Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Convenient Strategies for the Preparation of Modified 2(3H)-Benzothiazolethiones

Narayan C. Chaudhuri [a]

[a] Tata Research Development and Design Center, 1 Mangaldas Road, Pune, 411 001, India

Published online: 21 Aug 2006.

To cite this article: Narayan C. Chaudhuri (1996) Convenient Strategies for the Preparation of Modified 2(3H)-Benzothiazolethiones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:20, 3783-3790, DOI: 10.1080/00397919608003794

To link to this article: http://dx.doi.org/10.1080/00397919608003794

SYNTHETIC COMMUNICATIONS, 26(20), 3783-3790 (1996)

CONVENIENT STRATEGIES FOR THE PREPARATION OF MODIFIED 2(3*H*)-BENZOTHIAZOLETHIONES

Narayan C. Chaudhuri[1]

Tata Research Development and Design Center
1 Mangaldas Road, Pune 411 001, India

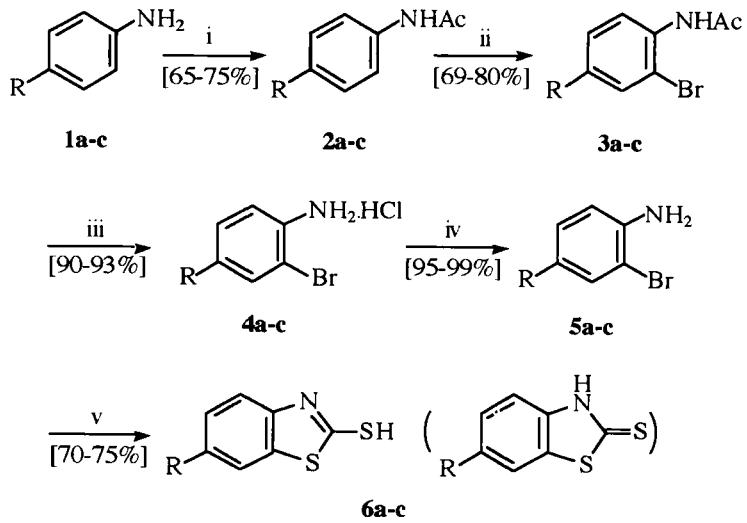
ABSTRACT: 4-Alkyl-2-bromoanilines and 4-alkoxy-2-chloroanilines were synthesized conveniently and submitted to cyclization reaction with potassium *O*-ethyl dithiocarbonate to afford 6-substituted 2(3*H*)-benzothiazolethiones in good yields.

In our program on the design, synthesis, and evaluation of novel surface-active chelating reagents for mineral processing applications, we needed to develop convenient procedures for the preparation of several 6-substituted 2(3*H*)-benzothiazolethiones in multigram quantities. 2(3*H*)-Benzothiazolethiones and their functionalized derivatives, besides being used as metal chelators in mineral beneficiation,[2] constitute an important class of heterocyclic compounds possessing a wide range of biological activities. They are used as highly effective insecticides, acaricides and herbicides,[3a] fungicides and bactericides,[3b,c] and some of them have been found useful in topical formulations such as drops or ocular inserts for treatment of elevated intraocular pressure.[3d] Among other applications, notable is their use as corrosion inhibitors for various metals[4] and the use of their metal complexes as catalysts in the polymerization of dienes[5] and vulcanization of rubber.[6] Yet, comprehensive strategies for their synthesis

involving easy routes to the key intermediates are lacking, barring some sporadic reports in the patent literature.[7] Some of these methods proceed with poor yields,[7a] some require special equipments to carry out condensations at high temperature and pressure,[7b] and other do not provide efficient strategies for the key intermediates.[7c,d]

Herein, we describe our facile methods for the synthesis of 6-substituted 2(3*H*)-benzothiazolethiones using anilines and phenols as readily available starting materials. As illustrated in Scheme I, 4-alkylanilines **1a-c** were converted in good yields to 4-alkyl-2-bromoacetanilides **3a-c** via the intermediacy of acetanilides **2a-c**. 4-Alkyl-2-bromoanilines **5a-c** were obtained in 86-92% yields (for two steps) from **3a-c** in a sequence of deacetylation by boiling with conc.HCl in 95% ethanol and treatment of the amine hydrochlorides **4a-c** with aqueous alkali at room temperature.[8] In each case, 4-alkyl-2-bromoaniline (**5**) was isolated as a heavy oil from the reaction mixture by extraction with diethyl ether and subsequent removal of ether at the rotary evaporator. Reaction of **5a-c** with freshly prepared potassium *O*-ethyl dithiocarbonate[9] in refluxing dimethyl formamide (DMF)[10] for 4 h afforded target molecules **6a-c** in 70-75% yields, after aqueous work-up and purification by recrystallization.

