[Chem. Pharm. Bull. 31(11)3946—3950(1983)]

A New Method for the Preparation of 2-Alkoxybenzoxazoles

MASATOSHI YAMATO,* YASUO TAKEUCHI, KYOKO HATTORI, and KUNIKO HASHIGAKI

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1–1–1, Okayama 700, Japan

(Received April 4, 1983)

A one-pot synthesis of 2-alkoxybenzoxazole (I) from benzoxazoline-2-thione (II) was achieved. Treatment of benzoxazoline-2-thione with methyl iodide followed by an alcohol at room temperature in the presence of sodium hydride gave I. The reaction involves the intermediate of 2-(methylthio)benzoxazole (IIIa), followed by substitution of the methylthio group by an alkoxide anion. The general applicability of this method is discussed.

Keywords——2-alkoxybenzoxazole; 2-(alkylthio)benzoxazole; benzoxazoline-2-thione; 2-(dialkoxymethylene)aminophenol; 4-*tert*-butylcyclohexanol

In the course of a study on the synthesis and biological activity of benzoxazole analogs, preparation of 2-alkoxybenzoxazoles (I) became necessary. A few congeners of I have been synthesized: Koyama *et al.* reported that the treatment of 6-methoxybenzoxazolin-2-one (coixol) with diazomethane gave 2,6-dimethoxybenzoxazole in 40% yield accompanied with 6-methoxy-3-methylbenzoxazolin-2-one in 60% yield.[1] Compound I has been generally synthesized from benzoxazoline-2-thione (II) *via* two steps: chlorination of II with phosphorus pentachloride or chlorine to give 2-chlorobenzoxazole[2] followed by replacement of the chlorine atom by an alkoxide anion.[3] Watanabe and Mukaiyama synthesized I from 2-fluorobenzoxazole.[4] However, 2-halobenzoxazoles are sensitive to hydrolysis and the yields of I from 2-halobenzoxazoles are not satisfactory.

We previously reported the solvent effect on the reaction of II with alkyl halide: the reaction of II with alkyl halide in dimethylformamide (DMF) in the presence of a base gives the corresponding 2-(alkylthio)benzoxazole (III), while the same reaction using methanol in place of DMF as a solvent gives 2-methoxybenzoxazole (Ia).[5] We were interested in this result and followed up this unexpected observation by a series of experiments. Consequently, we found new methods for the preparation of I from II.

Since we thought that the reaction of II with alkyl halides in methanol proceeded *via* the formation of III, the reaction of 2-(methylthio)benzoxazole (IIIa) with alkoxide anion was carried out. Stirring of a solution of IIIa and phenethyl alcohol in tetrahydrofuran (THF) in the presence of sodium hydride for 2 h at room temperature gave 2-(phenethyloxy)-benzoxazole (Id) in 59% yield. This finding led us to develop methods for one-pot synthesis of I from II. One of the methods (method A) involves removal of the methylthio group by an alkoxide ion. The reaction was performed by adding methyl iodide and 2 eq of sodium hydride to a THF solution of II at room temperature, followed after 2 h by addition of alcohol[6] (Table I).

The substitution rate of the methylthio group of IIIa by an alkoxyl group decreased in the order of primary, secondary, and tertiary alcohols. For example, the 2 h reaction of IIIa with primary alcohol gave Ia—g in moderate to high yields. On the other hand, the same reaction of IIIa with a secondary alcohol such as cyclohexanol gave 2-(cyclohexyloxy)-benzoxazole (Ih) in a poor yield. When the reaction time was prolonged to 6, 10, and 15 h,

