BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 50 (11), 3071—3072 (1977)

Convenient Synthesis of α-Mercaptoalkanoic Acid Esters Using *S*-Cyanomethyl Thiocarbamates

Yoshiro MASUYAMA, Yoshio UENO, and Makoto OKAWARA

Research Laboratory of Resources Utilization, Tokyo Institute of Technology, Nagatsuta-cho, Midori-ku, Yokohama 227

(Received June 18, 1977)

Synopsis. The reaction of cyanomethyl dithiocarbamate and *S*-cyanomethyl thiocarbamate with alkyl halides in aqueous medium selectively gave mono- and di-alkylated products. The treatment of the alkylated products with concd sulfuric acid gave α-mercaptoalkanoic acid esters.

Organic synthesis using phase-transfer catalyst in aqueous medium is one of the attractive subjects for effecting the C–C bond formation.[1] We previously reported the selective alkylation of cyanomethyl dithiocarbamate **1a** to give mono- (**2**) and di-alkylated cyanomethyl dithiocarbamates (**4**) and the subsequent ketone formation in aqueous medium.[2] On the other hand, it is well known that α-mercaptoalkanoic acids are useful as reducing and chelating agents in organic synthesis and medical fields.[3] Recently, α,α-diphenylmercaptoacetic acid was used effectively for the preparation of some hindered olefins.[4] α-Mercaptoalkanoic acids and their derivatives, however, have not been so easily accessible.

We wish to report here a convenient synthesis of α-mercaptoalkanoic acid esters **7** *via* stepwise alkylation and alcoholysis of cyanomethyl dithiocarbamate **1a** and *S*-cyanomethyl thiocarbamate **1b** in aqueous media.

Selective alkylation of **1a** with alkyl halides in the presence of catalytic amount of tetrabutylammonium iodide (TBA) in 50% aqueous sodium hydroxide has been previously reported.[2] Stepwise alkylation of **1b** was similarly achieved to give mono- (**3**) and di-alkylated thiocarbamates (**5**) in high yields. Dialkylated cyclic product **5d** was also obtained quantitatively by using 1,4-dibromobutane as an alkylating agent.

Alkaline hydrolysis of **4** in refluxing ethanol gave the corresponding ketones **6** in good yields.[2] On the other hand, α-mercaptoalkanoic acid esters **7** were obtained in good yields by the reaction of **4** with excess concd sulfuric acid (10 equiv) in refluxing ethanol for 20 h. The hydrolysis of **4** using lesser amounts of sulfuric acid (5 equiv) gave mainly (dimethylcarbamoylthio)acetic acid esters **9** (IR: ester C=O at 1725 and carbamoyl C=O at 1640 cm^{-1}). Meanwhile, treatment of thiocarbamates **3** and **5** with lesser amounts of concd sulfuric acid (5 equiv) gave **7** in good yields. Thus, *S*-cyanomethyl thiocarbamate **1b** seems to be a better starting material than dithiocarbamate **1a** for the preparation of α-mercaptoalkanoic acid esters **7**. Facile cleavage of the S–C bond with ethanolic sulfuric acid would be performed simultaneously with the conversion of nitrile into ester. Thiols **7** (IR: SH at 2550 cm^{-1}) were further converted to the corresponding disulfides **8** by air oxidation. The results are summarized in Scheme 1 and Table 1. The structures of all new compounds were confirmed by elemental analyses and spectral data.

TABLE 1. ALKYLATION OF **1b** AND HYDROLYSIS OF **3**, **4**, AND **5**

	R^1	R^2	Yield(%)		Yield(%)
3a	CH_3	H	86		
3b	$CH_3(CH_2)_4$	H	95	**7b**	61
5c	CH_3	$CH_3(CH_2)_5$	77	**7c**	66 (60)[a]
5d	$(CH_2)_4$		≈100	**7d**	75 (69)[a]

a) Figures in parentheses are yields *via* dithiocarbamates **4**.