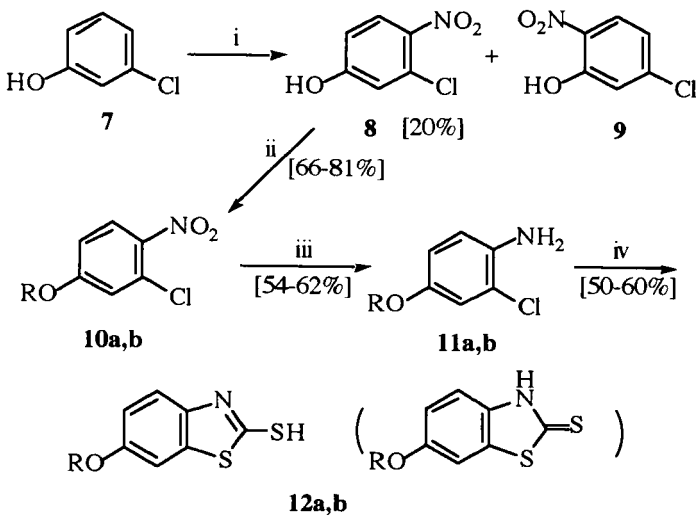
For the synthesis of 6-alkoxy-2(3*H*)-benzothiazolethiones (Scheme II), *m*-chlorophenol (**7**) was nitrated with aqueous $NaNO_3/H_2SO_4$.[11] Regioisomers **8** and **9** were separated by steam distillation, the ortho product **9** being steam-volatile. Although previous workers[11] reported 60% yield of the crude material **8**, yield of the purified product is not available from that report. We obtained pure 3-Chloro-4-nitrophenol (**8**) after repeated crystallizations from benzene in 20% yield, which was then alkylated with ethyl iodide or *n*-propyl bromide in presence of sodium ethoxide in absolute ethanol. 4-Alkoxy-2-chloronitrobenzenes (**10a,b**)



a : R = -CH_3; **b** : R = -CH_2CH_3; **c** : R = -$(CH_2)_2CH_3$

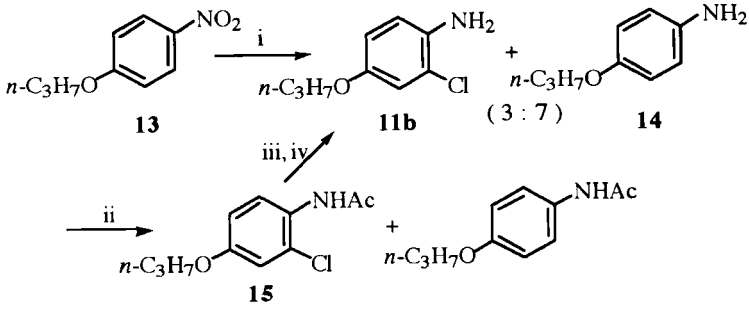
Scheme I: (i) AcOH, reflux, 3h; (ii) Br_2/AcOH, 55°C, 1-2h; (iii) Conc.HCl, 95% EtOH, reflux, 4h; (iv) Aq.NaOH, r.t., 30 min; (v) EtOC(=S)S^-K^+, DMF, 160°C, 4h.

which were isolated (66-81% yields) by aqueous work-up followed by extraction into diethyl ether, were found to be chromatograhically homogeneous in each case and hence no further purification was necessary. Reduction of the -NO_2 group in **10a,b** was accomplished with iron powder in conc. HCl according to published procedure[12] to obtain ortho-chloroanilines **11a,b** which were isolated by steam distillation (54-62% yields). These precursors **11a,b** underwent smooth cyclizations with potassium *O*-ethyl dithiocarbonate to afford 6-ethoxy-2(3*H*)-benzothiazolethione (**12a**) and 6-*n*-propoxy-2(3*H*)-benzothiazolethione (**12b**) in 60% and 50% yields respectively. In an alternative approach (Scheme III), *p*-

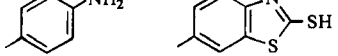
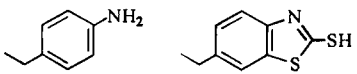
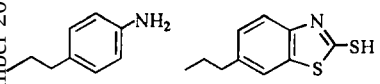
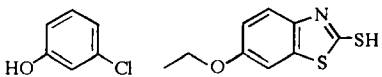
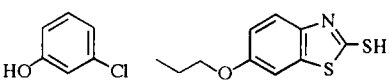


a : R = $-CH_2CH_3$; **b** : R = $-(CH_2)_2CH_3$

Scheme II: (i) Aq.$NaNO_3/H_2SO_4$, 25°C, 4h; (ii) NaOEt, RI or RBr, EtOH, reflux, 10h; (iii) Fe/HCl, EtOH, reflux, 6h; (iv) $EtOC(=S)S^-K^+$, DMF, 160°C, 4h.



