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Ultrafast and efficient continuous flow organic synthesis with a modified extruder-grinder system

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The study introduces a groundbreaking continuous system that combines an extruder and grinder to enable catalyst-free and solvent-free reactions under mild conditions. This temperature-controlled system facilitates the synthesis of highly functionalized chromenes, which have valuable applications in generating combinatorial libraries and complex target molecules. The newly developed mill extruder machine offers several advantages for industrial production on a large scale. It effectively reduces waste, saves energy, and enhances time efficiency. This system represents a significant advancement in the field, providing a new strategy for one-pot synthesis of various types of highly functionalized spirooxindoles and chromenes. Remarkably, these reactions can be accomplished within a short timeframe of 2–10 min, yielding impressive results of 75–98%. The results demonstrate superior performance compared to traditional reaction methods, making it an appealing tool and hotspot area of research in green chemistry.

Keywords Extruder-grinder, Continuous system, Catalyst-free, Solvent-free, Multicomponent synthesis, Chromenes, Green chemistry

Sustainability is playing an increasingly important role in environmental and industrial processes, and the expertise of sustainability professionals is essential in addressing the associated challenges. Solvents and catalysts are critical elements in numerous chemical processes, but their use can lead to environmental pollution due to the presence of hazardous chemicals¹. Specifically, the large quantities of volatile, flammable, and toxic organic solvents, as well as metal catalysts, contribute significantly to this issue². In recent years sustainable alternatives solvents and catalysts are being developed and implemented. Green solvents, eco-friendly catalysts and novel tools are being explored to minimize the environmental impact of chemical processes³.

Mechanochemistry has garnered significant interest among organic chemists as a versatile technique for conducting rapid, clean, and environmentally friendly synthesis without the need for harmful organic solvents⁴. This approach involves utilizing mechanical forces such as shearing, grinding, or milling to facilitate chemical reactions. Ball milling mechanochemistry, in particular, has proven to be a widely applicable method in solid-state phase reactions, offering advantages over conventional laboratory work involving stirrers and heaters⁵. Large-scale ball mills are utilized mainly for material processing but are not yet employed efficiently in organic chemistry⁶. Ball milling has indeed brought about a revolution in organic synthesis by enabling faster and simpler reactions in a solvent-free environment, leading to high conversion rates. However, there are two key areas that require attention and improvement in these methods: temperature control and scalability. Addressing these deficiencies is crucial given the significance of mechanical processes in organic synthesis⁶.

To eliminate these restrictions, scientists have introduced a twin-screw extrusion (TSE) (Fig. 1) in organic chemistry. Reactive extrusion is an innovative and efficient technique used in the synthesis of polymers. It involves combining polymerization or chemical reactions with the process of extrusion to produce functionalized or modified polymers⁷. This method offers several advantages over traditional polymer synthesis approaches, including improved reaction kinetics, enhanced control over the polymer structure, and simplified process integration. Furthermore, twin-screw extrusion has found applications beyond co-crystal synthesis, including the synthesis of diverse chemical species such as metal–organic frameworks (MOFs) and, deep eutectic solvents⁸.

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Figure 1. Twin-screw extrusion.

This study introduces reactive extruder-grinder (REG) as a new technique in continuous mechanochemical organic syntheses for the first time. Figure 2 shows the designed REG device, which is a combination of an extruder, a mortar, and a pestle. The REG operates in a continuous manner for mechanochemical organic syntheses. The materials are fed into the REG and mixed thoroughly within the extruder. They are then pushed into the conic part of the device. REG is capable of continuous reactive synthesizing of organic compounds in quantities ranging from milligrams to several grams and above. At the end of the cylinder, the conic part is designed to play the role of the mortar, and the final process of material grinding and heat-generating occurs in it. The conic part is the most critical part of the REG. By grinding the materials between the conic part wall and the pestle, the required heat is generated. The chemical reaction is carried out quickly due to the intensive grinding and generated heat. In REG, the screw and the pestle are designed in a single piece and alignment. The connection and coherence of these two parts have made the rotation and feeding uniform. The ability to continually enter the raw material and the regular withdrawal of the reaction product has made it an efficient device that can perform various condensation reactions quickly. The materials become mills intensively, and the reaction temperature increase due to the friction. The generated temperature can effectively cause the fulfillment of the multicomponent reactions (MCRs) that require heat. The twin-axis rotational speed of the screw and pestle was adjusted to control the reaction temperature by empirically controlling the screw and pestle rotational speed. The ability to continually enter the raw material and the regular withdrawal of the reaction product has made it an efficient device that can perform various condensation reactions quickly.

