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Microwave-assisted solid-phase Dötz benzannulation reaction: a facile synthesis of 2,3-disubstituted-1,4-naphthoquinones

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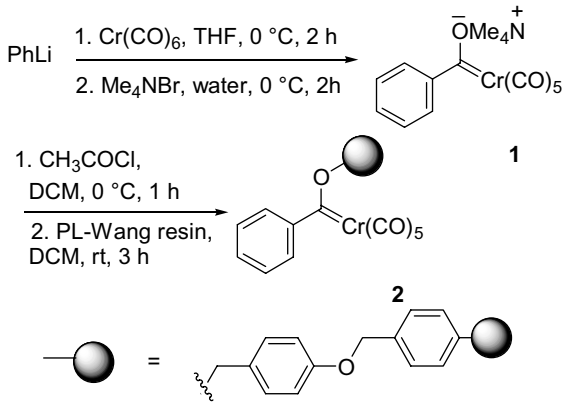
Abstract—A microwave-assisted solid-supported Dötz benzannulation of chromium carbene complexes with various alkynes has been developed. The oxidative cleavage of the resulting resin-bound 1,4-naphthols affords 2,3-disubstituted-1,4-naphthoquinone derivatives in good to moderate yields with high purities.

Transition metal-mediated reactions are extremely appealing for solid-phase organic synthesis (SPOS) due to their versatility, wide-ranging functional group compatibility and potential for synthesizing biologically active lead compounds. Although a wide range of Pd-mediated coupling reactions and transition metal-catalyzed olefin metathesis reactions have been utilized in SPOS,[1] the development of transition metal carbene chemistry remains relatively unexplored. Notable among transition metal carbene chemistry is the Dötz benzannulation of Fischer carbene complexes with alkynes to form substituted phenols.[2–4] While the Dötz benzannulation has been extensively applied to synthesize a diverse array of natural products,[3] no examples of its application to combinatorial library synthesis have yet been reported.

Due to the mechanistic complexity of the reaction, the product distribution of the Dötz benzannulation can vary among naphthol, indene, furan, and cyclobutanone products by slightly modifying reaction conditions such as the solvent, Fischer carbene, and alkyne concentrations and the nature of the alkyne.[5] Although there is precedent for the preparation of solid-supported triphenyl phosphine[6] Fischer carbene complexes and the application of a soluble Fischer carbene complex[7] to solid-phase peptide synthesis, their application to SPOS remains unexplored. Herein, we report the first example of the solid-supported Dötz benzannulation reaction and subsequent oxidative cleavage leading to biologically active 2,3-disubstituted-1,4-naphthoquinone derivatives in good to moderate yields.

Modifying the method originally developed by Connor and co-workers,[8] the synthesis of polymer-supported Fischer carbene complex **2** was obtained in four steps (Scheme 1) from commercially available chromium hexacarbonyl and phenyllithium by O-acylation of [tetramethylammonium][(2-phenyl)oxidocarbene]pentacarbonylchromium **1** with acetyl chloride followed by



Scheme 1.

Keywords: Solid-phase synthesis; Microwave; Dötz reaction; 1,4-Naphthoquinones; Fischer carbenes.
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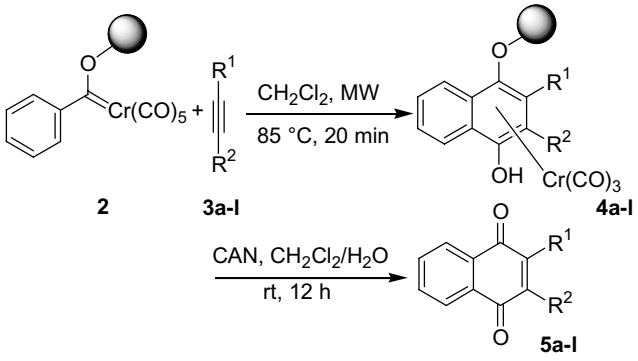
reaction with PL-Wang resin (Polymer Laboratories, 1% crosslinked 1.7 mmol/g) to produce resin-bound Fischer carbene complex **2** in 95% loading as determined by elemental analysis.[9] Resin loading of the carbene complex can be easily monitored qualitatively by colorimetric analysis, the beads turn to a dark red color. The appearance of characteristic Cr–CO stretches at 2061 and 1944 cm^{-1} in the IR spectrum of **2** corresponds to CO stretches found in analogous aryl carbene complexes.[10]

The reaction of **2** with 1-octyne (**3e**), followed by the oxidative cleavage of the resulting resin-bound phenol **4e** using cerium(IV) ammonium nitrate (CAN), provides a useful model system for reaction optimization of the solid-supported Dötz benzannulation reaction (Table 1). In contrast to traditional thermal and a recently reported microwave-assisted[11] Dötz benzannulation with soluble Fischer carbene complexes, CH_2Cl_2 was the optimal solvent affording **5e** in 63% yield (entry 1). While other solvents, such as acetonitrile, THF, toluene, and heptane, were also effective for the exclusive formation of **5e** under microwave conditions (entries 2–5), the use of butyl ether or DMF was less effective (entries 6 and 7). A brief examination of the effect of temperature on the reaction revealed that 85 °C was found to be the optimum temperature (entry 1 and entries 8–10) and extending the reaction time had little influence on the yield of **5e** (entry 1 and entries 11–13). The same reaction can be carried out under traditional thermal conditions with comparable yields (**5e**, 58% yield: entry 14); however, there is substantial 6-fold shortening of reaction times for the microwave conditions over traditional thermal conditions.

