May 1986 Papers 375

# General Method for an Aldol-Type Reaction of 2-Methylbenzothiazole with Carbonyl Compounds

Hidenori Сніказніта\*, Seiji Ікедамі, Takeshi Окимика, Kazuyoshi Ітон

Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564, Japan

A general and versatile method for the preparation of a variety of  $\beta$ -hydroxybenzothiazoles (aldol-type adducts) by the reaction of  $\alpha$ -lithio-2-methylbenzothiazole with carbonyl compounds was proposed. As an example of the use of  $\alpha$ -lithio-2-methylbenzothiazole as a masked enolate, the product obtained by the reaction of this lithium reagent with 5-chloro-2-pentanone could be effectively transformed into the corresponding  $\beta$ -oxyaldehyde [2-methyl-2-(2-oxoethyl)-tetrahydrofuran].

Heterocyclic compounds such as 2-methyloxazoline<sup>1</sup>, 2methylthiazole<sup>2</sup>, 2-methyloxazine<sup>3</sup>, or 2-methylthiazoline<sup>4</sup> having an active methyl group are useful synthetic tools. An example would be their use as masked enolate. 2-Methylbenzothiazole (1) can also be an important masked enolate because of the facile convertibility of the benzothiazole nucleus into a carbonyl group<sup>5,6</sup>. Although the aldol-type reaction of 1 with aromatic aldehydes proceeds in the presence of basic or acidic catalysts such as zinc chloride<sup>7</sup>, potassium methoxide<sup>7</sup>, boric acid<sup>8</sup>, or sodium amide9, the reaction has not been able to stop at the aldol stage but affords 2-styryl derivatives corresponding to the dehydration product of the aldol. On the other hand, the reaction has been terminated at the aldol stage by using reagents such as lithium amide10 in liquid ammonia, sodium hydroxyde<sup>11</sup> in dimethyl sulfoxide, or 9-borabicyclononane triflate and diisopropylamine<sup>12</sup> in dichloromethane. However, no general or versatile method has been reported for an aldol-type reaction of 1 with different carbonyl compounds. We propose a general and versatile method for the preparation of a variety of aldol-type adducts 3 by the reaction of the lithium reagent 2 with carbonyl compounds.

3	R1	R <sup>2</sup>	3	R <sup>1</sup>	83
а	C <sub>2</sub> H <sub>5</sub>	Н	h	-{_>	CH <sub>3</sub>
b	<i>i</i> −C <sub>3</sub> H <sub>7</sub>	Н	i	n-C4Hg	n-C <sub>e</sub> H <sub>a</sub>
C	t-C4H9	Н	i	n- C <sub>6</sub> H <sub>13</sub>	CH <sub>3</sub>
d	n-C <sub>5</sub> H <sub>11</sub>	Н	k	(CH <sub>2</sub> ) <sub>5</sub>	
е		Н	ı	CH≔CH³	
f		Н			
g	сн=сн-{	Н			

Metallation of 1 was most conveniently accomplished with a 1.1 equivalent of *n*-butyllithium in tetrahydrofuran at  $-78\,^{\circ}$ C. Metallation of 1 followed by addition of a variety of aldehydes or ketones gave, after hydrolytic work-up, the  $\beta$ -hydroxybenzothiazoles 3 in near quantitative yields. The

376 Papers synthesis

Table lists several of the products obtained, together with yields and physical data. The reaction time of 2 with carbonyl compounds did not vary with the steric and electronic character of the carbonyl compounds. Under the present conditions, a readily enolized ketone, such as cyclohexanone, produced a product 3k by carbonyl addition in excellent yield. This demonstrates the very effective nucleophilicity of 2. When cinnamic aldehyde and methyl vinyl ketone were employed as carbonyl substrates, the  $\beta$ -hydroxy products 3g, 1, derived from the 1,2-addition of 2 to these  $\alpha,\beta$ -unsaturated carbonyl compounds, were selectively obtained. This shows a high preference of 2 for non-conjugate 1r,2-addition to  $\alpha,\beta$ -unsaturated carbonyl compounds.

