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Nitrogenous Educts through Oxidative Amidation of Phenols: The Bimolecular Reaction

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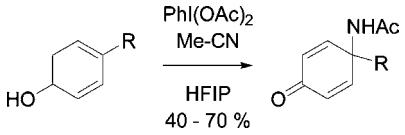
ABSTRACT

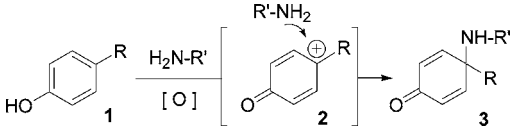


The elusive oxidative amidation of phenols to 4-aza-substituted dienones in the bimolecular mode may be achieved by treatment with iodobenzene diacetate ("DIB") in a mixture of hexafluoro-2-propanol and acetonitrile.

Phenols **1** are commonly advanced to products of type **3** (Scheme 1) through reaction with an *electrophilic* nitrogen species.[1] Conduct of the same reaction with a *nucleophilic* nitrogenous agent, that is, the oxidative amidation of a phenol to a dienone, remains unknown, probably because the selective oxidative activation of a phenol in the presence of a nitrogen nucleophile is technically difficult. The recent literature records examples of intramolecular variants of the chemistry of Scheme 1, for instance, the oxidative cyclization of phenolic oxazolines **4**[2] (moderate yields) or sulfonamides **5**[3] (excellent yields), as well as of phenolic secondary amines (moderate[4] to good[5] yields). These reactions involve treatment of the substrates with iodobenzene diacetate ("DIB"; Scheme 2) under Kita-type conditions.[6]

A major limitation of this technology is that it works well for the formation of 2-azaspiro[5.4]decanes, but it is inefficient for the preparation of 2-azaspiro[5.5]undecanes and of larger ring systems of the type found in many synthetically appealing natural products. A bimolecular version of the process would circumvent such a difficulty. To illustrate,

Scheme 1. Oxidative Amidation of Phenols



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(1) Leading references and noteworthy examples of reactions of this type: (a) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053. (b) Wardrop, D. J.; Burge, M. S.; Zhang, W.; Ortiz, J. A. *Tetrahedron Lett.* **2003**, *44*, 2587. (c) Wardrop, D. J.; Landrie, C. L.; Ortiz, J. A. *Synlett* **2003**, 1352. (d) Tanaka, K.; Mori, Y.; Narasaka, K. *Chem. Lett.* **2004**, *33*, 26. (e) Narasaka, K. *Pure App. Chem.* **2002**, *74*, 143. (f) Mitchell, H.; Leblanc, Y. *J. Org. Chem.* **1994**, *59*, 682. (g) Leblanc, Y.; Boudreault, N. *J. Org. Chem.* **1995**, *60*, 4268. (h) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739. (i) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *Heterocycles* **2003**, *59*, 149. (j) Prata, J. V.; Clemente, D.-T. S.; Prabhakar, S.; Lobo, A. M.; Mourato, I.; Branco, P. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 513. (k) Telma, D.; Clemente, V.; Lobo, A. M.; Prabhakar, S.; Marcelo-Curto, M. J. *Tetrahedron Lett.* **1994**, *35*, 2043. (l) Hartshorn, M. P.; Judd, M. C.; Vannoort, R. W.; Wright, G. J. *Aust. J. Chem.* **1989**, *42*, 689. (m) Ishizaki, T.; Hashimoto, Y.; Shudo, K.; Okamoto, T. *Heterocycles* **1983**, *20*, 1481. (n) Hashimoto, Y.; Ohta, T.; Shudo, K.; Okamoto, T. *Tetrahedron Lett.* **1979**, *20*, 1611. (o) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *Tetrahedron* **1987**, *43*, 2577. (p) Glover, S. A.; Goosen, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 653.

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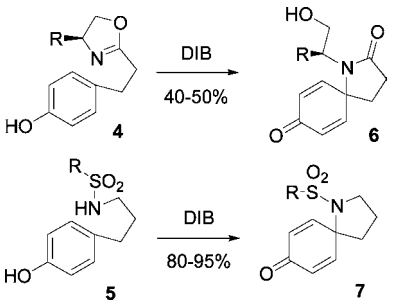
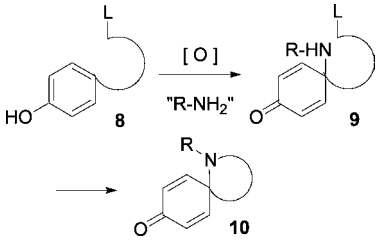
Scheme 2. Azaspirocycle Formation through Oxidative Cyclization of Phenolic Substrates



the hypothetical intermolecular oxidative coupling of a phenolic substrate **8** (L = leaving group) with a primary amine, or an equivalent thereof, would lead to dienone **9**, which subsequently could undergo cyclization to **10** (Scheme 3). Whereas the hurdles alluded to earlier become especially

