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Improved Procedure for the Bimolecular Oxidative Amidation of Phenols

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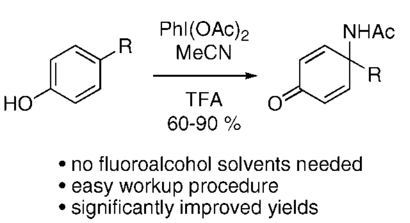
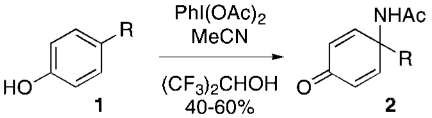


Trifluoroacetic acid (TFA) is an effective promoter of the bimolecular Ritter-like oxidative amidation of 4-substituted phenols induced by PhI(OAc)$_2$ in MeCN. This suppresses the need for fluoroalcohol cosolvents, increases the yields, and facilitates isolation/purification procedures.

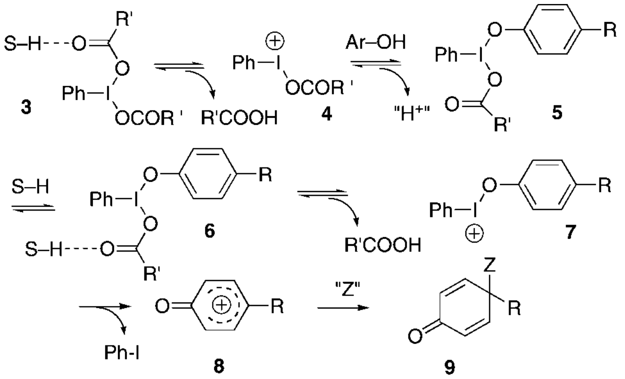
The oxidative amidation of phenols offers interesting opportunities in the synthesis of nitrogenous substances.[1] This appears to be especially true of the bimolecular variant of the process, which converts 4-substituted phenols **1** into dienones **2** (Scheme 1).[2] In its original form, the reaction entails attack of the phenol with PhI(OAc)$_2$ (DIB) in a mixture of MeCN and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). Products **2** emerge in 40−70% yield, at least on a small scale.

Research focusing on the application of this reaction to current synthetic problems has required substantial scaling-up of the original procedure. Reactions run on larger scales afford products contaminated with much polymeric matter, imposing the need for impractical, costly chromatographic purifications. Also, the cost of HFIP[3] becomes a significant issue during scale-up. The need for this cosolvent derives from the fact that the reaction of phenolic substrates with DIB proceeds poorly in an aprotic milieu such as plain MeCN,[4] whereas nucleophilic protic solvents such as alcohols or water (S−H in Scheme 2) promote clean conversion to products **9** (Z = OMe, OH, etc.), possibly by the mechanism of Scheme 2. Pioneering work by Kita[5] showed that solvolysis of (presumed) species **8** can be avoided by operating poorly nucleophilic fluoroalcohol media. This enables capture with various nucleophiles, both in an intra- and in an intermolecular mode.[6] Fluoroalcohol solvents have since become a standard feature of many such reactions.

SCHEME 1. Bimolecular Oxidative Amidation of Phenols



SCHEME 2. Possible Oxidative Amidation Mechanism



Z = OH or OMe if the reaction is carried out in H_2O or in MeOH
Z = external nucleophile if the reaction is run in fluoroalcohols

In accord with Wood,[7] we observed that the use of the more reactive PhI(OCOCF$_3$)$_2$ (PIFA) in lieu of DIB eliminates the need for HFIP. However, the formation of polymeric materials remains a serious problem; furthermore, PIFA is expensive.[8] We thus sought a method to induce DIB to react in the absence of HFIP and in such a manner as to minimize polymer formation. A solution emerged as detailed herein.

Protic solvents are likely to favor heterolysis of hypervalent iodine complexes, either by hydrogen bonding (cf. **3**, **6**) or by reversible protonation, thereby behaving as acidic promoters. Indeed, other acidic adjuvants capable of favoring dissociation of hypervalent iodine species, such as heteropolyacids or TMS-Br,[9] do induce DIB oxidations in nonprotic media. This suggested that HFIP might be replaceable with a suitable Lewis or Brønsted acid. On the other hand, polymeric byproducts are

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(1) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759.

(2) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175.

(3) About $1000 for 500 g (Sigma-Aldrich).

(4) This is true also for other polar, aprotic solvents such as MeNO$_2$, CH$_2$Cl$_2$, etc. See ref 1 and literature cited therein.

