Synthesis of 2-Arylbenzothiazoles by DDQ-Promoted Cyclization of Thioformanilides; A Solution-Phase Strategy for Library Synthesis

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Received 10 December 2006; revised 2 January 2007

Abstract: Several substituted benzothiazoles were synthesized by the intramolecular cyclization of thioformanilides using 2,6-dichloro-3,5-dicyano-1,4-benzoquinone (DDQ) in dichloromethane at ambient temperature in high yields. The resulting 2-arylbenzothiazoles were separated from the reduced DDQ byproduct 4,5-dichloro-3,6-dihydroxyphthalonitrile by treatment of the reaction mixture with a strongly basic ion-exchange resin. This protocol offers a high degree of flexibility with regard to the functional groups that can be placed on the benzothiazole ring or 2-aryl moiety, which in turn generates scaffolds for parallel synthesis.

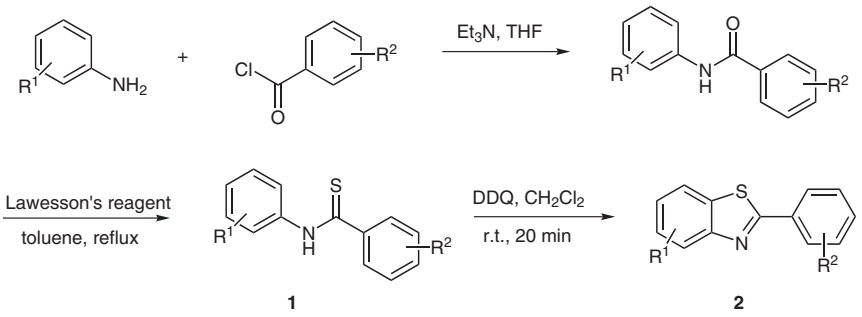
Key words: thioformanilide, solution phase, cyclization, 2,6-dichloro-3,5-dicyano-1,4-benzoquinone, benzothiazole, sulfanyl radical

In recent years, the privileged structure concept has emerged as a useful 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.[1] Arylbenzothiazoles bearing a substituent at C2 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, chemiluminescent agents, calcium channel antagonists, antituberculotics, antitumor agents, antiparasitics, and also as photosensitizers.[2–7]

Arylbenzothiazoles are most commonly synthesized by one of two major routes. The most commonly used method involves the condensation of 2-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 2-aminothiophenols bearing substituents. Another route is based on Jacobson's cyclization of thiobenzanilides.[9,10] Other general methods include microwave-mediated reaction of 2-aminothiophenol with β-chlorocinnamaldehydes, reaction of dibenzyl disulfides with 2-aminothiophenol, reduction of bis(2-nitrophenyl) disulfide, reaction of *S*-aryl thiobenzoate with arylhaloamines, ring transformation of 1,2,3-benzodithiazole 2-oxides, radical cyclization of benzyne intermediates, and Grignard reactions of aryl isothiocyanates.[11–16] More recently, arylbenzothiazoles have been prepared by oxidative coupling of thiophenols and aromatic nitriles[17] using ammonium cerium(IV) nitrate (CAN). However, the reported synthesis of 2-arylbenzothiazoles mediated by ammonium cerium(IV) nitrate is irreproducible; the only products formed in this reaction are di-4-tolyl disulfide and 4-tolyl 4-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 found that has significant practical value for the synthesis of 2-arylbenzothiazoles. To overcome these limitations, herein, we report an efficient intramolecular cyclization of thioformanilides mediated by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[19] without the use of a metal catalyst. DDQ is a well-known oxidizing agent and has proved to be a versatile reagent for various organic transformations including the 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.

