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Mechanochemical Strecker Reaction: Access to α -Aminonitriles and Tetrahydroisoquinolines under Ball Milling Conditions

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Abstract: A mechanochemical version of the Strecker reaction for the synthesis of α -aminonitriles was developed. The milling of aldehydes, amines and potassium cyanide in the presence of SiO₂ afforded the corresponding α -aminonitriles in good to high yields. The high efficiency of the mechanochemical Strecker-type multicomponent reaction allowed the one-pot synthesis of tetrahydroisoquinolines after a subsequent internal N-alkylation reaction.

Introduction

Mechanosynthesis of organic molecules has grown rapidly over the past two decades providing new alternatives to conduct chemical transformations faster, cleaner and more selectively.^[1] The current state of mechanochemical organic syntheses by milling, grinding or shearing, includes organocatalytic reactions.^[2] peptide syntheses,^[3] numerous metal-catalyzed reactions^[4] including C–H functionalizations,^[5] polymer formation,^[6] enzymatic reactions^[7] among others.^[8] Particularly interesting are the reports on mechanochemical multicomponent reactions (MCRs),^[9] which allow the efficient coupling of several building blocks in a single step to afford highly functionalized organic molecules. Recently, examples of the mechanochemically induced Biginelli, [9a] Ugi and Passerini reactions^[9b] have exemplified some of the advantages of mechanochemistry such as the reduction or elimination of the solvent, shorter reaction times, clean reaction mixtures and simple work-up procedures. Consequently, the combination between MCRs and mechanochemistry clearly strengthen the well-known advantages of both approaches in the effort to develop environmentally friendly synthetic strategies, since the generation of large amounts of waste, especially from solvents used in the reactions or during the purification of the intermediates is avoided.

The first documented, and perhaps the most symbolic MCR in organic synthesis is the Strecker reaction reported by Adolph Strecker as early as 1850.^[10] This three-component reaction between aldehydes, ammonia and hydrogen cyanide yields α -aminonitriles, which are extremely valuable intermediates for the synthesis of nitrogen containing heterocycles and natural products.^[11] However, probably the most important application of α -aminonitriles is found in the synthesis of α -amino acids upon

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hydrolysis of the nitrile group.^[12] In fact, α -aminonitriles have been considered as key intermediates in the classical Miller experiment to explain the formation of amino acids under simulated early earth conditions (methane, ammonia, water, and hydrogen) in spark-discharge flasks.^[13] Therefore, due to the fundamental importance of the Strecker reaction and particularly to the simple conditions required for the mechanochemical activation of a system in an early earth scenario (*e.g.* the collision of two stones), we wondered about the potential of ball milling to develop a mechanochemical version of the Strecker reaction for the formation of α -aminonitriles.

Results and Discussion

To test the idea of a mechanochemical version of the Strecker reaction, we began conducting a simple experiment milling benzaldehyde (1a), ammonium chloride and potassium cyanide (1.0:1.1:1.1 equiv) in a planetary ball mill using stones as the milling media (Scheme 1). To our delight, after 3 h of milling at 700 rpm the analysis of the reaction mixture by ¹H NMR revealed complete consumption of **1a** and the presence of the α aminonitrile 2 (65%), imine 3 (7%) and cyanohydrin 4 (27%) (Scheme 1). With the aim to suppress the formation of cyanohydrin 4, a step-wise experiment was conducted in the ball mill by first preforming the imine 3 (1 h of milling), followed by the addition of KCN (2 h of milling). The α -aminonitrile 2 formed upon milling was then acetylated by subsequent addition of Ac₂O into the milling vessel (1 h of milling), to facilitate its isolation as Ac-2 in 80% yield over three successive mechanochemical steps, representing an improvement to the typical solution-based procedures.^[14]



Scheme 1. Mechanosynthesis of the $\alpha\text{-aminonitrile}\ \textbf{2}$ using stones as milling media.

