Synthesis of mono- and *N*,*N*-disubstituted ureas

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Dedicated to Prof. Keiichiro Fukumoto on his 70th anniversary
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Abstract
Benzotriazole-1-carboxamide is a new efficient reagent for the preparation of mono- and *N*,*N*-disubstituted ureas. The title ureas **3** were obtained from benzotriazole-1-carboxamide with primary and secondary aliphatic amines and *p*-anisidine under mild conditions with simple purification in isolated yields of 61–96%. The procedure developed is suitable for solid-phase work.
Keywords: Urea, preparation, benzotriazole, substitution, solid-phase synthesis

Introduction

The urea functionality is a key structural element of many biologically active compounds such as enzyme inhibitors[1] and peptidomimetics.[2] Some compounds containing the urea functionality possess neuroprotective activity,[3] are tachykinin NK_3 selective antagonists,[4,5] show significant activity as neuropeptide Y1-selective receptor antagonist,[6] and have many other applications.

Recently, there have been extensive investigations into synthetic approaches to solid-supported ureas for the preparation of libraries of compounds with potential biological activities.[7] However, no reports of solid-phase work have described the preparation of mono- or *N*,*N*-disubstituted ureas.

Preparative routes to urea derivatives have been summarized.[8] Mono- or *N*,*N*-disubstituted ureas have been prepared, (i), by the reaction of unsubstituted urea with alkylamines or their hydrochloride salts, with the loss of ammonia or ammonium halide, to yield the expected substituted ureas, which in some cases may be contaminated with *N*,*N*′-disubstituted derivatives;[8,9] (ii), by aminolysis of isonitriles[10] or cyanamides;[11] (iii), by conversion of nitrourea into substituted ureas by the action of amines;[12] (iv), from the reaction of alkali metal cyanates with amines to form ureas;[13] and, (v), by reductive alkylation by which substituents may be introduced into ureas.[8,14] The above-mentioned methods usually provide moderate to good yields

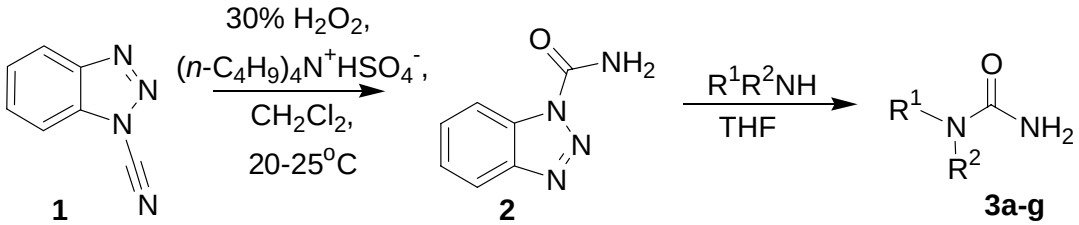
of the desired products; however, the toxic reagents and relatively harsh conditions required renders them unsuitable, in particular, for solid-phase work. Therefore, practical methods of obtaining urea-containing compounds are of great interest in the lead-optimization process of drug discovery. We now report on benzotriazole-1-carboxamide as a new convenient reagent for the preparation of mono- and *N,N*-disubstituted ureas.

Results and Discussion

The key compound, benzotriazole-1-carboxylic acid amide **2** was prepared by hydrolysis of 1-cyano-benzotriazole **1** with hydrogen peroxide. The 1-cyanobenzotriazole **1** was prepared by a previously published procedure.[15] Attempts to hydrolyze 1-cyanobenzotriazole **1** using, (i), hydrogen peroxide in DMSO in the presence of a catalytic amount of potassium carbonate,[16] or (ii), hydrogen peroxide in CH_2Cl_2 in the presence of a solution of 20% sodium hydroxide with tetrabutylammonium sulfate as a phase-transfer catalyst,[17] failed. The conditions that were found appropriate for the conversion of cyanobenzotriazole **1** into the desired compound **2** are as follows: hydrogen peroxide, CH_2Cl_2, room temperature, and tetrabutylammonium hydrogen sulfate as a catalyst (Scheme 1).