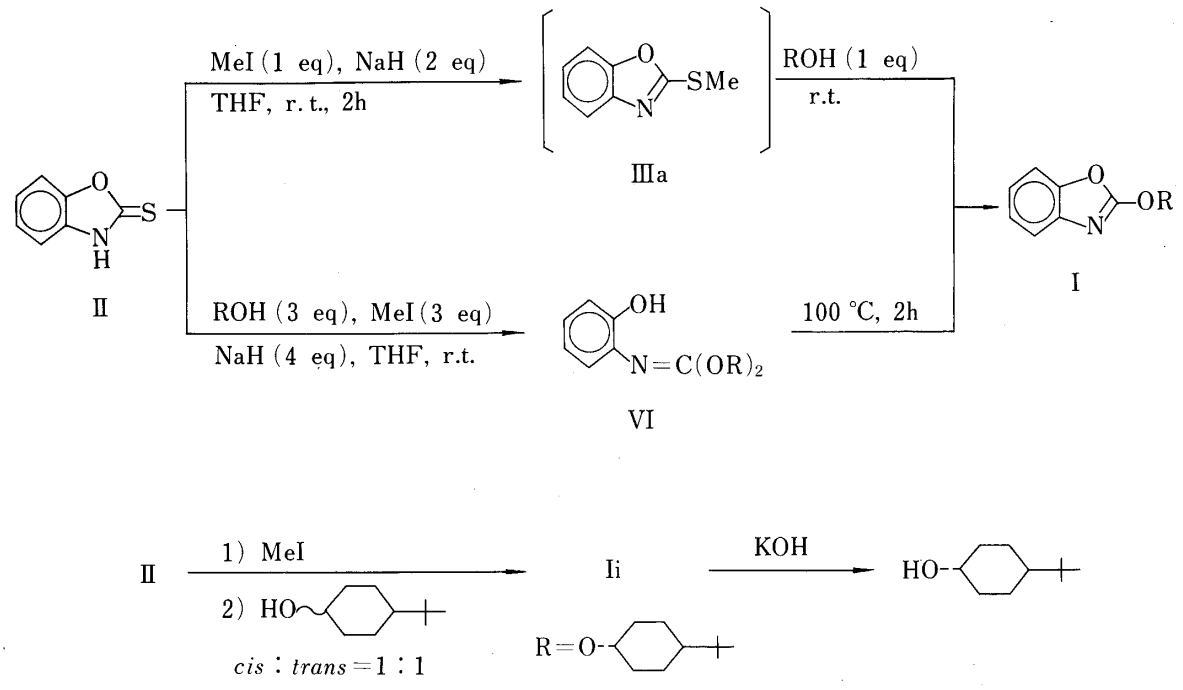


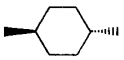
Chart 1

the yields of Ih increased to 42, 49, and 63%, respectively. In the case of *tert*-butyl alcohol, the yield of 2-*tert*-butoxybenzoxazole (Io) was less than 63% even if the reaction was carried out for 65 h.

A difference of substitution rate between the reactions of stereoisomeric alcohols with IIIa was also observed. The reaction of IIIa with *cis*-4-*tert*-butylcyclohexanol for 25 h gave 2-(*cis*-4-*tert*-butylcyclohexyloxy)benzoxazole (Ij) in 24% yield; the yield did not exceed 34% even after reaction for 6 d, while the similar reaction with *trans*-4-*tert*-butylcyclohexanol gave 2-(*trans*-4-*tert*-butylcyclohexyloxy)benzoxazole (Ii) in 52% yield. These findings prompted us to use IIIa as a separating agent for the stereoisomeric alcohols. For this purpose, the reaction of II with methyl iodide and 4-*tert*-butylcyclohexanol (*cis* : *trans* = 1 : 1) was undertaken (Chart 1). Treatment of a mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanol with IIIa prepared from II gave Ii in 71% yield, and this was hydrolyzed with potassium hydroxide to give *trans*-4-*tert*-butylcyclohexanol in 77% yield. *cis*-4-*tert*-Butylcyclohexanol was not detected in the product.

