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# The Preparation of Functionalized Amines and Amides Using Benzotriazole Derivatives and Organozinc Reagents

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***Abstract:*** Secondary and tertiary amines **6** are conveniently prepared in good yields by reacting organozinc halides with adducts **4**, which are derived from the corresponding amines, aldehydes and benzotriazole. The use of organozinc reagents enables the introduction of nitro, cyano or ester functionalities into amine mainframes. This methodology was also used to prepare functionalized amides **8**. 

## INTRODUCTION

The formation of a carbon-carbon bond at the α-position to a nitrogen atom is of great importance for the elaboration of amines and, in particular, the synthesis of nitrogen-containing natural products and biologically active compounds. Tertiary amines and amides can be prepared by a great variety of methods.[1] Work from our group has demonstrated that benzotriazole derivatives are versatile precursors for tertiary amines and amides.[2] While the benzotriazole anion is a good leaving group, in many cases benzotriazole derivatives are much more stable than the corresponding halogen analogs, and can be used efficiently in many synthetic transformations.[3] One such important reaction is the synthesis of tertiary amines and amides involving benzotriazole displacement in carbon-carbon bond forming reactions with organometallic reagents.

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*Dedicated to our friend Professor Madeleine Joullie in celebration of 40 years of distinguished teaching and research at the University of Pennsylvania.

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Grignard reagents have been the most frequently used organometallics in this type of reaction. Their high reactivity requires strictly anhydrous conditions and precludes their use in reactions with many functionalities such as organic halides or substrates bearing nitro, cyano or ester groups.

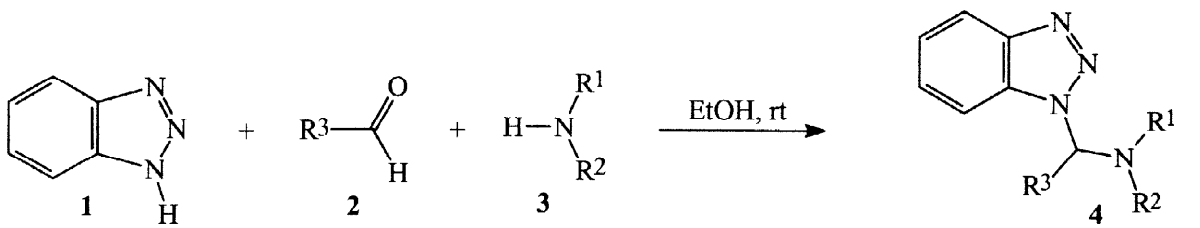
We now report that the use of organozinc reagents under modified Reformatsky conditions overcomes many of the limitations of the previously described method, and renders the preparation of secondary and tertiary amines or amides using benzotriazole methodology more general. The lower reactivity of organozinc reagents in comparison to Grignard reagents towards most organic electrophiles represents a potential advantage for the preparation of functionalized zinc reagents under mild conditions.[4-6] Organozinc halides can be prepared either by transmetalations of organolithium or Grignard reagents, or by the insertion of zinc into an organic halide.[7] The latter method is of special synthetic utility since it allows the one-step preparation of a variety of polyfunctional organozinc halides.[6,7] To improve the formation and reactivity of organozinc reagents several methods have been introduced, including chemical activation, using catalysts such as iodine or potassium iodide, 1,2-dibromoethane, trimethylsilylchloride, *etc.*, or physical activation, using ultrasonic irradiation.[7,8] Since organozinc reagents are less sensitive to moisture than Grignard reagents[7,9] it is possible to use technical grade DMF as a solvent.