Over the past decade, the synthesis of combinatorial libraries using both solution- and solid-phase methods have gained importance in pharmaceutical and academic institutions.[20] The preparation of compound libraries requires robust procedures for both synthesis and purification in order to obtain the final products in a pure form for biological screening. In continuation of our efforts towards the development of new methodologies in organic synthesis,[21] herein we describe a new and practical route for the synthesis of 2-arylbenzothiazoles using DDQ and its application to the synthesis of a 176-member compound library (Scheme 1). 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 and efficient and involves a simple workup procedure. Unlike previous methods, the reported protocol does not require high temperatures to produce benzothiazole derivatives. Solvents such as acetonitrile, tetrahydrofuran, methanol, and the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) proved to be effective. Furthermore, we expected that 4,5-dichloro-3,6-dihydroxyphthalonitrile (DDP), the reduced product of DDQ, could be easily removed from the reaction mixture by basic ion-exchange resins thereby enabling the solution-phase synthesis of the desired library. It should be noted that other

SYNTHESIS 2007, No. 6, pp 0819–0823
Advanced online publication: 08.02.2007
DOI: 10.1055/s-2007-965929; Art ID: Z25806SS



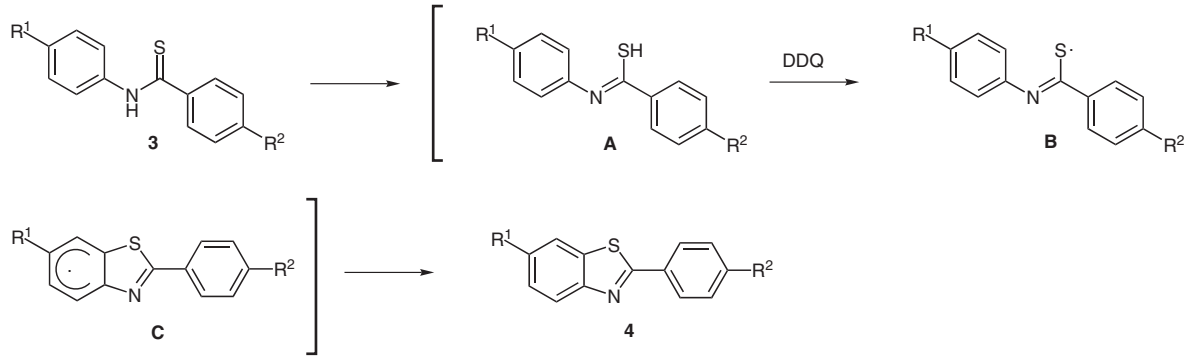
Scheme 1

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 **2**, which have substituents on both the phenyl and benzothiazolyl rings, began with benzanilides that were prepared by the reaction of benzoyl chlorides and arylamines in triethylamine. The benzanilides were converted into thioformanilides **1** with Lawesson's reagent[22] in refluxing anhydrous toluene.

To explore the generality and scope of this process, diverse thioformanilides **1** were studied in the synthesis of 2-arylbenzothiazoles **2** and the results are illustrated 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 high yields by this method. This contrasts, with the tributyltin hydride/2,2′-azobis(isobutyronitrile) 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 arylamines 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 of the target compounds. The method is compatible with many substituents such as alkoxy, nitro, and *tert*-butyl.

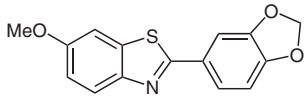
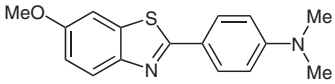
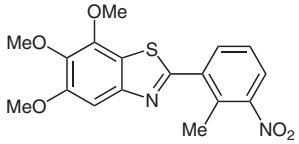
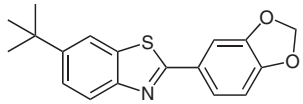
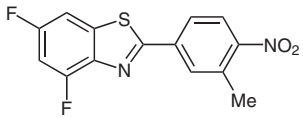
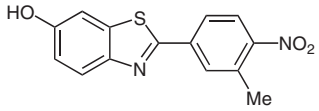
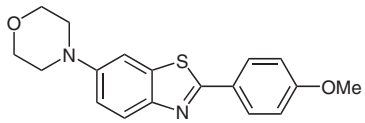
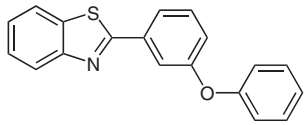
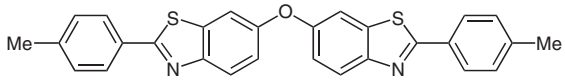
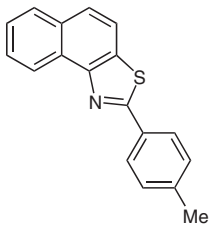
A plausible mechanism for the DDQ-promoted cyclization reaction is presented in Scheme 2. Arylthioformanilide **3** can exist as thioiminol **A**, which reacts with DDQ to produce sulfanyl radical **B**. Subsequently, 1,5-homolytic radical cyclization of **C** followed by aromatization of radical intermediate **1c** gives 2-arylbenzothiazole **4**.