The formation of **2** under such simple ball milling conditions prompted us to carry out a systematic study of the mechanochemical Strecker reaction. In order to expand the potential application of this approach, NH₄Cl was then replaced by benzylamine (**5a**) and the reaction was repeated (Table 1, entry 1). Also this time, the analysis of the reaction mixture by ¹H NMR after 3 h of milling indicated the complete consumption of benzaldehyde (**1a**) and showed the presence of the expected α aminonitrile **6a** in 16% (Table 1, entry 1). In contrast, a control experiment in solution (acetonitrile) under similar conditions generated mainly imine **7a** and only traces of the α -aminonitrile **6a** (<2%). In order to favor the formation of the α -aminonitrile,

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readily available silica gel (denoted as SiO₂) was added to the milling vessel along with the stones. SiO₂ is a common milling auxiliary in mechanochemistry,^[9b,15] and due to its intrinsic acidic properties and the ability to absorb moisture, SiO₂ was thought to be appropriate here to facilitate the formation of the imine and to enhance the cyanation step in the ball mill. Moreover, unlike many of the typical Brønsted and Lewis acid catalysts used for the Strecker reaction,^[11b] silica gel is inexpensive, easy to handle, non-toxic, and potentially a reusable promoter for this transformation. Pleasantly, in the presence of SiO₂, the milling of **1a**, **5a**, and KCN for 3 h led exclusively to the formation of the α -aminonitrile **6a** (Table 1, entry 2).

The use of inexpensive stones as the milling media in ball mills is perceived very advantageous from a practical and economical point of view. However, the difference in hardness between the milling vessels and the stones could in principle cause abrasion, thereby altering the total mass of the stones and potentially affecting the outcome of the experiments. In our case, however, the use of stones in combination with ZrO_2 milling vessels resulted in minimal wear of the milling media after several reactions, causing no effect on the selectivity or in the yield of the reaction. Nevertheless, in order to assure consistency in the following experiments, the mechanochemical Strecker reaction was subsequently conducted in stone-based agate milling vessels with balls of the same material giving identical results (Table 1, entries 2-3).

Intrigued by the excellent results observed using SiO₂ as a promoter, other additives such as fused sand and powder quartz were also tested in the ball mill. These additives also facilitated the formation of the α -aminonitrile **6a**, although to a lesser extent (Table 1, entries 4-5). Then, montmorillonite clays, which are known to function as Brønsted or Lewis solid acids were examined as potential activators of the mechanochemical Strecker reaction.^[11c,d] Under milling conditions, the commercial available montmorillonite K10 proved to be highly active affording α -aminonitrile **6a** almost exclusively (Table 1, entry 6). Similarly, other solid catalysts with Lewis acid sites such as titanium oxide and alumina were screened. Unfortunately, after 3 h of milling these oxides displayed a lower activity than SiO₂ to mediate the formation of the product 6a (Table 1, entries 8-9). Anhydrous MgSO₄, commonly used as a drying agent, was also found to promote efficiently the Strecker reaction yielding almost exclusively α -aminonitrile **6a** (Table 1, entry 10). A control experiment in the ball mill using anhydrous Na₂SO₄ instead, led to a mixture containing mainly imine 7a featuring the importance of the Lewis acidity of MgSO4 to facilitate the cyanation step (Table 1, entries 10-11). Recently, the properties of MgSO4 as Lewis acid in the N-alkylation of primary amides were observed to overweigh the originally intended role of MgSO4 as desiccant in the reaction in toluene.[16]

Out of the set of potential activators, which included typically considered "inert" milling auxiliaries, SiO_2 was chosen as the ideal promoter for the Strecker reaction based on its performance, availability and matching nature with the agate milling media (silicon dioxide). Further screening of the reaction conditions made evident one of the advantages of the mechanochemical Strecker approach when the milling time of the reaction was reduced from 3 h to 1 h without affecting the formation of **6a**. In contrast, control experiments by conventional

Table 1. Screening of the mechanochemical reaction conditions.^[a]



Entry	Additive	Vessel/ball bearing	Conv. [%] ^[b]	Ratio of 6a:7a [%] ^[b]
1		ZrO ₂ /stones ^[c]	99	16:84
2	SiO ₂	ZrO ₂ /stones	98	99:1
3	SiO ₂	Agate ^[d]	99	99:1
4	Powder quartz ^[e]	Agate	98	47:53
5	Sand	Agate	97	38:62
6	Montmorillonite K10 ^[f]	Agate	97	97:3
7	Montmorillonite K30 ^[f]	Agate	98	87:13
8	TiO ₂ ^[g]	Agate	99	33:67
9	$AI_2O_3^{[h]}$	Agate	99	68:32
10	MgSO ₄	Agate	99	98:2
11	Na_2SO_4	Agate	99	9:91

