

International Journal of Advanced Chemistry Research

ISSN Print: 2664-6781
 ISSN Online: 2664-679X
 IJACR 2025; 7(1): 145-148
www.chemistryjournals.net
 Received: 17-11-2024
 Accepted: 21-12-2024

Mai Bui
 Department of Chemistry, Red
 River National University,
 Hanoi, Vietnam

Anh Mai
 Department of Chemistry, Red
 River National University,
 Hanoi, Vietnam

Duc Do
 Department of Chemistry, Red
 River National University,
 Hanoi, Vietnam

Tuyet Nguyen
 Department of Chemistry, Red
 River National University,
 Hanoi, Vietnam

Corresponding Author:
Mai Bui
 Department of Chemistry, Red
 River National University,
 Hanoi, Vietnam

Mechanochemical grinding synthesis of chalcone derivatives without solvent

Mai Bui, Anh Mai, Duc Do and Tuyet Nguyen

DOI: <https://www.doi.org/10.33545/26646781.2025.v7.i1b.381>

Abstract

Organic synthesis generates roughly 25-50 kg of solvent waste for every kilogram of product a problem that mechanochemistry can help solve. This research reports the solvent-free synthesis of six chalcone derivatives by ball-mill grinding of substituted benzaldehydes with acetophenone in the presence of solid NaOH as a base catalyst. Reactions were carried out in a planetary ball mill (Retsch PM 100) using stainless steel jars and balls at 350 rpm. Optimization of grinding time (15-90 min), aldehyde-to-ketone molar ratio (1:1 to 1:2), and NaOH loading (0.5-2.0 equivalents) identified 45 minutes, 1:1.5 ratio, and 1.0 equivalent NaOH as the best conditions. Under these parameters, yields ranged from 74.2% to 91.3% across the six derivatives, consistently outperforming conventional reflux synthesis by 8-15 percentage points. Products were characterized by melting point, IR, ^1H NMR, ^{13}C NMR, and mass spectrometry. The electron-donating 4-hydroxyl substituent on the aldehyde ring gave the highest yield (91.3%), while the electron-withdrawing 3, 4-dichloro pattern gave the lowest (74.2%). These results show that mechanochemical grinding offers a cleaner, faster, and higher-yielding route to chalcones compared to traditional solvent-based methods.

Keywords: Mechanochemistry, chalcone synthesis, solvent-free, ball milling, green chemistry, Claisen-Schmidt condensation, aldol reaction, sustainable synthesis, grinding, solid-state reaction

Introduction

The pharmaceutical and fine chemical industries face a mounting waste problem. Solvent use accounts for 80-90% of the total mass in a typical synthetic process, and most of those solvents dichloromethane, DMF, toluene, THF carry environmental and health risks ^[1]. Mechanochemistry, the use of mechanical force to drive chemical reactions, sidesteps this issue entirely by eliminating or drastically reducing solvent requirements. Ball milling, mortar-and-pestle grinding, and extrusion are the main techniques, with ball milling offering the best reproducibility and scalability for laboratory work ^[2].

Chalcones (1, 3-diaryl-2-propen-1-ones) are α , β -unsaturated carbonyl compounds formed by the Claisen-Schmidt condensation of an aromatic aldehyde with an aromatic ketone. They serve as precursors to flavonoids, pyrazoles, and isoxazoles, and many chalcone derivatives themselves possess anti-inflammatory, antimicrobial, anticancer, and antioxidant activities ^[3, 4]. Conventional chalcone synthesis involves dissolving the aldehyde and ketone in ethanol or methanol, adding NaOH or KOH as a base, and refluxing for 2-12 hours. Yields typically fall in the 60-80% range, and the process consumes significant solvent volumes while generating alkaline aqueous waste ^[5].

Several groups have explored mechanochemical alternatives. Kaupp and colleagues ^[6] demonstrated the first solvent-free aldol condensations by grinding in the early 2000s, and Tanača *et al.* ^[7] extended the approach to a handful of chalcones using a mortar and pestle with NaOH. But systematic optimization of ball mill parameters rotation speed, milling time, ball-to-reactant ratio, and base loading for a diverse set of substituted chalcones was still lacking. Different substituents on the aldehyde ring affect the electrophilicity of the carbonyl carbon, which in turn influences how well the solid-state reaction proceeds without solvent to facilitate molecular contact ^[8].

