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Novel Method of Aromatic Coupling between *N*-Aryl Methanesulfonamide and Thiophene Derivatives

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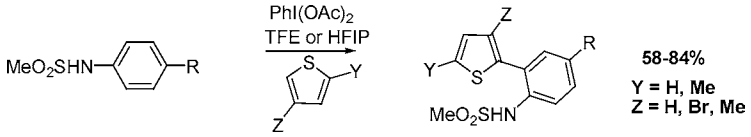
ABSTRACT



Oxidation of *N*-aromatic methanesulfonamides with iodobenzene diacetate in the presence of substituted thiophene promotes interesting coupling reactions in moderate to good yields.

The coupling of two aromatic units as an avenue to biaromatics has received much attention in recent years due to the large number of natural compounds that incorporate these systems,[1] to the use of axially chiral biaryls as ligands in asymmetric reactions,[2] and to the potential of bi- and polyaryls in materials chemistry and nanotechnology.[3] The first practical methods to effect aryl−aryl coupling are the Ullmann reaction[4] and variants thereof.[5] The scope of these transformations has been greatly extended with the advent of nickel[6]- and, especially, palladium[7]-mediated reactions. Nonetheless, the development of new, efficient, and environmentally benign methods for aryl−aryl coupling remains an active field of research.[8]

In that connection, a technique for the direct coupling of aromatic rings, i.e., one that removes the need to prepare halogen or metal derivatives of the aryl fragments prior to their actual union, would be quite useful. Indications of how such an objective could be achieved are apparent in the work of Kita,[9] who has shown that aromatics[10] may be oxidatively coupled in a bimolecular process under the influence of

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hypervalent iodine reagents. In this paper, we detail a technique for the direct oxidative coupling of aniline derivatives with thiophenes.

Ongoing work in our laboratory required rapid access to compounds of type **3** (Figure 1). A possible avenue to these

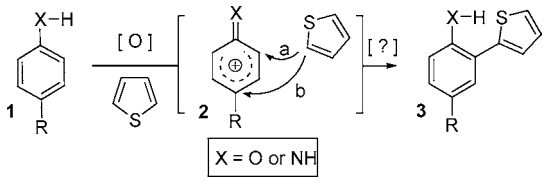
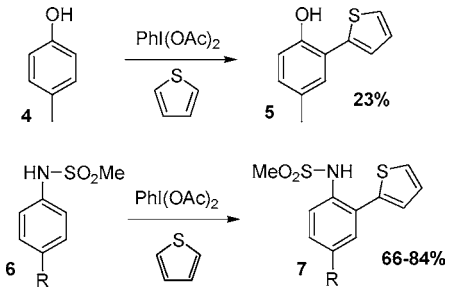


Figure 1. Possible avenue to compounds **3**

intermediates involves oxidative activation of substrate **1** and capture of the presumed intermediate **2**, at the *ortho* position, by thiophene (cf. pathway a). We note that while oxidative activation of phenols with various oxidants is well documented, it is also established that species such as **2** tend to react at the 4-position (cf. reaction mode b), at least with heteronucleophiles.[11]

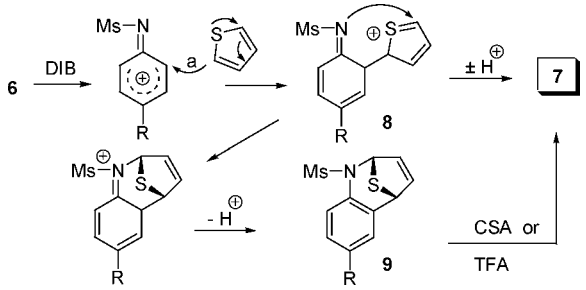
Initial attempts to induce the desired transformation in the phenol series produced disappointing results, even in the presence of a large excess of nucleophile. Thus, treatment of *p*-cresol and thiophene with iodobenzene diacetate (DIB) in hexafluoroisopropanol (HFIP; Kita conditions)[12] afforded **5** in a low 23% yield (Scheme 1).