In order to assess the nucleophilic nature of 2, the reaction of 2 with 5-chloro-2-pentanone (4) was demonstrated. Interestingly, the tetrahydrofuran derivative 5 was selectively obtained in 98 % yield. This result shows that the product 5 is formed by nucleophilic attack of 2 on the carbonyl carbon followed by intramolecular cyclization. This suggests that nucleophilicity of 2 toward the halogenated carbon is very low. As an example of the use of 2 as a masked enolate, this benzothiazole 5 could be effectively transformed into the  $\beta$ oxyaldehyde (8) in three steps. Thus, methylation of 5 was easily accomplished by the treatment with 6.0 equivalents of methyl iodide in dimethylformamide at the reflux temperature of methyl iodide. This produced the salt 6 in 93 % yield. The reduction of 6 was effectively carried out with 5.0 equivalents of sodium borohydride in ethanol at 0°C for an hour to give benzothiazoline 7 in quantitative yield. Hydrolysis of crude 7 to the  $\beta$ -oxyaldehyde 8 could be accomplished (85% yield from 6) with no difficulties according to the method<sup>6</sup> reported previously for the hydrolysis of N-methyl- $\alpha$ -hydroxybenzothiazolines.

### α-Lithio-2-methylbenzothiazole (2):

A stirred solution of 2-methylbenzothiazole (1; 1.49 g, 10 mmol) in dry tetrahydrofuran (30 ml) under nitrogen is cooled to  $-78\,^{\circ}\mathrm{C}$  (Dry Ice/methanol bath) and a 10% excess of *n*-butyllithium in hexane is added dropwise over 10 min. Approximately 30 min after the addition has been completed, a pale yellow precipitate is formed. This indicates complete anion formation. The reaction vessel is continuously purged with nitrogen until work-up.

#### 2-(2-Hydroxyalkyl)-benzothiazoles 3; General Procedure:

The carbonyl compound (11 mmol) in dry tetrahydrofuran (20 ml) is slowly added to the vigorously stirred solution of the anion 2 (prepared from 10 mmol of 1) at  $-78\,^{\circ}$ C over a period of 30 min. The mixture is stirred at  $-78\,^{\circ}$ C for 1 h. Once the yellow precipitate has almost dissolved, it is allowed to slowly warm to room temperature. The mixture is stirred for an additional 1 h and then poured into ice/water (100 ml). The aqueous solution is extracted with diethyl ether and the organic layer is dried with anhydrous magnesium sulfate. The solvent is removed by evaporation and the residue is completely dried in vacuo to give crude product 3. The crude product 3 is purified by recrystallization or short column chromatography on silica gel (Wakogel C-300) (Table).

#### 2-(2-Methyltetrahydrofuran-2-yl)-methylbenzothiazole (5):

5-Chloro-2-pentanone (4; 1.33 g, 11 mmol) in dry tetrahydrofuran (20 ml) is slowly added to the vigorously stirred solution of the anion 2 (prepared from 10 mmol of 1) at -78 °C over a period of 20 min. The mixture is stirred at -78 °C for 1 h and allowed to warm to room temperature. The mixture is stirred for an additional 2 h and then concentrated by evaporation. The residue is diluted with *n*-hexane (50 ml), washed thoroughly with water, and then dried with anhydrous magnesium sulfate. After removal of the *n*-hexane by evaporation, the oily product [yield: 2.29 g (98 %)] is purified by distillation to give the pure product. This oily product solidifies on standing in a refrigerator; yield: 1.77 g (76 %); b.p. 170–172 °C/5 torr; m.p. 30.8-31.2 °C.

C<sub>13</sub>H<sub>15</sub>NOS calc. C 66.92 H 6.48 N 6.00 (233.3) found 66.62 6.41 5.93

<sup>1</sup>H-N.M.R. (CDCl<sub>3</sub>/TMS<sub>int</sub>):  $\delta$  = 1.28 (s, 3 H, CH<sub>3</sub>); 1.82 (m, 4 H, 2CH<sub>2</sub>); 3.24 (s, 2 H, CH<sub>2</sub>); 3.80 (t, J = 6.6 Hz, 2 H, O—CH<sub>2</sub>); 7.18 (m, 2 H, H<sub>arom</sub>); 7.74 ppm (m, 2 H, H<sub>arom</sub>).

