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N-Acylbenzotriazoles: Neutral Acylating Reagents for the Preparation of Primary, Secondary, and Tertiary Amides

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Readily available N-acetylbenzotriazoles 2a–q efficiently acylate aqueous ammonia and primary and secondary amines to give primary, secondary, and tertiary amides in good to excellent yields. The wide applicability of the procedure is illustrated by the preparation of (i) α-hydroxamides from α-hydroxy acids and of (ii) perfluoroalkylated amides.

Introduction

Common routes to primary, secondary, and tertiary amides mostly involve the treatment of activated derivatives of acids, especially acyl halides, acid anhydrides, or esters, with ammonia or primary and secondary amines.1 However, limitations are associated with these methods. Reactions of ammonia or amines with acyl halides are highly exothermic. Acid anhydrides, especially cyclic anhydrides, easily form imides with ammonia and primary amines. Acylations of ammonia, primary and secondary amines by esters frequently require strongly basic catalysts and/or high pressure. Reactions of carboxylic acids themselves with ammonia or amines are seldom of preparative value.2 Other preparations of primary amides include the activation of carboxylic acids using 1-hydroxybenzotriazole (HOBt) and N,N′-dicyclohexylcarbodiimide (DCC)3 or the treatment of carboxylic acids with ammonium chloride, tertiary amine and primary amines. Acylations of ammonia, primary and secondary amines and primary amines with ammonia or primary amines mostly involve the treatment of activated derivatives of acids, especially acyl halides, acid anhydrides, or esters, with ammonia or primary and secondary amines.4 For these last two methods, difficulties can arise from the insolubility of starting materials and products or by competitive hydration of the activated carboxyl group.

As recently documented by Staab, Bauer, and Schröder,5 acyl azolides in general, and N-acylimidazoles in particular, are efficient acylating reagents. They have been widely reacted with ammonia or primary amines to give the corresponding primary amides6 or secondary amides.7 The classical azolide method normally involves two steps (which can, however, be combined in one pot): (i) reaction of the free carboxylic acid at 20 °C with (usually) 1,1′-carbonyldiimidazole (CDI) in a 1:1 molar ratio forms the carboxylic acid imidazole via elimination of CO2 and imidazole; (ii) after CO2 evolution has ceased, an equimolar amount of amine is added. Thus, two molar equivalents of the imidazole moieties are used. Furthermore, relatively few reports were located for reactions of N-acylimidazoles with secondary amines.

N-Acylbenzotriazoles have been previously used as acylating agents: in our group specifically for formylation8a and trifluoroacetylation8b and to provide oxamides9 and by others in isolated applications.9 We now report a simple, mild, and general procedure for the preparation of primary, secondary, and tertiary amides. Carboxylic acids are converted in a one-pot reaction into N-acylbenzotriazoles and subsequently treated with ammonia or primary or secondary amines. This methodology should be particularly applicable to solid-phase syntheses.

Results and Discussion

Preparation of N-Acylbenzotriazoles 2a–q. 1-(Trimethylsilyl)benzotriazole, readily available from benzotriazole and N,N-bis(trimethylsilyl)amine,10 was previously reacted with methanesulfonyl chloride to generate N-(1-methanesulfonyl)benzotriazole (1) in 60% yield.11 We now find that compound 1 is produced in 89% yield by direct treatment of benzotriazole with methanesulfonyl chloride in the presence of pyridine.

N-Acylbenzotriazoles 2a–m with R as aryl groups were readily prepared in 72–92% yields by the previously reported reaction of N-(1-methanesulfonyl)benzotriazole (1) with arene carboxylic acids (Scheme 1). We previously synthesized N-(alkanecarbonyl)- or N-(arylacetyl)-benzotriazoles 2 (R = alkyl, arylmethyl) by the reaction of benzotriazole with alkanecarbonyl chlorides or arylacetyl chlorides in the presence of triethylamine. The benzotriazoles byproducts benzbenzoate with a ratio of 9:1. The use of THF avoided the formation of esters byproducts.

Preparation of Primary Amides 3a–n from N-Acylbenzotriazoles 2 with Ammonia. Direct treatment of N-acylbenzotriazoles 2a–e and 2h–q with excess ammonium hydroxide (30% aqueous solution) in EtOH/THF (1:1) at room temperature for 2–4 h gave crude products, which were recrystallized from benzene to afford pure primary amides 3a–n (Scheme 1). The yields and melting points, as well as the literature melting points, for the primary amides 3a–n are summarized in Table 2; melting points and spectra of the products are in accord with literature data. The benzotriazole byproduct (BTH, pKa = 8.21) formed in these reactions dissolved in the excess aqueous ammonia solution.

