Intramolecular Cascade C–S Bond Formation: Regioselective Synthesis of Substituted Benzothiazoles

D. Subhas Bose,* Mohd. Idrees

Organic Chemistry Division III, Fine Chemicals Laboratory, Indian Institute of Chemical Technology, Hyderabad 500607, India
Fax +91(40)27160387; E-mail: dsb@iict.res.in; E-mail: bose_iict@yahoo.co.in

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Abstract: Carbon–fluorine bond fission has been coupled with C–S bond formation under metal-free conditions, which is seldom reported in the literature. The intramolecular C–S bond formation reaction takes place by fission of the carbon–fluorine bond in situ, and is believed to proceed through an S_NAr mechanism. The approach represents a practical and atom-economical approach for regioselective and metal-free cascade synthesis of substituted benzothiazoles. This one-pot, environmentally benign protocol involves 2-fluoroanilines, benzoyl chlorides and Lawesson's reagent under microwave irradiation (5 min) or conventional thermal conditions (3 h).

Key words: benzothiazole, metal-free, cascade reactions, S-arylation, regioselective

Large dissociation energies of C–F bonds in fluorocarbons are widely used to explain their low reactivity, and are caused mainly due to the small size and high electronegativity of the fluorine atom. The activation of C–F bonds in fluoroaromatic compounds has attracted the attention of many organometallic chemists and new routes that enable functionalization of these bonds are under intensive investigation. In this regard, a number of reports describing stoichiometric activation and functionalization of C–F bonds by transition-metal complexes have been reported.[1] Despite the recent advances in this field, catalytic transformations of C–F bonds using transition-metal centers have been only poorly developed and, moreover, only a few methods that enable fluorine to be replaced are currently available. However, among fluoroaromatic compounds, nickel-catalyzed activation of the C–F bond of 2-fluoropyridines and pyrimidines have been reported.[2]

In this context, we were interested in studying the anomalous reactivity of the fluorine atom towards aromatic nucleophilic substitution reactions (S_NAr). Halogen atoms generally show the reactivity trend F > Cl > Br > I towards S_NAr replacement reactions, which can be explained by considering the high electronegativity of the fluorine atom that facilitates the initial attack of nucleophile and stabilizes the transition state. This interesting property of the fluorine atom could be effectively investigated and demonstrated for the synthesis of biologically significant, privileged structures. From our part, we have focused on the development of environmentally benign and expeditious methodologies for the synthesis of privileged structures for use in drug discovery and development processes.

Benzothiazoles are an important class of privileged structures of medicinal significance due to their recognized biological and therapeutic activities.[3] As such, these heterocycles constitute key structural motifs that exhibit a wide range of biological properties, such as imaging agents for β-amyloid plaques,[4] photosensitizers,[5] inhibitors of stearoyl-coenzyme A δ-9 desaturase,[6] antitumor (**1**),[7] and antimicrobial[8] agents, LTD4 receptor antagonists,[9] orexin receptor antagonist (**2**),[10] and Gram-positive selective antibacterials[11] (**3**; Figure 1).

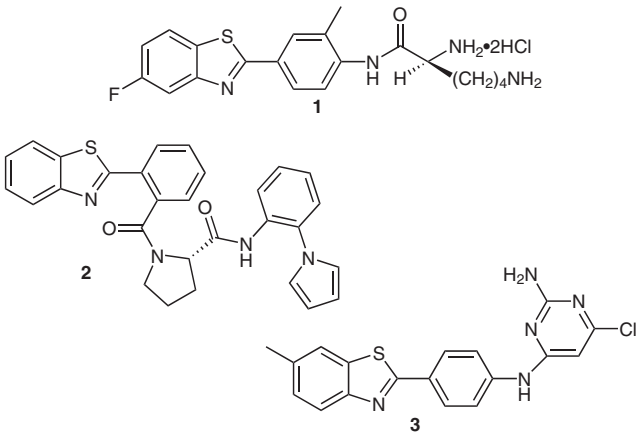

Figure 1 Structures of pharmaceutically important benzothiazoles

Although 2-substituted benzothiazoles play an important role in pharmaceutical science, the number of available synthetic strategies that lead to these compounds are limited compared with those that lead to the structurally related benzothiophene. Traditional methods for the preparation of the benzothiazole framework include condensation reactions of 2-aminothiophenols with substituted nitriles, aldehydes, carboxylic acids, acyl chlorides, or esters.[12] These methods, however, suffer from limitations such as difficulties encountered in the preparation of readily oxidizable 2-aminothiophenols bearing substituents. Some of these drawbacks have recently been overcome by the development of a novel and more sustainable process[13] that allows the efficient assembly of the target heterocycles under comparatively mild reaction conditions. Among those protocols, copper- or palladium-catalyzed Buchwald–Hartwig-type cross-coupling reactions

