
Green Synthesis of Amides through Direct Acid-Amine Coupling under Solvent-Free and Aqueous Conditions

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ABSTRACT

This study presented a green and efficient approach for the synthesis of amides through direct and acid-amine coupling under solvent-free mechanochemical and aqueous conditions, eliminating the need for coupling agents or activating reagents. Various carboxylic acids—benzoic acid, phenylacetic acid, acetic acid and p – nitrobenzoic acid were reacted with aniline, benzylamine, p-toluidine and ethylamine. Mechanochemical amidation was carried out by manual grinding in a porcelain mortar and pestle, while aqueous- phase reactions were performed on a magnetic stirrer with heating. Reaction progress was monitored by TLC and the resulting products were purified by recrystallization and characterized by melting point determination. Product yields ranged from 78–92% under mechanochemical conditions and 65–85% in aqueous media. The mechanochemical method consistently outperformed the aqueous approach, exhibiting atom economy (AE) values up to 92.6%, reaction mass efficiency (RME) up to 84.19 % and a low process mass intensity (PMI) of 1.19. A scale-up of benzanilide synthesis afforded 97.4% yield with enhanced AE (75%) and RME (77.83%). Overall, the solvent-free mechanochemical method demonstrates superior efficiency, atom economy and environmental performance highlighting its potential as a sustainable route for amide bond formation.

KEYWORDS: Green chemistry, amide synthesis, mechanochemistry, aqueous-phased reactions, spectroscopic analysis, green chemistry metrics.

INTRODUCTION

Amide formation is a keystone transformation in organic chemistry, playing a dynamic role in the synthesis of pharmaceuticals, agrochemicals and natural biomolecules such as peptides and proteins [1]. Conventional synthesis routes typically employ coupling reagents such as: dicyclohexylcarbodiimide, N, N^l-diisopropylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropyl)

carbodiimide in the presence of additives such as hydroxybenzotriazole or N-methylmorpholine, often in chlorinated or polar aprotic solvents. While effective, these methods raise substantial environmental and economic concerns due to their reliance on toxic reagents, volatile organic solvents and the generation of considerable waste streams [2].

In response to the growing emphasis on sustainable practices and the principles of green chemistry, recent research has focused on developing cleaner methodologies for amide bond formation. Mechanochemical synthesis, notably through ball milling has emerged as a favorable solvent-free alternative, enabling chemical transformations under ambient or mild heating conditions without solvents or coupling agents [3]. Parallel efforts in aqueous-phase chemistry have demonstrated that water, a non-toxic and sustainable medium can be used effectively in place of traditional organic solvents, especially under elevated temperatures or with catalytic assistance [4]. Despite these advances, many existing green approaches still depend on activating agents, specialized equipment or limited substrate scopes [5]. This study diverges by emphasizing practical, low-cost methods that require minimal equipment and no additives, making them particularly suitable for academic and resource-limited settings.

The present study introduces an environmentally benign and reagent-free protocols for amide bond synthesis through direct coupling of simple carboxylic acids and amines. The solvent-free mechanochemical method proceeds under completely reagent free conditions, whereas the aqueous approach employs only water as the reaction medium without any additional coupling or activating agents.

In view of the increasing demand for environmentally friendly and sustainable synthetic methodologies, this study aims to develop a green and efficient approach for the synthesis of amides through direct acid-amine coupling under solvent-free and aqueous conditions.

The study seeks to minimize or eliminate the use of hazardous organic solvents and activating agents commonly employed in conventional amidation reactions, thereby promoting safer and more sustainable chemical processes.

The objectives of this study are to compare the efficiency of solvent-free (mechanochemical) and aqueous-phase amidation methods in terms of yield and reaction time and to evaluate the environmental performance of both approaches using green chemistry metrics such as atom economy, E-factor and reaction mass efficiency. The synthesized amides were purified by recrystallization and their purity was confirmed by thin-layer chromatography (TLC) and melting

point determination. Overall, this clean, simple and eco – friendly methods can serve as viable alternatives to traditional amide synthesis routes.