Encouraged by these results, we were interested in exploring the possibility of generating a library of benzothiazole compounds. For this to be possible, the prerequisite is to remove the DDP in a high-throughput format. Among various purification methods available for solution-phase combinatorial synthesis, the treatment of reaction solutions with ion-exchange resins have proven effective in the removal of some acidic or basic byproducts, and there is a recent report demonstrating applicability to a 96-well format.[24] We assumed that basic ion-exchange resins could be a good option to neutralize and absorb acidic DDP. Amberlite IRA-900, which is a macroreticular resin with benzyltrialkylammonium functionality, proved to be the most efficient in this regard. The results are summarized in Table 1 as isolation B.[25] Thus, four grams of the aforementioned resin was freshly washed by methanol and used for the purification of each reaction on a 0.2-mmol scale, and this simple treatment gave the desired product in excellent purities. Since we used an exactly equal amount of DDQ in the reaction, which gave compa-



Scheme 2

Table 1 DDQ-Catalyzed Synthesis of 2-Arylbenzothiazoles

Entry	Product		Isolation[a] A Yield[b] (%)	Isolation[a] B Yield[c] (%)	Purity[d] (%)
1		**2a**	95	72	98
2		**2b**	89	68	91
3		**2c**	95	82	89
4		**2d**	88	85	92
5		**2e**	85	56	88
6		**2f**	82	61	86
7		**2g**	90	75	87
8		**2h**	95	90	97
9		**2i**	85	55	85
10		**2j**	89	72	93

[a] Isolation A, material produced by conventional synthesis on a 5-mmol scale as given in experimental section; Isolation B, material produced using the solution-phase library method.
[b] Yield refers to the pure isolated product.
[c] Crude yields after ion-exchange resin treatment.
[d] HPLC purities of Isolation B were determined by integration peak areas at 255 nm without calibration.

rable results to the aforementioned use of 1.1 equivalents of DDQ, there was no need to use a polymer-bound scavenger resin for removing DDQ from the reaction solutions.[26]

In summary, we have observed a novel DDQ-catalyzed cyclization of thioformanilides to give the corresponding 2-substituted benzothiazoles in high yields with complete selectivity. Moreover, the combination of this procedure with the use of basic ion-exchange resin allows for com-

binatorial library synthesis. The method described here represents the first example for benzothiazole library synthesis by a solution-phase strategy. Further investigations for broadening the synthetic application of this cyclization to develop a combinatorial version for structure–activity relationship studies of 2-arylbenzothiazoles for various pharmaceutical applications are currently in progress.

Compounds **2a**,**c**–**f**,**h**,**j** were characterized and found to have data comparable to those given in the literature.[20a]

Substituted 2-Arylbenzothiazoles 2a–j; General Procedure

DDQ (5.5 mmol) was added to a stirred soln of thioformanilide (5.0 mmol) in CH_2Cl_2 at r.t. The progress of the reaction was monitored by TLC. When the reaction was complete, it was quenched with H_2O (2 × 5 mL) and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried (anhyd Na_2SO_4) and the solvent was removed in vacuo, to afford the crude product which was purified by column chromatography (silica gel, petroleum ether–EtOAc, 8:1) to give **2a–j**; yield: 82–95%.

2-(Dimethylamino)-6-methoxybenzothiazole (2b)

Light brown solid; yield: 91%; mp 178–180 °C.