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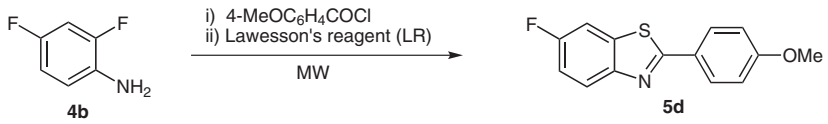
represent an elegant and straightforward synthetic approach to 2-substituted benzothiazoles, although some limitations still remain. For example, the palladium-catalyzed preparation of aryl thiols from aryl halides via thiol surrogates is difficult and can only be applied to a limited range of available starting materials.[14] Moreover, the high cost and air-sensitivity of palladium catalyst systems commonly limit their application to large- and industrial-scale formation of these bonds. The process is also inherently unfavorable from the point of view of atom economy. The replacement of one (or both) of these functionalized reagents by a metal-free protocol is thus a key goal in the development of green methods and is of particular appeal with respect to the organometallic reagents, which are often the least stable component and most difficult to prepare.

Over the past decade, extensive efforts have been made to develop methodologies that directly functionalize aromatic C–H bonds to construct C–C, C–N, C–O, and C–S bonds by using transition-metal catalysis.[15] Among the various intramolecular reactions, S-arylation is less studied, mainly due to the tendency of thiols to undergo oxidative self coupling (S–S coupling) and to undergo chelation to metals, which in turn leads to catalytic deactivation.[16,17] Despite the importance of sulfur-containing aromatic and heteroaromatic biologically active compounds, it is desirable to find novel procedures that provide efficient access to such highly useful organic products.[18] In this regard, we envisaged the application of a metal-free cascade intramolecular C–S bond formation protocol to obtain functionalized benzothiazoles from readily available *o*-fluoroanilines.

As part of our ongoing efforts to develop environmentally benign processes,[19] we examined the effect of microwave irradiation[20] on the formation of intramolecular C–S bonds. Thus, a mixture of 2,4-difluoroaniline (**4b**), *p*-anisoyl chloride, and Lawesson's reagent (LR)[21] was irradiated for five minutes in a domestic microwave oven (300 W, 115 °C) in toluene, to give the 2-arylbenzothiazole **5d**, albeit in trace amounts (Table 1). We then optimized the reaction conditions with respect to yield by varying the reaction time and temperature, and by using a range of solvents with suitable boiling points, with two commonly used ionic liquids, and with no added solvent (Table 1). These investigations revealed that compound **5d** could be obtained in 97% yield at 155 °C in *N*,*N*-diethylaniline under microwave irradiation for five minutes, whereas at 100 °C, intermediate thiobenzanilide **6b** was isolated (Scheme 1). The temperature was one of the key factors that improved the yields, but longer times and/or higher temperatures did not increase the yield further (Table 1). To check for the possible involvement of microwave effects, the reaction was also conducted using a pre-heated oil bath for the same duration and at the same final temperature as that measured at the end of the microwave-assisted synthesis. It was found that the reaction

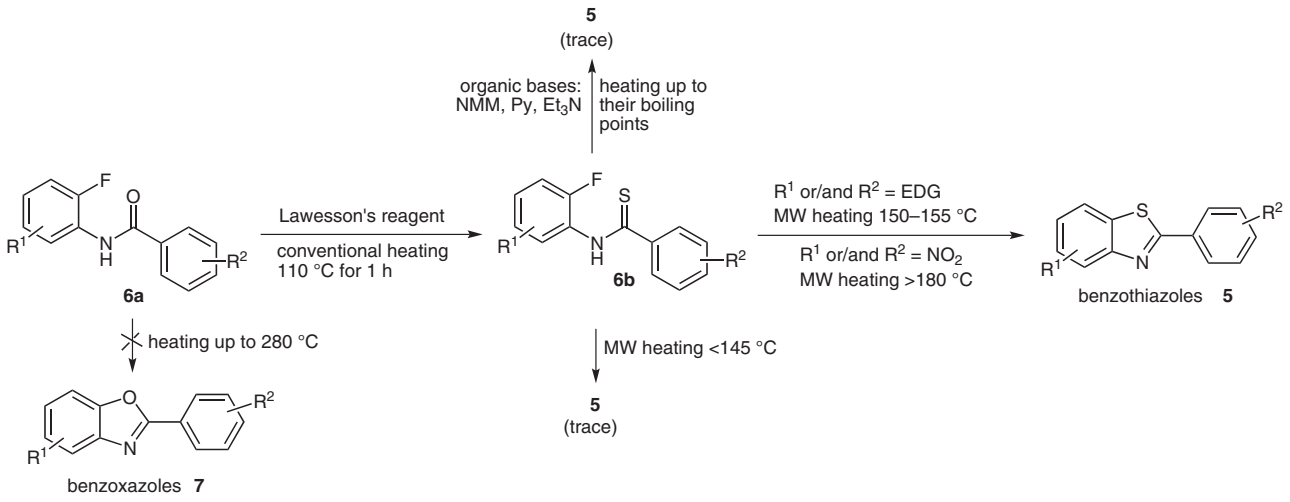
Table 1 Synthesis of Benzothiazoles via Cascade C–S Bond Formation[a]