Scheme III: (i) Sn/Conc.HCl; (ii) Ac_2O/NaOAc; (iii) Conc.HCl, 95% EtOH, reflux, 4h; (iv) Aq.NaOH, r.t., 30 min.

		75	184-185 (lit.[16]m.p 181 °C)	IR 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63-7.06 (3H, m, *aro* 2.46 (3H, s, -CH_3); MS m/z (rel. int.) 181 (M^+, 100), 18 (M^++1, 14), 183 (M^++2, 10).
		75	138-139	IR 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.85 (1H, br., S*H*), (3H, m, *arom.*), 2.7 (2H, q, J = 7.0 Hz, -CH_2CH_3), 1.23 t, J = 7.0 Hz, -CH_2CH_3); Anal. Calcd for $C_9H_9NS_2$: C 5 H 4.65%, N 7.17%; Found: C 55.53%, H 4.56%, N 6.97
		70	147-150	IR 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.9 (1H, br., S*H*), 7 (3H, m, *arom.*), 2.66 (2H, t, J =7.0 Hz, Ar-CH_2CH_2-), 1 m, Ar-CH_2CH_2-), 0.95 (3H, t, J = 7.0 Hz, -CH_2CH_3); M (rel.int.) 209 (M^+, 50), 210 (M^++1, 8), 211(M^++2, 6), 180 (M^+-C_2H_5, 100).
		60	196-199 (lit.[16]m.p 198 °C)	IR 1600 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6) δ 13.4 (1H, S*H*), 7.7-6.74 (3H, m, *arom.*), 4.1 (2H, q, J = 7.0 Hz, -OCH_2CH_3), 1.4 (3H, t, J = 7.0 Hz, -OCH_2CH_3); MS m (rel.int.) 211(M^+,100), 212 (M^++1, 15), 213 (M^++2, 12), 183 (M^+-C_2H_4, 81).
		50	161-165	IR 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6-6.9 (3H, m, *arom* (2H, t, J = 7.0 Hz, -OCH_2-), 2.1-1.6 (2H, m, -OCH_2CH_2 (3H, t, J = 7.0 Hz, -CH_2CH_3); MS m/z (rel. int.) 225 (M 226 (M^++1, 8), 227 (M^++2, 6), 183 M^+-C_3H_6, 100).

nitrophenyl *n*-propyl ether (**13**), when subjected to Sn/HCl reduction,[13] furnished a nuclear chlorinated aniline **11b** along with the normal reduction product **14** in 3:7 ratio. These were separated from the mixture by making acetyl derivatives followed by repeated fractional crystallization from aqueous ethanol and the desired chloro-acetanilide **15** was reverted to **11b** in pure form for the formation of 6-*n*-propoxy-2(3*H*)-benzothiazolethione (**12b**) as shown earlier in Scheme II.

In a typical experimental procedure for the cyclization reaction, freshly prepared potassium *O*-ethyl dithiocarbonate (3.6g. 22.5 mmol) was added in portions to a solution of 4-alkyl-2-bromoaniline (**5**) or 4-alkoxy-2-chloroaniline (**11**) (10 mmol) in 15 mL of anhydrous DMF. The pale yellow solution was heated in an oil bath of 160 °C for 4 h with constant stirring. The resultant dark solution was cooled, diluted with 25 mL of ice-cold water and acidified with 6 (N) HCl. Solid product that separated out on acidification, was isolated by Buchner filtration and purified by recrystallization from $CHCl_3$ / petroleum ether (60-80 °C). Yields and physical data of pure products are listed in the accompanying Table I (Entries 1-5).

In conclusion, we have developed convenient methods for the preparation of 6-alkyl- and 6-alkoxy-2(3*H*)-benzothiazolethiones using readily available starting materials and employing easy-to-execute synthetic strategies for the key intermediates. The transformations are simple and clean, and have been found good in large scale preparations. Results on their effectiveness in the processing of minerals of heavy metals will be reported elsewhere.

Acknowledgment: The author wishes to thank Dr. E. C. Subbarao, Director, TRDDC, Pune for providing research facilities and Prof. S. Chandrasekaran of the Department of Organic Chemistry, IISc, Bangalore for

helpful discussions. Financial assistance from the Department of Mines, Government of India, New Delhi is gratefully acknowledged.

References and Notes:

1. Current address: *Department of Chemistry, University of Illinois at Chicago, IL 60607, USA.*

2. Marabini, A. M.; Barbaro, M.; and Passariello, B. *Int. J. Miner. Process.* **1989**, *25*, 29; and the references cited therein.