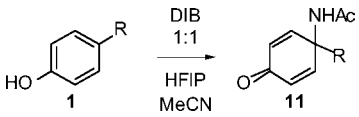
Scheme 3. Hypothetical Spirocycle Formation through Oxidative Amidation of Phenolic Substrates



troublesome in the bimolecular regime, the synthetic potential of the reaction appears to be substantial. This has provided us with an incentive to research appropriate solutions, and in this paper, we describe a technique to achieve such a transformation.

All attempts to intercept the electrophilic agent produced through DIB activation the phenol, and naively represented in Scheme 1 as structure **2**, with common nitrogen nucleophiles, such as primary or secondary amines, pyridine, imidazole, etc., in a bimolecular mode, met with failure.

Table 1. Bimolecular Oxidative Amidation of Phenols



entry	R	yield[a] (%)
a	Me	56
b	*n*-Pr	54
c	*i*-Pr	62
d	CH_2COOMe	58
e	$(CH_2)_3COOCH_2CF_3$	57
f	$(CH_2)_2CN$	67
g	$(CH_2)_3CN$	71
h	$(CH_2)_4CN$	71
j	$(CH_2)_3Br$	65
k	$(CH_2)_4Br$	72
l	$(CH_2)_3N_3$	42
m	$(CH_2)_4N_3$	49
n	$(CH_2)_2NHTs$	53
o	$(CH_2)_3O$-Piv	67

[a] Chromatographed.

Disappointing results were also obtained upon attempted capture of **2** with simple primary sulfonamides.[7] Recent work by Wood[8] suggested that products of the type **3**, R′ = Ac, may be accessible by intercepting **2** with a nitrile, in a Ritter-like mode. A number of phenols were recovered essentially unchanged upon treatment with DIB in, e.g., acetonitrile; however, we found that *acetamides **11** emerge in synthetically useful yields upon DIB oxidation of phenolic substrates in a 1:1 mixture of acetonitrile and hexafluoro-2-propanol*. Representative results appear in Table 1. It is apparent that the new oxidative reaction tolerates a range of useful spectator functionality on the aliphatic side chain of the substrates, including halogen, cyano, carbonyl, and protected alcohol substituents. Azido groups are also tolerated, except that yields are lower with these substrates (entries **l**, **m**). This may be due to competition between the intramolecularly positioned N_3 group and the external nitrile nucleophile for the presumed intermediate **2**. Side chain branching is also well tolerated (entry **c**). By contrast, methyl esters **12** and **13** (Scheme 4) are poor substrates for the reaction. Oxidation of these substances proceeded with formation of large amounts of hydroxylated derivatives **16** and **17**. This may be attributable to intramolecular capture of an intermediate of the type **2** by the carbonyl group of the substrate, resulting in probable formation of intermediates of the type **15**. These are likely to undergo hydrolysis to the observed **18** and **19** upon workup.[9] Compound **18** represented 95% of the crude product (NMR) obtained from **14**, while **19** amounted to 75% of the crude product obtained from

(2) (a) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667. (b) Braun, N. A.; Bray, J.; Ousmer, M.; Peters, K.; Peters, E.-M., Bouchu, D.: Ciufolini, M. A. *J. Org Chem.* **2000**, *65*, 4397. (c) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534.

(3) (a) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193 (b) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336; *Angew. Chem.* **2004**, *116*, 4436.

(4) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593.

(5) Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411.

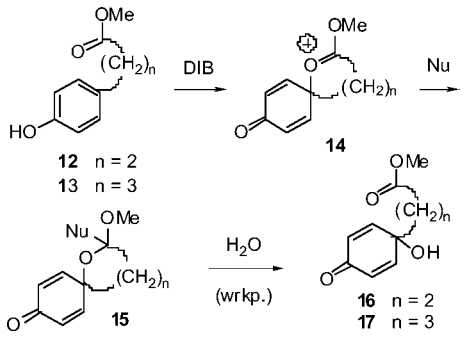
(6) This entails conduct of the reaction in fluorinated alcohol solvents such as hexafluoro-2-propanol (HFIP) or trifluoroethanol (TFE). Cf. (a) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857. (b) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (c) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435.