Amino-4H-chromenes are versatile organic compounds characterized by a chromene ring system with an attached amino group⁹. These compounds exhibit a range of biological activities, including antioxidant, anti-cancer, anti-inflammatory, antimicrobial, and potential antiviral effects¹⁰. Their unique chemical structure and diverse activities make them attractive candidates for drug discovery and development¹¹. With their potential to modulate various disease pathways, amino-4H-chromenes hold promise for the development of novel therapeutics targeting conditions such as cancer, inflammation, and infectious diseases¹². Continued research in this field aims to uncover their full therapeutic potential and optimize their pharmacological properties for clinical applications¹³.

The indole ring system, known for its biologically active derivatives, plays a crucial role in the structure of numerous pharmaceutical molecules¹⁴. Among these derivatives, spirooxindole compounds have gained recognition in diverse fields, particularly as inhibitors of microtubule assembly. Compounds such as spirotryprostatin A and B have shown potential in inhibiting microtubule assembly¹⁵. Additionally, spirooxindole derivatives have demonstrated their ability to modulate Muscarinic M1 and serotonin receptors, exemplified by compounds like pteropodine and isopteropodine¹⁶. Furthermore, spirooxindole compounds, including MK-0677, exhibit promise as nonpeptidyl growth-hormone secretagogues¹⁷. Given the significance of spiro compounds in organic chemistry and pharmacology, several synthetic protocols have been reported, and ongoing research efforts are exploring this subject¹⁸. The continued exploration of spirooxindole derivatives holds potential for the development of novel therapeutic agents and the advancement of organic chemistry.

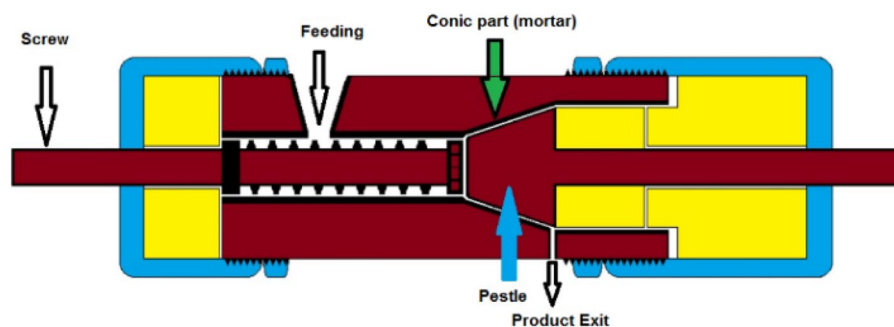


Figure 2. Reactive continuous extruder-milling (REG).

Knoevenagel condensation of malononitrile and chlorobenzaldehyde at room temperature, with only around 7% of the desired product obtained after 10 min in the solid state¹⁹. However, it has been demonstrated that conducting the reaction through a melting process at 150 °C without a catalyst can yield quantitative results. Stoichiometric Michael additions using dimedone at temperatures ranging from 100 to 130 °C have shown complete formation of 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromenes in quantitative yields¹⁹. Furthermore, it was shown that incorporating a mild catalyst (Na_2CO_3) during the milling process at ambient temperature led to quantitative yields of diverse chromene derivatives. The inclusion of Na_2CO_3 during kneading optimizes the overall efficiency of Knoevenagel condensations and Michael addition reactions, ensuring complete conversion. These findings underscore the significance of reaction conditions and catalysts in achieving high yields and complete conversion in the synthesis of chromene derivatives.

