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Microwave Assisted Solid-Supported Organic Synthesis: A Novel Methodology To Obtain 2,3-Disubstituted-1,4-Naphthoquinones

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MICROWAVE ASSISTED SOLID-SUPPORTED ORGANIC SYNTHESIS: A NOVEL METHODOLOGY TO OBTAIN 2,3-DISUBSTITUTED-1,4-NAPHTHOQUINONES

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Dedication

I dedicate this work to my unconditionally supportive family

Humberto Gérges García Serrano and Virginia Martínez Zavala

Humberto Esteban García Martínez

Daniel Adrian García Martínez

My Grandparents

Adrian Martínez Rodriguez (RIP) and Maria Zavala Cano

Humberto García Wagner (RIP) and Patricia Estela Serrano Fernández de Lara

MICROWAVE ASSISTED SOLID-SUPPORTED ORGANIC SYNTHESIS: A NOVEL DEVELOPMENT OF A METHODOLOGY TO OBTAIN 2,3-DISUBSTITUTED-1,4-NAPHTHOQUINONES

by

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DISSERTATION

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Abstract

This research focuses on the combinatorial solid phase organic synthesis (SPOS) of different bioactive compounds utilizing transition metal mediated reactions via microwave assisted organic synthesis (MAOS).

A microwave-assisted solid-supported Dötz benzannulation of chromium Fischer carbene complexes with various alkynes has been reported. The oxidative cleavage of the resulting resin-bound 1,4-naphthols affords 2,3-disubstituted-1,4-naphthoquinone derivatives in good to moderate yields with high purities.[1] We demonstrated that solid phase organic synthesis of naphthoquinones via conventional heating is limited due to their long reaction times and high temperatures. The products decompose leading to low yields and purities.[2] Microwave assisted synthesis of these naphthoquinones will increase the yields, reduce reaction times, temperatures and avoid decomposition of the products leading to new probes for chemical biology.

The previously reported synthesis procedure demands considerable effort and care to avoid decomposition of the intermediates.[1] Furthermore, contemporary synthesis of Fischer carbene complexes is limited by purification using column chromatography. A novel "Catch-Release" technique of Fischer carbene chromium complex has been accomplished to purify the organometallic complex. This technique produces both solid supported and solution phase

Fischer carbene complexes with good to moderate yields and high purities. The application of solid supported reagents will eliminate the need for column chromatography or liquid-liquid purifications thus provides a new synthetic approach to these types of organometallic moieties. The first "Catch-Release" synthesis of both solid- and non-supported chromium Fischer carbene complexes is presented.

Finally, "Click Chemistry" offers a versatile strategy for the construction of heterocyclic compounds that find wide spread applications in drug discovery programme.[2] In particular, Huisgen 1,3-dipoar cycloaddition of alkynes with azides to give triazole derivatives is a powerful example of this chemistry.[3] An efficient method for the solid-phase organic synthesis of 1, 2, 3-triazole containing 1,4-naphthoquinone derivatives through solid-supported Dötz benzannulation and Huisgen 1,3-dipolar cycloaddition reaction, followed by the oxidative cleavage of the resulting resin-bound click product is described.

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Chapter 1

SYNTHESIS OF 2,3-DISUBSTITUTED-1,4-NAPHTHOQUINONES VIA SPOS & MAOS

1.1. Introduction.

Synthesis of diverse analogs is a major practice during the development of new lead molecules in medicinal chemistry. The proficient application of small organic molecule parallel synthesis is one of the main methods to speed drug discovery.[5] These concepts can be misunderstood in terms of only chemistry or biology; hence, it is crucial to talk about a chemical biology field. Chemical biology is difficult to encapsulate, nevertheless, *Nature* states that: "chemical biology is both the use of chemistry to advance a molecular understanding of biology and the harnessing of biology to advance chemistry". Despite chemist's desires to have their compounds widely used by biologists, and biologist's to utilize chemical tools to enhance their understanding of biological systems, obstacles to chemist-biologist collaborations remain to be addressed.[6]

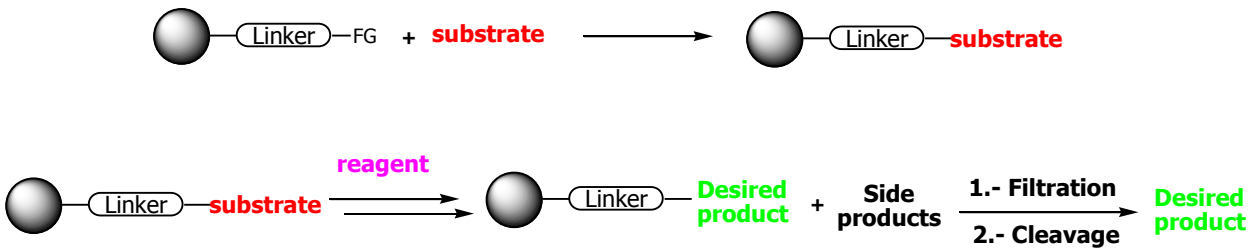
One of the most important chemical branches that help to address these barriers is organic chemistry. Organic reactions and reaction sequences for parallel synthesis to prepare target molecules should, if possible, be straightforward, rapid, efficient and resulting products should also be easily purified.[6]

Throughout the most common synthesis techniques there are two categories: liquid phase organic synthesis and solid phase organic synthesis. Liquid phase organic synthesis (LPOS) is considered classical organic synthesis performed in a homogenous environment, Scheme 1.1.

Scheme 1.1 - General representation of Liquid Phase Organic Synthesis.

1.1.1 Solid Phase Organic Synthesis (SPOS).

Solid Phase Organic Synthesis (SPOS) has been utilized as a major effort to create new lead compounds in medicinal chemistry. SPOS involves the application of solid supported reagents to conventional liquid phase chemistry, or synthesized on a solid support. In the latter application a bound intermediate is transformed to the synthetic target and then subsequently cleaved off the solid support, Scheme 1.2. [7]



Scheme 1.2 - General representation of solid phase organic synthesis; FG = Functional Group.

Expected reaction rate reductions due to the heterogeneous nature of SPOS are usually addressed by the application of microwave irradiation to speed up the rate of the reaction.[8]

1.1.2 Microwave Assisted Organic Synthesis (MAOS).

In the past few years, using microwave energy to heat and drive chemical reactions has become increasingly popular in the medicinal chemistry community.[9a] First described 20 years ago, this non-classical heating method has matured from a laboratory curiosity to an established technique that is heavily used in academia and industry. One of the many advantages of using rapid "microwave flash heating" for chemical synthesis is the dramatic reduction in reaction times, from days and hours to minutes and seconds.[9a] Microwaves lie in the electromagnetic spectrum between infrared waves and radio waves. They operate in a frequency range between 0.3 and 30 GHz. However, for their use in laboratory reactions, a frequency of 2.45 GHz is preferred.[9b] The fundamental mechanism of microwave heating involves agitation of polar molecules or ions that oscillate under the effect of an oscillating electric or magnetic field. In the presence of an oscillating field, particles try to orient themselves or be in phase with the field. However, the motion of these particles is restricted by resisting

forces (inter-particle interaction and electric resistance). These forces restrict the motion of particles therefore generating random motion, which produces heat.

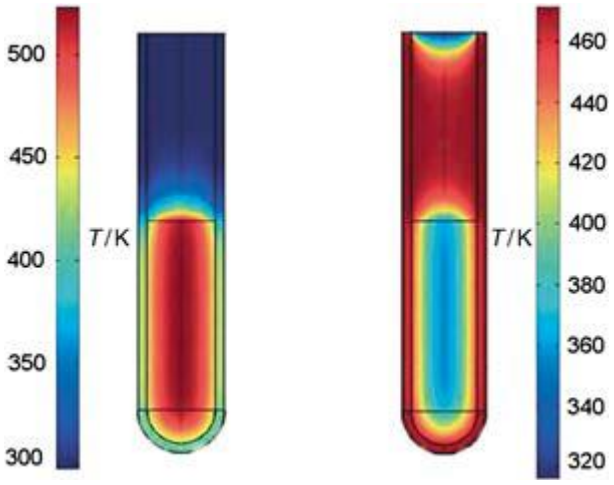


Figure 1.1: Thermal comparison between microwave irradiation vs. oil bath heating.

Figure 1.1 demonstrates the inverted temperature gradients in microwave versus oil bath heating: difference in the temperature profiles after 1 min of microwave irradiation (left) and treatment in an oil bath (right). Microwave irradiation simultaneously increases the temperature of the whole volume (bulk heating) whereas in the oil-heated tube, the reaction mixture in contact with the vessel wall is heated first.[9c]

One of the most important aspects of microwave energy is the heating rate. Microwaves will transfer energy in 10^{-9} seconds with each cycle of electromagnetic energy. The kinetic molecular relaxation from this energy is approximately 10^{-5} seconds. As a result, energy transfers at a faster rate than relaxation of the molecules, which results in non-equilibrium conditions and high

instantaneous temperatures that affect the kinetics of the system. This leads to enhancement in reaction rates and product yields.

In the Arrhenius reaction rate equation ($k=Ae^{-Ea/RT}$), the reaction rate constant is dependent on two factors: the frequency of collisions between molecules that have the correct geometry for a reaction to occur (A) and the fraction of those molecules with the minimum energy required to overcome the activation energy barrier ($e^{-Ea/RT}$).[9d] It is worthwhile to note that microwaves neither influence the orientation of collisions nor the activation energy. Activation energy remains constant for each particular reaction; however, microwave energy affects the temperature parameter in this equation. An increase in temperature causes greater movement of molecules which leads to a greater number of energetic collisions. This occurs much faster with microwave energy due to high instantaneous heating of the substances above the normal bulk temperature and is the primary factor for observed rate enhancements. Microwave heating is extremely useful in slower reactions where high activation energy is required.[9e]

Among many highly exploited reactions, synthesis of various microwave-assisted reactions involving metal catalysts or metal-based reagents often facilitates the discovery of novel reaction pathways. The extreme reaction conditions attainable by microwave heating sometimes lead to unusual reactivity by conventional heating. These conditions are not always reproducible during the

synthesis of new chemical entities and for discovering and probing new chemical reactivities.[9e] One type of natural product whose synthesis could be improved by the application of these techniques are 1,4-naphthoquinones.

1.1.3 Naphthoquinones.

The naphthoquinone moiety is present in a vast array of natural products (Figure 1.2). Some of these molecules participate in an important number of biological processes such as cellular respiration and electron transfer in mitochondria and have been shown to possess anti-infective activities such as antitumor, antifungal and biocide activity.[10] Furthermore, natural product naphthoquinones have also shown cytotoxicity attributed to DNA modification.[10]

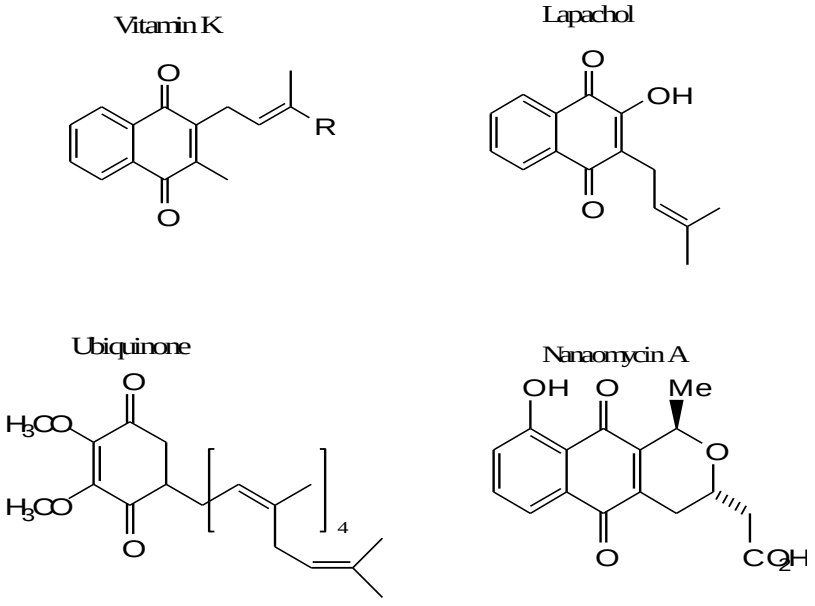


Figure 1.2.- Examples of natural products containing the quinone functionality.

Thus naphthoquinones are considered privileged structures. [12] They are compounds with a specific structural type, usually rigid heterocyclic systems, capable of inducing a wide array of biological activities (Figure 1.3).

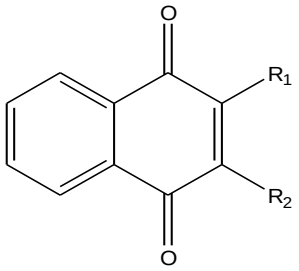
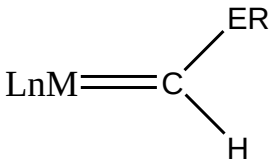


Figure 1.3 - 2,3-disubstituted 1,4-Naphthoquinone Moiety (R_1 = R_2 = H, aryl, alkyl.)

Potential pathways to synthesize biologically active lead compounds are transition metal-mediated reactions. They are extremely appealing for solid-phase organic synthesis (SPOS) due to their versatility and wide-ranging functional group compatibility. Although a wide range of Pd mediated coupling reactions and transition metal-catalyzed olefin metathesis reactions have been utilized in SPOS, [13] the development of transition metal Fischer carbene chemistry remains relatively unexplored.

1.1.4 Metal Fischer Carbene Complex.

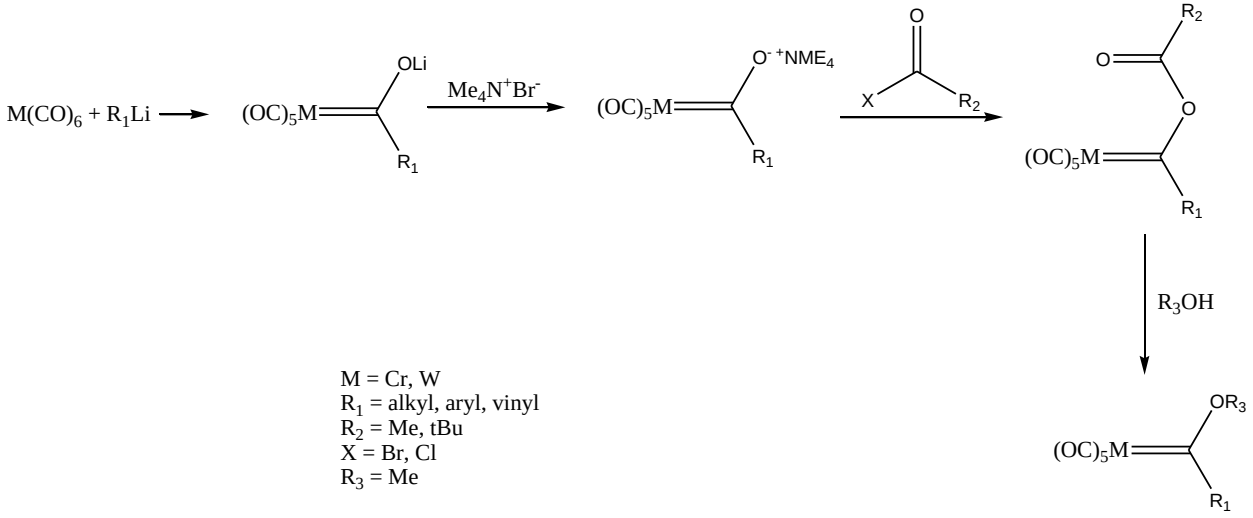
Fischer carbene complexes were named after Ernst Otto Fischer, [14a] they are typically found to be electron-rich, low oxidation state metal complexes (mid to late transition metals) containing pi-acceptor ligands, i.e.: Fe(0), Mo(0), Cr(0), W(0)[14b&c] (Figure 1.4).



R = alkyl, aryl, etc.
E = O, S, N.
M = Fe, Cr, Mo, W.

Figure 1.4 - General representation of a Fischer carbene complex.[15]

The most common synthesis for these Fischer carbene complexes is the one reported by Wulff, et.al, [16] (Scheme 1.3) consisting of reacting an organo-lithium molecule to chromium hexacarbonyl followed by alkylation at the oxygen with a hard alkylating agent.



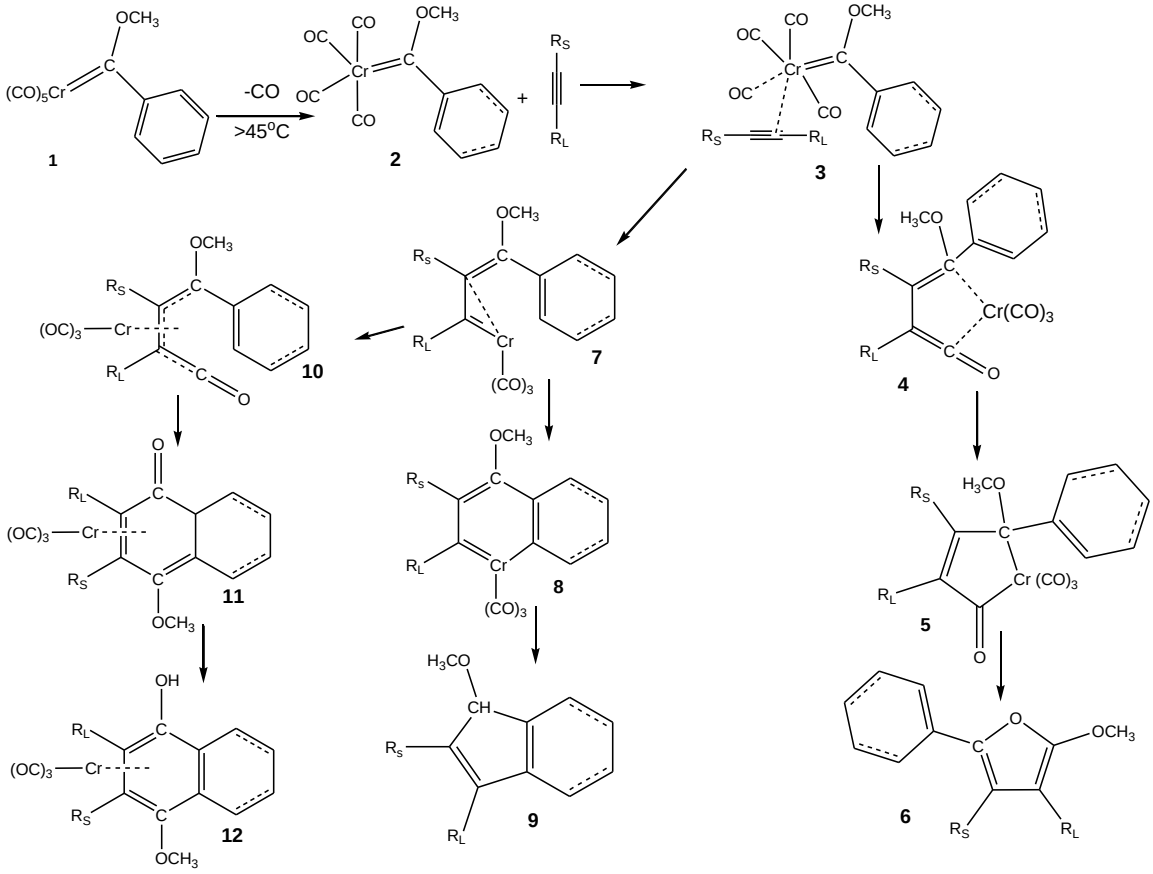
Scheme 1.3 - Commonly used reaction path to synthesize Fischer carbene complexes.

Notable among transition metal carbene chemistry is the Dötz benzannulation of Fischer carbene complexes with alkynes to form substituted phenols.[17]

1.1.5 [3+2+1] Dötz Benzannulation.

Developed by Karl Heinz Dötz in 1975, [17] the Dötz benzannulation is a reaction that utilizes a chromium Fischer carbene complex and an alkyne to obtain phenol derivatives. Its use is well documented in the literature [18] and reviews consist of the reaction of an α, β-unsaturated or an α-aryl-substituted metal (Cr(0), W (0), Mo (0)) carbene with an alkyne in a [3+2+1] cycloaddition fashion.

While the Dötz benzannulation has been extensively applied to synthesize a diverse array of natural products, [18] no examples of its application to combinatorial library synthesis have yet been reported. The mechanism of this [3+2+1] benzannulation is represented in Scheme 1.4 [19a]



Scheme 1.4 – General mechanism for [3+2+1] Dötz Benzannulation.

The Dötz benzannulation reaction gives multiple products depending on the polarity and nature of the solvent, if it is heated thermally or by other means such as photochemically or microwaves.[19b] Other factors to take into consideration are the reaction temperatures and the concentration of reactants, resulting in phenol **12**, indene **9**, furan **6**, and cyclobutanone products.[20] According to the benzannulation mechanism (Scheme 1.4), the rate determining step is the initial loss of a carbonyl ligand from the pentacarbonyl carbene

complex **1.** The generation of an unoccupied coordination site followed by the coordination of the alkyne generating complex **3** is the following step. The cycloaddition step and pericyclic ring opening forms a vinylcarbene complex **7**. Insertion of a CO moiety produces vinylketene **10** which undergoes ring closure and subsequent rearrangement produces phenol derivative **12**. The path to produce indenes occurs when vinylcarbene **7** does not undergo CO insertion and instead produces an intramolecular cyclization complex **9**. During the alkyne coordination, complex **4** can be favored when a carbonyl insertion followed by solvent assisted formation of metallocyclopentanone **5** leads to a furan complex **6**.[20]

One of the major advantages of solid phase synthesis is that provides pure products with a reduction in purification steps, along with the advantage that microwave enhanced synthesis decrease reaction times. The first description combining the advantages of both MAOS and SPOS was hydrolysis of amino acids from Merrifield resins by Wang. [21] The combination of these techniques has become extremely popular in the medicinal chemistry field where large libraries of clean products are synthesized very rapidly in the pharmaceutical industries. Aside from the advantages that each individual technique provides, the combination of both creates an additional benefit. Solid support reduces the use of reagents for a reaction mimicking high dilution techniques, as there is no need for column chromatography to purify final products. [22]

The fusion of these synthetic techniques provides an opportunity to produce large libraries of diversified compounds that promptly have natural product scaffolds. Synthetic chemists can increase the synthesis of natural small molecules such as naphthoquinones and benzofuran scaffolds under new synthetic methodologies that were not accessible before.

