Synthesis of Secondary Amines via *N*-(Benzoyloxy)amines and Organoboranes

O. Phanstiel, IV,* Q. X. Wang, D. H. Powell,† M. P. Ospina,† and B. A. Leeson

Center for Diagnostics and Drug Development, Department of Chemistry, University of Central Florida, Orlando, Florida 32816, and Department of Chemistry, University of Florida, Gainesville, Florida 32611

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A variety of primary amines (R−NH_2) were converted to their corresponding *N*-(benzoyloxy)amines (i.e., R−NHOCOPh) under biphasic conditions in excellent yields (63−90%). The intermediate *N*-(benzoyloxy)amines were converted to their *N*-ethylamine derivatives upon reaction with triethylborane in THF in good yield (54−89%). These experiments demonstrated the similar chemistry of *N*-chloro- and *N*-(benzoyloxy)amines with organoboranes.

Introduction

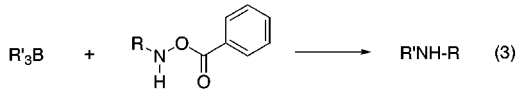
The synthesis of amines has long been of interest as a result of their unique biological activities and their potential as organic intermediates.[1] Organoborane technology allows access to substituted amines and protected amines by a variety of routes. For example, primary amines can be generated by the reaction of trialkylboranes with chloramine,[2−4] hydroxylamine-*O*-sulfonic acid,[5] or other *N*-activated reagents[6,7] (eq 1). Alternative methods allow for the generation of protected amine derivatives (e.g., sulfonamides) directly from trialkylboranes.[8] Borane-mediated amination reactions usually involve the regiospecific replacement of the boron atom by the amino group via an anionotropic rearrangement of an organoborate complex.[9,10] In addition, secondary amines can be accessed via *N*-chloro derivatives of primary amines[10] or organic azides[11,12] (eq 2). Many of these nitrogen-based reagents are unstable or corrosive and are typically generated just prior to use or in situ.[10,13] New reagents, which perform the same transformation, would clearly augment the existing methods of amine synthesis.

$$R'_3B + NH_2X \longrightarrow R'NH_2 \quad (1)$$

where X = Cl or OSO_3H

$$R'_3B + \begin{matrix}\text{RNH-Cl}\\ \text{or}\\ \text{RN}^{-}\text{-N}^{+}\equiv\text{N}\end{matrix} \longrightarrow R'NH\text{-}R \quad (2)$$

Because both the azide and *N*-chloro groups represent leaving groups appended to nitrogen, it seemed likely that *N*-(benzoyloxy)amines (R−NH−OCOPh), which contain a comparable motif, would also undergo similar chemistry with organoboranes. Having developed an improved entry to these systems,[14] our goal was to evaluate the *N*-(benzoyloxy)amines[15,16] as potential *N*-chloro replacements. Indeed, this paper introduces a new methodology for the synthesis of secondary amines via the reaction of organoboranes and *N*-(benzoyloxy)amine derivatives (eq 3).



Results and Discussion

When amine derivatives react with organoboranes, several factors have been shown to influence the reaction rate and product distribution. Previous work by Brown demonstrated that the degree of substitution on the carbon flanking the nitrogen (i.e., R in eq 2) influenced the yield of secondary amines (when generated from organic azides and trialkylboranes).[12] Later work demonstrated that the steric demands of both the reacting amine functionality and the alkylborane unit (R′) influenced the rate of the *N*-alkylation process.[9,10] In general, hindered motifs gave low yields of secondary amines. Therefore, the amine systems chosen for study included an adjacent 1°, 2°, and 3° substituted carbon center to observe the scope and limitations of the respective *N*-(benzoyloxy)amine reagents.

Several *N*-(benzoyloxy)amines (**1**−**7**) were prepared and isolated by a modification of our published method using benzoyl peroxide (BPO, see Scheme 1).[14] Prior

† University of Florida.

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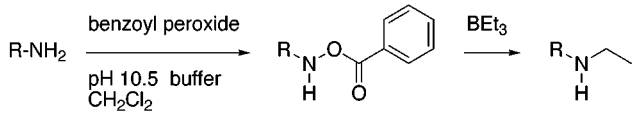
Scheme 1



experiments had indicated that 2 equiv of BPO provided high yields during the in situ oxidation of amine substrates.[14] However, we later found that using 1 equiv of BPO facilitated the chromatographic isolation of the intermediate *N*-(benzoyloxy)amines, which often had R_f values close to that of BPO. This modified procedure gave excellent yields of the desired *N*-(benzoyloxy)amines (63−90%, see Table 1).

