# A Convenient Method for the Preparation of ω-Dialkylaminoalkyl Isothiocyanates

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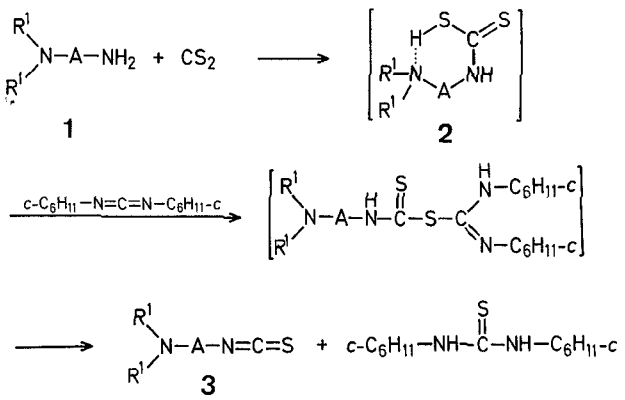
Isothiocyanates may be synthesized by a large variety of methods[1-11] some of which involve tedious multistep procedures or require starting materials such as thiocarbonyl chloride, alkyl carbonochloridates, or isocyanides. In order to avoid the use of such reagents, a mild method has been suggested[16] which consists of the reaction of a primary amine with carbon disulfide and dicyclohexylcarbodiimide. However, this method seemed to be limited to the synthesis of a few simple aliphatic[16] and aromatic[17] isothiocyanates. We wish to report here that this method constitutes a convenient approach to the synthesis of ω-dialkylaminoalkyl isothiocyanates (**3**) which are useful starting materials for the synthesis of several *N*-heterocyclic compounds containing water-solubilizing groups.



The reaction of *N,N*-dialkylalkanediamines (**1**) with carbon disulfide and dicyclohexylcarbodiimide is performed at 0 °C in ether in which the resultant *N,N'*-dicyclohexylthiourea is insoluble. Thus, filtration and removal of the solvent affords the crude isothiocyanate (**3**) which may be purified by distillation. The dithiocarbamic acid **2** may be regarded as an intermediate which reacts with the carbodiimide to give the isothiocyanate **3** and *N,N'*-dicyclohexylthiourea.

We report here three examples of the conversion of the ω-dialkylaminoalkyl isothiocyanates **3** into heterocyclic systems. The reaction of **3** with α-aminocarboxylic acids leads to the formation of the thiohydantoins **4**, the reaction with carboxylic acid hydrazides affords 4-dialkylaminoalkyl-5-thioxo-4,5-dihydro-1,2,4-triazoles (**5**), and the reaction with methyl anthranilate or 2-aminobenzonitrile affords 3-dialkylaminoalkyl-4-oxo-2-thioxo- or 3-dialkylaminoalkyl-4-imino-2-thioxo-1,2,3,4-tetrahydroquinazolines (**6**), respectively.

The formation of the thiohydantoins **4** may be used for the quantitative determination of α-amino acids. The water-soluble salts of compounds **5** and **6** are biologically active substances which have been investigated for their antithyroid and analgetic properties.

The $^1$H-N.M.R. spectra were determined with TMS as an internal standard using a Jeol JNM-MH 60 instrument. The I.R. spectra were measured on a Perkin-Elmer 177 spectrometer. The microanalyses were performed on a Perkin-Elmer CHN 240 apparatus.

**2-Morpholinoethyl Isothiocyanate (3c); Typical Procedure:**

A solution of carbon disulfide (3.8 g, 0.05 mol) in dry ether (50 ml) is slowly added, dropwise, to an ice-cooled stirred solution of 2-morpholinoethylamine (6.5 g, 0.05 mol) and dicyclohexylcarbodiimide (9.8 g, 0.05 mol) in anhydrous ether (200 ml). When the addition is complete, the ice bath is removed and the mixture stirred for 2 h. The precipitated *N,N'*-dicyclohexylthiourea is separated by filtration and the solvent evaporated under reduced pressure. The residue is distilled under high vacuum to give a clear colorless liquid; yield: 7.8 g (91%); b.p. 92–94 °C/0.1 torr; $n_D^{21.2}$: 1.5332.

| | | | | |
|---|---|---|---|---|
| $C_7H_{12}N_2OS$ | calc. | C 48.81 | H 7.02 | N 16.26 |
| (172.3) | found | 48.74 | 7.08 | 16.31 |

I.R. (neat): $\nu_{N=C=S} = 2100\ cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): δ = 3.65 (t, 4H, $CH_2$—O—$CH_2$); 2.52 (m, 4H, $CH_2$—N—$CH_2$); 1.50 ppm (m, 4H, N—$CH_2$—$CH_2$—N).

