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# A General and Straightforward Method for the Synthesis of 2-Trifluoromethylbenzothiazoles

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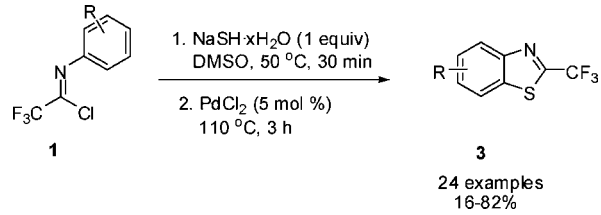
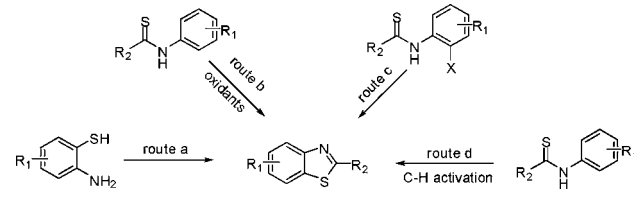
## ABSTRACT




**An efficient one-pot method for the synthesis of 2-trifluoromethylbenzothiazoles by the treatment of trifluoromethylimidoyl chlorides with sodium hydrosulfide hydrate using $PdCl_2$ as the sole catalyst in DMSO is described. The reaction proceeds via thiolation/C−H bond functionalization/C−S bond formation in moderate to high yields with good functional group tolerance.**

Benzothiazoles are a important class of heterocyclic compounds due to their wide range of biological properties such as antimicrobial,[1] antitumor,[2] antiviral,[3] and antiparasitic.[4] Synthesis of this privileged structure in medicinal chemistry has recently attracted much attention.[5] To date, these molecules are commonly prepared by the following methods (Scheme 1): (a) condensation of *o*-aminothiophenols with substituted carboxylic acids, aldehydes, nitriles, or esters;[6] (b) oxidative cyclization of thiobenzamides with various oxidants, including potassium ferricyanide(III),[7] ammonium cerium(IV) nitrate (CAN),[8] hypervalent iodine reagents (DMP, PIFA),[9] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ);[10] (c) palladium- or copper-catalyzed cyclization of *o*-halothio-benzamides;[11] and (d) palladium-

**Scheme 1.** Methods for Synthesis of Benzothiazoles

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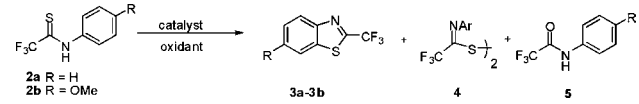
catalyzed cyclization of thiobenzamides through a C−H functionalization/C−S bond formation reaction.[12] These approaches suffer from some limitations such as the limited diversity of the starting materials (routes a and c), multistep synthesis especially utilizing the Lawesson's reagent (routes b, c, and d), the harsh reaction conditions (route a), and the lack of regioselectivity and functional group tolerance (route b). Although two elegant studies have been reported for the preparation of 2-substituted benzothiazoles via route d, the C−S bond formation via transition metal-catalyzed C−H bond functionalization is still limited.[13]

It is well-known that regioselective replacement of hydrogen on an aromatic or heterocyclic system by a fluorine atom or a fluoroalkyl group may have a profound influence on the biological and physical properties of such a molecule.[14] As part of our ongoing project to investigate new synthetic methods for fluorine-containing heterocycles,[15] we attempted to develop a mild and efficient process for the preparation of 2-trifluoromethylbenzothiazoles.[16] Inspired by the recent development of C−H bond functionalization[17] and the chemistry of trifluoromethylimidoyl halides as useful building blocks in synthetic organofluorine chemistry,[18] herein we wish to report a novel cascade synthesis of 2-trifluoromethylbenzothiazoles based on the reaction of the trifluoromethylimidoyl chlorides with sodium hydrosulfide hydrate by $PdCl_2$ as the sole catalyst in DMSO via the intermediate trifluoromethylthiobenzamides.