The use of Fischer carbene compounds to synthesize naphthoquinone moieties along with different alkynes via the Dötz benzannulation has been extensively applied to synthesize a diverse array of natural products. [18] This reaction typically results in the assembly of a mixture of products such as naphthols, indenes, furans and cyclobutanone. We reported a successful synthesis of naphthol moieties on solid support via the [3+2+1] cycloaddition.[1] The synthesis involves the SPOS of phenyl Fischer carbene complex to further react with alkynes to produce the naphthoquinone scaffolds after oxidative cleavage. Performing this reaction on solid support, only the six-membered naphthol adduct was obtained, supressing all the other byproducts produced according to the Dötz benzannulation mechanism. Benzoic acid is the only negligible byproduct obtained by the oxidation reaction of unreacted solid supported Fischer carbene complex.

It is worth to mention that the previously reported synthesis of Fischer carbene complexes on solid support produced molecules with low yields. These reaction procedures exposed the solid supported Fischer carbene to high

temperatures (120-140˚C) and destructive mechanical stirring which leads to degradation of the polymer support. Leachable products were found after the oxidative cleavage along with the desired molecules. [2]

The major innovation to improve this technique is the solid supported synthesis of 2,3-disubstituted-1,4-naphthoquinones via microwave enhanced Dötz benzannulation of Fischer carbene complexes.[1] We studied five main substrates that can be transformed into Fischer carbene complexes: phenyl, furan and three anisole molecules.

1.2 Results and Discussions.

The results from five Fischer carbene complexes (phenyl Fischer carbene, *o*-, *m*- and *p*-methoxy phenyl Fischer carbene and furan Fischer carbene) are presented in this section.

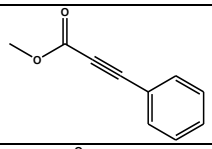
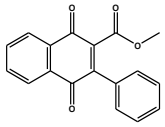
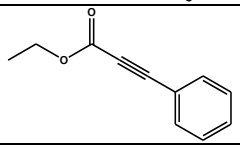
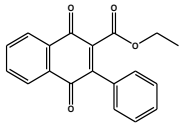
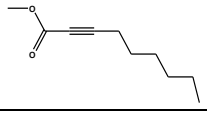
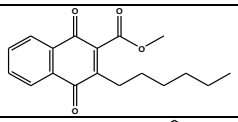
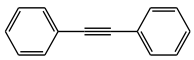
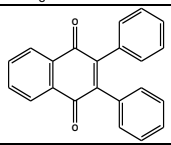
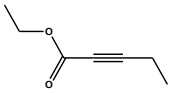
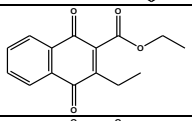
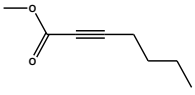
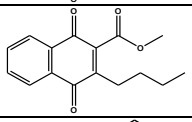
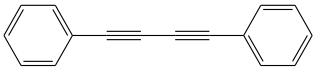
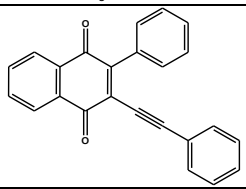
During this study, our chemistry was analyzed under two different microwave equipments. The equipments showed different results for three diverse reactions analyzed. Equipment A gives the best results. According to our study, discrepancies between equipments arise from the way the equipments were engineered. Equipment A has a tuner device right before the sample irradiation site. The microwaves that bounce back from the reaction vessel are tuned to make them additive to the waves coming into the sample instead of being destructive. Equipment B irradiates the sample in a circular fashion.

The microwaves do not irradiate the sample directly; instead they are bounced around a circular chamber with several windows. Once a wave finds a window it comes inside the heating chamber and irradiates the sample.

The drawback of this arrangement relies on the fact that microwaves can find each other inside the heating chamber and become destructive to each other. Refer to Appendix A for results.

1.2.1 - Results of Reactions Performed Between Resin-bound Phenyl Fischer Carbene Complexes with Several Alkynes under Microwave Assisted Dötz Benzannulation.

Table 1.1 shows a library of 2,3-disubstituted-1,4-naphthoquinones **16 b-s**, obtained by reacting phenyl Fischer carbene complex **13 a** with alkynes **14 b-s** utilizing MAOS-SPOS techniques.

Entry	Alkyne, **14**	2,3-disubstituted-1-4-naphthoquinone, **16**	Yield
b			89
c			84
d			78
e			76
f			74
g			73
h			68

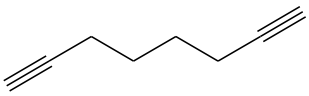
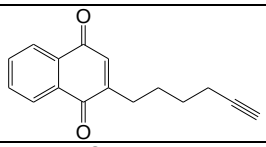
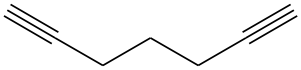
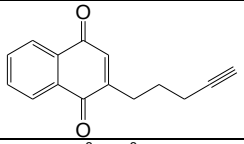
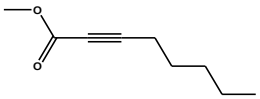
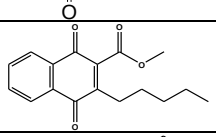
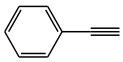
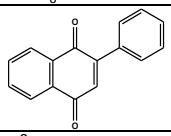
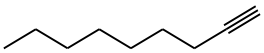
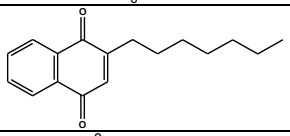
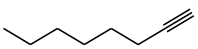
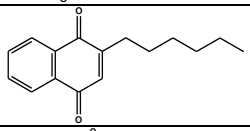
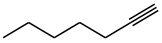
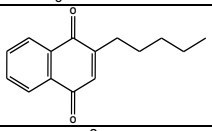
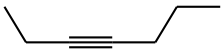
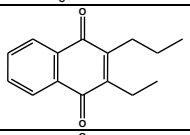
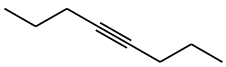
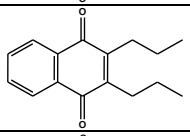
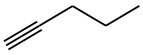
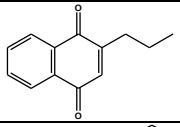
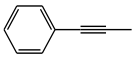
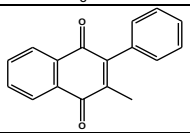
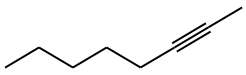
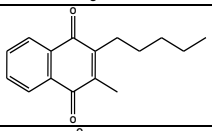
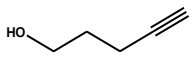
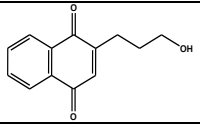
hh			68
hhh			67
i			67
j			67
k			63
l			62
m			58
n			57
o			55
p			53
q			50
r			50
s			50

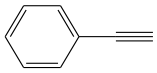
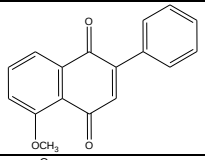
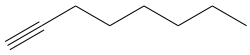
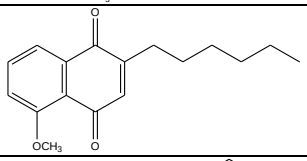
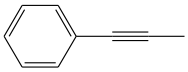
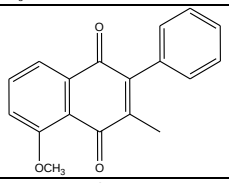
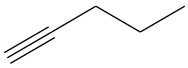
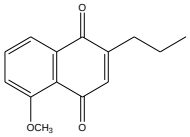
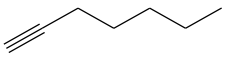
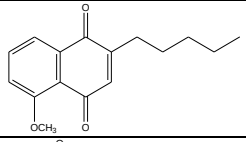
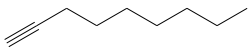
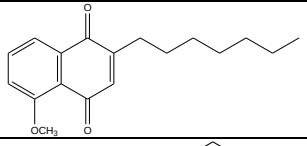
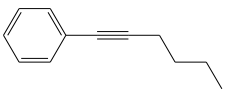
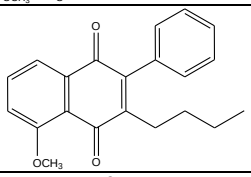
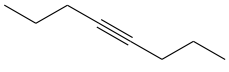
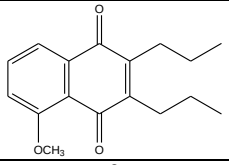
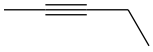
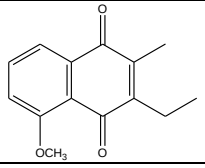
Table 1.1 - MAOS-SPOS reactions with phenyl Fischer carbene complex.

The 2,3-disubstituted-1-4-naphthoquinones were synthesized in high to moderate yields under SPOS-MAOS techniques (entries **16 b-s**, Table 1.1). According to these results, alkyl and aryl disubstituted propionates turned out to be the best alkynes to react with the solid supported phenyl Fischer carbene complex, followed by dialkyl substituted propionates, offering yields ranging from 67% to 89% (entries **16 b-d, f, g & i,** Table 1.1). Synthesis of this substrates lead to highly reactive dienophiles to utilize for further diversification. Similar high reactivity showed diphenylacetylene, 1,4-diphenylbuta-1,3-diyne, 2-(hex-5-ynyl)-1,4-naphthoquinone and 2-(pent-4-ynyl)-1,4-naphthoquinone 76%, 68%, 68% and 67% respectively (entries **16 e, h, hh** & **hhh** Table 1.1). Terminal aromatic alkynes followed by monosubstituted alkyl alkynes showed yields ranging from 58% to 67% (entries **16 j-m,** Table 1.1). Dialkyl alkynes followed by alkyl aryl alkyne give yields from 50% to 57%, (**16 n-s,** Table 1.1).

1.2.2 - Results of Reactions Performed Between Resin-bound *o*-Methoxy Phenyl Fischer Carbene Complexes with Several Alkynes under Microwave Assisted Dötz Benzannulation.

Table 1.2 shows a library of 2,3-disubstituted-5-methoxy-1,4-naphthoquinones **19 e, j-m, o-q, t-v**, obtained by reacting *o*-methoxy-phenyl

Fischer carbene complex **17 a** with alkynes **14 e, j-m, o-q, t-v,** utilizing MAOS-SPOS methodology.

Entry	Alkyne, **14**	5-methoxy-2,3-disubstituted-1-4-naphthoquinone, **19**	Yield %
j			80
l			73
q			73
m			72
p			70
k			69
t			60
o			55
u			48

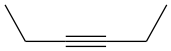
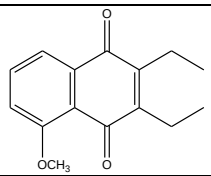
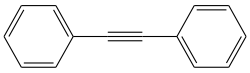
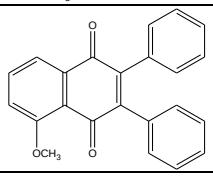
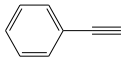
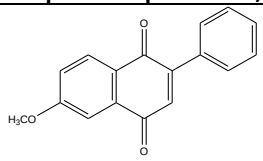
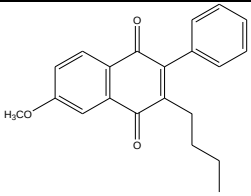
v			48
e			43

Table 1.2 - MAOS-SPOS reactions with *o*-methoxy-phenyl Fischer carbene complex.

The reactivity tendency observed in Table 1.2 for *o*-methoxy-phenyl Fischer carbene complex shows that terminal alkynes were the most reactive scaffolds, i.e. phenylacetylene, 80% (entries **19 j-m**, **p** & **q**, Table 1.2) followed by the internal unsymmetrical alkynes such as 2-pentyne, 48% (entries **19 t** & **u**, Table 1.2) leaving the symmetrical alkynes as the least reactive, i.e. diphenylacetylene, 43% (entries **19 o, v** & **e**, Table 1.2). The reactivity of the *o*-methoxy-phenyl Fischer carbene complex hold opposing views compared to the reactivity fashion of the phenyl Fischer carbene complex. In the first complex, one of the most reactive alkynes was diphenylacetylene, whereas in the *o*-methoxy-phenyl complex is the least reactive.

1.2.3 - Results of Reactions Performed Between Resin-bound *m*-Methoxy Phenyl Fischer Carbene Complexes with Several Alkynes under Microwave Assisted Dötz Benzannulation.

The reactivity of *m*-methoxy-phenyl complexes is being reported to be underprivileged due to electronic effects. [23] The presence of the electron donating methoxy group in the meta position related to the carbene, deactivates the aromatic ring. Hence, making it non susceptible of performing an efficient [3+2+1] cyclization and is not able to successfully compete with the formation of the aromatic system. Few reactions are reported for this substrate not only because of the low yields obtained but also because most did not proceed to completion, leaving behind oxidized unreacted complex as 3-methoxybenzoic acid. Results for products obtained with *m*-methoxy-phenyl Fischer carbene complex **17 a** are presented in Table 1.3.

Entry	Alkyne, **14**	6-methoxy-2,3-disubstituted-1-4-naphthoquinone, **19**	Yield %
j			28
t			13

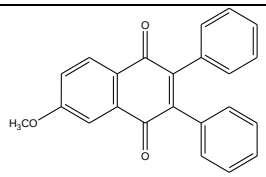
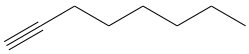
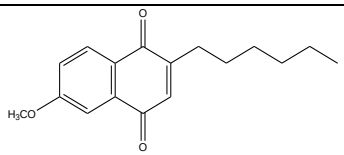
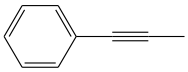
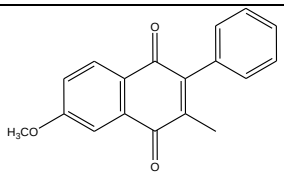
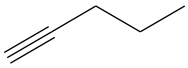
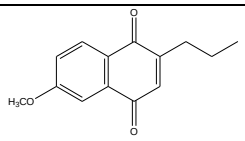
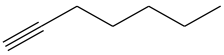
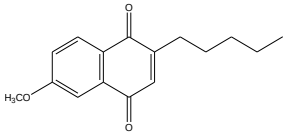
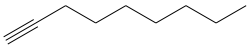
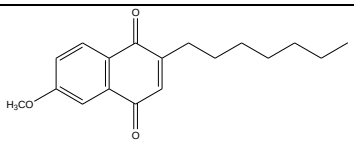
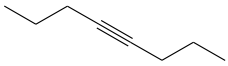
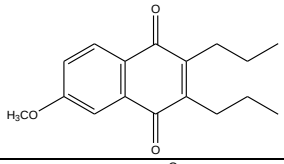
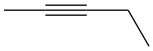
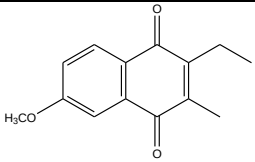
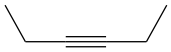
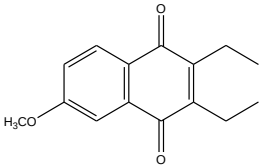
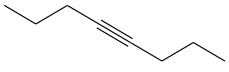
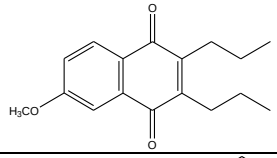
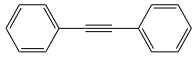
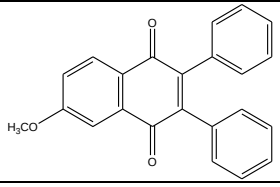
e			8
l			no
q			no
m			no
p			no
k			no
o			no
u			no
v			no

Table 1.3 - MAOS-SPOS reactions with *m*-methoxy-phenyl Fischer carbene complex.

In general, we obtained low yields and the *m*-methoxy phenyl Fischer complex reacted with 3 out of 11 alkynes. The most reactive alkyne was phenyl acetylene yielding 28% (entry **19 j**, Table 1.3) followed by 1-phenyl-1-hexyne, 13% (entry **19 t**, Table 1.3). Finally diphenylacetylene gave 8% yield (entry **19 e**, Table 1.3). It is difficult to determine a tendency for this substrate due to the underprivileged reactivity presented by the *m*-methoxy-phenyl Fischer carbene complex.

1.2.4 - Results of Reactions Performed Between Resin-bound *p*-Methoxy Phenyl Fischer Carbene Complexes with Several Alkynes under Microwave Assisted Dötz Benzannulation.

Results for products obtained with *p*-methoxy-phenyl Fischer carbene complex **17 a** are presented in Table 1.4.

Entry	Alkyne, **14**	7-methoxy-2,3-disubstituted-1-4-naphthoquinone, **19**	Yield %
o			56
e			49

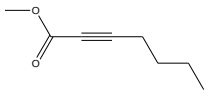
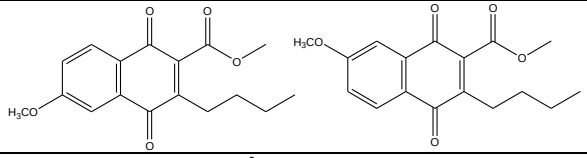
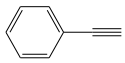
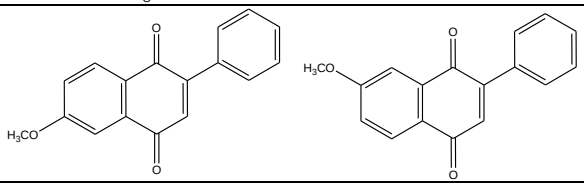
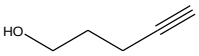
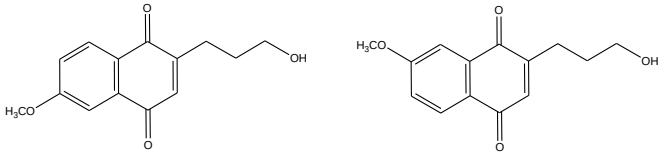
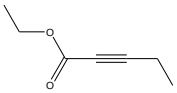
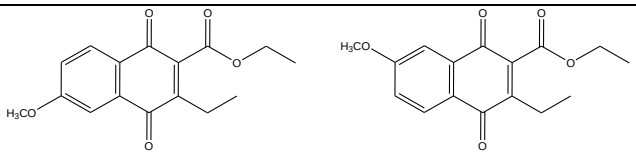
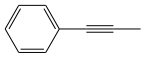
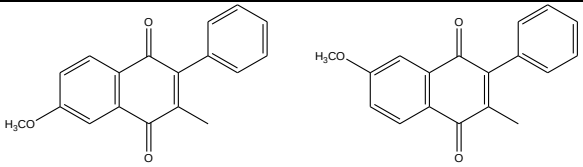
g			42
j			39
s			38
f			30
q			13

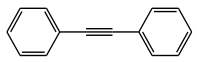
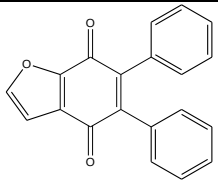
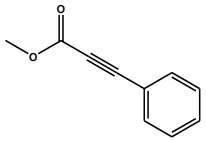
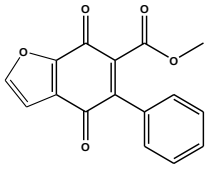
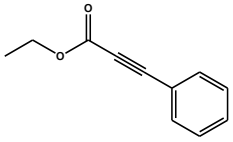
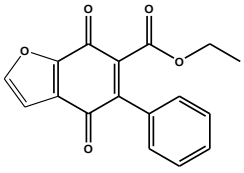
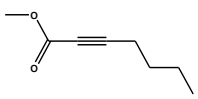
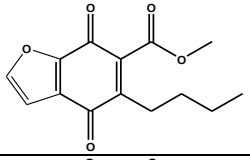
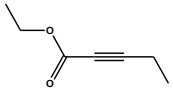
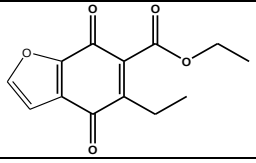
Table 1.4 - MAOS-SPOS reactions with *p*-methoxy-phenyl Fischer carbene complex.

The *p*-methoxy-phenyl Fischer carbene complex shows the tendency to react in moderate yields with internal symmetrical alkynes, i.e. 4-octyne 52% (entry **19 o**, Table 1.4), followed by diphenylacetylene 49% (entry **19 e**, Table 1.4). Terminal alkynes are next in the tendency, (entries **19 j** & **s**, 39 and 38%, Table 4) Finally, internal alkynes with shorter alkyl chain such as 2-(ethyl-carboxylate)-3-ethyl-6-methoxy-1,4-naphthoquinone (entry **19 f**, 30%, Table 1.4). The least reactive alkyne was the 1-phenyl-propyne (entry **19 q**, 13%). All

unsymmetrical alkynes (entries **19 g, j, s, f, q,** Table 1.4) resulted in two isomers with 50/50 distribution.

1.2.5 - Results of Reactions Performed Between Resin-bound Furan Fischer Carbene Complexes with Several Alkynes under Microwave Assisted Dötz Benzannulation.

Another substrate that was subjected to SPOS-MAOS methodology was the furan Fischer carbene complex, Table 1.5.

Entry	Alkyne, **14**	5,6-disubstituted-4,7-naphthoquinone, **22**	Yield
e			77
b			75
c			74
g			73
f			72

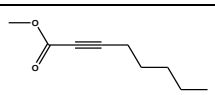
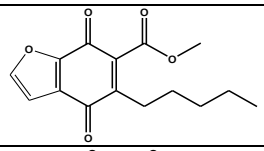
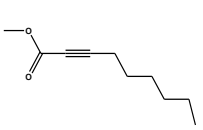
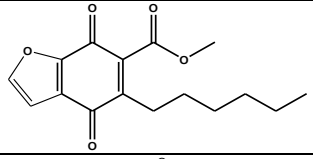
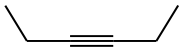
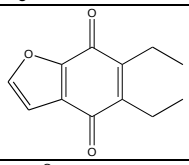
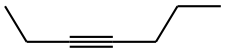
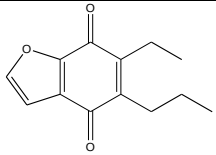
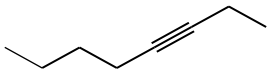
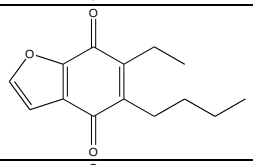
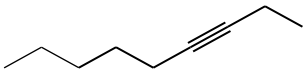
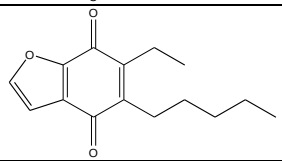
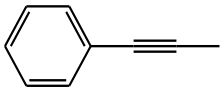
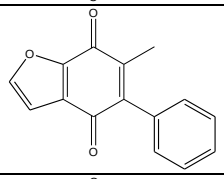
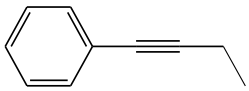
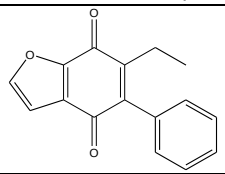
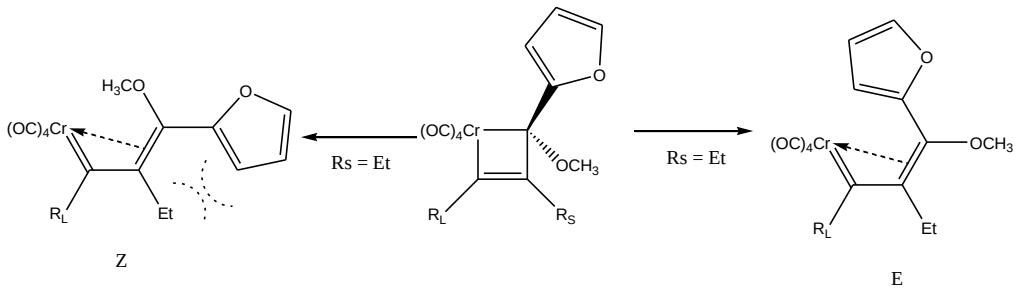
i			67
d			65
w			63
n			61
x			61
y			60
q			58
z			54

Table 1.5 - MAOS-SPOS reactions with furan Fischer carbene complex.