Preparation of Secondary Amides 4a–j from N-Acylbenzotriazoles 2 with Primary Amines. Treatment of N-acylbenzotriazoles 2 with 1 equiv of primary amines in THF at room temperature for 4 h furnished the corresponding secondary amides 4a–j in 70–100% yields (Scheme 1 and Table 3). After dilution of the concentrated residue in ethyl acetate, byproduct benzotriazole was easily washed away by a 2 M NaOH aqueous solution, and simple removal of EtOAc in vacuo gave secondary amides 4a–j, which were recrystallized from appropriate solvents to afford pure products. The primary amines used include arylamines (phenyl, 4-nitrophenyl) and alkylamines (n-butyl, cyclohexyl, sec-butyl, and tert-butyl).

Preparation of Tertiary Amides 5a–k from N-Acylbenzotriazoles 2 with Secondary Amines. When 1H-1,2,3-benzotriazol-1-yl(4-chlorophenyl)methanone was reacted with tetrahydro-1H-pyrrole at room temperature in EtOH, the crude ^4^H NMR spectrum showed that the isolated product was a mixture of (4-chlorophenyl)-(tetrahydro-1H-pyrrol-1-yl)methanone and ethyl 4-chlorobenzoate with a ratio of 9:1. The use of THF avoided the formation of esters byproducts.

Treatment of N-acylbenzotriazoles 2 with 1 equiv of secondary amines in THF at room temperature produced the corresponding tertiary amides 5a and 5d–k in good to excellent yields (Scheme 1 and Table 4). However,
When using N-ethyl-N-(1-methyl)ethylamine or N,N,N-bis-(1-methyl)ethylamine as a secondary amine, no desired N-ethyl-4-methyl-N-(1-methyl)ethyl)- or 4-methyl-N,N-bis(1-methyl)ethyl)benzamide (5b or 5c) was isolated, probably due to the heavily hindered nitrogen. Reaction of less hindered N,N-diethyl diazoline with 1H-1,2,3-benzotriazol-1-yl(4-methylphenyl)methanone (2g) produced N,N-diethyl-4-methylbenzamide (5a) in moderate yield (44%). A moderate yield (51%) was also obtained for N,N-diethylfuran-2-amine (5g) from N,N-diethylamine. These results show that the cyclic aliphatic amines, e.g., tetrahydro-1H-pyrrrole, produce the secondary amides in much better yields than the acyclic aliphatic amines, e.g., N,N-diethylamine.

**Preparation of α-Hydroxamides Using BtSO2CH3**

Development of synthetic methods for α-hydroxamides has attracted considerable interest, since they include valuable therapeutic agents and also possess synthetic utility. General routes to α-hydroxamides include: (i) the reduction of α-keto-amides with sodium borohydride,22 with other metal borohydrides, such as LiBEt3H, KEt2H, and Zn(BH4)2 or with magnesium- or titanium-based reagents;24 (ii) the hydrogenation of α-keto-amides in the presence of palladium on charcoal25 or neutral reaction condition is useful for ammoniation and subsequent reactions without separation, and indeed the reaction of benzotriazole with trifluoroacetic anhydride ([CF3CO]2O); thus, trifluoroacetic acid was formed as a byproduct. The analogous preparation of perfluoroacylbenzotriazoles, e.g., 1-(1H,1,2,3-benzotriazol-1-yl)-2,2,3,3,4,4-heptafluorobutan-1-one (8) and its perfluorocarboxylic acids to α-hydroxamides is their reaction with N-sulfynilamines (RNSO).28

After reaction of BtSO2CH3 with 2-hydroxy-2-phenylacetic acid (6) in the presence of triethylamine, we failed to isolate the corresponding α-hydroxy-N-acetylbenzotriazoles probably due to their unstability. However, when 1 equiv of aniline- or 4-methylaniline was added into the mixture obtained with refluxing 6, BtSO2CH3, and Et3N in dry THF for about 20 min, α-hydroxamides 7a and 7b were obtained in 68% and 72% yields, respectively (Scheme 2). Products 7a and 7b were not formed in the absence of BtSO2CH3. When n-butylamine or pyrrolidine was used as the amine reactant, no desired products were obtained. The role of BtSO2CH3 is as with other reactions.

**Preparation of 1-(1H,1,2,3-Benzotriazol-1-yl)-2,2,3,3,4,4-heptafluorobutan-1-one (8) and Its Perfluoroacylation with Primary and Secondary Amines**

In 1997, we reported (trifluoroacetyl)benzotriazole as a convenient trifluoroacylating agent for amines and alcohols,8b (Trifluoroacetyl)benzotriazole was prepared by the reaction of benzotriazole with trifluoroacetic anhydride ([CF3CO]2O); thus, trifluoroacetic acid was formed as a byproduct. The analogous preparation of perfluoroacylbenzotriazoles, e.g., 1-(1H,1,2,3-benzotriazol-1-yl)-2,2,3,3,4,4-heptafluorobutan-1-one (8) from (NF-CF3-CO)2O, means that half of the carbon–fluorine moiey is not utilized.

