

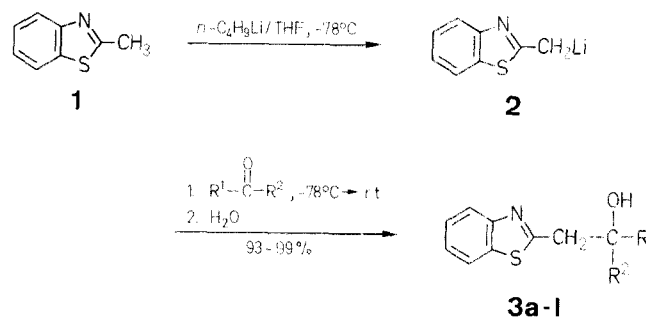
General Method for an Aldol-Type Reaction of 2-Methylbenzothiazole with Carbonyl Compounds

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A general and versatile method for the preparation of a variety of β -hydroxybenzothiazoles (aldol-type adducts) by the reaction of α -lithio-2-methylbenzothiazole with carbonyl compounds was proposed. As an example of the use of α -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 β -oxaldehyde [2-methyl-2-(2-oxoethyl)-tetrahydrofuran].

Heterocyclic compounds such as 2-methyloxazoline¹, 2-methylthiazole², 2-methyloxazine³, or 2-methylthiazoline⁴ 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^{5,6}. Although the aldol-type reaction of **1** with aromatic aldehydes proceeds in the presence of basic or acidic catalysts such as zinc chloride⁷, potassium methoxide⁷, boric acid⁸, 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 hydroxide¹¹ in dimethyl sulfoxide, or 9-borabicyclononane triflate and diisopropylamine¹² 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	R ¹	R ²	3	R ¹	R ²
a	C ₂ H ₅	H	h		CH ₃
b	<i>i</i> -C ₃ H ₇	H	i	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉
c	<i>t</i> -C ₄ H ₉	H	j	<i>n</i> -C ₆ H ₁₃	CH ₃
d	<i>n</i> -C ₅ H ₁₁	H	k	-(CH ₂) ₆ -	
e		H	l	-CH=CH-	CH ₃
f		H			
g	-CH=CH-	H			