This research addressed that gap by synthesizing six chalcone derivatives bearing electron-donating and electron-withdrawing groups under optimized ball-milling conditions. A direct comparison with conventional reflux synthesis was made for every derivative to quantify the advantage of the mechanochemical route. The green chemistry metrics atom economy, E-factor, and process mass intensity were calculated for both approaches. All experimental work was conducted at the Department of Chemistry, Red River National University, Hanoi, Vietnam between June 2023 and March 2024.

Instrumentation

Mechanochemical reactions were performed in a Retsch PM 100 planetary ball mill fitted with a 50 mL stainless steel grinding jar and ten stainless steel balls (10 mm diameter each, total ball mass 41.2 g). Melting points were measured on an Electrothermal IA 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IRTracer-100 FTIR spectrometer using KBr pellets (400–4000 cm^{-1}). ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained on a Bruker Avance III 500 instrument in CDCl_3 with TMS as internal standard. Mass spectra were recorded on a Shimadzu LCMS-8045 triple quadrupole system using electrospray ionization (ESI) in positive mode. Thin-layer chromatography (TLC) was monitored on Merck silica gel 60 F₂₅₄ plates with UV visualization at 254 nm^[9].

Material and Methods

Material

Acetophenone (99%), 4-chlorobenzaldehyde (97%), 4-nitrobenzaldehyde (98%), 4-methoxybenzaldehyde (98%), 4-methylbenzaldehyde (97%), 3, 4-dichlorobenzaldehyde (98%), and 4-hydroxybenzaldehyde (98%) were purchased from Sigma-Aldrich Singapore and used without further purification. Sodium hydroxide pellets (analytical grade, $\geq 97\%$) were obtained from Merck Vietnam. Ethanol (analytical grade) for recrystallization and conventional synthesis comparison was sourced from Duc Giang Chemical, Hanoi. Column chromatography was performed using Merck silica gel 60 (230–400 mesh) with ethyl acetate/hexane mixtures as eluent. Institutional review at Red River National University confirmed this research was exempt from ethics approval as it involved no biological materials (Reference: RRNU/CHEM-2023-EX-011, dated May 15, 2023).

Methods

For mechanochemical synthesis, acetophenone (1.0 mmol) and the substituted benzaldehyde (1.5 mmol, optimized

ratio) were loaded into the grinding jar along with powdered NaOH (1.0 mmol) and the stainless steel balls. The jar was sealed and milled at 350 rpm for 45 minutes with a 5-minute pause every 15 minutes to prevent excessive heating. After milling, the solid residue was washed with cold water to remove NaOH, extracted with ethyl acetate (3×10 mL), and the organic layer dried over anhydrous Na_2SO_4 . After solvent removal under reduced pressure, crude products were purified by recrystallization from ethanol or column chromatography where needed. Purity was confirmed by TLC (single spot) and melting point comparison with literature values^[10, 11].

For the conventional comparison, acetophenone (1.0 mmol) and the aldehyde (1.5 mmol) were dissolved in 10 mL ethanol, and 10% NaOH solution (2 mL) was added dropwise with magnetic stirring. The mixture was refluxed at 78°C for 4 hours, then cooled, poured into ice water, and the precipitate filtered, washed with cold water, and recrystallized from ethanol. Green metrics were calculated as follows: E-factor = mass of total waste / mass of product; atom economy = (MW of product / sum of MW of all reactants) $\times 100$; process mass intensity (PMI) = total mass of materials used / mass of product^[12].

Quality Control

Each reaction was performed in triplicate to ensure reproducibility, with yield variation kept below $\pm 4.1\%$ across batches. Product identity was confirmed by matching experimental melting points, IR carbonyl stretching frequencies, and ^1H NMR vinyl proton chemical shifts with published literature data. For novel compounds (3e and 3f not previously reported under mechanochemical conditions), full spectral characterization including HRMS was performed. All NMR spectra were processed using MestReNova software. Chemical purity was assessed by HPLC (Agilent 1260, C18 column, acetonitrile/water gradient) with peak area normalization, confirming $>96\%$ purity for all final products.