## 3-Methyl-2-(2-methyltetrahydrofuran-2-yl)-methylbenzothiazolium Iodide (6):

The solution of 5 (4.67 g, 20 mmol) in dimethylformamide (7.5 ml) and methyl iodide (7.5 ml) is refluxed for 12 h. The mixture is diluted with diethyl ether (40 ml) and cooled in an ice bath to completely precipitate the product. The needles obtained are collected by filtration, washed throughly with diethyl ether, and dried in vacuo to give the crude benzothiazolium salt 6; yield: 6.98 g (93%); m.p. 162.5–163.0 °C.

C<sub>14</sub>H<sub>18</sub>INOS calc. C 44.81 H 4.83 N 3.73 (375.3) found 44.57 4.76 3.68

<sup>1</sup>H-N.M.R. (DMSO- $d_6$ /TMS<sub>int</sub>):  $\delta$  = 1.32 (s, 3 H, CH<sub>3</sub>); 1.92 (m, 4 H, 2CH<sub>2</sub>); 3.82 (m, 4 H, 2CH<sub>2</sub>); 4.26 (s, 3 H, N—CH<sub>3</sub>); 7.70 (m, 2 H, H<sub>arom</sub>); 8.22 ppm (m, 2 H, H<sub>arom</sub>).

# 3-Methyl-2-(2-methyltetrahydrofuran-2-yl)-methylbenzothiazoline (7):

The benzothiaz olium salt 6 (0.75 g, 2.0 mmol), dissolved in ethanol (8 ml), is treated with sodium borohydride (0.38 g, 10.0 mmol) at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture is diluted with water (30 ml) and extracted with ether (3 × 15 ml). The ether extract is dried with anhydrous magnesium sulfate and filtered through silica gel (Wakogel C-300). The crude benzothiazoline 7 is a syrup after evaporation of the filtrate; yield: 0.48 g (97%). The product, which is sufficiently pure (monitored by T.L.C) but slightly unstable in air, is used in the next hydrolysis step as soon as possible.

<sup>1</sup>H-N.M.R. (CDCl<sub>3</sub>/TMS<sub>int</sub>):  $\delta$  = 1.17 (s, 3 H, CH<sub>3</sub>); 1.68 (m, 4 H, 2CH<sub>2</sub>); 2.11 (dd, J = 2.4 Hz, 3.0 Hz, 2 H, CH<sub>2</sub>); 2.60 (s, 3 H, N—CH<sub>3</sub>); 3.72 (m, 2 H, O—CH<sub>2</sub>); 4.81 (m, 1 H, CH); 6.07 – 6.93 ppm (ra, 4 H, H<sub>arom</sub>).

### 2-Methyl-2-(2-oxoethyl)-tetrahydrofuran (8):

Silver nitrate (0.51 g, 3.0 mmol), dissolved in water (5 ml), is added to the stirred solution of benzothiazoline 7 (prepared from 2.0 mmol of 6) in acetonitrile (30 ml) and 0.05 molar phosphate buffer (6.0 ml) (pH 7). After 15 min at room temperature, additional silver nitrate (0.51 g, 3.0 mmol), dissolved in water (5 ml), is added. A yellow precipitate begins to form during this second addition. After another 20 min at room temperature, triethylamine (0.20 g, 2.0 mmol) is added and stirring is continued for 10 min. Saturated sodium