[a] Reaction conditions: **1a** (53.1 mg, 0.5 mmol), **5a** (53.6 mg, 0.5 mmol), KCN (35.8 mg, 0.55 mmol), and the additive (240 mg) were milled in a planetary ball mill. [b] Determined by ¹H NMR spectroscopy. [c] Use of a 12 mL ZrO₂ milling vessel with 5 stones (5.50 g). [d] Use of a 12 mL agate milling vessel with 20 agate balls of 5 mm in diameter. [e] Powder quartz obtained after milling a natural quartz crystal. [f] The montmorillonite was dried at 120°C for 4 h prior to use. [g] TiO₂ as anatase. [h] Neutral Al₂O₃.

stirring in solution or under neat conditions were found to be less efficient leading to lower conversion and selectivity even after 3 h of reaction (Figure 1).

Subsequently, the recyclability of SiO₂ and scalability of the mechanochemical Strecker were evaluated. Both filtration and



Figure 1. SiO_2 -promoted Strecker reaction between 1a, 5a and KCN under neat, solution and ball milling conditions.

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Table 2. Mechanochemical Strecker reaction of aromatic and aliphatic aldehydes with benzylamine. $^{[a]}$

[a] Reaction conditions: **1a-I** (0.5 mmol), **5a** (53.6 mg, 0.5 mmol), KCN (35.8 mg, 0.55 mmol), and SiO₂ (240 mg) were milled in a planetary ball mill at 700 rpm for 3 h using a 12 mL agate jar with 20 agate balls of 5 mm in diameter.

centrifugation of the reaction mixture with a minimal amount of organic solvent allowed an easy separation of the silica gel, which upon washing with deionized water and drying at 120 °C for 4 h was reused. This recovered silica gel remained active in two subsequent milling cycles with just slight erosion in activity (2nd cycle: conv. 99%, **6a:7a**; 95:5; 3rd cycle: conv. 96%, **6a:7a** 87:13). On the other hand, a 10-fold scaled-up experiment in the planetary ball mill using a 45 mL milling vessel afforded the α -aminonitrile **6a** in 88% yield, which was consistent with the 90% of **6a** obtained in the standard 0.5 mmol scale reaction (Table 2, entry 1).

Next, the substrate scope of the mechanochemical Strecker reaction was evaluated. Again, benzylamine (5a) was used as the amine component and a series of aldehydes were tested in the presence of KCN and SiO₂ (Table 2). Various benzaldehydes bearing electron-donating groups afforded the corresponding α -aminonitriles **6a-c** in good yields (79-90%) after 3 h of milling. Aromatic aldehydes with electron-withdrawing substituents on the arene led to the formation of the α -aminonitriles 6d-g in high yields (91-97%). In the case of heterocyclic 3-pyridinecarboxaldehyde aldehvdes. (**1h**), 2-thiophenecarboxaldehyde (1i) and furfural (1j) the products (6h-j) were isolated in good yields (79-90%). Finally, cyclohexanecarboxaldehyde and cinnamaldehyde reacted with 5a and KCN providing the corresponding α -aminonitriles **6k** and **6l** in 70% and 93% yield respectively.

Then, the Strecker reaction was evaluated using different amines [aniline (5b), piperidine (5c), morpholine (5d) and methylammonium chloride (5e)] with benzaldehyde (1a) and KCN (Table 3, entries 1-4). Once again, the milling of the three



Table 3. Mechanochemical Strecker reaction of aldehydes, ketones and

various amines.

[a] Reaction conditions: carbonyl compound (0.5 mmol), amine (0.5 mmol), KCN (35.8 mg, 0.55 mmol), and SiO₂ (240 mg) were milled in a planetary ball mill at 700 rpm for 3 h using a 12 mL ZrO₂ milling jar with 20 agate balls of 5 mm in diameter. [b] Milling of **1a**, **5e** and KCN in the absence of silica also generated the product **8d**.

components in the presence of SiO₂ afforded the corresponding α -aminonitriles **8a-d** in yields ranging from 70% to 95%. In addition, the more challenging *p*-toluenesulfonamide (**5f**)^[17] was utilized as amino component. After 3 h of milling sulfonylamidonitrile **8e** was obtained in 45%. (Table 3, entry 5). This result was remarkable considering the low nucleophilicity of the sulfonamide. In accord with this notion the formation of **8e** was not observed when the reaction was performed in solution confirming the superiority of the ball milling process. Thus, stirring a mixture of **1a**, **5f**, KCN, and SiO₂ in acetonitrile-d₃ at ambient temperature for 3 h afforded none of the expected sulfonylamidonitrile but the corresponding sulfonylimine in trace quantities (as observed by ¹H NMR spectroscopy).