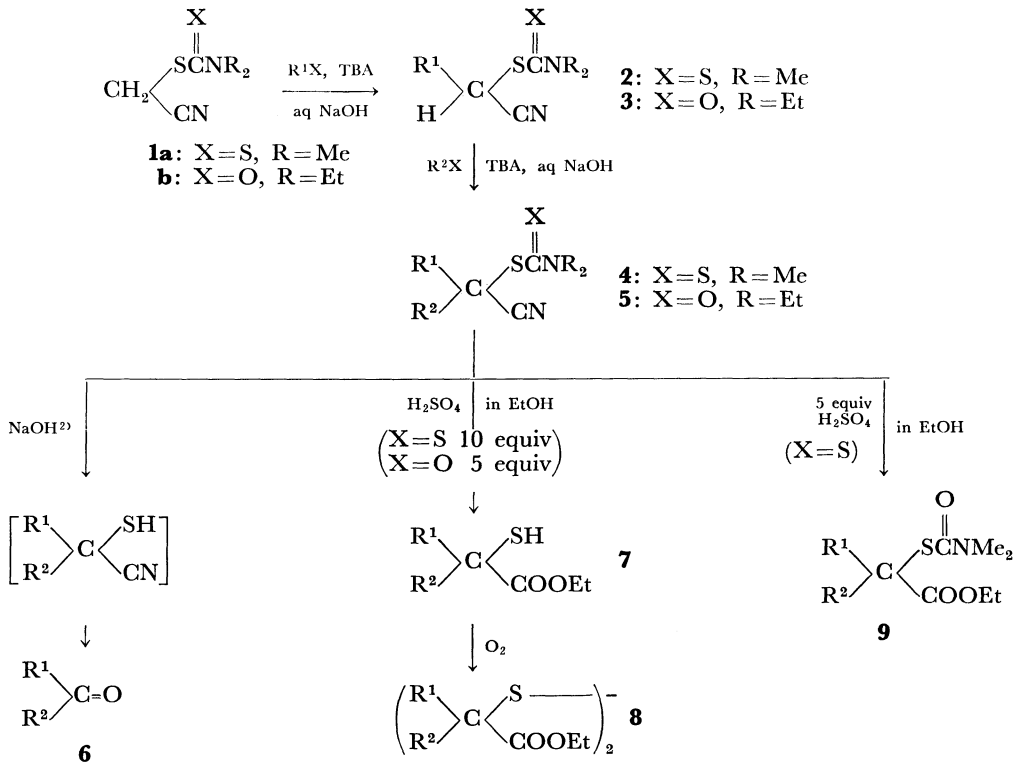
Experimental

*Dithiocarbamates **1a**, **2**, and **4**.* These compounds were prepared by the procedures described in our earlier paper.[2]

*S-Cyanomethyl Diethylthiocarbamate **1b**.* To 42 g (0.1 mol, 1.16 equiv) of 38% aq sodium diethylthiocarbamate in 25 ml of dimethylformamide was added dropwise 6.5 g (86 mmol) of chloroacetonitrile at 0—5 °C. The solution was stirred for 3 h at 25 °C, diluted with 50 ml of water, and extracted with two 50 ml portions of ether. The ether solutions were washed successively with three 30 ml portions of water and 50 ml of brine and dried over anhydrous sodium sulfate. Evaporation of the ether and distillation gave 14 g (95%) of **1b**; bp 135—136 °C/2.5 mmHg; IR (neat) 2270 (C≡N) and 1650 cm^{-1} (C=O); NMR (CCl_4) δ=1.20 (6H, t, J=7 Hz, CH_3), 3.40 (4H, q, J=7 Hz, N–CH_2), and 3.80 ppm (2H, s, S–CH_2); Found: C, 48.62; H, 7.07; N, 16.43%. Calcd for $C_7H_{12}N_2OS$: C, 48.83; H, 7.03; N, 16.27%.

