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Reaction of Benzoxazoline-2-thiones with Alkyl Halides

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The effect of the solvent on the reaction of benzoxazoline-2-thiones with alkyl halides was studied. The reaction of **1** with alkyl halides and potassium carbonate in dimethylformamide (DMF) gave the corresponding 2-alkylthiobenzoxazoles (**2**), but the same reaction gave 2-methoxybenzoxazoles (**4a**) when methanol was used in place of DMF as the solvent. On the other hand, the reaction of **1**, methyl iodide, alcohol, and sodium hydride in tetrahydrofuran (THF) gave 2-[*N*-(dialkoxymethylene)amino]phenols (**5**).

Keywords——benzoxazoline-2-thione; 2-alkoxybenzoxazole; 2-[*N*-(dialkoxymethylene)amino]phenol; alkylation; solvent effect

Substituted benzoxazoline-2-thiones are known to have various biological activities, and the preparation of 2-alkylthiobenzoxazoles has been achieved by several methods. For example, the reaction of benzoxazoline-2-thione with diazomethane or dimethyl sulfate[1,2] gave 2-methylthiobenzoxazole, and the reaction of benzoxazoline-2-thione with alkyl halides in the presence of phase transfer catalyst gave the corresponding 2-alkylthiobenzoxazole.[3] The preparation of 3-substituted benzoxazoline-2-thiones[4] and the reaction of 2-alkylthiobenzoxazole with alkyl halide and potassium hydroxide in methanol to give benzoxazolin-2-one and sulfide[5] were studied in our laboratory.

The present report describes the efrect of the solvent on the reactionof benzoxazoline-2-thiones with alkyl halides.

When a solution of 5-chlorobenzoxazoline-2-thione (**1**) and alkyl halide in dimethylformamide (DMF) was stirred in the presence of potassium carbonate at room temperature, the corresponding 2-alkylthio-5-chlorobenzoxazole (**2**) was obtained in a higher yield than in the reported methods.[3] For example, reaction of **1** with primary or secondary alkyl halides, such as methyl, ethyl, and isopropyl iodides or benzyl chloride gave 2-methylthio- (**2a**, 82%), 2-ethylthio- (**2b**, 78%), 2-isopropylthio-(**2c**, 68%), and 2-benzylthio- (**2d**, 76%) 5-chlorobenzoxazoles, respectively. However, similar reaction of **1** with *tert*-butyl bromide gave 3-(*tert*-butyl)-5-chlorobenzoxazoline-2-thione (**3e**) and 2-(*tert*-butylthio)-5-chlorobenzoxazole (**2e**) in 17 and 8% yields, respectively.

The reaction of **1** with excess benzyl chloride and potassium carbonate in methanol at room temperature gave unexpected compounds, 5-chloro-2-methoxybenzoxazole (**4a**) and dibenzyl sulfide, in 74 and 72% yields, respectively. Since the reaction of **1** with benzyl chloride in methanol was thought to proceed *via* the formation of 2-benzylthio-5-chlorobenzoxazole (**2d**) followed by the attack of methoxide anion at the C_2 carbon of **2d**, a solution of **2d**, benzyl chloride, and potassium carbonate in methanol was stirred at room

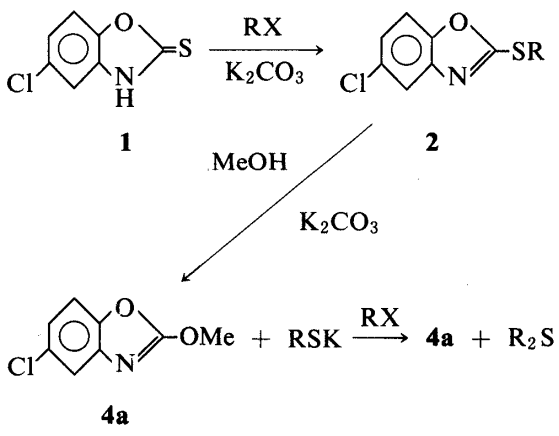


Chart 1

temperature. The resulting products were dibenzyl sulfide (77% yield) and **4a** (70% yield), as expected. Although the reaction of **2d** with methanol in the absence of potassium carbonate resulted in the recovery of **2d**, sodium hydride was found to be effective for this reaction as well as potassium carbonate.

