New 1*H*-Benzotriazole-Mediated Synthesis of *N,N'*-Disubstituted Thioureas and Carbodiimides

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1*H*-Benzotriazole reacts with an aldehyde and thiourea or an *N*-substituted thiourea to form Mannich-type condensation products which on treatment with sodium borohydride or benzylmagnesium chloride yield *N,N'*-disubstituted thioureas or carbodiimides, respectively.

Thioureas are important organic compounds: representatives possess high biological activity,[1] act as corrosion inhibitors[2] and antioxidants,[3] and are polymer components.[4]

Common methods for the preparation of *N,N'*-disubstituted thioureas include (i) the aminolysis of isothiocyanates[5,6] (but this is limited by the availability of starting isothiocyanates) and (ii) reaction of primary amines with carbon disulphide[7,8] (but this is used mainly for *N,N'*-diarylthioureas[5,9]). The addition of hydrogen sulphide to carbodiimides[10] is of low synthetic value since substituted thioureas themselves serve as starting materials for the carbodiimides.[11]

In certain cases other methods were used for the synthesis of *N,N'*-disubstituted thiourea derivatives. *N,N'*-Thiocarbonyldiimidazole and related heterocyclic compounds react with primary amines to yield thioureas.[12] Isothiouronium salts have been transformed into thioureas by reaction with thiolate anion.[13]

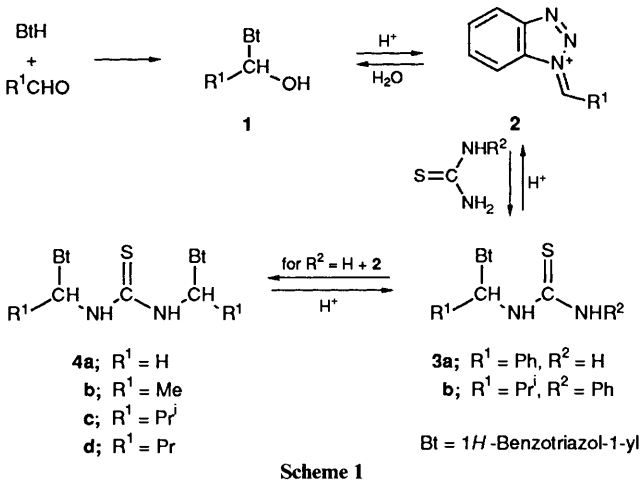
No generally applicable method has previously been available for the *N,N'*-dialkylation of thiourea. Alkylating agents have always converted thioureas into *S*-alkylisothiourea derivatives.[5,6] However, *N*-alkylation of thioamides[14] was recently reported from this laboratory as part of our application of 1*H*-benzotriazole as an efficient synthetic auxiliary for *N*-substitution of various nitrogen compounds. Mannich condensation of 1*H*-benzotriazole, an aldehyde and an NH-compound, followed by displacement of the 1*H*-benzotriazole moiety by a nucleophile, provided a convenient, selective and usually high-yielding method for the preparation of a wide variety of amines,[15] *N,N*-disubstituted hydroxylamines,[16] *N*-substituted amides[17] and amino acid derivatives.[18] We now report the extension of this strategy to the synthesis of *N,N'*-disubstituted thioureas and of carbodiimides.

Results

Reactions of Aldehydes with Benzotriazole and Thiourea.— Thiourea reacts with 2 mol equiv. of an aliphatic aldehyde and 2 mol equiv. of benzotriazole in glacial acetic acid at 85 °C to give the bis-condensation products **4** (Scheme 1, Table 1). The best yields in the synthesis of compound **4a** were achieved using 1-hydroxymethyl-1*H*-benzotriazole instead of 1*H*-benzotriazole and formaldehyde. The reactions all probably involve 1-(1-hydroxyalkyl)-1*H*-benzotriazole intermediates **1**.[15]

Under similar conditions, benzaldehyde, 1*H*-benzotriazole and thiourea, in the molar ratio 2:2:1, gave the product of monocondensation **3a** in good yield. The formation of compound **3a** is probably the result of the relatively low reactivity of benzaldehyde (Scheme 1).