As these materials (**1**−**7**) represent new "activated amine" sources, we evaluated their general storage properties. At room temperature, an uncapped vial containing the purified benzoyloxyamine **4** slowly decomposed (over several days) as evidenced by new spots on the TLC plate. This phenomenon was slowed upon storing the sample in a capped vial at 0 °C. Samples, which were stored under argon at 0 °C, remained in their pure state for several weeks. On the basis of these observations, these reactive intermediates are routinely stored under oxygen-free environments (i.e., Ar atmosphere) in the freezer.

As shown in Table 1, the *N*-(benzoyloxy)amines **1**−**7** were each reacted with 1 M triethylborane in THF to give their respective *N*-ethylamine derivatives. It should be noted that the reaction time during the ethylation step was dependent on the steric bulk of the R group (see Scheme 1). Although the reaction could be carried out at room temperature for many of the amines studied, the conversion rate became quite slow with the more hindered benzoyloxyamines (**5**−**7**). Refluxing THF (67 °C) was often required to achieve a convenient rate of reaction for these systems with triethylborane.

In general, reactions involving sterically demanding amine derivatives (or, for that matter, bulky trialkylborane substrates) often fail completely.[10,13] For example, a reaction involving the in situ generation of a *N*-chloroamine derivative (i.e., 1-methyloctylamine + sodium hypochlorite) and trihexylborane gave a 0% yield of the desired secondary amine.[10] Amines with adjacent 3° carbon centers are often precluded from such reactions. Not surprisingly, the reaction of hindered benzoyloxyamine **7** with triethylborane gave none of the anticipated *N*-ethylamine derivative **14**. Similar observations were found with the related *N*-chloro systems involving hindered substrates[10,13] and have been shown to involve a radical pathway.[10]

Systems containing 1° and 2° carbons adjacent to the amine center (**1**−**6**) gave good-to-excellent yields in the *N*-ethylation step (see Table 1). The adjacent secondary carbon present in **5** and **6** did not preclude the formation of the desired secondary amines **12** (54%) and **13** (86%). In comparison, *N*-chloro-2-octylamine and triethylborane generated amine **12** in a reported 85% yield.[13] Although the yield of **12** is lower than that reported via the *N*-chloro route, we found the yields for these reactions to be highly dependent on the workup procedure (especially for low molecular weight amine products). For example, by altering the workup method (see Experimental Section, Method A versus Method B), the yield of **13** was increased from 26% to 86%. This dramatic increase was obtained by a minor modification of the excellent procedure described by Kabalka.[6] Preacidification of the reaction mixture to pH 1 prior to removal of the THF and water mixture (under reduced pressure) limited significant losses of the low molecular weight, volatile amines **8** and **13**.

The *N*-ethylation reaction is analogous to the reaction of *N*-chloroalkylamines with organoboranes and presumably occurs via migration of an alkyl group from boron to nitrogen (see Scheme 2).[9,10] As the benzoyloxylation procedure is highly versatile,[14,17] this discovery opens up a promising new route to a diverse number of secondary amines with reagents that are stable to chromatography and completely soluble in THF and that tolerate appreciable steric bulk near the amine center.

In summary, this technology provides another source of "activated" amine (RNH−OCOPh), which is complementary to the published *N*-chloroamine and organic azide methods and utilizes classic organoborane chemistry to yield secondary amines in good yield.

Experimental Section

Materials and Methods. Reagents were purchased from either the ACROS Chemical Company or the Aldrich Chemical Co. All commercially available amines were distilled prior to use. An authentic sample of *N*-ethylcyclohexylamine (**13**) was purchased from the Aldrich Chemical Co. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer. The pH 10.5 buffer solution was prepared by combining 222 mL of 0.75 N aqueous $NaHCO_3$ and 78 mL of 1.5 N aqueous NaOH. The TLC and column chromatography solvents are expressed in volume %. ***Caution***: although we did not observe the *N*-benzoyloxyamines to be shock sensitive, proper safety procedures should be followed when handling these compounds.