MATERIALS AND METHODS

All reagents used in this study were of analytical grade and used without further purification. Benzoic acid ($\geq 99\%$, BDH Chemicals Ltd, Poole, England), acetic acid ($\geq 99.8\%$, Sigma–Aldrich, USA), phenylacetic acid ($\geq 98\%$, acetic acid, Sigma–Aldrich, USA) and p-nitrobenzoic acid ($\geq 99\%$, Merck, Germany). The amines selected for amidation included: aniline ($\geq 99.5\%$ BDH Chemicals Ltd. England), benzylamine ($\geq 99\%$, Sigma – Aldrich, USA), ethylamine (supplied as 70% aqueous solution) and p-toluidine. All compounds were used without further purification. Distilled water was used for all aqueous reactions and purifications. The key equipment included a Retsch MM400 ball mill (Retsch GmbH Germany) for solvent-free mechanochemical reactions and a magnetic stirrer with heating plate (IKA C – MAG HS7, IKA – Werke GmbH, Germany) for aqueous phase amidation. Reaction progress was monitored by thin – layer chromatography (TLC) using silica gel 60 F254 plates (Merck, Germany). Melting points were determined using a Stuart SMP30 digital melting point apparatus (Bibby Scientific Ltd, UK.).

Procedure for MechanochemicalAmidation

Manual mechanochemical reactions were carried out using a standard porcelain mortar and pestle allowing for intimate contact between solid reagents. For comparative studies and scale-up experiments, a Retsch planetary MM400 ball mill (Retsch GmbH Germany) equipped with stainless steel jars and balls was used [6]. Aqueous-phase reactions were conducted in glass test tubes with ground-glass stoppers, placed in temperature controlled water baths. Reaction progress was monitored by thin-layer chromatography using silica gel 60 F254 plates. Visualization was achieved using ultraviolet light at 254 nm [7]. Purification was performed via recrystallization using ethanol-water mixtures and cold-water washing followed by vacuum filtration [8]. An analytical balance (± 0.1 mg precision) was used for all reagent measurements and a rotary evaporator was employed for the concentration steps [9].

Approximately 122.1 mg of benzoic acid crystals were combined with 93.1 mg of aniline in a clean dry porcelain mortar. The mixture was ground manually using a pestle for 10 to 15 minutes [10]. During this process, the initial coarse solid and liquid blend gradually transformed

into a cohesive paste, indicating effective mixing and initial reaction onset due to local frictional heat and mechanical energy input. Following the grinding, the reaction mixture was transferred into a test tube, which was then sealed and placed in an oven maintained at 101°C.

The sealed tube was left undisturbed for 2 hours to promote the completion of the amidation reaction under solvent-free and additive-free conditions [11]. After cooling to ambient temperature, the solidified mass was triturated with 5 mL of cold distilled water to dissolve any unreacted starting materials or by-products. The resulting solid product was isolated by vacuum filtration, air-dried and further purified by recrystallization from 10 mL of hot ethanol.

The procedure was repeated for other acid-amine pairs. Approximately 136.2 mg of phenylacetic acid crystals was ground with 107.2 mg of benzylamine, 60.1 mg of acetic acid crystals was combined with 107.2mg of p-toluidine and 167.1 mg of p-nitrobenzoic acid was reacted with 64 μ L of the 70% aqueous solution of ethylamine.

Each combination followed the same procedure as already described, except that the heating of acetic acid and p-toluidine mixture was extended to 3 hours to ensure optimal yield. In the case of p-nitrobenzoic acid and ethylamine, the product crystallized directly upon washing and cooling and required no further purification [12].

Scale-up Mechanochemical Approach

Approximately 610.6 mg of benzoic acid crystals and 465.6 mg of aniline were introduced into a 25 mL stainless steel milling jar along with two stainless steel balls (10 mm diameter). The jar was sealed and subjected to milling at 400 revolutions per minute for 60 minutes. Upon completion, the contents of the jar were recovered using 5 mL of ethanol, filtered to remove impurities and washed thoroughly with cold distilled water. The product was then recrystallized from ethanol and air-dried. This scale-up method generally resulted in higher yields within shorter reaction times, due to more uniform energy transfer and mixing efficiency [13, 14].