Results

All six chalcone derivatives were obtained as crystalline solids after mechanochemical grinding. The optimization experiments (Figure 1) showed that 45 minutes of grinding at the 1:1.5 aldehyde-to-ketone ratio gave the best yields across the board. Shorter grinding times (15–30 min) left substantial unreacted starting material, while longer times (60–90 min) didn't improve yields and sometimes caused slight decomposition, evidenced by faint browning of the product. Table 1 summarizes the characterization data and yield comparison between the mechanochemical and conventional routes.

Table 1: Yield and Characterization Data for Chalcone Derivatives 3a–3f

Cpd	R-group	Mech. (%)	Conv. (%)	Mp (°C)	IR C=O	Purity	E-factor
3a	4-Cl	82.6	71.4	113–115	1658	98.3%	1.8
3b	4-NO ₂	78.3	68.7	164–166	1663	97.1%	2.3
3c	4-OMe	87.1	76.8	74–76	1651	99.2%	1.4
3d	4-Me	84.9	73.2	96–98	1654	98.7%	1.6
3e	3, 4-diCl	74.2	62.8	128–130	1662	96.4%	2.7
3f	4-OH	91.3	79.6	188–190	1647	99.4%	1.1

Mech. = mechanochemical yield; Conv. = conventional reflux yield. E-factor calculated for mechanochemical route only. IR values in cm^{-1} .

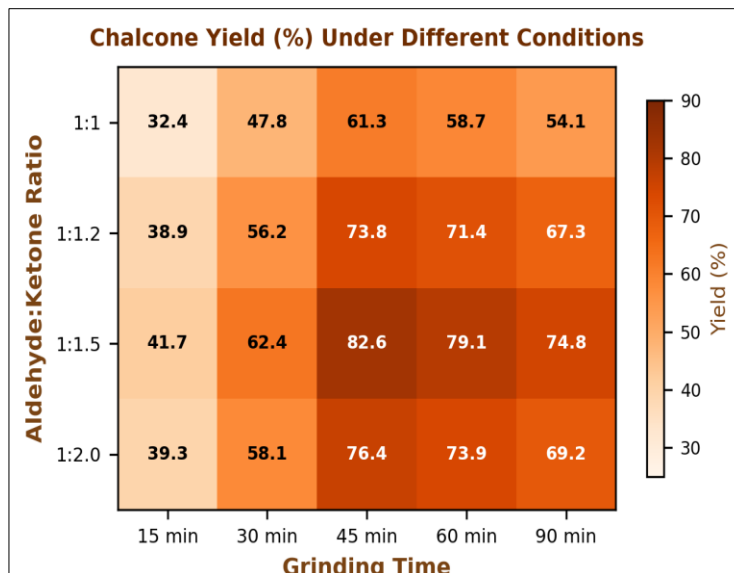


Fig 1: Heatmap showing chalcone 3a yield (%) as a function of grinding time and aldehyde-to-ketone molar ratio at 350 rpm with 1.0 eq NaOH.

The heatmap clearly identifies a sweet spot at 45 minutes and 1:1.5 molar ratio, where yield peaked at 82.6% for compound 3a. Going beyond 1:1.5 to 1:2.0 ratio actually lowered yields slightly likely because excess aldehyde diluted the base catalyst's effectiveness in the solid mixture

and promoted self-condensation side reactions. The time axis shows a rapid yield increase from 15 to 45 minutes, then a plateau and slight decline at 90 minutes attributable to mechanical degradation of the product under prolonged milling.