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Next, the potential use of ketones as carbonyl components was investigated. Pleasantly, substrates such as acetophenone (**7a**) and cyclohexanone (**7b**) proved also to be suitable for the mechanochemical Strecker reaction affording the corresponding α -aminonitriles **8f** and **8g** in good yields (Table 3, entries 6 and 7). On the other hand, benzophenone (**7c**) was found to be unreactive under neat the milling conditions, and no product formation was observed (Table 3, entry 8). Also the attempts to facilitate the Strecker reaction by liquid-assisted grinding (LAG),^[18] using either nitromethane or acetonitrile ($\eta = 0.25$) remained unsuccessful. As **7c**, 4-fluorobenzophenone and 3,3'-bis(trifluoromethyl)benzophenone did not react with benzylamine and KCN, indicating a general insufficient reactivity of diaryl ketones due to steric effects and increased aryl/carbonyl conjugation.

Finally, we decided to demonstrate the value of the mechanochemical approach by conducting a one-pot Strecker N-alkylation sequence synthesis. Milling *o*-formyl phenethyl bromide (**6m**) with benzylamine or aniline and KCN in the presence of SiO₂, afforded tetrahydroisoquinolines (THIQs) **9a-b** in high yields (Scheme 2). This one-pot three-component sequential reaction exemplifies an advance in complexity of mechanochemical design to generate privileged structural scaffolds such as THIQs, which are known for their broad biological activities and importance as building blocks in the synthesis of natural products containing the THIQ core.^[19]



Scheme 2. One-pot three-component mechanosynthesis of the tetrahydroisoquinolines 9a-b.

Conclusions

In summary, we developed an efficient mechanochemical approach to synthesize α -aminonitriles through a one-pot threecomponent Strecker reaction. The use of readily available materials such as Montmorillonite, MgSO4 and, in particular, SiO₂, proved to enhance the cyanation step affording the α aminonitriles derived from aldehydes, ketones, diverse amines and KCN in good to high yields. The high efficiency of the Strecker reaction allowed the one-pot synthesis of tetrahydroisoquinolines in excellent yields after a subsequent internal Nalkylation reaction. Finally, it is important to point out the remarkable chemical reactivity observed in the mechanochemical Strecker reaction by typically considered "inert" milling auxiliaries. This observation clearly indicates the latent potential of common additives to induce transformations in the ball mills. Hence, the intrinsic properties of added auxiliaries should also be taken into account during the early planning stage of a mechanosynthesis. The successful synthesis of α -aminonitriles in the ball mill now opens the possibility to explore the mechanochemical formation of α -amino acids upon enzymatic^[7] or chemical hydrolysis^[20] of the nitrile group, and research along these lines is currently ongoing in our group.

Caution! Potassium cyanide is toxic and may also release highly toxic hydrogen cyanide. All operations involving KCN should be conducted in a well-ventilated fume hood.

Typical procedure for the Strecker reaction in the planetary mill: A mixture of benzaldehyde (**1a**) (53.1 mg, 0.50 mmol), benzylamine (**5a**) (53.6 mg, 0.50 mmol), KCN (35.8 mg, 0.55 mmol) and SiO₂ (240 mg) was milled in a 12 mL agate milling vessel with 20 agate milling balls of 5 mm in diameter at 700 rpm for 3h. After the milling was complete, the resulting powdery reaction mixture was extracted with ethyl acetate or CH_2Cl_2 , washed with aqueous saturated NaHCO₃ solution and brine. The combined organic layers were dried over anhydrous Na₂SO₄, concentrated *in vacuo* and further dried under reduced pressure to furnish the product.

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Keywords: Mechanochemistry • Ball milling • Strecker reaction • SiO₂ • Tetrahydroisoquinolines.

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