Synthesis of α-Amino Isocyanides and α-Alkylthio Isocyanides

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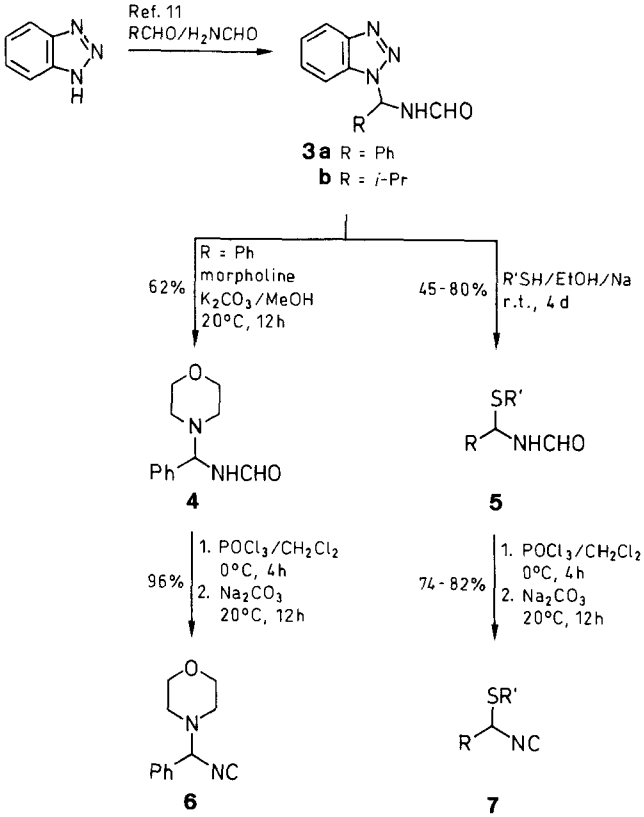
α-Morpholinobenzyl isocyanide and three 1-(aryl[or alkyl]thio)alkyl isocyanides are synthesized in good yields by the dehydration of *N*-(α-morpholinobenzyl)formamide and *N*-[1-(alkylthio)alkyl]formamides, themselves prepared from 1-(1-formylaminoalkyl)benzotriazoles with morpholine or with thiols.

The chemistry of isocyanides in general is well documented,[1] but far less work has been reported on functionalized, specifically α-substituted isocyanides **1**. Böhme and Fuchs reported the synthesis in three steps of (phenylsulfonyl)methyl isocyanide (**1**, Y = $PhSO_2$, R = H) and of *N*-(isocyanomethyl)phthalimide starting from the corresponding (formylaminomethyl)dialkylamine, but they failed to obtain (alkylthio)methyl isocyanides (**1**, Y = RS).[2] Diethyl isocyanomethylphosphonate [**1**, Y = $(EtO)_2P(O)$, R = H] was prepared from the reaction of triethyl phosphite and a (formylaminomethyl)trimethylammonium salt followed by treatment with phosphorus oxychloride ($POCl_3$) in the presence of triethylamine.[3] Other isocyanomethyl substituted phosphorus compounds have also been reported.[4-6] Treatment of *N*-(chloromethyl)-*N*-nitropropylamine with sodium cyanide/zinc(II) chloride gave *N*-(isocyanomethyl)-*N*-nitropropylamine (**1**, Y = O_2NNPr, R = H) which rearranged into its corresponding nitrile form.[7] 1-(Isocyanomethyl)azoles RCH_2NC (R = 1-imidazolyl-1,2,4-triazol-2-yl, 1-benzimidazolyl and benzotriazolyl) were synthesized by the reaction of RH with (formylaminomethyl)trimethylammonium iodide followed by dehydration of 1-(formylaminomethyl)azoles using $POCl_3$ or triphenylphosphine/carbon tetrachloride.[8] Preparations of a few α-(arylthio)methyl isocyanides (**1**, Y = ArS, R = H)[9] and 1-(arylthio)alkenyl isocyanides[10] have also been reported.