Procedure for Aqueous-Phase Amidation

Approximately 122.1 mg of benzoic acid crystals and 93.1 mg of aniline were combined in a clean glass test tube, to which 3.0 mL of distilled water was added. The mixture was stirred to ensure dispersion of the reactants and then sealed [15]. The test tube was placed in a water bath maintained at 95°C and heated a duration of 6 hours with intermittent manual shaking to ensure consistent mixing. On completion of the reaction, the mixture was allowed to cool to room temperature. A

solid precipitate was formed and allowed to cool. The product was collected by vacuum filtration, washed with 5 mL of cold water to remove soluble impurities and air-dried. Recrystallization was carried out using hot ethanol to further purify the product.

The procedure was repeated with other combinations of substrates under identical conditions. In the reaction between acetic acid and p-toluidine, complete precipitation occurred within 4 hours and the product was collected as described.

In the case of phenylacetic acid with benzylamine, the reaction produced a slightly emulsified suspension, which clarified upon cooling and led to solid product formation. When p-nitrobenzoic acid crystals was reacted with ethylamine, the amide product crystallized directly during the cooling phase and thus required only cold water washing before being dried and stored [16].

Thin Layer Chromatography and Purification Processes

Reaction progress was monitored by thin-layer chromatography. Small aliquots of each reaction mixture were extracted into ethanol and spotted on silica plates [17]. The eluent system used for most analyses was a 1:1 mixture of ethyl acetate and hexane, allowing effective separation of starting materials and products. Visualization was done under UV light at 254 nm [18].

Purification of the crude products was conducted basically through recrystallization using a 70:30 ethanol-water mixture, depending on the solubility characteristics of the target compound. Products were dried to constant mass in a desiccator and characterized by melting point analysis [19].

GREEN CHEMISTRY METRICS

The Green chemistry metrics employed in this study include: Atom Economy (AE), Reaction Mass Efficiency (RME), Process Mass Intensity (PMI) and Environmental Factor (E-Factor) [20].

Each of the factors was calculated using the experimental data. Atom economy is a theoretical measure based only on the stoichiometry of the chemical reactions. It is calculated with equation 1:

$$\% \text{ AE} = \frac{\text{Molar Mass of Desired Product}}{\sum \text{Molar Masses of Reactants}} \times \frac{100}{1} \quad (1)$$

Reaction Mass efficiency (RME) measures how efficiently the reactants are converted into products based on the actual yield. It is calculated using equation 2.

$$\% \text{ RME} = \frac{\text{Mass of Actual Product}}{\text{Mass of Reactants}} \times \frac{100}{1} \quad (2)$$

The Environmental Factor is relevant because it quantifies the amount of waste produced per unit of product, serving as a direct indicator of a process's environmental burden. Process Mass Intensity (PMI) measures total mass input relative to product output, reflecting overall resource efficiency and helping identify opportunities to reduce material consumption [20]. E-Factor and Process Mass Intensity (PMI) are calculated using equations 3, 4 and 5 below:

$$\text{E-factor} = \frac{\text{Mass of Total Waste}}{\text{Mass of Product}} \quad (3)$$

$$\text{Mass of Waste} = \text{Mass Input} - \text{Mass of Product} \quad (4)$$

$$\text{PMI} = \frac{\text{Total Mass of all Materials Used}}{\text{Mass of Product}} \quad (5)$$

RESULTS AND DISCUSSION

Table 1 below gives the percentage yields of amides synthesized by mechanochemical and aqueous-phase methods.

Table 1: Yields of Amide Products from Mechanochemical and Aqueous-Phase Methods

S/N	Reaction	Mechanochemical yield (%)	Aqueous Yield (%)
1.	Benzoic acid + Aniline	89.00 ± 0.98	83.00 ± 0.89
2.	Phenylacetic acid + Benzylamine	85.00 ± 0.96	72.00 ± 0.90
3.	Acetic acid + p-Toluidine	78.00 ± 1.00	65.00 ± 0.92
4.	p-Nitrobenzoic acid + Ethylamine	92.00 ± 0.95	85.00 ± 0.85

Values are expressed as mean ± standard deviation (n = 3)