In order to avoid the use of a large excess of alcohol in this reaction, tetrahydrofuran (THF) was used as a solvent. Namely, stirring of a solution of **1**, methyl iodide, benzyl alcohol, and sodium hydride in the molar ratio of 1:3:3:4 in THF at room temperature gave 2-benzyloxy-5-chlorobenzoxazole (**4d**) and an unexpected compound, 4-chloro-2-[*N*-(dibenzyloxymethylene)amino]phenol (**5d**), in 14 and 50% yields, respectively. Compound **5d** was also obtained in 56% yield by the reaction of **4d** with benzyl alcohol and sodium hydride in THF. The structure of **5d** was established on the basis of several instrumental analyses and the following facts.

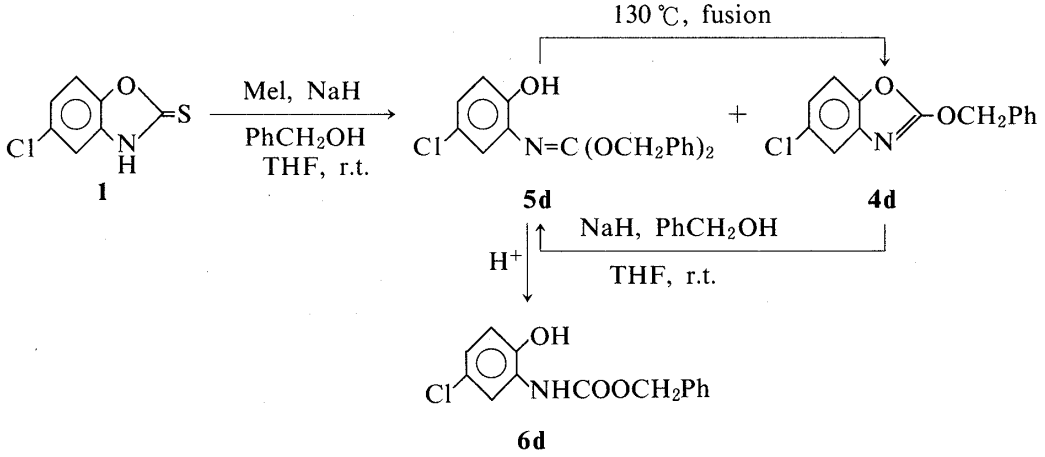
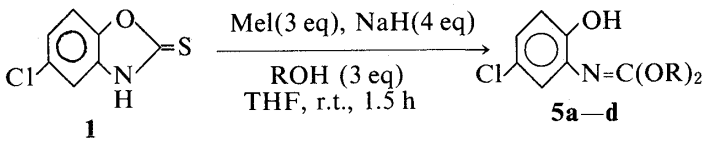


Chart 2

TABLE I. 4-Chloro-2-[*N*-(dialkoxymethylene)amino]phenols (**5**)



Product	R	Yield (%)	mp (°C)	Analysis (%) Calcd (Found) C	H	N	NMR (δ) in $CDCl_3$	MS (*m/e*)
5a	Me	39	88—91	50.13	4.67	6.50	3.90 (6H, s, CH_3×2)	217 (M^++2)
				(49.84	4.55	6.22)	6.77 (1H, br, OH)	215 (M^++2)
5b	Et	68	77—79	54.21	5.79	5.75	1.37 (6H, t, CH_3×2)	245 (M^++2)
				(53.89	5.78	5.38)	4.32 (4H, q, CH_2×2)	243 (M^++)
							6.80 (1H, br, OH)	
5c	Me_2CH	65	65—67	57.46	6.68	5.15	1.39 (12H, d, CH_3×4)	273 (M^++2)
				(57.18	6.73	5.00)	4.72—5.45	271 (M^++)
							(2H, m, CH_3×2)	
							6.89 (1H, br, OH)	
5d	$PhCH_2$	50	93—95	68.57	4.93	3.81	5.32 (4H, s, CH_2×2)	369 (M^++2)
				(68.41	4.72	3.66)	6.36 (1H, br, OH)	367 (M^++)

i) Compound **5d** gave a positive color test with ferrous chloride reagent.

