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# A convenient access to substituted benzothiazole scaffolds via intramolecular cyclization of thioformanilides

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**Abstract**—A new and practical method has been developed for the synthesis of substituted benzothiazoles via the intramolecular cyclization of thioformanilides using DDQ in $CH_2Cl_2$ at ambient temperature. The reaction proceeds in high yields via the thiyl radical to give novel oxybis-benzothiazole, and offers a high degree of flexibility with regard to the functional groups that can be placed on the benzothiazole nucleus or 2-aryl moiety which in turn generates scaffolds for parallel synthesis.


Over the past decade the privileged structure concept has emerged as a fruitful approach for the discovery of novel biologically active molecules. Privileged structures, with their inherent affinity for diverse biological receptors, represent an ideal source of core scaffolds and capping fragments for the design and synthesis of combinatorial libraries targeted at various receptors on a reasonable time scale.[1] Arylbenzothiazoles bearing a substituent at C-2 are of great interest as this structural framework has proved to be an important class of bicyclic privileged substructures owing to their potent utility as imaging agents for β-amyloid, as chemiluminescent agents, antitumour agents, calcium channel antagonists, antituberculotics, antiparasitics and also as photosensitizers.[2–7]

Arylbenzothiazoles are most commonly synthesized via one of 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 difficulties encountered in the synthesis of readily oxidizable *o*-aminothiophenols bearing substituents. Another route is based on Jacobson's cyclization of thiobenzanilides.[9,10] Other general methods include microwave-mediated reaction of *o*-aminothiophenol with β-chlorocinnamaldehydes, reaction of dibenzyl disulfides with *o*-aminothiophenol, reduction of *o*,*o*′-dinitrodiphenyl disulfide, reaction of *S*-aryl thiobenzoate with arylhaloamines, from 1,2,3-benzodithiazole-2-oxides, via radical cyclization of benzyne intermediates and Grignard reactions of arylisothiocyanates.[11–16] More recently, arylbenzothiazoles have been prepared by the oxidative coupling of thiophenols and aromatic nitriles[17] using ceric 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 a nitro functionality, thus requiring multistep synthesis. Therefore, a new alternative route needs to be explored having significant practical value for the synthesis of 2-arylbenzothiazoles. To overcome these limitations, herein, we report a highly efficient intramolecular cyclization of thioformanilides mediated by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[19] without using any metal catalyst. DDQ is a well-known oxidizing agent and has proved to be a versatile reagent for various organic transformations including deprotection of functional groups, cleavage of linker molecules from solid supports, introduction of unsaturation and potential applications for the construction of carbon–carbon and carbon–heteroatom bonds.

In continuation of our efforts towards the synthesis and development of new methodologies in organic

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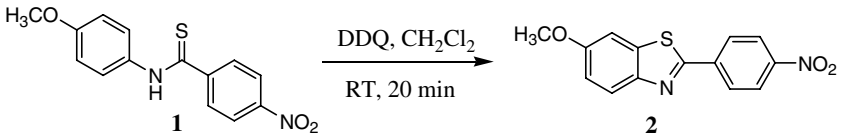
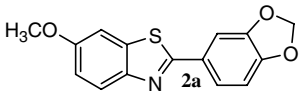
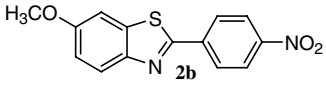
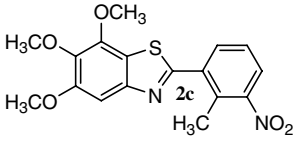
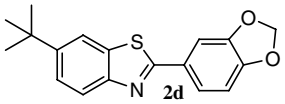
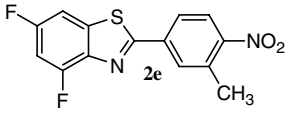
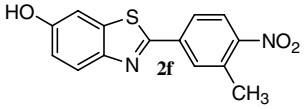
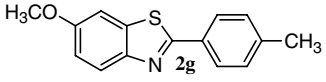
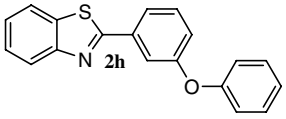
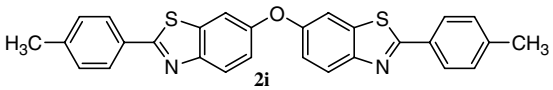
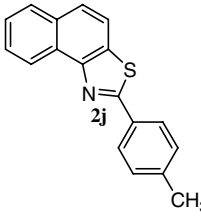