Table 2 gives the green chemistry metrics of the reactions

Table 2: Green Chemistry Metrics of the Reactions

S/N	Reactions	AE %	RME (Mech. %)	EF (Mech.)	PMI (Mech)	RME (aq %)	EF _(aq)	PMI (aq)
1.	Benzoic acid + Aniline	62.55	55.67	0.23	1.80	51.92	0.944	1.95
2.	Phenylacetic acid + Benzylamine	92.60	78.70	0.27	1.27	66.67	0.519	1.52
3.	Acetic acid + p-Toluidine	89.24	69.60	0.44	1.44	58.01	0.755	1.76
4.	p-Nitrobenzoic acid + Ethylamine	91.54	84.19	0.19	1.19	77.81	0.304	1.30

AE % = Percentage Atom Economy

RME (Mech. %) = Percentage Reaction Mass efficiency via Mechanochemical Reaction

EF (Mech) = Environmental Factor via Mechanochemical Reaction

PMI (Mech) = Process Mass Intensity via Mechanochemical Reaction

RME (aq %) = Percentage Reaction Mass efficiency via Aqueous-Phase Reaction

EF (aq) = Environmental Factor via Aqueous-Phase Reaction

PMI (aq) = Process Mass Intensity via Aqueous-Phase Reaction

Table 3 displays the green chemistry metrics for scale-up mechanochemicalamidation of benzoic acid with aniline

Table 3:Green chemistry Metrics for Scale-Up MechanochemicalAmidation of Benzoic Acid with Aniline

S/N	Metric	Value
1.	Isolated Yield (%)	97.4
2.	Atom Economy (AE %)	75.0
3.	Reaction Mass Efficiency (RME %)	77.83
4.	E-Factor	0.82
5.	Process Mass Intensity (PMI)	1.92

Table 4 gives melting points of the crystals obtained from mechanochemical methods

Table 4: Melting Points of the Crystals obtained from Mechanochemical Methods

S/N	Reaction	Proposed Compounds	Melting point	Standard melting point
1.	Benzoic acid + Aniline	Benzanilide	162 °C	161 – 164 °C
2.	Phenylacetic acid + Benzylamine	N-Benzyl-2-phenylacetamide	118.5 °C	118– 120 °C
3.	Acetic acid + p-Toluidine	p-Acetanilide	114 °C	113 – 115 °C
4.	p-Nitrobenzoic acid + Ethylamine	N-ethyl-p-Nitrobenzenamide	122.5 °C	122 – 125 °C

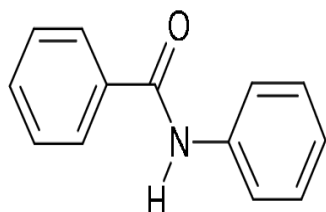


Fig 1: Benzanilide

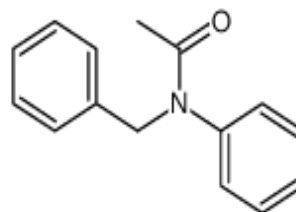


Fig 2: N-Benzyl-2-phenylacetamide

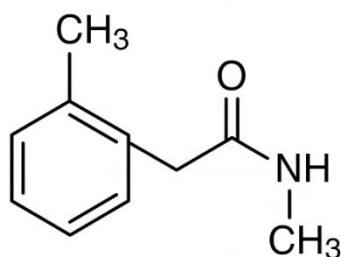


Fig 3: P-Acetanilide

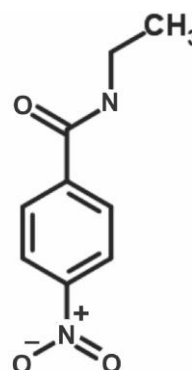


Fig 4: N-ethyl-p-nitrobenzamide

Table 1 gives the percentage yields of amides synthesized by mechanochemical and aqueous-phase methods. Both the mechanochemical and aqueous-phase techniques effectively facilitated direct amidation. The mechanochemical method resulted in faster product formation with solidification typically occurring during heating, while the aqueous method showed product precipitation during

the cooling phase. Visual cues such as crystal formation, colour change and reduction in heterogeneity were used to monitor progress qualitatively. Triplicate measurements confirm that mechanochemical methods consistently yielded higher and more reproducible outcomes with standard deviations approximately ± 1.00 % across all substrate pairs. For example, benzanilide which is the possible product obtained from benzoic acid and aniline was obtained at 89.0 ± 0.98 %, surpassing the aqueous method's 83.0 ± 0.89 %, reflecting both the efficiency and robustness of the solvent-free protocol.

