

## SOLVENT-FREE SYNTHESIS OF AMIDE: A NOVEL TECHNIQUE OF GREEN CHEMISTRY

CHIRAGKUMAR J GOHIL<sup>1\*</sup>, MALLESHAPPA N NOOLVI<sup>2</sup><sup>1</sup>Discipline of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India. <sup>2</sup>Department of Pharmaceutical Chemistry, Shree Dhanvantary Pharmacy College, Surat, Gujarat, India. Email: gohil2711@gmail.com

Received: 02 January 2021, Revised and Accepted: 16 March 2021

## ABSTRACT

**Objective:** Amide is one of the most important functional group presents in the chemicals, pharmaceuticals, and foods. Conventionally, it has been synthesized from the carboxylic acid and amines. This conventional reaction is lengthy and involves hazardous chemicals and solvents. Hence, it poses waste management, solvent removal, and environmental issues to the industries. To overcome this limitation, we have reported the green chemistry-based method for the synthesis of amide from carboxylic acid and urea.

**Methods:** In this reaction, we have used boric acid as a catalyst, it is a simple and readily available compound. It is simple, efficient, and solvent-free procedure which involves the trituration of the reactant mixture and subsequent, direct heating of the triturated mixture.

**Results:** The rate of reaction is very high and can synthesize the amide quickly.

**Conclusion:** Various amides were prepared in good yield by this technique.

**Keywords:** Carboxylic acid, Urea, Boric acid, Amides, Green chemistry, Solvent-free method, Trituration and direct heating.

© 2021 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2021v14i5.40688>. Journal homepage: <https://innovareacademics.in/journals/index.php/ajpcr>

## INTRODUCTION

Amides are a kind of organic compound or functional group which is most frequently found in the biological system, natural products, agrochemicals, polymers, and of course, in the pharmaceuticals [1-3]. Amide is a key intermediate in the synthesis of various bioactive molecules [4]. Amide or peptide bond is very much important for the drug synthesis and pharmaceutical industries [5]. Hence, amide synthesis is much concern in chemistry [6].

In general, amides are synthesized from the acid and amines. This reaction requires the activation of the carboxyl group. Activation of the carboxylic group can be done by converting the carboxylic group into the acyl halide, acyl azide, anhydride, and ester or by coupling reagents [7]. The most preferred process of the amide synthesis involves the conversion of acid into the acyl chloride and then this acyl chloride will react with the amine to give the amide [8] (Scheme 1).

However, this conventional reaction requires some of the hazardous and toxic reagents such as thionyl chloride, oxalyl chloride, and phosphorus pentachloride [9]. The various conventional methods have required the 6–16 h for the synthesis of amide.

Hence, it is a longer, tedious, and costly method. Moreover, at the industrial level, this reaction of the amide synthesis has produced hazardous waste. Moreover, pose the serious issue of waste disposal, waste solvent management, and increase the costs of waste disposal.

Therefore, it has required the atom economic, easy, convenient, and mild reaction for the amide synthesis [10,11].

## Greener approach for the synthesis

The use of toxic and hazardous solvents for the synthesis of chemicals arises environmental problems and waste management issues in industries. Hence, solvent-free or solid-state reaction is a potential

alternative. Solvent-free or solid-state reaction are kinds of reaction which is occur in the absence of solvent [12].

Solvent-free direct solid-solid reaction is a greener approach for synthesis. Moreover, it obeys 1, 2, 3, 4, 5, 6, 8, 9, and 12<sup>th</sup> principles of green chemistry [13].

Number of reactions can be done without the use of solvent [14]. Conventional reaction requires the workup and isolation of the solvent from the product, but solid-state reaction does not require it. Hence, it is economically cheap and easy to handle.

Advantages of solvent-free or solid-state or dry media reaction are as follow:

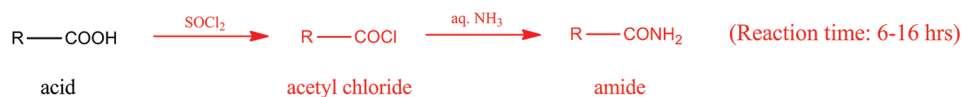
- Greener reaction
- Eco-friendly
- Minimize the waste or effluents
- Easy to handle
- Cheaper
- High rate of reaction
- High purity of product.