In our ongoing pursuit of environmentally friendly organic transformations²⁰, we present a groundbreaking study introducing the REG device as a reactive reactor for the solvent-free, catalyst-free, and additive-free multicomponent synthesis of diverse pyran, 2-amino-4-aryl-3-cyano-4H-chromene, and spiroindole derivatives. Importantly, this innovative method boasts the advantage of not relying on additives or catalysts, while ensuring remarkably short reaction times. The findings of this investigation were illustrated and presented in Fig. 3.

Results and discussion

To optimize the reaction parameters, a one-pot, multicomponent reaction (MCR) was performed involving 4-chlorobenzaldehyde (1a), malononitrile (2), and dimedone (3a) as the model reaction. The utilization of the REG device enabled the execution of a multicomponent reaction without the requirement of an external trigger. This innovative device facilitated the reaction to proceed spontaneously, eliminating the need for additional stimuli or initiators. Inside the REG device, the raw materials are initially mixed in the screw section, resulting in a uniform mixture that then enters the mortar section. In this section, the intensive friction and controlled rotation speed generate heat, which plays a crucial role in facilitating the cascade reaction of Knoevenagel condensation and Michael addition. The combination of intensive grinding and heat assistance within the REG device ensures the efficient and quantitative formation of the desired product.

Figure 4 presents the results obtained under optimized conditions for the multicomponent reaction involving various aldehyde derivatives and malononitrile with different reactants, including dimedone (3a) and 1,3-cyclohexanedione (3b). The table showcases that a wide range of aldehydes, encompassing both electron-donating and electron-withdrawing groups, yielded excellent to good yields within a remarkably short reaction time of 2–5 min. These findings demonstrate the efficiency and versatility of the reaction system in synthesizing the desired products using different aldehyde derivatives and reactants.

The scope and versatility of a one-pot reaction in REG were extended to activated phenol derivatives such as resorcinol (3c), α -naphthol (3d), and β -naphthol (3e). The results of these reactions are presented in Fig. 5. All activated phenol compounds were found to be good participants in this system, yielding good to excellent yields in short reaction times. The use of REG enabled ultrafast reactions to be conducted at ambient temperature without the need for any catalyst or additive on a 5 mmol scale. The experimental procedure was described as straightforward and easy. Initially, the raw materials were pre-mixed in a traditional mortar and pestle. The mixed materials then entered the first part of the REG machine, referred to as the screw, which featured a high homogeneous mixing rate. Subsequently, the well-mixed materials entered the mortar section of the REG system.

Spiroindole and its derivatives are considered privileged heterocyclic cores due to their presence in many natural products and pharmacological agents^{21–24}. These compounds have found extensive use in the pharmaceutical