ii) Heating of **5d** at 130°C gave **4d** in 85% yield.

iii) Stirring of a solution of **4d**, benzyl alcohol, and sodium hydride in THF at room temperature gave **5d** in 56% yield.

iv) Addition of one drop of conc. hydrochloric acid to a solution of **5d** in methanol gave benzyl 5-chloro-2-hydroxyphenylcarbamate (**6d**) in 40% yield. Similar reactions of **1** with several alcohols in THF to give the corresponding congeners of **5d** were carried out and the results are listed in Table I.

Experimental

Melting points (determined on a Yanagimoto micromelting point apparatus) are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken with a Hitachi R-24 spectrometer at 60 MHz, with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu-LKB 9000 spectrometer, and infrared (IR) spectra on a Nippon Bunko A-102 spectrometer.

General Procedure for the Alkylation of 1 with Alkyl Halides in DMF: 2-Benzylthio-5-chlorobenzoxazole (2d)———Benzyl chloride (7 g) was added dropwise to a mixture of **1** (8 g), K_2CO_3 (6 g), and DMF (100 ml). The mixture was stirred at room temperature for 1.5 h then poured into ice-water. The precipitate was collected by suction and recrystallized from cyclohexane to give 9 g (76%) of **2d**, mp76—77°C. *Anal.* Calcd for $C_{14}H_{10}ClNOS$: C, 60.9; H, 3.63; N, 5.08. Found: C, 61.17; H, 3.58; N, 5.23. NMR ($CDCl_3$) δ: 4.57 (2H, s, CH_2). MS *m/e*: 277 (M^++2), 275 (M^+).

Reaction of 1 with *tert*-Butyl Bromide———*tert*-Butyl bromide (10 g) was added dropwise to a mixture of **1** (5 g), K_2CO_3 (10 g), and dry DMF (100 ml) with cooling. The mixture was heated at 50°C for 20 h, poured into ice-water, and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried, and concentrated. The residue was chromatographed on a column of alumina. The first fraction eluted with cyclohexane gave 0.49 g (8%) of **2e**, mp 47—49°C, bp 125—130°C (5 mmHg). *Anal.* Calcd for $C_{11}H_{12}ClNOS$: C, 54.65; H, 5.00; N, 5.79. Found: C, 54.51; H, 4.99; N, 5.84. NMR ($CDCl_3$) δ: 1.69 (9H, s, $CH_3\times3$). MS *m/e*: 243 (M^++2), 241 (M^+). The second fraction eluted with benzene gave 1.13 g (17%) of **3e**, mp 103—104°C (from cyclohexane). *Anal.* Calcd for $C_{11}H_{12}ClNOS$: C, 54.65; H, 5.00; N, 5.79. Found: C, 54.46; H, 4.99; N, 5.77. NMR ($CDCl_3$) δ: 2.02 (9H, s, $CH_3\times3$). MS *m/e*: 243 (M^++2), 241 (M^+).

Reaction of 1 with Benzyl Chloride and Potassium Carbonate in Methanol———Benzyl chloride (5 g) was added dropwise to a mixture of **1** (3 g), K_2CO_3 (5 g), and methanol (100 ml). The mixture was stirred at room temperature for 26 h, then poured into ice-water, and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried, and concentrated. The residue was chromatographed on a column of silica gel. The first fraction eluted with cyclohexane gave 2.5 g (72%) of dibenzyl sulfide, mp 46—48°C, which was shown to be identical with an authentic sample by comparison of their NMR spectra. The second fraction eluted with benzene gave 2.2 g (74%) of **4a**, which was recrystallized from petr. ether, mp 82—84°C (Lit. 80.5—81.5°C[6]).

