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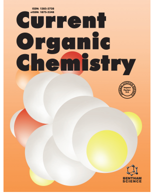
REVIEW ARTICLE



A Synopsis of Ball Milling Organic Synthesis in the Last 25 Years

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Abstract: Important progress in the transfer of organic reactions from solution conditions to automated solid-state synthesis was published a quarter of a century ago. Since then, ball-milling organic reactions have been slowly accepted by the chemical community as an additional synthetic tool, and the area of its application is rapidly expanding. These developments in mechanochemical synthesis are illustrated with selected literature examples.

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Keywords: Organic synthesis, solid-state reactions, mechanochemistry, mechanochemical synthesis, manual grinding, fullerene derivatives.

1. INTRODUCTION

Solid-state organic synthesis has been carried out initially with mortar at pestle by manual grinding [1]. It has been a quarter of the century since the seminal publication by Wang and co-workers [2], from Kyoto University on the application of ball milling in the organic synthesis of fullerenes. The practical problem of the very low solubility of fullerenes in common organic solvents led the research team to apply a home-made automated machine, a high-speed vibrational mill (HSVM) (Fig. **1**), which was previously used for sample grinding and homogenization of powder materials. Without the addition of solvent, fullerene was vigorously ball-milled in the presence of zinc dust and bromoethyl acetate to afford four products (Scheme **1**). Whereas the first two products were known and came from *in situ* formed Reformatsky reagent ($BrZnCH_2CO_2Et$), two entirely new products (**3** and **4**) were obtained. Indeed, the formation of novel and unexpected products (*via* reaction mechanisms different from the solution) is one of the synthetic advantages of the ball-milling technique.

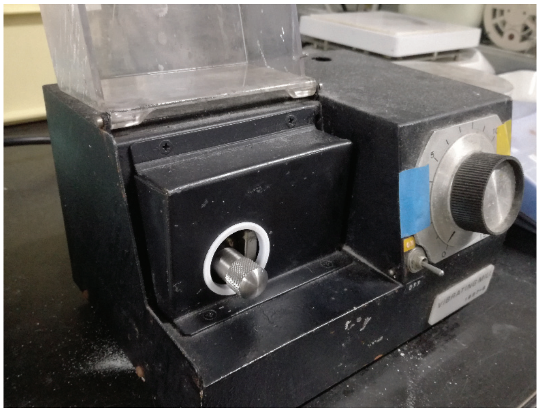

Fig. (1). High-speed vibrational milling machine, ICR, Kyoto University. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Once an advantageous mechanochemical method for fullerene derivatisation was developed, it was applied in the synthesis of various fullerene derivatives, such as fullerene [2+2] dimer C_{120} [3, 4] five structurally isomeric fullerene trimers C_{180} (Scheme **2**) [5] and silicon or germanium bridged dimers [6].

Whereas the high-speed vibration milling technique provides extra mechanical energy for activation of the reaction system, much more effectively than the shaker ball milling technique, the wider use of ball milling by organic chemists was triggered by the application of commercially available mill machines. Various types of mechanochemical ball mills are capable of bringing the reagents into very close contact and promoting the chemical reaction. It did not take long that organic chemists [7] to realize the advantages of the ball milling method. Amongst the advantages are reproducibility of the results, mild reaction conditions, novel reactions and mechanisms, a simple way of carrying out reactions, circumvention of poor solubility of reactants or their instability in solution and an environmentally more benign way to carry out the reaction. The green chemistry aspects of mechanochemistry (avoidance of solvents) are of particular importance for the reduction of the negative effects of chemical processes on the environment [8].