In an analogous way, phenylthiourea reacts with isobutyraldehyde and 1*H*-benzotriazole in a molar ratio of 1:1:1, yielding the monocondensation product **3b**. Condensation



Scheme 1

products of type **4** from 1*H*-benzotriazole, formaldehyde and thiourea or substituted thioureas were previously reported as formed in dioxane in the presence of copper(I) chloride:[19] however, the reported m.p. of compound **4a** was 205–206 °C instead of 223–224 °C, Table 1. No spectral data were given by the previous authors, and no aldehyde other than formaldehyde was investigated.

The structures of the products **3** and **4** were confirmed by their spectra (Tables 2 and 3). The ^{13}C NMR spectra showed benzotriazole ring-carbon chemical shifts close to those previously reported for 1-substituted 1*H*-benzotriazoles.[20] Thus the C-7 and C-7a signals appeared at δ 111.10–111.53 and 132.17–133.37, respectively. The C-3a and C-4 signals were slightly shielded and gave peaks at δ 144.49–145.54 and 119.05–119.71, whereas those of C-5 and C-6 appeared at δ 124.10–124.88 and 127.77–128.08, respectively. The thiocarbonyl group chemical shifts in compounds **3** and **4** were at δ 181.89–184.20. The NCHN signals appeared at δ 56.02–72.93 ppm.

In the ^1H NMR spectra of compounds **3** and **4** the most deshielded aromatic proton was assigned to C-4 of the benzothiazole.[20] The NH proton resonated at δ 9.04–9.79 and appeared in **3a,b** and **4b–d** as a doublet with a coupling constant in the range 8.4–8.9 Hz. The NCHN proton was observed at δ 6.5–7.7, except for compound **3a**, where this group was significantly deshielded (δ 8.38) due to the benzene ring. The latter signal appeared as a doublet (J 8.6 Hz) which became a singlet under deuterium-exchange conditions (CD_3SOCD_3–CD_3OD). Protons attached to C-β resonated in the region δ 2.1–2.7. The chemical shifts of two non-equivalent methyl groups in the adduct **4c** differed by *ca.* 0.33 ppm, and appeared as sharp doublets with coupling constant 6.6 Hz.

Table 1 Analytical data for *N*-[1-(benzotriazol-1-yl)alkyl]thioureas **3** and **4**

Compound (Formula)	Yield (%)	Solvent	M.p. (°C) (decomp.)	Found (%) (Required) C	H	N
3a ($C_{14}H_{13}N_5S$)	85	EtOH	178–179	59.1 (59.35)	4.6 (4.6)	24.9 (24.7)
3b ($C_{17}H_{19}N_5S$)	40	MeCN	170–171	62.9 (62.7)	5.9 (5.9)	21.8 (21.5)
4a ($C_{15}H_{14}N_8S$)	98	DMF	223–224[a]	52.85 (53.2)	4.2 (4.2)	33.5 (33.1)
4b ($C_{17}H_{18}N_8S$)	25[b]	Me_2CO	179–181	55.5 (55.7	4.9 (4.95)	30.8 (30.6)
4c ($C_{21}H_{26}N_8S$)	82	DMF	204–205	59.6 (59.7)	6.2 (6.2)	26.9 (26.5)
4d ($C_{21}H_{26}N_8S$)	42	Me_2CO	190–191	59.6 (59.7)	6.1 (6.2)	26.8 (26.5

[a] Lit.,[19] 205–206 °C. [b] Yield estimated from the ^1H NMR spectrum of the crude product, contained BtH (50%).