4b **5d**

Entry	Solvent[b]	Temp (°C)[c]	Time (min)[d]	Yield (%)[e]	
				Microwave	Thermal[f]
1	toluene	115	5	trace[g]	–
2	*o*-xylene	145	8	80[h]	–
3	anisole	154	5	84[h]	–
4	o-dichlorobenzene	165	7	88	–
5	*N*,*N*-diethylaniline	155, 188[i]	5	97	90
6	diphenyl ether	155, 188[i]	5	95	88
7	1-hexyl-3-methylimidazolium chloride	150	5	82	75
8	1-butyl-3-methylimidazolium tetrafluoroborate	145	7	80	–
9	no solvent	165	8	60	–

[a] Reaction conditions: **4b** (1.1 equiv), benzoyl chloride (1.0 equiv), LR (0.55 equiv), all reactions were carried out in a sealed tube.
[b] DMF and DMSO were avoided due to their reactivity with LR.
[c] Temperature of reaction mixture was recorded after the microwave irradiation at the given reaction time.
[d] The reactions were carried out in a domestic microwave oven with IR sensor.
[e] Yield of isolated product.
[f] Oil bath temperature 145–180 °C, 3 h, reflux.
[g] Benzene, THF and 1,4-dioxane gave intermediate thiobenzanilide **6b** (see Scheme 1).
[h] When the NO_2 group was present in *p*-anisoyl chloride, formation of **6b** was observed (see Scheme 1).
[i] When the NO_2 group is present.



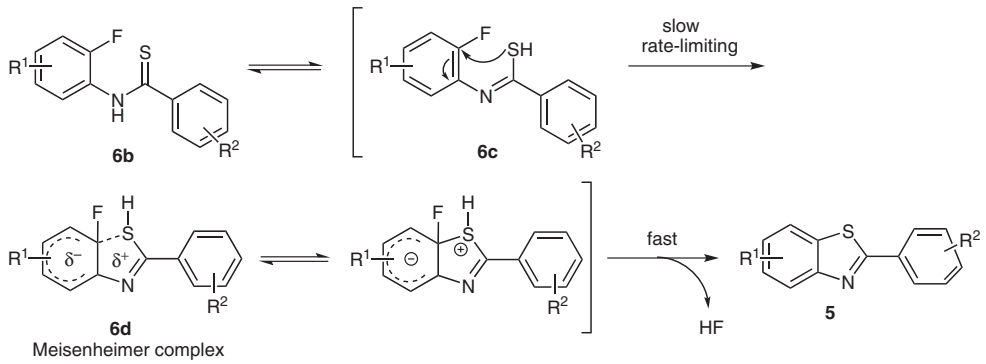
Scheme 1

proceeded slowly, with 5–10% yield in five minutes, whereas a 90% yield of **5d** was obtained after three hours under conventional heating at 155 °C (Table 1, entry 5). Interestingly, in derivatives of compound **4** containing other halogen atoms (R^1 = Cl, Br or I) in lieu of the fluorine atom, the same reaction did not produce the cyclized product **5d**. Instead, the reaction efficiently led to the formation of intermediate **6b** (Scheme 1), presumably due to relative differences in the size and electronegativity of the halogen atoms.

