An Improved Method for Preparation of *N*-Alkyl-2(3*H*)-benzothiazolone Analogs

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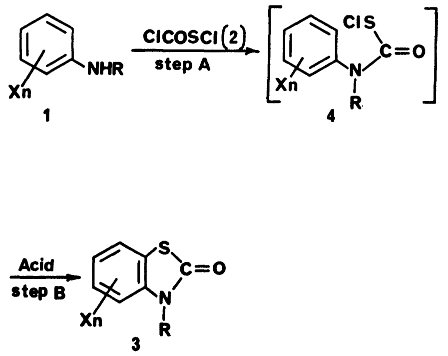
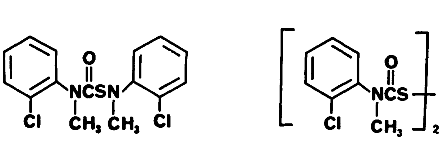
Synopsis. A number of *N*-alkyl-2(3*H*)-benzothiazolone analogs could be prepared from *N*-monosubstituted aniline and chlorocarbonylsulfenyl chloride. The new method consists of carbamoylation of aniline and successive Friedel-Crafts type ring closure of an intermediate carbamoylsulfenyl chloride in the presence of suitable Lewis or protic acid catalyst.

N-Alkyl-2(3*H*)-benzothiazolone derivatives (**3**) are well known as useful biologically active substances, *i.e.*, herbicides,[1] fungicides[2] and antiallergic drugs.[3] Therefore, synthesis of 2(3*H*)-benzothiazolone has been studied extensively, and the following two methods[4] which start from aniline are typical ones. According to the first method, *N*-alkyl-2(3*H*)-benzothiazolones (**3**) are prepared by the following series of reactions: 1) Condensation of aniline with thiocyanate ion to give phenylthiourea, 2) oxidative (*e.g.* Br_2 or SO_2Cl_2) cyclization to 2-aminobenzothiazole, 3) transformation of the 2-amino derivative to 2(3*H*)-benzothiazolone by diazotization and subsequent acid hydrolysis of the 2-chlorobenzothiazole, 4) *N*-alkylation to **3**. In the other method, a substituted aniline and carbon disulfide are coupled to give the corresponding 2-mercaptobenzothiazole, which is then converted to **3** by H_2O_2-oxidation followed by alkylation. The former method is general one to prepare *N*-alkyl-2(3*H*)-benzothiazolone, but requires several steps. The latter is of limited applicability, since the coupling reaction often requires drastic reaction conditions (high temperature (up to 150 °C) and pressure (≈3 atm)), and generally give low yields with certain exceptions such as 2-mercaptobenzothiazole.



Scheme 1.



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In contrast, Zumach *et al.* reported[5] a remarkable method for preparation of *N*-methyl-2(3*H*)-benzothiazolone (**3**) by condensation of *N*-methylaniline (**1**) and chlorocarbonylsulfenyl chloride (CCSC) (**2**), an effective "bifunctional" reagent,[7] and they described that the reaction proceeds stepwise as shown in Scheme 1: step A, carbamoylation of *N*-alkylaniline (**1**) with CCSC (**2**) and step B, ring-closure by way of Friedel-Crafts type C–S bond formation. When X_n on **1** is hydrogen atom or an electron donating group, the second step occurs spontaneously. However, when X_n is an electron-withdrawing group, such as halogen or cyano group, step B did not proceed and even a trace amount of benzothiazole (**3**) was not obtained, but the disulfide (**5**, Table 1,(c)) was found. The failure in the cyclization step seems to result from low reactivity of the benzene ring of the aniline (**1**) on the Friedel Crafts cyclization by an electron-withdrawing groups X_n.