The furyl Fischer carbene complex has the tendency to react in high to moderate yields. The highest yielding product was the reaction with diphenylacetylene 77% (entry **22 e**, Table 1.5), followed by aryl and alkyl methyl

or ethyl propionates 65-75% (entries **22 b-d**, **f**, **g** & **i**, Table 1.5). Internal dialkyl unsymmetrical alkynes are next in the trend, (entries **22 n, w-y,** 63 and 60%, Table 1.5). Finally, internal alkyl aryl alkynes such as 1-phenyl-1-butyne give 54% yield (entry **22 z**, Table 1.5). According to McCaullum, et al., [42] the electrocyclic ring opening of the chromacyclobutene intermediate produces the E and Z isomers of the vinylcarbene complex intermediate, and from a consideration of sterics the ring opening should be favored to the E isomer with disubstituted acetylenes where R_s is non-hydrogen to a greater degree than in the case of terminal acetylenes where R_s = H due to the anticipated greater interactions between and the aryl substituent than with the methoxy group.



Scheme 1.5 – Sterics leading to the predominant regioisomer for furan carbene Dötz benzannulation

The solid supported of furan Fischer carbene complex shows similar benefits than the phenyl or the substituted phenyl carbenes. The main distribution of products obtained after oxidative ceric (iv) cleavage is the desired 5,6-disubstituted-4,7-furanquinone along with furanic acid. The last one

produced by oxidation of unreacted furan Fischer carbene complex attached to the polymer support.

1.3 Conclusions.

According to these results the best solid supported Fischer carbene substrates employed to carry out microwave assisted Dötz benzannulation reactions are the phenyl Fischer carbenes (yields: 50-89%) followed by the furan Fischer carbene (yields: 54-77%).

The 2,3-disubstituted-1-4-naphthoquinones were synthesized in high to moderate yields. Alkyl and aryl disubstituted propionates turned out to be the best alkynes to react with this substrate, followed by dialkyl substituted propionates, offering yields ranging from 67-89% and producing highly reactive dienophiles. Similar high reactivity showed diphenylacetylene and 1,4-diphenyl-buta-1,3-diyne, 76% and 68% respectively. Terminal aromatic alkynes followed by monosubstituted alkyl alkynes showed yields ranging from 58-67%. Dialkyl alkynes followed by aryl alkyl alkynes give yields from 50-57%.

The reactivity tendency observed for *o*-methoxy-phenyl Fischer carbene complex showed that terminal alkynes were the most reactive scaffolds, i.e. phenylacetylene, 80%, followed by the internal unsymmetrical alkynes such as 2-pentyne, 48%, leaving as a least reactive the symmetrical alkynes, i.e. diphenylacetylene, 43%. The reactivity of the *o*-methoxy-phenyl Fischer carbene

complex hold opposing behavior compared to the reactivity fashion of the phenyl Fischer carbene complex. In the first complex, one of the most reactive alkynes was diphenylacetylene, whereas in the *o*-methoxy-phenyl complex it is the least reactive.

In general, the yields for the *m*-methoxy phenyl Fischer complex were low and only reacted with 3 out of 11 alkynes. The most reactive alkyne was phenyl acetylene yielding 28%, followed by 1-phenyl-1-hexyne, 13%. Finally diphenylacetylene gave 8% yield. It is difficult to determine a tendency for this substrate due to the underprivileged reactivity presented by this complex. [23]

The p-methoxy-phenyl complex showed the tendency to react in moderate yields with internal symmetrical alkynes, i.e. 4-octyne 52%, followed by diphenylacetylene 49%. Terminal alkynes are next with yields of 39 and 38%. Finally, Internal alkynes with shorter alkyl chain such as 1-ethyl propionate, 30%. The least reactive alkyne was the 1-phenyl-propyne, 13% yield. All unsymmetrical alkynes resulted in two isomers with 50/50 distribution.

The furan Fischer carbene shows similar behavior as the liquid phase Dötz benzannulation. It is more selective with disubstituted alkynes than with terminal or unsymmetrical alkynes. The highest yielding product for the furan complex was the reaction with diphenylacetylene, 77%, followed by aryl and alkyl methyl or ethyl propionates 65-75% leading to similar furan species highly reactive dienophile. Internal dialkyl unsymmetrical alkynes are next in the trend, 63 and

60% yield. Finally, internal alkyl aryl alkynes such as 1-phenyl-1-butyne give 54% yield.

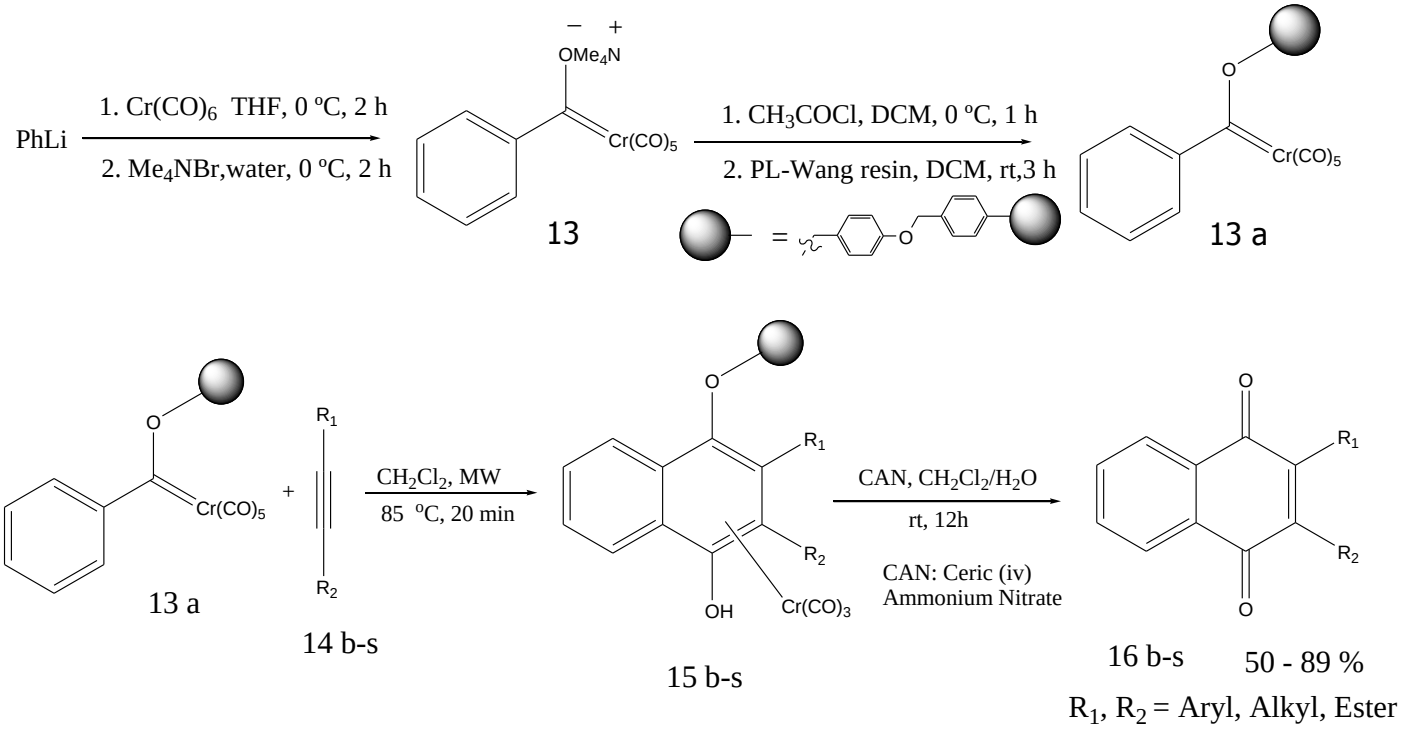
In summary, we have developed a new resin-bound Fischer carbene of chromium complexes. The solid-supported Dötz benzannulation reaction followed by CAN cleavage allows an efficient synthesis of various 1,4-naphthoquinone derivatives in good to moderate yields for five different substrates.

1.4 Experimental.

Due to the pyrophoric condition of the compounds and sensitivity of the products all reactions were carefully performed under inert gas atmosphere. During inert gas manipulations standard Schlenk line technique was used or a vacuum atmosphere dry box model MO-40M. Solids such as polymer support and chromium hexacarbonyl were purged with nitrogen to avoid decomposition. Solvents were purchased from EMD Chemicals and dried in a solvent-purification system mBRAUN or via distillation methods under nitrogen atmosphere. Dichloromethane (DCM) was distilled from calcium hydride, while tetrahydrofuran (THF) and diethyl ether were distilled from the sodium ketyl of benzophenone. Chromium hexacarbonyl was purchased from Strem Chemicals. The polymers for solid supported reactions and scavengers such as the PL-Wang and PL-HCO_3 were purchased from Varian Inc. (former Polymer Laboratories). All other chemical reagents were utilized without further purification and were purchased from Sigma-Aldrich, Alfa Aesar, VWR and Lancaster Chemical Companies. The microwave reactions were performed in a microwave synthesizer Emrys Optimizer from Biotage (former Personal Chemistry) and a Discover unit from CEM. The thermal reactions were performed in a solid supported synthesizer QUEST 210 by Argonaut Technologies. Infrared (IR) spectroscopy analysis was performed in a Bruker Tensor 27 FTIR spectrometer; for solids analysis, Pike ATR or KBr pellet and for liquids NaCl plates were utilized. The nuclear magnetic

resonance (NMR) analysis was recorded on a Bruker AM-300 (300MHz). The chemical shifts in ^{1}H NMR spectra are reported in δ in units of parts per million (ppm) with respect to chloroform-d, multiplicities are stated as follows: s (singlet), d (doublet), t (triplet), m (multiplet) and the integration value n (# of protons) are given by the value nH.

1.4.1 - Synthesis of Resin-bound Fischer Carbene Complexes and Microwave Assisted Dötz Benzannulation.



Scheme 1.6 - Synthesis of solid supported Fischer carbene complex and microwave assisted [3+2+1] Dötz benzannulation.

1.4.1.1 - Synthesis of Tetramethylammonium salt of (phenyl-methylene-carbene) pentacarbonyl chromium(0), 13.

Modifying the method originally developed by Connor and co-workers, [24] the synthesis of polymer-supported Fischer carbene complex **13 a** was obtained in four steps (Scheme 1.6). Starting from commercially available chromium hexacarbonyl and phenyllithium followed by O-acylation of [tetramethylammonium][(2-phenyl)oxidocarbene]pentacarbonyl chromium(0) **13**

with acetyl chloride. Finally support the carbene on PL-Wang resin (Polymer Laboratories, 1% crosslinked, loading capacity of 1.7 mmol/g) to produce resin-bound Fischer carbene complex **13 a** in 95% loading as determined by elemental analysis.

Chromium hexacarbonyl (3.00 g, 13.6 mmol) and dry THF (20.0 mL) were placed in a 100 mL two-necked round bottom flask under N_2 atmosphere. The flask was cooled to 0 °C and a solution of phenyllithium (20.5 mmol, 1.9 M in cyclohexane-ether, 10.8 mL) was slowly added over a period of 20 min and allowed to stir for 2 h. The solvent was removed under vacuum and the resulting orange red residue was added to a solution of tetramethyl ammonium bromide (4.19 g, 27.2 mmol) in 20.0 mL of oxygen-free water. The reaction mixture was allowed to stir at 0 °C for 2 h. The product was extracted with dry CH_2Cl_2 (2 x 50 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate. The solvent was concentrated under vacuum to afford 4.64 g (92%) of crude **13** as a red solid.

1.4.1.2 - O-linked pentacarbonyl (phenyl-methylene-carbene) chromium(0) on PL-Wang beads, 13 a.

To a stirred solution of crude red solid **13** (4.64 g, 12.5 mmol) in 10.0 mL of CH_2Cl_2 at 0 °C, acetyl chloride (1.27 g, 16.3 mmol) was added. After stirring at 0 °C for 1 h, the reaction mixture was allowed to warm to room temperature. The

solvent and the unreacted acetyl chloride were removed under reduced pressure. The bright red solid was diluted with 20.0 mL of CH_2Cl_2 and this solution was transferred via cannula to a 50.0 mL fritted funnel (solid-phase peptide synthesizer) containing PL-Wang resin (1.47 g, 2.5 mmol–1.7 mmol/g specified by manufacturer). The reaction mixture was shaken on a wrist shaker at room temperature for 3 h, after which the mixture was filtered and the resin was washed sequentially with CH_2Cl_2 (2 x 50 mL), THF (1 x 25 mL), CH_2Cl_2 (1 x 25 mL) and dried under vacuum to constant weight to give 2.17 g resin-bound complex **13 a**. Bright red complex supported in polymer beads FT-IR (KBr) 2061 and 1944 cm^{-1} (Elemental analysis: Cr, 5.67% 95% loading @ 1.7 mmol/g.)

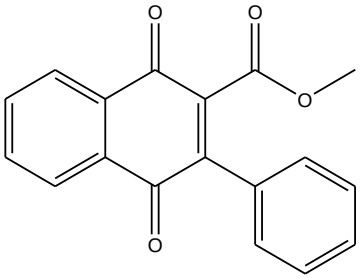
1.4.1.3 - Microwave assisted Dötz benzannulation reaction on solid support, 15.

To a microwave process vial (10.0 mL), resin **13a** (100 mg, 0.115 mmol) was added and the vial was sealed with an aluminum/Teflon crimp top. Then, a solution of alkyne **14** (0.575 mmol) in dry CH_2Cl_2 (2.0 mL) was added under nitrogen atmosphere. The reaction mixture was subjected to microwave irradiation (Biotage EmrysTM Optimizer—300 W maximum power) at 85˚C for 20 min. The reaction mixture was filtered and the resin was washed sequentially with CH_2Cl_2 (2 x 50 mL), THF (1 x 25 mL), CH_2Cl_2 (1 x 25 mL) and dried under vacuum for 1 h to afford resin-bound naphthols **15 b–s**.

1.4.1.4 - General procedure for cleavage of 15 employing ceric (IV) ammonium nitrate (CAN).

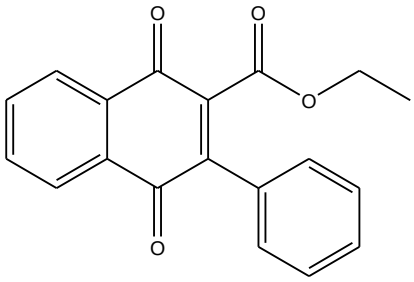
Resin-bound naphthols **15 b–s** (0.115 mmol) were suspended in a mixture of 3.0 mL of CH_2Cl_2 and ceric ammonium nitrate (0.315 g, 0.575 mmol) in 1.0 mL of water. The resulting suspension was stirred for 12 h and then filtered through a fritted glass funnel. The resin was washed with water (5.0 mL) and CH_2Cl_2 (5.0 mL). The resulting clear solution was washed with 10% NaOH (2 x 5 mL) and water (10.0 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed under vacuum to afford pure 2,3-Disubstituted-1,4-naphthoquinones **16 b–s**.

Figure 1.5 - 2-(methyl-carboxylate)-3-phenyl-1,4-naphthoquinone, **16 b.**



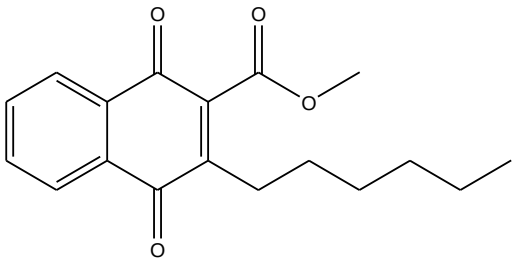
Yellow solid; ^1H NMR (300 MHz, $CDCl_3$): 7.80-7.70 (m, 2H); 7.70-7.60 (m, 2H); 7.40-7.28 (m, 5H); 3.78 (s, 3H).

Figure 1.6 - 2-(ethyl-carboxylate)-3-phenyl-1,4-naphthoquinone, **16 c.**



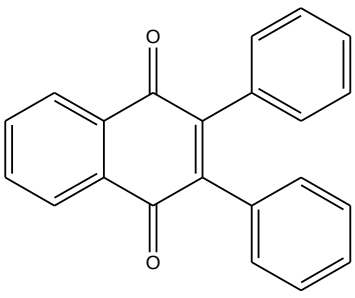
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.80-7.70 (m, 2H); 7.70-7.60 (m, 2H); 7.40-7.28 (m, 5H); 4.22(q, 2H); 1.32-1.30 (t, 3H).

Figure 1.7 - 2-(methyl-carboxylate)-3-hexyl-1,4-naphthoquinone, **16 d.**



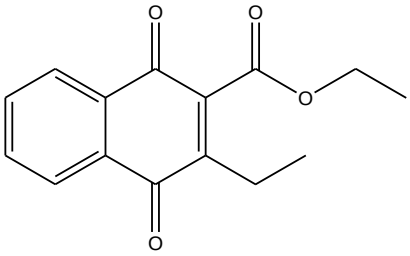
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.80-7.70 (m, 2H); 7.70-7.60 (m, 2H); 3.78(s, 3H); 2.10-1.98 (t, 2H); 1.50-1.30 (m, 8H); 1.0-0.96 (t, 3H).

Figure 1.8 - 2,3-diphenyl-1,4-naphthoquinone, **16 e.**



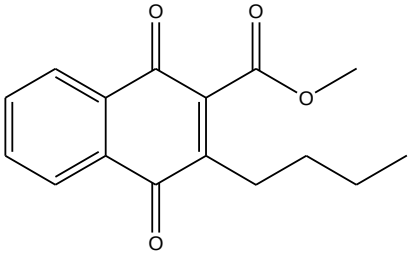
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.40-7.36 (m, 8H); 7.28-7.32 (t, 2H).

Figure 1.9 - 2-(ethyl-carboxylate)-3-ethyl-1,4-naphthoquinone, **16 f.**



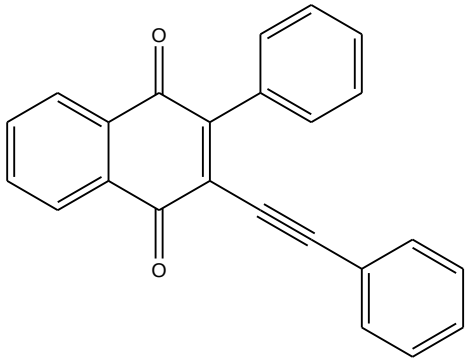
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 4.22(q, 2H); 2.10-1.98 (q, 2H); 1.32-1.30 (t, 3H); 1.0-0.96 (t, 3H).

Figure 1.10 - 2-(methyl-carboxylate)-3-butyl-1,4-naphthoquinone, **16 g.**



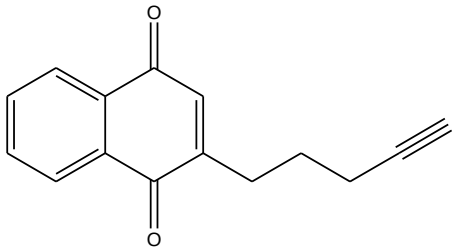
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 3.78(s, 3H); 2.10-1.9 (t, 2H); 1.35-1.25 (m, 4H); 1.0-0.96 (t, 3H).

Figure 1.11 - 2-phenyl-3-(phenylethynyl)-1,4-naphthoquinone, **16 h.**



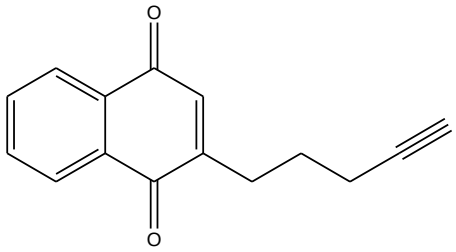
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.46-7.40 (m, 5H); 7.38-7.30 (m, 5H).

Figure 1.12 - 2-(hex-5-ynyl)-1,4-naphthoquinone**, 16 hh.**



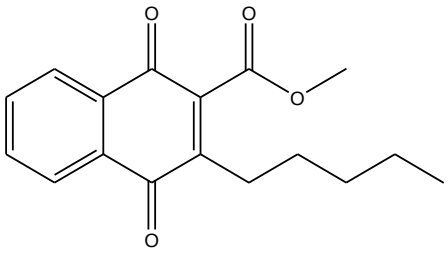
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.56 (s, 1H); 2.04-1.98 (t, 2H); 1.95-1.93 (t, 2H); 1.82 (s, 1H); 1.46-1.43 (t, 2H) 1.36-1.32 (m, 2H).

Figure 1.13 - 2-(pent-4-ynyl)-1,4-naphthoquinone**, 16 hhh.**



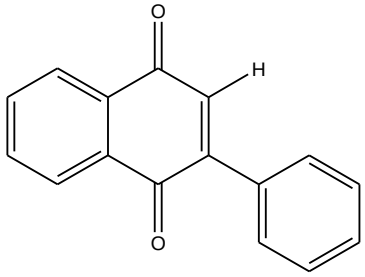
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.56 (s, 1H); 2.04-1.98 (t, 2H); 1.95-1.93 (t, 2H); 1.82 (s, 1H); 1.54-1.48 (m, 2H).