## RESULTS AND DISCUSSION

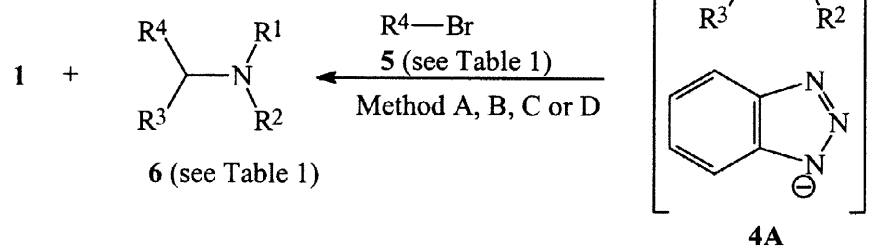
***Reactions of N-[1-(Benzotriazol-1-yl)alkyl]amines 4 with Organozinc Reagents.*** *N*-[1-(Benzotriazol-1-yl)alkyl]amines **4** are stable adducts, readily available from benzotriazole (**1**) and the corresponding aldehyde **2** and secondary amine **3** (Scheme 1). Our initial study on the preparation of tertiary amines **6** centered on the application of simple organozinc reagents prepared from metallic zinc and benzyl bromide or *n*-butyl bromide. Benzotriazole derivatives **4** reacted smoothly with 2 equivalents of zinc and 2 equivalents of benzyl bromide in DMF at room temperature over 24 hours to form amines **6a,b** in 72% and 89% isolated yields, respectively. The byproduct benzotriazole (**1**) was simply washed out during alkaline work up. When preparation of **6b** was carried out in dry THF as a solvent no significant difference in yields was observed. Formation of a carbon-carbon bond at the α-position to nitrogen is enabled by a partial ionization of compounds **4** in solution, producing a benzotriazolyl anion and iminium cation ion-pair **4A**, as shown, *inter alia,* by cross-over experiments.[10] The preparation of an organozinc reagent from *n*-BuBr required more vigorous conditions. Thus, to a mixture of 1 equivalent of Bt-derivative and 2 equivalents of Zn powder in DMF, 2 equivalents of butyl bromide and 1 equivalent of KI as a promotor were added. The mixture was stirred and heated at 60-70 °C for 6 hours than quenched with ice-cold $NH_4OH$ to give amine **6c** in 67% yield (Method B, Scheme 1, Table 1).

These preliminary results were sufficiently encouraging to turn our attention to the preparation of tertiary amines which are unavailable by the previously described method utilizing Grignard reagents. The

preparation of organozinc halides containing nitro, cyano and ester functionalities have been reported[4-7] and we anticipated that the use of organozinc reagents should thus enable the introduction of these groups into tertiary amine mainframes. *p*-Nitrobenzyl bromide and *p*-cyanobenzyl bromide each reacted in DMF smoothly at room temperature over 24 hours with 2 equivalents of zinc to form the corresponding organozinc reagents. The organozinc reagent from *p*-cyanobenzyl bromide reacted with the appropriate benzotriazole derivatives **4c** and **4d** to give amines **6e** and **6f** in 76% and 82% isolated yields, respectively. Using the same procedure, amine **6d** was prepared from *p*-nitrobenzyl bromide in 61% yield. Since there are possible side reactions of metallic zinc with cyano or nitro group, twofold excess of metallic zinc and alkyl halide, with respect to the starting adducts **4**, has to be used in order to provide sufficient amount of organozinc reagents to trap the corresponding iminium cations **4A** and to obtain maximum yields (Method A, Scheme 1, Table 1).




**4a**: $R^1$ = Me, $R^2$ = Ph, $R^3$ = H
**4b**: $R^1 = R^2 = (CH_2)_2O(CH_2)_2$, $R^3$ = H
**4c**: $R^1 = R^2 = (CH_2)_2O(CH_2)_2$, $R^3$ = *i*-Pr
**4d**: $R^1 = R^2 = (CH_2)_4$, $R^3$ = H
**4e**: $R^1 = R^2$ = 2-[$C_6H_4(CH_2)_3$], $R^3$ = H
**4f**: $R^1$ = *p*-$NCC_6H_4$, $R^2$ = H, $R^3$ = H
**4g**: $R^1$ = *p*-$EtO_2CC_6H_4$, $R^2$ = H, $R^3$ = H




Method A (Zn, DMF, rt); Method B (Zn, DMF, KI, Δ);
Method C (Zn, THF, $Me_3SiCl$, Δ); Method D (Zn, THF, Δ)

**Scheme 1**

Table 1. Preparation of Secondary and Tertiary Amines **6**.