The above method was applied to the preparation of various 2-alkoxybenzoxazoles and was found to be useful for the preparation of 2-[(ω-*N*,*N*-dialkylamino)alkoxy]benzoxazoles (Ie—g), which carry a substituent reactive to methyl iodide. The yields of Ia and 2-benzyloxybenzoxazole (Ic) by this method were relatively low. In the case of the preparation of Ia, benzoxazolin-2-one (IV) was obtained as a by-product in 20% yield and in the case of Ic, IV and benzyl methyl sulfide (Va) were produced in 20 and 22% yields, respectively. These compounds may be the products of attack of the methanethiolate anion, which was produced together with Ia or Ic, on the methoxy or benzyloxy group in Ia or Ic. The yields of IV and Va increased on increasing the reaction temperature of IIIa with benzyl alcohol. It seemed probable that attack of methanethiolate anion on the benzyloxy group in 2-(α-substituted benzyloxy)benzoxazole (I), which is produced by the reaction of II with methyl iodide and α-substituted benzyl alcohol, would be hindered. Therefore, the reaction of II with methyl iodide and α-substituted benzyl alcohol such as 1-phenethyl alcohol or diphenylmethyl alcohol was carried out. 2-(1-Phenethyloxy)benzoxazole (Ik) or 2-(diphenylmethoxy)benzoxazole (Im) was obtained in 76 or 63% yield and the corresponding sulfide and IV were not formed.

TABLE I. 2-Alkoxybenzoxazoles (I)

Run	ROH (R)	Method	R.T.[a] (h)	Product	Yield (%)	mp (°C) or bp (°C/mmHg)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR ($CDCl_3$) δ
1	Me	A	2	Ia	43	89–90/12[b]	$C_8H_7NO_2$	64.42 (64.06)	4.73 (4.85)	9.39 (9.45)	4.21 (3H, s)
2		B	2		74						
3	Et	A	2	Ib	68	97–98/10	$C_9H_9NO_2$	66.24 (66.03)	5.56 (5.49)	8.58 (8.36)	1.46 (3H, t, J=7.0 Hz), 4.62 (2H, q, J=7.0 Hz)
4	$PhCH_2$	A	2	Ic	40	49–50	$C_{14}H_{11}NO_2$	74.65 (74.50)	4.92 (4.83)	6.22 (6.04)	5.52 (2H, s)
5		B	1.5		57						
6	$PhCH_2CH_2$	A	2	Id	63	188–190/10[c]	$C_{15}H_{13}NO_2$	75.29 (75.62)	5.48 (5.40)	5.85 (5.42)	3.17 (2H, t, J=6.8 Hz), 4.75 (2H, t, J=6.8 Hz)
7	$Me_2NCH_2CH_2$	A	2	Ie·picrate	68	>300	$C_{17}H_{17}N_5O_9$	46.90 (47.01)	3.94 (3.82)	16.09 (15.79)	2.95 (6H, s),[d] 3.71 (2H, t, J=5.2 Hz), 4.97 (2H, t, J=5.2 Hz)
8	$Et_2NCH_2CH_2$	A	2	If·picrate	73	142–143	$C_{19}H_{21}N_5O_9$	49.24 (49.17)	4.57 (4.52)	15.11 (14.84)	1.43 (6H, t, J=7 Hz),[d] 3.46 (4H, q, J=7 Hz), 3.80 (2H, t, J=5.2 Hz), 5.02 (2H, t, J=5.2 Hz)
9	$Me_2NCH_2CH_2CH_2$	A	2	Ig·picrate	70	187–190	$C_{18}H_{19}N_5O_9$	48.11 (47.98)	4.26 (4.20)	15.59 (15.33)	2.14–2.49 (2H, m),[d] 2.89 (6H, s), 3.38 (2H, t, J=7.2 Hz), 4.72 (2H, t, J=5.0 Hz)
10		A	6	Ih	43	67–69	$C_{13}H_{15}NO_2$	71.86 (71.92)	6.96 (6.93)	6.45 (6.15)	1.10–2.46 (10H, m), 5.11 (1H, m, $w/2$=17.2 Hz)
11			10		49						
12			15		63						
13	*tert*-Bu 	A	25	Ii	52	70–71	$C_{17}H_{23}NO_2$	74.69 (74.33)	8.48 (8.59)	5.12 (5.06)	0.82–2.71 (10H, m), 0.84 (9H, s), 4.89 (1H, m, $w/2$=21.8 Hz)
14	*tert*-Bu 	A	24	Ij	24	50–52	$C_{17}H_{23}NO_2$	74.69 (74.29)	8.48 (8.71)	5.12 (5.01)	0.81–2.58 (10H, m), 0.88 (9H, s), 5.34 (1H, m, $w/2$=7.8 Hz)
15		A	6 d		34						
16	Ph(Me)CH	A	15	Ik	76	130–140/2	$C_{15}H_{13}NO_2$	75.29 (74.95)	5.48 (5.44)	5.85 (5.90)	1.66 (3H, d, J=6.8 Hz), 6.23 (1H, q, J=6.8 Hz)
17	Ph_2CH	A	37	Im	63	104–106	$C_{20}H_{15}NO_2$	79.71 (79.63)	5.02 (4.92)	4.65 (4.70)	7.04–7.77 (15H, m), 1.53 (6H, d, J=6.6 Hz), 5.63 (1H, septet, J=6.6 Hz)
18	iso-Pr	A	15	In	74	122–127/7	$C_{10}H_{11}NO_2$	67.78 (67.53)	6.26 (6.01)	7.91 (7.65)	1.53 (6H, d, J=6.6 Hz), 5.63 (1H, septet, J=6.6 Hz)
19	*tert*-Bu	A	65	Io	63	107–109/10	$C_{11}H_{13}NO_2$	69.09 (68.75)	6.85 (6.71)	7.33 (6.99)	1.65 (9H, s)

