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MECHANOCHEMICAL SYNTHESIS OF FLUORINE-CONTAINING HETEROCYCLES VIA BALL MILLING.

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Fluorine-containing heterocycles play a crucial role in the pharmaceutical, agrochemical, and materials industries. The pursuit of effective and sustainable synthesis methods has driven the development of mechanochemistry as a solvent-free, energy-efficient alternative to conventional chemical transformations. Among these approaches, ball milling has emerged as a particularly promising technique for facilitating chemical reactions. This review covers key achievements over the past decade in the mechanochemical synthesis of fluorinated heterocyclic compounds for bimolecular, trimolecular, and tetramolecular reactions as well as transformations classified as peripheral functionalization of the heterocyclic framework. This work serves as a valuable resource for researchers and practitioners seeking to develop sustainable and efficient catalytic systems for fluorinated heterocyclic synthesis.

Keywords: Fluorine, Heterocyclic Compounds, Fluorinated Pharmaceuticals, Mechanochemistry, Ball Milling, Green Chemistry, Sustainable Synthesis.

INTRODUCTION. Mechanochemistry, a subdiscipline of chemistry, instigates chemical transformations initiated by the direct application of mechanical energy in contrast to conventional thermal, photochemical, or electrochemical activation. These reactions are typically induced through techniques such as grinding, milling, and the exertion of mechanical force to instigate molecular transformations. Particularly effective in solid-state chemistry, mechanochemical forces can overcome activation energies by disrupting crystal lattices, breaking bonds, and enhancing reactant contact, frequently enabling solvent-free reactions and aligning with green chemistry principles. The unique activation mechanisms of mechanochemistry are finding growing utility in materials science, pharmaceuticals, and catalysis providing sustainable alternatives to traditional synthetic methodologies [1–7].

Ball milling, an innovative mechanochemical strategy in organic synthesis, involves the high-energy grinding of reactants within a rotating reactor, typically a cylindrical chamber charged with milling media such as ceramic, steel, or zirconia spheres, which provides the mechanical energy required for bond activation. Reaction progression is efficiently delivered through impact and frictional forces generated by the movement of the milling media, instigating molecular transformations. By significantly reducing or eliminating the use of hazardous organic solvents, ball milling offers enhanced substrate reactivity as the application of mechanical force effectively activates reactant molecules, often facilitating transformations that exhibit sluggish kinetics or require harsh conditions in traditional solution-phase methodologies. This can unlock unique reaction pathways, enabling challenging transformations such as carbon–carbon bond formation, oxidation reactions, and the selective functionalization of heterocyclic compounds with potentially enhanced regioselectivity [8–15].

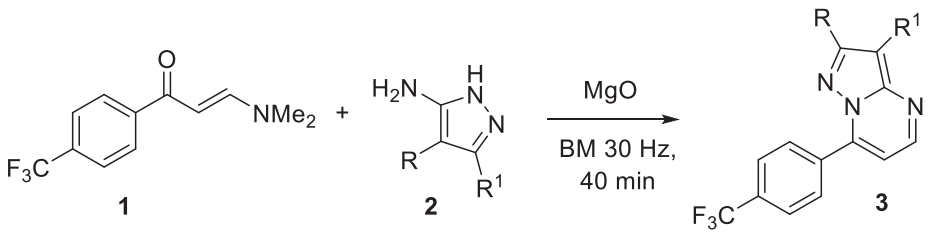
Scaling up mechanochemical processes, particularly ball milling techniques, from laboratory to industrial settings presents several challenges. Reactor design must ensure uniform energy distribution and effective mixing across larger volumes, a task complicated by the risk of uneven reactions and increased equipment wear at industrial scales. Additionally, mechanochemical systems lack the precise monitoring and control mechanisms found in solution-phase reactions, making it more difficult to regulate key parameters such as temperature, pressure, and reaction kinetics–especially in larger setups. Consequently, optimizing reaction conditions requires meticulous experimentation and refinement. Given these complexities, synthetically useful data reported in the literature serve as invaluable resources for practitioners seeking to advance mechanochemical methodologies [16–20].

As part of our expertise in modern pharmaceutical development [21–25], particularly in fluorine-containing drugs [26–31] and those derived from tailor-made amino acids [32–37], we continuously explore and assess innovative synthetic methodologies [38–42]. Given that heterocyclic compounds and amino acids form the structural foundation of over 85% and 35% of modern pharmaceutical drugs, respectively, we place special emphasis on advancements in these synthetic domains [43–52]. Heterocyclic compounds, in particular, serve as fundamental building blocks in medicinal chemistry with their broad biological activity and exceptional structural versatility making them indispensable for rational drug design [53–56].

As previously noted, mechanochemistry is an emerging research field with significant synthetic potential. In this review, we summarize the data published over the past decade on the mechanochemical synthesis of fluorine-containing heterocyclic compounds under ball milling conditions. The content is organized based on the number of reacting species covering bi-, tri-, and tetramolecular reactions with a final section dedicated to examples classified as peripheral functionalization of the heterocyclic framework. We believe this compilation will serve as a valuable resource and inspiration for researchers and practitioners in the fields of synthetic and medicinal chemistry as well as those interested in sustainable methodologies.

