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Novel formal [2+3] cycloaddition between substituted phenols and furan

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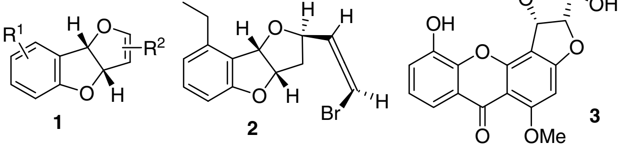
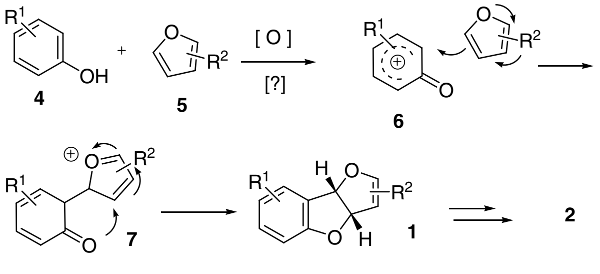
Abstract—Treatment of various substituted phenols in the presence of furan, iodobenzene diacetate, and trifluoroethanol promotes oxidative formal [2+3] cycloaddition in moderate to useful yields.

The unusual ring system **1** occurs in natural products such as panacene, **2**, a shark antifeedant,[1] psorofebrin, **3**, an antileukemic xanthone,[2] and other bioactive substances.[3] (Scheme 1). While a number of elegant routes to substructure **1** are known,[4] we have become interested in an approach that rests upon a hypothetical 'oxidative [2+3] cycloaddition' between a phenol and a furan, according to the format of Scheme 2. In this Letter, we disclose a methodology to effect this yet unknown transformation.



Scheme 1.



Scheme 2.

A key aspect of the new reaction is the use of iodobenzene diacetate ('DIB') as the oxidant. The potential of this environmentally benign reagent is especially apparent from the pioneering work of Kita.[5] In particular, DIB promotes noteworthy oxidative transformations of phenol[6] and aniline derivatives,[7] probably through cationic processes, in a manner consistent with the recent requirements for green chemical processes. As observed by Kita et al.,[8] DIB reactions generally occur best in solvents such as trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP).[9] Under these conditions, oxidative attack of phenols in the presence of unhindered heteronucleophiles[10] tends to proceed through pathway b (Scheme 3). However, we have recently determined that carbon-based nucleophiles such as thiophene[11] attack the presumed intermediate **6** at a position adjacent to the carbonyl group (pathway a), resulting in the formation of products **11**, albeit in low yield.

Interestingly, the use of furan in lieu of thiophene in the same reaction produces none of the furanyl phenols analogous to **11**. Interestingly, the use of furan in lieu of thiophene in the same reaction produces none of **11**. Instead, it efficiently leads to tricyclic compounds **12** resulting from a formal oxidative [2+3] cycloaddition (Scheme 4). Thus, various substituted phenols are converted to **12** in 38–61% yield, presumably by the mechanism depicted in Scheme 4. The reaction is best carried

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Keywords: Hypervalent iodine; Furan; Phenols; Cycloaddition [2+3].

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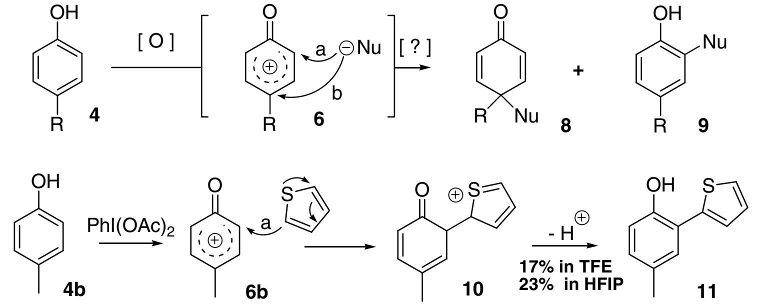
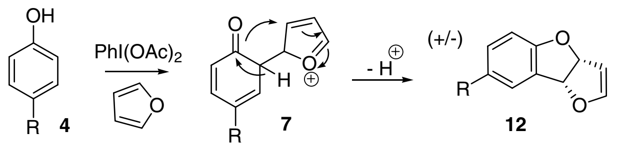


Scheme 3.



Scheme 4.

