

Ball-Milling-Assisted Synthesis of Aromatic Isothiocyanates and Thioureas: A Green and Versatile Synthetic Approach-Review

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Abstract

Mechanochemistry has emerged as an effective strategy for reducing solvent use and simplifying synthetic operations. The study considered here describes a straightforward ball-milling approach for converting substituted anilines into aromatic isothiocyanates and thioureas using carbon disulfide (CS_2) and inexpensive potassium hydroxide (KOH). The central feature of the methodology is the use of KOH as both base and decomposition reagent, thereby avoiding the harsh or toxic desulfurylating reagents frequently associated with conventional isothiocyanate synthesis. Under solvent-free milling, anilines were rapidly converted into isothiocyanates when 5.0 equivalents of CS_2 were employed, whereas reducing CS_2 to 1.0 equivalent redirected the reaction toward symmetrical thioureas. In addition, selected isothiocyanates generated in situ could be intercepted directly with a second aniline to furnish unsymmetrical thioureas in a one-pot sequence. This review-style presentation reorganizes the reported findings around reaction optimization, substrate scope, one-pot extension, selectivity, mechanistic rationale, and green-chemistry significance, while retaining the original reaction schemes and Tables 1–4 unchanged.

Keywords: mechanochemistry; ball milling; isothiocyanates; thioureas; carbon disulfide; potassium hydroxide; solvent-free synthesis; green chemistry

1. Introduction and Synthetic Context

Aromatic isothiocyanates constitute important sulfur-containing electrophiles and are useful intermediates for the preparation of sulfur–nitrogen heterocycles, thioureas, and biologically relevant molecules. Their reactivity also makes them valuable building blocks in chemoselective derivatization and bioconjugation. Despite this broad utility, conventional conversion of amines into isothiocyanates has commonly relied on thiophosgene or on alternative thiocarbonyl-transfer and desulfurylation reagents. The reported study places these approaches in the context of safety, functional-group compatibility, reagent availability, and work-up requirements, emphasizing the need for milder and operationally simpler alternatives.

A recurring strategy in isothiocyanate chemistry is the reaction of an amine with CS_2 in the presence of a base to generate a dithiocarbamate salt, followed by decomposition to the corresponding isothiocyanate. Although effective decomposition reagents have been developed, several reported procedures require hazardous or comparatively demanding reagents and may suffer from side reactions. The study therefore explores a solvent-free mechanochemical alternative in which mechanical energy and KOH replace conventional reaction conditions. The rationale is particularly attractive for isothiocyanates because avoiding prolonged exposure to solution conditions may also reduce problems associated with their instability.

The work represents an early example of applying ball milling to this specific transformation. The reported strategy is especially notable because product selectivity can be controlled by the amount of CS_2 : excess CS_2 favors isothiocyanate formation, while approximately stoichiometric CS_2 favors symmetrical thiourea formation. The same platform also provides access to unsymmetrical thioureas by trapping an in situ generated isothiocyanate with a second aniline.

2. Mechanochemical Strategy and Reaction Design

The synthetic sequence begins with an aniline and CS_2 in the presence of KOH. Mechanical milling at room temperature promotes rapid conversion through a dithiocarbamate-type intermediate. When 5.0 equivalents of CS_2 are used, the reaction is directed toward the corresponding aromatic isothiocyanate. The resulting isothiocyanate can either be isolated directly or, in selected cases, reacted further with another aniline without prior isolation. When the amount of CS_2 is reduced to 1.0 equivalent, the dominant pathway instead gives symmetrical thiourea.

Thus, the methodology can be viewed as a tunable reaction manifold rather than a single-product procedure. The principal variables are the physical mode of activation, base identity, solvent environment, and CS₂ loading. The optimization experiments show that the mechanochemical mode is decisive in accelerating conversion and that the base and CS₂ stoichiometry strongly influence chemoselectivity.