(5) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435. (c) Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627. (d) Dohi, T.; Ito, M.; Morimoto, K.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 4152.

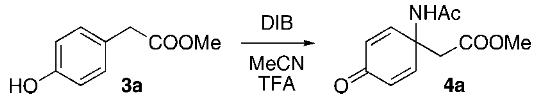
(6) Oxygen nucleophiles; cf. ref 5 as well as (a) Rodríguez, S.; Wipf, P. *Synthesis* **2004**, 2767. (b) Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469. (c) Li, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 385. Nitrogen nucleophiles: cf. refs 1, 2 as well as (d) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593. (e) Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411. (f) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397. (g) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534. (h) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336. Carbon nucleophiles: leading reviews of the massive volume of literature in this area: (i) Arisawa, M.; Toma, H.; Kita, Y. *Yakugaku Zasshi* **2000**, *120*, 1061. (j) Tohma, H.; Kita, Y. *Top. Curr. Chem.* **2003**, 224. Recent developments: (k) Berard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett.* **2007**, *48*, 8238. (l) Jean, A.; Cantat, J.; Berard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007**, *9*, 2553.

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

(8) Gram per gram, PIFA is about 3 times as costly as DIB, and more than 4 times as expensive on a molar basis.

10.1021/jo800267q CCC: $40.75

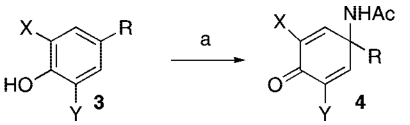
TABLE 1. Effect of TFA on the Yield of Desired Product[a]



mol ratio TFA:DIB	50	25	10	5	2.5	1.3	1.0	0.5	0
isolated yield (%) of 4a	75	75	79	85	86	86	80	36	0

[a] Slow addition of a MeCN solution of **3a** to a MeCN solution of 1.2 equiv of DIB and 1.3 equiv of TFA versus DIB, at rt. Final concentration = 8 mM.

TABLE 2. Comparison of the New versus the Old Procedure



entry	R	X	Y	yield %[a]
a	CH_2CO_2Me	H	H	86 (58[b], 35[c])
b	Et	H	H	87
c	*n*-Pr	H	H	82 (54[b])
d	*i*-Pr	H	H	40[d] (62[b])
e	Me	H	Me	41
f	CH_2CN	H	H	71 (31[b])
g	$(CH_2)_2CN$	H	H	81 (67[b])
h	$(CH_2)_2NHTs$	H	H	59 (53[b])
i	$(CH_2)_2Br$	H	H	57 (<10[b])
j	Me	H	H	89 (56[b])
k	Me	Br	Br	41 (24[b])
l	CH_2COOBn	H	H	65

[a] Slow addition of 4 mmol of substrate to 1.2 equiv of DIB and 1.3 equiv of TFA versus DIB, at rt, in a total of 500 mL of MeCN. [b] Yields in parentheses refer to the old procedure (ref 2). [c] Yield of reactions run on a 0.6 mmol scale as per ref 2. [d] Yield of reactions run as per ref 2, but on scales greater than 2−3 mmol. [e] The product of dienone−phenol rearrangement of **4d**, i.e., 3-isopropyl-4-acetamidophenol, was also isolated in 30% chromatographed yield.

likely to arise upon nucleophilic capture of an electrophile such as **8** by an intact molecule of substrate. If so, polymer formation could be contained by keeping the instant concentration of phenol low (operation in dilute solutions, slow addition, or both). Indeed, PIFA oxidation of **3a**[10] (cf. Table 1) in MeCN, run at a final substrate concentration of 500 mM, provided **4a** in 30% yield.[11] The yield improved to 53% at a final concentration of 110 mM and to 83% at 8 mM.

The search for an alternative to HFIP in DIB oxidations centered on the conversion of **3a** to **4a** (Tables 1 and 2) in a dilute MeCN solution. Lewis (BF_3•OEt_2, $TiCl_4$) and Brønsted (HCl,[12] 98% H_2SO_4, TsOH•H_2O, 85% H_3PO_4, 70% HNO_3, or AcOH) acids did promote the reaction, but they induced formation of mixtures of products. By contrast, clean, efficient oxidative amidation occurred in the presence of a slight molar excess of trifluoroacetic acid (TFA), which, as an added bonus, also greatly increased the solubility of DIB in MeCN: while the reagent is poorly soluble in acetonitrile, addition of TFA to a MeCN suspension of DIB results in rapid dissolution.[13] Table 1 summarizes the effect of TFA on the DIB-mediated oxidation of **3a** to **4a**. In each case, a MeCN solution of substrate was added over 10 min (syringe pump) to a MeCN solution of DIB and TFA. The final concentration was equivalent to 8 mmol/L of substrate. At least 1 equiv of TFA relative to DIB is required for efficient conversion. Excess acid complicates isolation procedures and diminishes the yields. Best results are obtained when a MeCN solution of the phenol (1 equiv) is slowly added to a MeCN solution of DIB (1.2 equiv vs substrate) and TFA (1.3 equiv vs DIB for small scales, 1.5 equiv vs DIB for large-scale work).