Herein, we report the solvent-free method for the synthesis of amides by direct reaction of acid and urea in the presence of boric acid (Scheme 2).

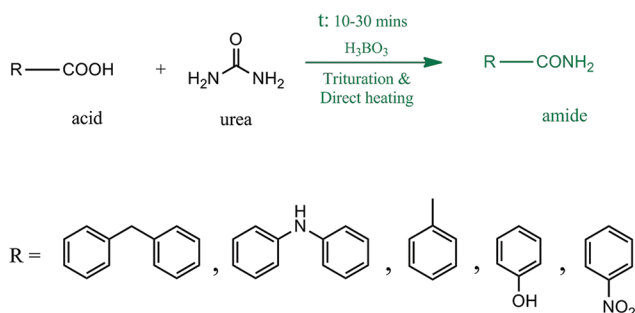
The scope of boric acid-catalyzed amidation has been discussed by various researchers [15]. Many pharmaceutical ingredients and steroid derivatives have synthesized by boric acid-catalyzed reactions [15].

Boric acid is cheap, readily available, and environmentally friendly compound. Moreover, urea is a good source of ammonia under solvent-free conditions [16].

The reported method in this study is a greener technique for the synthesis of amides by mixing and trituration of carboxylic acid, urea, and boric acid followed by direct reaction of the triturated mixture without the solvent.



Scheme 1: Conventional method of amide synthesis



Scheme 2: Greener method for amide synthesis (solvent-free direct heating)

## METHODS

### Experimental

All the chemicals and reagents/solvents were obtained from the commercial suppliers with high purity. The chemicals and reagents/solvents were used as received without further purification.

All the melting points were determined in one end open capillary tubes on a liquid paraffin bath and are uncorrected. The <sup>1</sup>H spectra were recorded in DMSO, using a Bruker 400 MHz FT-NMR Spectrometer Avance III, the solvents and reagents were used without further purification.

### General procedure for the synthesis of the amides

Weigh the carboxylic acid (0.06 mol), urea, and boric acid. The weigh amount was thoroughly mixed and triturated the mixture in mortar and pestle for 2–5 min. The triturated mixture was transferred into the beaker and was directly heated without the solvent at the 160–180°C for 10–30 min. During the course of reaction, the reaction mixture was completely melted and then reappeared as product (amide). Heating was removed and product (amide) was allowed to cool to room temperature. The aqueous ammonia solution (50–55 ml) was added to the crude product and heated with stirring, so unreacted acid was removed. Heating was stopped and filter to give a product. The collected product (amide) was successively washed with distilled water (100 ml) to remove residual boric acid and dried the product/amide at room temperature to give a corresponding amide with high purity.

Proportion ratio of urea and boric acid for any given acid:

g of acid \* 1.5 = Quantity of Urea, g of acid \* 0.4 = Quantity of Boric acid.

#### 2,2-Diphenylacetamide (C 01): Amorphous white

Diphenylacetic acid (12.67 g, 0.06 mol), urea (19 g), and boric acid (5.06 g) were mixed and triturated the mixture for 2–5 min. Then, the triturated mixture was directly heated without the solvent at the 160–180°C for 20–25 mins. During the course of reaction, the reaction mixture was completely melted and then reappeared as product. Heating was removed and product was allowed to cool to room temperature. The aqueous ammonia solution (50–55 ml) was added to the crude product and heated with stirring, so unreacted acid was removed. Heating was stopped and filter to give a product. The collected product was successively washed with distilled water (100 ml) to remove residual boric acid and dried the product at room temperature to afford C 01. The yield was 83–85 %, m.p. 164–166°C (lit), TLC (eluent:chloroform/methanol. 90:10 v/v) R<sub>f</sub>: 0.83, <sup>1</sup>H NMR (400 MHz, DMSO) δ<sub>H</sub>: 7.69–7.09

(10H, ArH), 6.82 (2H, NH<sub>2</sub>), 4.92 (1H, CH), MS (EI, 70 eV) m/z: 167, 183, 212 (M+1), 213 (M+2), 253, 254, 423, 424.