All these previously reported α-substituted isocyanides are isocyanomethyl derivatives (**1**, R = H). Our own group recently disclosed the synthesis of α-(benzotriazolyl)alkyl isocyanides (**1**, Y = benzotriazolyl, R = alkyl) by dehydration of 1-(1-formylaminoalkyl)benzotriazoles **3** which were prepared by the condensation of benzotriazole, an aldehyde and formamide.[11] (Benzotriazol-1-yl)-alkyl isocyanides have been used as versatile synthons for the preparation of unsymmetrical formamidines. *N*-(1-Benzotriazol-1-ylalkyl)amides are versatile α-amidoalkylation reagents, they react with CH acids[12] and reactive aromatics[13] to give the amidoalkylation products. They also give α-(alkoxyalkyl)amides by treatment with sodium alkoxides[14] and α-[(alkylthio)alkyl]amides with sodium alkylthiolates.[15] We now report for the first time the synthesis of an α-amino isocyanide (**1**, Y = R_2N, R = alkyl) and of elaborated α-alkylthio isocyanides (**1**, Y = RS, R = alkyl) from 1-(1-formylaminoalkyl)benzotriazoles.

α-Amino isocyanides and α-alkylthio isocyanides were prepared as shown in the Scheme. 1-[α-(Formylamino)benzyl]benzotriazole (**3a**) and 1-[1-(formylamino)-2-methylpropyl]benzotriazole (**3b**) were prepared from benzotriazole, formamide and the appropriate aldehyde as previously described.[11] Reaction of benzotriazole derivative **3a** with morpholine in methanol at room temperature in the presence of potassium carbonate gave *N*-(α-morpholinobenzyl)formamide (**4**) in 62% yield. Compounds **3a** and **3b** reacted with sodium salts of three aromatic and aliphatic thiols in ethanol at room temperature to afford the desired *N*-(alkylthioalkyl)formamides **5a–5c** in good yields. The byproduct sodium or potassium benzotriazolate, produced during these reactions, was easily removed during the aqueous workup. Dehydration of the *N*-(α-aminoalkyl)-(**4**) and *N*-(α-alkylthioalkyl)formamides **5a–5c** with $POCl_3$ in the presence of diisopropylamine gave the corresponding α-amino isocyanide **6** and α-alkylthio isocyanides **7a–7c** in good yields.



5, 7	R	R'
a	*i*-Pr	Ph
b	Ph	3-MeC_6H_4
c	Ph	*i*-Pr

Scheme

The dehydration of formamide derivatives with $POCl_3$ in the presence of an amine and other dehydrating reagents, such as tosyl chloride,[16] thionyl chloride and base[17] or triphenylphosphine in carbon tetrachloride[18] are well known. Therefore, the preparations of *N*-(α-aminoalkyl)- (**2**, Y = R_2N) and *N*-(α-alkylthioalkyl)formamides (**2**, Y = RS) are the key to the synthesis of the corresponding α-substituted isocyanides **1**. (Formylaminomethyl)dialkylamines have usually been synthesized by the condensation of formamide with formaldehyde and secondary amines, but the condensation is not, in general, applicable to other aliphatic nor to aromatic aldehydes.[2,19] Synthetic access to *N*-(alkylthiomethyl)formamides (**2**, Y = RS, R = H), the precursors for (alkylthio)methyl isocyanides, is available from the reactions of thiols with hydroxymethylformamide,[20] *p*-tosylmethylformamide[21,22] quaternary ammonium cations[2,9] and with chloromethylformamide.[23]

However, none of these methods has been used for the preparation of *N*-[1-(alkylthio)alkyl]formamides (**2**, Y = RS, R = alkyl). The novel aspect of our work is that using 1-(1-formylaminoalkyl)benzotriazoles now provides a convenient route to the preparation of both α-(formylaminoalkyl)dialkylamines and α-(formylaminoalkyl) alkyl sulfides in good yield; this method works particularly well with aromatic and aliphatic aldehydes under mild conditions.

N-(α-Morpholinobenzyl)formamide (**4**) and *N*-(α-alkylthioalkyl)formamides **5a–5c** were characterized by elemental analyses and by their ^1H and ^{13}C NMR spectra. In the ^1H NMR spectra of **4** and **5**, the NH protons appear as doublets at δ = 8.64 to 9.15 with coupling constants ranging from J = 9.3–10.0 Hz, and the formyl CH protons at δ = 8.28–7.78 with small coupling constants (0.9 Hz). In the ^{13}C NMR spectra, formyl carbonyl carbons appear at δ = 160.0–161.2 and CH carbons at δ = 68.9–52.9. All the α-substituted isocyanides are new compounds. The isocyanide structure is confirmed by the strong IR absorption band at ν = 2250 cm^{-1} for the compound **6** and ν = 2120 cm^{-1} for compounds **7**, and by the ^{13}C signals of the isocyanato carbons at δ = 159.7–160.4. The structures of isocyanide **6** is confirmed by elemental analysis and of compounds **7a–7c** by high resolution mass spectra.