Bimolecular reactions.

The synthesis of trifluoromethyl derivatives of 7-phenylpyrazolo[1,5-*a*]pyrimidine **3** is presented in Scheme 1. Using nanosized, powdered magnesium oxide as catalyst, unsaturated amino ketone **1** reacted with 1*H*-pyrazol-5-amine **2** under ball milling. For optimized conditions, the reaction proceeded at relatively high rates affording the target 7-phenylpyrazolo[1,5-*a*]pyrimidines **3** with excellent chemical yields. This mechanochemical process has a high degree of generality as 1*H*-pyrazol-5-amines **2** can carry various alkyl and aryl substituents.



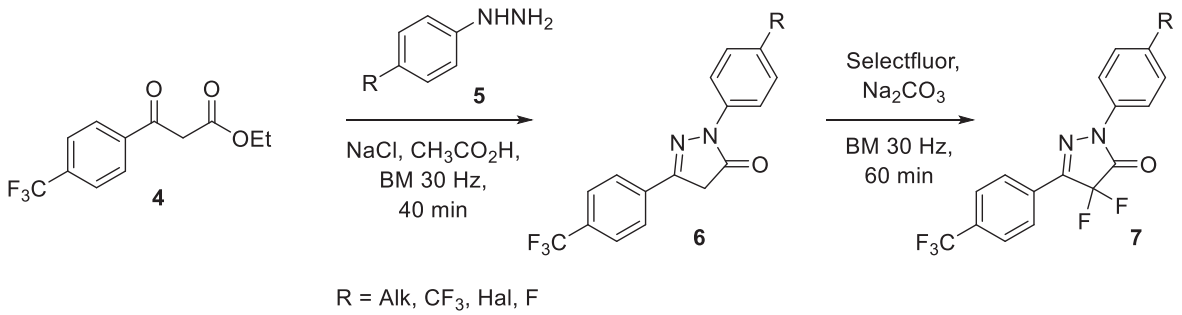
Scheme 1. Synthesis of trifluoromethyl derivatives of 7-phenylpyrazolo[1,5-*a*]pyrimidine **3** under ball milling (BM).

It is interesting to note that these structurally new fluorinated 7-phenylpyrazolo[1,5-*a*]pyrimidines **3** show promising antibacterial and anticancer properties [57].

The one-pot, two-step mechanochemical synthesis of fluorinated pyrazolones **6** and **7** is illustrated in Scheme 2. Trifluoromethyl-substituted β-keto ester **4** reacts with phenylhydrazines **5** under ball milling in the presence of NaCl (6 eq.) and acetic acid (0.5 eq.) yielding trifluoromethylated pyrazolones **6** in yields in excess of 90% [58]. Furthermore, the authors demonstrated that fluorination of **6** with Selectfluor [59] can also be achieved under mechanochemical conditions affording derivatives **7** in yields ranging from 40% to 60% featuring multiple fluorination patterns.

After meticulous optimization, the final protocol has been successfully applied to the synthesis of a library of 12 difluorinated pyrazolones **7** highlighting the synthetic versatility of ball milling. Due to their enhanced electrophilicity, fluorinated 1,3-dicarbonyl compounds exhibit high reactivity toward nucleophilic

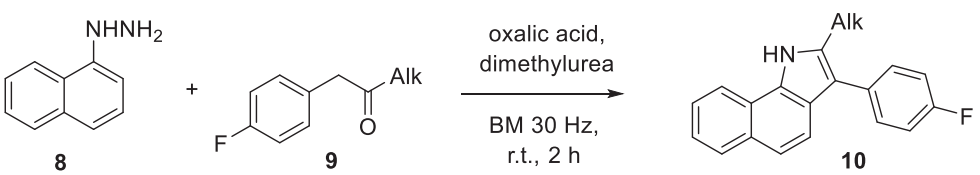
reagents [60], often posing challenges in controlling reaction selectivity. Consequently, the development of this mechanochemical protocol marks a significant achievement offering an efficient and reproducible method for the preparation of fluorinated pyrazolones **6** and **7**.



Scheme 2. Synthesis of fluorinated pyrazolones **6** and **7**.

Indoles are a crucial scaffold in drug design due to their versatile biological activity and ability to interact with various molecular targets. They are found in numerous natural and synthetic pharmaceuticals playing key roles in anticancer, antimicrobial, anti-inflammatory, and neuroprotective therapies. Their structural adaptability allows medicinal chemists to modify them for enhanced potency, selectivity, and bioavailability making them indispensable in modern drug discovery [61–64]. Numerous approaches have been developed for the preparation of variously substituted indole derivatives [65–67], including fluorine-containing variants [68–71].