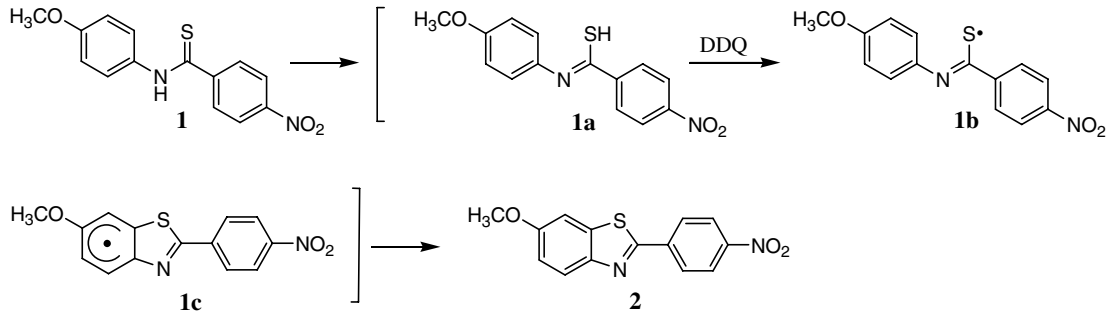

**Scheme 1.** DDQ-mediated intramolecular cyclization of thioformanilide.

synthesis,[20] we herein describe a new, efficient and practical route for the one-step conversion of thioformanilides into the corresponding benzothiazoles using DDQ in $CH_2Cl_2$ at room temperature in excellent yields (Scheme 1).[21] To the best of our knowledge, the generality and applicability of DDQ in the preparation of benzothiazoles from thioformanilides is not known. In addition, this reaction is very clean, efficient and

**Table 1.** DDQ-catalyzed synthesis of 2-arylbenzothiazoles

| Entry | Product | Yield[a] (%) |
|---|---|---|
| 1 |  | 95 |
| 2 |  | 87[9a] |
| 3 |  | 92 |
| 4 |  | 88 |
| 5 |  | 85 |
| 6 |  | 83 |
| 7 |  | 90 |
| 8 |  | 95 |
| 9 |  | 85 |
| 10 |  | 89 |

[a] Yield refers to the pure isolated product.




**Scheme 2.** A plausible mechanism for the DDQ-mediated intramolecular cyclization of thioformanilides.

involves a simple work-up procedure. Unlike previous methods, the reported protocol does not require high temperatures to produce benzothiazole derivatives. Solvents such as $CH_3CN$, THF, MeOH and the ionic liquid [BMIM]$PF_6$ proved to be effective. It should be noted that other reagents such as iodotrimethylsilane and molecular iodine were ineffective even after longer reaction times, demonstrating the unique ability of DDQ in this cyclization. The most versatile route to 2-arylbenzothiazoles bearing substituents on both the phenyl and benzothiazolyl rings started with benzanilides prepared by the reaction 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 for the synthesis of arylbenzothiazoles and the results are summarized in Table 1. As shown in Table 1, the synthesis of 2-arylbenzothiazoles bearing substituents on both rings was accomplished in high yields. It can be further seen that 2-arylbenzothiazoles bearing a nitro functionality on the aryl ring (entries 2, 3, 5 and 6) were obtained in quantitative yields by this method. This contrasts, with the $Bu_3SnH$/AIBN-promoted[23] cyclization of aryl radicals 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 bis(benzothiazole) possessing an oxygen bridge between the rings. Since a wide variety of aryl amines and acids are commercially available, this protocol offers a high degree of flexibility with regard to functional groups on the benzothiazole nucleus or 2-aryl moiety, thereby providing a means for understanding structure–activity relationships (SAR) of the target compounds. The method is compatible with many substituents such as alkoxy, nitro and *tert*-butyl.

A plausible mechanism for the DDQ promoted cyclization reaction is presented in Scheme 2. Arylthioformanilide **1** can exist as thioiminol **1a**, which reacts with DDQ to produce thiyl radical **1b**. Subsequently, 1,5-homolytic radical cyclization of **1b** followed by aromatization of radical intermediate **1c** gives 2-arylbenzothiazole **2**.

In summary, we have observed a novel DDQ-catalyzed cyclization of thioformanilides to give the corresponding 2-substituted benzothiazoles in high yields with a complete selectivity. Further investigations for broadening the synthetic application of this cyclization to develop a combinatorial version for the SAR studies of 2-arylbenzothiazoles for various pharmaceutical applications are currently in progress.

## Acknowledgement

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21. General procedure for the preparation of substituted 2-aryl benzothiazoles (**2a**–**j**): DDQ (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, the reaction was quenched with $H_2O$ ($2 \times 5$ ml) and the reaction mixture was extracted with $CH_2Cl_2$ ($2 \times 10$ 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 the eluent to give 2-arylbenzothiazoles **2a**–**j** in 83–95% yields. Compound **2a**: Pale yellow solid. Yield. 95%. Mp 164–166 °C, $^1$H NMR ($CDCl_3$) $\delta$ 3.88 (s, 3H), 6.02 (s, 2H), 6.83 (d, 1H, $J = 8.3$ Hz), 7.02 (dd, $J = 2.26$, 6.8 Hz, 1H), 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): $\delta$ 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. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{11}NO_3S$: 286.0537; found: 286.0537. Compound **2i**: Light yellow solid. Yield: 85%. Mp 216–217 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.48 (s, 6H), 7.18–7.28 (m, 6H), 7.51 (s, 2H), 7.89–8.02 (m, 6H). $^{13}$C NMR (75 MHz): $\delta$ 21.5, 111.0, 118.7, 124.0, 127.3, 129.7, 130.9, 136.3, 141.4, 150.3, 155.3. HRMS (ESI): *m*/*z* calcd for $C_{28}H_{21}N_2OS_2$ (M+H): 465.1095; found: 465.1100.
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