2,2,2-Trifluoro-*N*-phenylethanethioamide (**2a**), as the model substrate, was treated with several different oxidants and palladium sources to obtain the optimal reaction conditions, which was readily prepared in excellent yield from the reaction of 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (**1a**) with sodium hydrosulfide hydrate in EtOH at room temperature. As listed in Table 1, the product 2-trifluoromethylbenzothiazole (**3a**) was obtained in 40% yield when stoichiometric ferric chloride was used as the oxidant (entry 1). Unfortunately, only the starting material **2a** was recovered when DDQ was employed (entry 2). Utilizing phenyliodine(III) diacetate (PIDA) as the oxidant, disulfide **4a** was detected as the main product (entry 3), while acetylamide **5a** was formed when $Cu(OTf)_2$ was used as the catalyst (entry 4). After treatment of **2a** under air atmosphere with 10 mol % $PdCl_2$ in DMSO at 110 °C for 3 h, the desired product **3a** was obtained in 74% yield (entry 5). Other

**Table 1.** Optimization of Reaction Conditions




| entry | catalyst (mol %) | oxidant (2 equiv) | temp (degdC) | yield (%)[d] |
|---|---|---|---|---|
| 1[a] | | $FeCl_3$ | rt | **3a**/40 |
| 2[a] | | DDQ | rt | **2a** |
| 3[a] | | $PhI(OAc)_2$ | rt or 80 | **4a**/90 |
| 4[b] | $Cu(OTf)_2$ (20) | | 140 | **5a** |
| 5[b] | $PdCl_2$ (10) | | 110 | **3a**/74 |
| 6[b] | $PdCl_2(PPh_3)_2$ (10) | | 110 | **3a**/73 |
| 7[b] | $PdCl_2(CH_3CN)_2$ (10) | | 110 | **3a**/65 |
| 8[b] | Pd $(OAc)_2$ (10) | | 110 | **3a**/16 |
| 9[b] | $PdCl_2$ (10) | $Cu(OAc)_2$ | 110 | **3a**/64 |
| 10[b] | $PdCl_2$ (10) | DDQ | 110 | **3a**/43 |
| 11[c] | $PdCl_2$ (10) | | 110 | **3b**/83 |
| 12[c] | $PdCl_2$ (5) | | 110 | **3b**/82 |

[a] The reactions were carried out on a 0.4 mmol scale in $CH_2Cl_2$. [b] The reactions were carried out on a 0.4 mmol scale in DMSO for 3 h. [c] 2,2,2-Trifluoro-*N*-(4-methoxyphenyl)acetimidoyl chloride **1b** reacted with sodium hydrosulfide hydrate in DMSO at 50 °C for half an hour, followed by addition of $PdCl_2$ and elevated temperature to 110 °C; the mixture was stirred for 3 h. [d] Isolated yields.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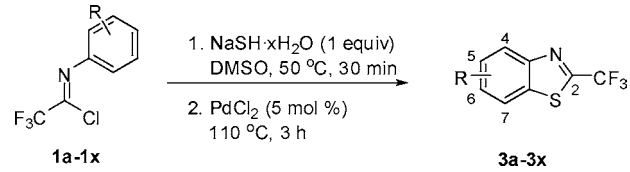
palladium salts were found to have comparable activity except for $Pd(OAc)_2$ (entries 6−8). Addition of oxidants ($Cu(OAc)_2$ or DDQ) to the system did not improve the yield of the desired product **3a** (entries 9 and 10). After screening the different solvents and temperature, the results showed that the solvent DMSO was crucial for this transformation and lower temperature gave no satisfactory results.

Encouraged by the results of the above experiments, we became interested in developing a tandem reaction to construct 2-trifluoromethylbenzothiazoles using imidoyl chlorides **1** as the starting substrates directly, which could eliminate the separation process of thiobenzamides **2**. Then 2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetimidoyl chloride **1b** was selected to confirm this hypothesis. However, none of the desired product **3b** was obtained when the mixture of **1b**, sodium hydrosulfide hydrate, and 10 mol % $PdCl_2$ in DMSO was stirred at 110 °C for 3 h. Interestingly, we were pleased to find that treating **1b** with sodium hydrosulfide hydrate at 50 °C for half an hour, followed by addition of 10 mol % $PdCl_2$ then elevating temperature to 110 °C for 3 h gave **3b** in 83% yield (entry 11). Decreasing the loading of $PdCl_2$ to 5 mol % under the same operation also gave a 82% yield (entry 12).

