



Digest paper

Recent advances in mechanochemical C–H functionalization reactions

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ARTICLE INFO

Article history:

Received 15 September 2017

Revised 4 December 2017

Accepted 6 December 2017

Available online 6 December 2017

Keywords:

Mechanochemical
C–H functionalization
Ball milling
Solvent-free

ABSTRACT

The mechanochemical synthesis has provided a greener alternative to solution-based approaches by eliminating the use of organic solvents and reducing the energy consumption. The C–H functionalization is among the most concise and economical synthetic strategies. The combination of the benefits from these two methods provides new opportunities to further increase the efficiency and sustainability of organic synthesis. In this digest, we aim to provide a brief overview of the recent advances in mechanochemical C–H functionalization reactions.

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Introduction

Sustainable and environmentally benign synthetic methods have been attracting increasing attention.¹ The pursuit of greener and more efficient processes and techniques to prepare various organic molecules continues challenging organic chemists and their synthetic capabilities. Mechanochemical organic synthesis offers a green alternative to solution-based synthetic approaches for the construction of diversified organic molecules by eliminating the use of organic solvents and lowering the energy consumption.² The mechanical forces coming from manual grinding or high energy ball-milling are usually utilized to drive the mechanochemical reactions under solvent-free or solvent-less conditions, which

allow intimate contacts between reactants during mechanochemical reactions. This interesting activation mode combined with some inherent characteristics of solid state matter, such as reduced molecular motion and ordered molecular alignment, often enables unique chemical behaviors distinct from those in solution. On the other hand, the C–H functionalization is among the most concise and economical synthetic strategies, which allows the direct modification of simple molecules without the need of pre-functionalization.³ Its versatility has resulted in an explosive increase in the use of C–H functionalization as a sustainable alternative to various synthetic transformations. Obviously, the implementation of mechanochemistry in C–H functionalization would provide new opportunities to further increase the efficiency and sustainability of organic synthesis and to explore new reactivity not readily accessible in solution-based reactions. In this digest, we aim to provide a brief overview of the recent advancements in

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mechanochemical reactions involving C–H bond functionalization. In addition, we would like to refer the interested reader to recently published excellent reviews relevant to mechanochemical organic synthesis.³

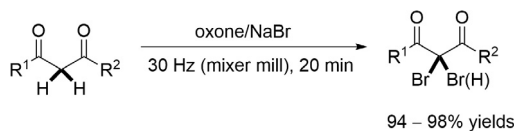
CH functionalization of activated methylene compounds

One of the simplest ways to achieve direct functionalization of C–H bonds is to produce carbanions or their synthetic equivalents from relatively acidic molecules. In this regard, active methylene compounds are ideal substrates for C–H functionalization because they undergo readily deprotonation and enolization. As no or only a minute amount of solvent is used, mechanochemical reactions usually proceed at the maximum concentrations with reaction rates higher than solution-based reactions. The mechanochemical bromination of 1,3-dicarbonyl compounds was demonstrated by the Wang group using a combination of oxone and sodium bromide as the brominating reagent (Scheme 1).⁴ It was found that the reaction with cyclic 1,3-dicarbonyl compounds selectively gave dibrominated products, whereas monobromination occurred exclusively with acyclic substrates even in presence of an excess amount of NaBr. This observation was attributed to the distinct reactivities of cyclic and acyclic substrates. Toxic and hazardous reagents were avoided in this method and the mechanochemical conditions allowed the reaction to proceed rapidly and selectively at room temperature.

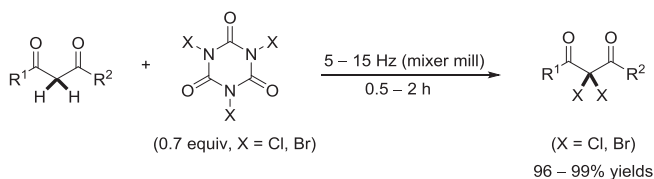
By using the trihaloisocyanuric acids as the halogenating reagents, Moorthy and coworkers found that both cyclic and acyclic 1,3-diketones underwent efficient dihalogenation under ball milling conditions, indicating the superior reactivity of trihaloisocyanuric acids over other halogenating reagents (Scheme 2).⁵

As a result of the unique electronic property of fluorine atom, the fluorinated molecules often display superior performances over their non-fluorinated counterpart. Accordingly, the synthetic methods to introduce fluorine atom(s) under mild reaction conditions have received increasing attention. Recently, a selective mechanochemical fluorination of 1,3-dicarbonyl compounds with Selectfluor™ was reported by Browne and coworkers (Scheme 3).⁶ The selectivity towards mono- and difluorinated products could be easily manipulated with different additives. Mono-fluorinated products were selectively obtained in presence of a small amount of acetonitrile, whereas the use of Na₂CO₃ as an additive promoted difluorination. Similar to other mechanochemical halogenations of activated methylene compounds, the fluorination under ball milling conditions proceeded more rapidly compared to solution-based reactions.

