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One-pot approach for the synthesis of 2-aryl benzothiazoles via a two-component coupling of *gem*-dibromomethylarenes and *o*-aminothiophenols

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ABSTRACT

One-pot synthesis of 2-aryl benzothiazoles from *gem*-dibromomethylarenes using 2-aminoarylthiols is described. Benzothiazoles were obtained in high chemical yields under mild conditions. This transformation would facilitate synthesis by short reaction times, large-scale synthesis, easy and quick isolation of the products, which are the main advantages of this procedure.

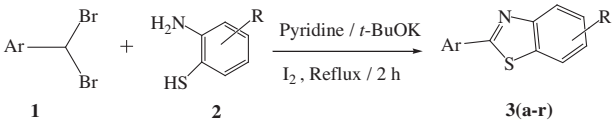
The exploration of privileged structures in drug discovery is a rapidly emerging area in medicinal chemistry. These structures represent a class of molecules capable of binding to multiple receptors with high affinity. By probing into these molecules, it enables the medicinal chemist to rapidly discover biologically active compounds across a wide range of therapeutic areas within a reasonable time scale. The substituted 2-arylbenzothiazoles have emerged in recent years as an important pharmacophore in a number of diagnostic and therapeutic settings and attractive features of drug candidates based on this benzothiazole scaffold include their synthetic accessibility as imaging agents for β-amyloid, antitumor agents, calcium channel antagonists, antituberculotics, antiparasitics, chemiluminescent agents and also as photosensitizers.[1–7]

A number of recent variants on the traditional solvent-based thermal synthetic conditions have been reported. For example, the classic methods for the synthesis of 2-aryl benzothiazoles are the condensation of *o*-aminothiophenol with aromatic carboxylic acids,[8] or aromatic aldehydes, followed by the oxidation with strong oxidants, such as molecular O_2,[9] H_2O_2,[10] MnO_2,[11] and co-oxidant DMSO[12] as described. We herein describe a new, efficient and straightforward approach starting from *gem*-dibromomethylarenes using *o*-aminobenzenethiols in the absence of strong oxidants, and this tandem process involving cyclization and aromatization, furnished 2-aryl benzothiazoles in high yields.

The substitution of carboxylic acid or aldehyde component with an alternative functional group has not been explored so far. Therefore, the development of a simple and stable substitute for these aromatic acids or aldehydes by using *gem*-dihalomethylarenes would extend the scope of the reaction in organic synthesis. Recently, *gem*-dihalomethylarenes have received considerable attention due to their application in the preparation of aldehydes,[13] the use of *gem*-dihalomethylarenes is limited to the synthesis of aldehydes and α,β-unsaturated carboxylic acids and esters.[14,15]

In continuation of our work[16] on the development of useful synthetic methodologies from *gem*-dibromomethylarenes, in this study we wish to report the one-step conversion of *gem*-dibromomethylarenes into the corresponding benzothiazoles by using aminobenzenethiols, potassium tertiary butoxide (*t*-BuOK) and catalytic amount of iodine in pyridine at reflux conditions with excellent yields (Scheme 1).[17,18]

In the preliminary stage of investigation we focused on the systematic evaluation of different base catalysts for the model reaction of *gem*-dibromomethylarenes and *o*-aminobenzenethiols at reflux conditions in pyridine. A wide variety of base catalysts including DBU, triethylamine, DABCO, K_2CO_3, Cs_2CO_3, and piperidine were



1 2 3(a-r)

Scheme 1. General approach to synthesis of 2-arylbenzothiazoles.

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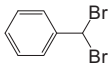
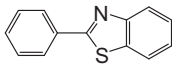
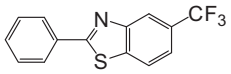
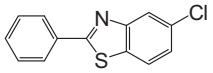
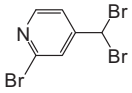
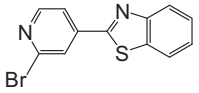
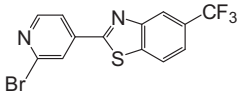
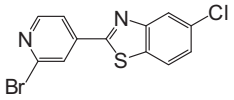
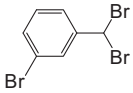
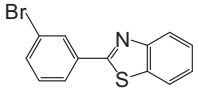
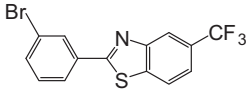
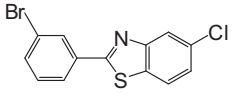
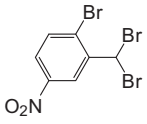
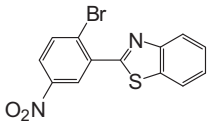
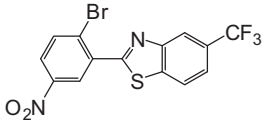
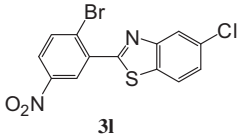
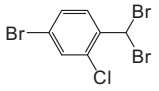
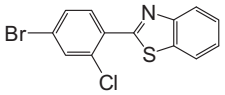
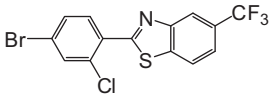
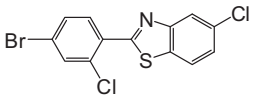
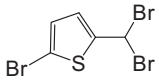
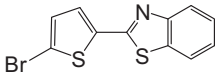
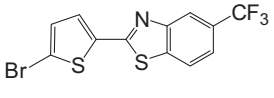
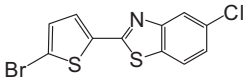
Table 1
Synthesis of benzothiazoles from *gem*-dibromomethlarenes using 2-amino benzenethiols

