Iron-Catalyzed Regioselective Synthesis of 2-Arylbenzoxazoles and 2-Arylbenzothiazoles via Alternative Reaction Pathways

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Abstract: A one-pot regioselective method for the preparation of 2-arylbenzoxazoles from N-arylbenzamides has been developed using iron(III)-catalyzed bromination of the aryl ring, followed by copper(I)-catalyzed O-cyclization with the benzamide side chain. In contrast, reaction of N-arylthiobenzamides with N-bromosuccinimide and iron triflimide led directly to the isolation of the corresponding 2-arylbenzothiazoles via intramolecular C–S bond formation. Mechanistic and control experiments suggest that in this case, bromination occurs at the sulfur atom, resulting in a reactive intermediate that can undergo electrophilic aromatic substitution and S-cyclization. The scope of both processes was explored yielding a range of structural analogues, including a pharmacologically active compound for the treatment of Duchenne muscular dystrophy and an affinity agent of the amyloid-beta protein in Alzheimer’s disease.

Introduction

Benzannulated heterocycles such as benzoxazoles and benzothiazoles are important structural motifs found in a wide range of natural products and pharmacologically active agents.[1] C2-Substituted systems, particularly aryl derivatives, have been shown to possess anticancer, antibacterial, antimicrobial or antiviral activity.[1] As a result of this biological and medicinal importance, there have been significant efforts in developing rapid and efficient syntheses of these heterocycles.[2,3] Traditional approaches include the reaction of 2-aminophenols and 2-aminothiophenols with carboxylic acid derivatives under acidic, dehydrating conditions.[2] Another common approach involves the reaction of 2-aminophenols and 2-aminothiophenols with aldehydes, followed by oxidative cyclization of imine intermediates.[2d]

More recently, transition metal-catalyzed methods involving O- or S-cyclization of N-arylbenzamides and N-arylthiobenzamides have been reported. For example, ligand-assisted, copper-catalyzed cyclization of N-haloaryl benzamides and thiobenzamides at elevated temperatures have produced the corresponding benzannulated heterocycles in good yields (Figure 1a).[4] To avoid the use of pre-activated, haloaryl systems, direct transition metal catalyzed cyclization of N-arylbenzamides and N-arylthiobenzamides under oxidative conditions has also been developed (Figure 1b).[5,6] Seminal work by Nagasawa and co-workers showed that benzoxazoles could be accessed directly from N-arylbenzamides using copper-catalysis and oxygen,[5a,5b] while the groups of Doi[6a,6c] and Batey[6b] used palladium catalyzed cyclization of N-arylthiobenzamides, under oxidative conditions for the synthesis of benzothiazoles. Further metal-mediated methods included an iron-catalyzed procedure for the synthesis of benzothiazoles that used sodium thiosulfate as the oxidant and was performed at lower temperatures.[6d] Similar cyclizations using oxidants such as TEMPO, oxone or oxygen, under photochemical,[7] electrochemical[8] or organocatalytic[9] conditions have also been described for the preparation of these benzannulated heterocycles.

(a) Copper-catalyzed cyclization of 2-haloanilides and 2-halothioanilides.

(b) Metal-catalyzed oxidative cyclization of 2-anilides and 2-thioanilides.

(c) This work: Iron-catalyzed synthesis via different reaction pathways.

Figure 1. Metal-catalyzed synthesis of benzoxazoles and benzothiazoles.