3. Reaction Optimization: From Solution Chemistry to Ball Milling

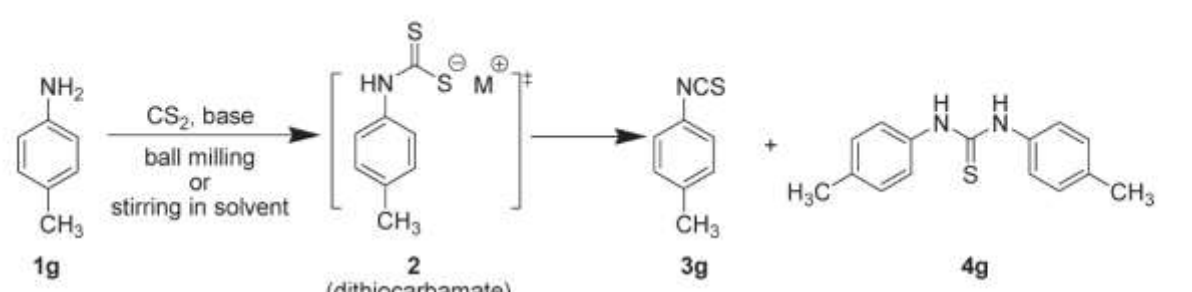
The optimization study used 4-methylaniline as the model substrate. Initial solution-phase experiments with CS₂ as solvent and several bases gave low conversion after 24 h. Carbonate bases afforded only trace isothiocyanate, whereas NaOH, KOH, and t-BuOK provided modest amounts of the desired product. Triethylamine gave a different outcome: although conversion was high, dithiocarbamate was the major product, accompanied by only partial formation of isothiocyanate and thiourea.

Changing from CS₂ as solvent to conventional polar solvents did not solve the selectivity problem. With KOH and 5.0 equivalents of CS₂, the reactions in dichloromethane, THF, acetone, methanol, DMF, and DMSO remained slow and/or favored thiourea. These observations indicate that simply increasing solvent polarity was not sufficient to achieve efficient, selective isothiocyanate formation under the investigated conditions.

A pronounced change occurred under ball milling. At a vibration frequency of 30 Hz, substantial conversion was achieved within 40 min with several bases. The strongest performance was obtained with KOH, which gave 98% of the target 4-methylphenyl isothiocyanate under the optimized conditions. The authors associate this acceleration with the high effective concentration of reactants in the absence of solvent and with the mechanical energy delivered during milling.

The optimization also establishes a clear stoichiometric effect of CS₂. With KOH under milling, 5.0 equivalents of CS₂ gave 98% isothiocyanate, whereas 3.0 equivalents gave 58% isothiocyanate together with 27% symmetrical thiourea. At 1.0 equivalent, isothiocyanate formation was suppressed and symmetrical thiourea reached 93%. Consequently, CS₂ loading functions as a practical selectivity switch within the reaction platform.

Table 1 Optimization of the reaction conditions for synthesis of 4-methyl-phenyl isothiocyanate (**3g**)^a

					
Entry	CS ₂ (equiv.)	Base	Solvent	Time	Product (yield) ^b
1	Solvent	Na ₂ CO ₃	CS ₂	24 h	3g (trace)
2	Solvent	K ₂ CO ₃	CS ₂	24 h	3g (trace)
3	Solvent	NaOH	CS ₂	24 h	3g (36%) + 4g (trace)
4	Solvent	KOH	CS ₂	24 h	3g (41%) + 4g (trace)
5	Solvent	^t BuOK	CS ₂	24 h	3g (45%) + 4g (trace)
6	Solvent	Et ₃ N	CS ₂	24 h	2 (major) + 3g (28%) + 4g (22%)
7	5.0	KOH	CH ₂ Cl ₂	24 h	3g (10%) + 4g (trace)
8	5.0	KOH	THF	24 h	3g (22%) + 4g (16%)
9	5.0	KOH	CH ₃ COCH ₃	24 h	3g (16%) + 4g (25%)
10	5.0	KOH	CH ₃ OH	24 h	3g (11%) + 4g (36%)
11	5.0	KOH	DMF	24 h	3g (trace) + 4g (45%)
12	5.0	KOH	DMSO	24 h	3g (trace) + 4g (49%)
13	5.0	Et ₃ N	ball milling	40 min	2 (major) + 3g (26%)
14	5.0	Na ₂ CO ₃	ball milling	40 min	3g (57%) + 4g (trace)
15	5.0	K ₂ CO ₃	ball milling	40 min	3g (61%) + 4g (trace)
16	5.0	NaOH	ball milling	40 min	3g (92%)
17	5.0	^t BuOK	ball milling	40 min	3g (86%)
18	5.0	KOH	ball milling	40 min	3g (98%)
19	3.0	KOH	ball milling	40 min	3g (58%) + 4g (27%)
20	1.0	KOH	ball milling	40 min	3g (trace) + 4g (93%)