*Alkylation of **1b**. 2-Diethylcarbamoylthioheptanenitrile **3b**:* To 0.86 g (5 mmol) of **1b** and 92 mg (0.25 mmol, 0.05 equiv) of TBA in 5 ml of 50% aq sodium hydroxide was added 0.62 ml (5 mmol) of 1-bromopentane. The solution was vigorously stirred for 10 h, diluted with 20 ml of water, and extracted with two 20 ml portions of ether. The ether solutions were washed successively with three 20 ml portions of water and 20 ml of brine and dried over anhydrous sodium sulfate. The crude product was purified by alumina column chromatography eluting with 4 : 1 hexane–chloroform to afford 1.16 g (95%) of **3b**; IR (neat) 2270 (C≡N) and 1655 cm^{-1} (C=O); NMR (CCl_4) δ=0.66—2.00 (11H, m), 1.17 (6H, t, J=7 Hz, N–C–CH_3), 3.35 (4H, q, J=7 Hz, N–CH_2), and 4.30 ppm (1H, t, J=7 Hz, S–CH); Found: C, 59.36; H, 9.44; N, 11.39%. Calcd for $C_{12}H_{22}N_2OS$: C, 59.48; H, 9.15; N, 11.56%.

*2-Diethylcarbamoylthiopropanenitrile **3a**:* As described above, 0.86 g (5 mmol) of **1b**, 92 mg (0.25 mmol) of TBA, and 0.62 ml (10 mmol, 2 equiv) of iodomethane were allowed to react for 8 h in 5 ml of 50% aq sodium hydroxide. After work-up, 0.80 g (86%) of **3a** was obtained; IR (neat) 2280 (C≡N) and 1660 cm^{-1} (C=O); NMR (CCl_4) δ=1.18 (6H, t, J=7 Hz, N–C–CH_3), 1.65 (3H, d, J=7.5 Hz, S–C–CH_3), 3.38 (4H, q, J=7 Hz, N–CH_2), and 4.33 ppm (1H, q, J=7.5 Hz, S–CH); Found: C, 51.67; H, 7.91; N, 15.09%. Calcd for



Scheme 1.

$C_8H_{14}N_2OS$: C, 51.58; H, 7.58; N, 15.04%.

2-Diethylcarbamoylthio-2-methyloctanenitrile **5c**: As described above, 0.93 g (5 mmol) of **3a**, 92 mg (0.25 mmol) of TBA, and 0.70 ml (5 mmol) of 1-bromohexane were allowed to react for 25 h in 5 ml of 50% aq sodium hydroxide. After work-up, 1.04 g (77%) of **5c** was obtained; IR (neat) 2270 (C≡N) and 1660 cm^{-1} (C=O); NMR (CCl_4) δ=1.15 (6H, t, J=7 Hz, N-C-CH_3), 0.77—2.00 (13H, m), 1.77 (3H, s, S-C-CH_3), and 3.33 ppm (4H, q, J=7 Hz, N-CH_2); Found: C, 62.21; H, 9.58; N, 10.34%. Calcd for $C_{14}H_{26}N_2OS$: C, 62.19; H, 9.69; N, 10.36%.

1-Diethylcarbamoylthiocyclopentanecarbonitrile **5d**: As described above, 0.86 g (5 mmol) of **1b**, 92 mg (0.25 mmol) of TBA, and 0.60 ml (5 mmol) of 1,4-dibromobutane were allowed to react for 20 h in 5 ml of 50% aq sodium hydroxide. After work-up, 1.12 g (≈100%) of **5d** was obtained; IR (neat) 2270 (C≡N) and 1655 cm^{-1} (C=O); NMR (CCl_4) δ=1.20 (6H, t, J=7 Hz, N-C-CH_3), 1.63—2.67 (8H, m), and 3.35 ppm (4H, q, J=7 Hz, N-CH_2); Found: C, 58.27; H, 8.27; N, 12.25%. Calcd for $C_{11}H_{18}N_2OS$: C, 58.39; H, 8.02; N, 12.38%.