Reactions run under these conditions require no aqueous workup.[14] Small-scale reactions may be neutralized with solid $NaHCO_3$ then filtered and concentrated as a prelude to chromatographic recovery of the product. However, and especially for large-scale operations, it is more expedient to concentrate the reaction mixture[15] and isolate the product by rapid filtration through a pad of silica gel, followed by crystallization in the case of solid materials.

The effect of temperature on the above transformation was examined in the range of −30 to +70 °C.[16] Chemical yields remained constant in this interval. Not unexpectedly, the rate of the reaction increases greatly as the temperature rises from −30 to +20 °C, at which point the conversion of **3a** to **4a** is virtually instantaneous. The reaction is thus most conveniently carried out at room temperature.

The new and previous oxidation procedures are compared in Table 2. All reactions were conducted by adding a solution of 4 mmol of substrate to a total volume of 500 mL of solvent, giving a final concentration of 8 mmol/L. This diminished polymer formation and improved the yields, sometimes by a factor of 2 or more. Efforts to further reduce the amount of polymeric byproducts centered on the oxidation of silyl ether derivatives of phenols **3**. This method proved to be inferior to the oxidation of unprotected substrates. The TBS ether of **3a** resisted the action of DIB, but it underwent oxidation in poor yield when TBAF was added to the reaction medium. The DIB/TFA system did convert TES and TMS ethers of **3a** to the expected **4a** in the absence of fluoride ion, but in only 33 and 81% yield, respectively. Silylation of the phenol thus offers no advantage.

The dilute conditions of the above experiments do reduce the extent of polymer formation, but they are problematic for process work, even though the MeCN utilized in such reactions may be recycled without purification and with no adverse effect on yields.[17] The effect of concentration on the efficiency of the reaction was therefore examined with **3a** and *para*-cresol, **3j**, as representative substrates (Table 3). Yields diminish with increasing concentration; however, good results are obtained by operating in the 0.1 M range, always with slow addition of substrate to the oxidant. It is worthy of note that the DIB−TFA system is more efficient than PIFA for the oxidation of **3a** at a final concentration of 110 mM (66 vs 53%). Preparative runs

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(9) (a) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007. (b) Hata, K.; Hamamoto, H.; Shiozaki, Y.; Kita, Y. *Chem. Commun.* **2005**, 2465.

(10) This phenol is of special interest in an ongoing synthetic venture.

(11) Slow addition of **3a** to 1.3 equiv of PIFA in MeCN at rt.

(12) Commercial 4 N HCl in dioxane.

(13) Mixed iodonium carboxylates such as PhI(OAc)($OCOCF_3$) may form under these conditions.

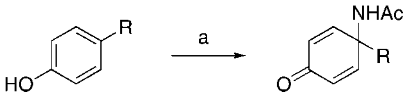
(14) Many compounds of the type **2** are water-soluble, a property that complicates aqueous workups.

(15) While most dienones **2** are sensitive to prolonged exposure to *excess* TFA (ref 1), the *small* amounts of TFA that accumulate in the solution during concentration of these reaction mixtures have little adverse effect on compounds **2** if R is a group possessing *poor* migratory aptitude in the dienone−phenol rearrangement, e.g., a primary (cf. **4b**,**c**,**e**,**j**) or an electronically deactivated (**4a**) alkyl substituent. Dienones incorporating secondary (cf. **4d**) or tertiary C-4 alkyls (cf. Scheme 3) are progressively more prone to undergo dienone−phenol rearrangement.

(16) A series of reactions were run at 15−20° C intervals within this range.

(17) The solvent may be recovered from the rotary evaporator and directly reused.