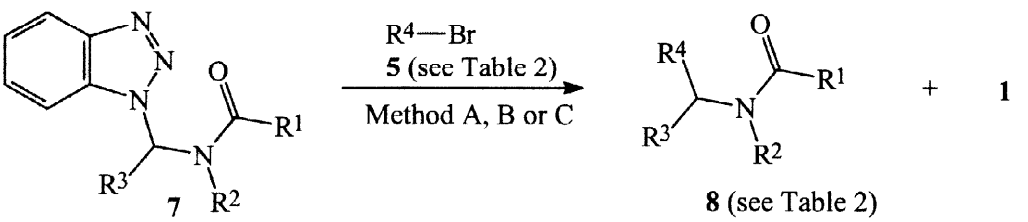
| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Method | Yield, % |
|---|---|---|---|---|---|---|
| **6a** | Me | Ph | H | $PhCH_2$ | A | 72 |
| **6b** | $-(CH_2)_2O(CH_2)_2-$ | | H | $PhCH_2$ | A | 89 |
| **6c** | $-(CH_2)_2O(CH_2)_2-$ | | H | *n*-Bu | B | 67 |
| **6d** | $-(CH_2)_2O(CH_2)_2-$ | | H | *p*-$O_2NC_6H_4$-$CH_2$ | A | 61 |
| **6e** | $-(CH_2)_2O(CH_2)_2-$ | | *i*-Pr | *p*-$NCC_6H_4$-$CH_2$ | A | 82 |
| **6f** | $-(CH_2)_4-$ | | H | *p*-$NCC_6H_4$-$CH_2$ | A | 76 |
| **6g** | $-(CH_2)_2O(CH_2)_2-$ | | H | $EtO_2CCH_2$ | C | 72 |
| **6h** | Me | Ph | H | $EtO_2CCH_2$ | C | 64 |
| **6i** | 2-[$C_6H_4(CH_2)_3$]- | | H | $EtO_2CCH_2$ | C | 71 |
| **6j** | *p*-$NCC_6H_4$ | H | H | $PhCH_2$ | D | 57 |
| **6k** | *p*-$EtO_2CC_6H_4$ | H | H | $PhCH_2$ | D | 61 |

Ethyl bromoacetate did not react satisfactorily using the general procedure "Method A". Hence, 1 equivalent of trimethylchlorosilane was added as a promotor to 2 equivalents of zinc powder in THF and the mixture stirred for 15 minutes at room temperature. Then 1 equivalent of Bt-derivative **4b**, **4a**, or **4e** in THF was added, the mixture heated to reflux, 2 equivalents of ethyl bromoacetate added, and the whole was stirred at reflux under nitrogen for 6 hours, cooled to room temperature, then quenched with $NH_4OH$ to give amines **6g-6i** respectively in 64-72% isolated yields (Method C, Scheme 1, Table 1).

As a continuation of the study we extended the reaction system to adducts **4f** and **4g**, which possess the sensitive cyano or ester groups as substituents. Thus, to a solution of the Bt-derivative **4f** or **4g** in THF benzylzinc bromide, prepared from 2 equivalents of benzyl bromide and 2 equivalents of Zn powder in THF, was added. The mixture was stirred at reflux for 12 hours under nitrogen, cooled to room temperature and quenched with ice-cold $NH_4OH$. After purification by column chromatography, the expected products **6j** and **6k** were isolated in 57% and 61% yield, respectively (Method D, Scheme 1, Table 1).

***Reactions of N-[1-(Benzotriazol-1-yl)alkyl]amides 7 with Organozinc Reagents.*** The new method was extended to prepare secondary and tertiary amides **8** from *N*-[1-(benzotriazol-1-yl)alkyl]amides **7**. The exclusive replacement of the benzotriazole group at the carbon attached to an amide nitrogen yielded the secondary or tertiary amides. This required some vigorous conditions: to a mixture of 1 equivalent of Bt-derivative **7** and 2 equivalents of Zn powder in DMF was added 2 equivalents of benzyl bromide. The mixture was stirred and heated at 70-80 °C under nitrogen for 12 hours, and then quenched with $NH_4OH$ to give the corresponding amides **8a**[2d] and **8b** in 68% and 74% yield, respectively. Ethyl bromoacetate reacted

satisfactorily using 1 equivalent of trimethylchlorosilane as a promotor. Thus, 1 equivalent of Bt-derivatives **7d** or **7c** in THF was added to 2 equivalents of zinc powder in THF and the mixture was heated to reflux, then 2 equivalents of ethyl bromoacetate added, and the whole was stirred at reflux under nitrogen for 9 hours, following with an alkali work-up to give amides **8c,d** in 76% and 87% isolated yields, respectively. The preparation of the β-amino acid derivatives **8c,d** extends our earlier work in this area[11] and is significant because of current interest in such compounds.[12] Bt-derivative **7c** reacted smoothly with 2 equivalents of zinc and 2 equivalents of *m*-cyanobenzyl bromide in DMF at room temperature over 48 hours to form amide **8e** in 59% yield (Method C, Scheme 2, Table 2).




**7a**: $R^1$ = Ph, $R^2$ = H, $R^3$ = *i*-Pr
**7b**: $R^1$= $R^2$ = $(CH_2)_3$, $R^3$ = Ph
**7c**: $R^1$ = Ph, $R^2$ = H, $R^3$ = Ph
**7d**: $R^1$ = Ph, $R^2$ = H, $R^3$ = H

Method A (Zn, DMF, Δ); Method B (Zn, THF, $Me_3SiCl$, Δ); Method C (Zn, DMF, rt)

**Scheme 2**

Table 2. Preparation of Secondary and Tertiary Amides **8**.