#### 2-(Phenylamino)benzamide (C 02): Purple color

N-Phenyl anthranilic acid (12.73 g, 0.06 mol), urea (19.09 g), and boric acid (5.09 g) were mixed and triturated the mixture for 2–5 min. Then, the triturated mixture was directly heated without the solvent at the 160–180°C for 19–20 mins. During the course of reaction, the reaction mixture was completely melted and then reappeared as product. Heating was removed and product was allowed to cool to room temperature. The aqueous ammonia solution (50–55 ml) was added to the crude product and heated with stirring, so unreacted acid was removed. Heating was stopped and filter to give a product. The collected product was successively washed with distilled water (100 ml) to remove residual boric acid and dried the product at room temperature to give C 02. The yield was 69–71 %, m.p. 165–169°C (lit), TLC (eluent: n-hexane/ethyl acetate. 70:30 v/v) R<sub>f</sub>: 0.82, MS (EI, 70 eV) m/z: 170, 196, 197, 213 (M+1), 214 (M+2), 239, 240, 266, 280.

#### 2-Phenylacetamide (C 03): Fluffy white

Phenylacetic acid (8.10 g, 0.06 mol), urea (12.15 g), and boric acid (3.24 g) were mixed and triturated the mixture for 2–5 min. Then, the triturated mixture was directly heated without the solvent at the 160–180°C for 29–30 mins. During the course of reaction, the reaction mixture was completely melted and then reappeared as product. Heating was removed and product was allowed to cool to room temperature. The aqueous ammonia solution (50–55 ml) was added to the crude product and heated with stirring, so unreacted acid was removed. Heating was stopped and filter to give a product. The collected product was successively washed with distilled water (100 ml) to remove residual boric acid and dried the product at room temperature to afford C 03. The yield was 87–89 %, m.p. 155–160°C (lit), TLC (eluent: n-hexane/ethyl acetate. 70:30 v/v) R<sub>f</sub>: 0.86, <sup>1</sup>H NMR (400 MHz, DMSO) δ<sub>H</sub>: 7.67–6.68 (5H, ArH), 6.42 (2H, NH<sub>2</sub>), 5.48 (2H, CH<sub>2</sub>), MS (EI, 70 eV) m/z: 91, 136 (M+1), 137 (M+2), 177, 178, 271, 272.

#### 4-Hydroxybenzamide (C 04): Pale yellow

p-hydroxybenzoic acid (8.22 g, 0.06 mol), urea (12.33 g), and boric acid (3.28 g) were mixed and triturated the mixture for 2–5 min. Then, the triturated mixture was directly heated without the solvent at the 160–180°C for 20–22 mins. During the course of reaction, the reaction mixture was completely melted and then reappeared as product. Heating was removed and product was allowed to cool to room temperature. The aqueous ammonia solution (50–55 ml) was added to the crude product and heated with stirring, so unreacted acid was removed. Heating was stopped and filter to give a product. The collected product was successively washed with distilled water (100 ml) to remove residual boric acid and dried the product at room temperature to afford C 04. The yield was 74–76%, m.p. 120–124°C (lit), TLC (eluent:n-hexane/ethyl acetate. 70:30 v/v) R<sub>f</sub>: 0.88, <sup>1</sup>H NMR (400 MHz, DMSO) δ<sub>H</sub>: 7.49–7.28 (2H, NH<sub>2</sub>), 7.27–7.19 (4H, ArH), 6.91 (1H, OH), MS (EI, 70 eV) m/z: 120, 137 (M), 138 (M+1), 161, 179, 234.

#### 4-Nitrobenzamide (C 05): Off white

p-nitro benzoic acid (9.96 g, 0.06 mol), urea (14.94 g), and boric acid (3.98 g) were mixed and triturated the mixture for 2–5 min. Then, the triturated mixture was directly heated without the solvent at the 160–180°C for 14–15 mins. During the course of reaction, the reaction mixture was completely melted and then reappeared as product. Heating was removed and product was allowed to cool to room

temperature. The aqueous ammonia solution (50–55 ml) was added to the crude product and heated with stirring, so unreacted acid was removed. Heating was stopped and filter to give a product. The collected product was successively washed with distilled water (100 ml) to remove residual boric acid and dried the product at room temperature to afford C 05. The yield was 78–80%, m.p. 180–183°C (lit), TLC (eluent: n-hexane/ethyl acetate. 70:30 v/v)  $R_f$ : 0.91, MS (EI, 70 eV) m/z: 98, 114, 124, 166 (M), 167 (M+1), 208.