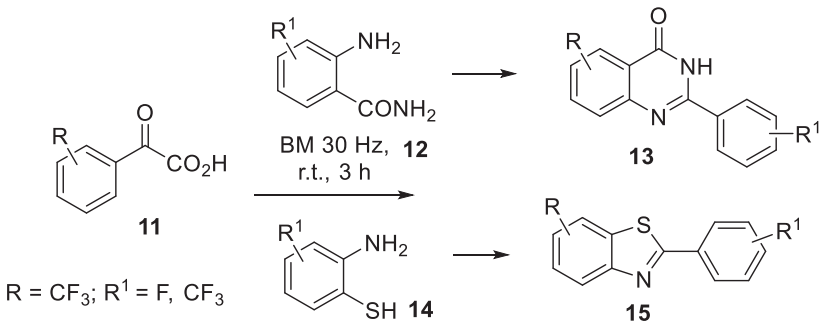
Scheme 3 presents a mechanochemical approach to Fischer indolization under ball milling conditions [72]. In this method, 1-naphthylhydrazine **8** reacts with fluorinated ketone **9** in the presence of oxalic acid and dimethylurea as catalysts together with a trace amount of acetic acid serving as a liquid-assisted grinding agent. The reaction is conducted in a ball mill at 30 Hz for two hours at ambient temperature providing fluoroindoles **10** in excellent yields of ~90%. Besides fluorine at the *para* position, ketones **9** can also accommodate other halogens and alkyl groups—including benzyl—highlighting the structural versatility of this mechanochemical approach for the synthesis of indole derivatives relevant to medicinal chemistry studies.



Scheme 3. Synthesis of fluoroindoles **10**.

Quinazolinones exhibit a broad spectrum of biological activities, including anticancer, antimicrobial, anti-inflammatory, antihypertensive, and antiviral properties. Their structural versatility makes them valuable scaffolds in drug design with many derivatives showing promising therapeutic effects [73–75]. Benzothiazoles are widely studied for their antitumor, antibacterial, antifungal, and neuroprotective properties. They are frequently explored in medicinal chemistry for their ability to interact with biological targets making them useful in Alzheimer's disease research, anticancer therapies, and antimicrobial drug development [76–79].

Scheme 4 illustrates a mechanochemical approach for the synthesis of fluorinated quinazolinones **13** and benzothiazoles **15** [80]. In this process, fluorine-containing α-keto acids **11** react with 2-aminobenzamides **12** under ball milling at 30 Hz and ambient temperature for 3 hours. Upon completion, the reaction mixture is quenched with $NaHCO_3$ and the target fluorinated quinazolinones **13** are purified either by recrystallization or column chromatography yielding products in good-to-excellent yields of 74–92%. Ball milling has been successfully scaled to gram quantities, though extended reaction times of up to 5 hours were required. Notably, fluorine substitution is well-tolerated on both starting compounds **11** and **12** enabling the design of quinazolinones **13** with varying degrees and positions of fluorine atoms and trifluoromethyl groups.



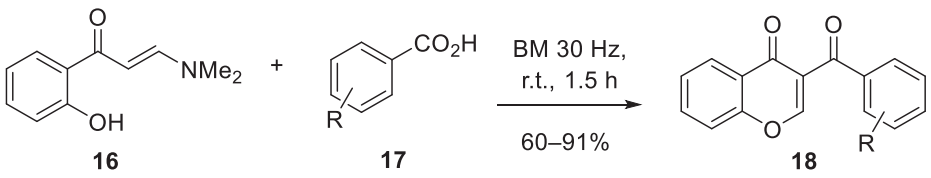
Scheme 4. Synthesis of fluorinated quinazolinones **13** and benzothiazoles **15**.

The synthesis of fluorinated benzothiazole derivatives **15** is carried out under the same ball milling conditions substituting 2-aminothiophenol **14** for 2-aminobenzamides **12**. The reactions proceed in similarly high yields of 80–90% yields providing a convenient and reliable route to fluorinated benzothiazoles **15** [82]. Both fluorine and trifluoromethyl groups can be incorporated into the starting compounds **11** and **12**, further highlighting the synthetic versatility of this mechanochemical approach.

The benzopyrone class of heterocyclic compounds, including chromones and coumarins, comprises naturally occurring biologically active molecules with diverse pharmacological properties. These compounds exhibit antioxidant, anti-inflammatory, antimicrobial, anticancer, and neuroprotective activities making them valuable in drug discovery. Their ability to regulate enzymatic pathways, oxidative stress, and inflammatory responses has driven their exploration for potential treatments of

neurological disorders, infections, and metabolic diseases [81–83].