Over time, many important organic chemistry transformations were successfully carried out by ball milling, and there has been a steady increase in the number of publications, and the topic was covered in review articles [9], book chapters [10] and books [11]. This technique is slowly becoming a standard piece of equipment in the synthetic laboratory, such as microwave reactors were introduced two decades ago. In the course of work on mechanochemical organic reactions, important developments were made, such as the activity of metal catalysts, the use of materials other than stainless steel for reaction vessels and milling balls [12] coupling mechanochemistry with photochemistry [13], gaseous reagent[14] and liquid-assisted grinding (LAG) [15]. Advances were also made in the mechanistic understanding of solid-state reactions by *in situ* reaction monitoring employing Raman spectroscopy [16] and powder X-ray diffraction [17] and temperature monitoring [18]. Mechanochemistry has found its way to various applications in pharmaceutical and fine organic chemicals, in preparation of polymorphs, [19]

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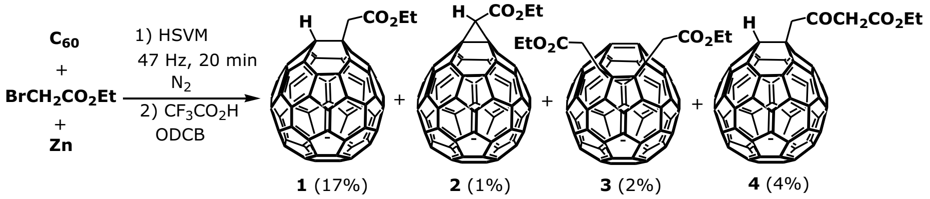
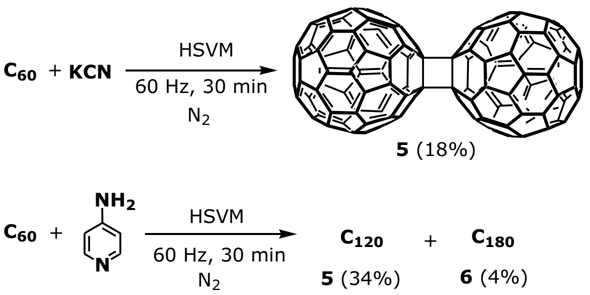


Scheme 1. Solid-state ball milling fullerene reaction.



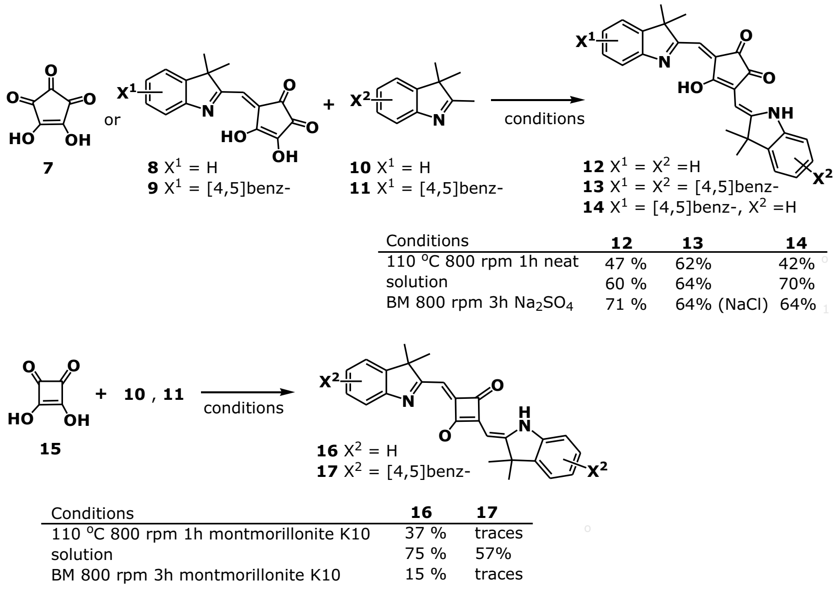
Scheme 2. Mechanochemical synthesis of fullerene dimers.

salts, [20] and cocrystals [21] of active pharmaceutical ingredients. Furthermore, ball milling has been a crucial tool for the preparation of various metal complexes, metal-organic frameworks (MOFs) [22] and coordination polymers [23].