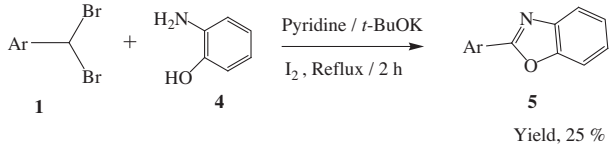
Entry	Substrate[a]	2-Aminobenzene thiols (R)	Product	Time (h)	Yield[b] (%)
1	 **1a**	R = –H **2a**	 **3a**	1.5	92
2	**1a**	R = $-CF_3$ **2b**	 **3b**	2	86
3	**1a**	R = –Cl **2c**	 **3c**	2	83
4	 **1b**	**2a**	 **3d**	2	87
5	**1b**	**2b**	 **3e**	2	90
6	**1b**	**2c**	 **3f**	2	85
7	 **1c**	**2a**	 **3g**	2	82
8	**1c**	**2b**	 **3h**	2	85
9	**1c**	**2c**	 **3i**	2	77
10	 **1d**	**2a**	 **3j**	2	82
11	**1d**	**2b**	 **3k**	2	83
12	**1d**	**2c**	 **3l**	2	86

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate[a]	2-Aminobenzene thiols (R)	Product	Time (h)	Yield[b] (%)
13	 **1e**	**2a**	 **3m**	2	81
14	**1e**	**2b**	 **3n**	2	85
15	**1e**	**2c**	 **3o**	2	81
16	 **1f**	**2a**	 **3p**	2	77
17	**1f**	**2b**	 **3q**	2	80
18	**1f**	**2c**	 **3r**	2	75

[a] Substrates are prepared from the commercial methyl analogs by radical bromination.
[b] Isolated yields.



Scheme 2. Synthesis of 2-phenylbenzoxazole.

employed to improve the yield for the specific synthesis of 2-aryl benzothiazoles. While piperidine catalysed the reaction to give quantitative yield in 4–5 h, the other bases did not promote this reaction. Interestingly, when the reaction was carried out in the presence of *t*-BuOK, it led to the desired product in high yields in 1.5–2.0 h; the results were tabulated in Table 1.

The synthetic approach starting from the corresponding commercially available methyl analogs using radical bromination is well documented.[13] Our approach was initiated using a mixture of *gem*-dibromomethylarenes (1.0 equiv) **1** and aminobenzenethiols (1.1 equiv) **2** with anhydrous pyridine in the presence of a *t*-BuOK (0.5 equiv) followed by the addition of iodine (0.2 equiv) and refluxing at 90 °C for 2 h. The starting material was consumed in 2 h as indicated by TLC analysis and the results are presented in Table 1. This transformation would extend the scope in organic synthesis, in addition, it is interesting to note that both aromatic and heteroaromatic *gem*-dibromomethylarenes bearing various functionalities such as chloro, bromo, nitro, and trifluoro methyl groups survived the reaction and provided high yields of corresponding benzothiazoles. The reaction was further probed by treating *gem*-dibromomethylarenes **1** with *o*-aminophenol **4** using the same procedure as described in Scheme 1 to obtain 2-phenylbenzoxazole (Scheme 2) in a very low yield (25%). Hence, *o*-aminophenol was not a good substrate for this protocol.

In summary, this one-step reaction presents an efficient method to convert *gem*-dibromomethylarenes to 2-aryl benzothiazoles. The mild reaction conditions offer the potential for the use of this method in the synthesis of complex molecules. It is anticipated that this methodology will have versatile applications in the practical syntheses of biologically important pharmaceutical molecules with benzothiazole moiety.

Acknowledgement

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Supplementary data

Supplementary data (compounds characterization data and copies of ^{1}H NMR, ^{13}C NMR of all the synthesized compounds described in scheme (1) are available as supplementary data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.055.