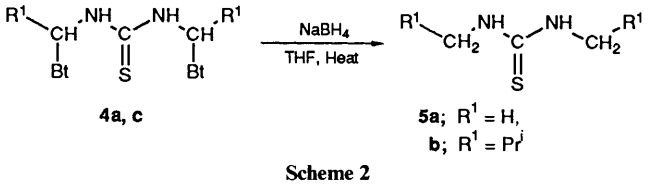
Table 2 ^{13}C NMR spectra[a] of *N*-[1-(benzotriazol-1-yl)alkyl]thioureas **3** and **4**

Compound	Solvent	Benzotriazole signals C=S	C-3a	C-7a	C-6	C-5	C-4	C-7	NCHN	R^1
3a	CD_3SOCD_3	183.88	145.54	132.59	128.08	124.66	119.71	111.44	70.34	126.77 129.36 129.43 137.35
3b[a]	CD_3SOCD_3	181.79	145.15	133.28	127.77	124.43	119.49	111.73	72.85	18.58 19.11 33.47
4a	CD_3SOCD_3	184.15	145.20	132.17	127.29	124.10	119.05	111.48	56.02	
4b[b]	$CDCl_3$	181.89	145.05	132.67	128.03	124.88	119.43	111.24	63.97	21.40
		181.89	144.87	132.47	127.91	124.75	119.27	110.97	63.91	21.70
4c	CD_3SOCD_3	184.20	145.10	133.21	127.78	124.43	119.55	111.53	72.93	18.33 18.77 33.73
4d[b]	$CDCl_3$	182.69	144.89	133.37	128.06	124.81	119.41	111.10	67.59	13.38 18.54 37.46
		182.67	144.74	133.12	127.96	124.70	119.26	110.97	67.40	13.61 18.71 37.71

[a] Phenyl signals: 123.54, 125.03, 128.89, 139.36. [b] Spectrum of major diastereoisomer is given in the upper line.

Compounds **4b–d** possess two chiral centres, and for **4b** and **4d** signals of both possible diastereoisomers were distinguished in the NMR spectra. The isomeric ratio was determined from the integrals of the proton spectra as *ca.* 1:1.3 in each instance; the major diastereoisomers of **4b** and **4d** were isolated pure by crystallization from acetone or washing with diethyl ether, respectively.

Reduction of N,N′-*Di*[1-(*benzotriazol*-1-*yl*)*alkyl*]*thioureas to* N,N′-*Dialkylthioureas*.—Sodium borohydride in boiling tetrahydrofuran (THF) cleaved benzotriazole from the Mannich bases **4a** and **4c** to give the *N*,*N*′-dialkylthioureas **5a** and **5b** in high yields (Scheme 2), which were characterized by comparison



4a, c **5a**; R^1 = H, **b**; R^1 = Pr^i

Scheme 2

with literature melting points and ^1H and ^{13}C NMR spectra (Table 4).

Conversion of N,N′-*Di*[1-(*benzotriazol*-1-*yl*)*alkyl*]*thioureas into Carbodiimides*.—Compounds **4b–d**, by treatment with benzylmagnesium chloride in a 1:4 molar ratio in a boiling THF–diethyl ether mixture, gave the new carbodiimides **7a–c**, the structures of which were confirmed by spectral evidence (Tables 4 and 5). Compounds **7** display the characteristic IR absorption bands[11] of the N=C=N group at 2120–2118 cm^{-1}. The ^{13}C NMR spectra of carbodiimides **7** displayed signals for the imine carbons in the expected region at 139.6–139.8 ppm,[11] and the methine carbons α to nitrogen resonated at 54.6–65.2 ppm. The spectra display double sets of certain carbon signals indicating the presence of diastereoisomers of the carbodiimides **7** (Table 5).