## RESULTS AND DISCUSSION

Our study is focused on the formation of an amide from the carboxylic acid and urea, catalyzed by boric acid [17]. It consists of two simple steps, (1) mixing and trituration of acid, urea, and boric acid (2) direct heating (without the solvent) of the triturated mixture to give a product/amide.

This reaction can be carried out directly in the beaker on the hot plate. The first and foremost important step in this technique is the mixing and trituration of the reactants. Mixing and trituration cause the melting point depression of the reaction components. Hence, they can be easily melted at the reaction temperature and formed the product/amide within 10–30 min. The product or amide not formed or formed in a minor amount when the reaction mixture not got melted at the reaction temperature.

During the course of reaction, pyrolysis of urea liberates the ammonia. Hence, urea is act as a suitable source for *in situ* generation of ammonia. Moreover, the carboxylic acid reacts with the boric acid to forms a mixed anhydride (actual acylating agent) [18].

Now, ammonia and mixed anhydride reacted together to forms the desired amides and regenerates the catalytically active boric acid. The possible mechanism of the reaction has shown in Fig. 1.

The mixed anhydride is an activated form of the acid and it is the actual reacting species [19]. In contrast to conventional methods, the mixed anhydride is *in situ* formed and only catalytic amount is present at any time during the course of reaction. As the reaction temperature is 160–180°C. Hence, the water liberated from the reaction getting continuously eliminated by evaporation. Hence, the reaction equilibrium got shifted in the direction of the product formation and the reaction rate noticeably increases.

We have synthesized the amides from the structurally diverse carboxylic acid. The method can tolerate a wide range of function groups ( $-\text{NO}_2$ ,  $-\text{OH}$ ,  $-\text{X}$ ,  $-\text{OCH}_3$ ) under given reaction conditions.

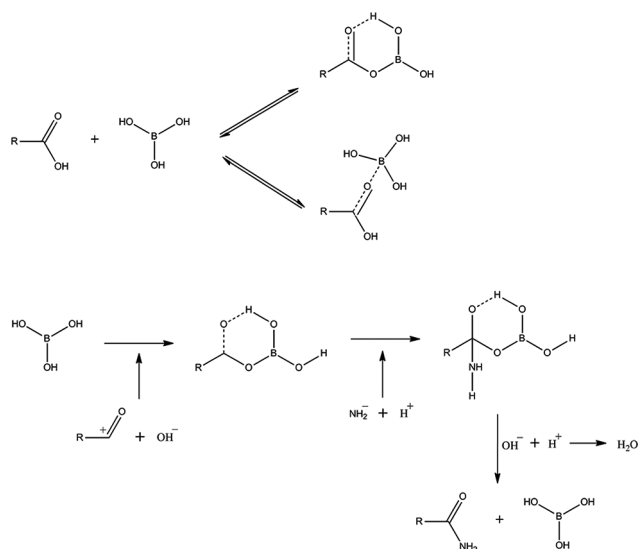


Fig. 1: Mechanism of the amide formation [17,19]

The presence of a hydroxyl group on the aromatic ring lowered the yield. Moreover, the presence of nitro group (electron-withdrawing groups) on the aromatic ring increases the rate of reaction and yields [7].

Our process has several advantages over the other processes are: It eliminates byproducts, minimizes impurity, and forms the products in good yield and purity [20].

The advantages are as follow:

- Greener method
- Simple procedure
- Short reaction time (6–16 h in other methods)
- Solvent-less/solid-state/dry media method.

The reported method can be applied to a wide range of acids. It can easily afford the amides in high purity. The main limitation of this method is that thermo-labile compounds get decomposed.

## CONCLUSION

We have developed a Greener method for the synthesis of amide under solvent-free condition. In this method, amide has been formed directly from the acid and urea in the presence of boric acid as a catalyst.

The process is quick, convenient, and includes the green catalyst. We have synthesized the amides from various types of acids, like unsubstituted, substituted, monocyclic, and bicyclic acid. Hence, this method can be applied to various amidation reactions. The reaction is having a high rate of reaction or shorter reaction time. It is a simple and solvent-less method; hence, it follows the principles of green chemistry. However, there is a need to evaluate the applicability of this method to the aliphatic acids.

## ACKNOWLEDGMENTS

The authors acknowledge the support provided by the Department of Pharmaceutical Chemistry, Shree Dhanvantary Pharmacy College, Kim(E), Dist.: Surat 394 110, Gujarat, India.