^{1}H NMR ($CDCl_3$): δ = 3.06 (s, 6 H), 3.88 (s, 3 H), 6.71 (d, *J* = 9.06 Hz, 2 H), 6.98 (dd, *J* = 9.06, 3.02 Hz, 1 H), 7.24–7.27 (m, 1 H), 7.80–7.88 (m, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 40.1, 55.8, 104.4, 111.7, 114.8, 121.6, 122.7, 128.5, 135.8, 148.9, 151.9, 157.0, 166.4.

MS (EI): *m*/*z* (%) = 284 (M^+, 100), 269 (80), 253 (55), 241 (75), 149 (75), 95 (50), 85 (50), 43 (75).

2-(4-Methoxyphenyl)-6-morpholin-4-ylbenzothiazole (2g)

Pale yellow solid; yield: 90%; mp 182–184 °C.

^{1}H NMR (DMSO-d_6): δ = 3.20 (t, *J* = 4.6 Hz, 4 H), 3.77 (t, *J* = 4.6 Hz, 4 H), 3.82 (s, 3 H), 7.07 (d, *J* = 8.6 Hz, 2 H), 7. 21 (dd, *J* = 8.9, 2.4 Hz, 1 H), 7.55 (d, *J* = 2.3 Hz, 1 H), 7.82 (d, *J* = 8.9 Hz, 1 H), 7.93 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 48.8, 55.4, 66.0, 106.3, 114.8, 116.2, 122.5, 125.7, 128.2, 136.0, 147.2, 149.0, 161.2, 163.3.

LC-MS (ESI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{18}N_2O_2S_2$: 326.11; found: 326.22.

Bis[4-(4-Tolyl)benzothiazol-6-yl Ether (2i)

Light yellow solid; yield: 85%; mp 216–217 °C.

^{1}H NMR ($CDCl_3$): δ = 2.48 (s, 6 H), 7.18–7.28 (m, 6 H), 7.51 (s, 2 H), 7.89–8.02 (m, 6 H).

^{13}C NMR (75 MHz): δ = 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* $[M + H]^+$ calcd for $C_{28}H_{21}N_2OS_2$: 465.1095; found: 465.1100.

Preparation of a 176-Member Library Using a Solution-Phase Method

Stock 0.1 M solns of 8 substituted anilines and 22 benzoyl chlorides in THF were prepared. They were then mixed in two 2-mL 96 (8 × 12) deep-well plates using substituted aniline (0.2 mL), benzoyl chloride (0.2 mL), and Et_3N (0.2 mL) in each well. The resulting plates were stirred at r.t. for 5 h. Et_3N and THF were then removed by a plate rotary evaporator and the resulting residue was redissolved using toluene (0.2 mL) and Lawesson's reagent (0.2 mL) in each well. The resulting plates were refluxed at 100 °C for 2 h. The toluene was then removed and the resulting residue was redissolved in CH_2Cl_2 (0.2 mL) in each well, which was subsequently treated with 0.1 M DDQ in 10% THF–CH_2Cl_2 (0.2 mL). The exact equivalent amount of DDQ was used in order to facilitate subsequent purification. The addition of THF was used to increase the solubility of DDQ. The reaction plates were agitated at r.t. for 2 h before the solns were transferred to the corresponding filter bottom plates loaded with freshly washed (MeOH) and dried Amberlite IRA-900 (0.4 g) in each well. Additional CH_2Cl_2 (0.4 mL) was added to each well. The plates were clamped and rotated slowly for 1 h before filtering the soln into collection plates. The higher freezing temperature of CH_2Cl_2 allowed the solns to be frozen so that possible leakage during the transfer was avoided. Finally, removal of solvents using a plate rotatory evaporator gave the desired compounds in the collection plates. The library was characterized by LC-MS. The purity of the individual compound determined by LC integration without calibration. As a result, 70% of the library showed purity >70%, while 10% of the compounds had purities <45%.

Acknowledgment

The authors thank CSIR (M.I.) and UGC (B.S.) New Delhi, for financial support.

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