An efficient conversion of carboxylic acids into Weinreb amides

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Dedicated to our good friend Mimmo Spinelli

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Abstract
Efficient conversions of carboxylic acids into Weinreb amides were achieved by treatment of *N*-acylbenzotriazoles **2a–i** with *N*,*O*-dimethylhydroxylamine hydrochloride under mild conditions. No racemization was found when optically active acids were employed.

Keywords: Weinreb amides, *N*-acylbenzotriazoles

Introduction

Recently, increasing attention has been paid to *N*-methoxy-*N*-methylamides (Weinreb amides) owing to their versatile reactivity with nucleophiles and selective reduction to aldehydes.[1] Weinreb amides derived from amino acids have found extensive use in the preparation of α-amino aldehydes[2] and α-amino ketones.[3]

Most direct conversions of carboxylic acids into the corresponding Weinreb amides have utilized peptide-coupling reagents such as benzotriazol-1-yl-*N*-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP) [4] *N*,*N*'-dicyclohexylcarbodiimide (DCC) [5] or propylphosphonic anhydride/*N*-ethylmorpholine.[6] Other reagents such as carbon tetrabromide/triphenylphosphine,[7] 2-chloro-1-methylpyridinium iodide (CMPI) and/or 2-bromide-1-methylpyridinium iodide (BMPI),[8] and [bis-(2-methoxyethyl)-aminosulfur trifluoride (deoxo-fluor reagent)[9] have also been used as coupling reagents in the preparation of *N*-methoxy-*N*-methylamides and involve *in situ* formation of the acyl halide. More recently, 2-mercaptopyridone-1-oxide-based thiouronium salts have been reported as effective coupling reagents for the synthesis of Weinreb amides from carboxylic acids.[10]

Acylbenzotriazoles are neutral acylating reagents.[11] Recently, our group has demonstrated advantageous methods for the preparation of acylbenzotriazoles from carboxylate anions and used the acylbenzotriazoles for the preparation of primary, secondary and tertiary amides,[12] and

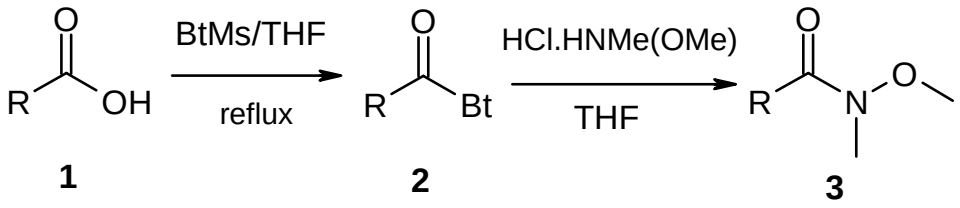
cinnamoyl hydrazides.[13] *N*-Formyl-,[14a] or *N*-trifluoroacetyl-benzotriazole,[14b] and 1,1'-(1,2-dioxoethane-1,2-diyl)bis-1*H*-bis-benzotriazole[14c] have been used advantageously for acylation. Very recently we have demonstrated that α-(Boc-amino) acids can be converted into stable chiral α-aminoacylating agents.[14d] We now report an efficient procedure for direct conversion of carboxylic acids into the corresponding Weinreb amides, with no racemization when optically active acids are employed.

Results and Discussion

The acylbenzotriazoles **2a–i** were readily prepared in 65–91% yields from the carboxylic acids **1a–i** by reaction with BtMs by a previously reported procedure[14]. Reactions of the *N*-acylbenzotriazoles **2a–i** with *N*,*O*-dimethylhydroxylamine hydrochloride in THF in the presence of a base at reflux afforded the corresponding Weinreb amides **3a–i** in 73–97% yields (Scheme 1, Table 1). The benzotriazole by-product formed in the reaction can easily be removed and recovered by washing with saturated Na_2CO_3. The product isolation can be carried out by column chromatography or recrystallization.