Reaction of compound **2** with an appropriate amine gave the desired mono- or *N,N*-disubstituted ureas **3** (Scheme 1, Table 1). Alkyl- and dialkyl amines gave the desired ureas **3b–g** in 88–96% yield. The reactions were performed at room temperature for 12–16h. Purification of the final ureas is simple: the reaction mixture was merely treated with dry potassium carbonate in order to remove benzotriazole. The pure ureas were obtained after filtration, evaporation of solvent, and recrystallization. Reactions of **2** succeeded with the hindered diisopropylamine, and the desired *N,N*-di-isopropylurea **3g** was obtained in 91% yield under the same mild conditions.

Attempts to prepare arylureas failed, except for 4-methoxyaniline which gave the desired 4-methoxyphenylurea **3a** in 61% yield. Its participation in the reaction is possibly due to the presence of a strong electron-donating group, which increases the nucleophilicity of 4-anisidine; the preparation of **3a** required two moles of compound **2**. In this case, equimolar amounts of anisidine and benzotriazole-1-carboxylic acid amide **2** were mixed together in dry THF and allowed to react under reflux overnight; but only after a second equivalent of **2** had been added did the anisidine completely react (TLC control). Addition of a base decomposes the excess of **2** and removes benzotriazole from the reaction mixture. Pure compound **3a** was obtained after evaporation of solvent and recrystallization.

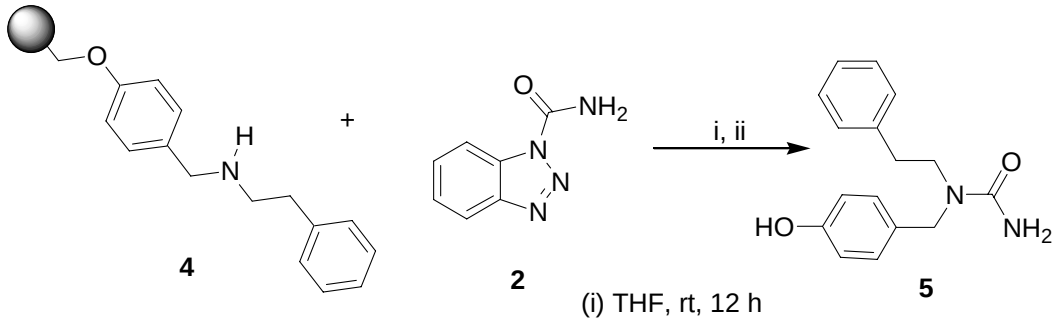


Scheme 1

Table 1. Preparation of mono- or *N*,*N*-disubstituted ureas **3a–g**

Entry	R^1	R^2	Yield, %
3a	$MeOC_6H_4$-	H-	61
3b	$C_6H_5CH_2$-	H-	93
3c	$C_6H_5CH_2CH_2$-	H-	88
3d	C_5H_{11}-	H-	88
3e	C_4H_9-	C_4H_9-	94
3f	$C_6H_5CH_2$-	$C_6H_5CH_2$-	96
3g	$(CH_3)_2CH$-	$(CH_3)_2CH$-	91

We have extended the use of benzotriazole-1-carboxylic acid amide **2** to the solid-phase preparation of substituted ureas. Wang's resin-linked secondary amine **4**, prepared according to a published procedure,[18] was reacted with benzotriazole-1-carboxylic acid amide **2** for 12h. Analysis of the residue obtained after the cleavage showed the formation of the urea **5** (Scheme 2, Figures 1, 2, see Supplemental Materials). Compound **5** was obtained in 63% yield after the purification by column chromatography on silica. Longer reaction time (24 h) decreased the yield of desired compound **5** to 30%.



Scheme 2

Conclusions

Mono- and *N*,*N*-disubstituted ureas **3a–g** were obtained in 61–96% yields from benzotriazole-1-carboxylic acid amide **2** in the reaction with primary and secondary aliphatic amines and *p*-anisidine. The desired ureas **3a–g** were obtained under mild conditions with simple purification. The procedure developed is suitable for solid-phase work.