In order to overcome the problem, we have extensively attempted a variety of Friedel-Crafts catalysts for the cyclization step B, and found that 1.5 mol of Lewis acid ($AlCl_3$, $FeCl_3$) or a large excess of protic acid (H_2SO_4,[8] CF_3CO_2H) gave *N*-alkyl-2(3*H*)-benzothiazolone (**3**) in

Table 1. Preparation of 4-chloro-*N*-methyl-2(3*H*)-benzothiazolone (**3a**)

Base/step A (equiv. *vs.* **1a**)	Acid/step B (equiv. *vs* **1a**)	Solvent	Yield/%
N,N-Dimethylaniline(1.1)	None	Toluene[a)]	–[c)]
N,N-Dimethylaniline(1.1)	$AlCl_3$(1.5)	Toluene[a)]	78.2
N,N-Dimethylaniline(1.1)	$FeCl_3$(1.5)	Toluene[b)]	48.4
N,N-Dimethylaniline(1.1)	$BF_3 \cdot Et_2O$(1.5)	Toluene[a)]	Trace
N,N-Dimethylaniline(1.1)	CF_3CO_2H(5.0)	Toluene[a)]	20.0
N,N-Dimethylaniline(1.1)	Conc H_2SO_4(10)	Toluene[b)]	76.1
N,N-Diethylaniline(1.1)	Conc H_2SO_4(10)	Toluene[b)]	76.5
Pyridine(1.1)	Conc H_2SO_4(10)	Toluene[b)]	42.8
Triethylamine(1.1)	Conc H_2SO_4(10)	Toluene[b)]	5.5
N,N-Dimethylaniline(1.1)	Conc H_2SO_4(10)	CH_2Cl_2[b)]	15.0
N,N-Dimethylaniline(1.1)	Conc H_2SO_4(10)	CCl_4[b)]	69.4
N,N-Dimethylaniline(1.1)	Conc H_2SO_4(10)	Hexane[b)]	Trace
N,N-Dimethylaniline(1.1)	Conc H_2SO_4(20)	Toluene[b)]	66.0
N,N-Dimethylaniline(1.1)	Conc H_2SO_4(5.0)	Toluene[b)]	18.0
2-Chloro-*N*-methylaniline(1.1)	Conc H_2SO_4(10)	Toluene[b)]	52.5

a) Refluxed for 3 h on step B. b) 0—5 °C for 1 h and r.t. for 8 h. c) Bis(*N*-(2-chlorophenyl) methylcarbamoyl) sulfide (**5**) was obtained in 30% yield as a main product.

Table 2. Preparation of *N*-alkyl-2(3*H*)-benzothiazolone (**3**) in concd H_2SO_4

Product[c)]	R	X_n	Yield/%
3a	CH_3	4-Cl	76.1
3b	CH_3CH_2	4-Cl	72.5
3c	$CH_2CO_2CH_2CH_3$	4-Cl	61.0
3d	CH_3	4-Cl, 6-Cl	57.8
3e	CH_3	6-Cl	78.2
3f	CH_3	6-CN	62.0
3g	CH_3	5-Cl, 7-Cl	59.5
3h	CH_3	4-Br	75.5
3i	CH_3	5-Cl[b)]	71.5

a) 10 mol equiv. *vs.* *N*-alkylaniline (**1**) was used. b) Containing a 10% of 7-chloro-*N*-methyl-2(3*H*)-benzothiazolone originated by the cyclization toward C-2 position of 3-chloroaniline. c) These physical and analitical data are given in experimental tail.

good yield. It is noteworthy that C–S bond formation between the aromatic carbon and the sulfenyl halide was successfully conducted in a protic acid media such as conc H_2SO_4.

Various types of amines were tried as acid scavenger in the step A. For example, in case of *N*-methyl-2-chloroaniline, *N,N*-dialkylaniline gave favorable yield of 4-chloro-*N*-methyl-2(3*H*)-benzothiazolone (**3a**), while pyridine and triethylamine gave poor yield. *N*-Methyl-2-chloro-aniline could also behave as an acid scavenger and gave 53% yield of (**3a**) and *N*-(2-chlorophenyl)-methylcarbamoyl 2-chloro-*N*-methylanilino sulfide (**6**) in 11% yield as a major by-product (Table 1). It was found that the reaction was very sensitive to solvents and bases. It seemed that solvents such as toluene, carbon tetrachloride, and certain tertiary amines such as *N,N*-dimethylaniline are favorable for the step A.