Under optimized conditions, the Dötz benzannulation of **2** was performed with various alkynes **3a**–**l** followed by the oxidative cleavage of the resulting resin-bound naphthols **4a**–**l** (Scheme 2).[12] Table 2 illustrates that various aryl and alkyl substituted alkynes produce 1,4-naphthoquinones **5a**–**i** in moderate to good yields (entries 1–9) with aryl substituted acetylenes producing 2,3-disubstituted-1,4-naphthoquinones in slightly higher yields than alkyl substituted acetylenes. In contrast to the solution-phase benzannulations, the solid-supported Dötz benzannulation reaction cleanly produces the quinone product without the indene, indenone, or cyclobutenone side products typically seen in these reactions as evidenced by GC, ^1H NMR, and mass data. An oxidized product of unreacted resin-bound Fischer carbene complex **2**, benzoic acid, was the only side product.[13]

The present solid-supported Dötz reaction tolerates alcohol and ester functionality on the alkyne (entries 10 and 11) and produces the corresponding 1,4-naphthoquinones in moderate yield. It is noteworthy that **5j** serves as a key intermediate for the synthesis of pyranonaphthoquinone, which has significant antitumor activity.[14] To further explore the synthetic scope of the reaction, the reaction was extended to conjugated diynes. In contrast to the solution-phase Dötz benzannulation with conjugated diynes,[15] the reaction of 1,4-diphenyl butadiyne (**3l**) with **2** under our standard conditions cleanly afforded the mono benzannulation product 2-phenyl-3-phenylethynyl-[1,4]naphthoquinone



Scheme 2.

Table 1. Effects of solvent, temperature, and time on the solid-supported Dötz benzannulation reaction of **2** with 1-octyne (**3e**), followed by the oxidative cleavage of resin-bound intermediate **4e**[a]

Entry	Solvent	Temp (°C)	Time (min)	Yield of **5e** (%)[b]
1	CH_2Cl_2	85	20	63
2	CH_3CN	85	20	61
3	THF	85	20	58
4	Toluene	85	20	56
5	Heptane	85	20	55
6	Butylether	85	20	40
7	DMF	85	20	35
8	CH_2Cl_2	135	20	50
9	CH_2Cl_2	110	20	35
10	CH_2Cl_2	60	20	50
11	CH_2Cl_2	85	50	61
12	CH_2Cl_2	85	30	61
13	CH_2Cl_2	85	10	57
14[c]	CH_2Cl_2	85	120	58

[a] Reactions of **2** (0.115 mmol) with 1-octyne (0.575 mmol) were carried out in the microwave at the specified temp for the specified time in 2.00 mL of the specified solvent followed by the oxidative cleavage of the resin using CAN (0.575 mmol).

[b] Isolated overall yields were calculated based on the loading of PL-Wang (1.7 mmol/g) by the supplier. Purity is >95% as determined by ^1H NMR spectroscopy.

[c] No microwave irradiation was employed.

Table 2. Results of the microwave-assisted solid-phase Dötz benzannulation of **2** with various alkynes **3a**–**l**, followed by the oxidative cleavage using CAN

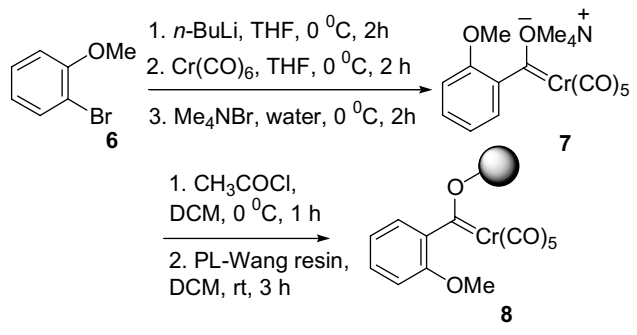
Entry	Alkyne	Product	R^1	R^2	Yield (%)[a]
1	**3a**	**5a**	Ph	Ph	76 (99)
2	**3b**	**5b**	H	Ph	67 (98)
3	**3c**	**5c**	Me	Ph	62 (99)
4	**3d**	**5d**	H	C_5H_{11}	58 (97)
5	**3e**	**5e**	H	C_6H_{13}	63 (97)
6	**3f**	**5f**	H	C_7H_{15}	62 (97)
7	**3g**	**5g**	C_3H_7	C_3H_7	55 (96)
8	**3h**	**5h**	Me	C_6H_7	50 (96)
9	**3i**	**5i**	C_2H_5	C_3H_7	57 (99)
10	**3j**	**5j**	H	C_3H_6OH	50 (93)
11	**3k**	**5k**	C_2H_5	CO_2Et	42 (98)
12	**3l**	**5l**	Ph	C≡CPh	68 (95)