Scheme 1. New Coupling Reaction



Interestingly, no products of addition to the para position were observed. We reasoned that the electronegativity of the oxygen atom in **1** (X = O) was likely to render this transient intermediate short-lived, excessively electrophilic, and therefore poorly selective in its reactivity. Replacement of the oxygen with a less electronegative nitrogen atom could then moderate the reactivity of **2** and allow the desired reaction to occur more efficiently. While free anilines failed to yield characterizable products, excellent results were obtained with methanesulfonamides **6**.[13] A typical procedure involves DIB treatment of a mixture of **6**[14] and excess thiophene in trifluoroethanol (TFE) or HFIP.[15] For reactions run in TFE, it is preferable to use 10−12 equiv[16] of thiophene to avoid formation of polymers and addition of TFE to the substrate by a Kita-type process.[12] With a less nucleophilic solvent such as HFIP, the reaction can be carried out with 5 equiv of thiophene.[16] The new reaction commonly affords a side product, **9** (5−10%),[17] which arises through a formal 4 + 3 cycloaddition of the substrate with thiophene. A mechanistic hypothesis for the formation of **9** is adumbrated in Scheme 2. We suppose that the addition of thiophene to the presumed

Scheme 2. Mechanistic Hypothesis



2 furnishes an initial sulfonium ion **8**, which may either undergo direct conversion to **7** or be nucleophilically intercepted by the nitrogenous functional group (Scheme 2). Interestingly, acid treatment (camphorsulfonic or trifluoroacetic acids) converts **9** to **7**. This observation has mechanistic ramifications, in that it could imply that **9** is the actual primary product of the reaction. The acidity of the reaction medium could then trigger the conversion of **9** to **7**.

A summary of representative experiments in TFE or in HFIP appears in Table 1. Product yields are generally higher when HFIP is used as the solvent.

It is interesting to observe that the reaction tolerates a free alcohol (entry **d**) on the aliphatic side chain, suggesting that

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(13) Examples of oxidative transformations of *N*-aryl sulfonamide: (a) Akai, S.; Kawashita, N.; Morita, N.; Nakamura, Y.; Iio, K.; Kita, Y. *Heterocycles* **2002**, *58*, 75. (b) Zawada, P. V.; Banfield, S. C.; Kerr, M. A. *Synlett* **2003**, 971.

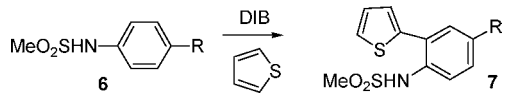
(14) Obtained in high yield by treatment of aniline with mesyl chloride and pyridine: Wang, Y.; Guziec, F.-S. *J. Org Chem.* **2001**, *66*, 8293.

(15) TFE (pK_a ca. 12.4, nucleophilicity ca. −2.8); HFIP (pK_a ca. 9.3, nucleophilicity ca. −4.2).

(16) Excess of thiophen is easily removed at the end of the reaction and could be recycled.

(17) An additional side product occasionally detected in crude reaction mixtures (5−10%) remains as of yet unidentified.

Table 1. Thiophene Coupling

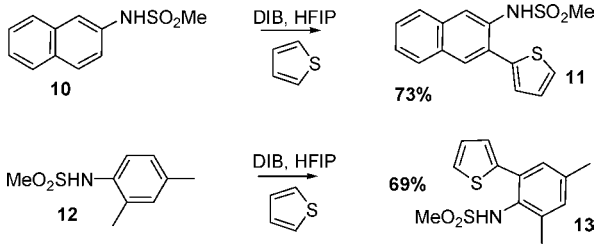


entry	R	yield[a] (%)	yield[b] (%)
a	Me	68	76
b	*n*-Pr	74	84
c	*i*-Pr	67	74
d	CH_2CH_2OH	68	75
e	Cl	66	72

[a] In TFE as solvent. [b] In HFIP as solvent.

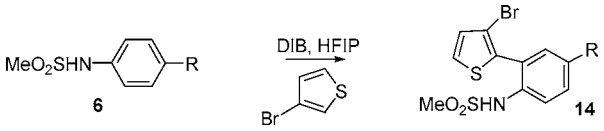
the new process may tolerate a range of spectator functional groups. The reaction also succeeds with substituted and polycyclic aromatic mesylamides **10** and **12** (Scheme 3).