^a Reactions were carried out with 4-methylaniline **1g** (10.0 mmol), CS₂ (designated usage) and base (10.0 mmol) at room temperature; 1800 rpm (30 Hz) vibration frequency for ball-milling and 15 mL solvent for stirring in solution. ^b Determined by HPLC analysis based on 4-methylaniline.

Table 1. Original reaction scheme and optimization data retained.

4. Scope of Aromatic Isothiocyanate Synthesis

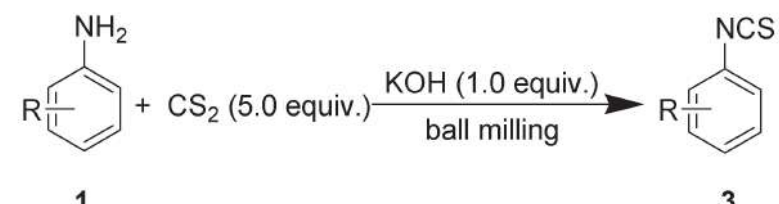
Following optimization, the authors examined a series of substituted anilines under the selected conditions (aniline, 5.0 equivalents of CS₂, 1.0 equivalent of KOH, room temperature, 30 Hz). The substrate scope includes ortho-, meta-, and para-substituted anilines and demonstrates that both electron-donating and electron-withdrawing substituents can be accommodated.

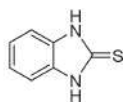
Electron-rich substrates were particularly responsive. Unsubstituted aniline afforded 85% of the corresponding isothiocyanate in 40 min, while 2-methyl-, 2-methoxy-, 3-methyl-, 4-methyl-, and 4-methoxy-substituted substrates provided 91–96% yields within 40–45 min. These results indicate that the mechanochemical environment can deliver rapid conversion for nucleophilic, electron-rich anilines without requiring a conventional solvent.

Electron-withdrawing substituents generally required longer milling times and gave moderate to good yields. For example, 4-bromo-, 4-chloro-, and 4-nitroanilines required 60–90 min and afforded 83%, 75%, and 61% yields, respectively. The 3,4-dichloro substrate was more demanding and gave 52%. The particularly important comparison was the 4-nitro substrate: conventional stirring with KOH and CS₂ for 48 h produced only a trace of the desired isothiocyanate, whereas ball milling for 90 min provided a 61% isolated yield.

The 2-aminophenyl substrate behaved differently. Instead of furnishing the corresponding simple isothiocyanate, it afforded the cyclic sulfur–nitrogen product represented as **4l** in the original table, in 97% yield after 40 min. This observation illustrates that additional nucleophilic functionality can redirect the reaction pathway and should be considered when evaluating the chemoselectivity of the method.

Table 2 Mechanochemical synthesis of phenyl isothiocyanates **3** from anilines **1** and CS₂ promoted by KOH^a

				
Entry	R	Product 3	Time (min)	Yield (%) ^b
1	H	3a	40	85
2	2-Me	3b	40	92
3	2-OMe	3c	40	91
4	2-Cl	3d	70	71
5	3-Me	3e	45	93
6	3-Cl	3f	90	72
7	4-Me	3g	40	96
8	4-OMe	3h	40	95
9	4-Br	3i	60	83
10	4-Cl	3j	90	75
11	4-NO ₂	3k	90	61
12	3,4-Cl	3l	90	52
13	2-NH ₂	4l	40	97



^a Reactions were carried out with aniline **1** (10.0 mmol), CS₂ (50.0 mmol) and KOH (10.0 mmol) at room temperature at a vibration frequency of 30 Hz. ^b Isolated yield combined from two parallel runs via Retsch MM400 ball miller, by direct separation of the reaction mixtures through short column chromatography.