[a] Isolated overall yields were calculated based on the loading of PL-Wang (1.7 mmol/g) by the supplier. Values given in parentheses represent purity of products as determined by GC.

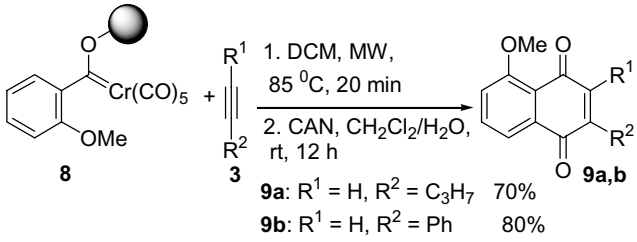
(**5l**) in 68% yield (entry 12) without any intermolecular double benzannulation or cyclobutenone product formed.

To understand the regioselectivity of the solid-supported Dötz benzannulation, the reaction with *o*-methoxyphenyl Fischer carbene complex **8**, synthesized as described in Scheme 3, was investigated. Under our standard conditions (Scheme 4), the reactions of **8** with unsymmetrical acetylenes 1-pentyne (**3k**) and phenylacetylene (**3b**) were highly regioselective and the regiochemistry was same as that of the solution-phase chemistry, affording the corresponding 2-substituted 1,4-naphthoquinone as the sole product by GC (**9a**: 70% yield—98% purity, **9b**: 80% yield—97% purity).[5b]

Several interesting features are noteworthy from this study. First, the present solid-supported Dötz reaction is highly insensitive to the nature of the solvents (Table 1, entries 1–7). Irrespective of the solvent under our standard conditions, the reaction afforded the single 1,4-naphthoquinone product and no other product was seen in the ^{1}H NMR spectrum. This is in sharp contrast to the solution-phase chemistry in which the Dötz reaction is highly solvent dependent. For example, the solution-phase reaction of phenyl Fischer carbene complex with diphenyl acetylene using heptane as the solvent at 80 °C for 30 min followed by the CAN oxidation afforded four different products,[5b] whereas the present solid-phase reaction of **2** with diphenyl acetylene using heptane as the solvent under microwave as well as thermal conditions afforded single product **5a** with 98% purity in 60% and 63% yields, respectively. Second, the only side product, benzoic acid, can be easily removed from the reaction mixture by washing with dilute base or by passage through a basic solid-phase extraction (SPE) column. Third, in contrast to the solution-phase Dötz benzannulation, the purification procedure for the present solid-supported methodology is quite simple and requires no column chromatography. The 1,4-naphthoquinone derivatives display a broad spectrum of biological activities[16] and preliminary screening of these compounds in our laboratories has showed significant cyctotoxic[17] and antimycobacterial activities.[18]



Scheme 3.



Scheme 4.

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. Further work in our laboratories is to utilize this methodology for the preparation of libraries of structurally diverse compounds, including natural products, and the screening of these compounds against a variety of biological targets is currently underway.

Acknowledgments

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9. Preparation of resin-bound Fischer carbene complex **2**: 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 (2×50 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 **1** as a red solid. To a stirred solution of crude red solid **1** (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 immediately. 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 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 (2×50 mL), THF (1×25 mL), and CH_2Cl_2 (1×25 mL) and dried under vacuum to constant weight to give 2.17 g resin-bound complex **2** as a red solid. IR (KBr) 2061, 1944 cm^{-1}. (Found: Cr, 5.67%. 95% loading @ 1.7 mmol/g requires Cr, 5.99%).
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12. General procedure for the preparation of 1,4-naphthoquinone derivatives **5a**–**l**. To a microwave process vial (10.0 mL), resin **2** (100 mg, 0.115 mmol) was added and the vial was sealed with an aluminum/Teflon crimp top. Then, a solution of alkyne **3** (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 Emrys™ Optimizer—300 W maximum power) at 80 °C for 20 min. The reaction mixture was filtered and the resin was washed sequentially with CH_2Cl_2 (2×50 mL), THF (1×25 mL), and CH_2Cl_2 (1×25 mL) and dried under vacuum for 1 h to afford resin-bound naphthols **4a**–**l**. Resin-bound naphthols **4a**–**l** (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 (2×5 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 1,4-naphthoquinones **5a**–**l**.
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