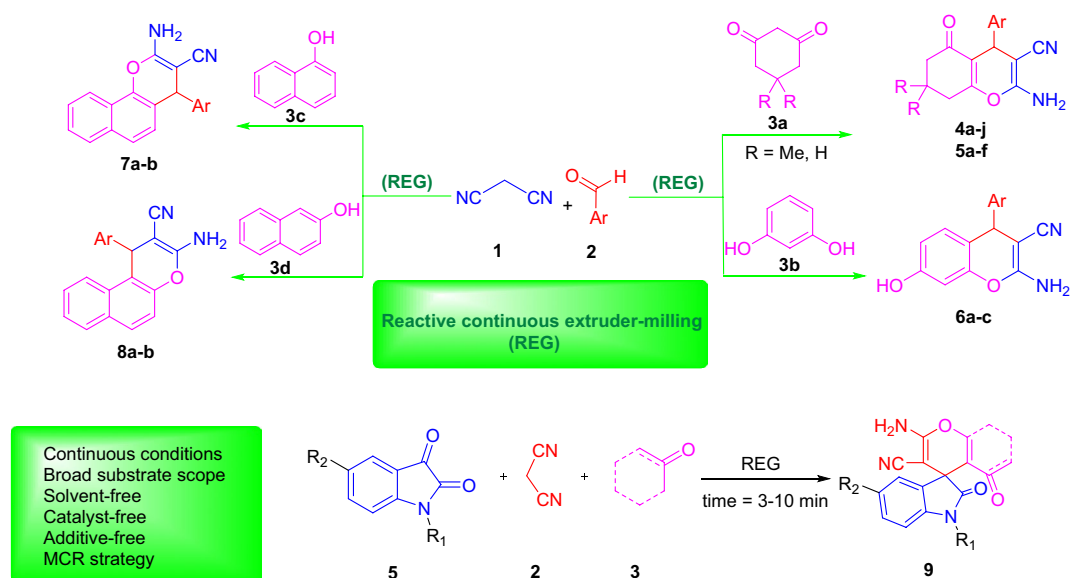


Figure 3. A schematic representation of prepared products in REG device.