3. a) Boehringer Sohn, C. H. *Chem. Abstr.* **1967**, *67*:73687x, **Neth. Appl. 6,612,312** (Cl. C 07*f*), 6 Mar 1967; b) Bujdakova, H.; Kuchta, T.; Sidoova, E.; and Gvozdjakova, A. *FEMS Microbiol. Lett.* **1993**, *112*, 329; c) Srivastava, S. K.; Gupta, A.; and Verman, A. *Egypt. J. Chem.* **1983,** *26*, 173; d) Woltersdorf, O. W., Jr.; Michelson, S. R.; Sondey, J. M.; and Schwam, H. (Merck and Co., Inc.) *Chem. Abstr.* **1983**, *99*:76881c, **Eur. Pat. Appl. EP 79,269** (Cl. A61K31/425), 18 May 1983, US Appl. 317,807, 03 Nov 1981.

4. a) Kumar, A.; and Singh, M. M. *Anti-Corros. Methods Mater.* **1993**, *40*, 4; b) Cho. T.; Shiraishi, Y.; Takahashi, T.; and Watanabe, M. (Mitsubishi Materials Corp.) *Chem. Abstr.* **1994**, *120*:277580e, **Jpn. Kokai Tokkyo Koho JP 06 10,166 [94 10,166]** (Cl. C23F 11/14), 18 Jan 1994, Appl. 92/192,999, 26 Jun 1992.

5. Kanbara, H.; Takahashi, A.; Nakano, M.; and Hirose, T. (Mitsui Chemical Industries Co., Ltd.) *Chem. Abstr.* **1969**, *70*:78965h, **JP 68 19,024** (Cl. 26B21), 19 Aug 1968, Appl. 18 Mar 1964.

6. a) Kacani, S.; and Stefanka, L. *Chem. Abstr.* **1968**, *69*:43905r, **Czech. 124,384** (Cl. C 07*d*), 15 Sep 1967, Appl. 20 Jul 1965; b) Pal, D.; and Basu, D. K. *Kautsch. Gummi, Kunstst.* **1983**, *36*, 358, *Chem. Abstr.* **1983**, *99*:23788w; c) Debnath, S. C.; and Basu, D. K. *J. Appl. Polym. Sci.* **1994**, *52*, 597.

7. a) Arventiev, B.; and Nicolaescu, T. *Bul. Inst. Politeh. Iasi, Sect. 2 : Chim. Ing. Chim.* **1980**, *26*, 117, *Chem. Abstr.* **1981**, *95* :132735q; b) Sanshin Chemical Industry Co., Ltd. *Chem. Abstr.* **1983**, *99* :5622h, **Jpn Kokai Tokkyo Koho JP 58 24,576 [83 24,576]** (Cl. C07D277/72), 14 Feb 1983, Appl. 81/121,949, 05 Aug 1981; c) Handte, R.; Willms, L.; and Blume, E. (Hoechst A.-G.) *Chem. Abstr.* **1982**, *96* :P6717t, **Ger. Offen. DE 3,008,225** (Cl. C07D277/72), 17 Sep 1981, Appl. 04 Mar 1980; d) Kretzschmar, E.; and Laban, G. (Arzneimittelwerk Dresden GmbH) *Chem. Abstr.* **1994**, *120* :164172e, **Ger. Offen. DE 4,230,923** (Cl. C07D285/14), 28 Oct 1993, DE Appl. 4,213,063, 21 Apr 1992.

8. Vogel, A. I. "*Textbook of Practical Organic Chemistry*," Longman Group Limited, London, 4th Edition, **1978**, pp. 709-710.

9. Vogel, A. I. *ibid.* p. 588.

10. At reflux DMF undergoes substantial decomposition, but this did not hamper the progress of the reaction.

11. Hodgson, H. H.; and Moore, F. H. *J. Chem. Soc.* **1925,** *127*, 1599.

12. Callaghan, P. D.; Gibson, M. S.; and Elliott, A. J. *J. Chem. Soc. Perkin Trans. I* **1975**,1386.

13. Hurst, W. G.; and Thorpe, J. F. *J. Chem. Soc.* **1915,** *107*, 934.

14. Melting points were determined using a capillary melting point apparatus and all are uncorrected.

15. Spectral and elemental analyses were carried out at: a) the Department of Chemistry, University of Poona, Pune; b) National Chemical Laboratory, Pune; and c) the Department of Organic Chemistry, IISc, Bangalore.

16. Sebrell, L. B.; and Boord, C. E. *J. Am. Chem. Soc.* **1923,** *45*, 2390.

(Accepted in the USA 19 May 1996)