a) Reaction time after addition of alcohol (Chart 1). *b*) Lit.[3] mp 32–33 °C. *c*) Lit.[4] bp 160–170 °C (2 mmHg). *d*) In DMSO-d_6.

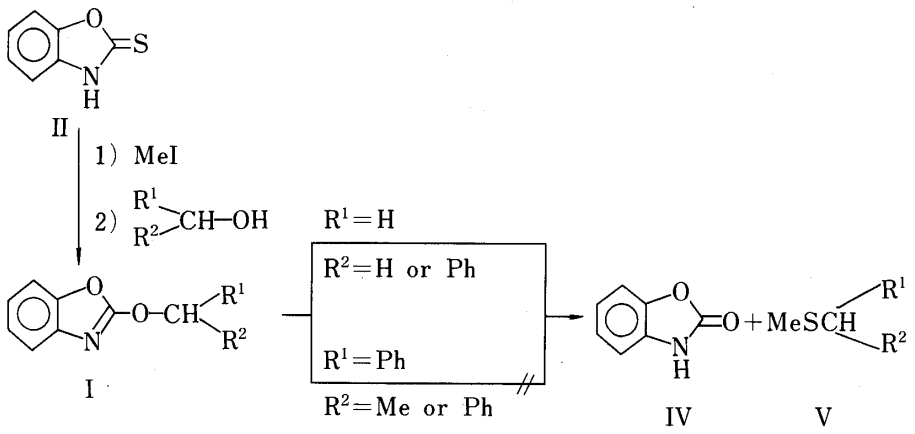


Chart 2

Compounds Ia and Ic were also prepared by another method, method B. Compound II was reacted with 3 eq of methyl iodide, 3 eq of an alcohol and 4 eq of sodium hydride in THF at room temperature for 2 h to give 2-(dialkoxymethylene)aminophenols (VI),[6] which on heating at 100 °C gave 2-alkoxybenzoxazoles (I). By this method, Ia and Ic were synthesized in 74 and 57% yields, respectively (Table I).