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Method | Yield, % | mp, °C |
|---|---|---|---|---|---|---|---|
| **8a** | Ph | H | *i*-Pr | $PhCH_2$ | A | 68 | 145-147[a] |
| **8b** | $-(CH_2)_3-$ | | Ph | $PhCH_2$ | A | 74 | 98-100 |
| **8c** | Ph | H | H | $EtO_2CCH_2$ | B | 76 | oil |
| **8d** | Ph | H | Ph | $EtO_2CCH_2$ | B | 87 | 87-89 |
| **8e** | Ph | H | Ph | *m*-$NCC_6H_4CH_2$ | C | 59 | 176-178 |

[a] Lit.[2d] mp = 146-148 °C

All new compounds were characterized by $^1H$ and $^{13}C$ NMR spectra and elemental analysis or HRMS.

In conclusion, functionalized amines **6** were conveniently prepared in good yields by reactions of organozinc halides with adducts **4**, which were derived from the corresponding amine, aldehyde and benzotriazole. The use of organozinc reagents enabled the introduction of nitro, cyano or ester functionalities

into amine mainframes, thus making the new method complementary to the described preparation of secondary and tertiary amines using Grignard reagents. Despite possible side reactions of metallic zinc with cyano, ester or nitro group, twofold excess of metallic zinc and alkyl halide, with respect to adducts **4**, provided sufficient amount of organozinc reagents to trap the corresponding iminium cations **4A**. This methodology was also used to prepare functionalized amides **8**.

## EXPERIMENTAL

***General.*** Melting points were determined on a Kofler hot stage apparatus and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian VXR-300 spectrometer at 300 MHz and 75 MHz respectively, with tetramethylsilane for $^{1}H$ and chloroform-*d* or dimethyl sulfoxide-$d_6$ for $^{13}C$ as internal references. Microanalyses were performed on a Carlo Erba 1106 elemental analyzer. THF was distilled from sodium/benzophenone directly prior to use. DMF (Aldrich)was dried over molecular sieves. Zinc powder was washed with 2% hydrochloric acid and air dried prior to use.

The following compounds were prepared according to the procedures described in the literature: *N*-methyl-*N*-phenyl-[(benzotriazol-1-yl)methyl]amine (**4a**),[13] *N*-[benzotriazol-1-yl)methyl]morpholine (**4b**),[14] *N*-[α-benzotriazol-1-yl)-β-methylpropyl]morpholine (**4c**),[14] *N*-[(benzotriazol-1-yl)methyl]pyrolidine (**4d**),[2c] *N*-[(benzotriazol-1-yl)methyl]-1,2,3,4-tetrahydroquinoline (**4e**),[15] *N*-[α-benzotriazol-1-yl)-β-methylpropyl]benzamide (**7a**),[17] *N*-[(benzotriazol-1-yl)phenylmethyl]pyrolidin-2-one (**7b**),[16] *N*-[(benzotriazol-1-yl)phenylmethyl] benzamide (**7c**),[17] *N*-[(benzotriazol-1-yl)phenylmethyl] benzamide (**7d**),[17] and 1-(hydroxymethyl)-benzotriazole.[18]

***Preparation of Substituted N-(Benzotriazol-1-yl)methylanilines 4f, 4g. General procedure.***
The mixture of 1-(hydroxymethyl)benzotriazole (1.49 g, 0.01 mol) and anilino derivative (0.01 mol) in ethanol (50 ml) was stirred at room temperature overnight. The precipitate formed was collected by filtration and washed with ethanol.

***N-(Benzotriazol-1-yl)methyl-4-cyanoaniline (4f).*** This compound was prepared from 4-cyanoaniline in 95% yield; white microcrystals; mp = 185-187 °C; $^{1}H$ NMR (DMSO-$d_6$) δ 6.27 (d, J = 6.9 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.57-7.65 (m, 4H), 8.08 (d, J = 8.6 Hz, 2H), 8.19 (t, J = 6.9 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$) δ 55.6, 98.8, 110.9, 112.9, 119.2, 119.8, 124.1, 127.4, 132.0, 133.5, 145.4, 149.8. Anal. Calcd for $C_{14}H_{11}N_5$: C, 67.46; H, 4.45; N, 28.09. Found: C, 67.35; H, 4.45; N, 28.31.