Scheme 3. Polysubstituted Aromatics



The use of 3-bromothiophene in the new reaction results in products with coupling at position 2 of the thiophene, due to the orientation effect of the bromine atom (Table 2).

Table 2. 3-Bromothiophene Coupling



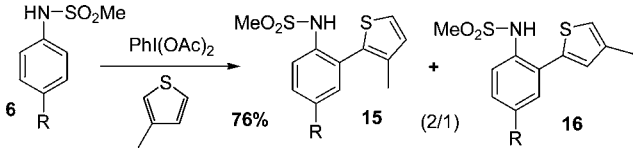
entry	R	yield (%)
f	Me	67
g	*n*-Pr	63
h	*i*-Pr	62
i	CH_2CH_2OH	64
j	Cl	64

It should be noted that metal-mediated coupling methods could be problematic with 3-bromothiophene, due to the reactivity of the halogen. This clearly illustrates the potential of the new method. The use of TFE as the solvent in reactions involving 3-bromothiophene results in formation of a byproduct of addition of TFE on the substrate (≈10%).[12]

This problem may be avoided by using HFIP as the solvent. It is noteworthy that under these conditions no cycloadduct of the type **9** is observed. The greater acidity HFIP-containing media relative to analogous TFE-containing mixtures may promote complete conversion of **9** to **7**.

Unfortunately, the reaction with 3-methylthiophene leads to an inseparable 2:1 mixture of **15** (major product; Scheme 4) and **16** (minor) in 76% yield. We believe that the product

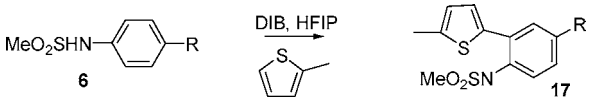
Scheme 4. 3-Methylthiophene Coupling



ratio reflects a balance between the electronic and the steric effect of the methyl group.

Reaction with 2-methylthiophene is less efficient, affording the expected **17** (Table 3) plus 10−20% of a cycloadduct of

Table 3. 2-Methylthiophene Coupling

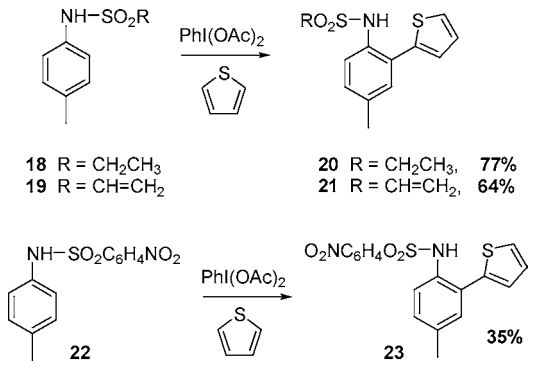


entry	R	yield (%)
k	Me	58
l	*n*-Pr	63
m	*i*-Pr	64

the type **9** and a byproduct of unidentified structure (10−15%). While the cycloadduct may be partially transformed into **17** by treatment with camphorsulfonic acid, the global yield of the latter is lower. Finally, different attempts to achieve coupling of **6** at the 3-position of 2,5-dimethylthiophene failed, as did all attempts to utilize compounds **7** in a second oxidative coupling step.

Oxidation of other aliphatic sulfonamides, such as ethanesulfonamide **18** or vinyl sulfonamide[18] **19**, gives similar

Scheme 5. Aryl Sulfonamide versus Aliphatic Sulfonamide



results and lets us suppose that this method can be generalized to different aliphatic sulfonamides (Scheme 5). However, uniformly unsatisfactory results were obtained with aromatic sulfonamides such as nosylamide **22** or tosylamide. Thus, compound **23** was obtained in a low yield of 35% (Scheme 5). The reason for these inefficient conversions remains unclear, but unfavorable steric effects engendered by the larger aryl groups may play a role.

In summary, a practical and new method for the bimolecular coupling of *N*-aryl methanesulfonamide and thiophene derivatives is now available. The transformation provides new strategic opportunities in the chemical synthesis of nitrogenous substances, and results in ongoing investigations with different aromatic derivatives, mild nucleophilic reagents, and their applications will be disclosed in due course.

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Supporting Information Available: Experimental procedures and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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