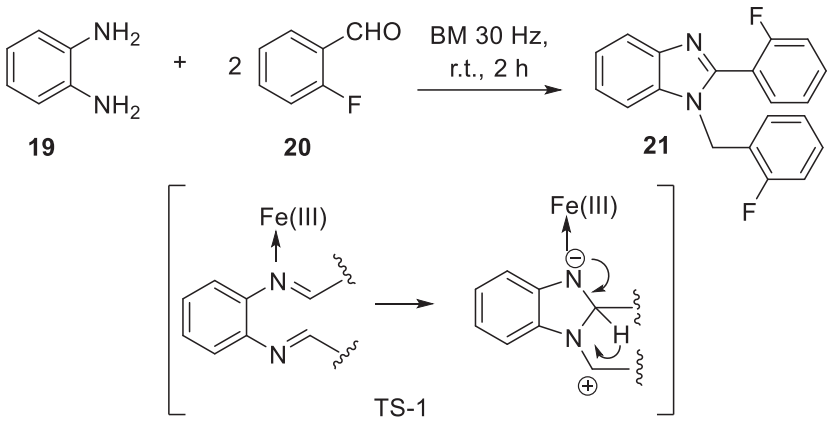
Scheme 5 illustrates the mechanochemical synthesis of fluorinated 3-acylchromones **18** [84]. The reaction of enaminones **16** with fluorine-containing benzoic acids **17** is efficiently catalyzed by $FeCl_3$ supported on nanocellulose under ball milling. The process exhibits a relatively fast reaction rate reaching completion within approximately 1.5 hours and in excellent yield.



Scheme 5. Synthesis of fluorine-containing chromones **18**.

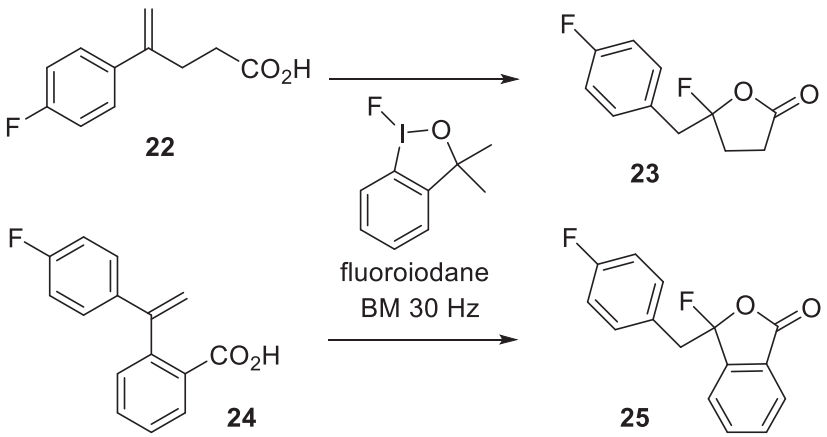
This mechanochemical approach is straightforward and accommodates a wide range of substitutions on the benzoic acid moiety. Specifically, one or two fluorine atoms, trifluoromethyl, and trifluoromethoxy groups can be introduced at the *ortho*, *meta*, or *para* positions within the target chromones **18**. Particularly noteworthy are derivatives containing the trifluoromethoxy group which is commonly found in the structures of successful pharmaceutical drugs and agrochemicals [85, 86].

Scheme 6 presents a compelling example of the mechanochemical synthesis of fluorinated 1,2-disubstituted benzimidazole **21** [87]. The reaction of benzene-1,2-diamine **19** with two equivalents of *o*-fluorobenzaldehyde **20** is catalyzed by $FeCl_3{\cdot}6H_2O$ under ball milling and involves the oxidation of one aldehyde residue together with the reduction of the other. This internal redox process is likely to proceed via transition state TS 1 featuring a key biomimetic 1,3-hydrogen transfer [88]. Fluorinated benzaldehydes are highly reactive and exhibit distinct reactivity patterns depending on the number and position of fluorine atoms on the aromatic ring [89, 90].



Scheme 6. Synthesis of fluorinated benzimidazole **21**.

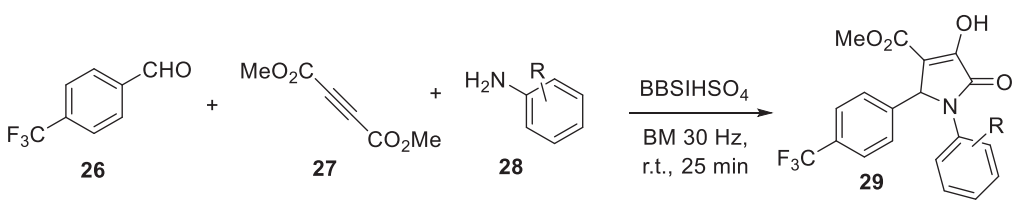
Scheme 7 illustrates examples of mechanochemical fluorination-cyclization reactions. The treatment of unsaturated carboxylic acid **22** with fluoroiodane under ball milling leads to the clean formation of fluorinated dihydrofuranone **23** in a good yield of 80%. Similarly, the reaction of aromatic acid **24** under identical mechanochemical conditions affords the corresponding benzofuranone **25** with comparable efficiency. Notably, both heterocyclic compounds **23** and **25** incorporate fluorine substitution at both aromatic and aliphatic positions, highlighting the versatility of this approach [91].



Scheme 7. Synthesis of fluorinated dihydrofuranone **23** and benzofuranone **25**.