No reaction occurred between BtSO2CH3 and N-CF3-COOH in the presence of Et3N. However, reaction of 1-(trimethylsilyl)benzotriazole (BtTMS) with 1 equiv of 2,2,3,3,4,4,4-heptafluorobutan-1-one chloride (n-CF3-COCl) gave 8 in 86% yield (NMR yield) as a sole Bt1 isomer, together with byproduct BtH, due to the easy hydrolysis of BtTMS. The 1H NMR spectrum of the mixture showed the molar ratio of 8 to BtH is about 6:1. Attempts to obtain pure 8 by washing with aqueous sodium hydroxide solution to remove BtH failed because of rapid hydrolysis of 8. Compound 8 cannot be separated from BtH by column chromatography, as they have almost identical Rf values. Nevertheless, the presence of BtH should not affect the perfluoroacylation of amines with n-CF3-CObt (8), which will also generate benzotriazole as a byproduct. Therefore, the mixture of 8 and BtH was used for the subsequent reactions without separation, and indeed treatment of primary and secondary amines with 8 readily produced the perfluoroalkylated amides 9a–d in good yields (Scheme 2).

In summary, a simple and efficient method for the preparation of primary, secondary and tertiary amides has been developed by the treatment of N-acylbenzotriazoles with primary, secondary and primary amines, respectively. Advantages of this procedure include: (1) neutral reaction condition is useful for ammoniation and amination of compounds possessing acidic or base-sensi-

### Table 4. Preparation of Tertiary Amines 5a–k

<table>
<thead>
<tr>
<th>R</th>
<th>R2</th>
<th>R3</th>
<th>yield (%)</th>
<th>mp (°C)</th>
<th>lit. mp (°C)</th>
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<td>4-CH2C6H4</td>
<td>C6H5</td>
<td>44</td>
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<tr>
<td>b</td>
<td>4-CH2C6H4</td>
<td>i-Pr</td>
<td>80</td>
<td>oil</td>
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<tr>
<td>c</td>
<td>4-CH2C6H4</td>
<td>i-Pr</td>
<td>80</td>
<td>oil</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>4-CN(CH2)4</td>
<td>i-Pr</td>
<td>96</td>
<td>73–74</td>
<td>b</td>
</tr>
<tr>
<td>e</td>
<td>C6H5</td>
<td>i-Pr</td>
<td>100</td>
<td>oil</td>
<td>al19</td>
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<tr>
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<td>i-Pr</td>
<td>98</td>
<td>oil</td>
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</tr>
<tr>
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<tr>
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<td>51–52</td>
<td>b</td>
</tr>
<tr>
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<td>C6H5</td>
<td>100</td>
<td>oil</td>
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</tr>
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<td>114–116</td>
<td>b</td>
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organic layers were dried over anhydrous MgSO₄. Evaporation of the solvent gave a solid, which was recrystallized from benzene to afford the pure primary amide 3a–n. The isolated yields, melting points, and reported melting points of 3a–n are summarized in Table 2.

**General Procedure for the Reaction of N-Acylbenzotriazoles 2 with Primary Amines.** The N-acylbenzotriazole 2 (1 mmol) was stirred with the appropriate primary amine (1 mmol) in THF (10 mL) at room temperature for 4 h. After evaporation of solvents in vacuo, the residue was added to 2 M NaOH (20 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO₄. Evaporation of the solvent gave a secondary amine 4a–j, which was recrystallized from appropriate solvents.

**General Procedure for the Reaction of N-Acylbenzotriazoles 2 with Secondary Amines.** The same procedure as the preparation of the secondary amines 4 afforded pure tertiary amines 5a–k.

**General Procedure for the Preparation of α-Hydroxyamides.** A mixture of BtSO₂CH₃ (0.49 g, 2.5 mmol), 2-hydroxy-2-phenylacetic acid (0.38 g, 2.5 mmol), and Et₂N (0.35 g, 3.5 mmol) was refluxed in dry THF for about 20 min, and then an appropriate amine (2.5 mmol) was added and the mixture was refluxed for 18 h. After the mixture was concentrated, EtOAc (50 mL) was added, and the organic phase was washed with 2 M NaOH and dried over anhyd MgSO₄. Removal of the solvent gave a solid, which was recrystallized from CHCl₃ to furnish the α-hydroxyamide 7a–b.