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While these methods provide flexible access to these ring systems, we were interested in developing processes that avoided pre-activated haloaryl starting materials, strong oxidants or precious transition metals. In recent years, we have reported the use of the super Lewis acid, iron(III)-triflimide for the activation of N-halosuccinimide reagents and the subsequent, highly regioselective halogenation of aryl rings.[10] We have also shown the combination of this halogenation reaction with copper(I)-catalyzed Ullmann-type N-arylations, thereby converting aryl C–H bonds to C–N bonds in a one-pot process.[11] An intramolecular version of this process has also been developed for the preparation of indolines and dihydrobenzofurans.[12] Building on this research programme, we were interested in extending the scope of these one-pot processes for the rapid synthesis of pharmaceutically relevant 2-arylbenzoxazoles and 2-arylbenzothiazoles. Herein, we now report the use of a one-pot iron(III)-catalyzed bromination and copper(I)-catalyzed O-cyclization of N-arylbenzamides for the preparation of 2-arylbenzoxazoles (Figure 1c). The reaction of iron(III)-triflimide and NBS with N-aryliodonium salts for the direct synthesis of 2-arylbenzothiazoles is also described. As well as exploring the scope of both reaction processes, the synthetic utility of these transformations for the preparation of pharmaceutically important targets is also demonstrated.

Results and Discussion

Initially, a series of N-arylbenzamides was prepared by the reaction of anilines with aryl acid chlorides in the presence of triethylamine.[13] N-(3,4-Dimethoxyphenyl)benzamide (1a) was used to optimize the one-pot process (Table 1). Investigation of each step separately showed that the use of copper iodide (10 mol-%), DMEDA (20 mol-%) and cesium carbonate at 130 °C each step separately showed that the use of copper iodide used to optimize the one-pot process (Table 1). Investigation of each step separately showed that the use of copper iodide (10 mol-%), DMEDA (20 mol-%) and cesium carbonate at 130 °C allowed efficient O-cyclization, however, the prior halogenation step required optimization. An initial attempt, involving the generation of iron triflimide from iron trichloride (5 mol-%) and the ionic liquid, [BMIM]NTf2 (15 mol-%), for the activation of N-iodosuccinimide (NIS) and subsequent reaction with 1a, resulted in slow iodination and gave a 36 % yield of 2a after copper-catalyzed O-cyclization (entry 1). It was proposed the slow reaction of 1a with NIS was due to steric hindrance and therefore, the smaller reagent, N-bromosuccinimide (NBS) was investigated. Under the same conditions, this allowed faster halogenation and led to an improved overall yield of 2a (entry 2). A solvent screen was then performed to investigate whether improved solubility of 1a in alternative solvents might lead to a more efficient bromination step. Issues with isolation of the final product 2a resulted in a lower yield when using DMF as the reaction solvent (entry 3). A combination of using toluene and THF (5:1) as co-solvents and a slightly elevated reaction temperature of 40 °C led to an improved yield of 51 % over the two steps (entry 4). Finally, the use of toluene and acetonitrile (5:1), resulted in clean and complete conversion to the brominated intermediate and the highest overall yield of 57 % for benzoxazole 2a (entry 5).

Having developed an optimized one-pot bromination and O-cyclization process, the scope of this transformation was explored for the preparation of various benzoxazoles (Scheme 1). Our previous studies in developing iron(III)-catalyzed halogenation of aryl systems have shown that electron-rich, activating substituents are required for this transformation to proceed.[10–12] Therefore, this study focused on the one-pot halogenation and cyclization of electron-rich N-arylbenzamides. Using N-(3,4-dimethoxyphenyl)benzamides (1a–1d) with a variety of substituents gave the corresponding benzoxazoles (2a–2d) as single regioisomers, in good overall yields (51–66 %). Higher yields were obtained from the one-pot bromination and O-cyclization of N-(3,4-methylenedioxyphenyl)benzamides 1e and 1f. As well as the synthesis of benzoxazole 2e, this gave 2f, which has been shown to have significant activity in a luciferase reporter assay of murine H2K cells, a predictive screening process for identifying compounds that have the potential for the treatment of Duchenne muscular dystrophy.[14] The use of the one-pot process with more demanding substrates was also explored. This included the iron-catalyzed bromination and copper-catalyzed O-cyclization of tri-substituted N-arylbenzamides 1g and 1h. As expected, the greater steric hindrance associated with the ortho,ortho-substituted aryl position required to undergo halogenation, resulted in isolation of benzoxazoles 2g and 2h in slightly reduced yields under the standard conditions. Surprisingly, less reactive aryl systems, bearing only one activating group, were found to be effective substrates for the one-pot process. N-Arylbenezamides 1i and 1j gave benzoxazoles 2i and 2j in 62 % and 72 % yields, respectively.