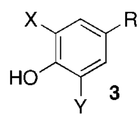
TABLE 3. Effect of Substrate Concentration on the Yield of Desired Product



[substrate][b] mmol/L	NMR yield[c]		chemical yield[d]	
	R = Me	R = CH_2CO_2Me	R = Me	R = CH_2CO_2Me
8	94	91	89	86
16	87	84	80	80
32	82	80	71	73
64	73	74	59	69
125	63	70	48	62
250	51	54	38	49
500	42	40	25	35

[a] Slow addition of 4 mmol of substrate to 1.2 equiv of DIB and 1.3 equiv of TFA versus DIB, in a total of 500 mL of MeCN. [b] Apparent final concentration. [c] NMR yields were determined by using 1,4-dioxane as an internal standard. [d] Yields of chromatographed products.

SCHEME 3. Poor Substrates for Oxidative Amidation



3

entry	R	X	X
m	$(CH_2)_2CO_2Me$	H	H
n	$(CH_2)_2NPht$	H	H
o	$(CH_2)_2I$	H	H
p	*tert*-Bu	H	H
q	I	H	H
r	Me	*tert*-Bu	*tert*-Bu

of this reaction carried out with 10−30 g batches of **3a** consistently gave yields in the 65−70% range.

The phenols shown in Scheme 3 are poor substrates for the reaction. The behavior of **3m**,**n** (Pht = phthalimido) is consistent with the tendency of suitably positioned carbonyl groups to intercept the electrophilic species (cf. **8**) produced upon DIB activation of the phenol.[18] Steric effects may complicate the reaction of BHT, **3r**. Phenol **3o** decomposes on standing at room temperature, and dissolution in MeCN may exacerbate this instability. The initial products of oxidative amidation of **3p**,**q** appear to undergo dienone−phenol rearrangement and quinonimine formation, respectively.

In summary, an improved procedure for the bimolecular oxidative amidation of phenols on preparatively useful scales is now available. Synthetic applications of this reaction will be reported in due course.

Experimental Section[19]

General Procedure for Oxidative Amidation of Phenols under Dilute Conditions. A MeCN (20 mL) solution of **3a** (53 mg, 0.32 mmol, 1 equiv) was added over 10 min (syringe pump) to a solution of DIB (123 mg, 0.38 mmol, 1.2 equiv) and TFA (47 mg, 0.4 mmol, 1.3 equiv vs DIB) in MeCN (20 mL) at rt with good stirring. The final concentration was equal to 8 mmol of substrate/L. At the end of the addition, the solution was light yellow. Solid $NaHCO_3$ (107 mg, 1.3 mmol, 4 equiv) was added, and the mixture was stirred for 15 min, then it was filtered through Celite and concentrated. Chromatographic purification (1% MeOH in EtOAc) yielded 61 mg (86% yield) of **4a**, off-white solid, mp 100−102 °C.

General Procedure for Preparative Scale Oxidative Amidation of Phenols. A MeCN (20 mL) solution of **3a** (9.1 g, 55.0 mmol, 1 equiv) was added over 3 h (syringe pump) to a solution of DIB (23.9 g, 74.0 mmol, 1.3 equiv) and TFA (6.4 mL, 82.5 mmol, 1.5 equiv vs DIB) in MeCN (480 mL) at rt with good stirring. The final concentration was equal to 110 mmol of substrate/L. The progress of the reaction was monitored by ^1H NMR. At the end of the addition, the solution had become light brown. The mixture was concentrated, and the residue was taken up with toluene (10 mL). The suspension was concentrated, and the procedure was repeated to azeotropically remove all residual TFA. The brown residue was filtered through a silica pad (45 g) using first 300 mL of Et_2O (removal of brown tar and PhI) and then 300 mL of Et_2O/CH_3CN (2.5:1, elution of the product). Concentration afforded a brown solid, which was refiltered through fresh silica gel using the same procedure (complete removal of polymeric material). The solid residue was taken up with 20 mL of EtOAc and kept at −20 °C for 5 h. The resulting precipitate was essentially pure **4a**. Concentration of the mother liquor afforded an additional crop of crystalline material. A total of 8.13 g (66% yield) of **4a** was obtained. A recrystallized sample (2:1 EtOAc/hexanes) had mp 100−102 °C.

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Supporting Information Available: Experimental protocols, characterization data, and spectra of all compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800267Q

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(18) (a) Wong, Y.-S. *Chem. Commun.* **2002**, 686. (b) Peuchmaur, M.; Wong, Y.-S. *J. Org. Chem.* **2007**, *72*, 5374. (c) Chang, J.; Chan, B.; Ciufolini, M. A. *Tetrahedron Lett.* **2006**, *47*, 3599 and refs cited therein.

(19) Experimental protocols are provided as Supporting Information.