(7) These experiments were inspired by the success of our sulfonamide-based methodology (ref 3).

(8) Drutu, I.; Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2002**, *4*, 493.

(9) A similar reaction forms the basis of an interesting synthesis of aculeatins A and B. Cf. Wong, Y. S. *J. Chem. Soc., Chem. Commun.* **2002**, 686.

Scheme 4. Behavior of Methyl Dihydrocinnamate and of Its Homolog

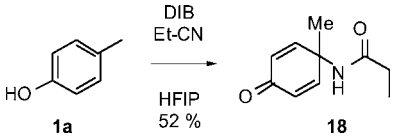


15, consistent with the earlier observation that such oxidative cyclizations are less facile when they lead to formation of six-membered rings, relative to five-membered rings.

In an effort to minimize formation of undesired **18**/**19**, we turned to the trifluoroethyl ester analogues of **14** and **15**, with the hope that the electron-withdrawing nature of the CF_3 group would diminish the nucleophilic character of the carbonyl system and disfavor cyclization to intermediates of the type **15**. This artifice did reduce the extent of formation of hydroxylated product from the trifluoroethyl ester analogue of **14**, but not to a synthetically useful degree. Much better results were observed with the homologous substrate **1e**: formation of the hydroxylated product was essentially suppressed and conversion to **11e** occurred in 57% yield (Table 1).[10]

Nitrile solvents other than MeCN may be used in the reaction. For instance, oxidation of *p*-cresol in the presence of propionitrile delivered **18**, the propionamide analogue of **11a** in 52% chromatographed yield (Scheme 5).

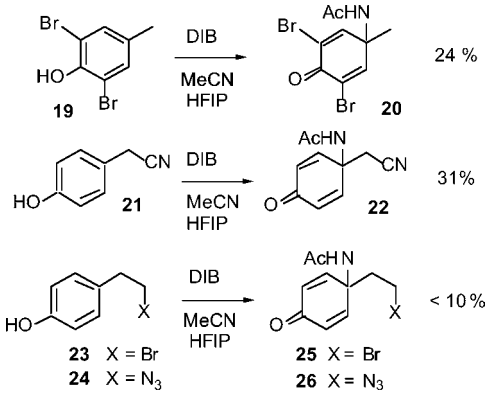
Scheme 5. Oxidative Amidation of *p*-Cresol with Propionitrile



Some limitations of the new process are outlined in Scheme 6. Unsatisfactory results were obtained with *o*,*o*′-dibromocresol **19**, which afforded the expected **20** in a low 24% yield. The reasons for this inefficient conversion remain unclear. Benzyl cyanide **21** furnished the anticipated **22** in

(10) General procedure: a solution of $PhI(OAc)_2$ ("DIB", 232 mg, 1.2 equiv) in $(CF_3)_2CHOH$ ("HFIP", 0.5 mL) was added dropwise over 30 s to a vigorously stirred solution of a phenol (0.6 mmol, 1 equiv) in MeCN (2 mL) and HFIP (1.5 mL) at 15 °C (ice/water bath). The mixture was stirred for 20 min and concentrated. Silica gel chromatography of the residue (first 50:50 AcOEt/hexanes to remove gross contaminants, then 5−10% MeOH in CH_2Cl_2) provided the pure product.

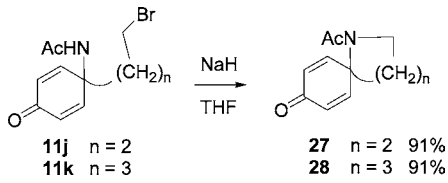
Scheme 6. Limitations of the New Reaction



modest yield. This product was accompanied by much polymeric material. We suspect that the phenolic OH in **21** might assist expulsion of the cyano group, leading to a reactive *p*-quinone methide, which may then polymerize. Finally, only trace amounts of the expected products were obtained from phenethyl substrates **23** and **24**.

As shown in Scheme 7, substances **11j** and **11k** underwent

Scheme 7. Cyclization of Bromides **11j**−**k**



facile base-promoted cyclization to azaspirocycles **27** and **28**. In both cases, the yield of spirocyclic product was 91%. The efficient formation of 2-azaspiro[5.5]undecanes such as **28** resolves a major limitation of the original methodology, as adumbrated in the Introduction.

In summary, a practical method for the bimolecular amidative dearomatization of phenols is now available. The transformation provides new strategic opportunities in the chemical synthesis of nitrogenous substances, and the results of ongoing investigations in that sense will be disclosed in due course.

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

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