JOC Notes

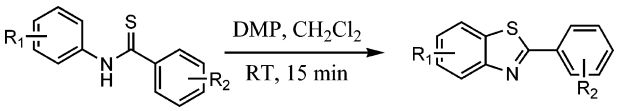
Hypervalent Iodine Mediated Intramolecular Cyclization of Thioformanilides: Expeditious Approach to 2-Substituted Benzothiazoles

D. Subhas Bose* and Mohd. Idrees

Organic Chemistry Division III, Fine Chemicals Laboratory, Indian Institute of Chemical Technology, Hyderabad, 500 007, India

dsb@iict.res.in; bose_iict@yahoo.co.in

Received May 5, 2006



A new, mild, and efficient method has been developed for the synthesis of 2-substituted benzothiazoles via the intramolecular cyclization of thioformanilides by using hypervalent iodine reagents in CH_2Cl_2 at ambient temperature. The reaction proceeds via a thiyl radical in high yields to give the novel compound oxybis benzothiazole and is also amenable to generating combinatorial libraries of heterocyclic compounds by solid-phase synthesis.

The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry. These structures represent a class of molecules capable of binding to multiple receptors with high affinity. The exploitation of these molecules enables the medicinal chemist to rapidly discover biologically active compounds across a wide range of therapeutic areas on a reasonable time scale. 2-Arylbenzothiazoles are an important class of bicyclic privileged substructures owing to their potent utility as imaging agents for β-amyloid, antitumor agents, calcium channel antagonists, antituberculotics, antiparasitics, chemiluminescent agents, and also as photosensitizers.[1−7]

Arylbenzthiazoles are most commonly synthesized via one of the two major routes. The most commonly used method involves the condensation of *o*-aminothiophenols with substituted nitriles, aldehydes, carboxylic acids, acyl chlorides, or esters.[8] This method, however, suffers from limitations such as the difficulties encountered in the synthesis of readily oxidizable *o*-aminothiophenols bearing substituent groups. Another route is based on the Jacobson's cyclization of thiobenzanilides.[9,10] Other general methods include the microwave-mediated reaction of *o*-aminothiophenol with β-chlorocinnamaldehydes, the reaction of dibenzyl disulfides with *o*-aminothiophenol, the reduction of *o*,*o*′-dinitrodiphenyl disulfide, the reaction of *S*-aryl thiobenzoate with arylhaloamines, from 1,2,3-benzodithiazole-2-oxides, radical cyclization of benzyne intermediates, and Grignard reactions of arylisothiocyanates.[11−16] More recently, arylbenzothiazoles have been prepared from the oxidative coupling of thiophenols and aromatic nitriles[17] using cerric ammonium nitrate (CAN). However, the reported synthesis of 2-arylbenzothiazoles mediated by CAN is irreproducible; the only products formed in this reaction are bis-(*p*-tolyl) disulfide and *p*-tolyl *p*-toluenethiosulfonate.[18] These strategies, however, were found to be incompatible with nitro functionality, requiring multistep synthesis, and therefore a new alternative route for the synthesis of 2-arylbenzothiazoles needs to be explored.

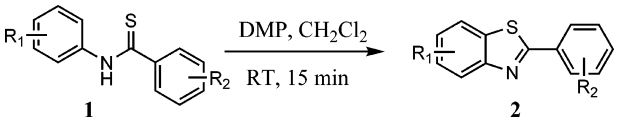
Over recent years, organic derivatives of hypervalent iodine reagents occupy an important place in the realm of natural and synthetic organic chemistry because of their potential applications for the construction of carbon−heteroatom and carbon−carbon bonds.[19] One of the field's most significant advances, the discovery of the Dess−Martin periodinane (DMP)[20] 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, opens the

* To whom correspondence should be addressed. Fax: +91-40-27160387.