Figure 1.14 - 2-(methyl-carboxylate)-3-pentyl-1,4-naphthoquinone, **16 i.**



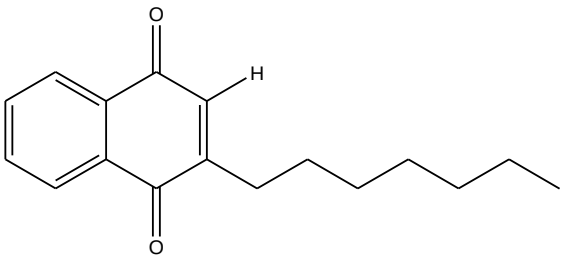
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 3.78(s, 3H); 2.10-1.9 (t, 2H); 1.45-1.35 (m, 6H); 1.0-0.96 (t, 3H).

Figure 1.15 - 2-phenyl-1,4-naphthoquinone, **16 j.**



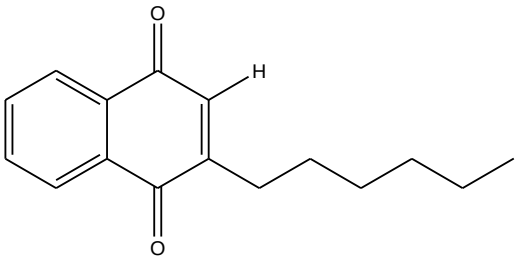
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.56 (s, 1H); 7.38-7.30 (m, 5H).

Figure 1.16 - 2-heptyl-1,4-naphthoquinone**, 16 k.**



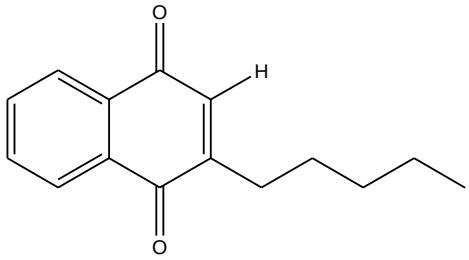
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.56 (s, 1H); 2.00-1.93 (t, 2H); 1.36-1.24 (m, 10H); 1.0-0.96 (t, 3H).

Figure 1.17 - 2-Hexyl-1,4-naphthoquinone**, 16 l.**



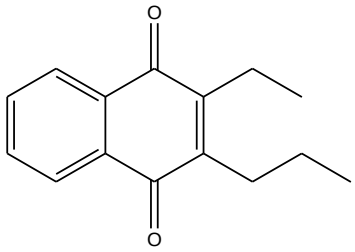
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.56 (s, 1H); 2.10-1.98 (t, 2H); 1.50-1.30 (m, 8H); 1.0-0.96 (t, 3H).

Figure 1.18 - 2-pentyl-1,4-naphthoquinone, **16 m**.



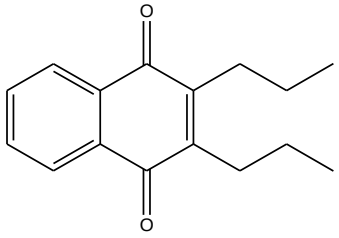
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.56 (s, 1H); 2.10-1.9 (t, 2H); 1.45-1.35 (m, 6H); 1.0-0.96 (t, 3H).

Figure 1.19 - 2-ethyl-3-propyl-1,4-naphthoquinone**, 16 n.**



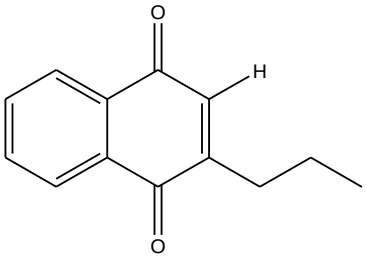
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 2.10-2.04 (t, 2H); 1.98-1.94 (t, 2H); 1.42-1.36(m, 2H); 1.06-1.00 (t, 3H); 0.98-0.95 (t, 3H).

Figure 1.20 - 2,3-dipropyl-1,4-naphthoquinone, **16 o.**



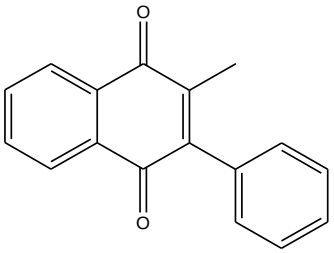
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 1.98-1.94 (t, 4H); 1.42-1.36(m, 4H); 0.98-0.95 (t, 6H).

Figure 1.21 - 2-propyl-1,4-naphthoquinone, **16 p**.



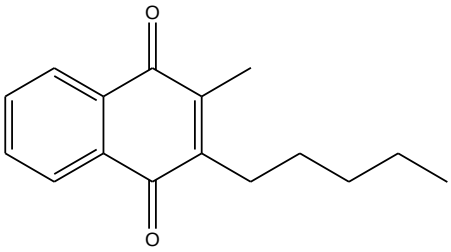
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 2.10-1.9 (t, 2H); 1.50-1.35(m, 2H); 1.0-0.96 (t, 3H).

Figure 1.22 - 2-methyl-3-phenyl-1,4-naphthoquinone, **16 q.**



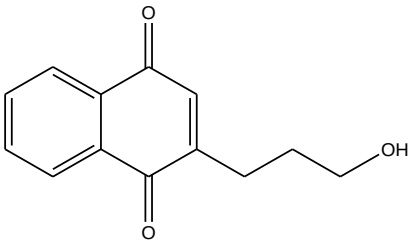
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.38-7.30 (m, 5H); 1.95 (s, 3H).

Figure 1.23 - 2-methyl-3-pentyl-1,4-naphthoquinone**, 16 r.**



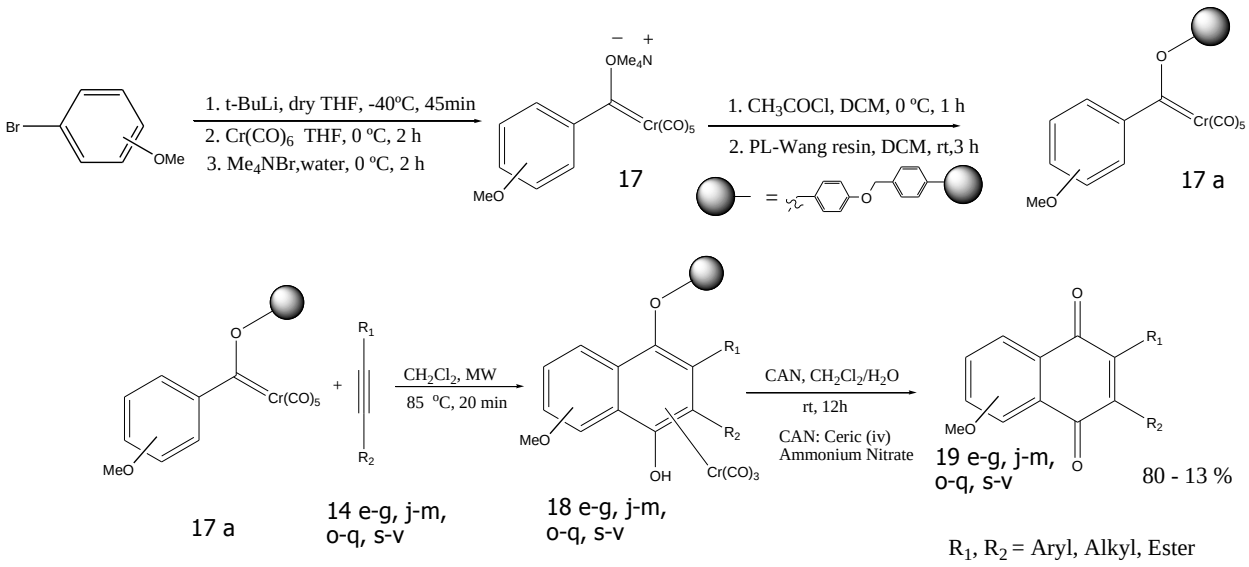
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 2.04-1.98 (t, 2H); 1.95 (s, 3H); 1.34-1.30 (m, 6H); 0.98-0.95 (t, 3H).

Figure 1.24 - 2-(3-hydroxypropyl)-1,4-naphthoquinone**, 16 s.**



Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 3.54-3.48 (t, 2H); 2.04-1.98 (t, 2H); 1.54-1.50 (m, 2H).

1.4.2 Synthesis of Resin-bound *o-, m-, p*-methoxy-phenyl Fischer Carbene Complexes and Microwave Assisted Dötz Benzannulation.



Scheme 1.7 - Synthesis of solid supported *o-, m-* or *p*-bromo methoxy-aryl Fischer carbene complex and microwave assisted [3+2+1] Dötz benzannulation.

1.4.2.1 - Synthesis of tetramethylammonium salt of (*o-, m-* or *p*-methoxy-aryl, methylene carbene] pentacarbonyl chromium(0), 17.

In a 50 mL round bottom flask equipped with stir bar, and septum wired down with 10mL of dry THF and 3mL of *o-, m-* or *p*-bromo anisole (2.41×10^{-2} mol; 1eq). The temperature of the solution is lowered to -40°C (slush bath) immediately followed by the addition of 28mL of tert-butyl lithium (4.82×10^{-2} mol; 2 eq.). Color changes from colorless to pale yellow. Stir for 45 minutes allowing the solution to warm up from -40°C (slush bath) to 0°C.

2.65gr ($1.2x10^{-2}$ mol, 1eq) of chromium hexacarbonyl is weighed on a round bottom flask equipped with stir bar, air free adaptor, and septum inside of the dry box. Under N_2, the prepared lithiated *o-, m-* or *p-* methoxy aryl Fischer carbene ($2.41x10^{-2}$ mol, 2eq) was transferred via cannula at 0°C (ice bath). The solution turned immediately from yellow to brown. After 2 hours, the resulting solution was a dark brown, and the chromium hexacarbonyl crystals had disappeared. The solvent was removed under reduced pressure on a vacuum line. The resulting brown slurry was dissolved in 15mL of nitrogen-saturated water (O_2 free), with 3.7 g ($2.41x10^{-2}$ mol, 2 eq) of tetramethylammonium bromide at 0°C. After 60 minutes, the organic layer was later extracted with 3x20mL of dry DCM. The combined organic extracts were promptly dried over $MgSO_4$, filtered, and the solvent was carefully removed under reduced pressure to yield a dark orange solid **17** (4.8g, 99%).

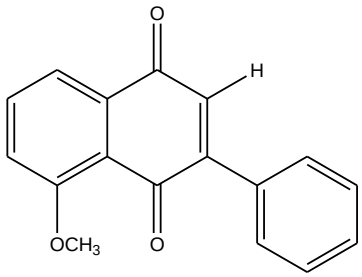
1.4.2.2 - O-linked pentacarbonyl (*o-, m-* & *p-*methoxy-aryl, methylene carbene) chromium(0) on PL-Wang beads, 17 a.

Add to a stirred solution of crude red solid **17** (4.8 g, 12 mmol) in 10.0 mL of CH_2Cl_2 at 0˚C, 1.7mL of acetyl chloride ($2.4x10^{-2}$ mol, 2eq). After stirring at 0˚C for 1 h, the reaction mixture was allowed to warm to room temperature. After 1 h, the solution's color turned from orange to dark red. The appearance of the dark red color is characteristic of the formation of the acetylated carbene

complex. The solvent and the unreacted acetyl chloride were removed under reduced pressure, washed with dry DCM to remove the traces of acetyl chloride. 1.42g of PL-Wang resin (2.4 mmol; 1.7 mmol/g bead, loading) was pre-swollen with 10mL of dry DCM for 20min. It is noted that *o-, m-* or *p*-methoxy-aryl acetoxy Fischer carbene complex are more sensitive than the phenyl Fisher carbene complex. Handling should be noted to maintain under N_2 and at low temperatures to avoid decomposition. The bright red solid was diluted with 20.0 mL of CH_2Cl_2 and this solution was transferred via cannula to a 50.0 mL fritted funnel (solid-phase peptide synthesizer) containing polystyrene PL-Wang resin (1.47 g, 2.5 mmol–1.7 mmol/g specified by manufacturer). The reaction mixture was shaken on a wrist shaker at room temperature for 3 h, after which the mixture was filtered and the resin was washed sequentially with CH_2Cl_2 (2 x 50 mL), THF (1 x 25 mL), CH_2Cl_2 (1 x 25 mL) and dried under vacuum to constant weight to give 2.2 g resin-bound complex **17 a** as a red solid.

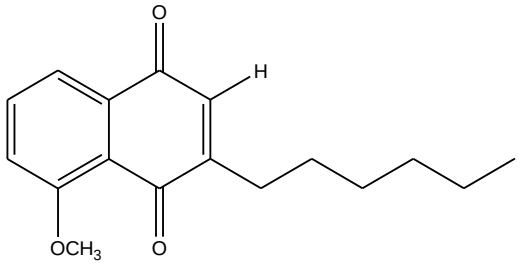
The microwave assisted Dötz benzannulation and the oxidative cleavage procedures are the same as reported previously for the phenyl Fischer carbene complex. Refer to sections 1.4.1.3 and 1.4.1.4 for details to perform microwave assisted Dötz benzannulation and oxidative cleavage respectively to obtain 2,3-disubstituted-(5-, 6- or 7-methoxy)-1,4-naphthoquinones **19 e-g, j-m, o-q, s-v**.

Figure 1.25 - 3-phenyl-5-methoxy-1,4-naphthoquinone, **19 j.**



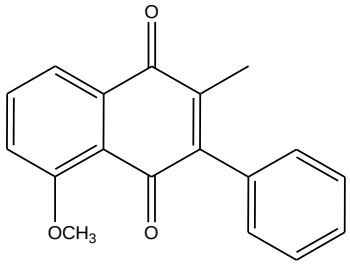
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.1 (s, 1H); 7.70-7.65 (t, 1H); 7.41-7.28 (m, 5H); 7.28-7.20 (d, 1H); 7.18-7.10 (d, 1H); 3.9(s, 3H).

Figure 1.26 - 3-hexyl-5-methoxy-1,4-naphthoquinone, **19 l**.



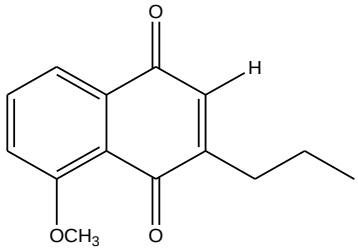
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.70-7.65 (t, 1H); 7.5 (s, 1H); 7.28-7.20 (d, 1H); 7.18-7.10 (d, 1H); 3.9 (s, 3H); 2.10-1.98 (t, 2H); 1.50-1.30(m, 8H); 1.0-0.96 (t, 3H).

Figure 1.27 - 2-methyl-3-phenyl-5-methoxy-1,4-naphthoquinone, **19 q.**



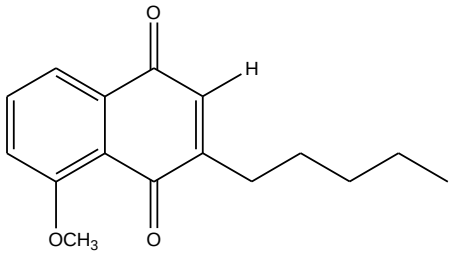
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.68-7.60(t, 1H); 7.42-7.26 (m, 5H); 7.27-7.23(d, 1H); 7.22-7.18 (d, 1H); 3.9 (s, 3H); 1.95 (s, 3H). Lit. reference [18]: ^{1}H NMR (CDCl3) δ 2.06 (s, 3H); 4.03 (s, 3H); 7.20 (d, 2H); 7.29 (d, 1H); 7.4-7.45 (M, 3H); 7.66 (t, 1H); 7.73 (d, 1H).

Figure 1.28 - 3-propyl-5-methoxy-1,4-naphthoquinone, **19 p**.



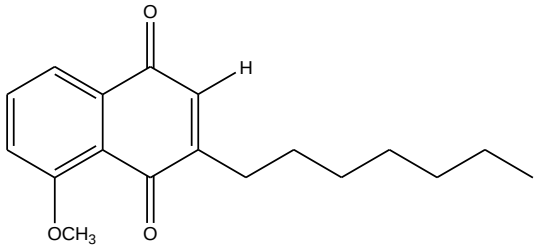
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.60-7.55 (t, 1H); 7.45 (s, 1H); 7.28-7.20 (d, 1H); 7.18-7.10 (d, 1H); 3.9 (s, 3H); 2.10-1.9 (t, 2H); 1.50-1.35(m, 2H); 1.0-0.96 (t, 3H).

Figure 1.29 - 3-pentyl-5-methoxy-1,4-naphthoquinone, **19 m**.



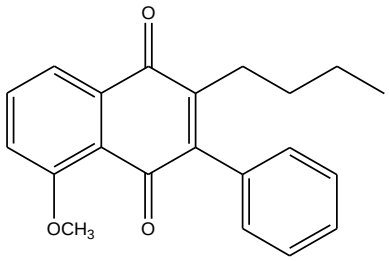
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.70-7.65 (t, 1H); 7.5 (s, 1H); 7.28-7.20 (d, 1H); 7.18-7.10 (d, 1H); 3.9 (s, 3H); 2.10-1.9 (t, 2H); 1.45-1.35(m, 6H); 1.0-0.96 (t, 3H).

Figure 1.30 - 3-heptyl-5-methoxy-1,4-naphthoquinone**, 19 k.**



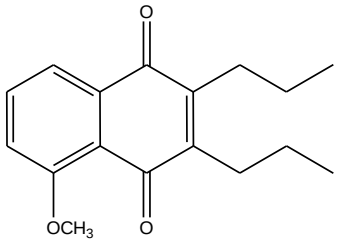
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.70-7.65 (t, 1H); 7.5 (s, 1H); 7.28-7.20 (d, 1H); 7.18-7.10 (d, 1H); 3.9 (s, 3H); 2.00-1.93 (t, 2H); 1.36-1.24(m, 10H); 1.0-0.96 (t, 3H).

Figure 1.31 - 2-butyl-3-phenyl-5-methoxy-1,4-naphthoquinone, **19 t.**



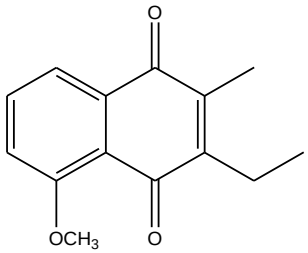
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.68-7.60(t, 1H); 7.42-7.26 (m, 5H); 7.27-7.23(d, 1H); 7.22-7.18 (d, 1H); 3.9 (s, 3H); 2.00-1.93 (t, 2H); 1.50-1.40(m, 4H); 1.0-0.96 (t, 3H).

Figure 1.32 - 2,3-dipropyl-5-methoxy-1,4-naphthoquinone, **19 o.**



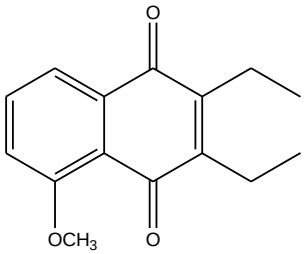
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.60-7.55 (t, 1H); 7.28-7.20 (d, 1H); 7.18-7.10 (d, 1H); 3.9 (s, 3H); 2.10-1.9 (t, 4H); 1.50-1.35(m, 4H); 1.0-0.96 (t, 6H).

Figure 1.33 - 2-methyl-3-ethyl-5-methoxy-1,4-naphthoquinone**, 19 u.**



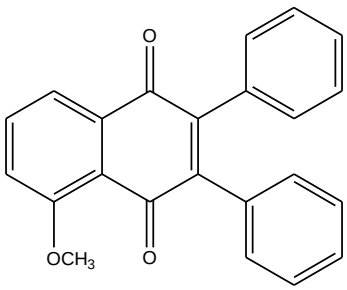
Yellow solid; 1H NMR (300 MHz, $CDCl_3$): 7.60-7.55 (t, 1H); 7.18-7.10 (d, 1H); 7.28-7.20 (d, 1H); 3.9 (s, 3H); 2.10-1.9 (q, 2H); 1.97(s, 3H); 1.0-0.96 (t, 3H).

Figure 1.34 - 2,3-diethyl-5-methoxy-1,4-naphthoquinone**, 19 v.**



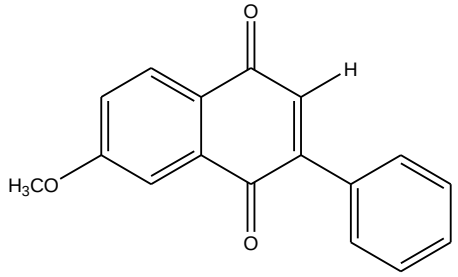
Yellow solid; ^1H NMR(300 MHz, $CDCl_3$): 7.60-7.55 (t, 1H); 7.18-7.10 (d, 1H); 7.28-7.20 (d, 1H); 3.9 (s, 3H); 2.10-1.9 (q, 2H); 1.0-0.96 (t, 3H).

Figure 1.35 - 2,3-diphenyl-5-methoxy-1,4-naphthoquinone**, 19 e.**



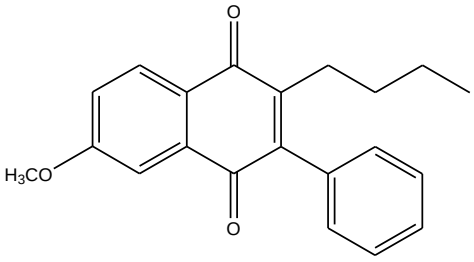
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.60-7.55 (t, 1H); 7.46-7.33 (m, 10H); 7.28-7.20 (d, 1H); 7.18-7.10 (d, 1H); 3.9 (s, 3H).

Figure 1.36 - 3-phenyl-6-methoxy-1,4-naphthoquinone, **19 j.**



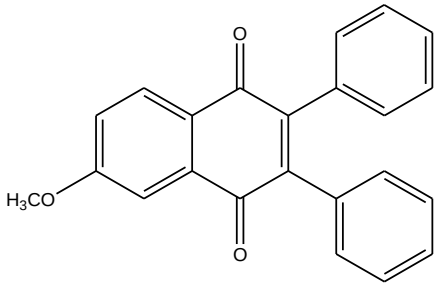
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.10 (s, 1H); 7.92-7.88 (d, 1H); 7.54 (s, 1H); 7.41-7.28 (m, 5H); 7.25-7.20 (d, 1H); 3.84 (s, 3H).