It should be noted that specific limitations were observed with some classes of substrates. Lower yields were obtained for mono-substituted N-arylbenzamides. For example, while N-(3-methoxyphenyl)benzamide 1k underwent successful transformation to benzoxazole 2k, competing bromination at the 4-position of the aryl ring meant that the target was isolated in 33 % yield (Scheme 1).[15] As mentioned above, electron-rich...
Scheme 1. Substrate scope for the synthesis of benzoxazoles. [a] Halogenation step required 12 h.

Based on the iron(III)-catalyzed activation of NBS, a mechanism for benzothiazole formation was proposed (Scheme 3a). In a similar fashion to the preparation of benzothiazoles by S-cyclization of N-arylthiobenzamides using the Jacobson method involving potassium ferricyanide and the Hugerschoff reaction with bromine, we propose that the iron(III) complexed NBS species results in activation of the sulfur atom, yielding S-bromide intermediate 5. Following formation of 5, the transformation is completed by an intramolecular electrophilic aromatic substitution step. Such a mechanism accounts for the lower yields observed for substrates such as 3i (Scheme 3b), in which the less activated aryl ring undergoes protodecupration.
electrophilic aromatic substitution more slowly, resulting in moderate yield (37 %) of the corresponding benzothiazole 4i. Further evidence for this mechanism was gained by the investigation of non-activated substrates such as N-(4-methylphenyl)thiobenzamide (3j). In this case, reaction of 3j under the standard S-cyclization conditions returned only N-arylbenzamide 11 in 67 % yield. During this transformation, we believe that N-arylthiobenzamide 3j is converted into the corresponding S-bromide intermediate. As the less activated aryl ring is not able to perform electrophilic aromatic substitution, the S-bromide intermediate is instead hydrolyzed, generating N-arylbenzamide 11.

Scheme 3. (a) Mechanism of iron(III) and NBS cyclization of N-arylthiobenzamides. (b) Mechanism elucidation experiments with N-arylthiobenzamides 3i and 3j.

Conclusions

In summary, two distinct methods for the synthesis of 2-arylbenzoxazoles and 2-arylbenzothiazoles have been developed using iron(III)-triflimide activation of NBS. N-Arylbenzamides were cyclized in a one-pot process using a regioselective iron(III)-catalyzed bromination reaction, followed by a copper(I)-catalyzed C-O bond forming process, while N-arylthiobenzamides were cyclized directly, by iron(III)-mediated bromination and a copper(I)-mediated C-S bond forming process, while iron(III)-catalyzed bromination reaction, followed by a copper(I)-mediated C-S bond forming process. The scope and limitations of both processes were explored with a range of substrates, leading to the synthesis of a small library of products, including two pharmaceutically important compounds. It should be noted that the single step C–O bond forming process is performed under milder conditions than is normally used for this type of cyclization and so generates these compounds very cleanly. Current work is investigating further applications of iron(III)-triflimide catalyzed aryl functionalization for the regioselective synthesis of substituted arenes and benzannulated heterocycles.

Experimental Section

All reagents and starting materials were obtained from commercial sources and used as received unless otherwise stated. N-bromosuccinimide was recrystallized from water and dried under high vacuum before use. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed in oven-dried glassware under an atmosphere of argon unless otherwise stated. Brine refers to a saturated aqueous solution of sodium chloride. Flash column chromatography was performed using silica gel 60 (35–70 μm). Aluminium-backed plates pre-coated with silica gel 60F254 were used for thin layer chromatography and were visualized with a UV lamp or by staining with potassium permanganate or ninhydrin. 1H NMR spectra were recorded on Bruker NMR spectrometers at either 400 or 500 MHz and data are reported as follows: chemical shifts in ppm relative to tetramethylsilane as the internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances). 13C NMR spectra were recorded on Bruker NMR spectrometers at either 101 or 126 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane or the solvent as internal standard (CDCl3, δ = 77.0 ppm), multiplicity with respect to hydrogen (deduced from DEPT experiments, C, CH, CH2 or CH3). Assignments are based on 2-dimensional COSY, HSQC and HMBC experiments. Infrared spectra were recorded on a FTIR spectrometer; wavenumbers are indicated in cm–1. Mass spectra were recorded using electron impact or electrospray techniques. HRMS spectra were recorded using a dual-focusing magnetic analyzer mass spectrometer. Melting points were determined on a Gallenkamp melting point apparatus.

