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Straightforward Synthesis of 2-Anilinobenzoxazoles and -benzothiazoles via Mechanochemical Ball-milling-promoted One-pot Reactions

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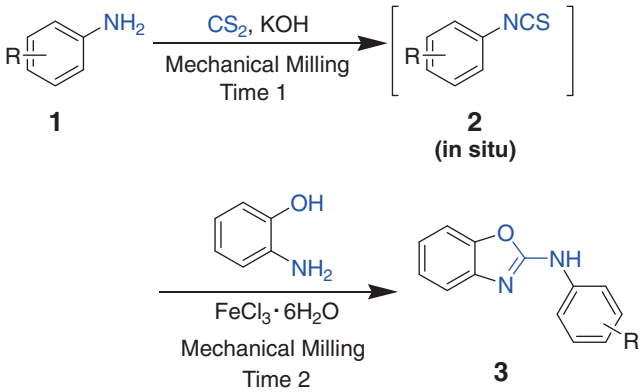
Under mechanochemical ball-milling and solvent-free conditions, a series of 2-anilinobenzoxazoles and -thiazoles were synthesized directly from the one-pot reaction of anilines, CS_2, and 2-aminophenol and -thiophenol. This protocol exhibits the following advantages: free or cheap use of a cyclodesulfurization reagent, no separation of in situ generated isothiocyanate, short reaction time, and simple work-up procedure.

Anilinobenzoxazoles and anilinobenzothiazoles have been attracting much attention due to their important structural motifs in medicinal chemistry.[1,2] Due to their great importance, considerable efforts have been made for the efficient construction of these units. Up to now, a large variety of synthetic methods have been documented.[3] These methods are generally efficient and high yielding, but most cases suffer from an expensive catalyst, drastic reaction conditions, pre-made starting materials such as toxic and unstable isothiocyanates, high temperatures, relatively long reaction times, or tedious purification work up. To circumvent these problems, mechanochemical ball milling, a powerful and greener way for the efficient promotion of various organic reactions,[4,5] may be an effective alternative. On the other hand, there are facts that: (a) cyclodesulfurization of the intermediates generated by 2-aminophenols and -thiophenols with isothiocyanates can afford 2-aminobenzoxazoles and -thiazoles efficiently;[6,7] (b) anilines can be smoothly transformed into isothiocyanates under high-speed ball milling.[8] Therefore, we explored and herein wish to report a solvent-free method for the one-pot synthesis of these compounds via the addition and cyclodesulfurization of 2-aminophenol or 2-aminothiophenol, with in situ generated isothiocyanates from anilines and CS_2 using the ball-milling technique.

After various attempts (see Supporting Information), $FeCl_3$ was optimized as the cyclodesulfurization catalyst for extension studies, considering its best efficiency, easy availability, low price, sustainability, nontoxicity, and environmentally friendly properties.[9] Usage of 0.25 molar equivalent is enough to promote the transformation completely. As outlined in Table 1, a series of 2-anilinobenzoxazoles were successfully synthesized in good to excellent yields from the corresponding anilines bearing either electron-donating or electron-withdrawing groups. In contrast, it is more efficient for anilines bearing electron-donating groups, which are easier to transform into the corresponding isothiocyanates **2**. However, when isothiocyanates **2** were formed, the addition–cyclodesulfurization process was accomplished more rapidly for cases involving electron-withdrawing groups (Entries 4–6). Furthermore, it is worthy to point out that all the products were obtained through a very simple work up, just including washing the resulting reaction mixture with water and recrystallization in $EtOH/H_2O$, without the need for isolation of in situ generated isothiocyanates **2** or any column chromatography work.[10]

Table 1. One-pot synthesis of 2-anilinobenzoxazoles **3** catalyzed by $FeCl_3$ under ball milling[a]



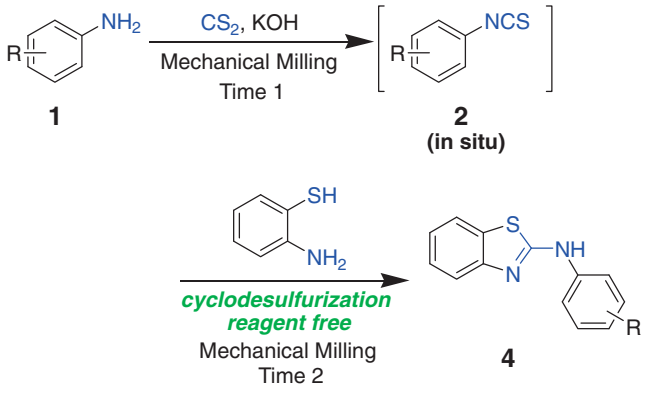
Entry	R	Product **3**	Time 1 /min	Time 2 /min	Yield /%[b]
1	H	**3a**	60	60	79
2	4-Me	**3b**	40	90	87
3	4-OMe	**3c**	40	90	90
4	4-Cl	**3d**	70	60	82
5	4-Br	**3e**	70	60	84
6	2-Cl	**3f**	90	60	72

[a]Reactions were carried out with aniline **1** (2.0 mmol), CS_2 (10.0 mmol), KOH (2.0 mmol), afterward added 2-aminophenol (2.0 mmol) and $FeCl_3 \cdot 6H_2O$ (0.5 mmol) under ball milling at room temperature with a vibration frequency of 30 Hz. [b]Isolated yield combined from two parallel runs.