***N-(Benzotriazol-1-yl)methyl-4-(ethoxycarbonyl)aniline (4g).*** This compound was prepared from 4-ethoxycarbonylaniline in 92% yield; white microcrystals; mp = 173-175 °C; $^{1}H$ NMR (DMSO-$d_6$) δ 1.26 (t, J = 7.1

Hz, 3H), 4.21 (q, J = 7.1Hz, 2H), 6.23 (d, J = 6.8 Hz, 2H), 6.94 (d, J = 6.8 Hz, 2H), 7.41 (t, J = 7.4 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.75 (d, J = 8.5 Hz, 2H), 8.00-8.08 (m, 3H); $^{13}$C NMR (DMSO-$d_6$) δ 14.2, 55.9, 59.8, 111.0, 112.1, 118.8, 119.1, 124.7, 127.3, 130.8, 132.1, 145.4, 150.1, 165.6. Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.99; H, 5.61; N, 19.11.

***Typical Procedures for the Preparation of Tertiary and Secondary Amines 6.***

***Method A:*** To a mixture of Zn powder (0.264 g, 4 mmol) and Bt-derivative **4** (2 mmol) in DMF (10 ml), the corresponding halide **5** (4 mmol) was added. The mixture was stirred at room temperature under nitrogen for 24 hours then quenched with ice-cold $NH_4OH$ (25%, 15 ml) and stirred until most of the solids were dissolved. Undissolved solids were filtered off, and the filtrate was extracted with $Et_2O$ (3 x 15 ml). The combined organic layers were washed with NaOH (10 ml) and water (3 x 20 ml) before being separated and dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure to give crude product (oily residue), which was purified by column chromatography on silica gel using the eluents specified to give pure product **6a**,**b**,**d-f**.

***Method B:*** To a mixture of Zn powder (0.264 g, 4 mmol) and Bt-derivative **4** (2 mmol) in DMF (10 ml), butyl bromide (4 mmol) and KI (0.32 g, 2 mmol) were added. The mixture was stirred and heated at 60-70 °C under nitrogen for 6 hours, cooled to room temperature, quenched with ice-cold $NH_4OH$ (25%, 15 ml) and stirred until most of solids were dissolved. The work-up procedure was the same as for method A, to give pure product **6c**.

***Method C:*** To a suspension of Zn powder (0.264 g, 4 mmol) in THF (10 ml) trimethylchlorosilane (0.03 ml, 2 mmol) was added and mixture was stirred for 15 min at room temperature. A solution of Bt-derivative **4** (2 mmol) in THF (10 ml) was added, the mixture was heated to reflux, than ethyl bromoacetate (0.668 g, 4 mmol) was added in one portion and the mixture was stirred at reflux under nitrogen for 6 hours, cooled to room temperature, quenched with ice-cold $NH_4OH$ (25%, 15 ml) and stirred until most of the solids were dissolved. The work-up procedure was the same as for method A, to give pure products **6g-i**.

***Method D:*** To a solution of Bt-derivative (2 mmol) in THF (15 ml) benzylzinc bromide, prepared from benzyl bromide (0.684 g, 4 mmol) and Zn powder (0.264 g, 4 mmol) in THF (10 ml), was added. The mixture was stirred and refluxed for 12 hours under nitrogen, cooled to room temperature, quenched with ice-cold $NH_4OH$ (25%, 15 ml) and stirred until most of the solids were dissolved. The work-up procedure was the same as for method A, to give pure products **6j**,**k**.

***N-Methyl-N-(2-phenylethyl)aniline (6a).*** This compound was isolated in 72% yield (eluent: $CHCl_3$); oil; $^1H$ NMR δ 2.85 (t, J = 7.5 Hz, 2H), 2.88 (s, 3H), 3.56 (t, J = 7.5 Hz, 2H), 6.69-6.76 (m, 3H), 7.20-7.36 (m, 7H); $^{13}C$ NMR δ 32.9, 38.4, 54.7, 112.2, 116.2, 126.1, 126.9, 128.5, 128.8, 129.2, 139.8. Anal. Calcd for $C_{15}H_{17}N_1$: C, 85.26; H, 8.11; N, 6.63. Found: C, 84.75; H, 8.37; N, 6.20.

