A facile synthesis of (*tert*-alkoxy)amines

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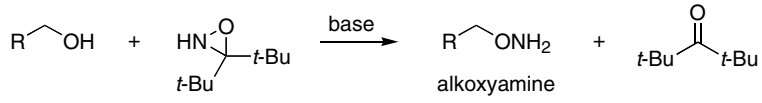
Abstract—Tertiary alcohols react with stoichiometric $BF_3{\cdot}Et_2O$ and *N*-hydroxyphthalimide to yield *N*-alkoxyphthalimides. Subsequent hydrazinolyses afford the title compounds.

1. Introduction

The condensation of a ketone or aldehyde with an alkoxyamine (aka aminooxy) has emerged as a powerful means for labelling liposome, bacterial and mammalian cell surfaces as well as for chemoselectively ligating small molecule 'recognition elements' onto polyfunctional substrates.[1] The robust oxime ether linkage formed in near quantitative yields in these reactions is ideal for applications in aqueous media; consequently, much effort has been devoted toward developing new, more efficient methods for the synthesis of alkoxyamines.[2–4] The existing methods for the preparation of alkoxyamines of the type $RONH_2$ can be divided into two principal approaches:[5] (i) hydroxyl group displacement and (ii) hydroxyl group amination. The former approach generally is performed using *N*-hydroxyphthalimide under Mitsunobu-like conditions[2] or by using *N*-protected hydroxylamine derivatives in nucleophilic substitution reactions.[3] The amination approach, which has the advantage of retention of alcohol stereochemistry, requires an electrophilic reagent, such as an appropriately substituted oxaziridine (Eq. 1).[4]

As might be expected, both the displacement and amination strategies suffer when the starting hydroxyl substrate is a tertiary alcohol. Indeed, most of the few reported syntheses of (*tert*-alkoxy)amines are characterized by modest to low yields.[4,6–8] We recently required access to sterically hindered alkoxyamines and, as a consequence, we developed an alternative method for their preparation. Herein, we describe the straightforward conversion of tertiary alcohols **1** (Table 1) to the corresponding (*tert*-alkoxy)amines **3** as well as conditions for isolation of low-molecular weight, water soluble members of this class of compounds.



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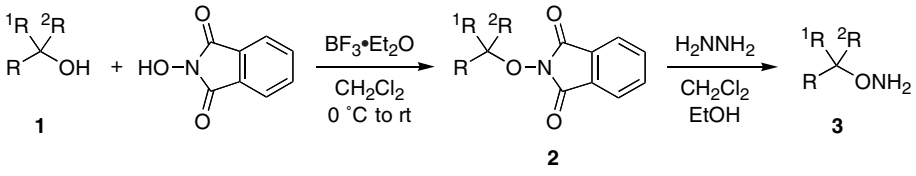
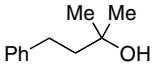
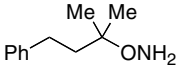
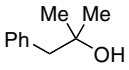
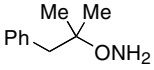
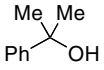
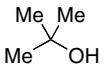
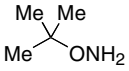
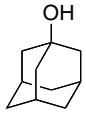
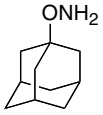
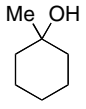
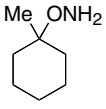
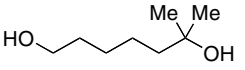
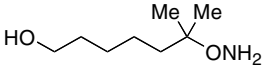


Table 1. Synthesis of (*tert*-alkoxy)amines[a]

Entry	Alcohol (**1**) (^{13}C NMR: R_3C–OH)[b]	Yield of **2**[c] (%)	Alkoxyamine (**3**) (^{13}C NMR: R_3C–ONH_2)[b]	Yield of **3**[d] (%)
a	 (δ 71.8)	74	 (δ 78.3)	A: 85
b	 (δ 70.9)	22[e]	 (δ 79.7)	A: 95
c		0		
d	 (δ 69.0)	74	 (δ 83.6)[f]	A: 0 B: 96
e	 (δ 68.0)	80	 (δ 76.1)	A: 87
f	 (δ 70.0)	52	 (δ 83.3)[f]	A: 0 B: 80
g	 (C(1) δ 63.1, C(6) δ 71.3)	45	 (C(1) δ 63.0, C(6) δ 79.2)	A: 75

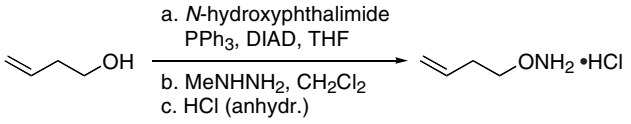
[a] All reactions were performed on ⩾1 mmol scale.
[b] Taken in $CDCl_3$.
[c] Isolated yield from **1**.
[d] Isolated yield from **2** using either Method A (aqueous work-up) or Method B (anhydrous conditions).
[e] Major product is β,β-dimethylstyrene (69%).
[f] HCl salt.

2. Results

The simple treatment of tertiary alcohols with stoichiometric $BF_3{\cdot}Et_2O$ and *N*-hydroxy-phthalimide in CH_2Cl_2 proceeds to give the corresponding *O*-alkyl phthalimides **2** in fair to good yields (Table 1, entries a, d–f). The use of TMSOTf or other Lewis acids to facilitate this transformation was less effective. In cases where alcohol elimination would provide a conjugated alkene (e.g., entries b and c), formation of the desired substitution product was minimal to nonexistent. We reasoned that *N*-hydroxyphthalimide did not competitively intercept the putative carbenium ion formed on alcohol reaction with BF_3 due, in part, to its poor solubility in CH_2Cl_2. However, our attempts at solubilizing *N*-hydroxyphthalimide using several polar and mixed solvent systems did not improve product yields in these facile elimination cases. We also noted that secondary alcohols do not afford *N*-hydroxyphthalimide substitution products under the BF_3 conditions. The reactions of cyclohexanol and 2-dodecanol resulted only in recovered starting alcohol. These results suggested the possibility for a chemoselective alcohol to alkoxyamine transformation. We examined this event using 6-methylheptane-1,6-diol (entry g) and found that only its tertiary alcohol reacted to give alkoxyamine **3g**.

