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COMMUNICATION

Mechanoredox Radical Annulation for the Solvent-Free Synthesis of 2-Substituted Benzothiophenes

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A mechanoredox-enabled radical annulation under ball-milling conditions affords 2-substituted benzothiophenes 3 from 2-(methylthio)benzenediazonium salts 1 and alkynes 2. Mechanical energy drives single-electron transfer without photoredox or electrochemical systems, providing a practical and environmentally benign approach to heterocycle synthesis.

Introduction

Radical intermediates can be generated under mild, functional-group-tolerant conditions, enabling diverse bond-forming reactions.[1] Recent advances, particularly in photoredox, electrochemical and mechanoredox strategies, have greatly expanded the synthetic toolbox for controlled radical chemistry.[2,3]

Mechanochemistry has emerged as a sustainable approach to bond construction, enabling solvent-free access to unique and efficient reactivity.[4-7] Building on these advances, we sought to develop a mechanoredox-based radical transformation that addresses limitations of conventional solution-phase methods.

In this context, the synthesis of 2-substituted benzothiophenes was chosen as a benchmark transformation, given the prominence of this heterocyclic scaffold in pharmaceuticals, functional materials and agrochemicals,[8-19] and its established accessibility via radical annulation strategies (Fig 1).[20,21]

Unlike solution-based approaches that require organic solvent (typically DMSO), specialised photochemical or electrochemical equipment, and in some cases stoichiometric additives, the mechanoredox protocol exploits mechanical energy alone to drive single-electron transfer, consistent with a mechanoredox SET process,[3,22] enabling a solvent-free and promoter-dependent alternative with competitive efficiency, selectivity, and sustainability. We acknowledge that ball milling itself requires dedicated equipment and that Al_2O_3 is used in stoichiometric quantities; these aspects are weighed against the advantages when evaluating the practical utility of the method.

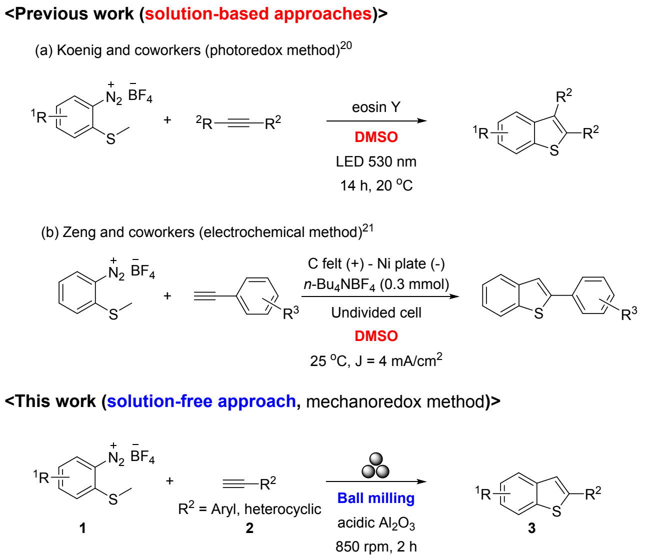

Figure 1. Synthesis of 2-substituted benzothiophenes **3** via radical annulation strategies

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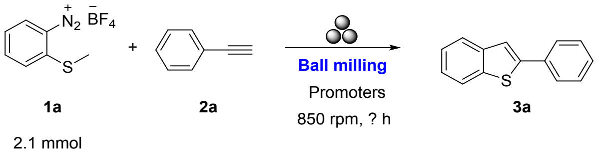
Results and discussion

Milling was carried out using a planetary micro mill (Pulverisette 7 Premium Line, Fritsch GmbH, Germany) equipped with a 20 mL ZrO_2 bowl[23] and ZrO_2 balls (10 mm in diameter).[24] When the planetary micro mill was equipped with 10 mm ZrO_2 balls, the maximum rotational speed was set to 850 rpm. Due to the maximum continuous milling time of 1 h, the process was conducted in two cycles of 1 h milling separated by 1 h cooling.[25]

Figure 2. Planetary ball mill used in this study: Fritsch Pulverisette 7 premium line (left), ZrO_2 bowl before grinding (right).

The reaction conditions were optimised, as summarised in Table 1. The reaction was conducted using five ZrO_2 balls at the maximum speed of 850 rpm. An optimization study of the number of ZrO_2 balls was performed, and detailed results are provided in the Supporting Information.

