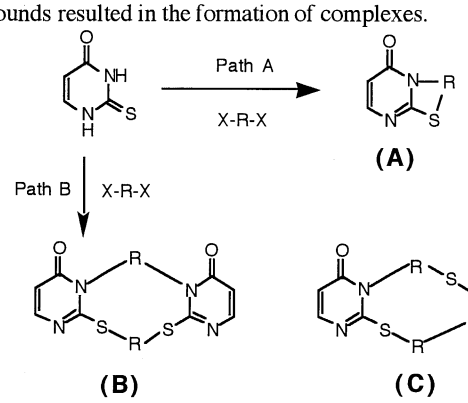
Preparation of Novel Heterocycles by Dimeric Alkylation of 2-Thiouracils and Formation of Complexes with Copper and Silver Ions

Toshio Itahara
Institute of Chemistry, College of Liberal Arts, Kagoshima University, Korimoto, Kagoshima 890

(Received September 3, 1996)

Dimeric Alkylation of 2-thiouracils with dihalomethanes and α,α'-dibromoxylenes gave novel heterocycles which were treated with copper(II) and silver(I) compounds to result in formation of complexes.

Although the cyclic alkylation of 2-thiouracils (**1**) with 1,2-dibromoethane[1a-d] and 1,3-dibromopropane[1d] has been reported to give the heterocyclic compounds (**A**) (Path A), little attention has been paid to dimeric alkylation of **1** (Path B). This paper describes an easy preparation of novel heterocycles (**B**) by the dimeric alkylation of **1** with dihalomethanes, α,α'-dibromo-*o*- and *p*-xylenes. However, compounds (**C**), which are the isomers of the heterocycles (**B**), were not isolated. The treatment of the heterocycles (**B**) with copper(II) and silver(I) compounds resulted in the formation of complexes.



Treatment of 2-thiouracil (**1a**) with CH_2I_2 or CH_2Br_2 in the presence of NaH in N,N-dimethylformamide (DMF) gave a novel dimeric heterocycle (**2a**) as a main product together with small amounts of a monomeric compound (**5a**) and a trimeric heterocycle (**7a**). The reaction of 2-thiothymine (**1b**) and 6-methyl-2-thiouracil (**1c**) also gave similar products such as **2b** and **2c** together with **7c**. Under similar conditions, treatment of **1a-c** with α,α'-dibromo-*o*-xylene gave dimeric compounds (**3a-c**) and monomeric compounds (**6a-c**). The reaction of **1a** with α,α'-dibromo-*p*-xylene also gave a dimeric product (**4a**), but any monomeric compounds were not obtained. These results are summarized in Table 1. The structures of the dimeric compounds (**B**) such as **2-4** were distinguishable from those of their isomers (**C**) on the basis of ^1H NMR and ^{13}C NMR spectral data.[2] Furthermore, the structures of the dimeric compounds and the monomeric compounds were differentiated on the basis of the mass spectral data, *e.g*, Mass, m/z (M^+, rel intensity, %): **2a**: 280 (100); **5a**: 140 (100); **7a**: 420 (80); **3a**: 460 (57); **6a**: 230 (100); **4a**: 460 (70).

Thus far the several types of macrocyclic thioethers have been prepared and are known to form complexes with several metal ions.[3] Furthermore, metal complexes with sulfur ligands

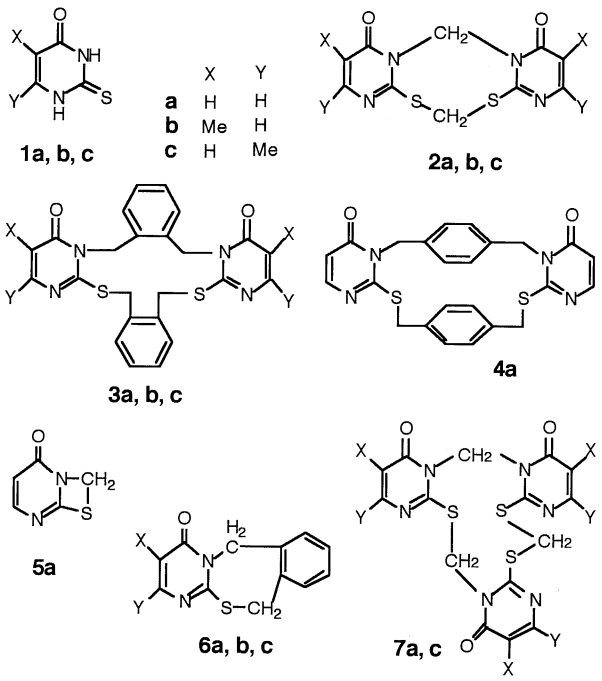


Table 1. Preparation of heterocycles from 2-thiouracils (**1**) and dihalogenated compounds (X-R-X)[a]