(1) Mathis, C. A.; Wang, Y.; Holt, D. P.; Huang, G.-F.; Debnath, M. L.; Klunk, W. E. *J. Med. Chem.* **2003**, *46*, 2740−2754.
(2) Hutchinson, I.; Jenninga, S. A.; Vishnuvajjala, B. R.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2002**, *45*, 744−747.
(3) Stevens, M. F. G.; Wells, G.; Westwell, A. D.; Poole, T. D. PCT Int. Appl., WO 0304479, 2003.
(4) Caujolle, R.; Loiseau, P.; Payard, M.; Gayral, P.; Kerhir, M. N. *Ann. Pharm. Fr.* **1989**, *47*, 68−73.
(5) Yamamoto, K.; Fujita, M.; Tabashi, K.; Kawashima, Y.; Kato, E.; Oya, M.; Iso, T.; Iwao *J. Med. Chem.* **1988**, *31*, 919−930.
(6) Yoshida, H.; Nakao, R.; Nohta, H.; Yamaguchi, M. *Dyes and Pigments* **2000**, *47*, 239−245.
(7) Petkov, I.; Deligeorgiev, T.; Markov, P.; Evstatiev, M.; Fakirov, S. *Polym. Degrad. Stab.* **1991**, *33*, 53−66.
(8) Ben-Alloum, A.; Bakkas, S.; Soufiaoui, M. *Tetrahedron Lett.* **1997**, *38*, 6395−6396.
(9) (a) Shi, D.-F.; Bradshaw, T. D.; Wrigley, S.; McCall, C. J.; Lelieveld, I. F.; Stevens, M. F. G. *J. Med. Chem.* **1996**, *39*, 3375−3384. (b) Klunk, W. E.; Mathis, C. A., Jr.; Wang, Y. PCT Int. Appl., 2004.
(10) Hein, D. W.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 427−429.
(11) Paul, S.; Gupta, M.; Gupta, R. *Synth. Commun.* **2002**, *32*, 3541−3547.
(12) Shirinian, V. Z.; Melkova, S. Yu.; Belen'kii, L. I.; Krayushkin, M. M.; Zelinsky, N. D. *Russ. Chem. Bull.* **2000**, *49*, 1859−1862.
(13) Zhong, W. H.; Zhang, Y. M.; Chen. X. Y. *J. Indian Chem. Soc.* **2001**, *78*, 316−318.
(14) Roe, A.; Tucker, W. P. *J. Heterocycl. Chem.* **1965**, *2*, 148−151.
(15) Stanetty, P.; Krumpark, B. *J. Org. Chem.* **1996**, *61*, 5130−5133.
(16) (a) Ares, J. J. *Synth. Commun.* **1991**, *21*, 625−633. (b) Majo, V. J.; Prabhakaran, J.; Mann, J. J.; Kumar, J. S. D. *Tetrahedron Lett.* **2003**, *44*, 8535−8537.
(17) Tale, R. H. *Org. Lett.* **2002**, *4*, 1641−1642.
(18) Nair, V.; Augustine, A. *Org. Lett.* **2003**, *5*, 543−544.
(19) (a) Varvoglis, A.; Spyroudis, S. *Synlett* **1998**, 221. (b) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1996; p 256. (c) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271−1287. (d) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Sugita, K. *J. Am. Chem. Soc.* **2002**, *124*, 2221−2232 and references therein. (e) Bose, D. S.; Reddy, A. V. N. *Tetrahedron Lett.* **2003**, *44*, 3543−3545. (f) Prakash, O.; Batra, A.; Sharma, V.; Saini, R.; Verma, R. S. *J. Indian Chem.* **2003**, *80*, 1031−1034. (g) Varma, R. S.; Saini, R. K.; Prakash, O. *Tetrahedron Lett.* **1997**, *38*, 2621−2622. (h) Aggarwal, R.; Sumran, G.; *Synth. Commun.* **2006**, *36*, 875−879. (i) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1996**, *61*, 8004−8005.

10.1021/jo0609374 CCC: $33.50
Published on Web 09/15/2006

SCHEME 1

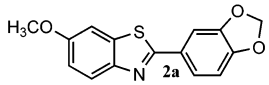
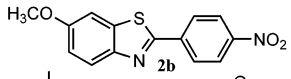
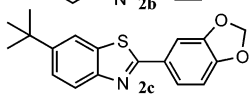
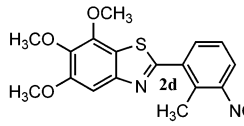
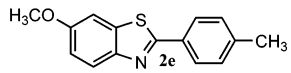
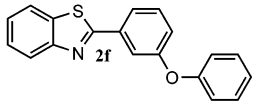
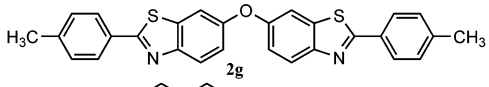
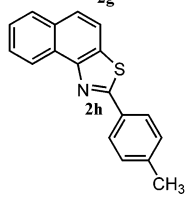