General Procedure for Amine Oxidation. A solution of benzoyl peroxide (BPO, 1 equiv) in CH_2Cl_2 (5 mL/mmol BPO) was added quickly to a mixture of the amine (1 equiv) and a pH 10.5 buffer solution (5 mL/mmol amine) at room temperature. [Note: using 1 equiv of BPO facilitated the isolation of the intermediate benzoyloxyamines, which often had R_f values close to that of BPO.] TLC was used to monitor the consumption of starting material, and the plates were typically stained (after solvent elution) with iodine vapor to visualize the amine starting materials. After the reaction was complete, the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was subjected to flash column chromatography.

General Procedure for Ethylation. Triethylborane (1 molar equiv) in THF (1 mL/mmol triethylborane) and an equivalent volume of a 0.4 M aqueous sodium carbonate solution were cooled to 0 °C while maintaining a nitrogen atmosphere. One molar equivalent of the *N*-(benzoyloxy)amine in THF (1 M solution) was then added dropwise. After the addition was complete, the solution was allowed to warm to room temperature. The disappearance of starting material was monitored by TLC. [Note: sluggish reactions were refluxed to facilitate conversion.]

Workup Method A. (Best for high molecular weight adducts) After the reaction was complete, the THF was removed under reduced pressure. The semisolid residue was dissolved in a minimum amount of water and extracted three times with diethyl ether. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The crude mixture was subjected to flash column chromatography to give the corresponding *N*-ethylamine.

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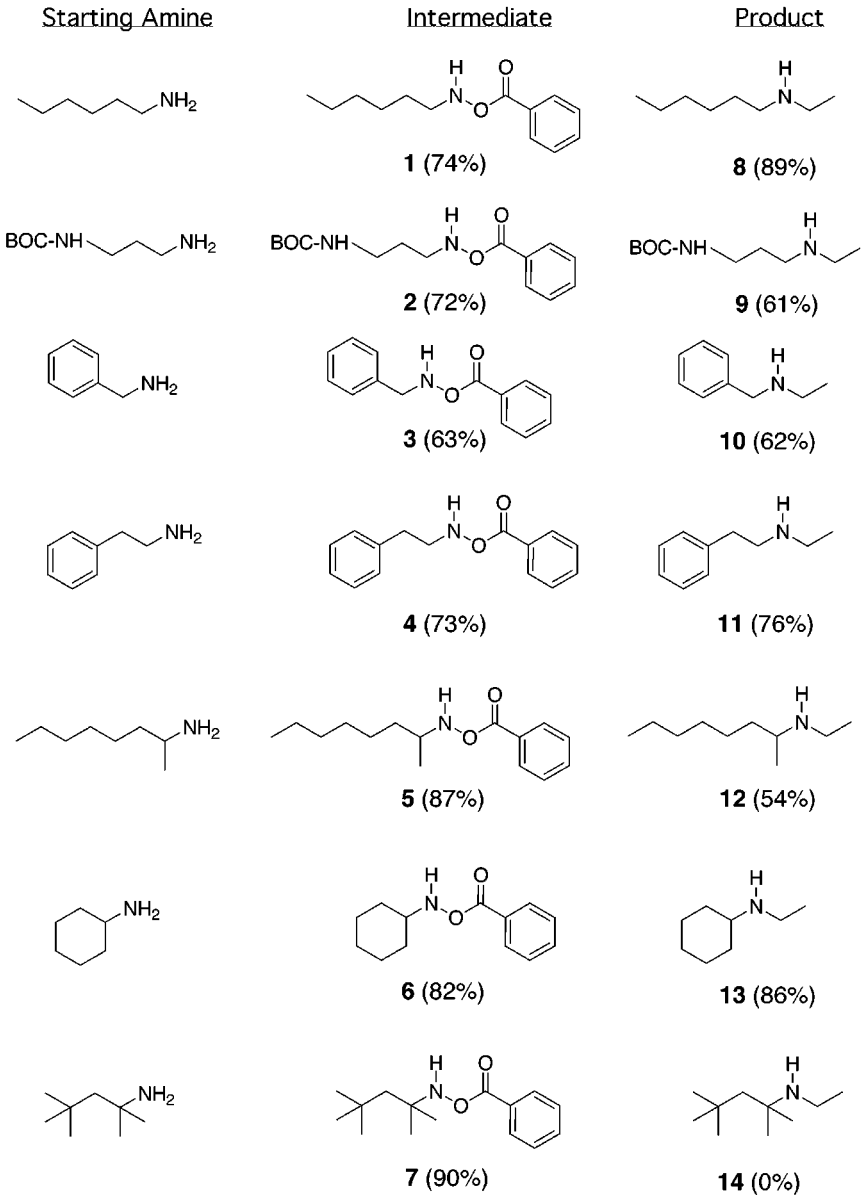
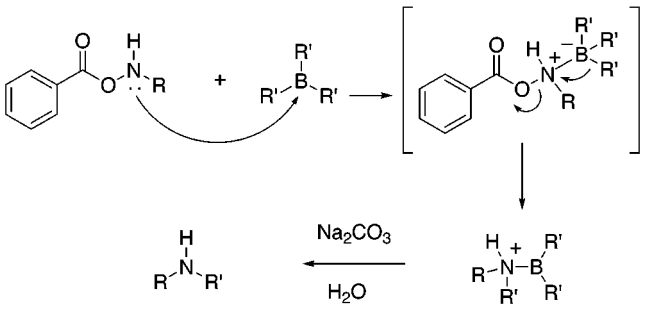
Table 1. Primary Amines Converted to *N*-Ethylamines