Table 1. An initial reaction optimization study[26]



Entry	**2a** (eq)	Promoters[a]	Reaction Time (h)	**3a** Yield (%)[b]
1	15	Al_2O_3 (acidic, 10eq)	0.5	27
2	15	None	0.5	<1
3	10	Al_2O_3 (acidic, 10eq)	1	40
4	10	Al_2O_3 (acidic, 10eq)	2	53
5	10	Al_2O_3 (acidic, 10eq)	3	53
6	10	Al_2O_3 (neutral, 10eq)	2	42
7	10	Al_2O_3 (basic, 10eq)	2	42
8	10	Al_2O_3 (10 eq), DMSO, no ball milling	2	<1[c]
9	10	$BaTiO_3$ (10eq)	2	35
10	10	TiO_2 (10eq)	2	4

[a]Commercially available Al_2O_3 (Brockmann Activity I, Sigma-Aldrich); acidic (pH ~4.5), neutral (pH ~7.0), basic (pH ~10.0). [b]After column chromatography. [c]Solution-phase control: reaction performed in DMSO without ball milling; confirms that mechanical activation is essential.

As shown in Table 1, the absence of a promoter completely suppressed the reaction (entry 2), highlighting the essential role of the promoter. A reaction time of 2 h was identified as optimal (entry 4). To probe the influence of surface acidity, three commercially available Al_2O_3 samples of defined acidity (acidic, neutral, and basic; Brockmann Activity I, Sigma-Aldrich) were evaluated under otherwise identical ball-milling conditions (entries 4–7). The acidic Al_2O_3 afforded the highest yield (53%, entry 4), while both neutral and basic Al_2O_3 gave a reduced but still appreciable yield of 42% (entries 6 and 7), indicating that surface Lewis acidity enhances, but is not solely responsible for, the mechanoredox SET process. Furthermore, conducting the reaction in DMSO solution in the presence of Al_2O_3 (entry 8) afforded no detectable product, confirming that mechanical activation—rather than chemical interaction with the solid additive alone—is the key driving force for the reaction. In contrast, replacement of Al_2O_3 with $BaTiO_3$ led to a reduced yield (entry 9), while TiO_2 was largely ineffective, affording only a very low yield (entry 10).

These results indicate that the presence of a promoter is essential for the reaction under mechanochemical conditions. A reaction time of 2 h was sufficient to achieve optimal conversion. In comparison, $BaTiO_3$ exhibited lower activity as a promoter, while TiO_2 was largely ineffective under the same conditions, suggesting that the activity as a promoter is strongly dependent on the nature of the promoter. The superior activity of Al_2O_3 relative to $BaTiO_3$ and TiO_2 argues against a purely piezoelectric mechanism[3] and is instead consistent with a mechanoredox SET process in which mechanical activation enables single-electron reduction of the diazonium substrate. The Lewis acidic surface sites of Al_2O_3 are further proposed to activate the diazonium substrate toward SET.

To explore the scope of the optimized reaction, 2-(methylthio)benzenediazonium salt **1** was reacted with a variety of ethynyl compounds, including aryl-, heterocyclic-, and alkyl-substituted ethynes **2**. Detailed results are provided in the Supporting Information. Among the ethynyl substrates examined, ethynylbenzene, 3-ethynylpyridine, and 3-ethynylthiophene, which afforded relatively high yields, were selected and subsequently reacted with variously substituted derivatives of 2-(methylthio)benzenediazonium salt **1** to synthesise a series of 2-substituted benzothiophenes **3** (Figure 3). Most of the compounds were isolated in moderate yields; notably, hetero–heterocyclic compounds (**3b** and **3c**) could also be readily obtained. These results compare favourably with those of related solution-phase methods: for the benchmark substrate **3a** (R^2 = Ph), the photoredox method of Koenig and

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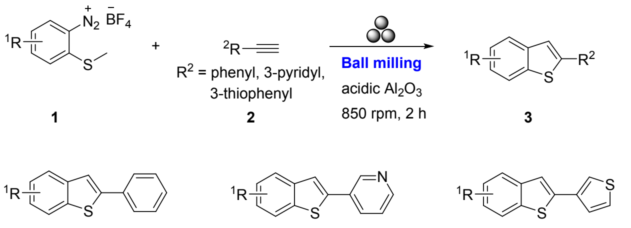
co-workers[20] affords 70–85% in 14 h in DMSO, and the electrochemical method of Zeng and co-workers[21] affords 60–75% in DMSO, compared with 53% in 2 h under solvent-free mechanochemical conditions in the present work. Notably, the hetero–heterocyclic products (**3b** and **3c** series, R^2 = 3-pyridyl and 3-thienyl) are, to the best of our knowledge, novel compounds not previously reported by either solution-phase method, further demonstrating the synthetic utility of the present approach. A comprehensive comparison for all directly comparable substrates is provided in Supporting Information Table S2.