The results were shown in Tables 1 and 2.

Experimental

Materials. CCSC (**2**) was prepared from CCl_3SCl and 95%-H_2SO_4.[6]

Analyses of the Products. Purity of *N*-Alkyl-2(3*H*)-benzothiazolone (**3**) were analyzed by GLC on a 1.5 m×3 mm XE-60 (5 wt%) column at 200 °C.

*4-Chloro-*N*-methyl-2(3*H*)-benzothiazolone (3a).* CCSC (**2**, 5.08 g, 3.83×10^{-2} mol) was added to a solution of 2-chloro-*N*-methylaniline (**1a**, 5.00 g, 3.53×10^{-2} mol) and *N,N*-dimethylaniline (4.73 g, 3.83×10^{-2} mol) in toluene (70 ml) at 0 °C and the solution was stirred at 0 °C for 1 h. After removal of *N,N*-dimethylaniline hydrochloride salt by filtration, the filtrate which contained sulfenyl halide intermediate (**4a**, was added to a suspension of $AlCl_3$ (7.66 g, 5.75×10^{-2} mol) in toluene (50 ml) at room temperature during 30 min, and heated under reflux for 3 h. Then the reaction mixture was poured into water (100 ml) and extracted with toluene. The organic layer was washed with sat. $NaHCO_3$ solution (100 ml) and dried with $MgSO_4$. The solvent was removed *in vacuo*, and the resultant crude crystals were recrystallized from EtOH to give **3a** (4.45 g, 78.2%). (Table 1). In the same manner, the intermediate sulfenyl halide (**4a**, X=2-Cl, R=CH_3) in toluene was added to conc H_2SO_4 (37 g, 0.38 mol) at 0—5 °C, and kept under stirring at room temperature for 5 h. The reaction mixture was worked up with ice (50 g) to give **3a** (4.43 g, 76.1%). (Tables 1 and 2): mp 124—128 °C (lit,[8] mp 130 °C); IR (Nujol) 2950, 1750 (C=O), 1440, 1210, 1160, 1100 and 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=6.08—7.50 (m, 3H, arom.) and 3.80 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ=169.93 (s, C=O), 133.91, 129.09, 124.82, 123.43, 121.15, 117.30 and 33.05 (s, N–$\underline{C}H_3$).

*4-Chloro-*N*-ethyl-2(3*H*)-benzothiazolone (3b)*: Mp 97.4 °C (lit,[2] mp 98—99 °C). *4-Chloro-*N*-(ethoxycarbonylmethyl)-2(3*H*)-benzothiazolone (3c)*: Mp 78.5 °C (lit,[1] mp 77 °C). *6-Chloro-*N*-methyl-2(3*H*)-benzothiazolone (3e)*: Mp 109.5—112.9 °C (lit,[2] mp 109 °C). *4-Bromo-*N*-methyl-2(3*H*)-benzothiazolone (3h)*: Mp 141.5 °C (lit,[2] mp 139—140 °C). *5-Chloro-*N*-methyl-2(3*H*)-benzothiazolone (3i)*: Mp 102 °C (lit,[9] mp 105—106 °C).

*4,6-Dichloro-*N*-methyl-2(3*H*)-benzothiazolone (3d)*: Mp 144—146 °C; ^{1}H-NMR ($CDCl_3$) δ=3.85 (s, 3H) and 7.05—7.55 (m, 2H); Found: C, 41.24; H, 2.11; N, 5.87; S, 13.95 Cl, 30.55%. Calcd for $C_8H_5NOSCl_2$: C, 41.05; H, 2.15; N, 5.99; S, 13.70; Cl, 30.29%.

*6-Cyano-*N*-methyl-2(3*H*)-benzothiazolone (3f)*: Mp 141 °C; ^{1}H-NMR ($CDCl_3$) δ=3.80 (s, 3H) and 7.05—7.65 (m, 3H); Found: C, 56.98; H, 3.15; N, 14.55; S, 16.86%. Calcd for $C_9H_6N_2OS$: C, 57.25; H, 3.18; N, 14.73; S, 16.86%.