Attempted preparations of 2-alkoxybenzimidazoles or 2-alkoxybenzothiazoles from benzimidazoline-2-thione or benzothiazoline-2-thione by method A were unsuccessful, and instead 1-methyl-2-(methylthio)benzimidazole or 2-(methylthio)benzothiazole was obtained.

Experimental

Melting points (determined on a Yanagimoto micro-melting 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.

Reaction of 2-(Methylthio)benzoxazole (IIIa) with Phenethyl Alcohol——NaH (50% in oil, 0.6 g) was added to a solution of IIIa[7] (2 g), methyl iodide (1.9 g), and phenethyl alcohol (1.5 g) in THF (100 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, dried, and concentrated. The residue was distilled under reduced pressure to give 2-phenethyloxybenzoxazole (Id), bp 188—190 °C (10 mmHg).

General Procedure for the Preparation of 2-Alkoxybenzoxazoles (Ib, d, h—o) (Method A)——NaH (50% in oil, 0.02 mol) was gradually added to a solution of II (0.01 mol) and methyl iodide (0.02 mol) in THF (100 ml) under cooling. The mixture was stirred at room temperature for 2 h, then an alcohol (0.01 mol) was gradually added and the whole was stirred at room temperature[6] for the time shown in the Table, then poured into ice water, and extracted with AcOEt. The AcOEt layer was washed, dried, and concentrated to leave a residue which was purified by crystallization or distillation.

Physical properties and analytical data for Ia—o are given in Table I.

General Procedure for the Preparation of 2-Alkoxybenzoxazole Picrates (Ie—g) (Method A)——NaH (50% in oil, 0.02 mol) was added to a solution of II (0.01 mol) and methyl iodide (0.02 mol) in THF (100 ml) under cooling. The mixture was stirred at room temperature for 2 h, then an ω-aminoalcohol (0.01 mol) was gradually added and the whole was stirred at room temperature, then poured into ice water, and extracted with benzene. Excess picric acid was added to the benzene layer. The resulting precipitate was filtered off and crystallized from MeOH or THF to give Ie—g.

2-Methoxybenzoxazole (Ia)——Method A: NaH (50% in oil, 3 g, 0.06 mol) was added to a solution of II (0.01 mol) and methyl iodide (0.02 mol) in THF (100 ml) under cooling. The mixture was stirred at room temperature for 2 h, then abs. MeOH (1 g, 0.03 mol) was added and the whole was stirred at room temperature for 2 h, poured into ice water, and extracted with AcOEt. The AcOEt layer was washed, dried, and concentrated. The residue was chromatographed on silica gel with a mixture of benzene and cyclohexane (1:2, v/v) to give 2 g (42%) of Ia.[3] The aqueous layer was made acidic with 10% HCl solution and extracted with AcOEt. The AcOEt layer was washed, dried, and concentrated. The residue was recrystallized from cyclohexane to give 0.9 g (20%) of benzoxazolin-2-one (IV), mp 137—139 °C (lit.[8] mp 140—141 °C).

Method B: NaH (50% in oil, 3.8 g, 0.08 mol) was added to a solution of II (3 g, 0.02 mol), methyl iodide (8.5 g,

0.06 mol), and MeOH (1.9 g, 0.06 mol) in THF under cooling. The mixture was stirred at room temperature for 2 h, then poured into ice water, and extracted with AcOEt. The AcOEt layer was washed, dried, and concentrated. The residue, without purification, was heated at 100 °C for 2 h to give 2.2 g (74%) of Ia, which was purified by distillation.