Experimental and theoretical investigations have indicated that more polar organic compounds absorb more microwave energy, which usually causes heating of the material. The different microwave energy absorption properties of the solvent and/or the reactants and/or intermediates can thus be advantageously used to alter the course of the reaction when it is carried out under microwave irradiation. On the basis of these ideas, we have studied the influence of the solvent on the formation of benzothiazoles from the corresponding anilines. Clearly, the nature of the solvent has a dramatic effect on the rate of reaction (Table 1), e.g., xylene (nonpolar, aprotic solvent) gave good yields and diphenylether or *N*,*N*′-diethylaniline (polar) afforded high yields, hence, these solvents are considered to be suitable solvents for this reaction.

The effects of some of the most common ionic liquids, which are known to have the ability to act as hydrogen bond acceptors, were also studied. The results were in accord with those obtained with the molecular solvents. Furthermore, thiobenzanilide (**6b**), when exposed to identical MW reaction conditions in DMF, resulted in the formation of **5** in a quantitative yield. However, in DMSO and polyethylene glycol (PEG) the reaction gave exclusively starting material. Because an additive, such as a base, was thought to be necessary for efficient S-arylation and high conversion into **5**, the use of several additives, including triethylamine, pyridinium tosylate, and *N*-methylmorpholine were explored. Ultimately, these additives were found to be unnecessary because changes to other parameters resulted in much higher yields of products (Scheme 1). Moreover, we conducted further investigations to see whether the benzoxazole ring system (**7**) was formed from the intermediate amide (**6a**) under the optimized conditions. Interestingly, we observed that the **6a** was found to be very stable even at temperatures up to 280 °C, and did not yield the expected benzoxazole.

The mechanism by which these reactions proceed is particularly intriguing, and we could find no literature precedence for benzothiazole formation from 2-fluorothioformanilide under cascade metal-free microwave irradiation. A proposed reaction mechanism is depicted in

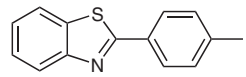
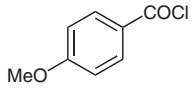
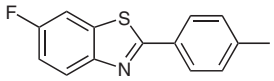
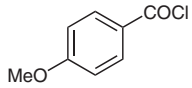
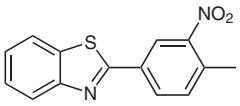
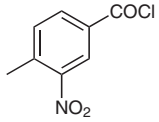
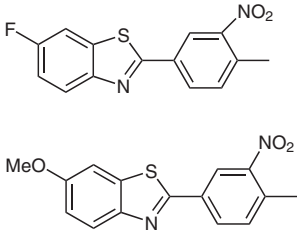
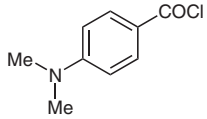
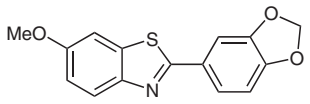
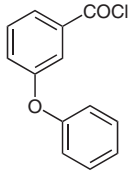


Scheme 2 S_NAr mechanism as the key step in the cascade sequence

Scheme 2. Nucleophilic aromatic substitution reactions involving activated substrates and good leaving groups are known to proceed through an addition–elimination[22] mechanism involving the formation of an intermediate Meisenheimer complex.[23] During the first step of this reaction, the nucleophilic sulfur attacks the fluorobenzene and bonds to the carbon that bears the halogen. This step, which involves the loss of aromaticity, generally proceeds slowly. In the second step, the complex formed loses the fluorine in a fast step, where the aromaticity of the ring is restored. The solvent can affect the rates of these reactions by interaction with starting materials, transition states, and/or the intermediate. In addition to simple dipole interactions between the transition sate and the solvent, it is important to consider the hydrogen bonding interactions that can occur between the sulfur/solvent, transition-state/solvent, and Meisenheimer complex/solvent.

Solvents with hydrogen-bond accepting properties can interact with the protons on the sulfur, increasing the electron density on the sulfur atom and therefore its nucleophilic character. This increase has been shown when ionic liquids, *N*,*N*-diethylaniline or diphenyl ether is used as the solvent for substituted anilines. Furthermore, the similarity between the transition state in these S_NAr reactions and the Meisenheimer complex intermediate pre-

Table 2 Synthesis of 2-Subtituted Benzothiazoles

Entry	2-Fluoroanilines **4**	Acid chloride	Product **5**[a]	Yield (%)[b]	
				MW	Thermal
1	**4a**		**5a**	92	90[24a]
2	**4a**		**5b**	93	89[24b]
3	**4b**		**5c**	95	90
4	**4b**		**5d**	95	92
5	**4a**		**5e**	90	86
6	**4b**		**5f**	95	88
7	**4c**		**5g**	92	90
8	**4c**		**5h**	85	85
9	**4c**		**5i**	92	85[13d]
10	**4a**		**5j**	95	90[13d]

[a] All reactions were carried out in diphenyl ether as solvent.
[b] Yield refers to the pure isolated product.

dicts that factors that contribute to the stabilization of the transition state will also tend to stabilize the complex.