2-Phenyl-5,6-dimethoxy-1,3-benzoxazole (2a):

Iron(III) chloride (1.62 mg, 0.0100 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (8.70 μL, 0.0300 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of N-bromosuccinimide (0.0360 g, 0.200 mmol) in toluene (0.5 mL). N-(3,4-Dimethoxyphenyl)benzamide (1a) (0.0510 g, 0.200 mmol) in toluene (0.5 mL) and acetoniitrile (0.2 mL) was then added and the mixture was stirred at 40 °C for 4 h. Upon completion of the bromination step, the reaction mixture was cooled to room temperature, diluted with toluene (1.0 mL) and cesium carbonate (0.130 g, 0.400 mmol), copper(I) iodide (3.80 mg, 0.0200 mmol), N,N′-dimethylethylenediamine (4.30 μL, 0.0400 mmol) and water (0.4 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 18 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with 1M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with brine (30 mL). The organic phase was dried (MgSO4), filtered and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (2a) (0.0286 g, 57 %) as a white solid. Mp 109–112 °C (lit.[19] 114–115 °C). 1H NMR (400 MHz, CDCl3): δ = 3.95 (s, 3H, OCH3), 3.96 (s, 3H, OCH3), 7.13 (s, 1H, 7-H), 7.25 (s, 1H, 4-H), 7.48–7.52 (m, 3H, 3′-H, 4′-H and 5′-H), 8.16–8.20 (m, 2H, 2′-H and 6′-H), 13C NMR (101 MHz, CDCl3): δ = 56.5 (CH3), 56.5 (CH3), 94.4 (CH), 101.8 (CH), 127.0 (2 × CH), 127.5 (C), 128.9 (2 × CH), 130.9 (CH), 135.0 (C), 145.2 (C), 147.8 (C), 148.4 (C), 162.3 (C). MS (ESI) m/z (%): 278 (100) [M + Na]+.
2-(4'-Methoxyphenyl)-5,6-dimethoxy-1,3-benzoxazole (2b): 2-(4'-Methoxyphenyl)-5,6-dimethoxy-1,3-benzoxazole (2b) was synthesized as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (2a) using 4'-methoxy-N-(3,4-dimethoxyphenyl)benzamide (1b) (0.057 g, 0.20 mmol) in toluene (1.0 mL) and acetonitrile (0.4 mL). The bromination step was carried out at 40 °C for 4 h and the O-arylation step at 130 °C for 48 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave 2-(4'-methoxyphenyl)-5,6-dimethoxy-1,3-benzoxazole (2b) (0.030 g, 52 %) as a light yellow solid. Mp 118–120 °C. IR (neat): 3300, 2928, 1605, 1481, 1250, 1219, 1128, 1057, 837. 1H NMR (500 MHz, CDCl3): δ = 3.88 (s, 3H, OCH3), 3.94 (s, 3H, OCH3), 7.01 (d, J = 8.9 Hz, 2H, 3'-H and 5'-H), 7.11 (s, 1H, 7-H), 7.23 (s, 1H, 4-H), 8.11 (d, J = 8.9 Hz, 2H, 2'-H and 6'-H). 13C NMR (101 MHz, CDCl3): δ = 112.8 (2 × CH), 132.7 (C), 135.0 (C), 138.7 (C), 145.7 (C), 146.4 (C), 162.6 (C). MS (ESI) m/z (%): 262 (100) [M+N]+.