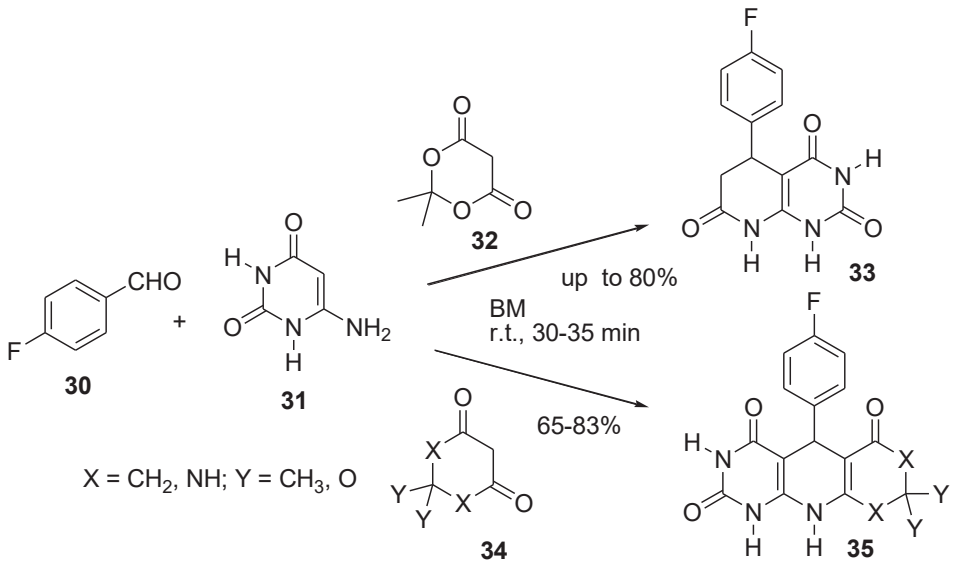
Trimolecular reactions.

Fluorine-containing benzaldehydes are highly reactive compounds widely utilized in the synthesis of various five-membered heterocyclic structures, either as final products or key intermediates [92, 93]. Benzaldehyde **26**, activated by a trifluoromethyl group in the *para* position, rapidly reacts with dimethyl acetylenedicarboxylate **27** and diverse anilines **28** under ball milling at ambient temperature yielding highly functionalized pyrrolidinones **29** in 25 minutes and in excellent 80–90% yields (Scheme 8). The reactions under ball milling are catalyzed by 1,1'-butylene bis(3-sulfo-3*H*-imidazol-1-ium) hydrogen sulfate ($BBSIHSO_4$), a reusable Brønsted acid ionic liquid catalyst [94].



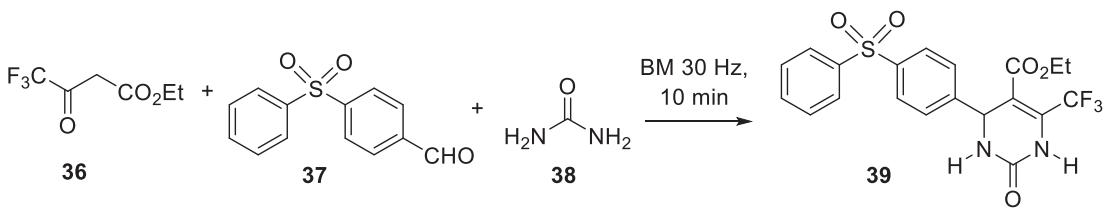
Scheme 8. Synthesis of trifluoromethyl-containing pyrrolidinones **29**.

A catalyst-free, solvent-free trimolecular reaction between fluorobenzaldehyde **30**, 6-aminouracil **31**, and 2,2-dimethyl-1,3-dioxane-4,6-dione **32** is performed under ball milling yielding fluoropyridopyrimidine **33** in excellent yields of 90% [95]. Due to the highly electrophilic nature of the malonic residue in diester **32**, it undergoes ring opening followed by decarboxylation, contributing only two carbon atoms to the structure of pyridopyrimidine **33**. Alternatively, employing more stable diamides (e.g., barbituric acid) or 1,3-diketones (e.g., dimedone), **34** results in a distinct chemical transformation enabling the synthesis of fluorinated tricyclic pyrimidoquinolines **35** (Scheme 9) in high yields of 90–97%.



Scheme 9. Synthesis of fluorine-containing pyridopyrimidines **33** and pyrimidoquinolines **35**.

Ethyl 4,4,4-trifluoro-3-oxobutanoate **36** (Scheme 10) is a highly reactive keto-ester widely utilized in the synthesis of fluorinated β-amino acids and their derivatives [96–98]. Under ball milling at ambient temperature, the trimolecular reaction of keto-ester **36** with aromatic aldehyde **37** and urea **38** proceeds at an exceptionally high rate reaching completion in approximately 10 minutes. The resulting multicomponent product, dihydropyrimidinone **39**, is isolated in yields of over 90% [99].



Scheme 10. Synthesis of trifluoromethyl-containing dihydropyrimidinone **39**.