Recently we reported that *N*-[1-(thioamido)alkyl]-1*H*-benzotriazoles with Grignard reagents yield the corresponding monoalkylthioamides.[21] In a similar way, the process described above converts thiourea **4** *via* the derivatives **6** and C–S bond cleavage into the substituted carbodiimides **7**. *N*,*N*′-Disubstituted thioureas are well-known as important starting materials for carbodiimides,[11] but normally the reaction simply consists of the elimination of hydrogen sulphide without the addition of any carbon atoms. By contrast, our synthesis allows the construction of carbon skeletons of considerable complexity. The new reaction proceeds under mild conditions in contrast to

Table 3 ^{1}H NMR spectra of *N*-[1-(benzotriazol-1-yl)alkyl]thioureas **3** and **4**

Compound	Solvent	NH	Benzotriazole signals				NCHN	R^1
			4-H	5-H	6-H	7-H		
3a	CD_3SOCD_3	9.45 (1 H, d, *J* 8.6)[a]	8.10 (1 H, d, *J* 8.1)	*b*	7.58 (1 H, m)	7.95 (1 H, d, *J* 8.3)	8.38 (1 H, d, *J* 8.6)	7.28–7.50 (8 H, m)[a,b]
3b[c]	CD_3SOCD_3	9.03 (1 H, d, *J* 8.4), 9.79 (1 H, s)	8.08 (1 H, d, *J* 8.4)	*b*	7.58 (1 H, dd, *J* 8.4, 7.2)	8.06 (1 H, d, *J* 8.4)	7.03 (1 H, dd, *J* 9.0, 8.7)	0.69 (3 H, d, *J* 6.6), 1.16 (3 H, d, *J* 6.6), 2.70 (1 H, m)
4a	CD_3SOCD_3	9.11 (2 H, br s)	8.05 (2 H, d, *J* 8.3)	7.40 (2 H, m)	7.53 (2 H, m)	8.03 (2 H, d, *J* 8.4)	6.47 (4 H, d, *J* 4.9)	
4b[d]	$CDCl_3$	9.43 (2 H, d, *J* 8.7)	8.17 (2 H, d, *J* 8.4)	7.47 (2 H, m)	7.61 (2 H, m)	8.12 (2 H, d, *J* 8.4)	7.70 (2 H, m)	2.11 (6 H, d, *J* 6.6)
4c	CD_3SOCD_3	9.04 (2 H, d, *J* 8.4)	8.06 (2 H, d, *J* 8.1)	7.41 (2 H, m)	7.56 (2 H, m)	7.97 (2 H, d, *J* 8.4)	6.77 (2 H, dd, *J* 8.7, 8.4)	0.64 (6 H, d, *J* 6.6), 0.97 (6 H, d, *J* 6.6), 2.56 (2 H, m)
4d[d]	$CDCl_3$	9.48 (2 H, d, *J* 8.9)	8.17 (2 H, d, *J* 8.3)	7.41–7.62 (6 H, m)[b]		8.08 (2 H, d, *J* 8.4)	*b*	0.86 (6 H, t, *J* 7.5), 1.09–1.38 (4 H, m), 2.30–2.63 (4 H, m)

[a] Broad NH_2 signal overlapped with phenyl protons. [b] Overlapped with aromatic protons. [c] Aromatic signals: 7.08–7.52 (6 H, m). [d] Spectrum of major diastereoisomer.

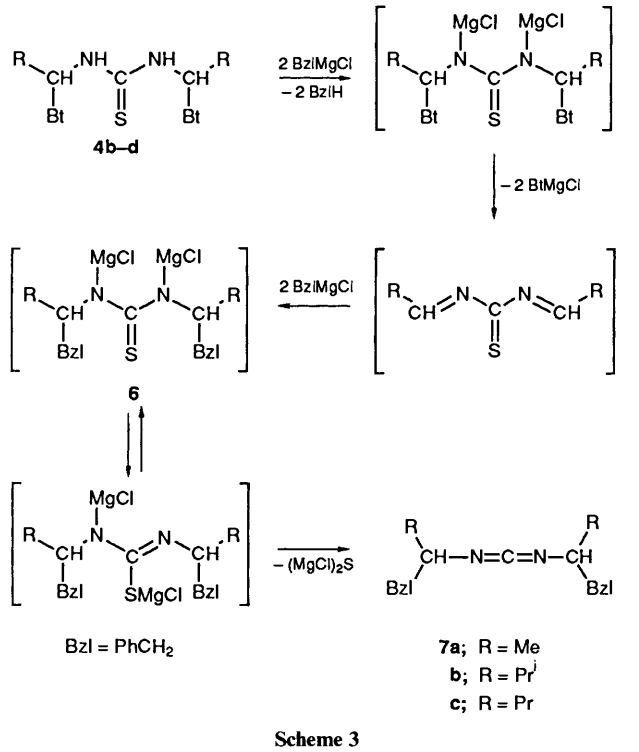
Table 4 Preparation of thioureas **5** and carbodiimides **7**

