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Diaryl Ethers Using Fischer Chromium Carbene Mediated Benzannulation

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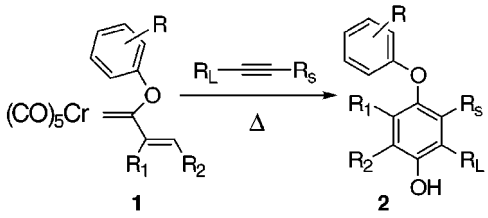
ABSTRACT



The biological relevance and irresistible synthetic challenge of compounds containing the diaryl ether linkage encourages the development of new methodologies targeted toward this structural subunit. The syntheses of diaryl ethers 2 using a benzannulation strategy that formally involves a [3 + 2 + 1] cycloaddition between aryloxy-substituted Fischer carbenes 1 and alkynes are described. This methodology provides a neutral near ambient temperature formation of diaryl ethers.

The diaryl ether moiety is crucial to a number of molecules with pronounced biological activity.[1] These range from K-13 a noncompetitive inhibitor of angiotensin I converting enzyme (ACE)[2] to the structurally more complex glycopeptide antibiotics such as vancomycin. Vancomycin is clinically used in the fight against methicillin-resistant *Staphylococcus aureus* and other gram-positive bacteria.[3] Oligomeric ellagitannins, important constituents in plant chemical defense systems, herbal medicines, leather tanning, and the food and beverage industry, result from an oxidative carbon−oxygen coupling to form a dehydrodigalloyl diaryl ether between monomeric ellagitannins. The dimeric ellagitannin sanguiin H-6 demonstrates an in vitro potency 100−250 times the clinically useful DNA topoisomerase II inhibitor etoposide (VP-16).[4] On another front, the diaryl ether thyroxine is an effective small molecule inhibitor of amyloid fibril formation in the amyloidogenic transthyretin (TTR) protein. Amyloid fibril formation of TTR and other normally soluble amyloidogenic proteins is thought to be the causative agent in human amyloid diseases.[5]

When considering syntheses of these compounds or structural variants for structure−activity relationship studies (SAR), the formation of the diaryl ether moiety plays a key role in the synthetic design. Current procedures for the formation of the diaryl ether subunit involve the following:[6] (1) Ullmann coupling strategies;[7] (2) thallium(III) trinitrate (TTN) oxidative phenolic coupling; (3) aromatic nucleophilic substitution (S_NAr); and (4) displacement of bromine from bromobenzoquinones with phenols to yield *O*-aryl benzoquinones. Given the interest in the synthesis of diaryl ethers and various disadvantages of the above-mentioned technologies, there is a great deal of activity in the development of new methods or improving existing technology. Several alternative approaches include complexation of haloaromatics

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Table 1. Diaryl Ethers from Benzannulation with Alkynes

Carbene	Alkyne	Product / Yield[a]
5a	TMS—≡, Ph—≡,	**8a** R = TMS, 61%; **8b** R = Ph, 88% **8c** R = $CH_3(CH_2)_3$, 60%
5b **5c** **5d**	Ph—≡—Ph	**9** R = *p*-OMe, 86%; **10** R = *m*-Br, 93% **11** R = *p*-*t*-Bu, 70%
6	Ph—≡—Ph	**12**, 76%
7a	Ph—≡	**13**, 73%
7b	BnO—≡,	**14**, R = OBn, 25%, (55%) **15**, R = $CH_3(CH_2)_2$, 42%, (59%)

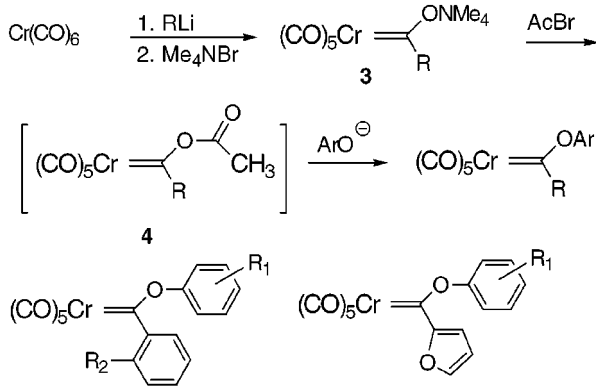
[a] Isolated purified yields and yields in parentheses are from ultrasonic irradiation

with ruthenium followed by displacement,[8] substitution of aryl iodonium salts by sodium phenolates,[9] ring opening of cyclohexenone oxides with phenols,[10] and substitution of 2,6-dihalo-substituted triazenes with phenols.[11] The palladium-catalyzed formation of diaryl ethers is also gaining increasing attention due to the efforts of Buchwald and Hartwig.[12]

Common to each of the above-mentioned strategies is the formation of the carbon−oxygen bond between two aromatic rings or their equivalents. Strategies that build the aromatic ring via a cycloaddition reaction benzannulation are much less common.[13] Olsen's Diels−Alder reaction between acetylenes and *O*-arylbutadienes leads to a model for isodityrosine[14] and Feldman's dimerization of orthoquinones provides an efficient route to the dehydrodigalloyl diaryl ether of the oligomeric ellagitannins.[15] This method is significant in that the steric crowding around the ether linkage and the electron-rich nature of the two-galloyl rings severely limits all the existing technologies for diaryl ether synthesis.