The optimized reaction conditions were also evaluated for a range of substituted precursors **1** in the presence of 5 mol % $PdCl_2$. As summarized in Table 2, a range of 2-trifluoromethylbenzothiazoles bearing electron-donating or electron-withdrawing groups were formed in moderate to high yields. A number of functional groups were tolerated in this reaction, such as the carbonyl group (entries 9 and 11), the cyano group (entry 10), the trifluoromethyl group (entry 22), and halogens (entries 5−8 and 13−15). Meta-substituted substrates could react regioselectively to afford 5-substituted products **3s**−**v** exclusively (entries 19−22), and this is in accordance with the results reported in many C−H bond functionalization reactions. *o*-Halogen-substituted compounds led to the products in good yields (entries 13−15) except *o*-iodide, which afforded the dehalogenated cyclized product **3a** in 63% yield (entry 16). Substrates bearing electron-withdrawing groups were dramatically affected by water, a better yield of **3** was obtained by using the corresponding thiobenzamides **2** as the substrates (entries 8−12), while addition of drying agents such as molecular sieves and $MgSO_4$ failed to improve the overall yield. When the trifluoromethyl groups were replaced by pentafluoroethyl or chlorodifluoromethyl groups, the corresponding benzothiazoles were generated in 52% and 16% yield, respectively (entries 23 and 24).

In summary, we have developed a novel and straightforward method for the synthesis of 2-trifluoromethylbenzothiazoles via Pd-catalyzed C−H bond functionalization from trifluoroimidoyl chlorides and sodium hydrosulfide. This one-pot protocol showed good functional group tolerance and utilized $PdCl_2$ as the sole catalyst without needing any other additives or oxidants.

**Table 2.** Synthesis of Various 2-Trifluoromethylbenzothiazoles[a]




1a-1x 3a-3x

| entry | substrate | R | product | yield (%)[c] |
|---|---|---|---|---|
| 1 | **1a** | H | **3a** | 72 |
| 2 | **1b** | *p*-OMe | **3b** | 82 |
| 3 | **1c** | *p*-Me | **3c** | 71 |
| 4 | **1d** | *p*-$NMe_2$ | **3d** | 66 |
| 5 | **1e** | *p*-F | **3e** | 69 |
| 6 | **1f** | *p*-Cl | **3f** | 77 |
| 7 | **1g** | *p*-Br | **3g** | 67 |
| 8 | **1h** | *p*-I | **3h** | 43 (83)[b] |
| 9 | **1i** | *p*-COOEt | **3i** | 51 70)[b] |
| 10 | **1j** | *p*-CN | **3j** | (60)[b] |
| 11 | **1k** | *p*-$COCH_3$ | **3k** | (57)[b] |
| 12 | **1*l*** | *p*-$NO_2$ | **3*l*** | (55)[b] |
| 13 | **1m** | *o*-F | **3m** | 65 |
| 14 | **1n** | *o*-Cl | **3n** | 65 |
| 15 | **1o** | *o*-Br | **3o** | 60 |
| 16 | **1p** | *o*-I | **3a** | 62 |
| 17 | **1q** | *o*-OMe | **3q** | 74 (78)[d] |
| 18 | **1r** | naphthyl | **3r** | 69 |
| 19 | **1s** | *m*-OMe | **3s** (R = 5-OMe) | 78 |
| 20 | **1t** | *m*-Me | **3t** (R = 5-Me) | 74 |
| 21 | **1u** | *m*-Cl | **3u** (R = 5-Cl) | 66 |
| 22 | **1v** | *m*-$CF_3$ | **3v** (R= 5-$CF_3$) | (61)[b] |
| 23 | **1w** ($CF_2CF_3$) | H | **3w** | (52)[b] |
| 24 | **1x** ($CF_2Cl$) | H | **3x** | (16)[b] |

[a] Imidoyl chloride **1** (1.0 mmol), sodium hydrosulfide hydrate (1.0 mmol), $PdCl_2$ (0.05 mmol), DMSO (3 mL). [b] Thiobenzamide **2** (1.0 mmol), $PdCl_2$ (0.05 mmol), DMSO (3 mL). [c] Yields of isolated products under condition a and yields in parentheses under condition b. [d] The second step was carried out at 140 °C.

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**Supporting Information Available:** Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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