***2-(Phenyl)ethylmorpholine (6b).*** This compound was isolated in 89% yield (eluent: $CHCl_3$); oil; $^1H$ NMR δ 2.50 (t, J = 4.6 Hz, 4H), 2.57 (t, J = 8.9 Hz, 2H), 2.79 (t, J = 8.9 Hz, 2H), 3.72 (t, J = 4.6 Hz, 4H), 7.18-7.35 (m, 5H); $^{13}C$ NMR δ 33.2, 56.6, 60.7, 66.8, 125.9, 128.2, 128.5, 140.0. Anal. Calcd for $C_{12}H_{17}N_1O_1$: C, 75.35; H, 8.96; N, 7.32. Found: C, 74.95; H, 9.32; N, 7.24.

***n-Pentylmorpholine (6c).*** This compound was isolated in 67% yield (eluent: $CHCl_3$); oil; $^1H$ NMR δ 0.90 (t, J = 7.1 Hz, 3H), 0.12-1.34 (m, 4H), 1.45-1.51 (m, 2H), 2. 32 (t, J = 7.7 Hz, 2H), 2.42 (t, J = 4.6 Hz, 4H), 3.72 (t, J = 4.6 Hz, 4H); $^{13}C$ NMR δ 13.9, 22.5, 26.2, 29.6, 53.7, 59.1, 66.9. Anal. Calcd for $C_9H_{19}N_1O_1$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.31; H, 12.61; N, 9.13.

***N-[2-(4-Nitrophen-1-yl)ethyl]morpholine (6d).*** This compound was isolated in 61% yield (eluents: $CHCl_3$ then $CHCl_3$: MeOH 5:1); oil; $^1H$ NMR δ 2.54 (t, J = 4.6 Hz, 4H), 2.65 (t, J = 7.6 Hz, 2H), 2.93 (t, J = 7.6 Hz, 2H), 3.75 (t, J = 4.6 Hz, 4H), 7.38 (d, J = 8.5 Hz, 2H), 8.16 (d, J = 8.5 Hz, 2H); $^{13}C$ NMR δ 33.0, 53.5, 59.7, 66.8, 123.5, 129.5, 146.8, 148.1. Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.36; H, 6.87; N, 12.15.

***(±)-1-(4-Cyanophenyl)-2-(morpholin-1-yl)-3-methylbutane (6e).*** This compound was isolated in 82% yield (eluents: $CHCl_3$ then $CHCl_3$: MeOH 20:1); oil; $^1H$ NMR δ 0.93 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 1.81-1.93 (m, 1H), 2.42-2.62 (m, 5H), 2.68-2.74 (m, 1H), 2.82-2.86 (m, 1H), 3.58 (br s, 4H), 7.32 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H); $^{13}C$ NMR δ 20.5, 21.1, 30.2, 34.3, 50.0, 67.5, 72.2, 109.0, 119.1, 129.9, 131.9, 132.1, 148.1. Anal. Calcd for $C_{16}H_{22}N_2O_1$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.36; H, 8.88; N, 11.18.

***1-(4-Cyanophenyl)-2-(pyrrolidin-1-yl)ethane (6f).*** This compound was isolated in 76% yield (eluents: $CHCl_3$ then $CHCl_3$: MeOH 20:1); oil; $^1H$ NMR δ 1.73-1.87 (m, 4H), 2.47-2.62 (m, 4H), 2.71 (t, J = 8.7 Hz, 2H), 2.86 (t, J = 8.7 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H); $^{13}C$ NMR δ 23.5, 35.9, 54.2, 57.4, 109.9, 119.0, 129.4, 132.1, 146.3. Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.99; H, 7.70; N, 14.08.

***N-[2-(Ethoxycarbonyl)ethyl]morpholine (6g).*** This compound was isolated in 72% yield (eluent: $CHCl_3$); oil; $^1H$ NMR δ 1.26 (t, J = 7.1 Hz, 3H), 2.45-2.49 (m, 6H), 2.69 (t, J = 7.4 Hz, 2H), 3.70 (t, J = 4.7 Hz, 4H), 4.15 (q, J = 7.1 Hz, 2H); $^{13}C$ NMR δ 14.2, 32.1, 53.4, 54.0, 60.4, 66.9, 172.4. HRMS Calcd for $C_9H_{17}N_1O_3$: 187.1208 ($M^+$). Found: 187.1207.