**1-(2-Morpholinoethyl)-5-oxo-2-thioxotetrahydroimidazole (4, $R^1$ $R^1$ = —$CH_2$—$CH_2$—O—$CH_2$—$CH_2$—, $R^2$ = H, A = —$CH_2$—$CH_2$—):**

To a stirred suspension of glycine ethyl ester hydrochloride (1.40 g, 0.01 mol) in dichloromethane (200 ml) is added triethylamine (1.38 ml, 0.01 mol), followed by the addition of a solution of 2-morpholinoethyl isothiocyanate (**3c**; 1.72 g, 0.01 mol) in dichloromethane (20 ml). The mixture is refluxed for 2 h, the solvent then distilled

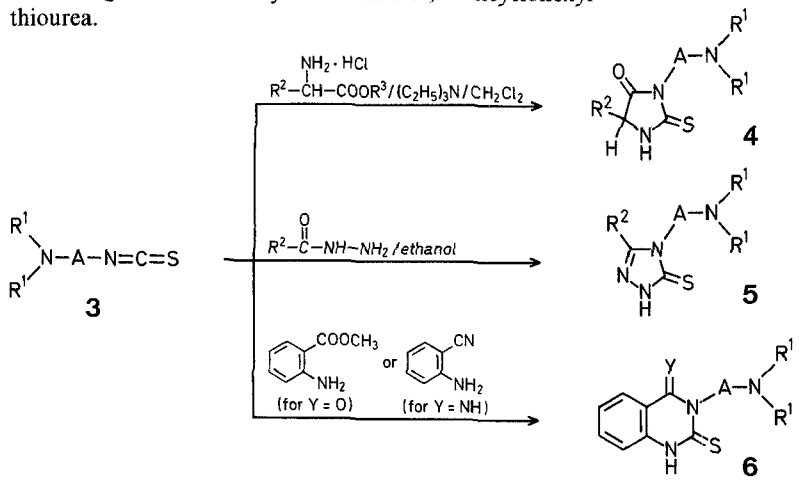


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**Table.** ω-Dialkylaminoalkyl Isothiocyanates (**3**)

| 3 | $R^1$ | $R^1$ | A | Yield [%] | b.p. [°C]/ 0.1 torr | Molecular formula[a] | |
|---|---|---|---|---|---|---|---|
| **a** | $CH_3$ | $CH_3$ | $(CH_2)_2$ | 87 | 135–137 | $C_5H_{10}N_2S$ | (130.2) |
| **b** | $-(CH_2)_5-$ | | $(CH_2)_2$ | 94 | 98–102 | $C_8H_{14}N_2S$ | (170.3) |
| **c** | $(CH_2)_2-O-(CH_2)_2$ | | $(CH_2)_2$ | 91 | 92–94 | $C_7H_{12}N_2OS$ | (172.3) |
| **d** | $C_2H_5$ | $C_2H_5$ | $(CH_2)_3$ | 85 | 90–92 | $C_8H_{16}N_2S$ | (172.3) |
| **e** | $-(CH_2)_5-$ | | $(CH_2)_3$ | 92 | 106–108 | $C_9H_{16}N_2S$ | (184.3) |

[a] The microanalyses were in good agreement with the calculated values: C, ±0.08; H, ±0.10; N, ±0.09.

off under reduced pressure, and the residue triturated with ice-cold water (100 ml) to give a solid red product; yield: 1.80 g (79%); m.p. 93–95 °C (from ethanol).

| | | | | |
|---|---|---|---|---|
| $C_9H_{15}N_3O_2S$ | calc. | C 47.14 | H 6.59 | N 18.33 |
| (229.3) | found | 47.06 | 6.63 | 18.39 |

I.R. (KBr): $\nu_{C=O} = 1745$; $\nu_{C=S} = 1530$ cm$^{-1}$.

$^1$H-N.M.R. (DMSO-$d_6$): $\delta = 10.00$ (s, 1H, NH); 4.13 (s, 2H, $N-CH_2-C-O$); 3.82 (t, 2H, $N-CH_2-CH_2-N-C-S$, $J = 6$ Hz); 3.58 (t, 4H, $CH_2-O-CH_2$, $J = 4$ Hz); 3.05 (t, 2H, $N-CH_2-CH_2-N-C-S$, $J = 6$ Hz); 2.46 ppm (t, 4H, $CH_2-CH_2-O-CH_2-CH_2$, $J = 4$ Hz).