Melting points were determined with a hot stage apparatus and were uncorrected. ^1H (300 MHz) NMR and ^{13}C (75 MHz) NMR spectra were recorded on a Varian VXR spectrometer with TMS as internal standard. HRMS were obtained on a Finnigan Mat 95 spectrometer and IR spectra were measured on a Perkin-Elmer Model 283B grating spectrometer.

N-(α-Morpholinobenzyl)formamide (4):
A mixture of 1-(α-formylaminobenzyl)benzotriazole (**3a**; 1.89 g, 7.5 mmol), morpholine (0.86 g, 10 mmol) and K_2CO_3 (2.25 g) in MeOH (20 mL) was stirred at 20 °C overnight. The solvent was evaporated, the residue dissolved in EtOAc (100 mL), washed with aq NaOH (3 × 20 mL, 10%), H_2O (2 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave a white solid which was recrystallized from EtOAc/hexane (3:1) to give **4** as white needles (1 g, 62%), mp 141–142 °C.

^1H NMR (DMSO-d_6): δ = 8.74 (d, 1 H, J = 9.3 Hz, NH), 8.28 (d, 1 H, J = 0.9 Hz, CHO), 7.47–7.30 (m, 5 H, ArH), 5.71–5.68 (d, 1 H, J = 9.6 Hz, CH), 3.57 (t, 4 H, J = 4.2 Hz), 2.38 (t, 4 H, J = 4.2 Hz).

^{13}C NMR: δ = 161.2 (CO), 138.6, 128.3, 128.2, 127.6, 127.2, 68.9 (CH), 66.2 (CH_2O), 48.3 (CH_2N).

$C_{12}H_{16}N_2O_2$	calc.	C 65.43	H 7.32	N 12.72
(220.3)	found	65.20	7.36	12.68

α-Morpholinobenzyl Isocyanide (6):
i-Pr_2NH (0.303 g, 3 mmol) was added to compound **4** (0.22 g, 1 mmol) in CH_2Cl_2 (40 mL). $POCl_3$ (0.20 g, 1.3 mmol) in CH_2Cl_2 was added dropwise at 0 °C with stirring. The solution was stirred for 4 h at 0 °C and aq Na_2CO_3 (8 mL, 20%) was added slowly. After stirring at 20 °C for 1 h, CH_2Cl_2 (20 mL) and H_2O (20 mL) were added. The organic layer was washed with H_2O (3 × 15 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to give a yellowish solid (0.19 g, 96%), mp 66–67 °C.

^1H NMR ($CDCl_3$): δ = 7.55–7.52 (m, 2 H, ArH), 7.43–7.37 (m, 3 H, ArH), 4.83 (s, 1 H, CH), 3.74 (m, 4 H, 2 × CH_2O), 2.60–2.57 (m, 4 H, 2 × CH_2N).

^{13}C NMR: δ = 132.3, 129.0, 128.8, 127.9, 115.1, 66.6, 62.3, 49.9.

IR (KB): ν = 2250.0 cm^{-1} (-NC).

$C_{12}H_{14}N_2O$	calc.	C 71.26	H 6.98	N 13.85
(202.2)	found	71.00	7.12	13.73

***N*-(2-Methyl-1-phenylthiopropyl)formamide (5a); Typical Procedure:**
A solution of PhSH (3.3 g, 30 mmol) and Na (0.72 g, 30 mmol) in abs. EtOH (60 mL) was added to a suspension of **3a** (3.27 g, 15 mmol) in abs. EtOH (30 mL) with stirring at r. t. The mixture was stirred for 4 d at r. t. EtOH was removed under reduced pressure and the residue dissolved in EtOAc (100 mL), washed with aqueous NaOH (3 × 20 mL, 10%) and H_2O (2 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent and recrystallization from EtOAc/hexane (3:1) gave **5a** as white needles (2.32 g, 74%), mp 65–66 °C.

^1H NMR ($CDCl_3$): δ = 8.61 (d, 1 H, J = 10.0 Hz, NH), 7.98 (d, 1 H, J = 0.9 Hz, CHO), 7.44–7.25 (m, 5 H, ArH), 5.31 (dd, 1 H, J = 9.9, 5.4 Hz, CH), 1.98 (m, 1 H, CH), 1.00 (m, 6 H, 2 × CH_3).