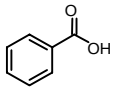
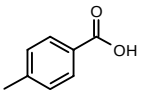
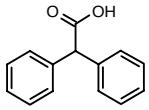
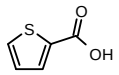
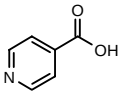
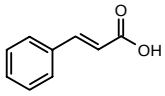
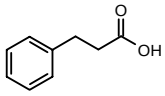
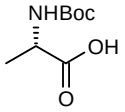
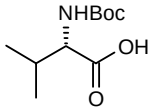
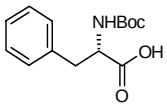
This methodology is applicable to a variety of carboxylic acids with sensitive functional groups. For example, *N*-protected amino acid amides can be prepared readily from the corresponding amino acids (entries **h–j**). These reactions proceed without detectable racemization of the chiral center, as evidenced by comparison with literature optical rotation values.[9]

In conclusion, we have developed a practical and convenient method for the synthesis of various Weinreb amides from the corresponding carboxylic acids without detectable racemization when chiral substrates are employed using benzotriazole methodology. The simplicity, easy operation, mild reaction conditions, and low cost are advantageous. The use of the previously mentioned peptide coupling reagents also gives high yields with retention of chirality in optically active substrates; however, difficult-to-remove by-products, toxic co-products (*e.g.*, hexamethylphosphoramide for the BOP reagent), or the high cost of scale-up, can be disadvantageous.



Scheme 1

Table 1. Yields of the *N*-acylbenzotriazoles **2** and Weinreb amides **3**

Entry	Acid **1**	**2** (Yield, %)			**3** (Yield, %)		
		PW	LW	Ref.	PW	LW	Ref.
a		89	89	12	78	80	8
b		91	91	12	74	91	17
c		89	89	12	73	95	16
d	 	96	89	15	82	76	9
e		93	84	12	77	/	/
f		94	90	13	89	76	8
g		98	84	12	83	86	9
h		65	/	/	80	75	8
i		83	/	/	71	99	18
j		81	/	/	75	89	9

* PW, Present Work; LW, Literature Work

Experimental Section

General Procedures. Melting points were determined on a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) and the solvent for ^{13}C (75 MHz) NMR. THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under argon atmosphere. Column chromatography was conducted on silica gel (230–400 mesh). For the preparation and characterization of *N*-acylbenzotriazoles **2a–g** see the literature.[12,13,15]

Typical procedure for the preparation of N-acylbenzotriazoles 2a–i

To a solution of the acid **1** (10mmol) in THF (10 mL), BtMs (11 mmol) and Et_3N (11mmol) were added at room temperature. The reaction mixture was refluxed 6–12 h. The solvent was removed *in vacuo* to dryness. The residue was dissolved in ethyl acetate and washed sequentially with satd. citric acid, satd. Na_2CO_3 and H_2O, and dried over $MgSO_4$. Concentration under reduced pressure gave the desired product, which was recrystallized from hexane–ethyl acetate.

***L-tert*-Butyl-*N*-[2-(benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (2h).** Needles from hexane–ethyl acetate (61%), m.p. 68–69 ^oC, $[\alpha]^D_{25}$= –17.7^o ($CHCl_3$); ^1H NMR δ 8.27 (d, *J* = 8.1 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.67 (dd, *J* = 7.5, 7.6 Hz, 1H), 7.52 (dd, *J* =7.5, 7.6 Hz, 1H), 5.74 (m, 1H), 5.36 (brs, 1H), 1.66 (d, *J* = 7.2 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR δ 172.7, 155.1, 146.0, 131.2, 130.6, 126.4, 120.3, 114.4, 80.3, 50.1, 28.2, 18.8. Anal. Calcd for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.25; N, 19.30. Found: C, 58.06; H, 6.44; N, 19.30.