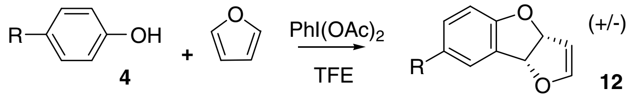
out in TFE as the solvent (not HFIP; vide infra) and in the presence of excess furan.[12]

A summary of the representative experiments with *para*-substituted phenols appears in Table 1.[13] It is worthy of note that the reaction tolerates moderately nucleophilic functionalities, such as a sulfonamide, that may be present on the substrate phenol (cf. entry **12e**). A 4-trimethylsilyl group is also readily tolerated (cf. **12f**).

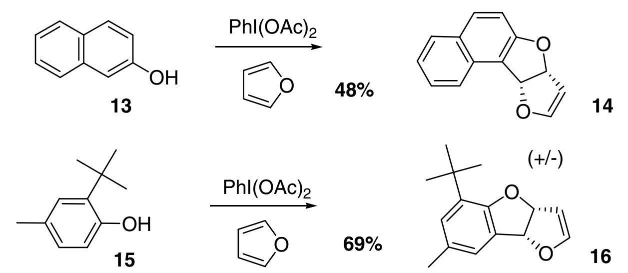
The reaction succeeds with polycyclic phenols such as 2-naphthol **13** and with polysubstituted ones such as **15**[14] (Scheme 5). The latter example seems to indicate that the process is fairly insensitive to steric effects. In fact, compound **15** is quickly converted to **16** in good yield despite the presence of a bulky *tert*-butyl group at the ortho position of the phenolic OH.

Oxidation of 3,4-xylenol leads to an inseparable ~1:1 mixture of compounds **18** and **19** in 41% yield (Scheme 6). Evidently, the methyl group at the meta position exerts an insufficient degree of regiocontrol. Regardless, the various examples provided herein suggest that the new reaction is fairly general and certainly synthetically useful.

Table 1.



Entry	R	Yield
a	*t*-Bu	61
b	Me	38
c	OMe	41
d	CH_2COOMe	52
e	CH_2CH_2NHTs	47
f	$SiMe_3$	59

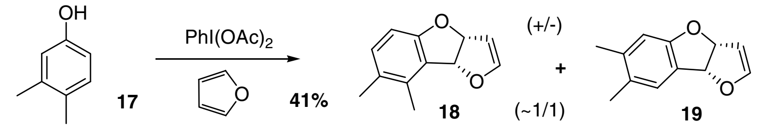


Scheme 5.

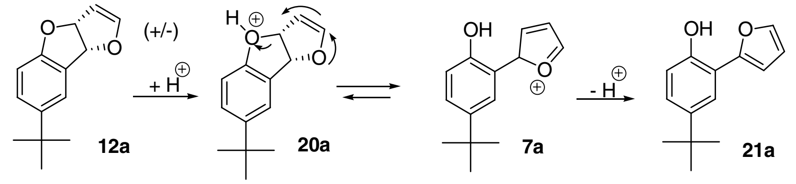
Compounds **12** are stable under neutral conditions and can be chromatographed without incident. However, sub-stoichiometric amounts of strong protonic acids, such as TFA, induce rapid and quantitative isomerization to biaryls. This is exemplified in Scheme 7 by the conversion of **12a** to **21a**.[15] Phenols **21** are significantly more electron-rich than the starting species **4**. Consequently, they are more readily oxidized by DIB than the corresponding starting phenols, resulting in the formation of intractable polymeric materials. Thus it is essential to minimize the formation of **21** during the main oxidative process. In a sense, the heterobicyclic system in **12** serves as a protecting group for the phenolic functionality, and it prevents undesirable side reactions of the latter.

Available evidence suggests that compounds **12** are fairly stable in media containing moderately acidic TFE. By contrast, the significantly more acidic HFIP appears to promote conversion to **21**, resulting in overoxidation and the ultimate formation of much polymeric matter. We believe this to be the reason why TFE, not HFIP, is the optimal reaction solvent in the present case. Even so, we suspect that some loss of product through the above sequence of events (formation of **21** and further oxidation) occurs even during reactions run in TFE, because more than 1 equiv of DIB is required to oxidize all the starting phenol.

The difference between the behavior of thiophene and of furan in otherwise identical reactions may be rationalized considering that the high electronegativity of the oxygen atom in **6** was likely to render this transient intermediate short-lived, excessively electrophilic and consequently very reactive with nucleophiles such as thiophene or furan. Formation of biaryl **11** versus tricyclic compound **12** depends on the stability of oxonium **7** ver-



Scheme 6.