Compound (Formula)	Yield (%)	M.p. (°C) or B.p. (°C/mmHg)	M^+ Calculated	M^+ Found
5a ($C_3H_8N_2S$)	75	50–51[a]		
5b ($C_9H_{20}N_2S$)	95	90–91[b]	188.1349	188.1347
7a ($C_{19}H_{22}N_2$)	72	110–115/0.3	279.1863[c]	279.1851[c]
7b ($C_{23}H_{30}N_2$)	60	135–140/0.2	335.2488[c]	335.2487[c]
7c ($C_{23}H_{30}N_2$)	62	95–100/0.2	335.2488[c]	335.2487[c]

[a] From light petroleum; lit.,[7] 51–52 °C. [b] From ethyl acetate–hexane; lit.,[7] 87–88 °C. [c] M + H.

Table 5 ^{13}C NMR spectra ($CDCl_3$) of carbodiimides **7**

Compound	R[1]	CH_2	Ph	NCH	N=C=N
7a	22.29	44.83, 44.86	126.46, 128.38, 129.46, 138.80	54.74, 54.63	139.69
7b	16.90, 16.96, 19.60, 19.72 32.18	39.99, 40.02	125.90, 125.94 128.02, 128.04, 129.13, 129.14, 139.15	65.17, 65.19	139.58, 139.74
7c	13.85, 19.51, 38.40	43.23, 43.25	126.30, 128.30, 129.46, 138.93	59.35, 59.42	139.66, 139.84



Scheme 3

the previously reported synthesis of carbodiimides by pyrolysis of bis(bromomagnesio)thioureas at 170–200 °C.[22] Facile fission of intermediate **6** probably reflects considerable steric hindrance at the nitrogen atom (Scheme 3). Attempted syntheses of carbodiimides from adduct **4a** and benzylmagnesium chloride, as well as from **4c** and phenylmagnesium bromide or isopropylmagnesium iodide under the above conditions failed.

In summary, 1*H*-benzotriazole–aldehyde–thiourea condensations enable both the *N,N'*-dialkylation of thiourea and the synthesis of carbodiimides.

Experimental

M.p.s were determined on a Fisher-Johns hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian XL300 or General Electric QE300 spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ or CD^3SOCD_3 referenced to Me_4Si for the proton spectra and the solvent signals for the carbon spectra. *J* Values are in Hz. High resolution mass spectra were recorded on a Kratos AEI MS30 spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium/benzophenone immediately before use.

N-[α-(1H-*Benzotriazol*-1-*yl*)*benzyl*]*thiourea* **3a**.—A mixture of 1*H*-benzotriazole (2.38 g, 20 mmol), benzaldehyde (2.12 g, 20 mmol) and thiourea (0.76 g, 10 mmol) was heated in glacial acetic acid (8 cm^3) at 85 °C for 2 h. The acetic acid was removed under reduced pressure at 80 °C, and the residue was triturated with diethyl ether (40 cm^3). The resulting solid was filtered off and washed with diethyl ether to yield the thiourea **3a** (2.41 g, 85%).