1	X-R-X	Conv.[b] %	Product Isolated Yield / %[c]
1a	CH_2I_2	62	**2a** / 70; **5a** / 3; **7a** / 4
1a	CH_2Br_2	58	**2a** / 67; **5a** / 4; **7a** / 5
1a	α,α'-Dibromo-*o*-xylene	51	**3a** / 30; **6a** / 46
1a	α,α'-Dibromo-*p*-xylene	47	**4a** / 15
1b	CH_2I_2	64	**2b** / 65
1b	CH_2Br_2	55	**2b** / 60
1b	α,α'-Dibromo-*o*-xylene	50	**3b** / 28; **6b** / 44
1c	CH_2I_2	70	**2c** / 70; **7c** / 4
1c	CH_2Br_2	55	**2c** / 68; **7c** / 3
1c	α,α'-Dibromo-*o*-xylene	52	**3c** / 32; **6c** / 48

[a] Reaction conditions are as follows: **1** (10 mmol), X-R-X (10 mml), NaH (20 mmol), DMF (100 ml), stirring at room temperature for 24 h. [b] Conversion based on the amount of **1** consumed. [c] Yield based on **1** consumed.

have been extensively studied.[4] These observations led us to attempt to form complexes of the heterocycles **2-4** with metal ions.

When AgOAc or CF_3SO_3Ag was added into the solution of **3a** in $CDCl_3$, the chemical shifts of signals of **3a** partially changed (Figure 1). The treatment of **3b,c** and **4a** with the silver compounds also resulted in similar changes of their signals, while the treatment of **2a-c** did not result in the changes. Therefore, it seemed reasonable to assume that the two benzene rings in **3** and **4** are essential for the complexation with silver(I) ion.

Adding of copper(II) ion into the solution of **2-4** in $CDCl_3$ resulted in changes of the chemical shifts and broadening of the signals on the ^1H NMR spectra. When $CuCl_2 \cdot 2H_2O$ was added into the solution of **3a** in $CDCl_3$, color of the solution changed to blue (λ_{max}=735 nm). It can be seen from Figure 1 that the signals of the proton of pyrimidine ring at 6-position of **3a** were not detected as a result of the broadening and those at 5-position were extremely broadened and shifted to lower field. Figure 1 also shows that the signal of the methylene group adjacent to sulfur atom (CH_2-S) was shifted to lower field, while that of CH_2-N was only slightly shifted to higher field. These results may be explained in terms of coordination of the thioether and the N_1 atom of the pyrimidine ring to the copper(II) ion.

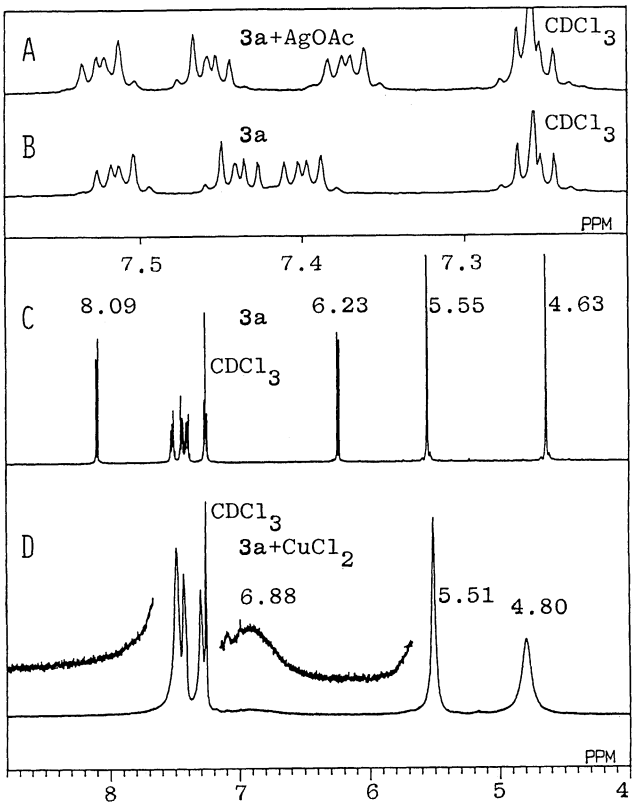


Figure 1. ^1H NMR Spectra of **3a** at 27 °C.
A: **3a** (10 mg) and AgOAc (1 mg) in $CDCl_3$ (0.6 ml).
B, C: **3a** (10 mg) in $CDCl_3$ (0.6 ml).
D: **3a** (10 mg) and $CuCl_2 \cdot 2H_2O$ (2 mg) in $CDCl_3$ (0.6 ml).