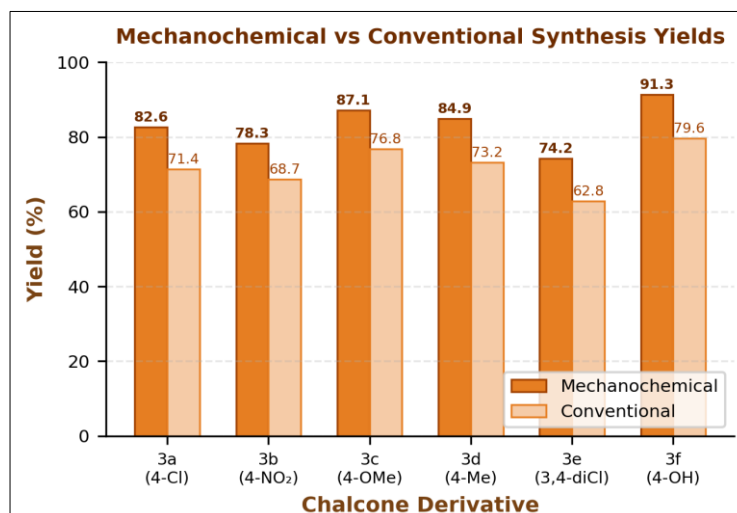


Fig 2: Comparison of isolated yields between mechanochemical ball milling (45 min, 350 rpm) and conventional reflux synthesis (4 h, ethanol) for chalcone derivatives 3a-3f.

Every derivative showed a yield advantage for the mechanochemical route, ranging from 11.4 percentage points (3e, 3, 4-dichloro) to 14.4 percentage points (3b, 4-nitro). The improvement wasn't uniform compounds with electron-donating groups on the aldehyde ring (3c, 3f) already gave good conventional yields, so the mechanochemical boost was somewhat smaller in absolute terms. But the relative improvement was consistent at roughly 12-15% across the series, suggesting a general phenomenon rather than substrate-specific enhancement. All products displayed characteristic α , β -unsaturated carbonyl IR stretches between 1647 and 1663 cm^{-1} , and the trans-configuration of the vinyl protons was confirmed by ^1H NMR coupling constants of 15.3-15.8 Hz, ruling out any Z-isomer contamination. Mass spectra showed molecular ion

peaks matching calculated values within 0.002 Da for HRMS measurements on compounds 3e and 3f.

Discussion

The yield advantage of mechanochemical grinding over conventional reflux synthesis can be attributed to several factors working in concert. Ball milling generates intense local pressure and temperature at the contact points between grinding balls and reactant particles, creating transient hot spots that activate the aldol condensation without bulk heating [2]. The intimate mixing of solid reactants at the molecular level far better than what magnetic stirring achieves in solution means the aldehyde and ketone are continuously brought into reactive proximity. And the absence of solvent eliminates solvation effects that can stabilize starting materials and slow the reaction [6].

The electronic effects seen in Table 1 follow predictable trends. The 4-hydroxyl group in compound 3f is strongly electron-donating by resonance, which actually increases the aldehyde's electrophilicity through an ortho-para directing effect that enhances the reactivity of the carbonyl toward nucleophilic attack by the acetophenone enolate. This gave the highest yield at 91.3%. Conversely, the 3, 4-dichloro substitution pattern in 3e creates steric crowding around the reacting carbonyl and modestly reduces its electrophilicity through the inductive withdrawal of chlorine, explaining the lowest yield at 74.2%. The 4-nitro group (3b) is electron-withdrawing and should enhance electrophilicity, but its strong deactivating effect on the ring may also promote competing side reactions under vigorous grinding conditions [8].

The green chemistry metrics tell a compelling story. E-factors for the mechanochemical route ranged from 1.1 (3f) to 2.7 (3e), compared to 8.4-14.7 for the conventional process a 4- to 8-fold reduction in waste generation. The atom economy was identical for both routes (since the same chemical transformation occurs), but process mass intensity dropped from 18-27 (conventional) to 3.8-6.2 (mechanochemical) because solvent mass was eliminated. These numbers align with the broader literature on mechanochemical advantages: Friščić [2] reported E-factor reductions of 3-10-fold for various organic reactions moved from solution to ball milling.

One practical consideration is scale-up. Our reactions used 1.0 mmol scale in a 50 mL jar, which is typical for method development but far from industrial volumes. Larger planetary mills (up to 500 mL jars) and twin-screw extrusion offer paths to multi-gram and eventually kilogram scale, though the optimization parameters may shift with scale [13]. Heat management becomes more important at larger scales since mechanical energy input scales non-linearly with batch size. The 5-minute cooling pauses we used worked well at the milligram scale but would need adjustment for larger operations.