***2-Aza-2-phenyl-5-oxo-6-oxaoctane (6h).*** This compound isolated in 64% yield (eluent: hexane:ethylacetate 5:1); oil; $^1H$ NMR δ 1.26 (t, J = 7.1 Hz, 3H), 2.56 (t, J = 7.4 Hz, 2H), 2.94 (s, 3H), 3.68 (t, J = 7.4 Hz, 4H), 4.13 (q, J = 7.1 Hz, 2H), 6.62-6.76 (m, 3H), 7.24 (t, J = 7.4 Hz, 2H); $^{13}C$ NMR δ 14.17, 31.8, 38.2, 48.6, 60.5, 112.5, 116.7, 129.1, 129.2, 172.5. Anal. Calcd for $C_{12}H_{17}N_1O_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.26; H, 8.09; N, 7.08.

***1-(1,2,3,4-Tetrahydroquinolin-1-yl)-3-oxo-4-oxahexane (6i).*** This compound was isolated in 71% yield (eluent: hexane:ethylacetate 9:1); oil; $^1H$ NMR δ 1.20 (t, J = 7.1 Hz, 3H), 1.88-1.99 (m, 2H), 2.57 (t, J = 7.4 Hz, 2H), 2.73 (t, J = 4.7 Hz, 4H), 3.27 (t, J = 4.7 Hz, 4H), 3.60 (t, J = 7.4 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 6.45-7.09 (m, 4H); $^{13}C$ NMR δ 14.2, 22.2, 28.0, 31.4, 47.1, 49.4, 60.5, 110.5, 116.0, 122.9, 127.1, 129.3, 144.5, 172.4. Anal. Calcd for $C_{14}H_{19}N_1O_2$: C, 72.07; H, 8.21. Found: C, 72.17; H, 8.19.

***N-(2-Phenylethyl)-4-(cyano)aniline (6j).*** This compound was isolated in 56% yield (eluent: $CHCl_3$); oil; $^1H$ NMR δ 2.91 (t, J = 6.9 Hz, 2H), 3.43 (q, J = 6.8 Hz, 2H), 4.25 (br s, 1H), 6.54 (d, J = 8.5 Hz, 2H), 7.19-7.35 (m, 5H), 7.40 (d, J = 8.5 Hz, 2H); $^{13}C$ NMR δ 35.1, 44.2, 112.3, 126.7, 128.7, 133.6, 133.7, 138.4, 151.1. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.58; H, 6.53; N, 12.52.

***N-(2-Phenylethyl)-4-(ethoxycarbonyl)aniline (6k).*** This compound was isolated in 61% yield (eluents: $CHCl_3$ then $CHCl_3$: MeOH 50:1); oil; $^1H$ NMR δ 1.33 (t, J = 7.1 Hz, 3H), 2.89 (t, J = 4.7 Hz, 2H), 3.40 (t, J = 4.7 Hz, 2H), 4.18 (br s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 6.52 (d, J = 8.5 Hz, 2H), 7.17-7.34 (m, 5H), 7.86 (d, J = 8.5 Hz, 2H); $^{13}C$ NMR δ 14.4, 35.2, 44.3, 60.1, 111.5, 126.5, 127.4, 128.6, 128.7, 131.5, 138.7, 151.6, 166.8. HRMS Calcd for $C_{17}H_{19}N_1O_2$: 269.1416 ($M^+$). Found: 269.1413.

***Typical Procedures for the Preparation of Secondary and Tertiary Amides 8.***

***Method A:*** The corresponding halide **5** (4 mmol) was added to a mixture of Zn powder (0.264 g, 4 mmol) and Bt-derivative **7** (2 mmol) in DMF (10 ml). The mixture was stirred and heated at 70-80 °C under nitrogen for 12 hours, cooled to room temperature, then quenched with ice-cold $NH_4OH$ (25%, 15 ml) and stirred until most of the solids were dissolved. Undissolved solids were filtered off, and the filtrate was extracted with $Et_2O$ (3 x 15 ml). The combined organic layers were washed with NaOH (10 ml) and water (3 x 20 ml) before being separated and dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure to give crude

product, which was purified by column chromatography on silica gel using the eluents specified to give pure products **8a,b**.

***Method B:*** Trimethylchlorosilane (0.012 ml, 1 mmol) was added to a suspension of Zn powder (0.132 g, 2 mmol) in THF (10 ml) and the mixture was stirred for 15 min at room temperature. A solution of Bt-derivative (1 mmol) in THF (10 ml) was added. The mixture was heated to reflux, then ethyl bromoacetate (0.334 g, 2 mmol) was added and the mixture stirred at reflux under nitrogen for 8 hours, cooled to room temperature, then quenched with ice-cold $NH_4OH$ (25%, 15 ml) and stirred until most of the solids were dissolved. The work-up procedure was the same as for method A, to give pure product **8c**. In the case of **8d** the crude product was triturated with ethyl acetate/hexane to give pure product.