2. SELECTED EXAMPLES

Many organic reactions could be transferred into solid-state ball-milling conditions. Often is achieved better reaction efficiency than in conventional solution reactions. For example, the synthesis of organic dyes croconaines and squaraines in a planetary ball mill was studied by Zappimbulso *et al.* and results were compared with solution conditions (Scheme **3**) [24]. Condensation of croconic derivatives **7**-**9** with indolenines **10** and **11** led to the formation of croconaines **12**-**14**. When squaric acid **15** was used instead of croconic derivatives, the corresponding squaraines **16** and **17** were obtained. Synthesis of croconaine **12** in ball milling conditions in the presence of grinding additive proceeds in better yields than the conventional solution reaction and also in comparison to magnetic stirring reaction heated at 110°C. These results exemplify the advantageous mechanochemical, room temperature conditions and short reaction times to obtain the product with equal efficiency. Similar results are obtained for the synthesis of **13**, whereas comparable yields are obtained for condensation of **14** for the solution and ball-milling reactions. In variance, condensations of indolenines **10** and **11** with squaric acid proceed well in solution, whereas solid-state reactions were sluggish in the case of **16** or did not take place at all in the case of squaraine **17**. As such, these findings illustrate the fact that not all chemical reactions will benefit from solid-state milling.

In addition to single-step reactions, several multi-step mechanochemical syntheses were also carried out, and each reaction step could have some advantage over the solution conditions. Further improvement in the simplicity of mechanochemical synthesis is the multi-step, one-pot procedure. In these reactions, when the first milling process is completed, additional reagents are introduced to the reaction jar, and a second chemical transformation is achieved by further milling. For this purpose, the first reaction step should be quantitative, employing equimolar amounts of reagents, and these

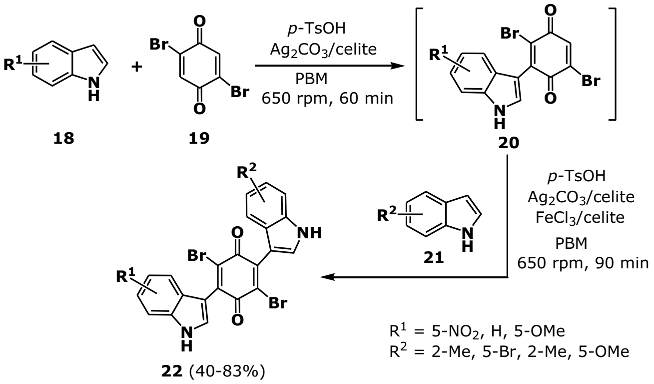


Conditions	12	13	14
110 °C 800 rpm 1h neat	47 %	62%	42%
solution	60 %	64%	70%
BM 800 rpm 3h Na_2SO_4	71 %	64% (NaCl)	64%

Conditions	16	17
110 °C 800 rpm 1h montmorillonite K10	37 %	traces
solution	75 %	57%
BM 800 rpm 3h montmorillonite K10	15 %	traces

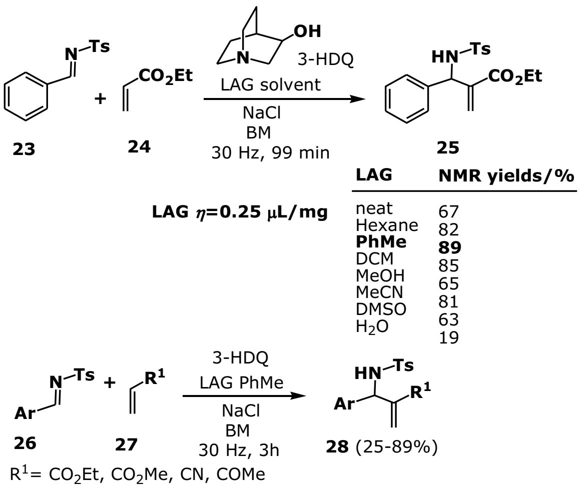
Scheme 3. Comparison of solution and mechanochemical synthesis.