R^1 = H, 53 % (**3a**)	R^1 = H, 48 % (**3b**)	R^1 = H, 38 % (**3c**)
5-chloro, 33 % (**3aa**)	5-chloro, 51 % (**3ba**)	5-chloro, 42 % (**3ca**)
6-chloro, 35 % (**3ab**)	6-chloro, 25 % (**3bb**)	6-chloro, 39 % (**3cb**)
5-methoxy, 42 % (**3ac**)	5-methoxy, 49 % (**3bc**)	5-methoxy, 20 % (**3cc**)
6-methoxy, 25 % (**3ad**)	6-methoxy, 39 % (**3bd**)	6-methoxy, 41 % (**3cd**)
6-methyl, 42 % (**3ae**)	6-methyl, 36 % (**3be**)	6-methyl, 33 % (**3ce**)
6-bromo, 39 % (**3af**)	6-bromo, 20 % (**3bf**)	6-bromo, 37 % (**3cf**)
6-fluoro, 40 % (**3ag**)	6-fluoro, 27 % (**3bg**)	6-fluoro, 38 % (**3cg**)
6-ethoxy, 33 % (**3ah**)	6-ethoxy, 38 % (**3bh**)	6-ethoxy, 28 % (**3ch**)

Figure 3. Scope of the optimized reaction

To gain insight into the mechanism of the mechanochemical reaction, radical trapping experiments were conducted. Ball milling of **1a** with TEMPO completely suppressed formation of **3a** (3% yield) and afforded the TEMPO adduct **4** in 80% yield, unambiguously confirming the intermediacy of a free aryl radical.[28] The formation of the TEMPO adduct **4** was confirmed by ^1H NMR spectroscopy. Based on literature reports,[3,20,21,22,28,29,30] together with our experimental results, a plausible reaction mechanism is proposed in Fig. 4; more detailed and rigorous mechanistic investigations are currently underway.

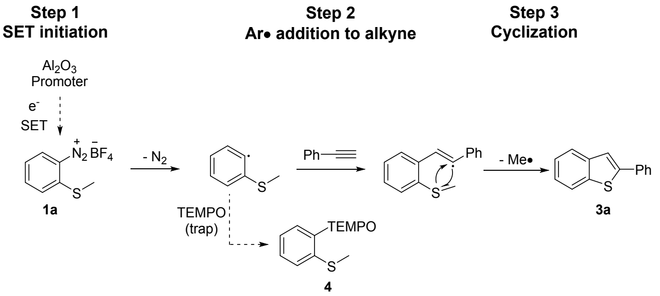


Figure 4. Proposed reaction mechanism

Conclusions

In summary, we have developed a mechanoredox-enabled radical annulation strategy for the synthesis of 2-substituted benzothiophenes **3** under solvent-free and promoter-dependent ball-milling conditions. This protocol exploits mechanical energy to drive single-electron transfer, providing a sustainable alternative to established photoredox and electrochemical approaches. A range of aryl- and heterocyclic-substituted ethynes **2** were successfully employed, affording the desired benzothiophenes **3** in generally moderate yields, including hetero–heterocyclic derivatives (**3b** and **3c**). Control experiments and promoter screening confirmed the crucial role of the promoter under mechanochemical conditions, while radical trapping studies support the involvement of radical intermediates. Overall, this study demonstrates the potential of mechanoredox chemistry as a practical and environmentally benign platform for radical heterocycle synthesis, expanding the synthetic toolbox for sustainable bond-forming reactions.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the Supplementary Information.

Acknowledgements

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23 A 20 mL milling bowl was used, as this was the smallest size commercially available from the manufacturer.

24 As comparable yields were obtained with 5 mm ZrO_2 balls, 10 mm ZrO_2 balls were used; larger balls could not be accommodated in the 20 mL milling bowl.

25 Safety note: Aryl diazonium tetrafluoroborate salts should be handled with appropriate care. Although these materials are substantially more thermally stable than diazonium chloride or nitrate salts, they should not be heated or subjected to friction in the dry state in large quantities. All milling experiments described herein were performed on a small scale (≤ 2.1 mmol of diazonium salt), using a sealed ZrO_2 milling jar at ambient temperature with the standard cooling cycle (1 h milling, 1 h rest, 1 h milling). Appropriate personal protective equipment (safety glasses, laboratory coat, and gloves) was worn at all times. No exothermic events or decomposition were observed during any experiment.

26 Among the conditions not included in Table 1, the use of 5 equiv. of ethynylbenzene **2a** led to damage of the milling bowl, preventing further experimentation. In addition, increasing the loading of Al_2O_3 to 15 or 20 equiv. did not result in a significant change in yield.

27 Supporting Information Table S2 compares the yields obtained in this work with those reported by Koenig and co-workers (photoredox) and Zeng and co-workers (electrochemical) for directly comparable substrates.

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The data supporting this article have been included as part of the Supplementary Information.