2-(4'-Chlorophenyl)-5,6-dimethoxy-1,3-benzoxazole (2c): 2-(4'-Chlorophenyl)-5,6-dimethoxy-1,3-benzoxazole (2c) was synthesized as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (2a) using 4'-chloro-N-(3,4-dimethoxyphenyl)benzamide (1c) (0.058 g, 0.20 mmol) in toluene (1.0 mL) and acetonitrile (0.2 mL). The bromination step was carried out at 40 °C for 4 h and the O-arylation step at 130 °C for 48 h. Purification by flash column chromatography (hexane/ethyl acetate, 7:3) gave 2-(4'-chlorophenyl)-5,6-dimethoxy-1,3-benzoxazole (2c) (0.038 g, 66 %) as a light yellow solid. Mp 160–161 °C. IR (neat): 3316, 2928, 1619, 1579, 1140, 1007, 883, 784. 1H NMR (500 MHz, CDCl3): δ = 3.95 (s, 3H, OCH3), 3.96 (s, 3H, OCH3), 7.11 (s, 1H, 7-H), 7.23 (s, 1H, 4-H), 7.46 (d, J = 8.7 Hz, 2H, 3'-H and 5'-H), 8.09 (d, J = 8.7 Hz, 2H, 2'-H and 6'-H). 13C NMR (101 MHz, CDCl3): δ = 115.7 (C), 135.5 (C), 136.5 (C), 145.7 (C), 146.9 (C), 161.2 (C). HRMS (ESI) m/z [M + Na]+ calcd. for C15H12Cl3NaO4: 321.0398, found 321.0391.

2-(4'-Cyano phenyl)-5,6-dimethoxy-1,3-benzoxazole (2d): 2-(4'-Cyano phenyl)-5,6-dimethoxy-1,3-benzoxazole (2d) was synthesized as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (2a) using 4'-cyano-N-(3,4-dimethoxyphenyl)benzamide (1d) (0.0565 g, 0.20 mmol) in toluene (1.0 mL) and acetonitrile (1.0 mL). The bromination step was carried out at 40 °C for 4 h and the O-arylation step at 130 °C for 48 h. Purification by flash column chromatography (dichloromethane/ethyl acetate, 9:1) gave 2-(4'-cyano phenyl)-5,6-dimethoxy-1,3-benzoxazole (2d) (0.028 g, 51 %) as a white solid. Mp 247–248 °C. IR (neat): 3450, 2928, 1619, 1481, 1329, 1273, 1192, 1161, 1134, 1003, 887, 839. 1H NMR (500 MHz, CDCl3): δ = 3.96 (s, 3H, OCH3), 3.98 (s, 3H, OCH3), 7.14 (s, 1H, 7-H), 7.26 (s, 1H, 4-H), 7.78 (d, J = 8.4 Hz, 2H, 3'-H and 5'-H), 8.26 (d, J = 8.4 Hz, 2H, 2'-H and 6'-H). 13C NMR (101 MHz, CDCl3): δ = 56.5 (CH3), 56.5 (CH3), 94.2 (CH), 101.8 (CH), 113.9 (C), 118.3 (C), 127.2 (2 × CH), 131.4 (C), 132.7 (2 × CH), 134.9 (C), 145.5 (C), 148.3 (C), 149.4 (C), 160.1 (C). HRMS (ESI) m/z [M]+ calcd. for C15H12CN3O4: 280.0848, found 280.0860.