reagents should be compatible with the second batch of reagents, which should not retard the reaction. Synthesis of non-symmetric bis-indolyl quinones **22** by Piquero *et al.* is an example of a two-step, single-pot mechanochemical reaction (Scheme **4**) [25]. Mono-indolyl quinones **20** were prepared by reacting 2,5-dibromo benzoquinone with the first indole in a planetary ball mill (PBM). This milling reaction is acid catalyzed by *p*-TsOH and intermediate oxidized by Fetizon's reagent (Ag_2CO_3 on celite). Once the first reaction step was completed, a second indole was introduced, as well as additional reagents and milling continued for another 90 min. By this procedure, several bis-indolyl quinones **22** were obtained in moderate to high yields.



Scheme 4. One-pot, three-step mechanochemical synthesis.

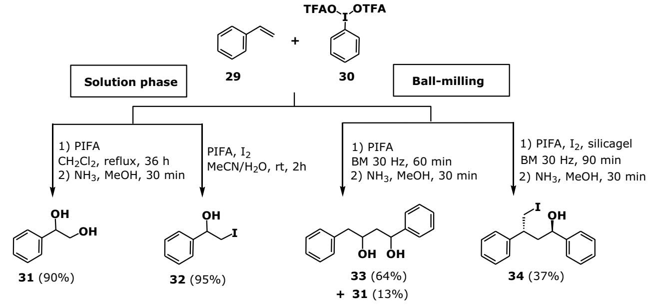
Beneficial effects on the addition of a small amount of solvent in a ball mill, *i.e.*, liquid-assisted grinding (LAG), could be illustrated by the optimization of model aza-Morita-Baylis-Hillman reaction (aza-MBH) described by Williams *et al.* (Scheme **5**) [26]. The reaction of tosyl-protected imine **23** with ethyl acrylate **24** in the presence of 3-hydroxy quinuclidine (3-HQD) as tertiary amine catalyst and NaCl as solid grinding additive led to the formation of β-amino acid derivative **25** after 99 min of milling. Neat grinding afforded product **25** in 67% yield, and the screening of LAG solvent has shown that this yield could be significantly improved by the employment of several solvents, in particular with toluene and DCM. In optimised reaction conditions, toluene was employed as LAG solvent, and various aza-MBH products **28** were synthesized in 25-89% yield.



LAG	NMR yields/%
neat	67
Hexane	82
PhMe	**89**
DCM	85
MeOH	65
MeCN	81
DMSO	63
H_2O	19

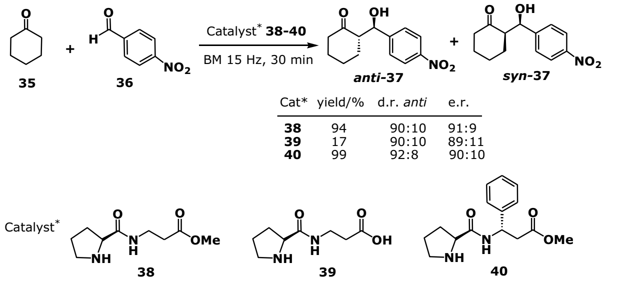
Scheme 5. LAG in the mechanochemical synthesis.

The formation of new, unexpected, different products than those obtained from conventional reactions in solution is a valuable feature of solid-state reactions, which makes them a complementary synthetic tool. In the course of these chemical reactions, novel reaction mechanisms often take place, further enriching the knowledge of organic chemistry. In addition to fullerene products described in Schemes **1** and **2**, products obtained by ball-milling which differ from conventional heating in solution are, for instance, described by Pan *et al.* (Scheme **6**) [27]. Solution reaction of styrene **29** with phenyl iodine bis(trifluoroacetate) (PIFA), a hypervalent iodine reagent **30**, provides (after hydrolysis of intermediate TFA esters by NH_3/MeOH) a 1,3-diol **31** as the sole product. In the solid-state ball-milling conditions, only a small amount of **31** was obtained; instead, an unexpected novel product, dimeric diol **34,** was obtained as the major product. When iodine was introduced in conjunction with PIFA, 1,2-dihydroxylation of styrene took place, forming product **31** in solution conditions. The product obtained in the ball-milling reaction is entirely different, 1,4-iodoalcohol **34** and its formation explained by changes in the reaction mechanism.