Our interest in benzannulation strategies to diaryl ethers led us to propose an approach to diaryl ethers **8**−**15** (Table 1) that involves the Dötz benzannulation[16] between aryloxy Fischer chromium carbene complexes **5**−**7** (Scheme 1) and alkynes.[17] While this work was in progress Wulff described the formation of aryloxy carbenes and their reaction with alkynes in a study probing electronic effects in the Dötz reaction.[18]

Scheme 1. Synthesis of Aryloxy Fischer Chromium Carbene Complexes **5**−**7**



5a R_1 = H, R_2 = H: 57%
5b R_1 = *p*-OMe, R_2 = H: 45%
5c R_1 = *m*-Br, R_2 = H: 64%
5d R_1 = *p*-*t*-Bu, R_2 = H: 41%
6 R_1 = H, R_2 = CH_3: 45%

7a R_1 = H: 94%
7b R_1 = *o*-Cl: 85%
7c R_1 = *o*-OCH_3: 62%
7d R_1 = *m*-CF_3: 90%
7e R_1 = *p*-I: 50%

This approach to diaryl ethers involves a formal [3 + 2 + 1] cycloaddition between an aryloxy -substituted Fischer chromium carbene complex and an alkyne. In general, Fischer carbene complexes are either alkoxy- or alkylamino-substituted and until recently only two aryloxy-substituted carbene complexes were known.[19] For our work the synthesis

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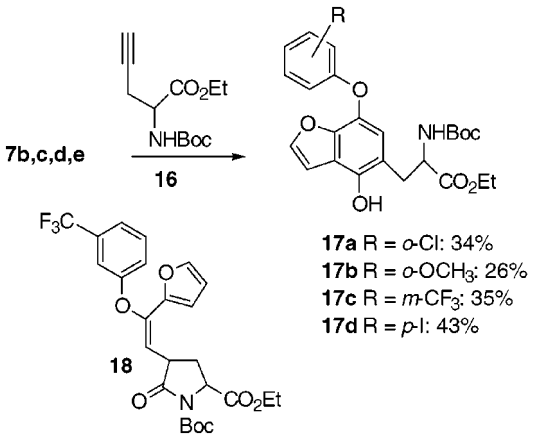
of aryloxy carbenes **5**−**7** follows a modification of Fischer's original procedure.[20] The optimum procedure involves addition of acetyl bromide to the ammonium ate complex **3**, resulting in the metal acyl complex **4**, followed immediately by the addition of lithium or sodium phenoxide (Scheme 1). Complexes **5**−**7** are isolated as deep red oils by standard chromatographic techniques and are stable to storage (−20 °C) under an inert atmosphere for several weeks.

With aryloxy carbenes **5**−**7** in hand, subsequent thermolysis with both internal and terminal acetylenes generally led to the desired diaryl ethers **8**−**15** in fair to excellent yields (Table 1). The reactions were complete in 16−36 h, at 50−55 °C, 0.05 M with 1.2 equiv of alkyne.

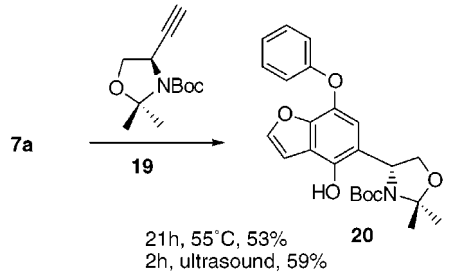
The regiochemistry of **8**−**15** is consistent with the accepted mechanism of the Dötz benzannulation that involves rate-limiting loss of CO from the carbene complex followed by alkyne coordination and insertion leading to a vinyl carbene complex. Subsequent insertion of CO forms a vinyl ketene which then undergoes electrocyclization and aromatization to yield the diaryl ethers.[21] Although these reactions are unoptimized, high intensity *ultrasound* significantly improves the yield and reduces the reaction time for the formation of **14** and **15**. For example, reaction of **7b** with *O*-benzyl propargyl alcohol gives the diaryl ether **14** in 25% after 33 h at 55 °C while *ultrasonic* irradiation gives a 55% yield after 5 h. The use of *ultrasound* is suggested to promote the rate-limiting loss of CO from the initial carbene complex.[22]

A general and very mild method of forming diaryl ethers is a valuable addition to the synthetic methods available for the construction of this important subunit. The neutral near ambient temperature formation of diaryl ethers with the Dötz benzannulation offers a potentially attractive method for the construction of diaryl ethers in synthetic endeavors toward complex natural products with sensitive functionality. To demonstrate this potential, treating complexes **7b**−**e** with propargylglycinate[23] **16** results in the diaryl ether phenylalanine analogues **17a**−**d**. The moderate yield of these



compounds is the result of the formation of lactams such as **18**, as a side product in these reactions. The lactams result from the attack of nitrogen on the intermediate ketene involved in the mechanism of the Dötz reaction.[21] Currently we are investigating the potential to form either the phenylalanine or lactam products depending on reaction conditions or substituent effects. The results of these studies will appear in due course.

In addition to the phenylalanine diaryl ethers, complex **7a** yields the protected diaryl ether glycinol derivative **20** upon reaction with the ethynylglycine equivalent **19** derived from Garner's aldehyde.[24]



Again, *ultrasound* significantly reduces the reaction time and results in an improved yield (59% after 2 h with sonication versus 53% after 21 h at 55 °C).

Each of the above examples lend further support to our hypothesis that aryloxy-substituted Fischer chromium carbene complexes can lead too highly functionalized diaryl ethers. These preliminary results provide a foundation to expand this methodology and demonstrate its usefulness in the synthesis of diaryl ethers with biological significance.

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Supporting Information Available: Experimental procedures for the preparation of **5**−**7**, **8**−**15**, **17**, and **20** and their characterization data. ^{1}H NMR and ^{13}C NMR spectra for **5b**−**d**, **6**, **7a**−**e** **8a**−**c**, **9**−**12**, **15**, **17b**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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