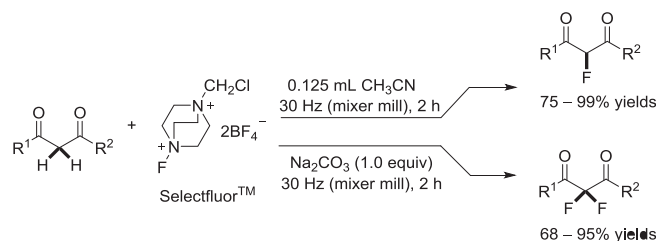
The enantioselective fluorination of 1,3-dicarbonyl compounds under mechanochemical conditions was achieved by the Xu group.



Scheme 1. Bromination of 1,3-dicarbonyl compounds.



Scheme 2. Halogenation of 1,3-diketones.

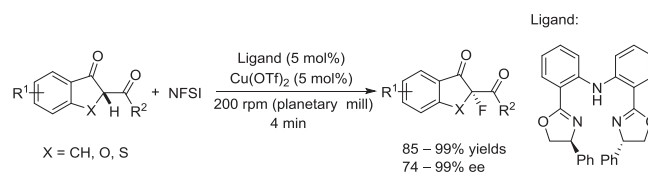


Scheme 3. Fluorination of 1,3-dicarbonyl compounds.

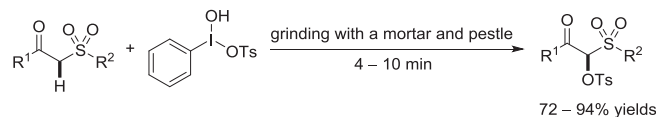
In presence of a diphenylamine-linked bis(oxazoline)-Cu(OTf)₂ complex, various fluorinated β -keto esters were produced in excellent yields with good enantioselectivities under ball-milling conditions using *N*-fluorobenzenesulfonimide (NFSI) as the fluorination reagent (Scheme 4).⁷ The reactions employing other Lewis acids, such as Ni(OTf)₂, Zn(OTf)₂, and Sc(OTf)₃ gave low enantioselectivities. Interestingly, the reaction in absence of a catalyst also proceeded effectively under the ball-milling conditions, which suggested that the enantioselective reaction pathway in presence of the chiral catalyst must be significantly faster than the non-catalyzed background reaction. For fluorination of acyclic β -keto esters, mechanochemical reactions allowed higher enantioselectivities compared to solution-based ones, which indicated the influence of structural flexibility under solvent-free conditions is not as significant as that in solution.

In addition to various halogenations, tosyloxylation of activated methylene compounds was also achieved under mechanochemical conditions. The Varma group found that the α -tosyloxylation of β -keto sulfones proceeded expeditiously at room temperature by simply grinding with [hydroxyl(tosyloxy)iodo]benzene (HTIB) for 4–10 min (Scheme 5).⁸ The mechanochemical activation was essential for this transformation as only a trace amount of the product was observed by keeping the homogenous mixture of β -keto sulfones and HTIB for 10 h. Notably, column chromatography was not required for the purification of the products, which suggested the high efficiency of the reaction under mechanochemical conditions.

Amino acids are important biologically active molecules, basic components for proteins, and valuable building blocks for chiral catalysts. The alkylation of glycine-derived Schiff bases is a straightforward method to prepare chiral amino esters, which could lead to chiral amino acids after deprotection. Traditionally, these reactions were carried out in a two-phase system as a result of the use of phase-transfer catalysts. Lamaty and coworkers demonstrated that the solvent-free ball-milling conditions were also effective for this transformation, by providing excellent conversions and yields (Scheme 6).⁹ The enantioselectivity of this



Scheme 4. Enantioselective fluorination of β -keto esters.



Scheme 5. Tosyloxylation of β -keto sulfones.

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