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

Table. 2-(2-Hydroxyalkyl)-benzothiazoles **3a**–**l** prepared

Product	Yield ^a [%]	m.p. ^b [°C] (solvent)	Molecular formula ^c or Lit. m.p. [°C]	¹ H-N.M.R. (CDCl ₃ /TMS _{int}) ^d δ [ppm]
3a	98	53.5–54.5° (hexane)	C ₁₁ H ₁₃ NOS (207.3)	1.00 (t, <i>J</i> = 6.2 Hz, 3H, CH ₃); 1.57 (m, 2H, CH ₂); 3.08 (t, <i>J</i> = 4.0 Hz, 2H, CH ₂); 3.65 (br.s, 1H, OH); 4.02 (m, 1H, CH); 7.23 (m, 2H, H _{arom}); 7.73 (m, 2H, H _{arom})
3b	98	61.5–62.5° (hexane)	C ₁₂ H ₁₅ NOS (221.3)	0.90 (d, <i>J</i> = 7.0 Hz, 3H, CH ₃); 1.02 (d, <i>J</i> = 7.0 Hz, 3H, CH ₃); 1.68 (m, 1H, CH); 3.03 (t, <i>J</i> = 4.0 Hz, 2H, CH ₂); 3.80 (m, 1H, CH); 4.00 (br.s, 1H, OH); 7.17 (m, 2H, H _{arom}); 7.67 (m, 2H, H _{arom})
3c	99	97.0–98.0° (hexane)	C ₁₃ H ₁₇ NOS (235.3)	1.01 (s, 9H, 3CH ₃); 3.15 (d, <i>J</i> = 3.0 Hz, 2H, CH ₂); 3.62 (br.s, 1H, OH); 3.80 (q, <i>J</i> = 3.0 Hz, 1H, CH); 7.28 (m, 2H, H _{arom}); 7.78 (m, 2H, H _{arom})
3d	95	56.0–57.0° (hexane)	C ₁₄ H ₁₉ NOS (249.4)	0.67–1.83 (br.s, 11H, C ₅ H ₁₁); 3.10 (t, <i>J</i> = 4.0 Hz, 2H, CH ₂); 3.86 (br.s, 1H, OH); 4.07 (m, 1H, CH); 7.27 (m, 2H, H _{arom}); 7.77 (m, 2H, H _{arom})
3e	96	159.5–161.0° (acetone)	155–156° ¹¹	3.38 (d, <i>J</i> = 6.0 Hz, 2H, CH ₂); 4.99 (q, <i>J</i> = 6.0 Hz, 1H, CH); 5.63 (d, <i>J</i> = 4.4 Hz, 1H, OH); 7.24 (m, 7H, H _{arom}); 7.82 (m, 2H, H _{arom})
3f	99	118.0–118.5° (acetone/hexane)	C ₁₃ H ₁₁ NO ₂ S (245.3)	3.52 (d, <i>J</i> = 6.0 Hz, 2H, CH ₂); 4.08 (br.s, 1H, OH); 5.21 (t, <i>J</i> = 6.0 Hz, 1H, CH); 6.17 (d, <i>J</i> = 1.6 Hz, 2H, H _{arom}); 7.25 (m, 3H, H _{arom}); 7.73 (m, 2H, H _{arom})
3g	93	143.6–144.3° (acetone)	C ₁₇ H ₁₅ NOS (281.4)	3.28 (d, <i>J</i> = 5.0 Hz, 2H, CH ₂); 3.80 (br.s, 1H, OH); 4.77 (q, <i>J</i> = 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	114.0–114.5° (acetone/hexane)	C ₁₆ H ₁₅ NOS (269.4)	1.60 (s, 3H, CH ₃); 3.50 (s, 2H, CH ₂); 4.88 (br.s, 1H, OH); 7.24 (m, 7H, H _{arom}); 7.73 (m, 2H, H _{arom})
3i	96	71.0–72.0° (hexane)	C ₁₇ H ₂₅ NOS (291.5)	0.67–1.83 (br.s, 18H, 2C ₄ H ₉); 3.18 (s, 2H, CH ₂); 3.80 (br.s, 1H, OH); 7.30 (m, 2H, H _{arom}); 7.80 (m, 2H, H _{arom})
3j	97	oil	C ₁₆ H ₂₂ NOS (276.4)	0.60–1.83 (br.s, 16H, CH ₃ + C ₆ H ₁₃); 3.16 (s, 2H, CH ₂); 4.10 (br.s, 1H, OH); 7.23 (m, 2H, H _{arom}); 7.75 (m, 2H, H _{arom})
3k	99	114.0–115.0° (acetone)	C ₁₄ H ₁₇ NOS (247.4)	1.53 (br.s, 10H, cyclo-C ₆ H ₁₀); 3.15 (s, 2H, CH ₂); 3.65 (br.s, 1H, OH); 7.23 (m, 2H, H _{arom}); 7.76 (m, 2H, H _{arom})
3l	96	oil	C ₁₂ H ₁₃ NOS (219.3)	1.38 (s, 3H, CH ₃); 3.23 (s, 2H, CH ₂); 4.52 (br.s, 1H, OH); 4.80–5.33 (m, 2H, =CH ₂); 5.70–6.13 (m, 1H, —CH=); 7.19 (m, 2H, H _{arom}); 7.73 (m, 2H, H _{arom})

^a Yield of isolated product.^b Not corrected.^c Satisfactory microanalyses obtained: C ± 0.26, H ± 0.14, N ± 0.28.^d Recorded at 60 MHz using a JEOL PMX-60 spectrometer.

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-*o*-aminothiophenol; 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.

C₇H₁₂O₂ calc. C 65.60 H 9.44
(128.2) found 64.70 9.66

¹H-N.M.R. (CDCl₃/TMS_{int}): δ = 1.28 (s, 3H, CH₃); 1.90 (m, 4H, 2CH₂); 2.50 (d, *J* = 2.8 Hz, 2H, CH₂); 3.78 (m, 2H, O—CH₂); 9.60 ppm (t, *J* = 2.8 Hz, 1H, CHO).

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Received: November 12, 1985