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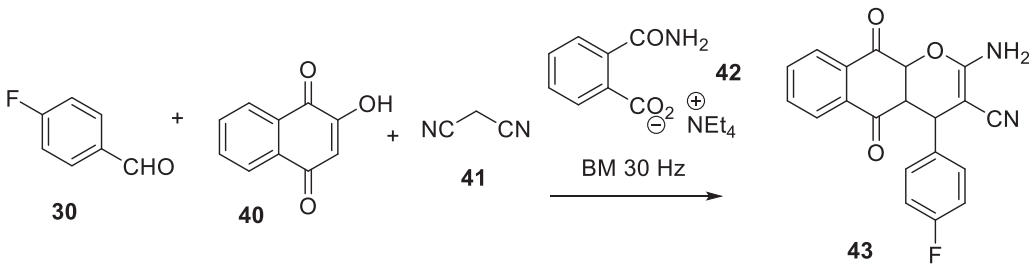
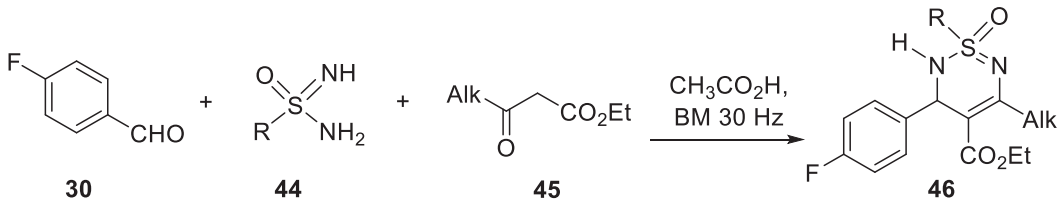
This variant of the Biginelli reaction [100] is efficiently catalyzed by zeolites. These porous materials provide both Brønsted and Lewis acid sites, offering key advantages such as high thermal stability, tunable acidity, and recyclability. Their compatibility with ball milling conditions further enhances their utility in sustainable and efficient catalysis.

Scheme 11 demonstrates another application of fluoro-aromatic aldehydes. *p*-fluorobenzaldehyde **30** undergoes a trimolecular reaction with 2-hydroxynaphthalene-1,4-dione **40** and malononitrile **41** yielding annulated pyran **43**. This transformation is performed under ball milling at ambient temperature. A key feature of this reaction is the catalyst tetraethylammonium (carbamoyl) benzoate **42**, a bifunctional organocatalyst that efficiently facilitates the process under ball milling [101].



Scheme 11. Synthesis of fluorine-containing pyran **43**.

Scheme 12 presents a variant of the Biginelli-type multicomponent reaction employing *p*-fluorobenzaldehyde **30**, sulfonimidamides **44**, and β-keto esters **45** to efficiently synthesize 2,3-dihydro-1,2,6-thiadiazine 1-oxides **46** in high yields [102]. The reaction is carried out under solvent-free ball milling at ambient temperature using acetic acid as a catalyst.



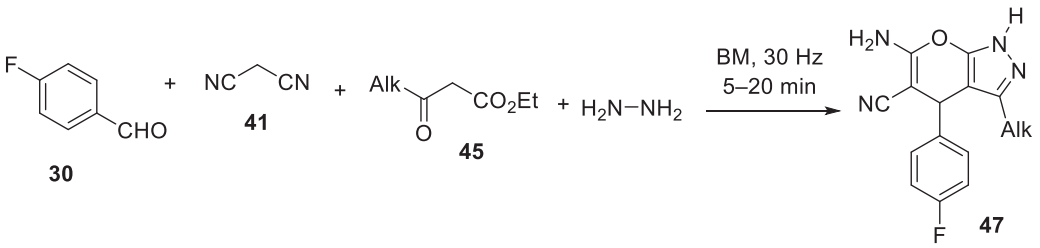
Scheme 12. Synthesis of fluoro-substituted thiadiazine **46**.

Tetramolecular reactions.

Tetramolecular reactions, while synthetically valuable, are rare. These transformations resemble a finely tuned orchestra where each component harmonizes perfectly with all others. As a result, successfully executing tetramolecular reactions evokes a sense of awe, particularly when they proceed with high efficiency. Accordingly, mechanochemical tetramolecular reactions hold both practical and aesthetic significance in synthetic chemistry.

The mechanochemical synthesis of fluorinated pyranopyrazoles **47** (Scheme 13) was successfully achieved by ball milling a mixture

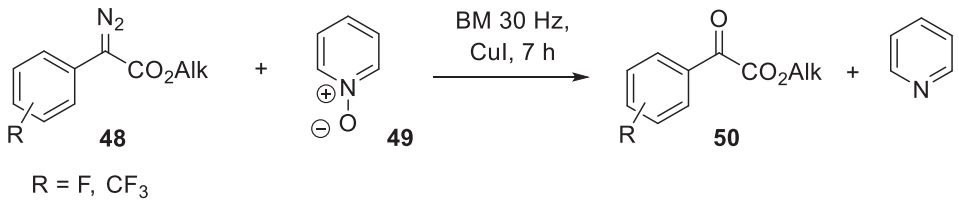
of *p*-fluorobenzaldehyde **30**, malononitrile **41**, β-keto esters **45**, and hydrazine hydrate at ambient temperature [103, 104]. The key to this success is a specially designed nanocatalyst, synthesized using silica/aminoethylpiperazine, which significantly enhances reaction efficiency.