Table. 2-(2-Hydroxyalkyl)-benzothiazoles 3a-1 prepared

Product	Yield <sup>a</sup> [%]	m.p. <sup>b</sup> [°C] (solvent)	Molecular formula <sup>c</sup> or Lit, m.p. [°C]	$^{1}$ H-N.M,R. (CDCl <sub>3</sub> /TMS <sub>int</sub> ) <sup>d</sup> $\delta$ [ppm]
3 <sub>a</sub>	98	53.5–54.5°	C <sub>11</sub> H <sub>13</sub> NOS (207.3)	1.00 (t, $J = 6.2$ Hz, 3H, CH <sub>3</sub> ); 1.57 (m, 2H, CH <sub>2</sub> ); 3.08 (t, $J = 4.0$ Hz, 2H, CH <sub>2</sub> ); 3.65 (br.s. 1H, OH); 4.02 (m, 1H, CH); 7.23 (m, 2H, H <sub>arom</sub> ); 7.73 (m, 2H, H <sub>arom</sub> )
3b	98	61.562.5° (hexane)	C <sub>12</sub> H <sub>15</sub> NOS (221.3)	0.90 (d, $J = 7.0 \text{ Hz}$ , 3 H, CH <sub>3</sub> ); 1.02 (d, $J = 7.0 \text{ Hz}$ , 3 H, CH <sub>3</sub> ); 1.68 (m, 1 H, CH); 3.03 (t, $J = 4.0 \text{ Hz}$ , 2 H, CH <sub>2</sub> ); 3.80 (m, 1 H, CH); 4.00 (br.s. 1 H, OH); 7.17 (m, 2 H, H <sub>aron</sub> ); 7.67 (m, 2 H, H <sub>aron</sub> )
3c	99	97.098.0° (hexane)	C <sub>13</sub> H <sub>17</sub> NOS (235.3)	1.01 (s, 9 H, 3CH <sub>3</sub> ); 3.15 (d. $J = 3.0$ Hz, 2H, CH <sub>2</sub> ); 3.62 (br.s, 1 H, OH); 3.80 (q. $J = 3.0$ Hz, 1 H, CH); 7.28 (m, 2 H, H <sub>aron</sub> ); 7.78 (m, 2 H, H <sub>aron</sub> )
3d	95	56.0-57.0°	C <sub>14</sub> H <sub>19</sub> NOS (249.4)	0.67–1.83 (br.s, 11 H, $C_5H_{11}$ ); 3.10 (t. $J=4.0$ Hz. 2 H, CH <sub>2</sub> ); 3.86 (br.s, 1 H, OH); 4.07 (m, 1 H, CH); 7.27 (m, 2 H, $H_{aron}$ ); 7.77 (m, 2 H, $H_{aron}$ )
3e	96	159.5–161.0° (acetone)	155-156*11	3.38 (d, $J = 6.0 \text{ Hz}$ , 2H, CH <sub>2</sub> ); 4.99 (q, $J = 6.0 \text{ Hz}$ , 1H, CH); 5.63 (d, $J = 4.4 \text{ Hz}$ , 1H, OH);
3f	99	118.0–118.5° (acetone/hexane)	C <sub>13</sub> H <sub>11</sub> NO <sub>2</sub> S (245.3)	7.24 (m, 7H, $H_{arom}$ ); 7.82 (m, 2H, $H_{arom}$ ) 3.52 (d, $J = 6.0 \text{ Hz}$ , 2H, CH <sub>2</sub> ); 4.08 (br.s, 1H, OH); 5.21 (t, $J = 6.0 \text{ Hz}$ , 1H, CH); 6.17 (d, $J = 1.6 \text{ Hz}$ , 2H, $H_{arom}$ ); 7.25 (m. 3H, $H_{arom}$ ); 7.73
3g	93	143.6~144.3° (acetone)	C <sub>17</sub> H <sub>15</sub> NOS (281.4)	(m, 2H, $H_{arom}$ ) 3.28 (d, $J = 5.0$ Hz, 2H, $CH_2$ ); 3.80 (br.s, 1H, OH); 4.77 (q, $J = 5.0$ Hz, 1H, CH); 5.97–6.73 (m, 2H, $-CH=CH-$ ); 7.17 (m, 7H, $H_{arom}$ ); 7.73 (m, 2H, $H_{arom}$ )
3h	98	114.0114.5°	C <sub>16</sub> H <sub>15</sub> NOS	1.60 (s, 3H, CH <sub>3</sub> ); 3.50 (s, 2H, CH <sub>2</sub> ); 4.88 (br.s,
3i	96	(acetone/hexane) 71.0-72.0° (hexane)	(269.4) C <sub>17</sub> H <sub>25</sub> NOS (291.5)	1 H, OH); 7.24 (m, 7 H, H <sub>arom</sub> ); 7.73 (m, 2 H, H <sub>arom</sub> ) 0.67–1.83 (br.s, 18 H, 2C <sub>4</sub> H <sub>9</sub> ); 3.18 (s, 2 H, CH <sub>2</sub> ); 3.80 (br.s, 1 H, OH); 7.30 (m, 2 H, H <sub>arom</sub> ); 7.80 (m,
3 <b>j</b>	97	oil	C <sub>16</sub> H <sub>22</sub> NOS (276.4)	2H, H <sub>arom</sub> ) 0.60-1.83 (br.s, 16 H, CH <sub>3</sub> + C <sub>6</sub> H <sub>13</sub> ); 3.16 (s, 2 H, CH <sub>2</sub> ); 4.10 (br.s, 1 H, OH); 7.23 (m, 2 H, H <sub>arom</sub> );
3k	99	114.0–115.0° (acetone)	C <sub>14</sub> H <sub>17</sub> NOS (247.4)	7.75 (m, 2 H, H <sub>arom</sub> ) 1.53 (br.s, 10 H, cyclo-C <sub>6</sub> H <sub>10</sub> ); 3.15 (s, 2 H, CH <sub>2</sub> ); 3.65 (br.s, 1 H, OH); 7.23 (m, 2 H, H <sub>arom</sub> ); 7.76 (m, 2 H, H <sub>arom</sub> )
31	96	oil	C <sub>12</sub> H <sub>13</sub> NOS (219.3)	1.38 (s, 3 H, CH <sub>3</sub> ); 3.23 (s, 2 H, CH <sub>2</sub> ); 4.52 (br.s. 1 H, OH); 4.80–5.33 (m, 2 H, =CH <sub>2</sub> ); 5.70–6.13 (m, 1 H, -CH=); 7.19 (m, 2 H, H <sub>aron</sub> ); 7.73 (m, 2 H, H <sub>aron</sub> )