Next, this strategy was extended to the synthesis of 2-anilinobenzothiazoles **4** using 2-aminothiophenol instead of 2-aminophenol. To our delight, in these cases, various desired products were still efficiently obtained even without using any cyclodesulfurization reagents (Table 2). This higher efficiency may be ascribed to the fact that thiophenol has stronger acidity, which would result in easier cyclodesulfurization.

In summary, a straightforward and environmentally friendly method for the direct transformation of various anilines into the corresponding 2-anilinobenzoxazoles or 2-anilinobenzothiazoles has been successfully developed using the mechanochemical ball-milling technique. This protocol exhibits several promising advantages including the use of cheap $FeCl_3$ or even no using cyclodesulfurization catalyst, simple isolation work up, no need of pre-made toxic and unstable isothiocyanates, which make it a very efficient, economical, and practical alternative to traditional methods for the synthesis of this kind of compound.

Table 2. One-pot and cyclodesulfurization reagent-free synthesis of 2-anilinobenzothiazoles **4** under ball milling[a]



Entry	R	Product **4**	Time 1 /min	Time 2 /min	Yield /%[b]
1	H	**4a**	60	90	83
2	4-Me	**4b**	40	90	85
3	4-OMe	**4c**	40	90	92
4	4-F	**4d**	90	70	82
5	4-Cl	**4e**	70	80	79
6	4-NO_2	**4f**	90	90	71
7	4-Br	**4g**	70	70	81
8	3-NO_2	**4h**	90	90	74

[a]Reactions were carried out with aniline **1** (2.0 mmol), CS_2 (10.0 mmol), KOH (2.0 mmol) and afterward added 2-aminothiophenol (2.0 mmol) under ball milling at room temperature with a vibration frequency of 30 Hz. [b]Isolated yield combined from two parallel runs.

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Supporting Information is available electronically on J-STAGE.

References and Notes

1 M. A. P. Martins, C. P. Frizzo, D. N. Moreira, L. Buriol, P. Machado, *Chem. Rev.* **2009**, *109*, 4140.

2 a) S. Ueda, H. Nagasawa, *Angew. Chem., Int. Ed.* **2008**, *47*, 6411. b) P. Yogeeswari, D. Sriram, L. R. J. Sunil Jit, S. S. Kumar, J. P. Stables, *Eur. J. Med. Chem.* **2002**, *37*, 231.

3 a) B. Liu, M. Yin, H. Gao, W. Wu, H. Jiang, *J. Org. Chem.* **2013**, *78*, 3009. b) S. K. Rout, S. Guin, J. Nath, B. K. Patel, *Green Chem.* **2012**, *14*, 2491. c) G. Shen, X. Lv, W. Bao, *Eur. J. Org. Chem.* **2009**, 5897.

4 For recent reviews, see: a) R. M. Claramunt, C. López, D. Sanz, J. Elguero, *Adv. Heterocycl. Chem.* **2014**, *112*, 117. b) E. Boldyreva, *Chem. Soc. Rev.* **2013**, *42*, 7719. c) G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668. d) L. Takacs, *Chem. Soc. Rev.* **2013**, *42*, 7649. e) S.-E. Zhu, F. Li, G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7535.

5 For some recent examples, see: a) D. Tan, V. Štrukil, C. Mottillo, T. Friščić, *Chem. Commun.* **2014**, *50*, 5248. b) M. Hestericová, R. Šebesta, *Tetrahedron* **2014**, *70*, 901. c) L. Chen, B. E. Lemma, J. S. Rich, J. Mack, *Green Chem.* **2014**, *16*, 1101. d) M. Ferguson, N. Giri, X. Huang, D. Apperley, S. L. James, *Green Chem.* **2014**, *16*, 1374. e) A. Bose, P. Mal, *Tetrahedron Lett.* **2014**, *55*, 2154. f) M. Zille, A. Stolle, A. Wild, U. S. Schubert, *RSC Adv.* **2014**, *4*, 13126.

6 a) H. Ogura, S. Mineo, K. Nakagawa, *Chem. Pharm. Bull.* **1981**, *29*, 1518. b) H. S. Chang, G. H. Yon, Y. H. Kim, *Chem. Lett.* **1986**, 1291.

7 a) D. Fajkusova, P. Pazdera, *Synthesis* **2008**, 1297. b) X. Zhang, X. Jia, J. Wang, X. Fan, *Green Chem.* **2011**, *13*, 413.

8 Z. Zhang, H.-H. Wu, Y.-J. Tan, *RSC Adv.* **2013**, *3*, 16940.

9 a) A. Correa, O. G. Mancheño, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108. b) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500.

10 Typical procedures for synthesis of **3** or **4**: aniline (2.0 mmol), CS_2 (10.0 mmol), and KOH (2.0 mmol), together with a stainless ball of 7.0 mm in diameter, were introduced into a stainless jar (25 mL). The same mixture was also introduced into a second parallel jar. The two reaction vessels were sealed with screw caps, fixed on the vibration arms of a ball-milling apparatus (mixer mill MM400, Retsch GmbH, Germany) and were vibrated vigorously at a rate of 30 Hz at room temperature for designated time. The vessels were opened, and 2-aminophenol or 2-aminothiophenol (2.0 mmol) with $FeCl_3 \cdot 6H_2O$ (0.5 mmol, none for **4**) were added into each resulted mixture. The vessels were sealed again and continued to vibrate for designated time at 30 Hz. The reaction mixtures combined from two parallel vessels were immersed in 5% HCl (30 mL) with the aid of ultrasonic irradiation. After Büchner filtration followed by washing with water for several times up to colorless filtrate, the crude product was collected and recrystallized from EtOH/H_2O to afford the desired product.