door to a mild oxidation procedure allowing a myriad of alcohols to be converted to the corresponding carbonyl compounds. As part of our ongoing program on the synthesis and development of new methodologies in organic synthesis,[21] we herein describe a new, efficient, and practical route for the one-step conversion of thioformanilides into the corresponding benzothiazoles by using Dess−Martin periodinane in CH_2Cl_2 at room temperature in excellent yields for a short period of time as required to complete the reaction (TLC) (Scheme 1). To the best of our knowledge, the generality and applicability of DMP in the preparation of benzothiazoles from thioformanilides is not known. The most versatile route to 2-arylbenzothiazoles bearing substituents in both phenyl and benzothiazolyl rings started with benzanilide prepared by the interaction of benzoyl chlorides and arylamines in triethylamine. The benzanilides were converted to thiobenzanilides with Lawesson's reagent[22] in refluxing dry toluene.

To explore the generality and scope of this process, diverse thioformanilides were studied to illustrate this novel and general method for the synthesis of arylbenzothiazoles, and the results are summarized in Table 1. As shown in the table, the synthesis of 2-arylbenzothiazoles bearing substituents in both the rings is accomplished in high yields. It is further seen that 2-arylbenzothiazoles bearing nitro functionality on the aryl ring (entries 2 and 4) are obtained in quantitative yield by this method. This contrasts, however, with the Bu_3SnH/AIBN-promoted[23] cyclization of aryl radical onto thioamides for the synthesis of arylbenzothiazoles, where under these conditions thioamides containing a nitro functionality on the aryl ring underwent decomposition rather than benzothiazole formation. Furthermore, we have synthesized for the first time a new type of bis(benzothiazoles) having an oxygen bridge between the rings. Since a wide variety of arylamines and acids are commercially available, this protocol would offer a higher degree of flexibility with regard to functional groups that can be placed on the 2-aryl moiety, thereby providing a better understanding of this structure activity relationship (SAR) of the target compounds. The usefulness of this methodology lies in the fact that the reactions are carried out rapidly under extremely mild conditions to give the product 2-arylbenzothiazoles (entries **2a**−**h**) in high yields. Moreover, the method is compatible with many substituents such as alkoxy, nitro, *tert*-butyl, etc. in the substrate.

Among the hypervalent iodine reagents such as IBX, DAIB was studied for this transformation, DMP was found to be the most effective in terms of conversion and reaction rates. A plausible mechanism proposed for Dess−Martin periodinane promoted cyclization reaction is presented in Scheme 2. Arylthioformanilide **1** can exist as thioiminol **1a**; the latter reacts with DMP to produce thiyl radical **1b** while iodine(V) is reduced to iodine(IV) at the same time. Subsequently, 1,5-homolytic radical cyclization of **1b** followed by aromatization of radical **1c** gives 2-arylbenzothiazole **2**.

TABLE 1. Results of DMP-Promoted Synthesis of 2-Arylbenzothiazoles

entry	product	Yield (%)[a]
1		95
2		94[24]
3		92
4		87
5		90
6		95
7		85
8		91

[a] Yield refers to the pure isolated product.

In conclusion, the short reaction period, the simple workup, the good yield, and the fairly mild conditions of this method offer advantages over other procedures, and this approach should be of further interest in synthetic chemistry. Future work will be undertaken to develop a combinatorial version of this synthesis for the SAR of 2-arylbenzothiazoles for various pharmaceutical applications.

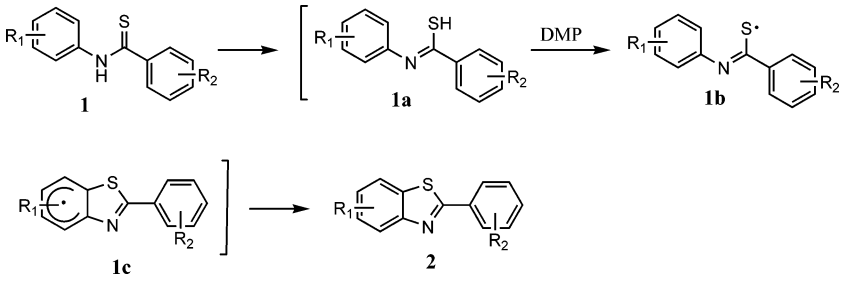
Experimental Section

General Procedure for the Preparation of Substituted 2-Aryl Benzothiazole (2a−h). Dess−Martin periodinane (5.5 mmol) was added to a stirred solution of thioformanilide (5.0 mmol) in CH_2Cl_2 at room temperature. The progress of the reaction was monitored by TLC. After completion, it was quenched with H_2O (2 × 5 mL), and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed in vacuo, to afford the crude product which was purified by column chromatography on silica gel using petroleum ether/EtOAc 8:1 as eluent to give 2-arylbenzothiazole **2a**−**h** (85−95%).