Scheme 7.

sus sulfonium **10** generated in the media. These results may be explained if we consider that furan has a weaker aromatic character than thiophene. Thus, the formed oxonium can be trapped by the nucleophilic hydroxy and leads to **12**, whereas the sulfonium is transformed faster to thiophene derivative **11** and probably overoxidized into polymers. This may explain the low yield (17%) of this transformation with thiophene.

In summary, a practical and new method to induce a formal 'oxidative [2+3] cycloaddition' between substituted phenols and furan is now available. The transformation provides new strategic opportunities in the chemical synthesis of oxygenated substances, and results in ongoing investigations in this domain will be disclosed in due course.

Acknowledgments

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12. *Experimental procedure:* At −10 °C (ice/NaCl), a solution of PhI(OAc)$_2$ ('DIB', 98 mg, 0.3 mmol, 1.5 equiv) in CF$_3$CH$_2$OH ('TFE', 0.35 mL) was added dropwise for 1 min to a vigorously stirred solution of phenol (0.2 mmol, 1 equiv) in furan (164 mg, 2.4 mmol, 12 equiv) and TFE (0.6 mL). The mixture was then stirred for 20 s, diluted with 6 mL of ethyl acetate, poured into a separatory funnel, washed with 3 mL of a saturated solution of K$_2$CO$_3$ and 3 mL of brine. The solution is concentrated under vacuum and the residue is purified by silica gel chromatography with an appropriate mixture of ethyl acetate/hexane.
13. *NMR data:* a: ^{1}H (300 MHz, CDCl$_3$ $\delta = 7.48$ (d, 1H, $J = 1.8$ Hz), 7.34 (dd, 1H, $J = 8.2$, 1.8 Hz), 6.82 (d, 1H, $J = 8.2$ Hz), 6.65 (d, 1H, $J = 2.9$ Hz), 6.06 (d, 1H, $J = 7.6$ Hz), 5.97 (dd, 1H, $J = 7.6$, 2.3 Hz), 5.31 (t, 1H, $J = 2.3$ Hz), 1.33 (s, 9H). ^{13}C (75 MHz, CDCl$_3$ $\delta = 157.1$, 151.1, 143.8, 128.4, 124.1, 122.9, 110.1, 100.0, 89.0, 85.5, 34.3, 31.6. b: ^{1}H (300 MHz, CDCl$_3$ $\delta = 7.24$ (d, 1H, $J = 1.8$ Hz), 7.08 (dd, 1H, $J = 8.2$, 1.8 Hz), 6.77 (d, 1H, $J = 8.2$ Hz), 6.63 (d, 1H, $J = 2.9$ Hz), 6.03 (d, 1H, $J = 7.6$ Hz), 5.97 (dd, 1H, $J = 7.6$, 2.3 Hz), 5.31 (t, 1H, $J = 2.3$ Hz), 2.31 (s, 3H). ^{13}C (75 MHz, CDCl$_3$) $\delta = 157.2$, 151.0, 131.8, 130.1, 126.5, 124.5, 110.4, 100.1, 88.8, 85.3, 20.6. c: ^{1}H (300 MHz, CDCl$_3$ $\delta = 6.99$ (d, 1H, $J = 2.7$ Hz), 6.86 (dd, 1H, $J = 8.8$, 2.7 Hz), 6.78 (d, 1H, $J = 8.8$ Hz), 6.63 (d, 1H, $J = 2.7$ Hz), 6.03 (d, 1H, $J = 7.6$ Hz), 5.97 (dd, 1H, $J = 7.6$, 2.7 Hz), 5.29 (t, 1H, $J = 2.7$ Hz), 