Scheme 2



Workup Method B. (Best for low molecular weight adducts) After the reaction was complete, the reaction mixture was acidified with 10% (by volume) HCl to pH < 2. The volatiles were removed under reduced pressure. The resultant residue was suspended in water and washed with diethyl ether. [Note: TLC and ^{1}H NMR analysis of this ether layer confirmed the presence of benzoic acid, the expected byproduct. This ether layer was then discarded.] Next, 2 N NaOH was added to the water layer until pH >12. The water phase was then extracted three times with diethyl ether. These ether layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the pure *N*-ethylamine. One spot was observed by TLC (2% concentrated NH_4OH/MeOH). The yield and the product were confirmed by ^{1}H NMR using a known amount of a diphenylmethane (DPM) standard. In general, comparison of the integration value determined for the DPM singlet at 3.95 ppm and the H−C−N multiplet (typically near 2.6 ppm) provided the yields listed in Table 1. Although structure-dependent, the ^{1}H NMR *N*-ethyl group pattern was usually observed as a quartet near 2.6 ppm and a triplet at 1.1 ppm.

***N*-Benzoyloxy-hexylamine (1).** Hexylamine (1.62 g, 16 mmol) was reacted with benzoyl peroxide using the general procedure. TLC (2% concentrated NH_4OH/MeOH, $R_f = 0.41$) was used to monitor the consumption of hexylamine. The crude product was subjected to flash column chromatography ($CHCl_3$, $R_f = 0.45$) to give *N*-benzoyloxy-hexylamine **1** (2.62 g, 74%): ^{1}H NMR ($CDCl_3$) δ 8.03 (d, 2H), 7.50 (m, 3H), 3.13 (t, 2H), 1.61 (m, 2H,), 1.35 (m, 6H), 0.88 (t, 3H). Anal. Calcd for $C_{13}H_{19}N_1O_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.45; H, 8.72; N, 6.32.

***N*^{3}-Benzoyloxy-3-(*tert*-butoxycarbonylamino)propylamine (2).** 3-(*tert*-Butoxycarbonylamino)propylamine[17] (5.22 g, 30 mmol) was reacted with benzoyl peroxide using the general procedure. TLC (4% concentrated NH_4OH/MeOH) was used to monitor the consumption of N^1-BOC-propane diamine. The crude product was subjected to flash column chromatography (40% ethyl acetate/hexane, $R_f = 0.43$) to give the known amine **2** (6.35 g, 72%):[17] ^{1}H NMR ($CDCl_3$) δ 8.03 (d, 2H), 7.52 (m, 3H), 4.81 (broad m, 1H), 3.22 (m, 4H), 1.82 (m, 2H), 1.41 (s, 9H); HRMS−FAB calcd for $C_{15}H_{23}N_2O_4$ (M + 1) 295.1658, found 295.1645.

***N*-Benzoyloxy-benzylamine (3).** Benzylamine (1.71 g, 16 mmol) was reacted with benzoyl peroxide using the general procedure. TLC (2% concentrated NH_4OH/MeOH, $R_f = 0.56$) was used to monitor the consumption of benzylamine. The crude product was subjected to flash column chromatography (10% ethyl acetate/hexane, $R_f = 0.33$) to give *N*-benzoyloxybenzylamine **3** (2.29 g, 63%): ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 2H), 7.40 (m, 8H), 4.27 (s, 2H). Anal. Calcd for $C_{14}H_{13}N_1O_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.91; H, 5.76; N, 6.14.