Scheme 13. Synthesis of fluorinated pyranopyrazoles **47**.

Peripheral functionalization of the heterocyclic framework.

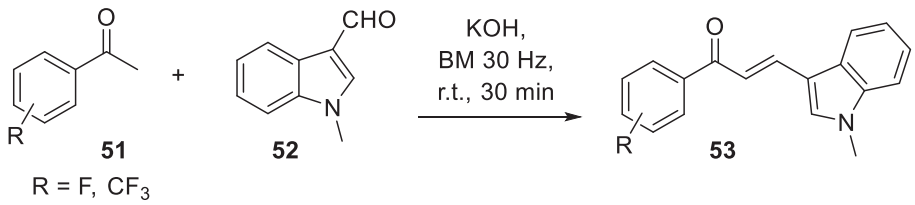
As emphasized throughout this review, fluorine-containing carbonyl compounds are highly valuable synthetic building blocks exhibiting significantly enhanced reactivity compared to their non-fluorinated counterparts [105–107]. Consequently, their preparation via mechanochemistry is of particular interest. Scheme 14 illustrates the synthesis of α-keto esters **50** under ball milling [108]. The process involves an anaerobic oxidation of aryl diazo esters **48** with pyridine *N*-oxide **49** catalyzed by CuI under ball milling to afford α-keto esters **50**. Mechanistic studies highlighted the role of CuI in forming a copper–carbenoid intermediate which facilitates the oxygenation process. The scalability of this method was validated by gram-scale reactions and its utility was demonstrated in the synthesis of various natural product and pharmaceutical intermediates.



Scheme 14. Synthesis of fluorinated α-keto esters **50**.

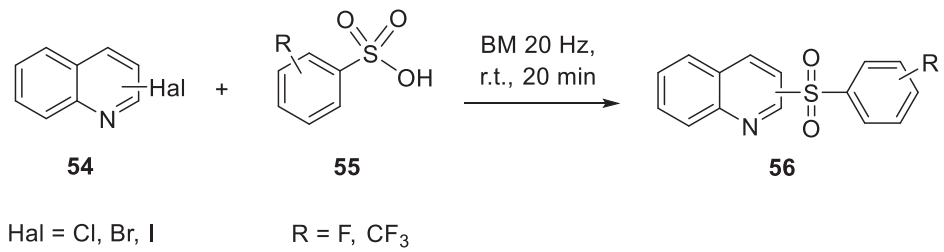
Scheme 15 illustrates the synthesis of indoylchalcones **53** under ball milling [109]. The reaction between fluorine-containing aromatic ketones **51** and 1-methylindole-3-carboxaldehyde **52** was optimized for Claisen–Schmidt condensation under high-energy ball milling. The optimal protocol, utilizing KOH as a catalyst and ethanol (100 μL) as a liquid-assisted grinding additive, proceeds efficiently at ambient temperature and is completed within 15 minutes. Under these conditions, a series of indoylchalcones **53** incorporating fluorine atoms and/or trifluoromethyl groups were synthesized in yields of 50–92%. Notably, the

presence of electron-withdrawing trifluoromethyl groups significantly enhanced reactivity. Additionally, ball milling considerably reduced reaction time compared to conventional solution-based approaches, highlighting its efficiency and practicality.



Scheme 15. Synthesis of fluorine-containing indoylchalcones **53**.

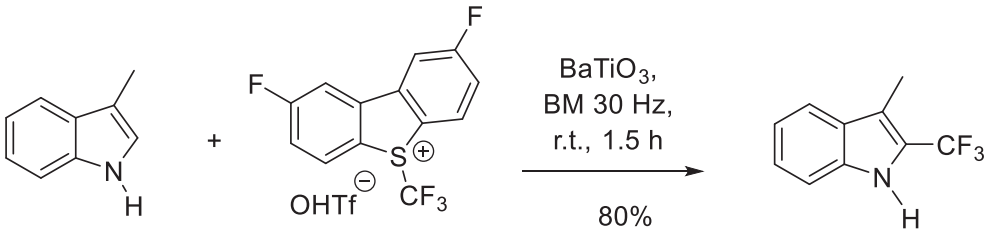
Scheme 16 presents a synthetically valuable mechanochemical procedure for the preparation of sulfonyl quinolines **56** [110]. This method involves the coupling of haloquinolines **54** with sulfonic acids **55** showcasing the advantages of mechanochemistry over conventional approaches that typically rely on metal catalysts, solvents, and harsh reaction conditions. Notably, this procedure eliminates the need for metals, solvents, or additives making it a more sustainable and efficient alternative. Fluorine atoms incorporated into the aromatic sulfonic acid residues, either as fluorine directly attached to the aromatic ring or as trifluoromethyl groups attached to the aromatic ring at various positions, further demonstrate structural diversity and potential applications of the methodology.



Scheme 16. Synthesis of fluorine-containing sulfonyl quinolines **56**.

