An Improved Alkylation of 2*H*-1,4-Benzothiazin-3(4*H*)-one and Related Heterocyclic Anilides

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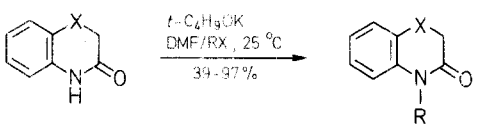
Various *N*-substituted derivatives of 2*H*-1,4-benzothiazin-3(4*H*)-one are obtained in high yields employing functionalized alkyl halides and potassium *tert*-butoxide in dimethylformamide. The method is mild, regioselective and tolerates a variety of functional groups.

Benzothiazine and its various derivatives continue to receive considerable attention both from a synthetic and a pharmacological point of view. Of particular importance are the biological roles which they play as antiinflammatory,[1,2] antihypertensive[3,4] and CNS agents.[5,6] While exploring potential biological activities of certain benzothiazine derivatives we required a simple and efficient preparation of various functionalized *N*-substituted 2*H*-1,4-benzothiazin-3(4*H*)-ones **6**. Although alkylations of benzothiazine have been reported previously,[7–10] these methods all make use of sodium hydride or potassium hydroxide as a base and often require high temperature (100–150 °C). While these conditions are well-suited for simple alkylating agents (e.g. methyl iodide or benzyl bromide), reactions with functionalized alkylating agents usually proceed in very poor yield or not at all. For example, Prasad and Tietje[7] were unable to satisfactorily alkylate a benzothiazine using sodium hydride and ethylchloroacetate in dimethylformamide. In order to obtain the desired 4-ethoxycarbonyl methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (**6k**), sodium amide in refluxing toluene was employed as a base giving **6k** in only 19% yield. Since we required large quantities of *N*-functionalized derivatives milder reaction conditions were sought for compatibility with a variety of functional groups and to provide the final products on a large scale in good overall yield.

After studying a variety of conditions and methods, including copper-catalyzed coupling reactions,[11] we report here a simple and efficient benzothiazine alkylation procedure which makes use of potassium *tert*-butoxide as a base in dimethylformamide at room temperature. This simple one pot procedure consists of dissolving benzothiazine in dimethylformamide at room temperature followed by addition of a slight excess of potassium *tert*-butoxide (1.05–1.15 eq) and the alkylating agent. As soon as these reagents are combined, a slightly exothermic reaction occurs followed by a fine deposit of white solid (presumably potassium halide) which usually indicates completion of the reaction. As seen from the Table, excellent yields of various functionalized derivatives of benzothiazine are obtained. Reactions are usually over in several hours, although in the cases of less reactive alkylating agents longer periods are required (12–18 h). A high degree of regioselection was observed since C-3 or O-alkylation products were not detected in any significant amounts. The reaction proceeds equally well with 2*H*-1,4-benzoxazin-3(4*H*)-one (**2**)[12] and 3,4-dihydro-2(1*H*)-quinoline (**1**)[12] but it is much less satisfactory with indoles, giving a variety of products (presumably mixtures of N, C, and O-alkylations).