## AUTHORS' CONTRIBUTIONS

Both the authors contributed equally.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## SOURCE OF FUNDING

This paper was not supported by any grant or funding.

## SUPPLEMENTARY MATERIAL

<sup>1</sup>H NMR and mass spectra are available in the compressed file attach with the manuscript.

## REFERENCES

1. Valeur E, Bradley M. Amide bond formation: Beyond the myth of coupling reagents. *Chem Soc Rev* 2009;38:606-31.
2. Machetti F, Bucelli I, Indiani G, Kappe CO, Guarna A. Parallel synthesis of an amide library based on the 6,8-dioxo-3-azabicyclo[3.2.1]octane scaffold by direct aminolysis of methyl esters. *J Comb Chem* 2007;9:454-61.
3. Pattabiraman VR, Bode JW. Rethinking amide bond synthesis. *Nature* 2011;480:471-9.
4. Xiao F, Liu Y, Tang C, Deng GJ. Peroxide-mediated transition-metal-free direct amidation of alcohols with nitroarenes. *Org Lett* 2012;14:984-7.
5. Ghose AK, Viswanadhan VN, Wendoloski JJ. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. *J Comb Chem* 1999;1:55-68.
6. Lanigan RM, Sheppard TD. Recent developments in amide synthesis:

- Direct amidation of carboxylic acids and transamidation reactions. *Eur J Org Chem* 2013;2013:7453-65.
7. Khalafi-Nezhad A, Mokhtari B, Soltani Rad MN. Direct preparation of primary amides from carboxylic acids and urea using imidazole under microwave irradiation. *Tetrahedron Lett* 2003;44:7325-8.
  8. Leggio A, Belsito EL, De Luca G, Di Gioia ML, Leotta V, Romio E, *et al.* One-pot synthesis of amides from carboxylic acids activated using thionyl chloride. *RSC Adv* 2016;6:34468-75.
  9. Swamy T, Raviteja P, Subba Reddy BV, Ravinder V. Efficient method for the synthesis of benzamides from benzoic acids and aryl isothiocyanates using  $K_2HPO_4$ . *ChemistrySelect* 2017;2:7612-4.
  10. Crochet P, Cadierno V. Catalytic synthesis of amides via aldoximes rearrangement. *Chem Commun* 2015;51:7612-4.
  11. Constable DJ, Dunn PJ, Hayler JD, Humphrey GR, Leazer JL Jr., Linderman RJ, *et al.* Key green chemistry research areas--a perspective from pharmaceutical manufacturers. *Green Chem* 2007;9:411-20.
  12. Kidwai M. Dry media reactions. *Pure Appl Chem* 2001;73:147-51.
  13. Ivanković A, Dronjić A, Bevanda AM, Talić S. Review of 12 principles of green chemistry in practice. *Int J Sustain Green Energy* 2017;6:39-48.
  14. Marvaniya HM, Modi KN, Sen DJ. Greener reactions under solvent free conditions. *Int J Drug Dev Res* 2011;3:42-51.
  15. Mylavarapu RK, Kondaiah GC, Kolla N, Veeramalla R, Koilkonda P, Bhattacharya A, *et al.* Boric acid catalyzed amidation in the synthesis of active pharmaceutical ingredients. *Org Process Res Dev* 2007;11:1065-8.
  16. Kamali M, Shockravi A, Doost MS, Hooshmand SE. One-pot, solvent-free synthesis via Biginelli reaction: Catalyst-free and new recyclable catalysts. *Cogent Chem* 2015;1:1081667.
  17. Ge C, Li L, Zhang R, Wang R, Zhang X. Amidation of aromatic amine and benzoic acid under boric acid catalysis. *Asian J Chem* 2014;26:6805-7.
  18. Tang T. Boric acid catalyzed amide formation from carboxylic acids and amines: N-benzyl-4-phenylbutyramide. *Org Synth* 2005;81:262-72.
  19. Arce G, Carrau G, Bellomo A, Gonzalez D. Greener synthesis of an amide by direct reaction of an acid and amine under catalytic conditions. *World J Chem Educ* 2015;3:27-9.
  20. Jursic BS, Zdravkovski ZA. Simple preparation of amides from acids and amines by heating of their mixture. *Synth Commun* 1993;23:2761-70.