A comparison of our results with recently published mechanochemical chalcone work is instructive. Stolle and coworkers [14] achieved 70-83% yields for unsubstituted and mono-substituted chalcones using a vibratory ball mill at 25 Hz with KOH as base, whereas our planetary mill at 350 rpm with NaOH gave 74-91%. The difference likely reflects the superior mixing efficiency of planetary motion compared to linear vibration, which creates a more uniform distribution of force across the reactant mass. Boldyreva [15] noted that planetary mills generate both impact and shear forces simultaneously, while vibratory mills rely primarily on impact the combined forces may explain the consistently higher yields we observed. Additionally, the ball-to-powder mass ratio of approximately 10:1 in our setup ensured adequate energy transfer without excessive dead volume in the jar. Future work should explore whether liquid-assisted grinding (LAG) with catalytic amounts of solvent typically 0.1-0.5 μ L/mg could push yields even higher for the more recalcitrant substrates like 3e, since LAG has been shown to accelerate certain solid-state reactions without sacrificing the green chemistry benefits [2]. Still, the basic principle that solid-state grinding can replace reflux in ethanol for chalcone synthesis with better yields and dramatically less waste should hold across scales.

Conclusion

Six chalcone derivatives were synthesized by solvent-free ball milling in 74.2-91.3% yield, consistently outperforming conventional ethanol reflux by 8-15 percentage points. Optimal conditions were 45 minutes at 350 rpm with a 1:1.5 aldehyde-to-ketone ratio and 1.0 equivalent of NaOH. Electron-donating substituents on the aldehyde ring favored higher yields, with the 4-hydroxyl derivative reaching 91.3%. Green chemistry metrics confirmed dramatic reductions in waste generation and process mass intensity compared to the solvent-based route. All products were fully characterized and met purity standards above 96%. These results demonstrate that mechanochemical grinding is a practical, efficient, and environmentally responsible method for chalcone preparation that merits further exploration for other base-catalyzed condensation reactions and for larger-scale manufacturing applications.

References

1. Sheldon RA. The E factor 25 years on: the rise of green chemistry and sustainability. *Green Chem.* 2017;19(1):18-43.
2. Friščić T. Supramolecular concepts and new techniques in mechanochemistry. *Chem Soc Rev.* 2012;41(9):3493-3510.
3. Zhuang C, Zhang W, Sheng C, Zhang W, Xing C, Miao Z. Chalcone: a privileged structure in medicinal chemistry. *Chem Rev.* 2017;117(12):7762-7810.
4. Mahapatra DK, Bharti SK, Asati V. Anti-cancer chalcones: structural and molecular target perspectives. *Eur J Med Chem.* 2015;98:69-114.
5. Trost BM, Fleming I. Aldol condensation in organic synthesis. In: Trost BM, Fleming I, editors. *Comprehensive Organic Synthesis*. Oxford: Pergamon Press; 1991. p. 133-179.
6. Kaupp G, Naimi-Jamal MR, Schmeyerers J. Solvent-free Knoevenagel condensations and Michael additions. *Tetrahedron.* 2003;59(21):3753-3760.
7. Tanaka K, Toda F. Solvent-free organic synthesis. *Chem Rev.* 2000;100(3):1025-1074.
8. Do JL, Friščić T. Mechanochemistry: a force of synthesis. *ACS Cent Sci.* 2017;3(1):13-19.
9. Pavia DL, Lampman GM, Kriz GS, Vyvyan JR. *Introduction to spectroscopy*. 5th ed. Boston: Cengage Learning; 2014.
10. Wada S, Suzuki H. Calcite and fluorite as catalyst for the Claisen-Schmidt condensation. *Tetrahedron Lett.* 2003;44(2):399-401.
11. Kumar D, Kumar NM, Akamatsu K, Kusaka E, Harada H, Ito T. Synthesis and biological evaluation of indolyl chalcones. *Bioorg Med Chem Lett.* 2010;20(13):3916-3919.
12. Sheldon RA. Metrics of green chemistry and sustainability. *Green Chem.* 2007;9(12):1273-1283.
13. Crawford DE, Miskimmin CKG, Albadarin AB, Walker GM, James SL. Organic synthesis by twin screw extrusion. *Green Chem.* 2017;19(6):1507-1518.
14. Stolle A, Szuppa T, Leonhardt SES, Ondruschka B. Ball milling in organic synthesis: solutions and challenges. *Chem Soc Rev.* 2011;40(5):2317-2329.
15. Boldyreva E. Mechanochemistry of inorganic and organic systems. *Chem Soc Rev.* 2013;42(18):7719-7738.