***N*-Benzoyloxy-2-phenethylamine (4).** Phenethylamine (0.484 g, 4 mmol) was reacted with benzoyl peroxide using the general procedure. TLC (2% concentrated NH_4OH/MeOH, $R_f = 0.53$) was used to monitor the consumption of phenethylamine. The crude product was subjected to flash column chromatography (20% ethyl acetate/hexane, $R_f = 0.47$) to give *N*-benzoyloxy-2-phenethylamine **4** (0.70 g, 73%): ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 2H), 7.35 (m, 8H), 3.45 (t, 2H), 2.98 (t, 2H); HRMS−FAB calcd for $C_{15}H_{15}N_1O_2$ (M + 1) 242.1209, found 242.1204. Anal. Calcd: C, 74.67; H, 6.27; N, 5.81. Found: C, 75.04; H, 6.45; N, 5.86.

***N*-Benzoyloxy-1-methyl-heptylamine (5).** 1-Methyl-heptylamine (1.03 g, 8 mmol) was reacted with benzoyl peroxide using the general procedure. TLC (2% concentrated NH_4OH/MeOH, $R_f = 0.30$) was used to monitor the consumption of 1-methyl-heptylamine. The crude product was subjected to flash column chromatography (10% ethyl acetate/hexane, $R_f = 0.25$) to give **5** (1.73 g, 87%): IR (neat) 3234, 3064, 2930, 1720, 1601, 1452, 1270, 1092, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07 (t, 2H), 7.54 (m, 3H), 3.20 (m, 1H), 1.30 (m, 13 H), 0.87 (t, 3H); HRMS−FAB calcd for $C_{15}H_{23}N_1O_2$ (M + 1) 250.1807, found 250.1821. Anal. Calcd: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.58; H, 9.43; N, 5.67.

***N*-Benzoyloxy-cyclohexylamine (6).** Cyclohexylamine (1.58 g, 16 mmol) was reacted with benzoyl peroxide using the general procedure. TLC (2% concentrated NH_4OH/MeOH, $R_f = 0.41$) was used to monitor the consumption of cyclohexylamine. The crude product was subjected to flash column chromatography (10% ethyl acetate/hexane, $R_f = 0.40$) to give **6** (2.90 g, 82%): ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 2H), 7.72 (s, 1H), 7.53 (m, 3H), 3.05 (m, 1H), 1.98 (m, 2H), 1.80 (m, 2H), 1.68 (m, 1H), 1.28 (br s, 5H). Anal. Calcd for $C_{13}H_{17}N_1O_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.15; H, 7.79; N, 6.31.

***N*-Benzoyloxy-*tert*-octylamine (7).** *tert*-Octylamine (1.03 g, 8 mmol) was reacted with benzoyl peroxide using the general procedure. TLC (2% concentrated NH_4OH/MeOH, $R_f = 0.33$) was used to monitor the consumption of *tert*-octylamine. The crude product was subjected to flash column chromatography (10% ethyl acetate/hexane, $R_f = 0.25$) to give **7** (1.79 g, 90%): IR (neat) 3221, 3050, 2954, 1718, 1600, 1451, 1272, 1093, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04 (t, 2H), 7.47 (m, 3H), 1.59 (s, 2H), 1.25 (s, 6H), 1.07 (s, 6H); HRMS−FAB calcd for $C_{15}H_{23}N_1O_2$ (M + 1) 250.1807, found 250.1821. Anal. Calcd: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.30; H, 9.29; N, 5.65.