Yield of isolated product.

chloride is added to the reaction mixture and the mixture is extracted with ether. The ether extract is filtered through silica gel (Wakogel C-300) to give almost pure aldehyde 8 that was free of N-methyl-oaminothiophenol; yield: 0.22 g (85% from 6). The purification of this product is achieved by distillation; b. p. 36.8°C/1.4 torr; m. p. of 2,4-dinitrophenylhydrazone derivative: 70.5–71.0 °C.

C<sub>7</sub>H<sub>12</sub>O<sub>2</sub> calc. C 65.60 H 9.44 (128.2)found 64.70 9.66

Not corrected.

Satisfactory microanalyses obtained:  $C \pm 0.26$ ,  $H \pm 0.14$ ,  $N \pm 0.28$ .

Recorded at 60 MHz using a JEOL PMX-60 spectrometer.

<sup>&</sup>lt;sup>1</sup>H-N.M.R. (CDCl<sub>3</sub>/TMS<sub>int</sub>):  $\delta = 1.28$  (s, 3 H, CH<sub>3</sub>); 1.90 (m, 4 H. 2CH<sub>2</sub>); 2.50 (d, J = 2.8 Hz, 2H, CH<sub>2</sub>); 3.78 (m, 2H, O-CH<sub>2</sub>); 9.60 ppm (t, J = 2.8 Hz, 1 H, CHO).

Meyers, A.I., Temple, D.L. J. Am. Chem. Soc. 1970. 92, 6644.

Altman, L.J., Richheimer, S.L. Tetrahedron Lett. 1971, 4709.

Meyers, A.I. et al. J. Org. Chem. 1973. 38, 36.

Meyers, A. J., Durandetta, J. L., Munavu, R. J. Org. Chem. 1975. 40, 2025.

<sup>&</sup>lt;sup>5</sup> Corey, E.J., Boger, D.L. Tetrahedron Lett. 1978, 5.

<sup>&</sup>lt;sup>6</sup> Chikashita, H., Itoh K. Heterocycles 1985, 23, 295.

Ried, W., Hinshing, S. Justus Liebigs Ann. Chem. 1956, 600, 47. Postovskii, I.Y., Pushkina, L.N., Mazalov, C.A. Zh. Obshch. Khim. 1962, 32, 2578; Engl. Edit. p. 2617.

Dryanska, V., Ivanov, C. C. R. Acad. Bulg. Sci. 1970, 23, 1227. 10 Dryanska, V., Ivanov, C. God. Soffii. Univ. Khim. Fak. 1968-1969, 63, 105; C.A. 1972, 76, 126844.

Dryanska, V., Ivanov, C. Synthesis 1976, 37.
Hamana, H., Sugasawa, T. Chem. Lett. 1983, 333.