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ONE POT AND SOLVENT-FREE SYNTHESIS OF POLYHYDROQUINOLINE BY MECHANOCHEMICAL GRINDING

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ABSTRACT:
The synthesis of polyhydroquinoline derivatives using a solvent-free, mechanochemical approach has been proven to be both highly effective and environmentally benign. A mortar and pestle is used to grind α,β-unsaturated ketones with dimedone and ammonium formate in this reaction, which does not require solvents or outside catalysts. The procedure, which is carried out at room temperature, produces the target compounds quickly and in high yields. In complete accord with the fundamental ideas of green chemistry, this simple and environmentally friendly process provides an efficient path for the synthesis of biologically important polyhydroquinolines.

KEYWORDS: Mechanochemistry, Solvent-Free Synthesis, Dimedone, α,β-Unsaturated Ketones, Polyhydroquinolines, Cyclization

INTRODUCTION:

A significant class of nitrogen-containing heterocycles with a variety of pharmacological characteristics are polyhydroquinolines (PHQs), particularly those with the 1,4-dihydropyridine (1,4-DHP) core[i,ii]. These substances have a variety of biological properties, such as antioxidant and antibacterial[iii], antituberculosis[iv], anti-diabetics[v], antihypertensive[vi] and anticancer effects[vii]. Their structural similarity to popular calcium channel blockers like nifedipine further emphasizes their medical significance, making them useful scaffolds in drug discovery and development[viii].

Traditionally, PHQs are made using the Hantzsch multicomponent reaction, which usually consists of an aldehyde, a β-ketoester, a 1,3-dicarbonyl compound like dimedone, and a nitrogen source like ammonium acetate[ix,x]. This procedure requires organic solvents, high temperature, and expensive or hazardous catalysts. These not only make the method less

feasible for large-scale or environmentally friendly applications, but they also increase the environmental burden[xi,xii].

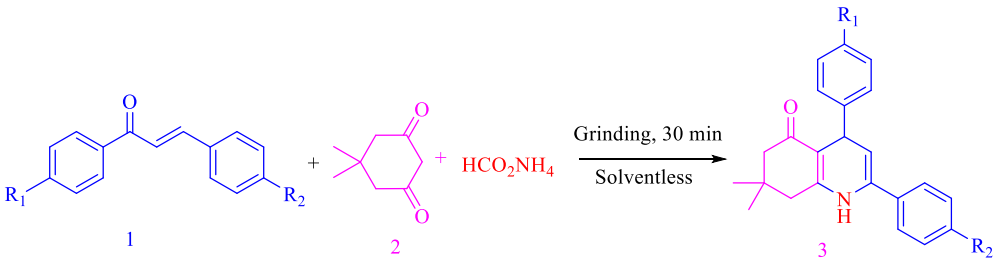
Green chemistry has significantly advanced the creation of more environmentally friendly, solvent-free, and catalyst-free synthetic approaches in response to the drawbacks of conventional techniques. Among these, mechanochemistry, which applies mechanical energy through ball milling or grinding, has drawn interest as a potent, environmentally friendly method that frequently does not require solvents, high temperatures, or external catalysts[xiii,xiv]. These strategies enhance reaction efficiency, mitigate environmental detriments, facilitate purification, and reduce waste generation.

Despite numerous studies examining the synthesis of polyhydroquinolines under solvent-free conditions[xv] utilising various catalytic systems, such as microwave irradiation[xvi,xvii], magnetically recyclable nanoparticles[xviii], ionic liquids[xix], and organocatalysts, there remains a necessity for simpler, truly catalyst-free methodologies[xx].

Here, we describe a simple, solvent-free mechanochemical grinding method for the synthesis of polyhydroquinoline derivatives in a single pot. Using a mortar and pestle and room temperature, this method directly reacts α,β-unsaturated ketones with dimedone and ammonium formate. Without the use of solvents or catalysts, the process proceeds quickly and produces the desired products in high yields. This is one of the rare documented instances of polyhydroquinoline synthesis that is entirely mechanochemical and catalyst-free, as far as we are aware.

EXPERIMENTAL

A combination of chalcone derivative (2 mmol), dimedone (2.2 mmol), and ammonium formate (3 mmol) was placed in a mortar and meticulously crushed at room temperature to achieve a homogeneous mixture. The resultant mixture was incessantly milled under solvent-free conditions for 30 minutes as shown in **scheme 1**. The reaction's progress was assessed using thin-layer chromatography (TLC). Following completion, the reaction mixture was extracted using ethyl acetate. The organic layer was washed with brine, dried with anhydrous sodium sulphate, filtered, and concentrated under reduced pressure.



a: R_1=R_2=H
b: R_1=H, R_2= OMe d: R_1= H, R_2=NO_2
c: R_1= OMe, R_2=H e: R_1=NO2, R_2=Furfuryl

Scheme 1: General reaction for solvent-free synthesis of polyhydroquinolines.

RESULTS AND DISCUSSION

A solvent-free grinding technique was established for the effective synthesis of polyhydroxyhydroquinoline derivatives utilising chalcones, dimedone, and ammonium formate. The reaction progressed well at ambient temperature using basic mortar and pestle grinding. Ammonium formate, functioning as an eco-friendly reducing agent, facilitated the

transition without requiring solvents or catalysts. This mechanochemical method produced the target compounds (3a–3c) with high yields (78-92%) in a brief reaction period. The method illustrates a sustainable and operationally straightforward approach to valuable polyhydroquinoline structures.