N-[1-(1H-*Benzotriazol*-1-*yl*)-2-*methylpropyl*]-N'-*phenylthiourea* **3b**.—Benzotriazole (1.19 g, 10 mmol), isobutyraldehyde (0.72 g, 10 mmol) and phenylthiourea (1.52 g, 10 mmol) were heated in glacial acetic acid (4 cm^3) at 85 °C for 3 h. Acetic acid was removed under reduced pressure at 80 °C and the residue was recrystallized from diethyl ether (25 cm^3) to yield He thiourea **3b** (1.30 g, 40%).

General Procedure for the Preparation of N,N'-*Dialkylthioureas* **4**.—1*H*-Benzotriazole (2.38 g, 20 mmol), the aldehyde (20 mmol) and thiourea (0.76 g, 10 mmol) were heated in glacial acetic acid (8 cm^3) at 85 °C for 2 h. In the synthesis of **4a** 1-hydroxymethyl-1*H*-benzotriazole (2.98 g, 20 mmol) was used instead of 1*H*-benzotriazole and formaldehyde. The crystalline products *N,N'*-bis[(1*H*-benzotriazole-1-yl)methyl]thiourea **4a** and N,N'-*bis*[1-(1H-*benzotriazol*-1-*yl*)-2-*methylpropylthiourea* **4c** were filtered off from the reaction mixtures cooled to room temperature and washed with diethyl ether. Compound **4b** and **4d** were isolated as described below. Analytical samples were recrystallized from the solvent given in Table 1.

N,N'-*Bis*[1-(1H-*benzotriazol*-1-*yl*)*ethyl*]*thiourea* **4b**. The solvent was removed under reduced pressure at 80 °C. The crude product was triturated with diethyl ether (40 cm^3) at 0 °C. The resulting crystals were collected and washed with diethyl ether (2 × 10 cm^3) to yield the thiourea **4b** (0.92 g, 25%).

N,N'-*Bis*[1-(1H-*benzotriazol*-1-*yl*)*butyl*]*thiourea* **4d**. The reaction mixture was maintained at 0 °C for 12 h. The resulting crystals were collected and washed with diethyl ether (2 × 15 cm^3) to yield one diastereoisomer of **4d** (0.63 g, 15%). The combined filtrates were again evaporated under reduced pressure at 80 °C and triturated with a mixture of diethyl ether and petroleum (b.p. 35–60 °C) (1:1; 40 cm^3). The resulting precipitate was filtered off and washed with diethyl ether (2 × 15 cm^3) to give additional thiourea **4d** (1.14 g, 27%).

General Procedure for the Preparation of N,N'-*Disubstituted Thioureas* **5**.—A mixture of compound **4a** or **4c** (2 mmol) and sodium borohydride (0.46 g, 12 mmol) in dry THF (20 cm^3) was stirred under reflux for 4 h. The solvent was evaporated under reduced pressure at 30 °C. Water (5 cm^3) was added to the residue and the mixture extracted with chloroform

(4×10 cm^3). The organic layer was washed with 5% aqueous NaOH (10 cm^3), and dried ($MgSO_4$). The solvent was evaporated to afford *N,N'*-dimethylthiourea **5a** or *N,N'*-diisobutylthiourea **5b**.

General Procedure for the Preparation of Carbodiimides **7**.—To a suspension of the appropriate thiourea **4** (7 mmol) in dry THF (56 cm^3), a solution of benzylmagnesium chloride (30 mmol) in diethyl ether (30 cm^3) was added dropwise with stirring at room temperature over *ca.* 35 min. The mixture was stirred for 3 h and refluxed for 1 h. The solvent was removed under reduced pressure at 35 °C, and the residue extracted with dry hexane (4×50 cm^3). The combined hexane extracts were evaporated under reduced pressure at 70 °C to yield the crude carbodiimides *bis*(1-*phenylpropan*-2-*yl*)*carbodiimide* **7a**, *bis*(3-*methyl*-1-*phenyl*(*butan*-2-*yl*)*carbodiimide* **7b** and *bis*(1-*phenylpentan*-2-*yl*)*carbodiimide* **7c** which were purified by vacuum distillation (for analytical data see Tables 4 and 5).

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