(20) (a) Dess, D. B.; Martin. J. C. *J. Org. Chem*. **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem*. **1994**, *59*, 7549−7552.

(21) (a) Bose, D. S.; Jayalakshmi, B. *J. Org. Chem*. **1999**, *64*, 1713−1714. (b) Bose, D. S.; Kumar, R. K. *Tetrahedron Lett*. **2006**, *47*, 813−816. (c) Bose, D. S.; Rudra Das, A. P.; Mereyala, H. B. *Tetrahedron Lett*. **2002**, *43*, 9195−9197. (d) Bose, D. S.; Fatima, L.; Rajender, S. *Synthesis* **2006**, 1863−1867. (e) Bose, D. S.; Chary, M. V.; Mereyala, H. B. *Heterocycles* **2006**, *68*, 1217−1224.

SCHEME 2



Preparation of 6-Methoxy-2-[3,4-methylenedioxyphenyl]benzothiazole (2a). Dess−Martin periodinane (2.33 g, 5.5 mmol) was added to a stirred solution of thioformanilide (1.43 g, 5.0 mmol) in CH_2Cl_2 at room temperature. The progress of the reaction was monitored by TLC. After completion, it was washed with H_2O (2 × 5 mL); and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed in vacuo, to afford the crude product which was purified by column chromatography on silica gel using petroleum ether/EtOAc 8:1 as eluent to give subtituted benzothiazole **2a** (1.35 g, 95%) as a pale yellow solid: mp 164−166 °C. ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H), 6.02 (s, 2H), 6.83 (d, 1H, J = 8.3 Hz), 7.02 (dd, 1H, J = 2.26 Hz), 7.25 (1H, d, J = 3.0 Hz), 7.48−7.58 (m, 2H), 7.85 (d, 1H, J = 9.0 Hz). ^{13}C NMR (75 MHz): δ 55.8, 101.6, 104.4, 107.3, 108.6, 115.4, 122.0, 123.5, 128.3, 136.3, 148.4, 148.7, 149.8, 157.7. MS (EI): m/z (%) = 285 (M^+, 100), 270 (80), 242 (15), 143 (13), 95 (20). Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.88; N, 4.90; S, 11.24. Found: C, 63.05; H, 3.82; N, 4.96; S, 11.15.

Preparation of 6,6′-Oxybis-2-[4-methylphenyl]benzothiazole (2g). Dess−Martin periodinane (4.66 g, 11 mmol) was added to a stirred solution of thioformanilide (2.34 g, 5.0 mmol) in CH_2Cl_2 at room temperature. The progress of the reaction was monitored by TLC. After completion, it was washed and diluted with H_2O (2 × 5 mL), and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed in vacuo, to afford the crude product which was purified by column chromatography on silica gel using petroleum ether/EtOAc 8:1 as eluent to give oxybis benzothiazole **2g** (1.98 g, 85%) as a pale yellow solid: mp 216−217 °C. ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H), 7.18−7.28 (m, 3H), 7.51 (s, 1H), 7.89−8.02 (m, 3H). ^{13}C NMR (75 MHz): δ 21.5, 111.0, 118.7, 124.0, 127.3, 129.7, 130.9, 141.4, 150.3, 155.3. MS (ESI): m/z (%) = 465 (M^+, 55), 145 (100), 102 (78). Anal. Calcd for $C_{28}H_{20}N_2OS_2$: C, 72.38; H, 4.34; N, 6.02; S, 13.80. Found: C, 72.32; H, 4.30; N, 5.94; S, 13.72.

Acknowledgment. M. Idrees thanks CSIR, New Delhi, for financial support.

Supporting Information Available: Experimental procedure, copies of ^{1}H NMR, and ^{13}C NMR spectra of **2a**, **2c**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0609374

(22) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth*. **1984**, *62*, 158−164.

(23) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119−10128.

(24) Shi, D.-F.; Bradshaw, T. D.; Wrigley, S.; McCall, C. J.; Lelieveld, P.; Fichtner, I.; Stevens, M. F. G. *J. Med. Chem.* **1996**, *39*, 3375−3384.