To explore the generality and scope of this method, a range of 2-fluoroanilines and acid chlorides were studied for the synthesis of arylbenzothiazoles (**5a–j**) and the results are illustrated in Table 2. It is noteworthy that both acid-sensitive and alkaline-sensitive groups were completely unaffected under the reaction conditions. Furthermore, it appears that electron-donating or electron-withdrawing groups do not significantly affect the rate of reaction. It is pertinent to mention here that when a nitro group was present in the benzoyl chloride, an optimum reaction temperature of 180 °C was required.

In summary, we have developed a novel and regioselective, metal-free cascade intramolecular S-arylation reaction, which represents a simple, practical and straightforward approach towards 2-aryl-substituted benzothiazole derivatives from readily available starting materials. Further investigations into the detailed mechanistic aspects and expanded scope of this protocol for the construction of novel heterocyclic ring systems are underway in our laboratory.

All chemicals were obtained from Sigma-Aldrich and used without further purification. Column chromatography was performed using Acme silica gel (60–120 mesh). Common solvents for chromatography (petroleum ether, EtOAc) were distilled prior to use. Routine monitoring of the reaction was made using thin layer chromatography (TLC) on glass plates precoated with silica gel (Merck 60 F-254) of 0.25 mm thickness and visualized with iodine or UV light (254 nm) or by coloration with cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concd H_2SO_4 (60 mL), H_2O (940 mL)]. Optical rotations were measured on a Jasco P-1030 polarimeter. IR spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on either a Bruker Avance 300 spectrometer (300.132 MHz for ^1H, 75.473 MHz for ^{13}C), or a Varian FT-200 MHz (Gemini) spectrometer using CDCl3 as a solvent. Chemicals shifts are reported in parts per million relative to tetramethylsilane (δ = 0.0 ppm) as an internal standard. Melting points were obtained using a precision digital melting point Veego VMPDS apparatus and are uncorrected. Elemental analyses were performed on a Elementar's Vario EL microanalyzer. Low-resolution mass spectra (ESI-MS) and HRMS were recorded on Quattro LC (Micromass) and Q STAR XL (Applied Biosystems), respectively.

Preparation of Substituted Benzothiazoles 5a–j; General Procedure

A heterogeneous mixture of 2-fluoroaniline (11.0 mmol), benzoyl chloride (10.0 mmol), Lawesson's reagent (5.0 mmol, corresponding to the intermediate amide formed in situ) in *N*,*N*-diethylaniline (or diphenyl ether; 5 mL), was irradiated in a sealed tube with microwaves in a domestic microwave oven fitted with an IR sensor to measure temperature, for 5–8 min at 145–180 °C (Method A) or using conventional heating at 145–180 °C for 3 h under N_2 (Method B). After cooling to r.t., the reaction mixture was transferred to a stirred solution of dilute HCl (2 M, 5 mL) followed by 1 N NaOH (10 mL). The precipitated product was filtered, washed with H_2O (2 × 5 mL) and dried in vacuo to give crude **5**, which was further purification by column chromatography (EtOAc–hexane, 1:5 v/v) to afford pure 2-arylbenzothiazoles **5a–j** [60–97% (A), 75–90% (B)] as crystalline solids. This procedure was carried out on a 5–20 mmol scale and some experiments were carried out on larger scales in slightly more concentrated solution and slightly extended overall heating time in the microwave oven.

6-Methoxy-2-(3,4-methylenedioxyphenyl)-1,3-benzothiazole (5i)

White solid; mp 164–166 °C (Lit.[13d] 165–166 °C).

^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 3.88 (s, 3 H), 6.04 (s, 2 H), 6.84–6.87 (d, J = 8.31 Hz, 1 H), 6.99–7.04 (dd, J_1 = 9.06, J_2 = 2.26 Hz, 1 H), 7.27–7.28 (d, J = 3.02 Hz, 1 H), 7.48–7.58 (m, 2 H), 7.85 (d, J = 9.06 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.8, 101.6, 104.4, 107.3, 108.6, 115.4, 122.1, 123.5, 128.3, 136.3, 148.4, 148.7, 149.7, 157.7, 165.1.

MS (EI): *m*/*z* (%) = 285 (100) $[M]^+$, 270 (80), 242 (15), 143 (13), 95 (20).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{11}NO_3S$: 286.0537; found: 286.0537.

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.

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