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17. Representative procedure for the synthesis of 2-phenylbenzothiazole analogs **3(a–r)** (Scheme 1).
18. To a mixture of benzal bromide **1a** (25 g, 100 mmol) and 2-aminobenzenethiol **2a** (13.75 g, 110 mmol) in pyridine (100 mL) was added *t*-BuOK (6.25 g, 500 mmol) followed by the addition of iodine (2.62 g, 20 mmol) and the reaction mixture was refluxed at 90 °C for 2 h. The completion of the reaction was confirmed by TLC. The black reaction mixture was concentrated and the residue obtained was dissolved in water, and then extracted with ethyl acetate (2 × 500 mL), the combined organic phase was washed with water and brine solution, and dried over anhydrous sodium sulfate. The organic phase was evaporated and the crude product was purified by column chromatography (10% EtOAc/hexanes) to afford the title compound **3a** (19.5 g, 92%) as a white solid. Mp 112–114 °C (lit.[19] 111–115 °C). Calcd for $C_{13}H_9NS$: C, 73.9; H, 4.29; N, 6.63; S, 15.18. Found: C, 74.03; H, 4.24; N, 6.69; S, 15.13. *ν* max (liquid film): 2923, 2544, 1479, 1314, 1225, 963, 765 cm^{-1}; δ_H (DMSO-d_6, 400 MHz): 8.15–8.06 (4H, m, Ar–H), 7.6–7.53 (4H, m, Ar–H), 7.48–7.44 (1H, m, Ar–H); δ_C (DMSO-d_6, 100.6 MHz): 167.7, 154.0, 134.9, 133.3, 131.8, 129.8, 127.6, 127.1, 126.0, 123.3, 122.8; MS (Maldi) calcd for $C_{13}H_9NS$ ($M+H^+$) 211.2804; found, 211.2801.

Selected spectral data: Compound **3g**: 182 mg, (82%) was isolated as wine red solid. Mp: 81–83 °C (lit.[20] 83–84 °C). Calcd for $C_{13}H_8NSBr$: C, 53.81; H, 2.78; N, 4.83; S, 11.05. Found: C, 53.73; H, 2.73; N, 4.89; S, 11.0. *ν* max (liquid film) 2965, 2498, 1702, 1481, 1348, 785 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 8.34–8.33 (1H, t, Ar–H), 8.14–8.12 (1H, d, *J* = 8.4 Hz, Ar–H), 8.06–8.03 (1H, m, Ar–H), 7.98–7.96 (1H, d, *J* = 8.8 Hz, Ar–H), 7.68–7.65 (1H, m, Ar–H), 7.58–7.54 (1H, m, Ar–H), 7.49–7.47 (1H, d, *J* = 8.0 Hz, Ar–H), 7.46–7.44 (1H, d, *J* = 8.0 Hz, Ar–H); δ_C ($CDCl_3$, 100.6 MHz): 156.2, 135.5, 134.4, 133.8, 132.6, 130.5, 129.8, 129.6, 128.3, 126.1, 125.2, 122.0); MS (Maldi) calcd for $C_{13}H_8NSBr$ ($M+H^+$) 291.7531; found, 291.7529.

Compound **3p**: 170 mg, (77%) was isolated as wine red solid. Mp: 105–107 °C (lit.[21] 106–108 °C). Calcd for $C_{11}H_6NS_2Br$: C, 44.6; H, 2.04; N, 4.73; S, 21.65. Found: C, 43.72; H, 2.01; N, 4.7; S, 21.5. *ν* max (liquid film) 2972, 2521, 1681, 1491, 1279, 895 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 8.0–7.98 (1H, d, *J* = 8.0 Hz, Ar–H), 7.76–7.74 (1H, d, *J* = 8.0 Hz, Ar–H), 7.4–7.36 (2H, m, Ar–H), 7.34–7.31 (2H, m, Ar–H); δ_C ($CDCl_3$, 100.6 MHz,), 131.0, 130.2, 129.7, 129.5, 128.9, 128.6, 128.8, 128.4, 125.9, 122.8, 122.1; MS (Maldi) calcd for $C_{11}H_6NS_2Br$ [$M+H^+$]: 297.7420; found, 297.7415.

Compound characterization data for: 2-phenylbenzoxazole **5** (Scheme 2). 81.0 mg, 25%) as an off white solid. Mp: 101–103 °C (lit. 102–104 °C). Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.91; H, 4.56; N, 7.21. *ν* max (KBr) 2996, 2932, 2789, 1643, 1532, 1276, 810 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 7.94–7.91 (1H, m, Ar–H), 7.54–7.49 (3H, m, Ar–H), 7.37–7.30 (2H, m, Ar–H), 7.22–7.18 (2H, m, Ar–H), 7.03–7.01 (1H, d, *J* = 8.0 Hz, Ar–H); δ_C ($CDCl_3$, 100.6 MHz), 157.1, 131.7, 129.7, 129.0, 128.9, 128.4, 128.0, 127.6, 127.6, 120.1, 116.0; MS (Maldi) calcd for $C_{13}H_9NO$ ($M+H^+$) 196.0710; found, 196.0703.
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