3.77 (s, 3H). ^{13}C (75 MHz, CDCl$_3$) $\delta = 154.1$, 150.9, 150.9, 125.0, 117.8, 111.1, 110.7, 100.2, 89.0, 85.5, 56.0. d: ^{1}H (300 MHz, CDCl$_3$) $\delta = 7.36$ (d, 1H, $J = 1.8$ Hz), 7.18 (dd, 1H, $J = 8.2$, 1.8 Hz), 6.82 (d, 1H, $J = 8.2$ Hz), 6.63 (d, 1H, $J = 2.3$ Hz), 6.04 (d, 1H, $J = 7.6$ Hz), 5.97 (dd, 1H, $J = 7.6$, 2.3 Hz), 5.30 (t, 1H, $J = 2.3$ Hz), 3.69 (s, 3H), 3.58 (s, 2H). ^{13}C (75 MHz, CDCl$_3$) $\delta = 172.2$, 151.2, 132.2, 130.3, 127.1, 126.2, 125.0, 110.8, 99.9, 89.2, 85.0, 52.0, 40.3. e: ^{1}H (300 MHz, CDCl$_3$) $\delta = 7.69$ (d, 2H, $J = 8.2$ Hz), 7.28 (d, 2H, $J = 8.2$ Hz), 6.97 (dd, 1H, $J = 8.2$, 1.7 Hz), 6.74 (d, 1H, $J = 8.2$ Hz), 6.61 (d, 1H, $J = 2.7$ Hz), 5.97 (m, 2H), 5.29 (t, 1H, $J = 2.7$ Hz), 4.56 (t, 1H, $J = 7.1$ Hz), 3.17 (q, 2H, $J = 7.2$ Hz), 2.70 (t, 2H, $J = 7.2$ Hz), 2.42 (s, 3H). ^{13}C (75 MHz, CDCl$_3$) $\delta = 154.1$, 150.9, 150.9, 125.0, 117.8, 111.1, 110.7, 100.2, 89.0, 85.5, 56.0. f: ^{1}H (300 MHz, CDCl$_3$) $\delta = 7.59$ (d, 1H, $J = 1.6$ Hz), 7.42 (dd, 1H, $J = 8.2$, 1.6 Hz), 6.87 (d, 1H, $J = 8.2$ Hz), 6.61 (d, 1H, $J = 2.7$ Hz), 6.04 (d, 1H, $J = 7.7$ Hz), 5.94 (dm, 1H, $J = 7.7$ Hz), 5.28 (t, 1H, $J = 2.7$ Hz), 0.23 (s, 9H). ^{13}C (75 MHz, CDCl$_3$) $\delta = 160.1$, 151.2, 136.5, 131.8, 131.4, 124.4, 110.5, 99.9, 88.9, 85.1, −0.8.
14. *NMR data:* Compound **14**: ^{1}H (300 MHz, CDCl$_3$) $\delta = 7.92$ (d, 1H, $J = 8.2$ Hz), 7.84 (d, 1H, $J = 8.2$ Hz), 7.82 (d, 1H, $J = 8.2$ Hz), 7.56 (td, 1H, $J = 8.2$, 1.2 Hz), 7.37 (td, 1H, $J = 8.2$, 1.2 Hz), 7.15 (d, 1H, $J = 9.4$ Hz), 6.69 (d, 1H, $J = 2.9$ Hz), 6.52 (d, 1H, $J = 7.6$ Hz), 6.17 (dm, 1H, $J = 7.0$ Hz), 5.38 (t, 1H, $J = 2.9$ Hz). ^{13}C (75 MHz, CDCl$_3$) $\delta = 157.5$, 151.2, 137.4, 132.4, 130.9, 130.1, 128.6, 127.5, 123.3, 122.1, 112.8, 99.9, 89.8, 85.1. Compound **16**: ^{1}H (300 MHz, CDCl$_3$) $\delta = 7.12$ (s, 1H), 7.04 (s, 1H), 6.60 (d, 1H, $J = 2.3$ Hz), 6.03 (d, 1H, $J = 8.2$ Hz), 5.96 (dm, 1H, $J = 8.2$ Hz), 5.30 (t, 1H, $J = 2.3$ Hz), 2.32 (s, 3H), 1.35 (s, 9H). ^{13}C (75 MHz, CDCl$_3$) $\delta = 150.5$, 133.8, 129.7, 128.5, 125.0, 123.9, 100.5, 87.8, 85.3, 34.0, 29.1, 20.8.
15. *NMR data:* ^{1}H (300 MHz, CDCl$_3$) $\delta = 7.54$ (m, 2H), 7.25 (dd, 1H, $J = 8.2$, 2.3 Hz), 7.04 (br, 1H), 6.92 (d, 1H, $J = 8.2$ Hz), 6.72 (d, 1H, $J = 3.5$ Hz), 6.55 (dd, 1H, $J = 3.5$, 1.8 Hz), 1.34 (s, 9H). ^{13}C (75 MHz, CDCl$_3$) $\delta = 150.1$, 143.3, 141.1, 131.1, 126.5, 122.8, 116.7, 115.7, 111.6, 106.3, 34.1, 31.4.