Table 2. Original reaction scheme and substrate-scope data retained unchanged

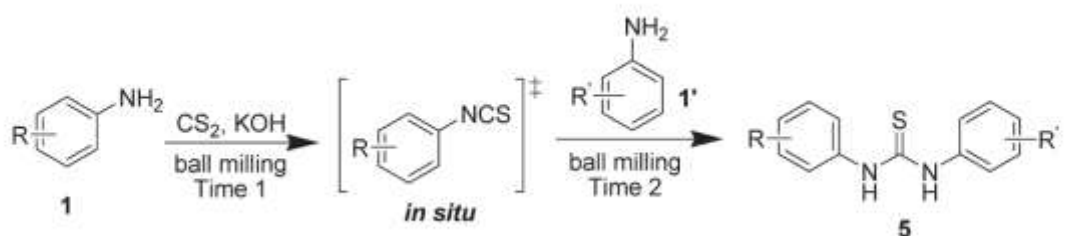
5. One-Pot Access to Unsymmetrical Thioureas

A major extension of the method is the direct use of selected in situ generated isothiocyanates as electrophilic partners for a second aniline. This approach avoids the preliminary isolation and handling of isothiocyanates, which can otherwise introduce an additional operation and safety concern. In the reported sequence, the first aniline is milled with CS₂ and KOH to generate the isothiocyanate, after which an equimolar second aniline is introduced and milling is continued.

The second coupling step was rapid, generally requiring 30–75 min, and gave unsymmetrical phenylthioureas in 85–96% isolated yields. The examples include combinations of methyl-, methoxy-, bromo-, chloro-, and unsubstituted anilines. The highest reported yield in this series was 96% for product 5k. Importantly, the two-stage operation is performed in one reaction vessel, while isolation is accomplished after the reaction by treatment with diluted HCl, ultrasonic irradiation, and Büchner filtration.

From a review perspective, this one-pot extension is one of the most useful aspects of the study because it converts the mechanochemical generation of an unstable or reactive intermediate into a direct bond-forming sequence. The approach therefore illustrates how mechanochemistry can be used not merely to accelerate an individual transformation, but also to integrate consecutive synthetic operations.

Table 3 Mechanochemical one-pot synthesis of unsymmetrical phenylthioureas **5** by addition of phenyl amines **1'** on in situ generated isothiocyanates^a



Entry	R	R'	Product 5	Time 1 (min)	Time 2 (min)	Yield (%) ^b
1	4-Me	2-Me	5a	40	35	89
2	4-Me	3-Me	5b	40	35	92
3	4-Me	4-OCH ₃	5c	40	30	95
4	4-Me	4-Br	5d	40	45	92
5	4-Me	4-Cl	5e	40	60	87
6	4-Me	H	5f	40	40	94
7	4-OMe	4-Cl	5g	40	60	90
8	4-OMe	3-Cl	5h	40	60	89
9	4-OMe	2-Cl	5i	40	75	85
10	4-OMe	4-Br	5j	40	60	94
11	3-Me	4-OMe	5k	45	40	96
12	3-Me	4-Br	5l	45	60	91

^a Reactions were carried out with aniline **1** (10.0 mmol), CS₂ (50.0 mmol), KOH (10.0 mmol) and afterward added aniline **1'** (10.0 mmol) at room temperature at a vibration frequency of 30 Hz. ^b Isolated yield combined from two parallel runs.