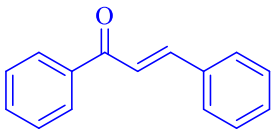
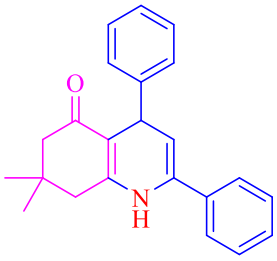
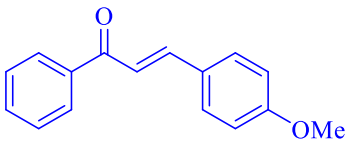
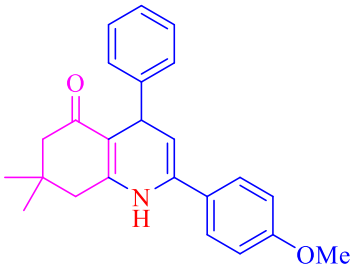
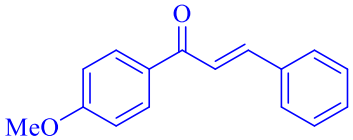
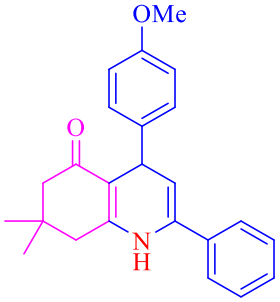
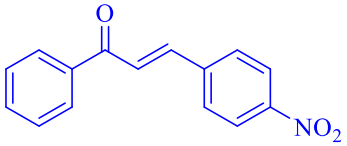
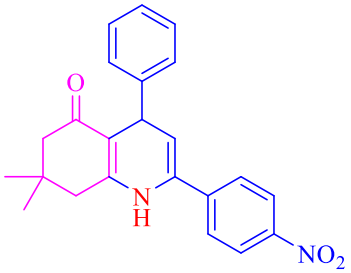
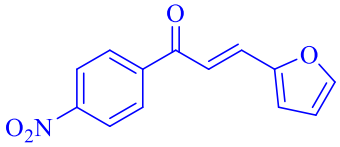
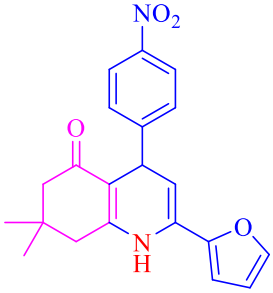
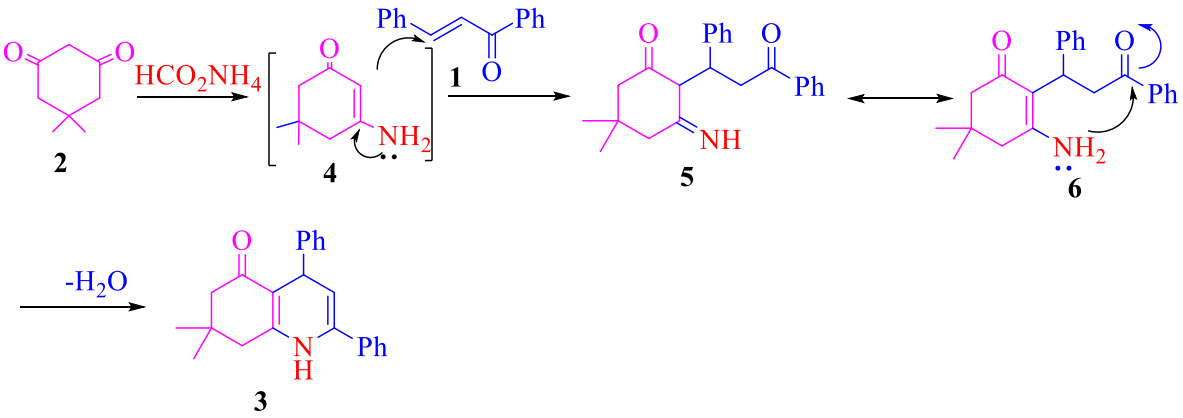
Sr. No.	**Chalcones (1a-e)**	**Products (3a-e)**	**M.P (°C)**	**Time (min.)**	**% Yield**
1			204-206	30	90
2			255-257	30	78
3			256-258	30	85
4			245-247	30	92
5			226-228	30	82

Table1: Derivatives of polyhydroxyquinolines(3a-e). All products were previously reported and characterized by ^{1}H NMR, IR and MS[xxi].

Proposed reaction mechanism:

Based on prior research in the literature, we suggest a tenable route. An enamine intermediate (4) is probably formed initially in the reaction and is then added to the α,β-unsaturated ketone in a Michael-type manner. The final polyhydroquinoline product (3) is obtained by intramolecular cyclization and dehydration after this process produces intermediates (5),(6) as shown in **Scheme 2** [xxii].



Scheme 2: Proposed reaction mechanism of synthesis of polyhydroquinolines (3a).

CONCLUSION:

We have developed a sustainable and efficient method for synthesizing polyhydroquinolines using a solvent-free grinding process. Ammonium formate mediated mechanochemical synthesis offers a scalable, catalyst-free, and clean route to these physiologically significant compounds. This approach adheres to the goals of green chemistry by reducing waste and avoiding hazardous reagents or solvents.

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