Cleavage of the phthalimide groups of **2a**–**b**,**e**,**g** using standard hydrazinolysis conditions (Method A: excess hydrazine hydrate, 1:5 CH_2Cl_2–EtOH, rt, 12 h)[9] gave the (*tert*-alkoxy)amine products in good yields.[10] The consistent, slight ^{13}C NMR downfield shift of the alkoxyamine ONH_2-bearing carbon relative to starting alcohol is a convenient means for analyzing the transformation (see Table 1). The cleavage products of phthalimides **2d** and **2f** had appreciable solubility in water and this precluded their straightforward isolation. However, by adopting a non-aqueous method for phthalimide cleavage (Method B: methylhydrazine, CH_2Cl_2; HCl),[11] we were gratified to isolate alkoxyamines **3d**

and **3f** as their hydrochloride salts in good yields.[10] In our experience, application of this method to other low-molecular weight phthalimides also dramatically improved product isolation (e.g., Eq. 2; Method A: 7%, Method B: 98%).



(2)

3. Representative anhydrous hydrazinolysis (Method B)

To a solution of *N*-(*tert*-butoxy)phthalimide **2d** (1.0 g, 4.6 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added methylhydrazine (0.32 mL, 6.0 mmol) dropwise. The reaction was gradually warmed to room temperature and stirred for 12 h. After re-cooling to 0 °C, the reaction mixture was filtered to remove precipitated solids. HCl(g) then was bubbled through the filtrate at 0 °C for 15 min. The resulting slurry was stirred at 0 °C for an additional 30 min and subsequently filtered. Concentration of the filtrate in vacuo afforded **3d** as an off-white solid (0.55 g, 96%). Mp 154.0–155.4 °C; ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 9H), 10.57 (br s, 3H); ^{13}C NMR ($CDCl_3$): δ 26.6, 83.6.

In conclusion, we have presented a straightforward two-step method for the transformation of tertiary alcohols to (*tert*-alkoxy)amines. The method uses inexpensive reagents and is amenable to large scale synthesis.

Acknowledgements

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References and notes

1. For recent examples, see: (a) Lemieux, G. A.; Yarema, K. J.; Jacobs, C. L.; Bertozzi, C. R. *J. Am. Chem. Soc.* **1999**, *121*, 4278–4279; (b) Perouzel, E.; Jorgensen, M. R.; Keller, M.; Miller, A. D. *Bioconjug. Chem.* **2003**, *14*, 884–898; (c) Sadamoto, R.; Niikura, K.; Ueda, T.; Monde, K.; Fukuhara, N.; Nishimura, S.-I. *J. Am. Chem. Soc.* **2004**, *126*, 3755–3761.
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9. Sasaki, T.; Minamoto, K.; Itoh, H. *J. Org. Chem.* **1978**, *43*, 2320–2325.
10. Alkoxyamines **3b**,**d**–**f** have been previously described. Characterization data for the new compounds is as follows: Compound **2a**: mp 78.6–80.1 °C; ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 6H), 1.98 (m, 2H), 2.86 (m, 2H), 7.15 (m, 1H), 7.27 (m, 4H), 7.63 (m, 2H), 7.74 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 25.2, 30.5, 42.3, 88.0, 123.1, 123.2, 125.7, 128.3, 129.1, 134.3, 142.2, 165.5; HRMS [M+Na$^+$] Calcd for $C_{19}H_{19}NO_3$: 332.1257, found: 332.1262. Compound **3a**: ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 6H), 1.99 (m, 2H), 2.76 (m, 2H), 4.93 (br s, 2H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 24.4, 30.5, 40.8, 78.3, 125.6, 128.3, 142.9; HRMS [M+Na$^+$] Calcd for $C_{11}H_{17}NO$: 202.1202, found: 202.1206. Compound **2g**: mp 55.5–56.6 °C; ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 6H), 1.59 (m, 8H), 3.68 (t, $J = 6.6$ Hz, 2H), 7.76 (m, 2H), 7.84 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 24.3, 25.4, 26.4, 32.9, 40.6, 63.0, 89.1, 123.7, 129.5, 134.7, 166.1; HRMS [M+Na$^+$] Calcd for $C_{16}H_{21}NO_4$: 314.1363, found: 314.1362. Compound **3g**: ^{1}H NMR ($CDCl_3$): δ 1.09 (s, 6H), 1.29 (m, 4H), 1.50 (m, 4H), 3.58 (t, $J = 6.6$ Hz, 2H), 3.81 (br s, 2H); ^{13}C NMR ($CDCl_3$): δ 24.1, 24.6, 26.6, 33.0, 39.1, 63.0, 79.2; HRMS [M+Na$^+$] Calcd for $C_8H_{19}NO_2$: 184.1308, found: 184.1306.
11. We modified the procedure described in the following reference to obviate column chromatography: Bailey, S.; Harnden, M. R.; Jarvest, R. L.; Parkin, A.; Boyd, M. R. *J. Med. Chem.* **1991**, *34*, 57–65.