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Efficient conversion of primary and secondary alcohols to primary amines

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Abstract—A convenient single-vessel conversion of primary and secondary alcohols to primary amines is reported. Use of this method results in substantially cleaner crude products than similar procedures reported in the literature. A simple work-up also makes this procedure ideal for parallel synthesis.
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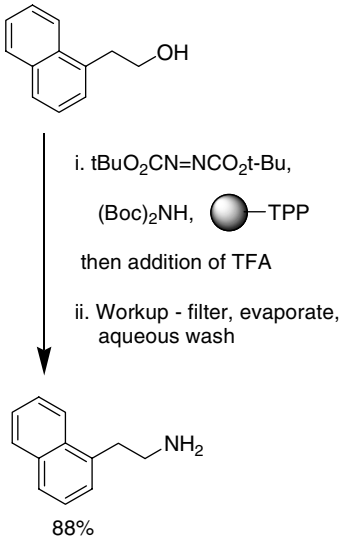
The conversion of alcohols to amines is one of the most common transformations in organic chemistry. Typical procedures involve 2–3 steps encompassing alcohol activation, nucleophilic displacement, and manipulation of the post-nucleophile product to an amine.[1] Each step generally requires isolation and purification making it cumbersome, particularly for parallel synthesis procedures. In spite of the frequency of this conversion and the accompanying inconvenience of intermediate characterization and purification there are only a few methods describing this functional group manipulation in a single operation.[2–4] Each of these methods has limitations due to harsh conditions required to drive the reaction to completion, narrow scope and/or purification of desired products contaminated with triphenylphosphine oxide and other significant byproducts of the Staudinger and Mitsunobu reactions.

Several years ago we reported a variant of the Mitsunobu reaction in which all byproducts and excess reagents were removed using standard workup procedures including aqueous wash, filtration, and evaporation.[5] Products were usually isolated in high yield and better than 90% purity *before* chromatography. Judicious choice of reagents, allowing for easy removal of excess reagent as well as reagent by-products, was key to this convenient procedure. We now report an extension of this technique to generate primary amines from primary and secondary alcohols. Addition of the key acidic nitrogen component, bis-*t*-butyliminodicarbonate, into the reaction scheme allows for the isolation of the primary amines with few byproducts. Further purification by normal or reversed phase chromatography occurs without an incident.

An example of the conversion is shown in Scheme 1. Hence, a mixture of 2-(1-naphthyl)ethanol (1.0 equiv),



Abbreviations: $(Boc)_2NH$ = bis-*tert*-butyliminodicarbonate, TFA = trifluoroacetic acid, ●-TPP = polystyrene resin bound triphenylphosphine.

Scheme 1. Conversion of 2-(1-naphthyl)ethanol to 2-(1-naphthyl)ethylamine in a single operation.

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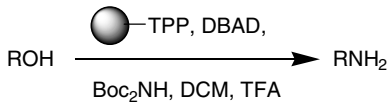
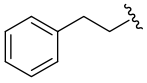
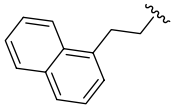
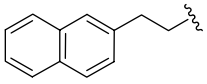
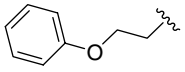
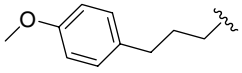
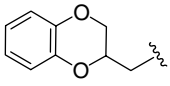
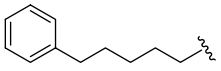
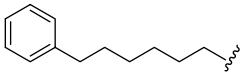
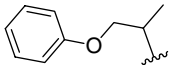
Table 1. Single-vessel conversion of primary and secondary alcohols to amines[a]



Entry	Structure (R)[b]	Yield (%)
1		91
2		88
3		86
4		79
5		74
6		87
7		83
8		90
9		55

[a] Abbreviations: DCM = dichloromethane, DBAD = Di-*tert*-butyldicarbonate, see scheme for others.
[b] Products characterized by ^{1}H NMR and MS.

bis-*tert*-butyliminodicarboxylate (4.0 equiv) and polystyrene resin bound triphenylphosphine (4.0 equiv) in dichloromethane was treated with di-*tert*-butylazodicarbonate (3.0 equiv) and stirred for 30 min. The mixture was treated with trifluoroacetic acid (TFA) and stirred an additional hour. Following filtration and evaporation of solvents the crude product was subjected to typical aqueous workup. The product, 2-(1-naphthyl)ethylamine was obtained in 88% yield and >90% purity (HPLC). It is important to note that no unreacted reagents or reagent byproducts were detected in the product. Further purification to obtain the product in >99% purity (HPLC, NMR) was easily accomplished with reversed phase, semi-preparative HPLC.[6] Table 1 shows several other alcohols converted to amines using this method. Yields are generally high. In the case of the secondary alcohol (Table 1, entry 9) a reasonable yield of 55% is obtained.

In summary, primary and secondary alcohols are readily converted to primary amines via a modified Mitsunobu reaction protocol. The method requires reagents and/or converted reagents that are readily removed from the reaction mixtures via typical workup conditions. In addition, all reagents used in the process are commercially available from several vendors.

Acknowledgments

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6. Typical experimental details: 2-(1-naphthyl)ethanol (0.050 g, 0.29 mMol), triphenylphosphine resin (3 mMol/g, 0.4 g, 1.2 mMol) and di-*t*-butyl iminodicarboxylate (0.252 g, 1.2 mMol) were mixed in anhydrous dichloromethane (4 mL) in an oven-dried, N_2-purged 8 mL vial. The mixture was magnetically stirred and cooled in an ice bath for 10 min. Di-*t*-butylazodicarbolylate (DBAD, 0.2 g, 0.87 mMol) was added all at once and the reaction mixture stirred for 30 min. The ice bath was removed and trifluroacetic acid (TFA, 1 mL) was added. After an hour the reaction mixture was filtered through Celite®, the residue was washed with a mixture of methanol and dichloromethane (1:1, 15 mL) and the combined filtrate was treated with saturated aqueous Na_2CO_3 solution (30 mL). The mixture was extracted with ethyl acetate (2×20 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by reversed phase PREP-HPLC (5–95% acetonitrile in water with 0.05% TFA buffer), to afford a yellow solid **2** (43 mg, 88%). ^{1}H NMR (MeOH-d_4): δ 8.04 (d, $J = 8.5$ Hz, 1H), 7.88 (d, $J = 7.5$ Hz, 1H), 7.80 (d, $J = 7.5$ Hz, 1H), 7.56 (t, $J = 8.2$ Hz, 1H), 7.51 (t, $J = 8.1$ Hz, 1H), 7.38–7.44 (m, 2H), 3.41 (t, $J = 7.3$ Hz, 2H), 3.24 (t, $J = 7.3$ Hz, 2H); MS (ES): 171.9; HRMS [M+H]: 172.1114 (calculated, 172.1121); HPLC: retention time: 5.6 min; purity: 100%.