Scheme 6. Mechanochemical route to novel products.

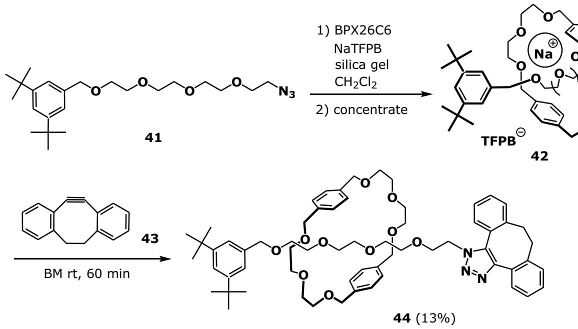
Important results were obtained in the development of solid-state enantioselective reactions, which demonstrate that ball milling conditions are applicable for this type of reaction [28]. For instance, the enantioselective aldol reaction of cyclohexanone **35** with 4-nitrobenzaldehyde **36**, which is catalyzed by several (*S*)-dipeptides **38-40** was reported by Machuca *et al.* (Scheme **7**) [29]. In short milling time, *anti*-aldol isomer **37** was obtained in high yield and good d.r. It was demonstrated that these reaction conditions could be applied to a series of aldol reactions of cyclohexanone, cyclopentanone and acetone with aromatic aldehydes which provide *anti*-isomer aldol products in 31-98% yields, with *anti/syn* d.r. ranging from 35:65 to 92:8 and e.r. between 66:34 and 98:2.



Cat*	yield/%	d.r. *anti*	e.r.
38	94	90:10	91:9
39	17	90:10	89:11
40	99	92:8	90:10

Scheme 7. Enantioselective mechanochemical aldol reaction.

The operationality of weak, non-covalent interactions in solid-state milling, besides in enantiocatalyzed reactions, is evidenced by the applications in supramolecular chemistry [30]. Synthesis of the [2]rotaxane **44** was completed by ball-milling by Wu *et al.* (Scheme **8**) [31]. Thread-like polyether molecule **41** was pre-mixed with bis-*p*-xylyl[26]crown-6 (BPX26C6), sodium tetrakis(3,5-trifluoromethyl phenyl)borate (NaTFPB) and silica. Evaporation of solvent affords the [2]pseudorotaxane **42**, which was stoppered by an azide-alkyne click reaction with the diphenyl cyclooctyne **43** in a ball mill. The [2]rotaxane **44** was prepared in 13% yield after one hour of milling at room temperature.



Scheme 8. Mechanochemical synthesis of rotaxane.

CONCLUSION

Future use of mechanochemical synthesis on an industrial scale lies in the scaling up of the reactions by moving from batch to continuous process, which is now an area of intensive research and the employment of the twin-screw extrusion technique [32] is a major step forward. With the rapid growth of the research publications, review articles [9] and books [11], as well as the realization of the importance and usefulness of mechanosynthesis by the organic chemical community, dedicated chemical conferences were organized, and EU-COST action was launched [33]. The International Union of Pure and Applied Chemistry (IUPAC) has recently recognized mechanochemistry among 10 chemistry innovations that will change the world.

LIST OF ABBREVIATIONS

IUPAC = International Union of Pure and Applied Chemistry
LAG = Liquid-assisted Grinding
HSVM = High-speed Vibrational Mill
PBM = Planetary Ball Mill

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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