Table 3. Original reaction scheme and unsymmetrical thiourea data retained

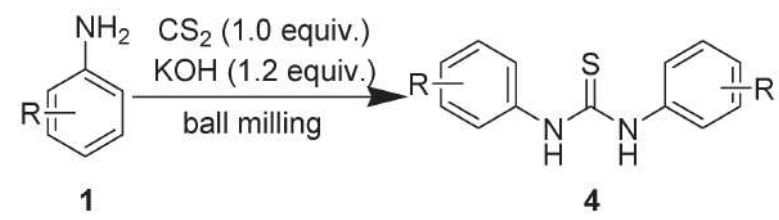
6. Chemoselective Formation of Symmetrical Thioureas

The same reaction platform can be redirected toward symmetrical thioureas by lowering the CS₂ loading to 1.0 equivalent. The optimized conditions for this branch employ aniline (5.0 mmol), CS₂ (5.0 mmol), and KOH (6.0 mmol) at room temperature and 30 Hz. A broad set of substituted anilines was examined, and the products were obtained in generally good to excellent yields.

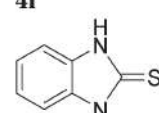
Electron-rich anilines again performed particularly well. The parent thiourea **4a** was obtained in 86%, while the 4-methyl and 4-methoxy derivatives gave 93% and 95%, respectively. The 2-amino substrate afforded **4l** in 97% yield. In contrast, the electron-deficient 4-nitro substrate gave 43%, confirming that substrate electronics remain an important determinant of efficiency even under mechanochemical conditions.

The comparison between Tables 2 and 4 highlights the synthetic flexibility of the protocol. With essentially the same mechanochemical activation and base, altering the CS₂ stoichiometry changes the dominant product class from isothiocyanate to symmetrical thiourea. This tunability provides a simple way of adapting the method to different synthetic objectives without changing the fundamental reaction platform.

Table 4 Mechanochemical synthesis of symmetrical phenylthioureas **4** from anilines **1** and CS₂ promoted by KOH^a



Entry	R	Product 3	Time (min)	Yield (%) ^b
1	H	4a	45	86
2	2-CH ₃	4b	45	84
3	2-OCH ₃	4c	50	87
4	2-Cl	4d	90	74
5	3-CH ₃	4e	50	88
6	3-Cl	4f	75	75
7	4-CH ₃	4g	40	93
8	4-OCH ₃	4h	40	95
9	4-Br	4i	60	82
10	4-Cl	4j	80	77
11	4-NO ₂	4k	90	43 ^c
12	2-NH ₂	4l	40	97



^a Reactions were carried out with aniline **1** (5.0 mmol), CS₂ (5.0 mmol) and KOH (6.0 mmol) at room temperature at a vibration frequency of 30 Hz. ^b Isolated yield combined from two parallel runs. ^c Isolated yield from column chromatography.

Table 4. Original reaction scheme and symmetrical thiourea data retained

7. Reaction Pathway and Selectivity Considerations

The reported chemistry is consistent with an initial reaction between the aniline and CS₂ under basic conditions to form a dithiocarbamate salt. The original optimization scheme explicitly depicts this species as intermediate 2. Subsequent decomposition gives the isothiocyanate when excess CS₂ is present. The study does not establish a detailed step-by-step mechanistic sequence, so the mechanistic interpretation should be regarded as a reaction-pathway rationale rather than a fully demonstrated mechanism.

The observed product distribution nevertheless provides useful evidence for the role of reaction parameters. Triethylamine favors accumulation of the dithiocarbamate intermediate, whereas KOH strongly favors conversion toward isothiocyanate under milling. In addition, insufficient CS₂ increases the relative formation of thiourea. These results suggest that both the basicity of the reaction medium and the availability of CS₂ control the competition among dithiocarbamate, isothiocyanate, and thiourea pathways.

Mechanochemistry adds a further dimension to this selectivity. The reported acceleration under solvent-free conditions is attributed to the high effective concentration of reactants and the mechanical energy supplied by the mill. The results therefore support the broader concept that physical activation can alter reaction efficiency and practical selectivity in addition to simply replacing a conventional heating or stirring step.

8. Green-Chemistry and Process Advantages

Several features of the methodology are consistent with the objectives of greener synthesis. First, the core isothiocyanate formation is conducted without an added reaction solvent. Second, inexpensive KOH serves both as base and decomposition reagent, eliminating the need for separate harsh or toxic desulfurylating reagents. Third, the

reactions are performed at room temperature and reach completion rapidly for many substrates. Fourth, the one-pot thiourea sequence avoids isolation and handling of selected intermediate isothiocyanates.