1 X = CH_2
2 X = O
3 X = S

4 X = CH_2
5 X = O
6a-o X = S

Table. *N*-Substituted Derivatives of 2*H*-1,4-Benzothiazin-3-(4*H*)-one

Product	R	Yield[a] (%)	m.p. (°C)[b] (solvent) or b.p. (°C)/mbar	Molecular Formula[c] or Lit. Data	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR(CDCl$_3$/TMS)[e] δ (ppm)	MS[f] *m/e* (M$^+$) (rel. inten., %)
6a	CH_3	97	m.p. 53–55 (hexane)	m.p. 53.5–55.5[7]			
6b	n-C_4H_9	94	b.p. 128–130/3	$C_{12}H_{15}NOS$ (221.3)	1650	0.95 (t, 3H, J = 7.95 Hz); 1.35 (m, 2H); 1.6 (m, 2H); 3.36 (s, 2H); 4.0 (t, 2H, J = 7.95 Hz); 7.0–7.4 (m, 4H)	221 (67)
6c	$C_6H_5CH_2$	79	m.p. 83–85 (hexane)	m.p. 84–85.5[7]			
6d	$C_6H_5(CH_2)_2$	39[g]	m.p. 54–57 (hexane)	$C_{16}H_{15}NOS$ (269.3)	1590, 1665	2.95 (m, 2H, J = 7.95 Hz); 3.4 (s, 2H); 4.2 (m, 2H); 7.0–7.4, m, 9H)	269 (13)
6e	$C_6H_5CH=CHCH_2$	80	m.p. 61–63.5 (hexane)	$C_{17}H_{15}NOS$ (281.3)	1580, 1655	3.45 (s, 2H); 4.75 (m, 2H); 6.3 (m, 1H); 6.55 (d, 1H, J = 15.8 Hz); 7.0–7.4 (m, 9H)	281 (26)
6f	4-$(CO_2C_2H_5)C_6H_4CH_2$	86	m.p. 108–110 (toluene/hexane)	$C_{17}H_{15}NO_3S$ (313.3)	1660, 1715	3.55 (s, 2H); 3.90 (s, 3H); 5.3 (s, 3H); 6.9–7.42 (m, 5H); 8.0 (dd, 2H, J = 7.95 Hz)	313 (49)
6g	2-$CNC_6H_4CH_2$	80	m.p. 121–123 (toluene/hexane)	$C_{16}H_{12}N_2OS$ (280.3)	1670, 2220	3.55 (s, 2H); 5.48 (s, 2H); 6.9–7.0 (m, 8H)	280 (25)
6h	$HC\equiv C-CH_2$	87	m.p. 110–111 (toluene/hexane)	m.p. 111–112[7]	–	–	–
6i	$H_2C=CH-CH_2$	75	b.p. 149/4	b.p. 124/0.4[7]	–	–	–
6j	$(CH_3)_2NCH_2CH_2$	88[13]	b.p. 132–136/0.7	b.p. 146–149/0.3[9]	–	–	–
6k	$C_2H_5O_2CCH_2$	94	m.p. 48–50 (ether/pet.ether)	m.p. 48.5–50.5[7]	–[h]	–[h]	–[h]
6l	$C_2H_5O_2C(CH_2)_3$	94	b.p. 202–203/3	$C_{14}H_{17}NO_3S$ (279.3)	1660, 1720	1.2 (t, 3H, J = 7.95 Hz); 2.0 (m, 2H); 2.38 (t, 2H, J = 7.8 Hz); 3.38 (s, 2H); 4.0–4.2 (m, 4H); 7.0–7.4 (m, 4H)	279 (56)
6m	CH_3COCH_2	55	m.p. 73–75 (toluene/hexane)	$C_{11}H_{11}NO_2S$ (221.2)	1675, 1730	2.25 (s, 3H); 3.45 (s, 2H); 4.7 (s, 2H); 6.75 (dd, 1H, J = 7.95, 1.98 Hz); 7.0–7.3 (m, 2H); 7.4 (dd, 1H, J = 7.95, 1.98 Hz)	221 (75)
6n	$(CH_3)_3SiCH_2$	75	b.p. 133–135/3	$C_{12}H_{17}NOSSi$ (251.0)	1380, 1650	0.1 (br s, 9H); 3.35 (s, 2H); 3.6 (s, 2H); 7.0–7.45 (m, 4H)	251 (26)
6o	$(CH_3O)_2CHCH_2$	60	b.p. 143–144/1.3	$C_{12}H_{15}NO_3S$ (253.3)	1660	3.4 (s, 2H); 3.45 (s, 6H); 4.05 (d, 2H, J = 0.6 Hz); 4.65 (t, 1H, J = 0.6 Hz); 7.0–7.5 (m, 4H)	253 (17)

[a] Yield of pure products isolated by silica gel column chromatography.
[b] Uncorrected, measured with a Thomas-Hoover capillary melting point apparatus.
[c] Satisfactory microanalysis obtained: C ±0.39, H ±0.33, N ±0.3.
[d] Recorded on Perkin-Elmer 283B Infrared Spectrometer.
[e] Obtained on Bruker 250 MHz spectrometer.
[f] Recorded on a A.E.I. MS-30 spectrometer.
[g] Attempts to improve overall yield by various modifications failed, apparently due to rapid elimination of bromide.
[h] See experimental.

In conclusion, alkylation of benzothiazine with potassium *tert*-butoxide as a base offers a very mild and useful synthetic route to various functionalized *N*-substituted derivatives. The method is compatible with esters, acetals and silyl functionalized alkylating agents and provides a distinct advantage over previously reported methods. Considering these advantages, we believe that this method should have substantial utility and be the method of choice in preparation of *N*-substituted derivatives of benzothiazines, benzoxazines, and tetrahydroquinolinones.