Reaction of 2d with Benzyl Chloride and Potassium Carbonate in Methanol———Benzyl chloride (2.5 g) was added dropwise to a mixture of **2d** (3 g), K_2CO_3 (3 g), and methanol (100 ml). The mixture was stirred at room temperature for 11 h and treated as described for the reaction of **1** with benzyl chloride and potassium carbonate in methanol to give 1.4 g (70%) of **4a** and 1.8 g (77%) of dibenzyl sulfide.

Reaction of 1 with Methyl Iodide, Benzyl Alcohol, and Sodium Hydride in THF———Sodium hydride (50% dispersion in oil, 2.1 g) was added portion-wise to a mixture of **1** (2 g), benzyl alcohol (3.5 g), and THF (100 ml), then methyl iodide (4.6 g) was added. The mixture was stirred at room temperature for 1.5 h, poured into ice-water, and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried, and concentrated. The residue was purified by fractional recrystallization from cyclohexane. Initially, 2 g (50%) of **5d** was obtained, mp 93—95°C. Analyticl data are listed in Table I. Next, 0.4 g (14%) of **4d** was obtained, mp 90—92°C. *Anal.* Calcd for $C_{14}H_{10}ClNO_2$: C, 64.73; H, 3.85; N, 5.39. Found: C, 64.38; H, 3.83; N, 5.17. NMR ($CDCl_3$) δ: 5.58 (2H, s, CH_2). MS *m/e*: 261 (M^++2), 259 (M^+).

General Procedure for the Reaction of 4d with Alcohol and Sodium Hydride———A Typical Example: Sodium hydride (50% dispersion in oil, 0.2 g) was added portionwise to a mixture of **4d** (1 g), benzyl chloride (0.5 g), and THF (50 ml). The mixture was stirred at room temperature for 2 h, poured into ice-water, and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried, and concentrated. The residue was recrystallized from cyclohexane to give 0.8 g (56%) of **5d**, which was identical with an authentic sample.

Conversion of 5d to 4d———One gram of **5d** was heated at 130°C for 1 h. The resulting product was recrystallized to give 0.6 g (85%) of **4d**, which was identical with an authentic sample.

Benzyl 5-Chloro-2-hydroxyphenylcarbamate (6d)———One drop of conc. HCl was added to a solution of **5d** (1 g) in THF (50 ml) and H_2O (50 ml), then the solution was stirred at room temperature for 5 min. The resulting solution was extracted with AcOEt and the AcOEt layer was washed with H_2O, dried, and concentrated. The residue was recrystallized from benzene to give 0.3 g (40%) of **6d**, mp 160—162°C. *Anal.*

Calcd for $C_{14}H_{12}ClNO_3$: C, 60.54; H, 4.32; N, 5.04. Found: C, 60.22; H, 4.25; N, 4.75. IR ν_{max}^{Nujol} cm^{-1}: 3440, 3200, 1710. NMR (DMSO-d_6) δ: 5.25 (2H, s, CH_2), 8.61 (1H, br, NH), 10.22 (1H, s, OH). MS m/e: 279 (M^++2), 277 (M^+).

References and Notes

1) H. Zinner and N. Niendorf, *Chem. Ber.*, **89**, 1012 (1956).
2) *a*) S. Hunig and K.H. Fritsch, *Justus Lieligs Ann. Chem.*, **609**, 143 (1957); *b*) B. Beilenson and F.M. Hamer, *J. Chem. Soc.*, **1939**, 143.
3) J. Henri, P. Hassanaly, J. Kister, and J. Metzger, *Phosphorus Sulfur*, **3**, 355 (1977).
4) M. Yamato, Y. Takeuchi, K. Hashigaki, K. Hattori, K. Muroga, and, T. Hirota, *Chem. Pharm. Bull.*, "accepted."
5) M. Yamato, Y. Takeuchi, K. Hattori, and K. Hashigaki, *Synthesis*, **1982**, 1014.
6) J. Sam and J.N. Plampin, *J. Pharm Sci.*, **53**, 538 (1964).