***Method C:*** *m*-Cyanobenzyl bromide (2 mmol) was added to a suspension of Zn powder (0.132 g, 2 mmol) and Bt-derivative **7c** (1 mmol) in DMF (10 ml). The mixture was stirred at room temperature under nitrogen for 48 hours, than quenched with ice-cold $NH_4OH$ (25%, 15 ml) and stirred until most of the solids were dissolved. The work-up procedure was the same as for method A, to give crude product which was triturated with ethyl acetate/hexane to give pure product **8e**.

***(±)-1-Phenyl-2-phenylcarbamido-3-methybutane (8a).*** This compound was isolated in 68% yield (eluent: $CHCl_3$); white microcrystals; mp = 145-147 °C (lit.[2d] mp = 146-148 °C); $^1$H NMR δ 1.00 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 1.95-2.03 (m, 1H), 4.64 (q, J = 12.0 Hz, 2H), 5.32 (dt , J = 6.3 Hz and 9.6 Hz, 1H), 6.34 (d, J = 9.6 Hz, 1H), 7.26-7.41 (m, 5 H), 7.43-7.60 (m, 3 H), 7.76 (d, J =7.2 Hz, 2H); $^{13}$C NMR δ 17.6, 17.9, 33.5, 70.5, 84.2, 126.8, 126.9, 127.5, 127.7, 128.3, 128.7, 131.8, 167.6.

***(±)-1-Pyrolidin-2-on-1-yl-1,2-diphenylethane (8b).*** This compound was isolated in 74% yield (eluent: $CHCl_3$); white microcrystals; mp = 98-100 °C; $^1$H NMR δ 1.75-1.86 (m, 2H), 2.13-2.33 (m, 2H), 3.01-3.38 (m, 4H), 5.68 (dd, J = 6.3 Hz and 9.9 Hz, 1H), 7.18-7.39 (m, 10 H); $^{13}$C NMR δ 18.0, 31.2, 36.5, 42.9, 54.6, 126.5, 127.6, 128.4, 128.6, 128.7, 137.7, 139.3, 174.6. Anal. Calcd for $C_{18}H_{19}N_1O_1$: C, 81.48; H, 7.22; N, 5.28. Found: C, 81.13; H, 7.40; N, 5.41.

***Ethyl benzamidopropionate (8c).*** This compound was isolated in 76% yield (eluent: $CHCl_3$); oil; $^1$H NMR δ 1.29 (t, J = 7.1 Hz, 3H), 2.66 (t, J = 6.0 Hz, 2H), 3.74 (q, J = 6.0 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 7.41-7.52 (m, 4H), 7.76-7.87 (m, 2H); $^{13}$C NMR δ 14.2, 34.0, 35.3, 60.8, 126.9, 127.2, 128.5, 131.5, 131.9, 167.3, 170.5. Anal. Calcd for $C_{12}H_{15}N_1O_3$: C, 65.14; H, 6.83. Found: C, 64.48; H, 6.71.

***(±)-Ethyl 1-phenyl-1-benzamidopropionate (8d).*** This compound was isolated in 87% yield; white microcrystals; mp = 87-89 °C; $^1$H NMR δ 1.19 (t, J = 7.1 Hz, 3H), 2.91-3.08 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 5.61-5.70 (m, 1H), 7.28-7.87 (m, 11H); $^{13}$C NMR δ 14.0, 39.9, 49.9, 60.9, 126.2, 127.5, 127.0, 127.3, 127.6, 127.9, 128.6, 128.7, 131.5, 131.6, 140.6, 166.5, 171.6. Anal. Calcd for $C_{18}H_{19}N_1O_3$: C, 72.71; H, 6.44. Found: C, 73.07; H, 6.32.

***(±)*-1-(3-Cyanophenyl)-2-phenyl-2-phenylcarbamidoethane (8e).** This compound was isolated in 59% yield; white microcrystals, mp = 176-178 °C; $^1$H NMR δ 3.17-3.24 (m, 1H), 3.35-3.41 (m, 1H), 5.34-5.45 (m, 1H), 6.42 (d, J = 6.4 Hz, 1H), 7.26-7.50 (m, 10 H), 7.69-7.92 (m, 4 H); $^{13}$C NMR δ 42.0, 55.2, 125.9, 126.8, 127.2, 128.1, 128.7, 129.0, 129.2, 131.7, 132.1, 132.9, 168.0. Anal. Calcd for $C_{22}H_{18}N_2O_1$: N, 8.58. Found: N, 8.40.

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