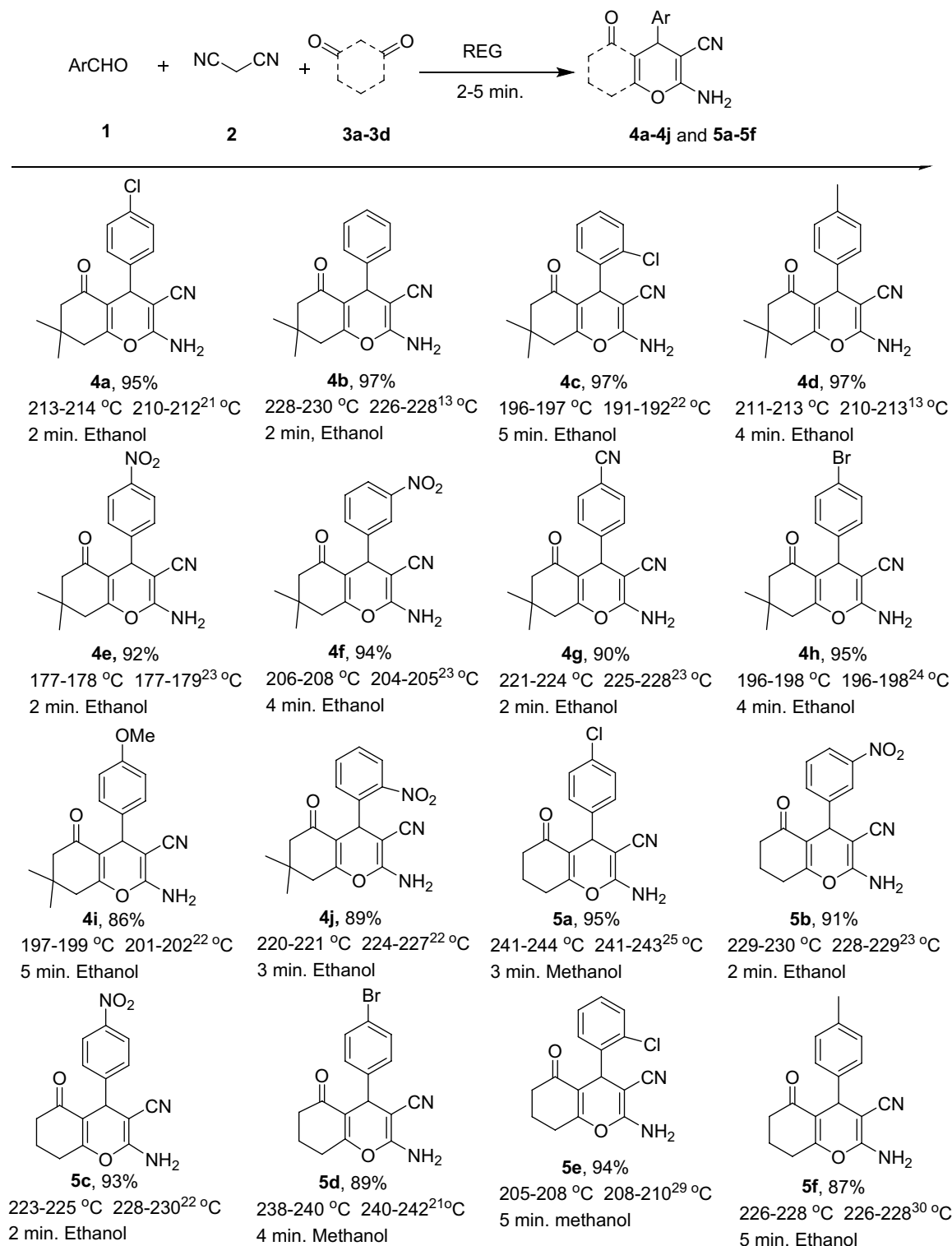


Figure 4. Synthesis of various 4*H*-chromene in REG in optimized reaction conditions. ^aIsolated pure product. ^bRecrystallization solvents.

industry due to their versatile role in numerous biologically active substances²⁵⁻²⁷. These characteristics have made them highly valuable in the development of novel pharmaceutical agents²⁸.

In the continued exploration of the method, the REG system was employed for the green synthesis of different types of spirooxindoles (Fig. 6). This synthesis involved the use of isatin derivatives (5), malononitrile (2), and various types of Michael acceptors (3). By employing different combinations of these reactants, the selected multicomponent reaction (MCR) proceeded efficiently, resulting in the synthesis of the desired products with excellent yields within a short reaction time. The REG system, played a crucial role in facilitating this green

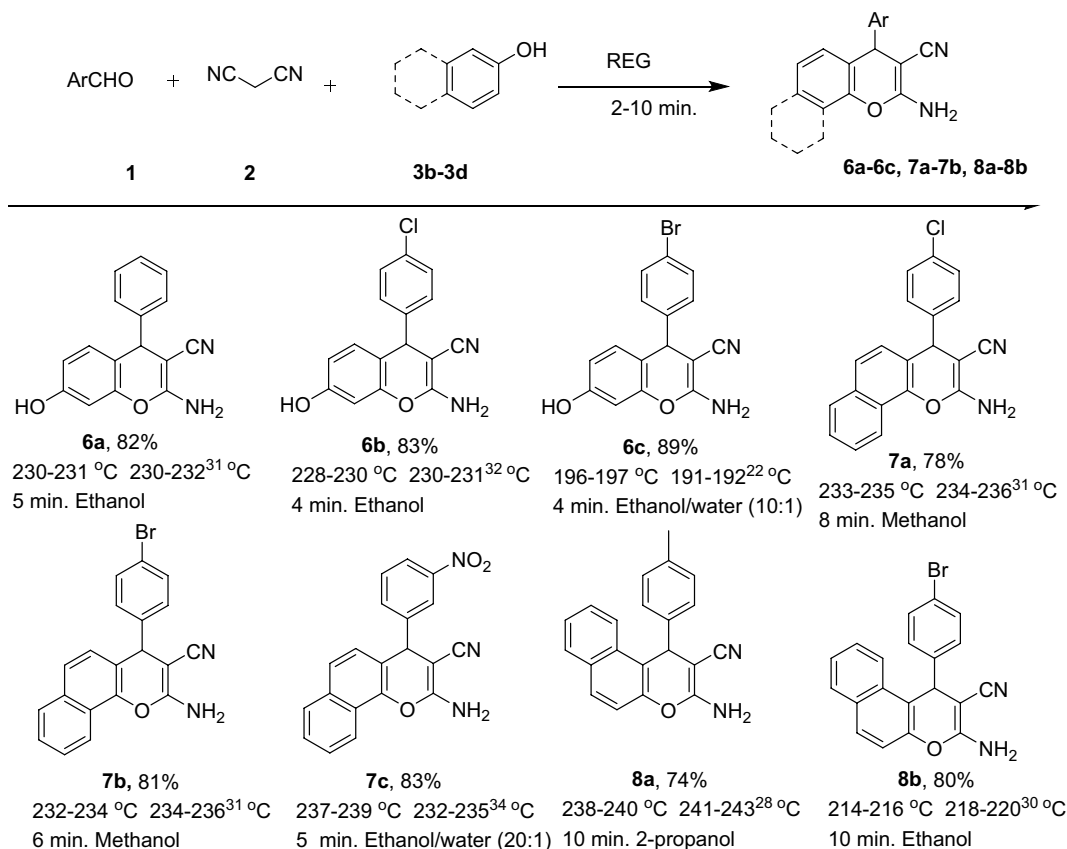


Figure 5. Synthesis of various 4H-chromene in REG in optimized reaction conditions. ^aIsolated pure product. ^bRecrystallization solvents.