***L-tert*-Butyl-*N*-[1-(1*H*-benzotriazol-1-ylcarbonyl)-2-methylpropyl]carbamate (2i)**. Prisms from hexane–ethyl acetate (83%), m.p. 120–121 ^oC, $[\alpha]^D_{25}$= –47.5^o (CH_3OH); ^1H NMR δ 8.28 (d, *J* = 8.1 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.68 (dd, *J* = 7.4, 7.3 Hz, 1H), 7.54 (dd, *J* =7.4, 7.5 Hz, 1H), 5.70–5.66 (m, 1H), 5.33 (d, *J* = 8.4 Hz, 1H), 2.47–2.17 (m, 1H), 1.46 (s, 9H), 1.11 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR δ 171.9, 155.6, 145.9,130.9, 130.5, 126.3, 120.2, 114.3, 80.1, 58.9, 31.4, 28.2, 19.6, 16.9. Anal. Calcd for $C_{16}H_{22}N_4O_3$: C, 60.36; H, 6.96; N, 17.60. Found: C, 60.56; H, 7.13; N, 17.72.

***L-tert*-Butyl- *N*-[2-(1*H*-benzotriazol-1-yl)-1-benzyl-2-oxoethyl]carbamate (2j).** White solid from hexane–ethyl acetate (81%), m.p. 143.5–144.5 ^oC; ^1H NMR δ 8.26 (d, *J* = 7.8 Hz, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 7.68 (dd, *J* = 6.9, 7.8 Hz, 1H), 7.55 (dd, *J* = 7.5, 7.8 Hz, 1H), 7.28–7.18 (m, 5H), 6.03 (brs, 1H), 5.28 (brs, 1H), 3.48–3.30 (m, 1H), 3.22–3.09 (m, 1H), 1.41 (s, 9H). ^{13}C NMR δ 171.5, 155.3, 146.2, 135.5, 131.3, 131.2, 130.9, 129.5, 128.9, 127.5, 126.7, 120.6, 114.6, 80.6, 55.5, 39.1, 28.4. Anal. Calcd for $C_{20}H_{22}N_4O_3$: C, 65.56; H, 6.05; N, 15.29. Found: C, 65.68; H, 6.38; N, 14.90.

Typical procedure for the preparation of Weinreb amides 3a–i

To a solution of *N*-acylbenzotriazole **2** (2 mmol) in dry THF (10 mL), a solution of *N*,*O*-dimethylhydroxylamine in THF (prepared from 2.2 mmol of *N*,*O*-dimethylhydroxylamine

hydrochloride, and 2.2 mmol of triethylamine in 5 mL of dry THF was added at 20 °C over 5 min. The reaction mixture was stirred at r.t. for 24 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc. The organic layer was washed sequentially with saturated citric acid, satd. Na_2CO_3, H_2O, and dried over $MgSO_4$. Evaporation *in vacuo* to dryness gave the desired products, which were recrystallized from the appropriate solvent.

***N*-Methoxy-*N*-methylbenzamide (3a).** Colorless oil [8] (78%); 1H NMR δ 7.67 (d, *J* = 6.6 Hz, 2H), 7.41 (m, 3H), 3.56 (s, 1H), 3.37 (s, 1H); ^{13}C NMR δ 170.2, 134.2, 130.8, 128.3, 128.2, 61.2, 34.0.

***N*-Methoxy-4,*N*-dimethylbenzamide (3b).** Colorless oil [9] (74%); ^{1}H NMR δ 7.60 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 3.56 (s, 3H), 3.35 (s, 3H), 2.39 (s. 3H); ^{13}C NMR δ 170.2, 141.1, 131.3, 128.9, 128.5, 61.2, 34.1, 21.7.

***N*-Methoxy-*N*-methyl-2,2-diphenyl-acetamide (3c).** White crystals (73%), m.p. 106–107 °C (lit.[16] 108–108.5.5 °C); ^{1}H NMR δ 7.32–7.20 (m, 10H), 5.54 (s, 1H), 3.49 (s, 3H), 3.23 (s, 3H); ^{13}C NMR δ 173.1, 139.4, 128.9, 128.4, 126.9, 61.4, 52.8, 32.3.