2-Phenyl-5,6-methylene dioxy-1,3-benzoxazole (2e): 2-Phenyl-5,6-methylene dioxy-1,3-benzoxazole (2e) was synthesized as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (2a) using N-(3,4-methylene dioxyphenyl)benzamide (1e) (0.0513 g, 0.213 mmol) in toluene (1.6 mL) and tetrahydrofuran (0.4 mL). The bromination step was carried out at 40 °C for 3 h and the O-arylation step at 130 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 19:1) gave 2-phenyl-5,6-methylene dioxy-1,3-benzoxazole (2e) (0.0351 g, 69 %) as a white solid. Mp 142–143 °C (lit. 147–148 °C). 1H NMR (500 MHz, CDCl3): δ = 6.03 (s, 2H, OCH2), 7.06 (s, 1H, 7-H), 7.17 (s, 1H, 4-H), 7.46–7.52 (m, 3H, 3'-H, 4'-H and 5'-H), 8.12–8.18 (m, 2H, 2'-H and 6'-H). 13C NMR (126 MHz, CDCl3): δ = 92.6 (CH), 99.5 (CH), 101.7 (CH3), 126.9 (2 × CH), 127.4 (C), 128.9 (2 × CH), 130.9 (CH), 136.1 (C), 145.7 (C), 145.8 (C), 146.4 (C), 162.6 (C). MS (ESI) m/z (%): 262 (100) [M+N]+.