Aromatic trifluoromethylation is a fundamental transformation in fluorine chemistry widely employed in the synthesis of key building blocks and bioactive compounds [111–113]. Accordingly, the development of a mechanochemical version of this reaction holds significant synthetic value. Scheme 17 presents a notable example of this approach [114] representing the first instance of using piezoelectricity to generate trifluoromethyl radicals. In this method, Umemoto reagent **58** [115] and piezoelectric tetragonal $BaTiO_3$ are utilized in a ball milling trifluoromethylation reaction of indole **57** yielding fluorinated indole **59**. Compared to conventional solution-phase methodologies, this mechano-redox C–H

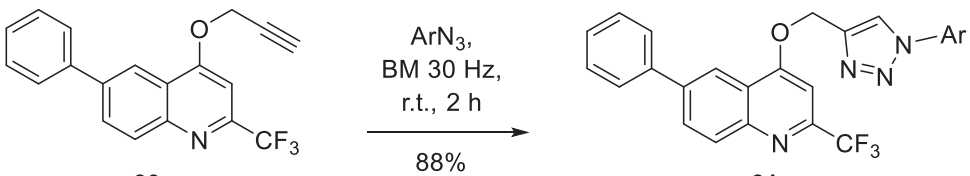
trifluoromethylation technique offers a more environmentally sustainable and efficient route for synthesizing a broad range of trifluoromethylated N-heterocycles and peptides which serve as essential scaffolds in modern drug discovery. This advancement marks a significant step forward in the application of mechano-redox systems for pharmaceutical and biomedical research [114].



57 **58** **59**

Scheme 17. Mechanochemical trifluoromethylation of indole **57** to yield fluorinated indole **59**.

Scheme 18 illustrates the mechanochemical synthesis of 2-(trifluoromethyl)quinolines featuring an aryl-1,2,3-triazole moiety at O-4 in **61** [116]. The reaction is performed under ball milling in the presence of Cu(II) [117], Cu(I), and Cu(0) as catalysts for azide–alkyne cycloaddition in the presence of Hünig's base [118]. Notably, this mechanochemical approach yields significantly higher efficiencies compared to conventional solution-based methods [116, 117].



60 **61**

Scheme 18. Mechanochemical azide-alkyne cycloaddition.

CONCLUSIONS. The scalability of mechanochemical methods, particularly ball milling processes, offers significant potential for industrial applications but presents key challenges. Their ability to eliminate solvents reduces environmental impact and costs while aligning with green chemistry principles. High efficiency and rapid reaction rates further enhance their appeal, potentially lowering energy demands and shortening processing times. However, scaling up requires overcoming hurdles such as ensuring uniform energy distribution, preventing uneven reactions, and mitigating equipment wear at larger volumes. Mechanochemical processes also lack the precise control mechanisms of solution-based reactions rendering parameters like temperature and kinetics harder to regulate. Most systems still operate in batch mode, limiting throughput compared to continuous processing that is favored in industry. Additionally, high-energy milling may degrade sensitive reactants or produce

unintended by-products, necessitating careful material selection. To address these challenges, researchers are exploring advanced reactor designs, real-time monitoring technologies, and hybrid approaches integrating mechanochemistry with techniques like microwave or ultrasound assistance.

The presented data clearly demonstrates that fluorine-containing compounds serve as versatile starting materials for all types of mechanochemical reactions. Notably, fluorinated carbonyl compounds are favored due to their significantly enhanced reactivity compared to their non-fluorinated counterparts. In particular, fluorinated aromatic aldehydes and keto acid derivatives frequently appear as key starting materials in numerous examples throughout this review, highlighting their strategic importance in mechanochemical synthesis.

Given the critical role of fluorinated heterocyclic compounds in the pharmaceutical, agrochemical, and materials industries, along with the benefits of mechanochemical reactions, research in this field is expected to expand significantly.

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МЕХАНОХІМІЧНИЙ СИНТЕЗ ФТОРВМІСНИХ ГЕТЕРОЦИКЛІВ ЗА ДОПОМОГОЮ КУЛЬОВОЇ МЛИНАРКИ

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Фторвмісні гетероцикли відіграють вирішальну роль у фармацевтичній, агрохімічній та промисловості матеріалів. Пошук ефективних та екологічно сталих методів синтезу стимулював розвиток механохімії як безрозчинникової та енергоефективної

альтернативи традиційним хімічним перетворенням. Серед цих підходів кульова млинарка стала особливо перспективною технікою для сприяння хімічним реакціям.

Цей огляд охоплює ключові досягнення останнього десятиліття в механохімічному синтезі фторованих гетероциклічних сполук для бімолекулярних, тримолекулярних та тетрамолекулярних реакцій, а також перетворень, класифікованих як периферійна функціоналізація гетероциклічного каркасу. Ця робота слугує цінним ресурсом для дослідників та практиків, які прагнуть розробляти екологічно сталі та ефективні каталітичні системи для синтезу фторованих гетероциклів.

Ключові слова: фтор, гетероциклічні сполуки, фторовані фармацевтичні препарати, механохімія, кульова млинарка, зелена хімія, екологічно сталий синтез.

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