Figure 1.37 - 2-butyl-3-phenyl-6-methoxy-1,4-naphthoquinone, **19 t.**



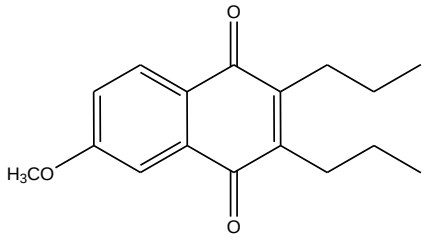
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.92-7.88 (d, 1H); 7.54 (s, 1H); 7.41-7.28 (m, 5H); 7.25-7.20 (d, 1H); 3.84 (s, 3H); 2.00-1.93 (t, 2H); 1.38-1.30(m, 4H); 1.0-0.96 (t, 3H).

Figure 1.38 - 2,3-diphenyl-6-Methoxy-1,4-Naphthoquinone**, 19 e.**



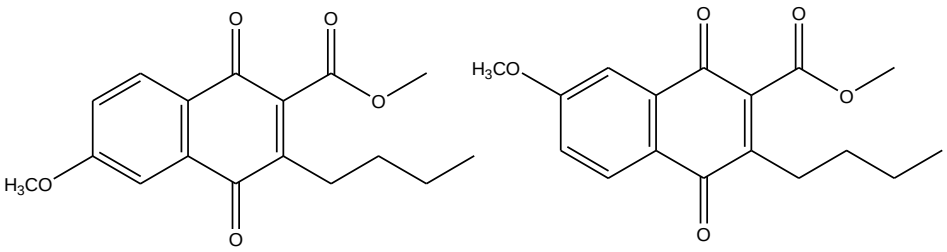
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.92-7.88 (d, 1H); 7.54 (s, 1H); 7.46-7.42 (d, 8H); 7.32-7.28 (t, 2H); 7.25-7.20 (d, 1H); 3.84 (s, 3H).

Figure 1.39 - 2,3-dipropyl-6-methoxy-1,4-naphthoquinone, **19 o.**



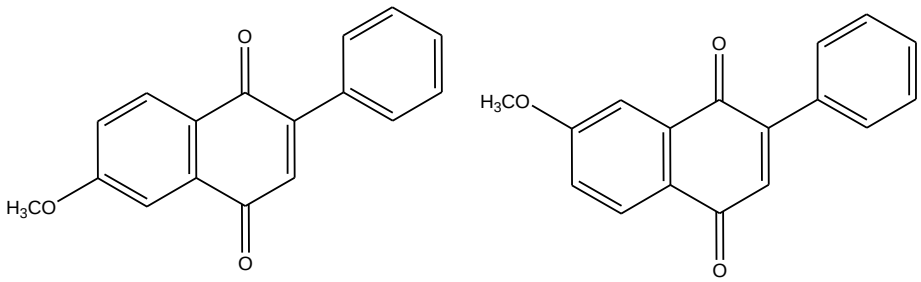
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.92-7.88 (d, 1H); 7.54 (s, 1H); 7.25-7.20 (d, 1H); 3.9 (s, 3H); 2.10-1.9 (t, 4H); 1.50-1.35(m, 4H); 1.0-0.96 (t, 6H).

Figure 1.40 - 2-(methyl-carboxylate)-3-butyl 6 & 7-methoxy-1,4-naphthoquinone, **19 g.**



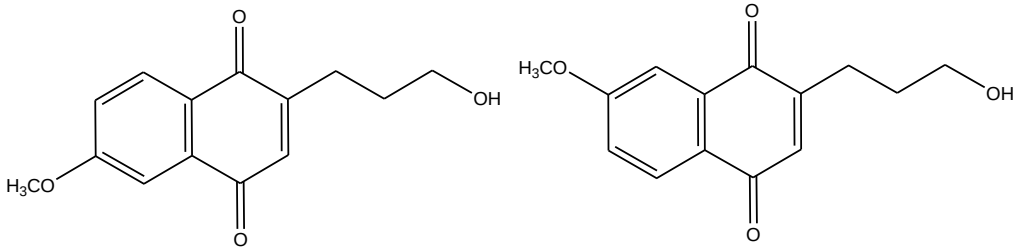
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.92-7.88 (d, 2H); 7.54 (s, 2H); 7.25-7.20 (d, 2H); 3.78(s, 6H); 2.10-1.9 (t, 4H); 1.35-1.25 (m, 8H); 1.0-0.96 (t, 6H).

Figure 1.41 - 2-phenyl-6 & 7-methoxy-1,4-naphthoquinone**, 19 j.**



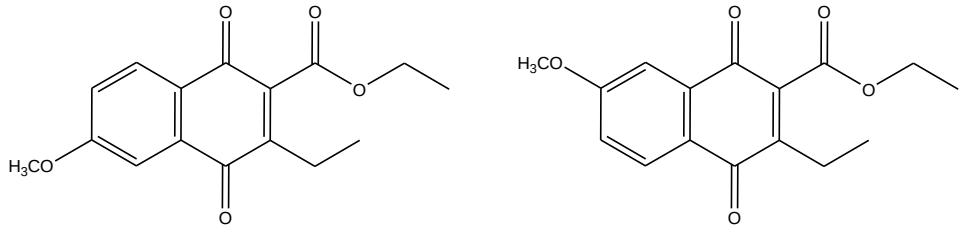
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.10 (s, 2H); 7.92-7.88 (d, 2H); 7.54 (s, 2H); 7.41-7.28 (m, 10H); 7.25-7.20 (d, 2H); 3.84 (s, 6H).

Figure 1.42 - 2-(3-hydroxypropyl)-6 & 7-methoxy-1,4-naphthoquinone**, 19 s.**



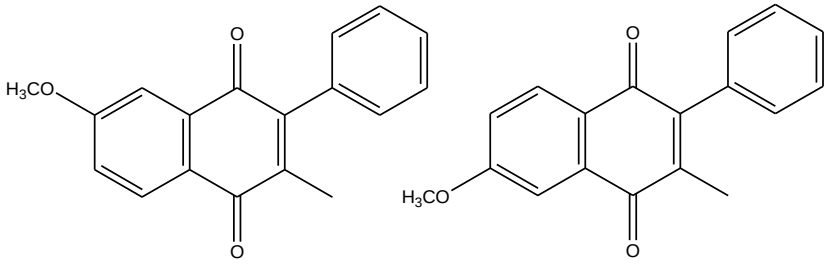
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.92-7.88 (d, 2H); 7.54 (s, 2H); 7.25-7.20 (d, 2H); 7.45 (s, 2H); 3.84 (s, 6H); 3.54-3.48 (t, 4H); 2.04-1.98 (t, 4H); 1.54-1.50 (m, 4H).

Figure 1.43 - 2-(ethyl-carboxylate)-3-ethyl-6 & 7-methoxy-1,4-naphthoquinone, **19 f.**



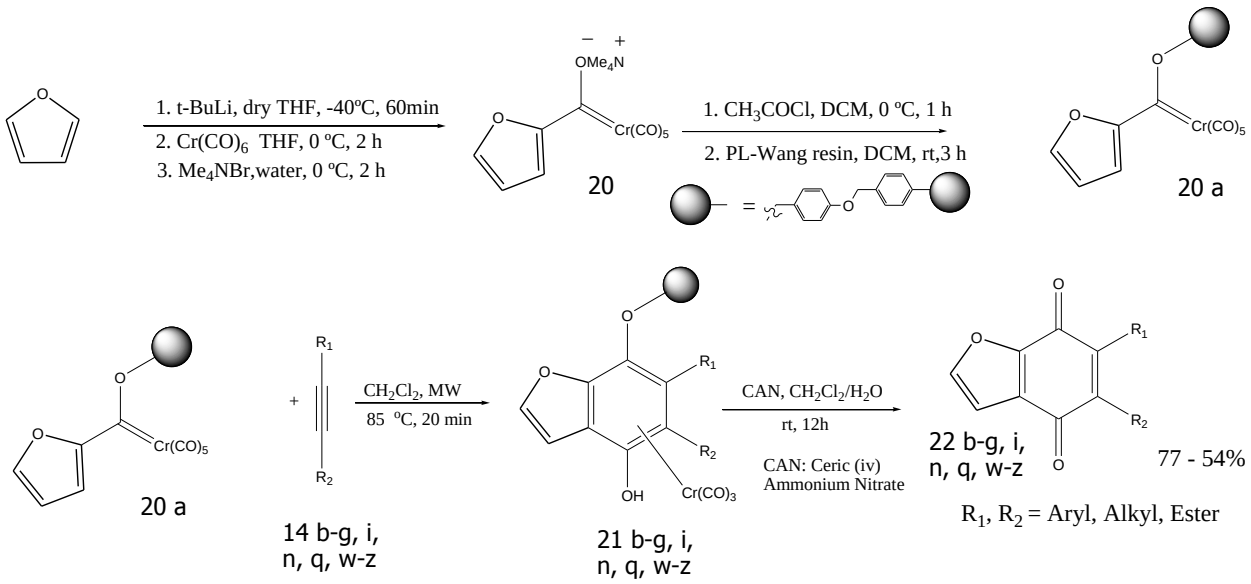
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.92-7.88 (d, 2H); 7.54 (s, 2H); 7.25-7.20 (d, 2H); 4.22(q, 4H); 3.84 (s, 6H); 2.10-1.98 (q, 4H); 1.32-1.30 (t, 6H); 1.0-0.96 (t, 6H).

Figure 1.44 - 2-methyl-3-phenyl-6 & 7-methoxy-1,4-naphthoquinone, **19 q.**



Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.92-7.88 (d, 2H); 7.54 (s, 2H); 7.42-7.26 (m, 10H); 7.25-7.20 (d, 2H); 3.84 (s, 6H); 1.95 (s, 6H).

1.4.3 - Synthesis of Resin-bound furan Fischer Carbene Complexes and Microwave Assisted Dötz Benzannulation.



Scheme 1.8 - Synthesis of solid supported furan Fischer carbene complex and microwave assisted [3+2+1] Dötz benzannulation.

1.4.3.1 - Synthesis of tetramethylammonium salt of (furyl-methylene carbene] pentacarbonyl chromium(0), 20.

In a 50 mL round bottom flask equipped with stir bar, and septum wired down with 10mL of dry THF. Subsequent addition of furan (2.5 ml, d = 0.936 g/mL; $3.47x10^{-2}$ mol 1eq) after that add tert-Buthyl lithium (30.7 mL, $5.21x10^{-2}$ mol, 1.7M, 1.5 eq). Stir for 45 min from -40°C (slush bath) to room temperature. 3.83gr ($1.74x10^{-2}$ mol, 1eq) of chromium hexacarbonyl is weighed on a round bottom flask equipped with stir bar, air free adaptor, and septum inside of the dry box. Under N_2, the prepared lithiated furan ($2.41x10^{-2}$ mol, 2eq) was

transferred via cannula to the flask with chromium at 0°C (ice bath). The solution turned immediately from yellow to brown. After 2 hours, the resulting solution was a dark brown, and the chromium hexacarbonyl crystals had disappeared. The solvent was removed under reduced pressure on a vacuum line. The resulting brown slurry was dissolved in 15mL of nitrogen-saturated water (O_2 free), with 5.34 g ($3.47x10^{-2}$ mol, 2 eq) of tetramethylammonium bromide, all done at 0°C. After 60 minutes, the organic layer was later extracted with 3x20mL of dry DCM. The combined organic extracts were promptly dried over $MgSO_4$, filtered, and the solvent was carefully removed under reduced pressure to yield 6.26 g of a dark orange solid (**20**), 99 %. No further purification was carried out.

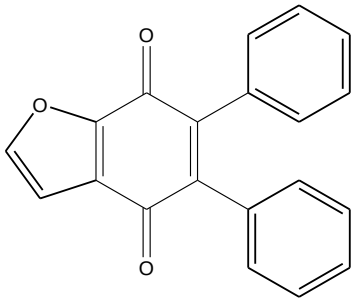
1.4.3.2 - O-linked pentacarbonyl (furyl methylene carbene) chromium(0) on PL-Wang beads, 20 a.

Add to a stirred solution of crude orange solid **20** (6.28 g, $1.74x10^{-2}$ mol) in 10.0 mL of CH_2Cl_2 at 0˚C, 2.1 mL of acetyl chloride ($2.95x10^{-2}$ mol, 1.7 eq). The solution was left stirring for 1 hour until its color turned from orange to dark red. The appearance of the dark red color is characteristic of the formation of the acetylated furyl carbene complex. Afterwards, the solvent was quickly removed with vacuum, washed again with dry dichloromethane to get rid of acetyl chloride traces and removed with vacuum again. In the meantime, 2.05g of PL-Wang resin ($3.48x10^{-3}$; 0.2 eq; loading: 1.7 mmol/g bead) were preswell with 10

mL of dry dichloromethane. The next step is transfer acetylated furyl carbene to the beads container. Since this complex is oxigen and moisture sensitive, the acetoxy furyl Fischer carbene complex is transferred via cannula, all under a N_2 atmosphere. The flask was then placed on a wrist-action shaker for 120 minutes and the beads were gently shaken until they retained the red color of the solution. The beads were then washed with 3x5 mL of dry and N_2 saturated dichloromethane and 3x5 mL of dry and N_2 saturated tetrahydrofurane, after which, they retained a bright red color, **20 a**. This product has to be stored under N_2 atmosphere and low temperature to avoid decomposition. The obtained loading by weight was 93%.

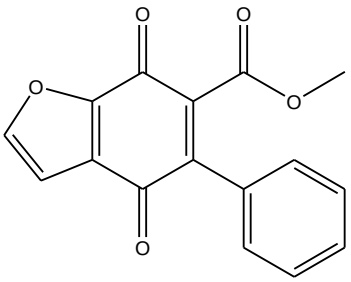
The microwave assisted Dötz benzannulation and the oxidative cleavage procedures are the same as reported previously for the phenyl Fischer carbene complex. Refer to sections 1.4.1.3 and 1.4.1.4 for details to perform microwave assisted Dötz benzannulation and oxidative cleavage respectively to obtain 5,6-disubstituted-4,7-furanquinone **22 b–g, i, n, q, w-z**.

Figure 1.45 - 5,6-diphenyl-4,7-furanquinone, **22 e.**



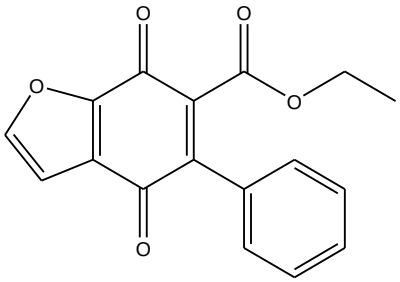
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 7.46-7.33 (m, 10H); 6.98-6.92 (d, 1H).

Figure 1.46 - 5-phenyl-6-(methyl-carboxylate)-4,7-furanquinone, **22 b.**



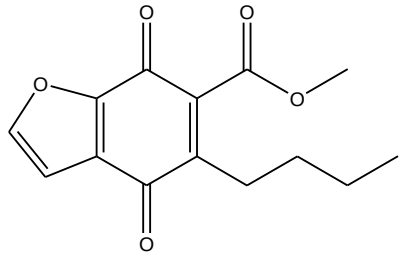
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 7.38-7.34 (m, 5H); 6.98-6.94 (d, 1H); 3.74 (s, 3H).

Figure 1.47 - 5-phenyl-6-(ethyl-carboxylate)-4,7-furanquinone, **22 c.**



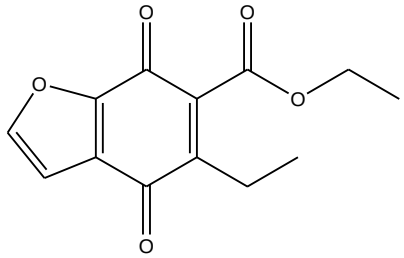
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 7.38-7.34 (m, 5H); 6.98-6.94 (d, 1H); 4.22(q, 2H); 1.32-1.30 (t, 3H).

Figure 1.48 - 5-butyl-6-(methyl-carboxylate)-4,7-furanquinone, **22 g.**



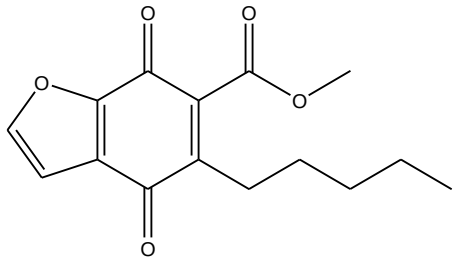
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 6.98-6.94 (d, 1H); 3.74 (s, 3H); 2.10-1.98 (t, 2H); 1.35-1.25 (m, 4H); 1.32-1.30 (m, 4H); 1.0-0.96 (t, 3H).

Figure 1.49 - 5-ethyl-6-(ethyl-carboxylate)-4,7-furanquinone, **22 f.**



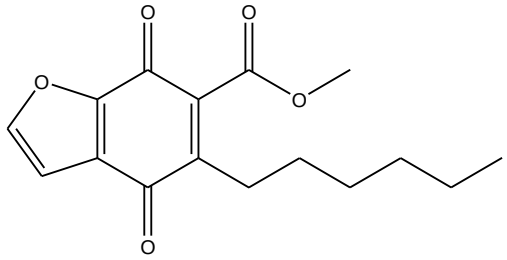
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 6.98-6.94 (d, 1H); 4.22(q, 2H); 2.10-1.98 (q, 2H); 1.32-1.30 (t, 3H); 1.0-0.96 (t, 3H).

Figure 1.50 - 5-pentyl-6-(methyl-carboxylate)-4,7-furanquinone, **22 i.**



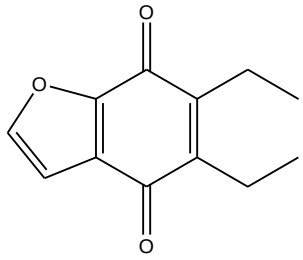
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 6.98-6.94 (d, 1H); 3.78(s, 3H); 2.10-1.9 (t, 2H); 1.45-1.35 (m, 6H); 1.0-0.96 (t, 3H).

Figure 1.51 - 5-hexyl-6-(methyl-carboxylate)-4,7-furanquinone, **22 d.**



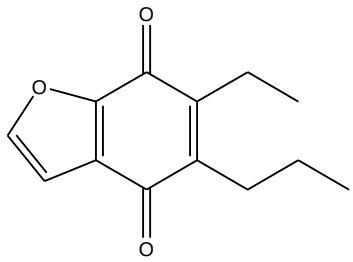
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 6.98-6.94 (d, 1H); 3.78(s, 3H); 2.10-1.98 (t, 2H); 1.50-1.30 (m, 8H); 1.0-0.96 (t, 3H).

Figure 1.52 - 5,6-diethyl-4,7-furanquinone, **22 w.**



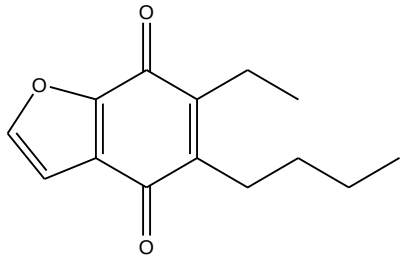
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 6.98-6.94 (d, 1H); 2.10-1.98 (q, 4H); 1.0-0.96 (t, 6H).

Figure 1.53 - 5-propyl-6-ethyl-4,7-furanquinone, **22 n.**



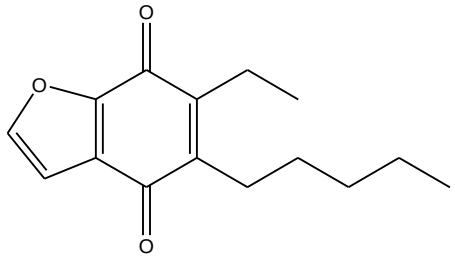
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 6.98-6.94 (d, 1H); 2.10-2.04 (t, 2H); 1.98-1.94 (t, 2H); 1.42-1.36(m, 2H); 1.06-1.00 (t, 3H); 0.98-0.95 (t, 3H).

Figure 1.54 - 5-butyl-6-ethyl-4,7-furanquinone, **22 x.**



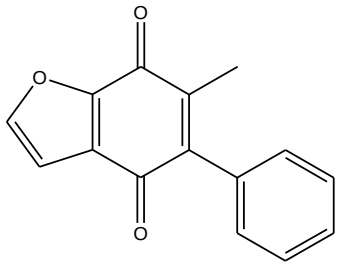
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 6.98-6.94 (d, 1H); 2.10-2.04 (m, 2H); 1.98-1.94 (t, 2H); 1.42-1.36(m, 4H); 1.06-1.00 (t, 3H); 0.98-0.95 (t, 3H).

Figure 1.55 - 5-pentyl-6-ethyl-4,7-furanquinone, **22 y.**



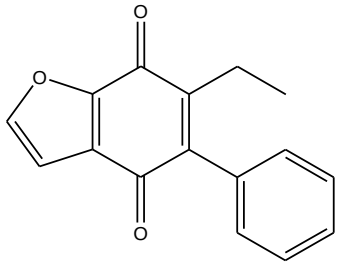
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 6.98-6.94 (d, 1H); 2.10-2.04 (m, 2H); 1.98-1.94 (t, 2H); 1.42-1.36(m, 6H); 1.06-1.00 (t, 3H); 0.98-0.95 (t, 3H).

Figure 1.56 - 5-phenyl-6-methyl-4,7-furanquinone, **22 q.**



Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 7.38-7.30 (m, 5H); 6.98-6.94 (d, 1H); 1.95 (s, 3H).

Figure 1.57 - 5-phenyl-6-ethyl-4,7-furanquinone, **22 z.**



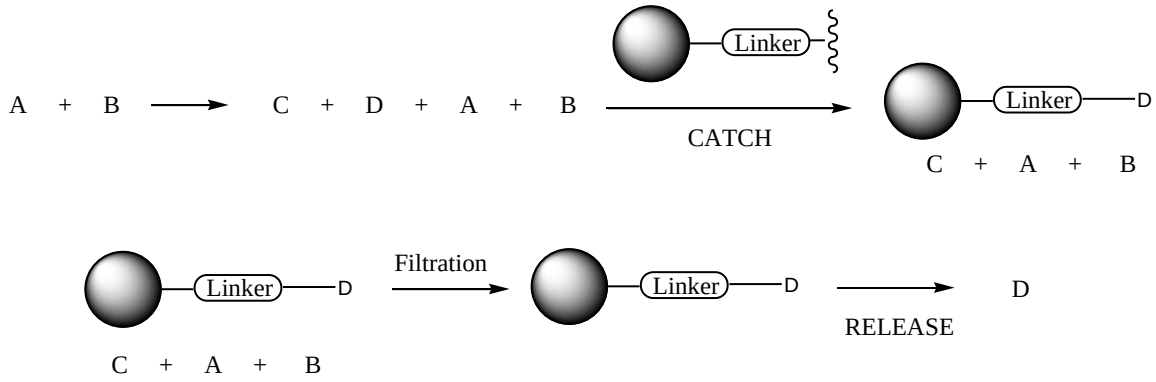
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.60 (d, 1H); 7.38-7.30 (m, 5H); 6.98-6.94 (d, 1H); 1.98-1.94 (t, 2H); 1.06-1.00 (t, 3H).