**4-(2-Morpholinoethyl)-5-thioxo-4,5-dihydro-1,2,4-triazole (5, $R^1-R^1 = -CH_2-CH_2-O-CH_2-CH_2-$, $R^2 = H$, $A = -CH_2-CH_2-$):**

A solution of formylhydrazine (3 g, 0.05 mol) in ethanol (100 ml) is added to a stirred solution of 2-morpholinoethyl isothiocyanate (**3c**; 8.6 g, 0.05 mol) in ethanol (50 ml). Stirring is continued under reflux for 6 h. The solvent is removed under vacuum and the resultant solid is collected, washed with ether, and dried; yield: 10.50 g (98%); m.p. 142–143 °C (from ethanol).

| | | | | |
|---|---|---|---|---|
| $C_8H_{14}N_4OS$ | calc. | C 44.84 | H 6.59 | N 26.15 |
| (214.3) | found | 44.91 | 6.59 | 26.18 |

M.S.: *m/e* (relative intensity) = 214 (5%, $M^+$), 113 (100).

I.R. (KBr): $\nu_{NH} = 3300$; $\nu_{C=S} = 1560$ cm$^{-1}$.

$^1$H-N.M.R. (DMSO-$d_6$): $\delta = 13.80$ (s, 1H, NH); 8.33 (s, 1H, $N-CH-N$); 4.00 (t, 2H, $N-CH_2-CH_2-N-C=S$, $J = 6$ Hz); 3.55 (t, 4H, $CH_2-O-CH_2$, $J = 4$ Hz); 2.58 (t, 2H, $N-CH_2-CH_2-N-C-S$, $J = 6$ Hz); 2.40 ppm (t, 4H, $CH_2-CH_2-O-CH_2-CH_2$, $J = 4$ Hz).

**3-(2-Morpholinoethyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline (6, $R^1-R^1 = -CH_2-CH_2-O-CH_2-CH_2-$, $A = -CH_2-CH_2-$, Y = O):**

A solution of methyl anthranilate (1.51 g, 0.01 mol) in methanol (20 ml) is added to a stirred solution of 2-morpholinoethyl isothiocyanate (**3c**; 1.72 g, 0.01 mol) in methanol (10 ml). Stirring is continued for 1 h at room temperature, and the mixture then refluxed for 3 h. The reaction is followed by T.L.C. on silica plates with dichloromethane/methanol elution. After the completion of the reaction, the solvent is evaporated and the residue is triturated in ether. The crude solid product is filtered, washed with ether, and dried; yield: 2.50 g (85%); m.p. 230–232 °C (from methanol).

| | | | | |
|---|---|---|---|---|
| $C_{14}H_{17}N_3O_2S$ | calc. | C 57.71 | H 5.88 | N 14.42 |
| (291.4) | found | 57.65 | 5.91 | 14.48 |

I.R. (KBr): $\nu_{C=O} = 1695$; $\nu_{C=S} = 1630$ cm$^{-1}$.

$^1$H-N.M.R. (DMSO-$d_6$): $\delta = 13.10$ (s, 1H, NH); 8.20–7.45 (m, $4H_{arom}$); 4.60 (t, 2H, $N-CH_2-CH_2-N-C=S$, $J = 6$ Hz); 3.58 (t, 4H, $CH_2-O-CH_2$, $J = 4$ Hz); 2.45 ppm [m, 6H, $CH_2-N(CH_2)-CH_2$].

**4-Imino-3-(2-morpholinoethyl)-2-thioxo-1,2,3,4-tetrahydroquinazoline (6, $R^1-R^1 = -CH_2-CH_2-O-CH_2-CH_2-$, $A = -CH_2-CH_2-$, Y = NH):**

A solution of 2-aminobenzonitrile (2.36 g, 0.02 mol) in methanol (30 ml) is added dropwise to a stirred solution of 2-morpholinoethyl isothiocyanate (**3c**; 3.44 g, 0.02 mol) in methanol (20 ml). The mixture is stirred at room temperature for 1 h and under reflux for 3 h and then allowed to stand at ambient temperature until no more crystals are formed. The product is isolated by suction, washed with ether, and dried: yield: 5.10 g (88%); m.p. 216 °C (from ethanol).

| | | | | |
|---|---|---|---|---|
| $C_{14}H_{17}N_4OS$ | calc. | C 57.91 | H 6.25 | N 19.29 |
| (290.4) | found | 58.03 | 6.21 | 19.29 |

I.R. (KBr): $\nu_{C=S} = 1620$ cm$^{-1}$.

$^1$H-N.M.R. (DMSO-$d_6$): $\delta = 12.05$ (s, 1H, NH); 9.27 (s, 1H, =NH); 8.20–7.00 (m, $4H_{arom}$); 4.62 (t, 2H, $N-CH_2-CH_2-N-C=S$, $J = 6$ Hz); 3.60 (t, 4H, $CH_2-O-CH_2$, $J = 4$ Hz); 2.50 ppm [m, 6H, $CH_2-N(CH_2)-CH_2$].

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