Hydrolysis of **3b**, **4**, *and* **5**. *Ethyl 2-Mercaptoheptanoate* **7b**: To 486 mg (2 mmol) of **3b** in 5 ml of ethanol was added 1.2 ml (ca. 5 equiv) of concd sulfuric acid. The mixture was refluxed for 20 h, cooled, diluted with 10 ml of water, and extracted with two 20 ml portions of ether. The combined ether solutions were washed successively with three 20 ml portions of water and 20 ml of brine and dried over anhydrous sodium sulfate. The solvent was evaporated to yield 232 mg (61%) of **7b**; IR (neat) 2550 (SH) and 1735 cm^{-1} (C=O). **7b** was confirmed as the corresponding disulfide **8b** by allowing to stand for 2 days in contact with air; IR (neat) 1735 cm^{-1} (C=O); NMR (CCl_4) δ=0.67—2.00 (11H, m), 1.27 (3H, t, J=7 Hz, O-C-CH_3), 3.47 (1H, t, J=7 Hz, S-CH), and 4.22 ppm (2H, q, J=7 Hz, O-CH_2). An analytical sample was prepared by silica gel column Chromatography eluting with 1 : 1 hexane–chloroform; Found: C, 57.05; H, 9.12%. Calcd for $C_{18}H_{34}O_4S_2$: C, 57.12; H, 9.06%.

Ethyl 2-Mercapto-2-methyloctanoate **7c**: As described above, 540 mg (2 mmol) of **5c** and 1.2 ml (ca. 5 equiv) of concd sulfuric acid were allowed to react for 30 h in 5 ml of refluxing ethanol. After work-up, 288 mg (66%) of **7c** was obtained. **7c** was confirmed as the corresponding disulfide **8c** by air oxidation; IR (neat) 1730 cm^{-1} (C=O); NMR (CCl_4) δ=0.70—1.93 (13H, m), 1.27 (3H, t, J=7 Hz, O-C-CH_3), 1.40 (3H, s, S-C-CH_3), and 4.20 ppm (2H, q, J=7 Hz, O-CH_2); Found: C, 60.46; H, 9.92%. Calcd for $C_{22}H_{42}O_4S_2$: C, 60.80; H, 9.74%.

Ethyl 1-Mercaptocyclopentanecarboxylate **7d**: As described above, 452 mg (2 mmol) of **5d** and 1.2 ml (ca. 5 equiv) of concd sulfuric acid were allowed to react for 25 h in 5 ml of refluxing ethanol. After work-up, 261 mg (75%) of **7d** was obtained. **7d** was confirmed as the corresponding disulfide **8d** by air oxidation; IR (neat) 1735 cm^{-1} (C=O); NMR ($CDCl_3$) δ=1.28 (3H, t, J=7 Hz, O-C-CH_3), 1.48—2.35 (8H, m), and 4.22 ppm (2H, q, J=7 Hz, O-CH_2); Found: C, 55.57; H, 7.90%. Calcd for $C_{16}H_{26}O_4S_2$: C, 55.48; H, 7.57%.

The hydrolysis of dithiocarbamates **4** was carried out similarly to the hydrolysis of thiocarbamates **5** except using 10 equiv of concd sulfuric acid. These products were identified by comparison of physical properties with those of disulfides **8** obtained from thiocarbamates **5**.

References

1) E. V. Dehmlow, *Angew. Chem. Int. Ed. Engl.*, **13**, 170 (1974); M. Makosza, *Pure Appl. Chem.*, **43**, 439 (1975).

2) Y. Masuyama, Y. Ueno, and M. Okawara, *Tetrahedron Lett.*, **1976**, 2967.

3) Kirk-Othmer, "Encyclopedia of Chemical Technology," 2nd ed., Interscience Publishers, Vol. 20, New York (1969), p. 198.

4) D. H. R. Barton and B. J. Willis, *J. Chem. Soc. Perkin Trans. 1*, **1972**, 305.