References and Notes

1 a) N. G. Pashkurov and V. S. Reznik, *Khim. Geterotsikl. Soedin,* **1968**, 918 (*Chem. Abstr.*, **71**, 13088 (1969)); b) G. R. Brown and W. R. Dyson, *J. Chem. Soc. C*, **1971**, 1527; c) E. Campaigne, K. Foiting, J. C. Huffman, and T. P. Selby, *J. Heterocycl. Chem.*, **18**, 575 (1981); d) P. Pecorari, M. Rinaldi, and M. Paola Costi, *J. Heterocycl. Chem.*, **26**, 1701 (1989).

2 All new compounds were characterized by elemental analyses, and ^1H NMR, ^{13}C NMR and Mass spectral data. The analytical and NMR spectral data of **2a-7a** are as follows.

2a: Mp 232-235 °C; ^1H NMR ($CDCl_3$) δ 8.25 (d, 2H, J = 5.6 Hz), 8.21 (d, 1H, J = 6.0 Hz), 6.71 (d, 1H, J = 15.0 Hz), 6.44 (d, 2H, J = 5.6 Hz), 5.38 (d, 1H, J = 6.0 Hz), 4.29 (d, 1H, J = 15.0 Hz); ^{13}C NMR ($CDCl_3$) δ 169.52, 166.05, 158.86, 103.93, 81.11, 33.35. Found: C, 42.90; H, 2.74; N, 19.94%. Calcd for $C_{10}H_8N_4O_2S_2$: C, 42.85; H, 2.88; N, 19.99%.

3a: Mp 228-230 °C; ^1H NMR (Figure 1); ^{13}C NMR ($CDCl_3$) δ 171.52, 167.96, 157.64 , 135.30, 134.69, 130.58, 130.57, 129.29, 127.90, 103.41, 65.18, 33.36. Found: C, 61.78; H, 4.47; N, 12.03%. Calcd for $C_{24}H_{20}N_4O_2S_2 \cdot 1/2H_2O$: C, 61.39; H, 4.51; N, 11.93%.

4a: Mp 268-271 °C; ^1H NMR ($CDCl_3$) δ 8.24 (d, 2H, J = 5.6 Hz), 7.01 (s, 4H), 6.87 (s, 4H), 6.49 (d, 2H, J = 5.6 Hz), 5.65 (s, 4H), 4.26 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 171.22, 168.54, 158.18, 137.28, 136.26, 128.10, 126.14, 103.85, 66.09, 33.65. Found: C, 62.63; H, 4.47; N, 11.98%. Calcd for $C_{24}H_{20}N_4O_2S_2$: C, 62.59; H, 4.38; N, 12.16%.

5a: Mp 127-128 °C; ^1H NMR ($CDCl_3$) δ 7.77 (d, 1H, J = 7.0 Hz), 6.23 (d, 1H, J = 7.0 Hz), 5.17 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 161.58, 158.03, 155.37, 113.22, 47.56. Found: C, 42.65; H, 2.88; N, 19.75%. Calcd for $C_5H_4N_2OS$: C, 42.85; H, 2.88; N, 19.99%.

6a: Mp 188-190 °C; ^1H NMR ($CDCl_3$) δ 7.58 (d, 1H, J = 6.0 Hz), 7.53 (dd, 1H, J = 7.0 Hz and 2.0 Hz), 7.30-7.40 (m, 3H), 6.18 (d, 1H, J = 6.0 Hz), 5.46 (s, 2H), 4.36 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 162.16, 161.46, 152.69, 135.43, 135.27, 130.07, 130.05, 129.43, 128.38, 111.66, 43.67, 35.99. Found: C, 62.42; H, 4.26; N, 12.02%. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16%.

7a: Mp 193-196 °C; ^1H NMR ($CDCl_3$) δ 8.38 (d, 1H, J = 5.6 Hz), 8.35 (d, 1H, J = 5.6 Hz), 8.27 (d, 1H, J = 5.6 Hz), 6.59 (d, 1H, J = 5.6 Hz), 6.50 (d, 1H, J = 5.6 Hz), 6.45 (d, 1H, J = 5.6 Hz), 6.23 (s, 2H), 5.98 (s, 2H), 4.91 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 170.84, 170.11, 168.74, 168.66, 167.48, 167.16, 159.11, 158.84, 158.11, 104.83, 104.29, 104.26, 85.88, 66.74, 31.91. Found: C, 42.58; H, 2.63; N, 19.95%. Calcd for $C_{15}H_{12}N_6O_3S_3$: C, 42.85; H, 2.88; N, 19.99%.

3 a) S. R. Cooper, *Acc. Chem. Res.*, **21**, 141 (1988); b) H. Xianming, R. M. Kellogg, and F. van Bolhuis, *J. Chem. Soc. Perkin Trans. 1*, **1994**, 707.

4 a) S. Toyota, Y. Matsuda, M. Oki, and H. Akashi, *Chem. Lett.*, **1995**, 31; b) D. Sellmann, D. Haussinger, F. Knoch, and M. Moll, *J. Am. Chem. Soc.*, **118**, 5368 (1996).