Experimental Section

General Procedures. Melting points were determined using a Fluka 51 capillary melting point apparatus equipped with a digital thermometer. ^{1}H- and ^{13}C- NMR spectra were recorded on a Gemini 300 MHz NMR spectrometer (300- and 75 MHz, respectively). Tetrahydrofuran (THF) was distilled from sodium/benzophenone under nitrogen immediately before use. Column chromatography was conducted with silica gel, grade 230–400 mesh (for compound **5**). All other reagents were of reagent grade and were used without purification.

1-Cyano-1*H*-benzotriazole (1). Benzotriazole (5.96 g, 50 mmol) was dissolved in dry THF (100 ml) with stirring. Sodium hydride (60% in mineral oil, 2.20 g, 55 mmol) was added to the solution at 0–5 °C. The mixture was allowed to react at the same temperature for 30 min. A solution of cyanogen bromide (5.82 g, 55 mmol) in dry THF (25 ml) was added rapidly to this vigorously stirred solution of sodium benzotriazole, and was allowed to react at ambient temperature for an additional 1.5 h. The precipitate obtained was filtered off and washed with THF. Evaporation of THF from the filtrate afforded a solid which was sublimed on Kugelrohr apparatus (200–250 °C, 0.1mm/Hg) to give the desired product as off-white microcrystals (6.45 g, 90%), m.p. 74–76°C (lit. m.p.[15] 74–76 °C); ^{1}H NMR ($CDCl_3$) δ 7.58–7.68 (m, 1H), 7.76–7.87 (m, 2H), 8.23 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 103.8, 109.6, 121.5, 126.9, 131.6, 132.7, 143.4.

1*H*-Benzotriazole-1-carboxylic acid amide (2). A solution of hydrogen peroxide (30%, 6.35 ml, 56 mmol) was added in small portions (0.8 mL each hour) over an 8 h period to a stirred mixture of 1-cyano-1*H*-benzotriazole (1.0 g, 7 mmol) and tetrabutylammonium hydrogensulfate (3.56 g, 10.5 mmol) in DCM (3 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature after addition of each portion. The white solid obtained was filtered off, washed with DCM and dried to give pure product as white microcrystals (0.9 g, 79%), m.p. 160–161 °C (lit.[19] m.p. 160–162 °C); ^{1}H NMR (DMSO-d_6) δ 7.52 (t, J = 7.7 Hz, 1H), 7.68 (t, J = 7.7 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 8.27 (br. s, 1H), 8.59 (br. s, 1H); ^{13}C NMR (DMSO-d_6) δ 113.8, 119.8, 125.5, 129.9, 131.4, 145.6, 150.0.

4-Methoxyphenylurea (3a). *p*-Anisidine (0.25 g, 2.0 mmol) was added to a solution of 1*H*-benzotriazole-1-carboxamide **2** (0.32g, 2.0 mmol) in THF (10 mL). The mixture was allowed to react under reflux for 24 h. Further 1*H*-benzotriazole-1-carboxamide **2** (0.32g, 2.0 mmol) was added and the reaction mixture heated under reflux for an additional 72h. The reaction's progress was monitored by TLC. Upon completion, the reaction mixture was cooled, dry K_2CO_3 (2 g) was added, and the mixture stirred for 5–6 hours. The reaction mixture was filtered through Celite 545–silica gel to remove K_2CO_3, and then concentrated under reduced pressure. The crude residue was purified by recrystallization from propan-2-ol to give the desired urea **3a** as white needles (0.20 g, 61%, m.p. 168–169 °C; lit. m.p.[20] 170 °C. ^{1}H NMR (DMSO-d_6) δ3.69 (s, 3H),

5.74 (br. s, 2H), 6.80 (d, J = 8.9 Hz, 2H), 7.28 (d, J = 8.9 Hz, 2H), 8.36 (br. s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.1, 113.8, 119.5, 133.7, 153.9, 156.2.

General procedure for the preparation of substituted ureas 3b–g

The appropriate amine (1.0 mmol) was added to a solution of 1*H*-benzotriazole-1-carboxamide **2** (0.16 g, 1.0 mmol) in THF (5 mL). The mixture was allowed to react at room temperature for 48 hours, the reaction being monitored by TLC. Upon completion of the reaction, dry K_2CO_3 was added and the mixture was stirred for 5–6 hours. The reaction mixture was filtered through Celite 545–silica gel to remove K_2CO_3, then concentrated under reduced pressure. The crude ureas were purified by recrystallization (except **3e**) from an appropriate solvent to give the desired products **3b–g**. Compound **3e** was obtained in satisfactory purity without additional purification (see Figures 3,4).