The work-up is also relatively simple. Isothiocyanates were isolated by short-column chromatography using hexane/ethyl acetate (20:1, v/v), while the unsymmetrical thioureas were isolated after diluted-HCl treatment, ultrasonic irradiation, and filtration. These operations are substantially simpler than procedures that require preparation and handling of activated thiocarbonyl reagents.

At the same time, a balanced assessment should recognize limitations. The protocol uses a relatively large excess of CS₂ for selective isothiocyanate formation, and electron-deficient substrates generally require longer milling times and may give lower yields. The study also reports complicated selectivity for 1,4-phenylenediamine, showing that multifunctional substrates are not universally compatible. In addition, the work was conducted at laboratory scale, so questions concerning scale-up, milling energy efficiency, equipment design, CS₂ recovery, and broader process metrics were not addressed in the reported study.

9. Comparative Interpretation of the Reported Reaction Classes

Taken together, the four original data sets reveal a coherent reaction-design principle. Table 1 establishes the optimal mechanochemical environment and demonstrates that KOH/CS₂ stoichiometry controls product selectivity. Table 2 shows that the optimized conditions can accommodate a range of substituted anilines for isothiocyanate synthesis. Table 3 demonstrates that selected in situ generated isothiocyanates can be intercepted directly by a second aniline to form unsymmetrical thioureas. Table 4 then shows that lowering the CS₂ loading provides an independent route to symmetrical thioureas.

The most significant conceptual outcome is therefore the convergence of three transformations on a common mechanochemical platform: formation of aromatic isothiocyanates, one-pot formation of unsymmetrical thioureas, and direct formation of symmetrical thioureas. Rather than treating these as unrelated reactions, the study demonstrates how reagent stoichiometry and intermediate capture can be used to navigate among different thiocarbonyl products.

10. Limitations and Future Perspectives

The reported findings suggest several directions for further development. Expansion beyond the demonstrated aniline series would help define the functional-group tolerance of the methodology, particularly for aliphatic amines, heteroarylamines, multifunctional substrates, and more complex molecular frameworks. Greater attention to the behavior of strongly electron-withdrawing substrates could also improve the practical utility of the method.

From a process perspective, future studies could examine the minimum effective CS₂ loading, solvent-free recovery strategies, milling parameters, scale-up, and energy consumption. Continuous or larger-scale mechanochemical equipment could potentially address some of these issues, although such developments are outside the scope of the reported work.

The authors also point toward a broader synthetic opportunity: in situ generated isothiocyanates could be combined with other nucleophiles to access additional thiocarbonyl compounds and sulfur–nitrogen-containing heterocycles in one-pot operations. This proposal is a logical extension of the demonstrated intermediate-capture strategy and provides a useful framework for subsequent mechanochemical synthesis development.

11. Conclusion

The study provides a concise demonstration of how mechanochemical activation can simplify the synthesis of aromatic isothiocyanates and thioureas. Ball milling with KOH and CS₂ overcomes the poor conversion and selectivity observed in the investigated solution-phase experiments, while the amount of CS₂ provides a practical means of controlling product class. Under optimized conditions, a broad range of substituted anilines affords isothiocyanates in 52–97% isolated yield, with many electron-rich substrates reacting within 40–45 min. Selected in situ generated isothiocyanates can then be converted directly into unsymmetrical thioureas in 85–96% yield, whereas 1.0 equivalent of CS₂ enables formation of symmetrical thioureas in 43–97% yield.

Overall, the methodology illustrates the value of solvent-free mechanical activation for improving reaction rate, simplifying work-up, and avoiding conventional harsh decomposition reagents. Its principal strengths are operational

simplicity, inexpensive reagents, rapid reaction times, and the ability to access several product classes from a common starting-material platform. Its limitations—particularly the need for excess CS₂ in the isothiocyanate branch, reduced performance with strongly electron-deficient substrates, and limited scale-up information—also define clear opportunities for future research.

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