Chapter 2

SYNTHESIS OF RESIN-BOUND FISCHER CARBENE COMPLEXES VIA "CATCH-RELESE" METHODOLOGY

2.1 Introduction.

During the last 10 years the application of solid phase synthesis and solution-phase protocols with the aid of scavenger resins and polymer-bound reagents of small molecules have become a widely used methodology.[23] Also known as "Catch-Release", this methodology has been relatively unexplored in organometallic chemistry. [25] "Catch-Release" procedures can be particularly useful since the reaction product can be separated from solution by immobilization onto an activated resin. Simple filtration can then be performed to eliminate purification steps such as chromatography, distillation or recrystalization and reduce reaction work up times. The desired product can then be released off the solid support for additional chemistry (Scheme 2.1). In order to purify the organometallic Fischer carbene complex utilized in the previously described reactions, a "Catch-Release" method has been developed which produces both solid supported and solution phase Fischer carbene complexes with high purities.

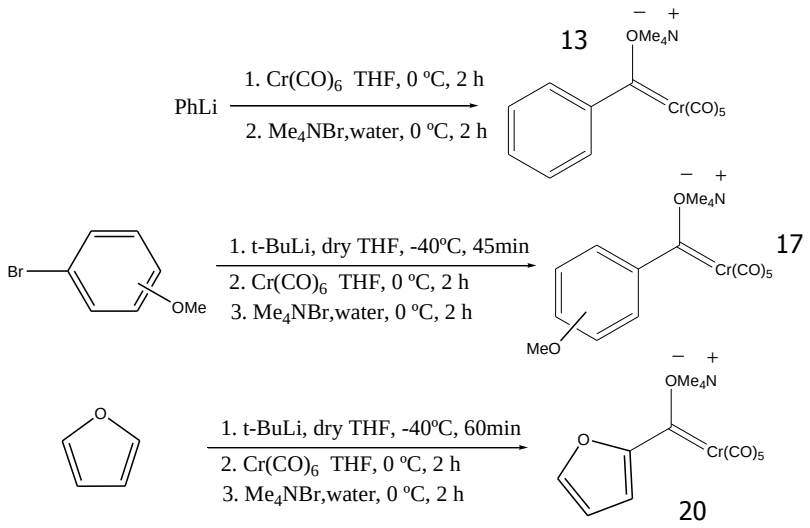


Scheme 2.1 - General procedure of "Catch-Release" methodology.

Previously we reported the synthesis of Fischer carbene chromium complexes on solid support.[1] A novel "Catch-Release" technique to catch phenyl Fischer carbene complex and further release it for future chemistry has been accomplished. Throughout this procedure, it is possible to afford both solid supported and solution phase phenyl Fischer carbene complexes with good to moderate yields and high purities.

2.2 Results and Discussions.

The results from the synthesis of phenyl Fischer carbene complex via "Catch-Release" technique is presented in this section. The "Catch-Release" methodology help us to avoid purification steps such as liquid-liquid extraction, which in most cases exposes the reaction to oxygen and leads to decomposition and degradation of the substrate.



Scheme 2.2 – Key step to avoid decomposition of the carbene complexes.

The key step is the reaction with the tetramethyl ammonium bromide to transform the lithiated carbene into a tetramethyl ammonium carbene salt. A reaction between the solid carbene complex and the salt dissolved in oxygen free water during 2 hour agitation, requires a liquid-liquid extracton to isolate the carbene salt. This is the risky step on the synthesis pathway. Chromium can easily get oxidize with oxygen from air.

2.2.1 - Results for synthesis and support of trimethylammonium salt of [(oxy)(aryl)carbene] pentacarbonyl chromium(0) on polymer support PL-HCO_3, 13 b.

The loading obtained in the "Catch" step was 97%. Although the complex is fairly stable in this solid support, the FTIR analysis has to be performed as soon as possible to avoid decomposition of the carbene. The synthesis procedure demands considerable effort and care to avoid decomposition of the intermediates which are oxygen and temperature sensitive.

2.2.2 - Results for O-linked pentacarbonyl (phenylmethylene) chromium(0) on PL-Wang beads, 13 a.

The comparison of carbene **13 a** obtained by this methodology and the one obtained by the previous methodology [1] reveals that the "Catch-Release" technique works proficiently to avoid difficult purification processes that can also lead to decomposition of the carbene intermediate. The yields and the purities of the products for both methodologies are comparable with the previously reported synthesis. [26]

2.2.3 - Results from synthesis of phenyl methylene methoxy carbene chromium(0) pentacarbonyl, 13 d.

The evidence of cleaving off the polymer bead or "Release" the phenyl Fischer carbene from the solid support is confirmed by the FTIR analysis and its comparison with the previous literature reported data [26a] leads us to prove the "Catch –Release" technique is effective.

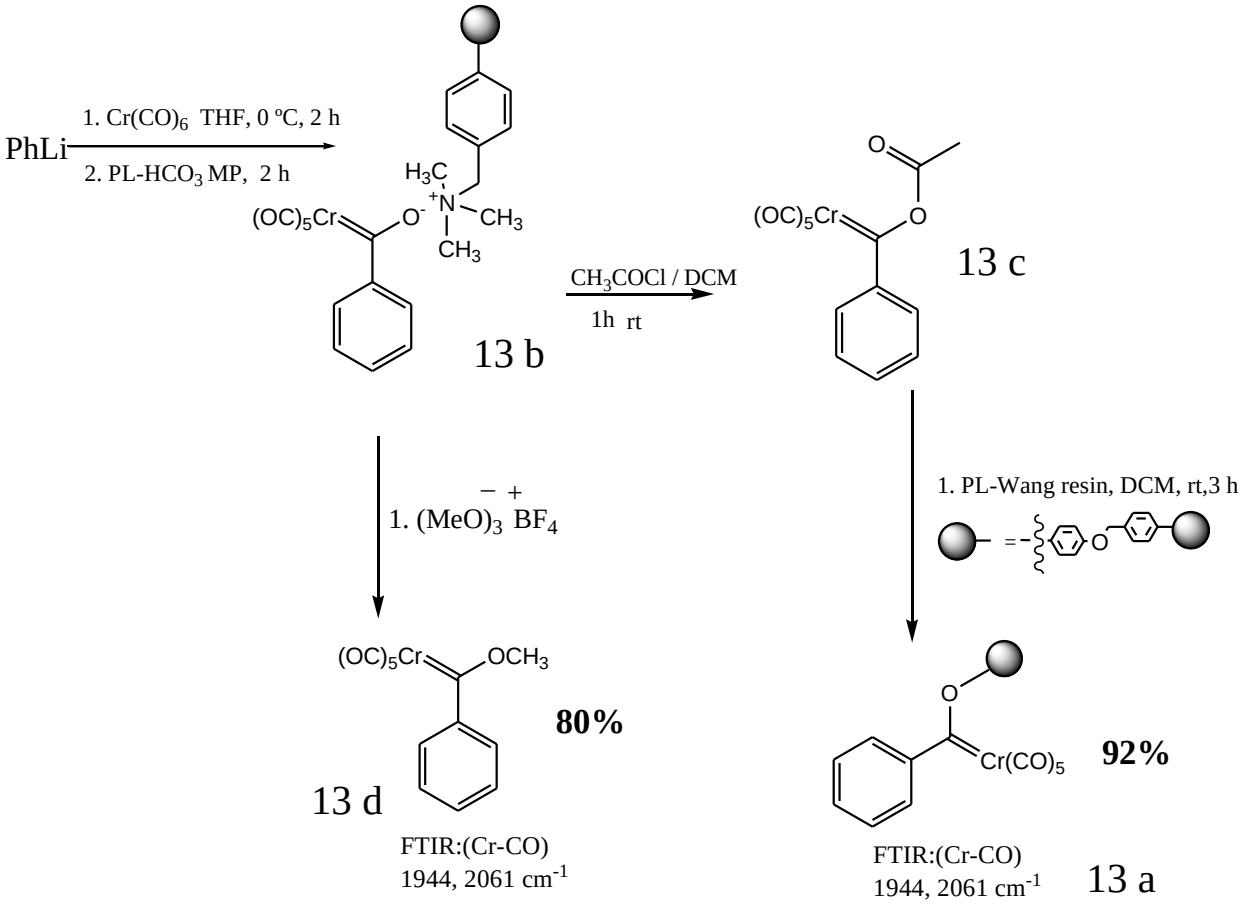
2.3 Conclusions.

It has been demonstrated that solid phase organic synthesis of naphthoquinones via solid supported Fischer carbene complexes and its microwave assisted synthesis increased the yields, reduce reaction times, temperatures and avoid decomposition of the products. The application of solid supported reagents to the synthesis of Fischer carbene complexes eliminated the need for long time period purifications providing a new synthesis approach to these types of organometallic moieties. It is worth to draw attention that the yields of both solid supported and non-supported Fischer carbene complexes are comparable with the synthesis of Fischer carbenes previously reported in the literature. [18]

2.4 Experimental.

Due to the pyrophoric condition of the compounds and sensitivity of the products all reactions were carefully performed under inert gas atmosphere. During inert gas manipulations standard Schlenk line technique was used or a vacuum atmosphere dry box model MO-40M. Solids such as polymer support and chromium hexacarbonyl were purged with nitrogen to avoid decomposition. Solvents were purchased from EMD Chemicals and dryed in a solvent-purification system mBRAUN or via distillation methods under nitrogen atmosphere: dichloromethane (DCM) was distilled from calcium hydride, tetrahydrofuran (THF) and diethyl ether were distilled from the sodium ketyl of benzophenone. chromium hexacarbonyl was purchased from Strem Chemicals. The polymers for solid supported reactions and scavengers such as the PL-Wang and PL-HCO_3 were purchased at Varian Inc. (former Polymer Laboratories). All other chemical reagents were utilized without further purification and were purchased from Sigma-Aldrich, Alfa Aesar, VWR, Lancaster Chemical Companies. The microwave reactions were performed in a microwave synthesizer Emrys Optimizer from Biotage (former Personal Chemistry) and a Discover unit from CEM. The thermal reactions were performed in a solid supported synthesizer QUEST 210 by Argonaut Technologies. Infrared (IR) spectroscopy analysis was performed in a Bruker Tensor 27 FTIR spectrometer; for solids analysis, Pike ATR or KBr pellet and for liquids NaCl plates were utilized. The nuclear magnetic resonance (NMR)

analysis was recorded on a Bruker AM-300 (300MHz). The chemical shifts in ^{1}H NMR spectra are reported in δ in units of parts per million (ppm) with respect to chloroform-d, multiplicities are stated as followed: s (singlet), d (doublet), t (triplet), m (multiplet), the integration value n (# of protons) are given by the value nH.



Scheme 2.3 - Synthesis of solid supported and liquid phase phenyl Fischer carbene complex.

2.4.1 - Synthesis and support of trimethylammonium salt of [(oxy)(aryl)carbene] pentacarbonyl chromium(0), 13 b.

1.5gr (6.81 mmol, 1eq) of chromium hexacarbonyl was weighed on a round bottom flask equipped with stir bar, air free adaptor, and septum inside of the dry box. Then, under nitrogen atmosphere, 10 mL of dry THF and 5.68 mL of phenyllithium (1.8M solution in t-Bu_2O, 10.22 mmol, 1.5 eq) was carefully added drop wise over a period of 5-10 minutes at 0°C (ice bath). The solution turned gradually from yellow to brown. The reaction was left stirring for 2 hours, time after which it adopted a dark brown, and the chromium hexacarbonyl crystals were dissolved. The solvent was removed in vacuum. The resulting brown solution (2.07g, 6.81 mmol) of phenyl Fischer complex was then transferred to 1.18g (2.27mmol, with 1.92 mmol/g bead of loading) of polymer support PL-HCO_3 MP resin at a ratio of complex 3:1 resin (6.81 mmol), 3**:**1 resin (2.27 mmol), all done at rt. The solution was left stirring for 2hr. The polymer beads were washed with 3x20mL dry THF 1.80g of bright red polymer beads (97 % loading, 2.20 mmol) were collected.

2.4.2 - O-linked pentacarbonyl(phenylmethylene) chromium(0) on PL-Wang beads, 13 a.

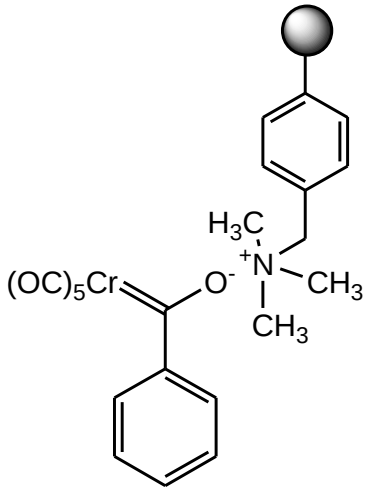
The beads loaded with the carbene **13 b** (1.80g, 2.20 mmol) are treated with 468 µL of acetyl chloride (6.6 mmol, 3 eq, FW=78.5g/mol, d=1.1051g/ml) dissolved in 10 ml of DCM for 2 hr in order to release the carbene complex from the polymer beads. The appearance of the dark red color is characteristic of the formation of the acetylated carbene complex **13 c**. The solvent and excess of acetyl chloride are quickly removed with vacuum. In the mean time, 940 mg of PL-Wang resin (1.7mmol /g bead, Acetoxy (2.20 mmol) **:** PL-Wang (1.10 mmol), 2**:**1) were preswell with 10 mL of dry dichloromethane. The compound **13 c** is dissolved in DCM and cannulated to the previously prepared PL-Wang resin. The flask is then placed on a wrist-action shaker for 2 hr and until the beads absorbed the red color of the solution. The beads were then washed with 3x5 mL of dry and N_2 saturated dichloromethane, after which they retained a bright red color **13 a**. This product has to be stored under N_2 atmosphere and low temperature to avoid decomposition.

2.4.3 - Phenyl methylene methoxy carbene chromium(0) pentacarbonyl, 13 d.

The beads loaded with the Fischer carbene **13 b** (1.80g, 2.20 mmol) were treated with 0.976 g trimethyloxonium tetrafluoroborate (FW = 147.91g/mol;

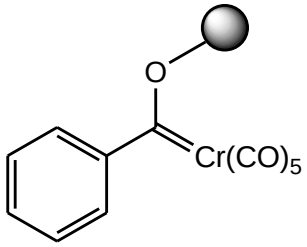
6.60 mmol, 3 eq) dissolved in 10 mL of dry DCM and shook for 2 hr to release the carbene complex from the beads. The product is isolated by regular filtration and the solvent is removed under vacuum to obtain a bright red pure phenyl chromium Fischer carbene complex.

Figure 2.1 - Trimethylammonium salt of [(oxy)(aryl)carbene] pentacarbonyl chromium(0) on polymer support PL-HCO_3, (**13 b**).



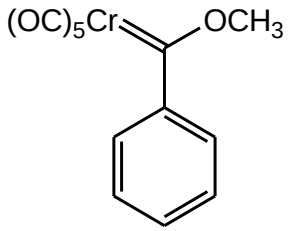
Bright red complex supported in polymer beads: FT-IR (ATR): 2032, 1947, 1904, 1875, 1859 (Cr-CO); 1144 ($C_{carbene}$-O).

Figure 2.2 - O-linked pentacarbonyl (phenylmethylene) chromium(0) on PL-Wang beads, **13 a**.



Bright red complex supported in polymer beads FT-IR (KBr) 2061 and 1944 cm^{-1} (Elemental analysis: Cr, 5.67% 95% loading @ 1.7 mmol/g.)

Figure 2.3 - Phenyl methylene methoxy carbene chromium(0) pentacarbonyl, **13 d**.



Bright red solid: FT-IR (KBr): 2060, 1935, 1901, 1875, 1851 (Cr-CO); 1142 ($C_{carbene}$-O). Literature data: [32] 2054s, 1957ss, 1912ss, 1887ss, 1862ss (Cr-CO); 1146 ($C_{carbene}$-O).

Chapter 3

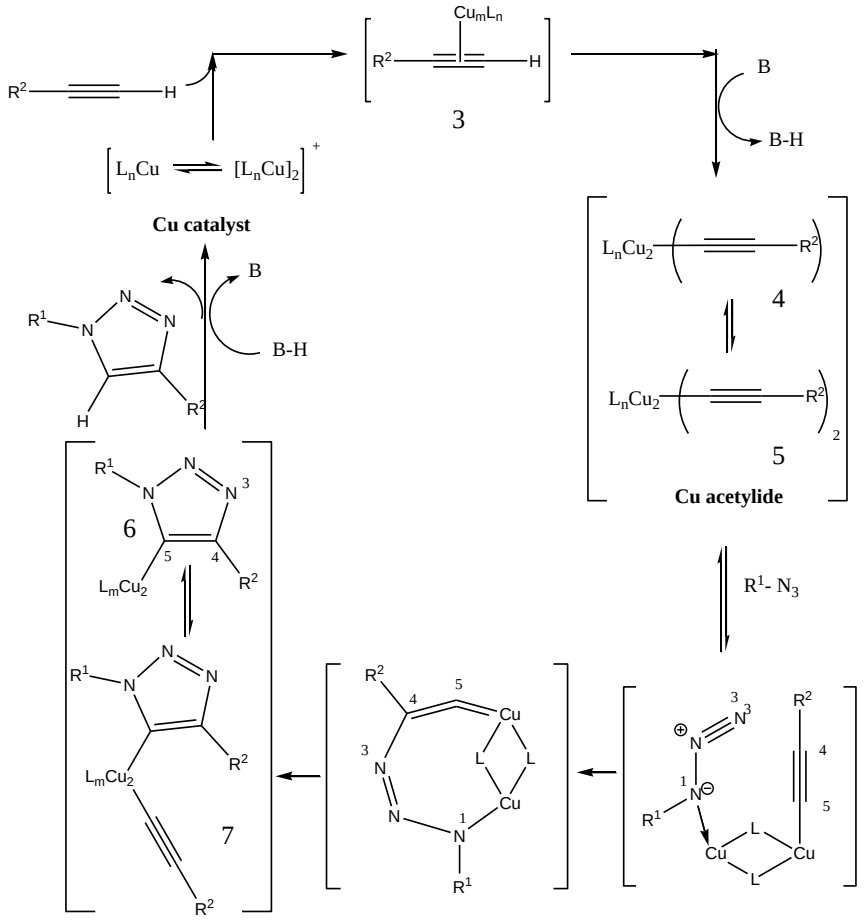
MICROWAVE-ASSISTED SOLID-SUPPORTED CLICK CHEMISTRY: AN EFFICIENT ROUTE TO SYNTHESIZE TRIAZOLE CONTAINING 1,4-NAPHTHOQUINONE DERIVATIVES

3.1 Introduction.

Click chemistry is a chemical philosophy introduced by K. Barry Sharpless in 2001 in which reactive molecular building blocks are designed to "click" together selectively and covalently. [27] This is inspired by the fact that nature also generates substances by joining small modular units. The products might be biological inhibitors, molecular-electronics components, sensor probes, nonlinear optical materials, light-harvesting compounds, or compounds with any number of other useful properties. [28]

The mechanism behind the reaction is better known as the Cu^{I} catalyzed variant of Huisgen 1,3-dipolar cycloaddition. The catalytic cycle begins with formation of Cu^{I} acetylide species via the π complex **3** (Scheme 3.1). Alkyne π complexation requires ligand dissociation and is endothermic in acetonitrile by 0.6 kcal/mol. In aqueous solution, however, the formation of copper species **4** is exothermic by 11.7 kcal/mol, therefore, it can be accelerated in water. Calculations also indicate that copper coordinations lowers the pK_a of the alkyne C-H by up to 9.8 pH units, thus making deprotonation in aquous systems possible without the addition of a

base. Following the formation of the active copper acetylide species, azide displacement of one ligand generates a copper acetylide-azide complex, such as the dicopper species **9**. Complexation of the azide activates it toward nucleophilic attack of acetylide carbon C(4) at N(3) of the azide (numbers based on traditional triazole nomenclature), generating metallocycle **8**. Consistent with this mechanism, experimental results indicate that electron-withdrawing substituents on the alkyne accelerate CuI-catalyzed alkyne–azide coupling. This metallocycle positions the bound azide properly for subsequent ring contraction by a transannular association of the N(1) lone pair of electrons with the C(5)–Cu π^* orbital. Protonation of triazole-copper derivative **7** followed by dissociation of the product ends the reaction and regenerates the catalyst (Scheme 3.1).



Scheme 3.1 - General Mechanism for Cu^I Catalyzed Variant of Huisgen 1,3-dipolar Cycloaddition.

As we previously reported, 1,4-naphthoquinone skeleton is found in many natural products. [10, 11] On the other hand, 1, 2, 3-triazole finds use in research as a building block for more complex chemical compounds, such as pharmaceutical drugs like tazobactam. [29] Tazobactam (Figure 3.1) in combination with piperacillin (PIP/TAZ) is a β-lactam/β-lactamase inhibitor combination with in vitro activity against a broad spectrum of aerobic and anaerobic, Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*. [30, 31]

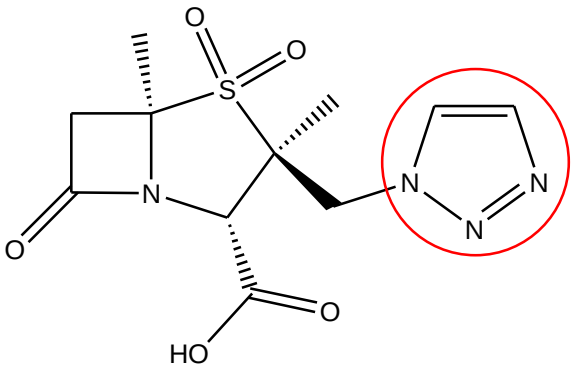


Figure 3.1 - Tazobactam drug including 1,2,3 triazole scaffold.

Given the biological importance of 1,4-naphthoquinone and triazole derivatives, it was of our interest to synthesize molecules that have both 1,4-naphthoquinone and triazole units in order to study their chemical biology. As previously described, the microwave assisted solid supported Dötz benzannulation reaction was extended to diynes to afford resin-bound naphthol derivatives with additional alkyne functionality. This observation prompted us to explore the possibility of click chemistry through this resin-bound Dötz intermediate.