4-Ethoxycarbonylmethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (6k); Typical Procedure:

2*H*-1,4-Benzothiazin-3(4*H*)-one (**3**; 2.5 g, 15.13 mmol) is dissolved in dry dimethylformamide (40 ml) under a nitrogen atmosphere at room temperature and treated in one portion with potassium *tert*-butoxide (1.95 g, 17.4 mmol). The resulting homogeneous mixture is stirred at room temperature for 15 min followed by the dropwise addition of ethyl bromoacetate (1.85 ml, 16.6 mmol) in dry dimethylformamide (10 ml). The mixture turns slightly exothermic. Stirring is continued at room temperature and progress is monitored by TLC (silica gel/dichloromethane). TLC analysis after 1.5 h indicated formation of a major less polar product and nearly complete consumption of starting 2*H*-1,4-benzothiazin-3(4*H*)-one (**3**). Following stirring at room temperature overnight, the mixture is poured into ice water (500 ml) and acidified to pH 1 with 2 normal hydrochloric acid. Extraction with ethyl acetate (2 × 450 ml) followed by washing of the ethyl acetate extracts with water (2 × 400 ml) and brine (400 ml), drying with sodium sulfate and removal of solvent *in vacuo* gives a light yellow oil. The crude product is purified on a silica gel column using dichloromethane as eluent to afford a light yellow oil; yield: 3.56 g (94%), which solidifies upon cooling. Recrystallization from ether/petroleum ether (1:1) gives a white crystalline product **6k**; m.p. 48–50°C (Lit.[7] m.p. 48.5–50.5°C).

$C_{12}H_{13}NO_3S$	calc.	C 57.35	H 5.21	N 5.57
(251.3)	found	57.39	5.15	5.55

IR (KBr) ν = 1680, 1740 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.95 (t, 3H, J = 5.07 Hz); 3.36 (s 2H); 4.17 (q, 2H, J = 5.85 Hz); 4.55 (s, 2H); 6.81 (d, 1H, J = 5.07 Hz); 6.95 (t, 1H, J = 5.85 Hz); 7.15 (t, 1H, J = 5.85 Hz); 7.30 ppm (d, 1H, J = 7.8 Hz).

MS: m/e = 251.0460 (M^+; calcd for $C_{12}H_{13}NO_3S$ = 251.0610).

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(1) Lombardino, J.G., Wiseman, E.H. *Med. Res. Rev.* **1982**, *2*, 127.
(2) Krapcho, J., Turk, C.F. *J. Med. Chem.* **1973**, *16*, 776.
(3) Cecchetti, V., Fravolini, A., Schiaffella, F., De Regis, M., Orzalesi, G., Volpato, I. *Farmaco. Ed. Sci.* **1983**, *38*, 35.
(4) Prasad, R.N. *J. Med. Chem.* **1969**, *12*, 290.
(5) Poepel, W., Leban, G., Gaust, G., Dietz, G. *Pharmazie* **1980**, *35*, 266.
(6) Sianesi, E., Redaelli, R., Magistretti, M.J., Massarini, E. *J. Med. Chem.* **1973**, *16*, 1133.
(7) Prasad, R.N., Tietje, K. *Can. J. Chem.* **1966**, *44*, 1247.
(8) Funke, A., Funke, G., Millet, B. *Bull. Soc. Chem. Fr.* **1961**, 1524.
(9) Krapcho, J. *U.S. Patents* 3 767 653 (1973) and 3 984 405 (1976).
(10) Worley, J.W., Ratts, K.W., Cammack, K.L. *J. Org. Chem.* **1975**, *40*, 1731.
(11) Employing these conditions,[14] compound **6c** was obtained at best in 10–20% after tedious silica gel column chromatography. Various *N*-aryl and *N*-heteroaryl-3-oxo-3,4-dihydro-2-*H*-1,4-benzothiazine derivatives were obtained in excellent yield employing Cu(I) catalyzed coupling reactions of 2*H*-1,4-benzothiazin-3-(4*H*)-one (**3**) and the appropriate aryl halide [ArX, (X = Br, I) CuBr, K_2CO_3, 1-methyl-2-pyrrolidinone, 180–190°C, 20–40 h].
(12) 3,4-Dihydro-1-methylquinolin-2-one (**4a**, R = CH_3) and 4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine (**5a**, R = CH_3) were prepared in 83% and 84% yield, respectively, employing the general procedure described for synthesis of **6k**.
(13) In this particular experiment, 2*H*-1,4-benzothiazin-3(4*H*)-one (**3**) and 2-dimethylaminoethyl chloride hydrochloride were combined and dissolved in dry dimethylformamide, followed by addition of excess (2.5 eq) potassium *tert*-butoxide. The reaction mixture was allowed to stir at room temperature for 3 days.
(14) Harbert, C.A., Plattner, J.J., Welch, W.M., Weissman, A., Koe, B.K. *J. Med. Chem.* **1980**, *23*, 635.