2-Hydroxy-N,N-diphenylacetamide (7a): yield 68% colorless flakes; mp 143–144 °C (lit.28 mp 150–151 °C); 1H NMR δ 8.98 (br s, 1H), 7.59–7.51 (m, 2H), 7.49–7.40 (m, 2H), 7.40–7.20 (m, 5H), 7.07 (t, J = 7.4 Hz, 1H), 6.07 (br s, 1H), 5.13 (s, 1H); 13C NMR δ 170.5 (C₁O), 139.7, 137.2, 128.4, 127.9, 127.6, 126.3, 123.7, 119.2, 73.8. Anal. Calcd for C₁₂H₁₀NO: C, 79.99; H, 5.77; N, 11.6. Found: C, 79.72; H, 5.91; N, 11.4.

2-Hydroxy-N-(4-methylphenyl)-2-phenylacetamide (7b): yield 72% colorless flakes; mp 169–170 °C (lit.28 mp 170–172 °C); 1H NMR δ 9.02 (br s, 1H), 7.53–7.45 (m, 4H), 7.37–7.24 (m, 1H), 7.33 (d, J = 7.5 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 6.11 (d, J = 4.4 Hz, 1H), 5.14 (d, J = 4.2 Hz, 1H), 2.29 (s, 3H); 13C NMR δ 170.2 (C₁O), 139.9, 134.7, 133.1, 128.8, 127.8, 127.5, 126.3, 119.1, 73.7, 20.3. Anal. Calcd for C₁₃H₁₂NO: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.43; H, 6.07; N, 5.77.

Preparation of 1-1H-1,2,3-Benzotriazol-1-yl)-2,2,3,3,4,4,4-heptafluorobutan-1-one (8). To a solution of BTMS (1.9 g, 10 mmol) in dry THF (20 mL) under argon was added dropwise n-C₇F₇COCl (10 mmol) in toluene (30 mL). The mixture was then stirred overnight at room temperature. ACOEt (150 mL) and H₂O (100 mL) were added. The organic layer was separated, successively washed with water and brine, and dried over anhydrous MgSO₄. Removal of solvents in vacuo gave a solid, which was recrystallized from benzene to afford N-(1-methanesulfonyl)benzotriazole (1) (1.97 g, 89%) as colorless needles: mp 110–112 °C (mp11,29 110–112 °C).

**General Procedure for the Preparation of N-Acylbenzotriazoles 2.** A mixture of aromatic or aliphatic (10.0 mmol) and 1-(methylsulfonyl)benzotriazole 1 (1.97 g, 10.0 mmol) and triethylamine (2.0 mL, 14.0 mmol) were refluxed in THF (50 mL) overnight. The solvent was evaporated and the residue was dissolved in chloroform (100 mL). The organic layer was washed with water, dried over anhydrous MgSO₄, and evaporated to give a crude product, which was recrystallized from an appropriate solvent to give pure N-(arylacarbonyl)- or N-(alkancarbonyl)benzotriazole 2a–q.

1H-1,2,3-Benzotriazol-1-yl(2-hydroxyphenyl)methanone (2b): yield 72% colorless flakes (recrystallized from ethanol); mp 96–97 °C; 1H NMR δ 8.38 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.63–7.50 (m, 3H), 7.14–7.05 (m, 2H), 3.77 (s, 3H); 13C NMR δ 166.9 (C₁O), 157.8, 146.0, 133.5, 131.4, 130.2, 130.1, 126.1, 122.6, 120.4, 120.0, 114.4, 111.7, 55.7 (CH₃). Anal. Calcd for C₁₀H₇NO: C, 66.88; H, 4.38; N, 16.60. Found: C, 66.53; H, 4.41; N, 16.66.

1H-1,2,3-Benzotriazol-1-yl(2-hydroxyphenyl)methanone (2c): yield 74% colorless needles (recrystallized from chloroform/hexane); mp 120–121 °C; 1H NMR δ 8.38 (d, J = 8.4 Hz, 1H), 8.20–8.11 (m, 3H), 7.75–7.65 (m, 2H), 7.60–7.53 (m, 2H); 13C NMR δ 165.3 (C₁O), 145.7, 134.6, 133.6, 133.1, 132.1, 131.5, 130.6, 129.8, 129.7, 126.6, 120.3, 114.7. Anal. Calcd for C₁₀H₈ClNO: C, 60.60; H, 3.13; N, 16.31. Found: C, 60.75; H, 3.01; N, 16.38.

**General Procedure for the Reaction of N-Acylbenzotriazoles 2 with Aqueous Ammonia.** The N-acylbenzotriazole 2 (2.5 mmol) was stirred with ammonium hydroxide (30% aqueous solution, 5 mL, 43 mmol) in EtOH (5 mL) and THF (5 mL) at room temperature for 2–4 h. After evaporation of solvents in vacuo, 2 M NaOH (20 mL) was added to the residue and the mixture was extracted with EtOAc. The combined

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Supporting Information Available: 1H and 13C NMR spectra data and CHN analyses or HRMS for compounds 2d–f, 1d–n, 4c–f, 5d, f, h, i, k, and 9a–d. This material is available free of charge via the Internet at http://pubs.acs.org.