In more hydrophobic systems such as phenylacetic acid with benzylamine, the mechanochemical yield of 85.0 ± 0.96 % significantly exceeded the aqueous method's 72.0 ± 0.90 % likely due to limited miscibility of reactants in water. This supports the interference that the solid-state method provides a better environment for less polar substrates. In the case of acetic acid and p-toluidine, moderate yields were achieved in both methods, with mechanochemical reactions yielding 78.00 ± 1.0 % and aqueous giving 65.0 ± 0.92 %. Acetic acid's volatility and partial solubility in water account for these lower values, particularly under aqueous conditions. The highest yields were consistently observed with p-nitrobenzoic acid and ethylamine, where enhanced electrophilicity due to the nitro group facilitated a highly efficient amidation, yielding 92.0 ± 0.95 % mechanochemically and 85.0 ± 0.85 % in the aqueous method. These results validate the mechanistic assumption that electron-deficient carboxylic acids enhance nucleophilic attack by amines.

Table 2 shows the calculated Green Chemistry Metrics of the study. Atom Economy (AE) values are consistently high (62 – 92%) across all reactions as expected for straightforward condensation reactions where water is the only by-product.

Reaction Mass Efficiency (RME) better reflects practical yield and waste reduction. Mechanochemistry consistently outperforms aqueous amidation with RME values up to 84.2% compared to 52 – 77.8% in aqueous media. This can be attributed to better energy transfer and minimized solvent effects in mechanochemical systems.

E-Factor and Process Mass Intensity (PMI), which penalize excess mass and waste generation highlight the sustainability advantage of solvent-free synthesis. Mechanochemical factors remain below 0.50 in all cases (as low as 0.19), whereas aqueous systems exhibit significantly higher values up to 0.944 primarily due to the inclusion of water as process waste. Process Mass Intensity

(PMI) values follow a similar trend, underscoring that even relatively benign solvents such as water can substantially impact the overall mass footprint.

Overall, mechanochemistry offers a superior green profile, combining high atom economy with excellent mass efficiency and minimal waste. The inclusion of water in aqueous processes inflates the E-Factor and PMI values, demonstrating the importance of solvent minimization even when the solvent is non-toxic.

Table 3 gives the green chemistry metrics for scale-up mechanochemicalamidation of benzoic acid with aniline. The optimized scale-up mechanochemicalamidation yielded 97.4% of the product, reflecting highly efficient conversion under solvent-free conditions. The process achieved a notable atom economy of 75% reflecting efficient incorporation of reactant atoms into the final product with minimal byproduct formation. The reaction mass efficiency of 77.83% further demonstrates the practical utility of this method. Importantly, the E-factor of 0.82 and PMI of 1.92 signify low waste generation and excellent material economy, surpassing conventional solution-based approaches.

These metrics collectively underscore the sustainability and scalability of mechanochemicalamidation, making it a compelling strategy aligned with green chemistry principles.

Table 4 gives the melting points of the synthesized and purified compounds obtained from mechanochemical methods. It reveals a close relationship between the determined melting points and the standard references of the proposed amides.

Figure 1 shows the chemical structure of benzanilide, the amide obtained from the reaction between benzoic acid and aniline.

Figure 2 shows the chemical structure of N-Benzyl-2-phenylacetamide, the amide obtained from the reaction between phenylacetic acid and benzylamine.

Figure 3 shows the chemical structure of p-Acetanilide, the amide obtained from the reaction between acetic acid + p-Toluidine while Figure 4 shows the chemical structure of N-ethyl-p-nitrobenzamide, the amide obtained from the reaction between p-Nitrobenzoic acid and ethylamine.

CONCLUSION

The study demonstrated that both aqueous phase and mechanochemical approaches are effective for green amidation, with mechanochemical method showing superior efficiency and environmental performance based on green chemistry metrics. Pure crystalline amides were successfully obtained through TLC isolation and recrystallization, as confirmed by melting point analysis. Overall, the mechanochemical route proved to be a more sustainable and practical alternative for amide synthesis.

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