*5,7-Dichloro-*N*-methyl-2(3*H*)-benzothiazolone (3g)*: Mp 97—100 °C; ^{1}H-NMR ($CDCl_3$) δ=3.85 (s, 3H) and 7.20—7.60 (m, 2H); Found C, 41.16; H, 2.16; N, 5.96; S, 13.10; Cl, 30.82%. Calcd for $C_8H_5NOSCl_2$: C, 41.05; H, 2.15, N, 5.99; S, 13.70; Cl, 30.29%.

*Bis(*N*-(2-chlorophenyl)methylcarbamoyl) Sulfide (5)*: A solution of the sulfenyl halide intermediate (**4a**, X=2-Cl, R=CH_3) in toluene (20 ml) prepared from 2-chloro-*N*-methylaniline (2.00 g, 1.41×10^{-2} mol) in the same manner to those described for **3a**, was heated under reflux for 3 h. Then the solvent was removed in vacuo and the residue was poured into water (40 ml) and extracted with $CHCl_3$ (40 ml×2). The organic layer was washed with aqueous 10% HCl (50 ml×2), sat. $NaHCO_3$ solution (50 ml) and dried with $MgSO_4$. The solvent was removed *in vacuo*, and the resultant product were subjected to column chromatography (silica gel using $CHCl_3$ as an eluent) to give **5** (1.25 g, 30%), mp 172—174 °C; IR (Nujol) 2720, 1680 (C=O), 1465, 1260, 850, and 720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=6.50—7.80 (m, 8H, arom) and 3.30 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ=164.57 (s, C=O), 137.91, 134.64, 134.52, 131.79, 131.06, 128.32 and 37.90 (s, N–CH_3); Found: C, 47.67; H, 3.50; N, 6.91; S, 15.50; Cl, 17.61%; Calcd for $C_{16}H_{14}Cl_2N_2O_2S_2$: C, 47.89; H, 3.52; N, 6.98; S, 15.98; Cl, 17.67%.

*M-(2-Chlorophenyl)methylcarbamoyl (2-Chloro-*N*-methylanilino Sulfide (6).* CCSC (**2**, 5.08 g, 3.83×10^{-2} mol) was added to a solution of 2-chloro-*N*-methylaniline (**1a**, 10.0 g, 7.06×10^{-2} mol) in toluene (70 ml) at 0 °C and the solution was stirred at 0 °C for 1 h. After removal of 2-chloro-*N*-methylaniline hydrochloride by filteration, the filtrate was treated by the same procedure employed in the preparation of **3a.** 6.50 g of crude material was obtained after work up. The crude material was purified by column chromatography (silica gel using $CHCl_3$ as an eluent) to give **3a** (4.16 g, 59%) and **6** (0.66 g, 11%). oil; IR (film) 2920, 1740 (C=O), 1660, 1580, 1480, 1340, 1280 and 1120 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ=6.55—7.80 (m, 8H, arom.), 3.35 (s, 3H), and 3.17 (s, 3H); MS: (70 ev, DI) *m/e* (rel intensity)=340 (M^+, 40), 168 (100), 140 (68), and 77 (24).

References

1) For example, Benazoline® (4-chloro-*N*-(carboxymethyl)-2(3*H*)-benzothiazolone), British Patent 862226 (The Boots Co. Ltd., 1965).

2) T. Uematsu, Japan Patent 90261 (Sumitomo Chemical Co. Ltd., 1978).

3) I. Ueda, Japan Patent 92952 (Fujisawa Pharmaceutical Co. Ltd., 1979).

4) R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, New York (1957), p. 484.

5) V. G. Zumach and E. Kühle, *Angew. Chem., Int. Ed. Engl.*, **82**, 63 (1970).

6) CCSC (**2**) is also commercially available from Fulka Chemical Corp.

7) For example, see K. Pilgram and R. D. Skiler, *J. Org. Chem.*, **38**, 1575 (1973).

8) As indicated in Table 2, the yield of **3** decreased significantly when 5.0 equiv. of concd H_2SO_4 was used in the step B.

9) E. Hoggarth. *J. Chem. Soc.*, **1949**, 3315.