***N*-Ethylhexylamine (8).** *N*-(Benzoyloxy)hexylamine **1** (0.774 g, 3.5 mmol) was reacted with triethylborane using the general procedure. After it warmed to room temperature, the reaction was refluxed to facilitate complete conversion. The reaction was cooled to room temperature, and the amine **8** (0.40 g, 89%) was isolated by Method B: ^{1}H NMR ($CDCl_3$) δ 2.60 (m, 4H), 1.75 (broad s, 1H), 1.49 (m, 2H), 1.20 (m, 9H), 0.85 (t, 3H); consistent with literature spectrum.[18]

***N*^{1}-Ethyl-3-(*tert*-butoxycarbonylamino)propylamine (9).** N^1-Benzoyloxy-3-(*tert*-butoxycarbonylamino)propylamine **2** (0.735 g, 2.5 mmol) was reacted with triethylborane using the general procedure for ethylation. TLC ($R_f = 0.42$, 40% ethyl acetate/hexane) was used to monitor the disappearance of **2**. The crude mixture was subjected to flash column chromatography (2% NH_4OH/MeOH, $R_f = 0.28$) to give **9** (0.31 g, 61%): ^{1}H NMR ($CDCl_3$) δ 5.35 (br s, 1H), 3.19 (virtual q, 2H), 2.63 (m, 4H), 1.75−1.50 (m, 3H), 1.43 (s, 9H), 1.1 (t, 3H); HRMS−FAB calcd for $C_{10}H_{22}N_2O_2$ (M + 1) 203.1760, found 203.1759.

***N*-Ethylbenzylamine (10).** *N*-Benzoyloxy-benzylamine **3** (0.568 g, 2.5 mmol) was reacted with triethylborane using the general procedure for ethylation. The reaction solution was refluxed for 24 h. TLC ($R_f = 0.33$, 10% ethyl acetate/hexane) was used to monitor the disappearance of **3**. The crude mixture was subjected to flash column chromatography (2% NH_4OH/MeOH, $R_f = 0.41$) to give **10** (0.21 g, 62%): ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 3.79 (s, 2H), 2.67 (q, 2H), 1.65 (br s, 1H), 1.10 (t, 3H), consistent with literature spectrum.[18]

***N*-Ethylphenethylamine (11).** *N*-Benzoyloxy-phenethylamine **4** (0.60 g, 2.5 mmol) was reacted with triethylborane using the general procedure for ethylation. The reaction solution was refluxed for 4 h. TLC ($R_f = 0.34$, 10% ethyl acetate/hexane) was used to monitor the disappearance of **4**. The crude mixture was subjected to flash column chromatography (2% NH_4OH/MeOH, $R_f = 0.40$) to give **11** (0.28 g, 76%): ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 5H), 2.85 (m, 4H), 2.66 (q, 2H), 1.52 (br s, 1H), 1.08 (t, 3H), consistent with literature spectrum.[18]

***N*-(Ethyl)-1-methyl-heptylamine (12).** *N*-Benzoyloxy-1-methyl-heptylamine **5** (0.99 g, 4 mmol) was reacted with triethylborane using the general procedure for ethylation. The reaction solution was refluxed for 5 h. TLC ($R_f = 0.25$, 10% ethyl acetate/hexane) was used to monitor the disappearance of **5**. The crude mixture was subjected to flash column chromatography (2% NH_4OH/MeOH, $R_f = 0.42$) to give **12** (0.34 g, 54%): ^{1}H NMR ($CDCl_3$) δ 2.55 (m, 3H), 1.35 (br m, 1H), 1.30−1.10 (br s, 10H), 1.03 (t, 3H), 0.95 (d, 3H), 0.80 (t, 3H); HRMS−FAB calcd for ($C_{10}H_{23}N_1$) (M + 1) 158.1869, found 158.1889.

***N*-Ethylcyclohexylamine (13).** *N*-Benzoyloxy-cyclohexylamine **6** (0.88 g, 4.02 mmol) was reacted with triethylborane using the general procedure for ethylation. The reaction solution was refluxed overnight, and *N*-ethylcyclohexylamine **13** (0.44 g, 86%) was isolated via Method B: ^{1}H NMR ($CDCl_3$) δ 2.66 (q, 2H), 2.40 (m, 1H), 1.92−1.49 (m, 6H), 1.40−0.9 (m, 8H); matched the ^{1}H spectrum ($CDCl_3$) of a commercial sample of **13**.

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(18) ^{1}H NMR spectral data for *N*-ethylamine derivatives; for compound **8**, see: Pienemann, T.; Schafer, H.-J. *Synthesis* **1987**, 1005−1007. **10**: Pouchert, C. J.; Campbell, J. R. *The Aldrich Library of NMR Spectra* **1974**, Vol. V, 97. **11**: Ishihara, Y.; Kato, K.; Goto, G. *Chem. Pharm. Bull.* **1991**, *39*, 3225−3235.