2-(4'-Chlorophenyl)-5,6-methylene dioxy-1,3-benzoxazole (2f): 2-(4'-Chlorophenyl)-5,6-methylene dioxy-1,3-benzoxazole (2f) was synthesized as described for 2-phenyl-5,6-dimethoxy-1,3-benzoxazole (2a) using 4'-chloro-N-(3,4-methylene dioxyphenyl)benzamide (1f) (0.055 g, 0.20 mmol) in toluene (1.0 mL) and acetonitrile (1.0 mL). The bromination step was carried out at 40 °C for 3 h and the O-arylation step at 130 °C for 24 h. Purification by flash column chromatography (dichloromethane/hexane, 7:3) gave 2-(4'-chlorophenyl)-5,6-methylene dioxy-1,3-benzoxazole (2f) (0.0412 g, 75 %) as a white solid. Spectroscopic data were consistent with the literature. [14] Mp 252–254 °C. 1H NMR (500 MHz, CD3OCDMSO): δ = 6.13 (s, 2H, OCH2), 7.36 (s, 1H, 7-H), 7.49 (s, 1H, 4-H), 7.65 (d, J = 8.6 Hz, 2H, 3'-H and 5'-H), 8.10 (d, J = 8.6 Hz, 2H, 2'-H and 6'-H). 13C NMR (126 MHz, CD3OCDMSO): δ = 93.5 (CH), 99.7 (CH), 102.4 (CH2), 126.0 (C), 128.7 (2 × CH), 129.9 (2 × CH), 135.8 (C), 136.4 (C), 145.9 (C), 146.1 (C), 146.9 (C), 161.2 (C). MS (EI) m/z (%): 273 (100) [M]+.
ethyl acetate, 9:1) gave 2-phenyl-5-methoxy-6-methyl-1,3-benzoazole (2b) (0.042 g, 62 %) as a white solid. Spectroscopic data were consistent with the literature.\textsuperscript{1,21} Mp 137–138 °C.\textsuperscript{1} 1H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta = 2.34\) (s, 3H, 6-CH\textsubscript{3}), 3.89 (s, 3H, OCH\textsubscript{3}), 7.18 (s, 1H, 4-H), 7.33 (s, 1H, 7-H), 7.47–7.53 (m, 3H, 3'-H, 4'-H and 5'-H), 8.17–8.24 (m, 2H, 2'-H and 6'-H).\textsuperscript{12} 13C NMR (101 MHz, CDCl\textsubscript{3}): \(\delta = 17.2\) (CH\textsubscript{3}), 55.8 (CH\textsubscript{3}), 100.4 (CH), 111.6 (CH), 125.3 (C), 127.3 (2 × CH), 127.5 (C), 128.9 (2 × CH), 131.1 (CH), 140.7 (C), 145.0 (C), 155.7 (C), 162.7 (C). MS (ESI) m/z (%): 262 (100) [M + Na]\textsuperscript{+}. 2-(4'-Chlorophenyl)-5-methoxy-6-methyl-1,3-benzoazole (2j): \(\delta = 2.68\) (s, 3H, 6-CH\textsubscript{3}), 7.16 (d, \(J = 8.8\) Hz, 2H, 3'-H and 5'-H), 8.10 (d, \(J = 8.8\) Hz, 2H, 2'-H and 6'-H).\textsuperscript{13} 13C NMR (101 MHz, CDCl\textsubscript{3}): \(\delta = 17.2\) (CH\textsubscript{3}), 55.8 (CH\textsubscript{3}), 100.4 (CH), 111.5 (CH), 125.7 (C), 126.0 (C), 128.5 (2 × CH), 129.2 (2 × CH), 137.2 (C), 140.6 (C), 145.0 (C), 155.8 (C), 161.7 (C). HRMS (ESI) m/z [M + Na]\textsuperscript{+}: 272 (100) [M + H]\textsuperscript{+}. 2-(4'-Methoxyphenyl)-5-methoxy-6-methyl-1,3-benzoazole (2a): \(\delta = 2.68\) (s, 3H, 6-CH\textsubscript{3}), 6.98 (d, \(J = 8.9\) Hz, 2H, 3'-H and 5'-H), 7.28 (s, 1H, 7-H), 7.52 (s, 1H, 4-H), 7.97 (d, \(J = 8.9\) Hz, 2H, 2'-H and 6'-H).\textsuperscript{13} 13C NMR (126 MHz, CDCl\textsubscript{3}): \(\delta = 55.4\) (CH\textsubscript{3}), 56.1 (CH\textsubscript{3}), 56.3 (CH\textsubscript{3}), 102.6 (CH), 104.6 (CH), 114.3 (2 × CH), 126.7 (C), 126.7 (C), 128.5 (2 × CH), 148.3 (C), 148.6 (C), 149.4 (C), 161.5 (C), 166.2 (C). MS (EI) m/z (%): 301 (100) [M]\textsuperscript{+}, 286 (30), 258 (16), 215 (12), 151 (9), 125 (7), 82 (8). 2-(4'-Chlorophenyl)-5-methoxy-6-methyl-1,3-benzoazole (4c): 2-(4'-Chlorophenyl)-5-methoxy-6-methyl-1,3-benzoazole (4c) was synthesized as described for 2-phenyl-5-methoxy-6-methyl-1,3-benzoazole (2a) using 4'-chloro-N-(3,4-dimethoxyphenyl)thiobenzamide (3b) (0.0607 g, 0.200 mmol) in acetonitrile (2.6 mL) and dichloromethane (0.2 mL). The yellow precipitate was collected, washed with aqueous 1 M sodium thiosulfate solution (5 mL) and water (10 mL). Recrystallization from hot acetonitrile gave 2-(4'-methoxyphenyl)-5-methoxy-6-methyl-1,3-benzoazole (4b) (0.033 g, 55 %) as a yellow solid. Mp 163–165 °C (lit.