2-Benzyloxybenzoxazole (Ic)——Method A: NaH (50% in oil, 1.3 g, 0.027 mol) was added to a solution of II (2 g, 0.013 mol) in THF (50 ml) under cooling. The mixture was stirred at room temperature for 2 h, then benzyl alcohol (1.4 g, 0.012 mol) was added and the whole was stirred at room temperature for 2 h, poured into ice water, and extracted with AcOEt. The AcOEt layer was washed, dried, and concentrated. The residue was chromatographed on silica gel. The first eluate with cyclohexane gave 0.4 g (22%) of benzyl methyl sulfide (Va), bp 80—81 °C (5 mmHg) [lit.[9] bp 195—198 °C (760 mmHg)]. The second eluate with cyclohexane–benzene (1 : 1, v/v) gave 1.1 g (40%) of Ic, mp 49—50 °C. The aqueous layer was made acidic with 10% HCl solution, and the resulting precipitate was filtered off and crystallized from cyclohexane to give 0.36 g (20%) of IV.

Method B: Compound Ic was prepared according to the described procedure of method B for the preparation of Ia.

Reaction of II with Methyl Iodide and Benzyl Alcohol in Boiling THF——NaH (50% in oil, 1.3 g) was added to a solution of II (2 g) and methyl iodide (1.9 g) in THF (100 ml). The mixture was stirred at room temperature for 2 h, then benzyl alcohol (1.4 g) was added and the whole was refluxed for 1 h, poured into ice water, and extracted with Et_2O. The Et_2O layer was washed, dried, and concentrated. The residue was distilled under reduced pressure to give 1.3 g (71%) of Va. The aqueous layer was made acidic with 10% HCl solution, then the resulting precipitate was filtered off and crystallized from cyclohexane to give 1.7 g (67%) of IV.

Reaction of II with Methyl Iodide and 4-*tert*-Butylcyclohexanol——NaH (50% in oil, 0.65 g, 13 mmol) was added to a solution of II (1 g, 6.6 mmol) and methyl iodide (1 g, 7 mmol) in THF (50 ml). The mixture was stirred at room temperature for 2 h, then 4-*tert*-butylcyclohexanol (*cis* : *trans* = 1 : 1) (1 g) was added and the whole was stirred at room temperature for 2 h, poured into ice water, and extracted with Et_2O. The Et_2O layer was washed, dried, and concentrated. The residue was chromatographed on silica gel with benzene–cyclohexane (1 : 5, v/v) to give 0.62 g (71%) of 2-(*trans*-4-*tert*-butylcyclohexyloxy)benzoxazole (Ii), mp 70—71 °C.

Hydrolysis of Ii——A mixture of Ii (0.5 g), 10% KOH solution (2 ml), and EtOH (50 ml) was refluxed for 2 h, then excess EtOH was evaporated off *in vacuo*. The residue was extracted with Et_2O. The Et_2O layer was washed with 10% KOH solution and brine, dried, and concentrated. The residue was crystallized from petr. ether to give 0.22 g (77%) of *trans*-4-butylcyclohexanol, mp 83—85 °C (lit.[10] mp 81—82 °C).

References and Notes

1) T. Koyama, M. Yamato, and K. Kubota, *Yakugaku Zasshi*, **77**, 989 (1957).
2) P. Seidel, *J. Prakt. Chem.*, **42**, 454 (1890).
3) L. T. Darlage, T. H. Kinstle, and C. L. McIntosh, *J. Org. Chem.*, **36**, 1088 (1971).
4) Y. Watanabe and T. Mukaiyama, *Chem. Lett.*, **1978**, 348.
5) M. Yamato, Y. Takeuchi, K. Hashigaki, and T. Hirota, *Chem. Pharm. Bull.*, **31**, 733 (1983).
6) The reaction temperature must be kept at room temperature. When these reactions are carried out at a high temperature, 2-alkoxybenzoxazole (I) is converted to benzoxazolin-2-one (IV) and alkyl methyl sulfide (V) by the reaction of I with sodium methanethiolate formed in the reaction mixture.
7) J. Henri, P. Hassanaly, J. Kister, and J. Metzger, *Phosphorus Sulfur*, **3**, 355 (1977).
8) R. T. Williams, *Biochem. J.*, **41**, 1 (1947).
9) J. Overmeyer, *Chem. Ber.*, **20**, 2926 (1887).
10) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **79**, 5562 (1955).