***N*-Methoxy-*N*-methyl-2-thiophenecarboxamide (3d).** Colorless oil [9] (82%); ^{1}H NMR δ 7.97 (dd, *J* = 1.1, 3.8 Hz, 1H), 7.56 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.11 (dd, *J* = 4.8, 4.0 Hz, 1H), 3.78 (s, 3H), 3.38 (s, 3H); ^{13}C NMR δ 162.4, 134.6, 133.4, 132.4, 127.0, 61.7, 33.2.

***N*-Methoxy-*N*-methylisonicotinamide (3e)**. Colorless oil (77%); ^{1}H NMR δ 8.72 (d, *J* = 6 Hz, 2H), 7.55 (d, *J* = 6 Hz, 2H), 3.55 (s, 3H), 3.37 (s, 3H); ^{13}C NMR δ 173.6, 167.1, 149.4, 141.6, 125.2, 121.8, 61.1, 32.8.

(*E*)-*N*-Methoxy-*N*-methyl-3-phenyl-2-propenamide (3f). Colorless oil [7] (89%); ^{1}H NMR δ 7.75 (d, *J* = 15.6 Hz, 1H), 7.58 (d, *J* = 3.9 Hz, 1H), 7.56 (d, *J* = 1.8 Hz, 1H), 7.39 (m, 3H), 7.05 (d, *J* = 15.9 Hz, 1H), 3.77 (s, 1H), 3.32 (s, 1H); ^{13}C NMR δ 167.0, 143.5, 135.1, 129.8, 128.8, 128.0, 115.7, 61.9, 32.5.

***N*-Methoxy-*N*-methyl-3-phenylpropionamide (3g).** Colorless oil [17] (83%); ^{1}H NMR δ 7.32–7.17 (m, 5H), 3.60 (s, 3H), 3.18 (s, 3H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR δ 173.5, 141.2, 128.3, 128.3, 125.9, 61.0, 33.6, 32.0, 30.5.

***tert*-Butyl *N*-((1*S*)-2-[methoxy(methyl)amino]-1-methyl-2-oxoethyl) carbamate (3h).** White crystals (71%), α^{D}_{25}= -27.8 (c=1, methanol) m.p.[9] 145–146 °C; ^{1}H NMR δ 5.26 (d, *J* = 7.8 Hz, 1H), 4.68 (m, 1H), 3.77 (s, 3H), 3.21 (s, 3H), 1.44 (s, 9H), 1.31 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR δ 173.7, 155.2, 79.5, 61.6, 46.5, 32.1, 28.3, 18.6.

***tert*-Butyl *N*-((1*S*)-1-[methoxy(methyl)amino]carbonyl-2-methylpropyl)carbamate (3i).** Oil [18] (71%); α^{D}_{25}= –13.6 (c=2.5, methanol) ^{1}H NMR δ 5.14 (d, *J* = 8.7 Hz, 1H), 4.56 (brs, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 1.85 (m, 1H), 1.43 (s, 9H), 0.94 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H). ^{13}C NMR δ 172.9, 155.8, 79.4, 61.5, 54.9, 31.9, 31.3, 28.3, 19.4, 17.4.

***tert*-Butyl *N*-{(1*S*)-1-benzyl-2-[methoxy(methyl)amino]-2-oxoethyl}carbamate (3j).** Yellow crystals (75%), m.p. 135–135.5 °C [18]; ^{1}H NMR δ 7.30–7.16 (m, 5H), 5.23 (d, *J* = 7.5 Hz, 1H), 4.96 (m, 1H), 3.66 (s, 3H), 3.17 (s, 3H), 3.06 (dd, *J* = 6.0, 13.5 Hz, 1H), 2.88 (dd, *J* = 7.2, 13.2 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR δ 172.3, 155.2, 136.5, 129.4, 128.3, 126.7, 125.6, 79.6, 61.5, 51.5, 38.8, 32.1, 28.3.

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