\textsuperscript{13} 159–160 °C).\textsuperscript{1} 1H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta = 3.87\) (s, 3H, OCH\textsubscript{3}), 3.96 (s, 3H, OCH\textsubscript{3}), 9.38 (s, 3H, OCH\textsubscript{3}), 6.98 (d, \(J = 8.9\) Hz, 2H, 3'-H and 5'-H), 7.28 (s, 1H, 7-H), 7.52 (s, 1H, 4-H), 7.97 (d, \(J = 8.9\) Hz, 2H, 2'-H and 6'-H).\textsuperscript{13} 13C NMR (126 MHz, CDCl\textsubscript{3}): \(\delta = 55.4\) (CH\textsubscript{3}), 56.1 (CH\textsubscript{3}), 56.3 (CH\textsubscript{3}), 102.6 (CH), 104.6 (CH), 114.3 (2 × CH), 126.7 (C), 126.7 (C), 128.5 (2 × CH), 148.3 (C), 148.6 (C), 149.4 (C), 161.5 (C), 166.2 (C). MS (EI) m/z (%): 301 (100) [M]\textsuperscript{+}, 286 (30), 258 (16), 215 (12), 151 (9), 125 (7), 82 (8). 2-(4'-Fluorophenyl)-5-methoxy-6-methyl-1,3-benzoazole (4d): 2-(4'-Fluorophenyl)-5-methoxy-6-methyl-1,3-benzoazole (4d) was synthesized as described for 2-phenyl-5-methoxy-6-methyl-1,3-benzoazole (2a) using 4'-fluoro-N-(3,4-dimethoxyphenyl)thiobenzamide (3d) (0.0583 g, 0.200 mmol). Purification by flash column chromatography (dichloromethane/hexane, 9:3 to dichloromethane), followed by recrystallization from hot acetonitrile gave 2-(4'-fluorophenyl)-5-methoxy-6-methyl-1,3-benzoazole (4d) (0.0371 g, 57 %) as a white solid. Mp 146–148 °C. IR (neat): \(\nu_{max} = 2959\), 1510, 1463, 1329, 1294, 1221, 1161, 1003.\textsuperscript{1} 1H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta = 3.87\) (s, 3H, OCH\textsubscript{3}), 3.96 (s, 3H, OCH\textsubscript{3}), 7.29 (s, 1H, 7-H), 7.44 (d, \(J = 8.5\) Hz, 2H, 3'-H and 5'-H), 7.53 (s, 1H, 4-H), 7.95 (d, \(J = 8.5\) Hz, 2H, 2'-H and 6'-H).\textsuperscript{13} 13C NMR (126 MHz, CDCl\textsubscript{3}): 56.1 (CH\textsubscript{3}), 56.3 (CH\textsubscript{3}), 102.4 (CH), 104.7 (CH), 127.1 (C), 128.2 (2 × CH), 129.2 (2 × CH), 132.4 (C), 136.4 (C), 148.5 (C), 148.8 (C), 149.6 (C), 164.7 (C). HRMS (ESI) m/z [M + Na]\textsuperscript{+}: 296.0443. Found 296.0443.
2-Phenyl-5,6-dimethoxy-1,3-benzothiazole (4e): 2-Phenyl-5,6-dimethoxy-1,3-benzothiazole (4e) was synthesized as described for 2-phenyl-5,6-dimethoxy-1,3-benzothiazole (4a) using \( N(3,4\text{-dime} \text{thoxy})\)thiohydroxamic acid (3e) (0.0315 g, 0.122 mmol). Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave 2-phenyl-5-methoxy-6-methyl-1,3-benzothiazole (4f) (0.0646 g, 0.250 mmol). Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave 2-phenyl-5-methoxy-6-methyl-1,3-benzothiazole (4f) (0.0238 g, 0.37 %) as a yellow solid. Mp 156–157 °C.

\( ^{1}C \text{ NMR} \) (CDCl3): \( \delta = 100.2 \) (CH), 101.8 (CH2), 102.7 (CH), 127.0 (2 × CH2), 128.3 (2 × CH), 130.4 (CH), 133.8 (C), 146.9 (C), 149.3 (C), 166.4 (C). HRMS (ESI) m/z \([ \text{M} + \text{Na}^+ \]) calcd. for \( \text{C}_{14}\text{H}_{12}\text{FNNaO}_2\text{S} \) 311.9851, found 311.9851.

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Keywords: Heterocycles · Benzoxazoles · Benzothiazoles · Homogeneous catalysis · Reaction mechanisms

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Iron(III) triflimide catalyzed bromination of N-(3-methoxyphenyl)benzamide 1k gave a 1:1 ratio of 4- and 6-brominated regioisomers.
Methods involving iron-catalysis for the synthesis of 2-arylenzoxazoles and 2-arylenzotriazoles from the corresponding N-arylenzamide or N-arylenzothiobenzamide have been developed. While the arylen ring of N-arylenzamides are activated by bromination and then cyclized by copper-catalysis, treatment of N-arylenzothiobenzamides with NBS led directly to the cyclized product.

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