^{13}C NMR: δ = 160.4 (CO), 133.8, 131.1, 128.9, 126.9, 60.9, 33.1, 19.4, 18.2.

$C_{11}H_{15}NOS$	calc.	C 63.12	H 7.22	N 6.69
(209.2)	found	62.99	7.33	6.66

N-[α-(3-Methylphenylthio)benzyl]formamide (**5b**): white needles (EtOAc/hexane), 45%, mp 132–133 °C.

^1H NMR ($CDCl_3$): δ = 9.05 (d, 1 H, J = 9.6 Hz, NH), 7.78 (s, 1 H, CHO), 7.36–6.86 (m, 9 H, ArH), 6.32 (d, 1 H, J = 9.6 Hz, 1 H), 2.04 (s, 3 H, CH_3).

^{13}C NMR: δ = 160.0 (CO), 138.9, 138.3, 133.2, 131.9, 128.8, 128.5, 128.4, 128.2, 128.1, 126.8, 56.8, 20.8.

$C_{15}H_{15}NOS$	calc.	C 70.1	H 5.88	N 5.44
(257.9)	found	69.57	5.78	5.34

N-[α-(1-methylethylthio)benzyl]formamide (**5c**): needles (EtOAc/hexane), 80%, mp 62–63 °C.

^1H NMR (DMSO-d_6): δ = 9.15 (d, 1 H, J = 9.6 Hz, NH), 8.13 (d, 1 H, J = 0.6, CHO), 7.49–7.26 (m, 5 H, ArH), 6.26 (d, 1 H, J = 9.6 Hz, CH), 3.03 (m, 1 H, CH), 1.32 (d, 3 H, J = 6.6 Hz, CH_3), 1.19 (d, 3 H, J = 6.6 Hz, CH_3).

^{13}C NMR: δ = 160.1, 139.7, 128.4, 127.7, 126.6, 52.9, 34.6, 23.7, 22.5.

$C_{11}H_{15}NOS$	calc.	C 63.12	H 7.22	N 6.69
(209.2)	found	63.34	7.19	6.65

2-Methyl-1-phenylthiopropyl Isocyanide (7a); Typical Procedure:
This compound was prepared as an oil (81%) from **5a** by the same procedure as described for **6**.

^1H NMR ($CDCl_3$): δ = 7.57–7.54 (m, 2 H), 7.32–7.32 (m, 3 H, ArH), 4.50 (d, 1 H, J = 4.8 Hz, CH), 2.12 (m, 1 H, CH), 1.13 (d, 3 H, J = 5.1, CH_3), 1.11 (d, 3 H, J = 5.1 Hz, CH_3).

^{13}C NMR: δ = 158.8, 133.5, 131.5, 129.2, 128.8, 67.2, 32.9, 19.2, 17.5.

IR (KBr): $\nu = 2120\,cm^{-1}$ (NC).

HRMS: *m/z*, $C_{11}H_{13}NS$, calc.: 191.0752; found: 191.0752.

α-(3-Methylphenylthio)benzyl Isocyanide (**7b**): oil (82%).

^1H NMR ($CDCl_3$): δ = 7.40–7.22 (m, 9H, ArH), 5.81 (s, 1H, CH), 2.33 (s, 3H, CH_3).

^{13}C NMR: δ = 160.4, 139.1, 135.4, 133.9, 131.8, 131.7, 131.6, 130.2, 129.1, 128.7, 126.3, 62.8 (CH), 21.1.

IR (KBr): $\nu = 2120.1\,cm^{-1}$ (–NC).

HRMS: *m/z*, $C_{15}H_{13}NS$, calc.: 239.0769 (HRMS); found: 239.0769.

(1-Methylethylthio)benzyl Isocyanide (**7c**): oil (74%).

^1H NMR ($CDCl_3$): δ = 7.49–7.34 (m, 5H, ArH), 5.74 (s, 1H, CH), 3.27 (m, 1H, CH), 1.43 (d, 3H, $J = 6.6$ Hz, CH_3), 1.29 (d, 3H, $J = 6.6$ Hz, CH_3).

^{13}C NMR: δ = 159.7, 134.2, 128.9, 128.1, 125.1, 58.1, 36.3, 23.2, 22.1.

IR (KBr): $\nu = 2120.1\,cm^{-1}$ (–NC).

HRMS: *m/z*, $C_{11}H_{13}NS$, calc.: 191.0772; found: 191.0770.

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