Click chemistry offers a versatile strategy for the construction of heterocyclic compounds that find wide spread applications in drug discovery programme. [33] In particular, Huisgen 1,3-dipoar cycloaddition of alkynes with azides to give triazole derivatives is one of the powerful examples of this chemistry. [4] Although this cycloaddition has been known for several decades, the

reaction suffers from the drawback of poor regioselectivity. The recent copper-catalyzed reaction offers a great solution to this regioselectivity issue and forms exclusively the corresponding 1,4-regioisomers. [34, 35] However, the use of Cu(I) catalyst is not suitable for this chemistry because of the side product obtained from the dimerization of alkynes, but the *in-situ* generation of Cu(I) catalyst by the reduction of Cu(II) catalyst circumvent this problem. [34] The development of solution-phase Cu(I) catalyzed reaction has led to interesting applications in the field of target-oriented synthesis and activity based protein-profiling. [33, 36] Recently, Appukkuttan *et al*. reported that the Cu(I) catalyzed reaction of terminal alkynes with azides showed shortening of reaction time under microwave conditions. [37] While the use of solution-phase click chemistry is well documented in the literature, the exploration of the solid-supported click chemistry is underdeveloped. [35]

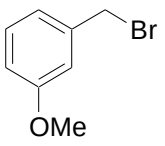
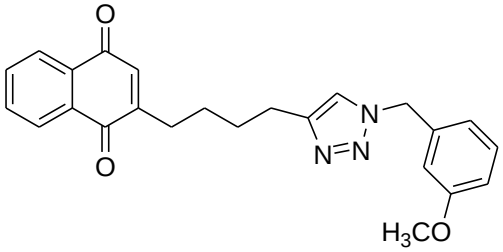
1,4-naphthoquinone skeleton is found in many natural products such as menadione, plumbagin, lapachol, vitamin K_3, frenolycin B, eleutherin, nanamycin, pentalongin, and juglone which is associated with various pharmaceutical applications. [38, 39] Structures incorporating this moiety have shown marked antibacterial, antifungal, antiplatelet, anticancer, and antiviral activities. [38] There is an interest to synthesize molecules that have both 1,4-naphthoquinone and triazole units in order to study their chemical biology. We recently reported an efficient combinatorial synthesis of 2,3-disubstituted 1,4-naphthoquinone

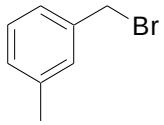
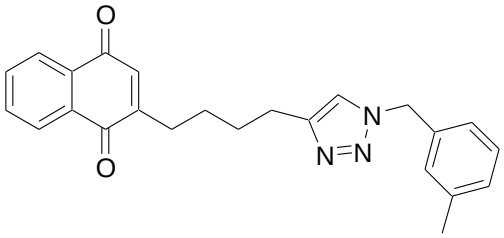
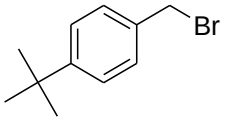
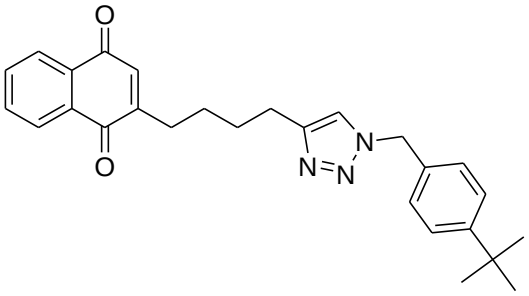
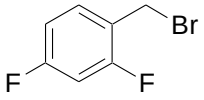
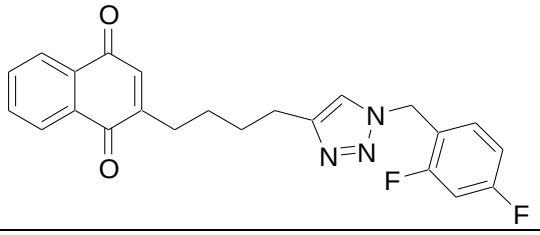
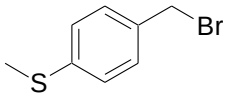
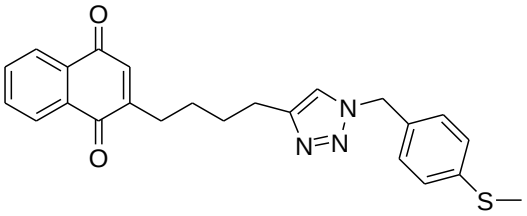
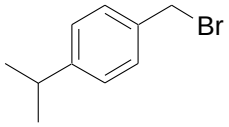
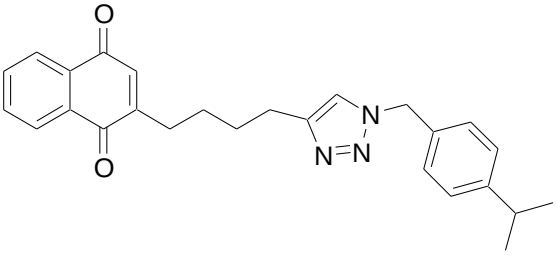
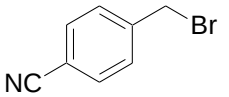
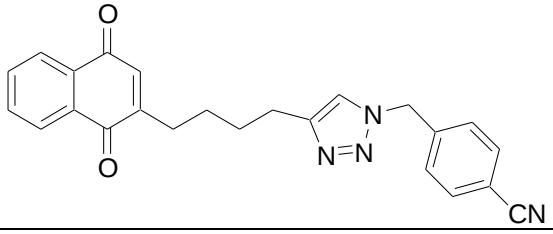
derivatives through solid-supported Dötz benzannulation of resin-bound Fischer carbene complex with alkynes, followed by its resulting oxidative cleavage. [1] In addition to alkynes, the reaction was extended to diynes to afford the resin-bound alkyne substituted naphthol derivatives. This observation prompted us to explore the possibility of click chemistry through this resin-bound Dötz intermediate.

3.2 Results and Discussions.

Herein, we report an efficient synthesis of 1, 2, 3-triazole containing 1,4-naphthoquinone derivatives through microwave-assisted solid-supported click chemistry.

3.2.1 - Results for the synthesis of phenyl Fischer carbene with 1,7-octadiyne and its subsequent click chemistry reaction.

Entry	Halide, **14**	Product **25**	Yield
i			53

ii			50
iii			48
iv			46
v			45
vi			42
vii			41

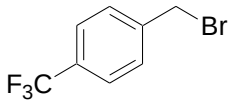
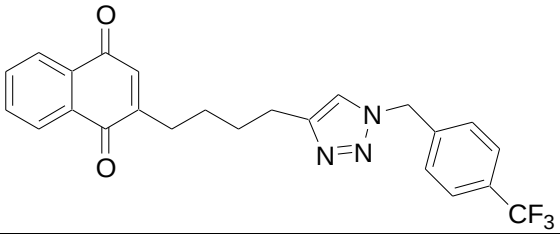
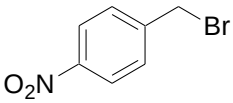
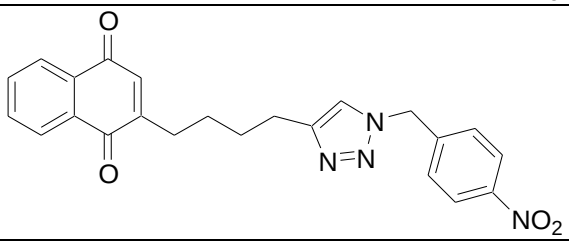
viii			40
ix			40

Table 3.1 - Results of the MAOS-SPOS Click chemistry of **15 a** with Various Benzyl Bromides and Sodium Azide, Followed by the Oxidative Cleavage of **24 i-ix.**

The oxidative cleavage using ceric ammonium nitrate (CAN) of **24 i-ix** afforded the corresponding 1, 2, 3-triazole containing 1,4-naphthoquinone derivative **25 i-ix.** In addition to **14 a**, the CuI catalyzed reactions of **15 a** with sodium azide and various benzyl bromide with electon-donating groups **14 ii-vii,** followed by the oxidative cleavage afforded the corresponding triazole containing 1,4-naphthoquinones **25 ii-vii** in moderate yields (entries i-vii, Table 3.1). Furthermore, reactions with electron-withdrawing groups on the benzyl bromide **14 viii-ix** undergo smooth reaction to produce the corresponding compounds **25 viii-ix** in 42 and 41% yields, respectively (entries viii and ix, Table 3.1). It is noteworthy that the present solid-supported CuI catalyzed reaction tolerates a

wide variety of functional groups such as methoxy, fluoro, thio, cyano, and nitro on the benzyl bromide (Table 3.1).

3.2.2 - Results for the synthesis of phenyl Fischer carbene with 1,6-heptadiyne and its subsequent click chemistry reaction.

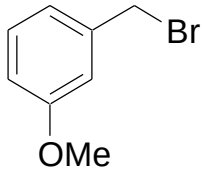
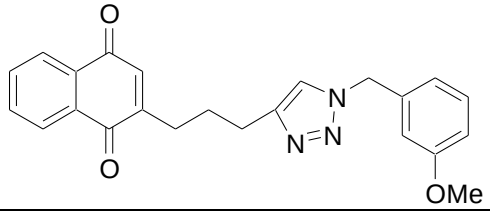
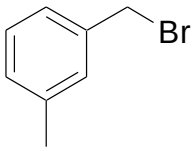
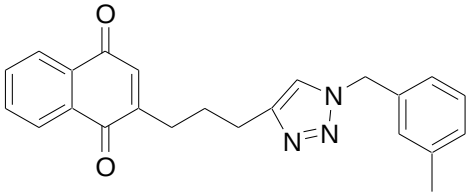
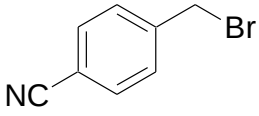
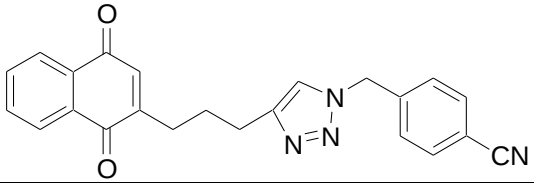
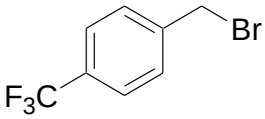
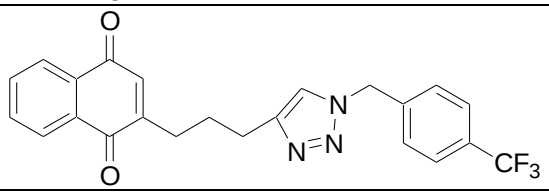
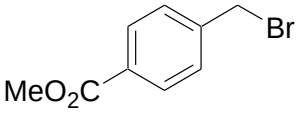
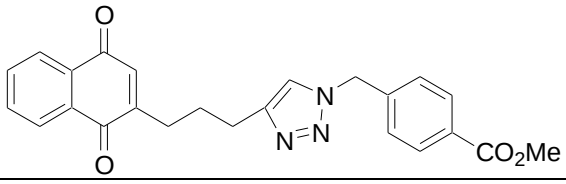
Entry	Halide, **14**	Product **27**	Yield
i			52
ii			51
vi			47
viii			45
x			45

Table 3.2 - Results of the MAOS-SPOS Click chemistry of **15 a** with Various Benzyl Bromides and Sodium Azide, Followed by the Oxidative Cleavage of **25 i, ii, vi, viii,** & **x.**

The oxidative cleavage using ceric ammonium nitrate (CAN) of **26** moieties afforded the corresponding 1, 2, 3-triazole containing 1,4-naphthoquinone derivative **27** products. In addition to **14 aa**, the CuI catalyzed reactions of **15 aa** with sodium azide and various benzyl bromide with electon-donating groups **14 i** & **ii,** followed by the oxidative cleavage afforded the corresponding triazole containing 1,4-naphthoquinones in moderate yields, 52 & 51% (entries **27 i** & **ii**, Table 7). Furthermore, reactions with electron-withdrawing groups on the benzyl bromide **14 vi, viii** & **x** undergo smooth reaction giving 45 and 47% yields, respectively (entries **27 vi**, **viii** and **x**, Table 7). It is also worthy that the present solid-supported CuI catalyzed reaction also tolerates functional groups such as methoxy, methyl, cyano, methyl ester and trifluoro methyl benzyl bromide (Table 3.2).

3.3 Conclusions.

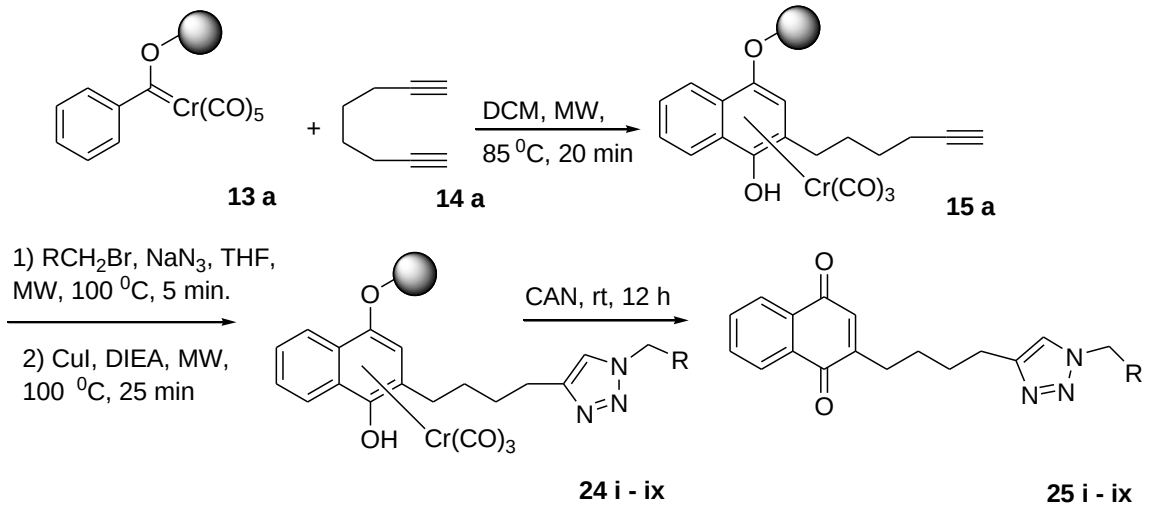
New microwave-assisted solid-supported click chemistry was reported. The CuI catalyzed solid-supported reaction is highly regioselective and tolerates a wide variety of functional groups on the benzyl bromide. This methodology leads to an efficient synthesis of triazole containing 1,4-naphthoquinone derivatives in moderate yields. There are three interesting features that are noteworthy from the present microwave-assisted solid-supported click chemistry. First, the solid-supported Dötz reaction with diynes afforded exclusively the mono Dötz benzannulation product with no double product formation probably due to the

presence of solid-support. This result is in contrast to the solution-phase Dötz reaction with diynes in which double Dötz benzannulation was observed. [40] Second, unlike solution-phase Cu(I) catalyzed cycloaddition, no dimerization of alkynes was observed. Third, the purification procedure of final product is quite simple and requires no column chromatography.

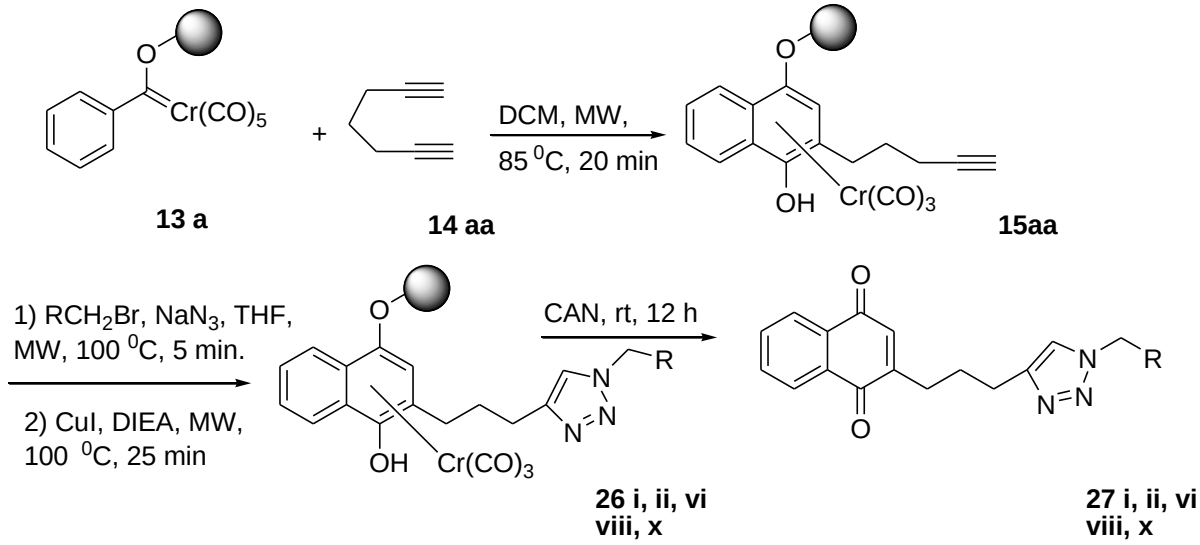
3.4 Experimental.

The experimental procedure for both different alkynes (1,7-octadiyne and 1,6-Heptadiyne) is the same the only differences is that not all the benzyl halides used for the first substrate were used for the second.

3.4.1 - MAOS-SPOS-Click chemistry procedure to synthesize 3-(butyl & propyl[1-p-substituted benzyl]-1,2,3-triazole), 1,4-naphthoquinone from 13 a, 1,7 octadiyne or 1,6 heptadiyne, and benzyl halides i-x.



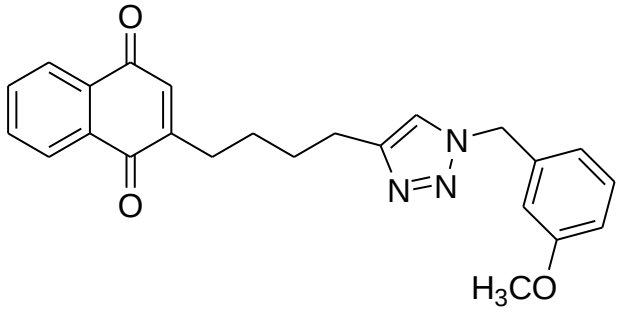
Scheme 3.2 - Synthesize of 3-(butyl[1-p-substituted benzyl]-1,2,3-triazole), 1,4-Naphthoquinone derivatives.



Scheme 3.3 - Synthesize of 3-(propyl[1-p-substituted benzyl]-1,2,3-triazole), 1,4-Naphthoquinone derivatives.

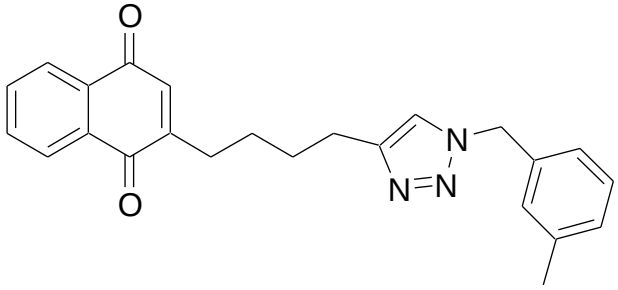
Polymer-Wang resin (Polymer Laboratories, 1% cross linked 1.7 mmol/g) was used as a solid support in the preparation of resin-bound phenyl Fischer carbene complex **13 a**. [1] The solid-supported Dötz benzannulation of **13 a** with 1,7-octadiyne **14 a,** or 1,6-heptadiyne **14 aa** in the presence of DCM as the solvent at 85 ^{0}C under microwave conditions afforded the resin-bound alkyne substituted naphthol derivative **15 a/15 aa**. Treatment of 3-methoxy benzyl bromide (**i**) with sodium azide under microwave conditions, followed by the reaction with **15 a/15 aa** in the presence of CuI as the catalyst and DIEA as the base under microwave conditions afforded the resin-bound 1,2,3-triazole derivative **24 i/26 i**. The oxidative cleavage using ceric ammonium nitrate (CAN) of **24 i/26 i** afforded the corresponding 1, 2 ,3-triazole containing 1,4-naphthoquinone derivatives, **25 i/27 i**.

Figure 3.2 – 2-butyl(1-{3-methoxybenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **25 i**.



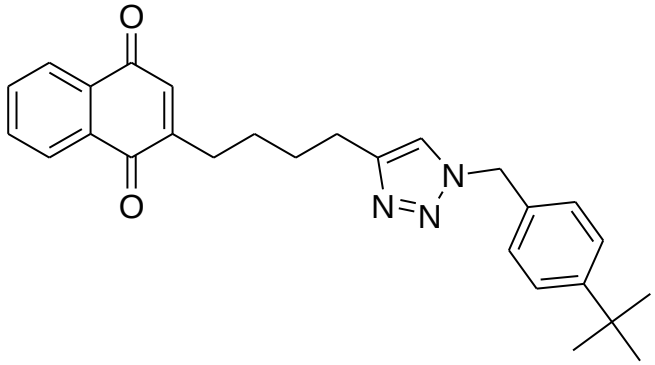
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.04-7.02 (t, 1H); 6.62-6.60 (d, 1H); 6.59-6.57 (d, 1H); 6.56 (s, 1H); 5.01-4.98 (s, 2H); 3.84 (s, 3H); 2.56-2.52 (t, 2H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H); 1.35-1.31 (m, 2H).

Figure 3.3 – 2-butyl(1-{3-methylbenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **25 ii**.



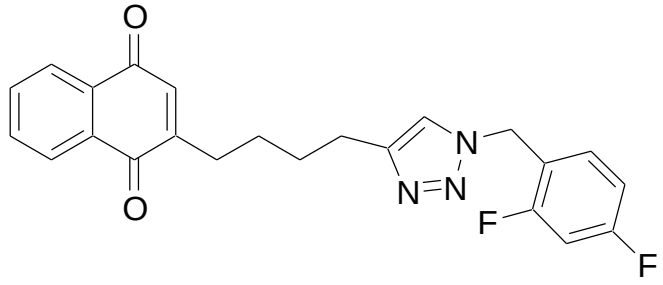
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.05-7.03 (t, 1H); 6.92-6.90 (d, 1H); 6.88-6.86 (d, 1H); 6.85 (s, 1H); 5.01-4.98 (s, 2H); 2.56-2.52 (t, 2H); 2.34 (s, 3H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H); 1.35-1.31 (m, 2H).