Benzylurea (3b). Colorless needles (2-propanol), m.p. 148–149 °C (lit. m.p.[21] 148–149 °C); ^{1}H NMR (DMSO-d_6) δ 4.17 (d, *J* = 5.9 Hz, 2H), 5.54 (br. s, 2H), 6.41 (br. t, *J* = 5.9 Hz, 1H), 7.16–7.38 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 42.8, 126.5, 127.0, 128.2, 141.0, 158.7.

Phenethylurea (3c). White microcrystals (benzene), m.p. 110–111 °C (lit. m.p.[22] 112 °C); ^{1}H NMR (acetone-d_6) δ 2.76 (t, *J* = 7.2 Hz, 2H), 3.25–3.42 (m, 2H), 5.16 (br. s, 2H), 5.74 (br. s, 1H), 7.12–7.33 (m, 5H); ^{13}C NMR (acetone-d_6) δ 37.5, 42.4, 126.9, 129.2, 129.7, 141.0, 159.6.

***n*-Pentylurea (3d).** Colorless needles (benzene), m.p. 99 °C (lit. m.p.[23] 99.5 °C); ^{1}H NMR (DMSO-d_6) δ 0.86 (t, *J* = 6.4 Hz, 3H), 1.12–1.42 (m, 6H), 2.93 (q, *J* = 6.4 Hz, 2H), 5.37 (br. s, 2H), 5.91 (br. s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.0, 21.9, 28.7, 29.7, 39.2, 158.8.

***N*,*N*-Di-*n*-butylurea (3e).** Colorless oil;[24] ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.3 Hz, 6H), 1.31 (sextet, *J* = 7.5 Hz, 4H), 1.46–1.62 (m, 4H), 3.18 (t, *J* = 7.5 Hz, 4H), 5.00 (br. s, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.0, 30.4, 47.1, 158.7.

***N*,*N*-Dibenzylurea (3f).** White needles (2-propanol), m.p. 125–126°C (lit. m.p.[21] 125 °C); ^{1}H NMR (DMSO-d_6) δ 4.47 (s, 4H), 4.88 (br. s, 2H), 7.1$\tilde{8}$7.39 (m, 10H); ^{13}C NMR (DMSO-d_6) δ 50.2, 127.1, 127.4, 128.7, 137.2, 159.5.

***N*,*N*-Diisopropylurea (3g).** Colorless prisms (hexanes), m.p. 105–106 °C (lit. m.p.[25] 103–104 °C); ^{1}H NMR ($CDCl_3$) δ 1.25 (d, *J* = 6.9 Hz, 12H), 3.89 (septet, *J* = 6.9 Hz, 2H), 4.70 (br. s, 2H); ^{13}C NMR ($CDCl_3$) δ 21.1, 45.3, 158.0.

***N*-(4-Hydroxybenzyl)-*N*-phenethylurea (5).** A resin-bound amine **4** (0.89 mmol/g), prepared by a previously published procedure,[18] was placed in a solution of 1*H*-benzotriazole-1-carboxamide **2** (10 eq, conc. 0.25 mmol/mL) in THF and allowed to react for 12–14 h at room temperature. The resin was separated and washed successively several times with THF, CH_2Cl_2 and MeOH (5mL of solvent was used for each 100 mg of resin). The resin was dried in vacuum during 14 h and cleaved with a 20% solution of TFA in CH_2Cl_2 for 30 min. The residue obtained after the removal of solvents was purified by gradient column chromatography (chloroform to chloroform/methanol, 20/1) to give the urea **5** in 63% yield, as white microcrystals, m.p. 177–178 ^{o}C. The ^{1}H NMR in $CDCl_3$ and DMSO-d_6 showed a mixture of rotamers (Figures 1 and 2, see Supplemental Materials). The composition and purity of **5** were confirmed by combustion

analysis. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.09; H, 6.93; N, 10.59%.

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