synthesis process. By providing a suitable reaction environment, the REG system allowed for the efficient and rapid formation of spirooxindoles from the selected reactants. The utilization of the REG system in this context eliminated the need for additional catalysts or additives, emphasizing its utility as an environmentally friendly and efficient method for synthesis of various spirooxindole compounds.

Scalability holds immense importance in the industry due to the cost efficiency, the resilience and reliability of industrial systems. The scalability of the reaction was evaluated using the model reaction involving 4-chlorobenzaldehyde (**1a**), malononitrile (**2**), and dimedone (**3a**) on a 100 mmol scale. The reaction was successfully conducted on a larger scale, yielding the desired 4H-pyran derivatives with 97% isolated yields in just 50 min. However, it is important to note that precise control of reactant feeding is crucial for maintaining the temperature of the REG system within the desired range, preferably not exceeding room temperature. In larger-scale reactions, the feeding speed of reactants tends to be slower due to the need for careful monitoring and control. As a result, the overall reaction time slightly increase compared to smaller-scale reactions. Nonetheless, by ensuring proper control over the reactant feeding process, it is possible to maintain the desired temperature conditions and successfully carry out the reaction on a larger scale.

Conclusion

To summarize, the study presents a highly efficient and additive-free method for synthesizing industrial-grade 2-amino-4-aryl-3-cyano-4H-chromenes, pyran, and spiroindole derivatives using a mechanochemical approach. The method has distinct advantages over traditional ball mills, such as the ability to perform temperature-dependent reactions without external heating and its continuous operation, enabling easy scale-up. The heat generated during the reaction is a result of the speed of the rotating mortar and the friction between the conical part and the rotating mortar, making the process more energy-efficient. Overall, this approach represents a significant advancement in sustainable and efficient methods for organic synthesis.

Experimental section

Material and methods

In this study, the REG utilized for the experiments was custom-designed and manufactured within the laboratory conducting the research. The REG system was constructed using stainless steel 316 alloy for all its components. This choice of material ensures the system's durability and resistance to corrosion, which is important for maintaining the integrity of the equipment during the experimental process. The grinding frequency employed during the experiments using the REG system ranged between 15 and 20 Hz. This indicates the rate at which the