Figure 3.4 – 2-butyl(1-{4-tert-butylbenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **25 ii**.



Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.42-7.40 (d, 2H); 7.31 (s, 1H); 6.99-6.97 (d, 2H); 5.01-4.98 (s, 2H); 2.56-2.52 (t, 2H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H); 1.35-1.31 (m, 2H); 1.33 (s, 9H).

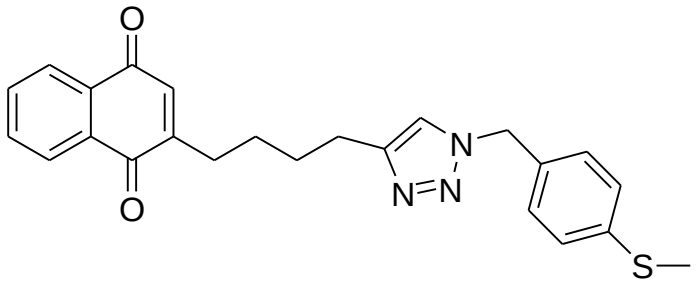
Figure 3.5 – 2-butyl(1-{2,4-difluorobenzy}-1,2,3-triazole)-1,4-naphthoquinone, **25 iv**.



Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.03-7.01 (d, 1H); 6.64 (d, 1H); 6.55 (s, 1H); 5.01-

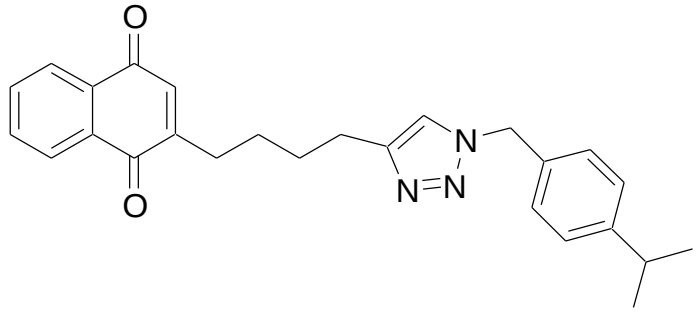
4.98 (s, 2H); 2.56-2.52 (t, 2H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H); 1.35-1.31 (m, 2H).

Figure 3.6 – 2-butyl(1-{4-[methylthio]benzyl}-1,2,3-triazole)-1,4-naphthoquinone, **25 v**.



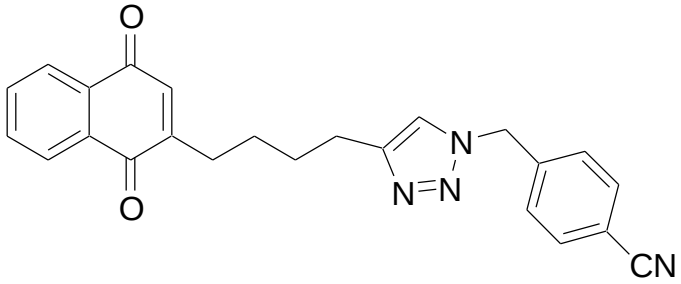
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.08-7.06 (d, 2H); 6.96-6.94 (d, 2H); 5.01-4.98 (s, 2H); 2.56-2.52 (t, 2H); 2.45 (s, 3H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H); 1.35-1.31 (m, 2H).

Figure 3.7 – 2-butyl(1-{4-isopropylbenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **25 vi**.



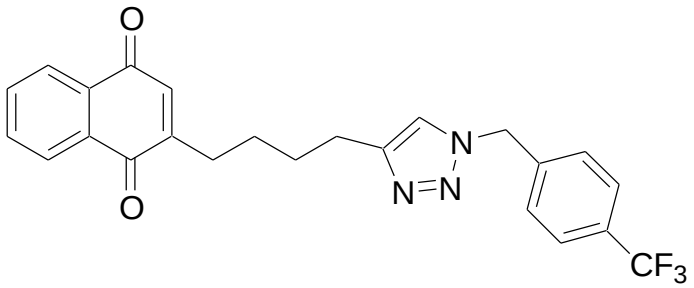
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.20-7.18 (d, 2H); 6.98-6.96 (d, 2H); 5.01-4.98 (s, 2H); 2.56-2.52 (t, 2H); 2.87-2.85 (m, 1H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H); 1.35-1.31 (m, 2H); 1.19 (d, 6H);

Figure 3.8 – 2-butyl(1-{4-cyanobenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **25 vii**.



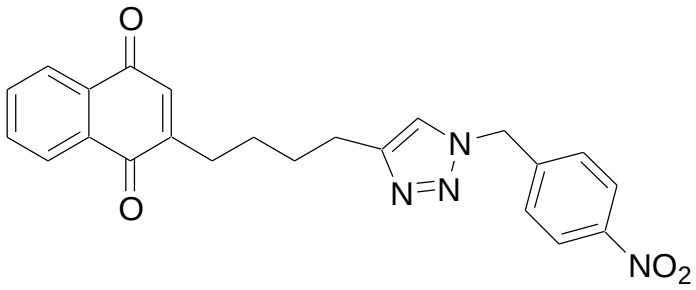
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.38-7.36 (d, 2H); 7.25-7.21 (d, 2H); 5.01-4.98 (s, 2H); 2.56-2.52 (t, 2H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H); 1.35-1.31 (m, 2H).

Figure 3.9 – 2-butyl(1-{4-trifluoromethylbenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **25 viii**.



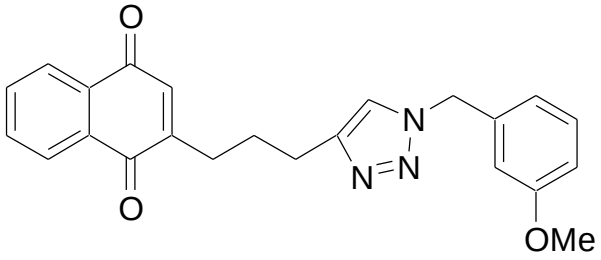
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.56-7.52 (d, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.02-6.98 (d, 2H); 5.01-4.98 (s, 2H); 2.56-2.52 (t, 2H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H); 1.35-1.31 (m, 2H).

Figure 3.10 – 2-butyl(1-{4-nitrobenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **25 ix**.



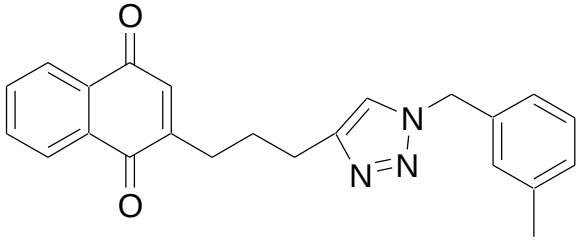
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 8.17-8.15 (d, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.34-7.32 (d, 2H); 7.31 (s, 1H); 5.01-4.98 (s, 2H); 2.56-2.52 (t, 2H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H); 1.35-1.31 (m, 2H).

Figure 3.11 – 2-propyl(1-{3-methoxybenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **27 i**.



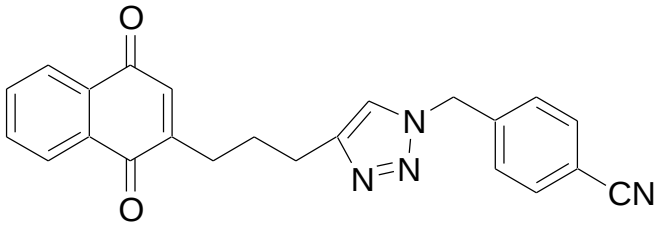
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.04-7.02 (t, 1H); 6.62-6.60 (d, 1H); 6.59-6.57 (d, 1H); 6.56 (s, 1H); 5.01-4.98 (s, 2H); 3.84 (s, 3H); 2.56-2.52 (t, 2H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H).

Figure 3.12 – 2-propyl(1-{3-methylbenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **27 ii**.



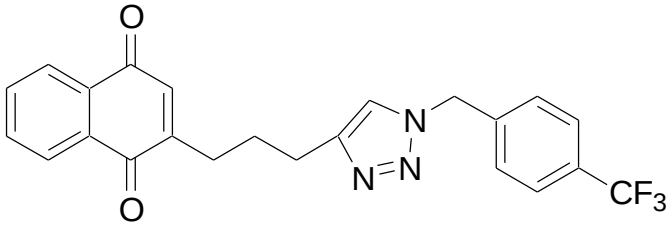
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.05-7.03 (t, 1H); 6.92-6.90 (d, 1H); 6.88-6.86 (d, 1H); 6.85 (s, 1H); 5.01-4.98 (s, 2H); 2.56-2.52 (t, 2H); 2.34 (s, 3H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H).

Figure 3.13 – 2-propyl(1-{4-isopropylbenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **27 vi**.



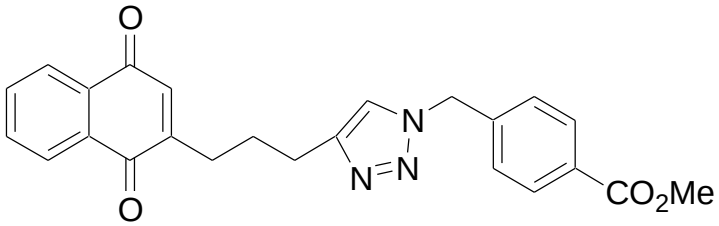
Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.20-7.18 (d, 2H); 6.98-6.96 (d, 2H); 5.01-4.98 (s, 2H); 2.56-2.52 (t, 2H); 2.87-2.85 (m, 1H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H); 1.19 (d, 6H).

Figure 3.14 – 2-propyl(1-{4-trifluoromethylbenzyl}-1,2,3-triazole)-1,4-naphthoquinone, **27 viii**.



Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.82-7.68 (q, 2H); 7.56-7.52 (d, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.02-6.98 (d, 2H); 5.01-4.98 (s, 2H); 2.56-2.52 (t, 2H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H).

Figure 3.15 – 2-propyl(1-{methylbenzoate}-1,2,3-triazole)-1,4-naphthoquinone, **27 x**.



Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.22-8.18 (q, 2H); 7.91-7.89 (d, 2H); 7.82-7.68 (q, 2H); 7.45 (s, 1H); 7.31 (s, 1H); 7.19-7.17 (d, 2H); 5.01-4.98 (s, 2H); 3.84 (s, 3H); 2.56-2.52 (t, 2H); 1.99-1.95 (t, 2H); 1.68-1.64 (m, 2H).

References.

1. Shanmugasundaram, M.; Garcia-Martinez, I.; Martinez, L. E., et.al.; *Tetrahedron Lett*, **2005,** *46*, 7545–7548.
2. Li, Q. M.S. Thesis, University of Texas at El Paso, May **2002**.
3. **a)** Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew Chem., Int. Ed.* **2001**, *40*, 2004. **b)** Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128
4. Huisgen, R. *In 1,3-dipolar cycloaddition chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.
5. Xiang, X-D; Sun, X.; Briceño, G.; Lou, Y.; Wang, K.A.; Chang, H.; Wallace-Freedman, W.G.; Chen, S.W.; Schultz, P.G. *Science* **1995**, *268*, 1738-1740.
6. http://www.rsc.org/ScienceAndTechnology/Policy/Bulletins/Issue3/Chemicalbiology.asp
7. Gordon, E.M.; Gallop, M.A.; Patel, D.V. *Acc. Chem. Res.* **1996**, *29*, 144-154.
8. O'Neill, Jennifer C.; Blackwell, Helen E.*; Combinatorial Chemistry & High Throughput Screening*, Vol. 10, No. 10, December **2007**, 857-876.
9. **a)** Kappe, O. C. and Dallinger, D.; *Nature Review Drug Discovery*, **2006**, 5, 1, 51-63. **b)** Taylor, M., Atri, B. S., Minhas, S.; *Evalueserve***, 2005,**

Developments in Microwave Chemistry. **c)** J.-S. Schanche, Mol. Diversity **2003**, 7, 293 – 300; Biotage AB (formally Personal Chemistry AB), www.personalchemistry.com; www.biotage.com **d)** Kappe, O. C., *Angew. Chem. Int. Ed.* **2004**, 43, 6250–6284. **e)** Hayes, B. L., *Microwave Synthesis, Chemistry at the speed of light*, CEM publishing, **2002**, chapter 2, pp 29.

10. Besson, T, Chosson, E.; *Combinatorial Chemistry & High Throughput Screening*, Vol. 10, No. 10, December **2007**, pp. 903-917.
11. **a)** Huang, L. J.; Chang, F.C.; Lee, K.H.; Wang, J.P.; Teng, C.M.; Kuo, S.C. *Bioorganic & Medicinal Chemistry,* **1998**, *6*,12, 2261. **b)** Ahn, J. H.; Cho, S. Y.; Ha, J. D.; Chu, S. Y.; Jung, S. H.; Jung, Y. S.; Baek, J. Y. ; Choi, I. K.; Shin, E. Y.; Kang, S. K.; Kim, S. S.; Cheon, H. G.; Yang, S. D.; Choi, J. K., *Bioorganic & Medicinal Chemistry Letters*, **2002**, *12,* 15, 1941. **c)** Bringmann, G.; Messer, K.; Brun, K.; Mudogo V*., J. Nat. Prod.,* **2002**, *65*, 1096.
12. Sacau, E. P.; Estévez-Braun, A.; Ravelo, A. G.; Ferro, E. A.; Tokuda, H.; Mukainaka, T.; Nishino, H.; *Bioorg. Med. Chem.* **2003**, *11(4)*, 483-488.
13. Mason, J. S.; Morize, I.; Menard, P. R.; Cheney, D. L.; Hulme, C.; Labaudiniere, R. F. *J. Med. Chem.* **1999**, *42*, 3251-3264.

14. **a)** Fischer, E.O. *Pure & Applied Chem.* **1970***,* 24, 2, 407 **b)** Fischer, E.O., Shubert, U. *J. of Organometallic Chem.* **1975** *100, 1,* 59. **c)** Fischer, E.O.; *Advances in Organometallic Chemistry* **1976***, 14,* 1.

15. Fischer, E.O. *Angew. Chemie* **1974,** *86,* 651.

16. Wulff, W. D.; Challner, C. A.; *J. Organometallic Chem.* **1987***, 334*, 9.

17. Dötz, K.H. *Angew. Chem. Int. Ed. Engl.* **1975***, 14,* 644.

18. **a)** Dötz, K.H. *Angew. Chem.* **1984***, 96,* 573. **b)** Dötz, K.H. *Angew. Chem. Int. Ed. Engl.* **1964***, 23,* 587. **c)** Dötz, K.H. *Organometallics in organic synthesis. Aspects of a modern Insterdisciplinary Field.* (Eds. DeMeijere, A., Dieck, H.,) Springer Berlin **1987**. **d)** Wulff, W.D. *Advances in Metal-Organic Chemistry*, Vol. 1, (Eds. Liebeskind, L. S.) JAI, Landon **1989**. **e)** Wulff, W.D. in *Comprenhensive Organic Synthesis* Vol. 5 (Ed; Trost, B.M., Fleming, I.; Paquette, L.A.) Pergamon, Oxford, **1991**. **f)** Wulff, W.D. in *Comprenhensive Organic Synthesis II*, Vol. 12 (Ed; Abel, E.W., Stone, F. G. A.; Hegedeus, L.S.) Pergamon, New York, **1995**.

19. **a)** Waters et al. *J. Am. Chem. Soc.* **1999**, 121, 27, 6404. **b)** Wulff, W. D. ; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J., *Organometallics* **1994**, 13, 1, 102

20. Hegedus, L.S. *Topics in Organometallic Chem.* **2004***, 13 (Metal Carbenes in Org. Synthesis),* 157.

21. Wang, K.T.; Yu, H. M.; Chen, S. T.; Chiou, S. H. *J. Chromatgr.* **1998**, 456, 357.

22. **a)** Brain, Christopher T.; Brunton, Shirley A. *Synlett* , **2001**, 3, 382. **b)** Besson, T.; Brain, C. T. *Microwave Assisted Organic Synthesis*, **2005**, 44, 77.

23. Dötz, K.H. *Pure & Appi. Chem.*, Vol. 55, No. 11, pp. 1689—1706, **1983**.

24. **a)** Connor, J. A.; Jones, E. M. *J. Chem. Soc. A* 1971, **1974**; **b)** Connor, J. A.; Jones, E. M. *J. Chem. Soc., Chem. Commun.* **1971**, 570; **c)** Söderberg, B. C.; Hegedus, L. S*. Organometallics* **1990**, 9, 3113; **d)** Söderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, 112, 4364.

25. **a)** S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, J. Chem. *Soc. Perkin Trans*. *1* **2000**, 3815 – 4196; **b)** S. V. Ley, I. R. Baxendale, *Nat. Rev. DrugDiscovery* **2002**, 1, 573–586; **c)** A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem. Int. Ed.* **2001**, 40, 650 –679; **d)** C. C. Tzschucke, C. Markert,W. Bannwarth, S. Roller, A. Hebel, R. Haag, *Angew. Chem*. **2002**, 114, 4136 – 4173; *Angew. Chem. Int. Ed*. **2002**, 41, 3964 – 4000. **e)** G. A. Strohmeier, C. O. Kappe, *Angew. Chem. Int. Ed*. **2004**, 43, 621 –624

26. **a)** Wulff, W.D.; *Tetrahedron,* **1985**, Vol. 41. No. 24. 5813-5832; **b)** Wulff, W.D; et al., *J. Am. Chem. Soc.* **1981**, *103,* 7677-7678.

27. Sacau, E. P.; Estévez-Braun, A.; Ravelo, A. G.; Ferro, E. A.; Tokuda, H.; Mukainaka, T.; Nishino, H.; *Bioorg. Med. Chem.* **2003**, *11(4)*, 483-488.

28. Kolb, H. C. and Sharpless, K. B.; *Drug Discovery Today,* Vol. 8, No. 24 December **2003.**

29. Shea, K.M. et al., *International Journal of Antimicrobial Agents*, 34, **2009**, 429–433.

30. Gin A, Dilay L, Karlowsky JA, Walkty A, Rubinstein E, Zhanel GG. *Expert Rev Anti Infect Ther.* **2007**; 5, 365–383.

31. Snydman DR, Jacobus NV, McDermott LA.; *Antimicrob. Agents Chemother.* **2008**; 52, 4492–4496.

32. Fischer, E.O.; Maasböl, A.; *Chem. Ber.* **1967**, *100*, 2445.

33. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew Chem., Int. Ed.* **2001**, *40*, 2004.

34. Rostovstev, V. V.; Green, L. G.; Finn, V. V.; Sharpless, K. B., *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

35. Tornoe, C. W.; Christensen, C.; Meldal, M., *J. Org. Chem*. **2002**, *67*, 3057.

36. Krasinski, A.; Radic, Z.; Manetsch, R.; Raushel, J.; Taylor, P.; Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc*. **2005**, *127*, 6686.

37. Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Eycken, E. V. *Org. Lett*. **2004**, *6*, 4223.

38. **a)** Thompson, R. H., *Naturally Occurring Quinones*; 2nd ed.; Academic Press: London and New York, **1971**. **b)** Naruta, Y.; Maruyama, J., Recent Advances in the Synthesis of Quinoid Compounds. In *The Chemistry of Quinoid Compounds*, Patai, S., Rappoport, Z., Eds.; Wiley: New York, **1988**, Vol. II, p-24.

39. **a)** O'Brien, P. J., Molecular mechanisms of quinone cytotoxicity. *Chem. Biol. Interact*. **1991**, *80*, 1. **b)** Kesteleyn, B.; Kimpe, N. D.; Puyvelde, L. V., *J. Org. Chem.* **1999**, *64*, 1173-1179

40. Bao, J.; Wulff, W. D.; Fumo, M. J.; Grant, E. B.; Heller, D. P.; Whitcomb, M. C.; Yeung, S.-M. *J. Am. Chem. Soc.* **1996**, *118*, 2166.

41. Aponick, A.; Buzdygon, R. S.; Tomko, R. J., Jr.; Fazal, A. N.; Shughart, E. L.; McMaster, D. M.; Myers, M. C.; Pitcock, W. H., Jr.; Wigal, C. T.; *J. Org. Chem.* **2002**, *67*, 242-244.

42. McCallum, et al., *Organometallics*, Vol. 7, No. 11, **1988**.

Appendix A.

Equipment	Time	Temperature	Solvent	Conversion
A	5 min ramp 15 min hold	180ºC	THF	64%
B	15 min	180ºC	THF	25%
A	5 min ramp 10 min hold	180ºC	Bu_2O	74%
B	15 min	180°C	Bu_2O	18%
A	5 min ramp 10 min hold	200ºC	Bu_2O	46%
B	15 min	200ºC	Bu_2O	9%

Curriculum Vita

Israel García-Martínez was born in México City, México, the second born of Humberto G. García Serrano and Virginia Martinez Zavala. He earned his bachelor degree in Chemical Engineering with honors from Universidad Nacional Autonoma de Mexico. He worked as a chemical engineer for PEMEX (Petróleos Mexicanos) a petroleum refining company and for CIP-COMEX (Centro de Investigación en Polímeros), a paint company in Mexico City. He joined the Master of Science program at the University of Texas at El Paso during fall 2002. In 2007, he transferred to the chemistry doctoral degree program. He graduated with his doctoral degree in December 2009.

Dr. Garcia-Martinez has been the recipient of the scholarship from Consejo Nacional de Ciencia y Tecnologia, CONACYT, to complete his doctoral studies at the University of Texas at El Paso. While pursuing his degree, Dr. Garcia-Martinez worked as a teaching assistant and research associate for the department of chemistry.

Dr. Garcia-Martinez's published the work on microwave assisted synthesis of naphthoquinones utilizing solid supported Fischer carbene complexes (*Tetrahedron Lett.*, **2005,** *46*, 7545–7548). He has presented his research at national and international conferences such as the 227th American Chemical Society (ACS), national meeting in Anaheim, CA during March of 2004 and the 2ª Reunion de la Academia Mexicana de Química Orgánica in March of 2006. He participated as an active member of ACS student affiliates at UTEP, SACNAS-Paso del Norte student chapter. He collaborated as a scientific judge for the Research Expo at UTEP during the 2007-2009 events.

Dr García-Martínez's dissertation entitled, "Microwave Assisted Solid-Supported Organic Synthesis: A Novel Development of a Methodology to Obtain 2,3-Disubstituted-1,4-Naphthoquinones", was supervised by Dr. Luis E. Martinez.

Dr. García-Martínez is currently working at University of Texas at San Antonio synthesizing compounds for photo-harvesting applications under the supervision of Dr. George R. Negrete.

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