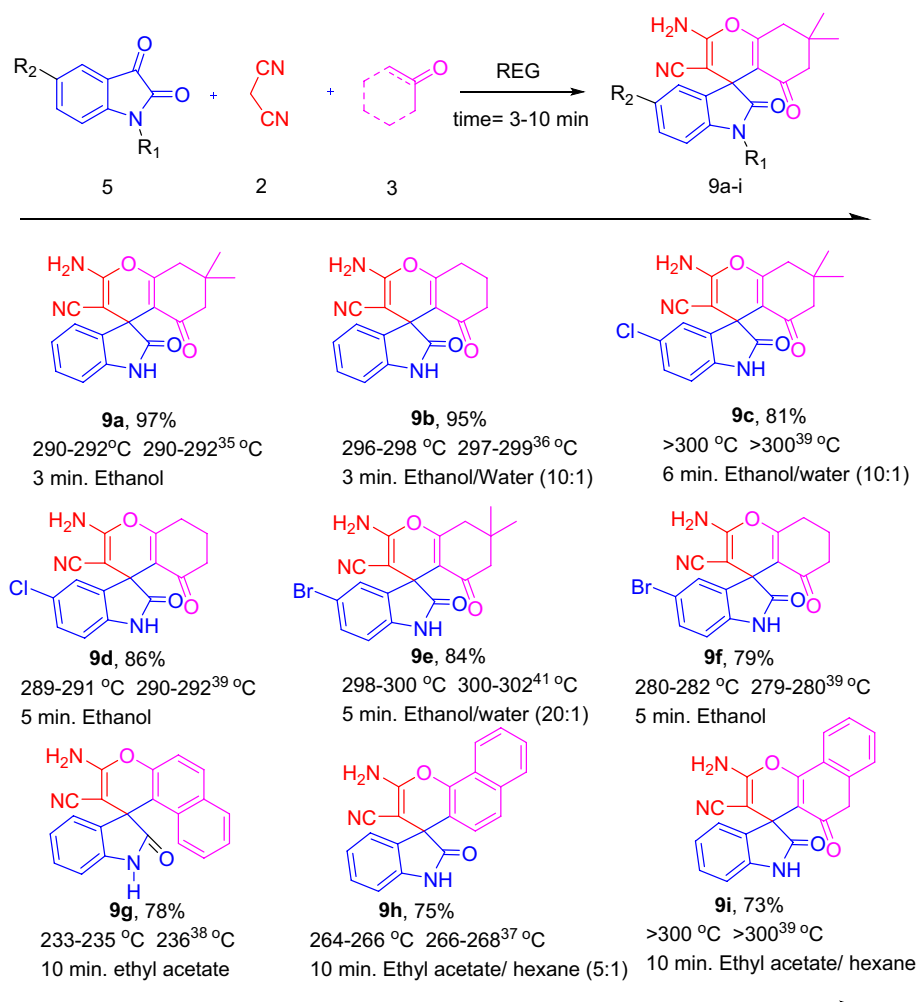


Figure 6. Synthesis of spiroindole derivatives using REG. ^aYields refer to isolated pure product ^bCrystallization Solvents.

grinding action took place within the system. The specific frequency chosen for the experiments depended on the optimization of the reaction conditions, considering factors such as the nature of the reactants, desired reaction kinetics, and the efficiency of mixing and grinding within the REG system. During the grinding process, it was observed that malononitrile, which has a melting point of 32 °C, undergoes melting when mixed with other reactants, resulting in a paste-like consistency. To determine the melting points of the compounds accurately, the Buchi B-545 Melting Point apparatus was employed.

For nuclear magnetic resonance (NMR) analysis, 500 MHz ¹H NMR spectra were acquired using a Bruker DRX-500 Avance spectrometer. Additionally, 250 MHz spectra were obtained using a Bruker Avance DPX-250 spectrometer (Supplementary Information). In the experiments, solid reagents were obtained from commercial sources and used without additional purification. However, liquid reagents underwent distillation before being used. Thin-layer chromatography (TLC) was performed on silica gel plates using a 1:5 ratio of ethyl acetate to hexane as the eluent (Supplementary Information).

Typical procedure for the synthesis of 2-amino-3-cyano-4-aryl-4H-chromenes

In a typical experiment, a stoichiometric mixture of an aromatic aldehyde (1) (5.0 mmol) or isatin derivatives (5) (5.0 mmol), malononitrile (2) (5.0 mmol), dimedone (3a) or other Michel acceptors (5.0 mmol) were introduced in REG system and grinded for the required duration (Fig. 3). Upon confirming the completion of the reaction using TLC, (in few cases only a single spot is observed on a TLC plate). The absence of solvents, catalysts, or additives in the reaction system simplifies the workup procedure, making it easier and more straightforward. The resulting precipitate obtained after the reaction was collected, and a recrystallization process was employed using the solvents illustrated in Figs. 4, 5, and 6 to further purify the product and obtain a highly pure compound. The synthesized products were previously known compounds^{21–42}, and their identification and structural characterization were confirmed.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

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Author contributions

All authors contributed to the study's conception and design. Omid Hosseinchi Qareaghaj performed material preparation, data collection and analysis. The first draft of the manuscript was written by Najmedin Azizi. Mohammad Ghaffarzadeh was supervised. All authors read and approved the final manuscript.

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Competing interests

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Additional information

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