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A Highly Efficient and Convergent Approach to Direct Synthesis of Carboxamide by C-N Bond Formation

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Abstract: A cost-effective and eco-friendly straightforward protocol for direct amide (C-N) bond formation between carboxylic acids and amines/acid hydrazides by using EDC.HCl/PEG-400 was successfully achieved. The merit of this protocol is highlighted by its operational simplicity, avoids use of expensive additives and hazardous organic solvents, efficient utilization of all the reactants and clean reaction profile.

Keywords: Carboxamide, EDC.HCl, PEG-400, *N*-Phenylbenzamides

1. Introduction

Among the fundamental chemical transformations of organic chemistry, amide synthesis is truly one of the most useful and having wide range of applications.¹ It is ubiquitous in life, as proteins and plays crucial role in almost all biological processes such as enzymatic catalysis,² transport/storage (haemoglobin) and immune protection (antibodies). Amides are also found in the structures of several synthetic commodity chemicals such as agrochemicals, polymeric materials, nutraceuticals, and insecticides.³ Amide bond formation is one of the most prevalent transformations in the pharmaceutical industry, accounting for 16% of

all reactions carried out in medicinal chemistry laboratories.^{4,5}

A straightforward and elegant approach for amide (C-N) bond formation is often overlooked as a contemporary challenge in synthetic organic chemistry. Recently, several new improved strategies have been developed for amide bond formation included, reaction between amines and carboxylic acids in toluene,⁶ using radiofrequency heating under neat conditions,⁷ transamidation of amides under solvent-free conditions,⁸ metal-based catalytic systems using Cp_2ZrCl_2 ,⁹ $\text{Ti}(\text{O}^i\text{Pr})_4$,¹⁰ and ZrCl_4 ,¹¹ microwave irradiated direct amidation,¹² oxidative amidation of methylarenes,¹³ boron-reagents

catalyzed amidation,¹⁴ oxidative coupling of alcohols with amines,¹⁵ mechanochemical synthesis of amides¹⁶ and hydroamination of olefins.¹⁷ All the reported methods have some limitations, such as long reaction time, limited substance scope, modest yields, expensive additives and cumbersome work-up procedures. Therefore, there is an obvious need to develop an efficient synthetic method that would synthesize amides under milder conditions and in an environmentally benign manner.

Nowadays, the most conventional methods are coupling of amines with stoichiometrically activated carboxylic acids, (anhydride, ester or acyl chloride)¹⁸ accounting for 93% of amidation in 128 drugs synthesis.^{14a} Carbodiimides were the first and extremely important class of compounds for the efficient activation of carboxylic acids and subsequently formation of amide bond, but encountered with the intricacy of epimerization.¹⁹ In order to reduce the epimerization level and to increase the yields of the products, various hydroxyl-*1H*-benzotriazoles (HOBt, HOAt, HOBN, 6-Cl-HOBt), HATU, HBTU etc are introduced as an additives.^{1,20} These additives are expensive, exotic and show explosive properties when heated under closed vessels or when subjected to mechanical stimulus.²¹

Within the framework of green chemistry, solvents occupy a strategic place. There is scanty information on carbodiimides used with green solvents for the synthesis of amides. In this context, surrogation of toxic and volatile organic solvents as reaction media with environmentally acceptable alternatives is an area of paramount importance.²² Polyethylene Glycol (PEG) is one such green alternative as it is inexpensive, thermally stable, reusable, non-toxic media and phase transfer catalysts. PEG-400 is a routinely used and easily available chemical with immense potential as medium and catalyst.²³ In recent years, the chemistry of

PEG-400 has been expanded rapidly because of interest in their two active sites *i.e.* free hydroxyl groups, ethereal oxygen linkages and their hydrogen bonding ability with different functional groups.²⁴

Considering the synthetic utilities of PEG-400 and in the context of our program directed toward the exploitation of PEG-400 as a catalyst in organic synthesis,²⁵ herein we report a new catalytic system carbodiimide in PEG-400 (EDC.HCl/PEG-400), able to efficiently promote amide (C-N) bond formation at room temperature. We describe the coupling of various aryl/heteryl carboxylic acids and acid hydrazides/amines using EDC.HCl as activator of acid and PEG-400 as a reaction medium and additive which afforded carboxamides in higher yields.

2. Material and Methods

General

All the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ¹H NMR spectra were recorded with a Bruker Avance 400 spectrometer operating at 400 MHz using DMSO-*d*₆ solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm. ¹³C NMR spectra were recorded on Bruker Avance 300 MHz on Jeol. Mass spectra were recorded on a Sciex, Model; API 3000 LCMS/MS Instrument. The purity of each compound was checked by TLC using silica-gel, 60F₂₅₄ aluminum sheets as adsorbent and visualization was accomplished

General procedure for synthesis of *N*'-Benzoyl substituted benzohydrazide (**3a-o**)

To a round-bottomed flask containing PEG-400 (4 mL) at 0-10 °C, carboxylic acids (**1a-j**) (0.004 mmol) and EDC.HCl (0.004 mmol) were added and the mixture was stirred. After 30 min, acid

hydrazides (**2a-g**) (0.004 mmol) were added to the reaction mixture at cooled condition. Reaction progress was monitored by TLC using ethyl acetate:hexane (3:7) as solvents. Then, after 8 h of stirring at room temperature (30 °C), reaction mass was poured on crushed ice. Thus obtained crude products were filtered and crystallized.

General procedure for synthesis of N-phenylbenzamides (3p-w)

To a round-bottomed flask containing PEG-400 (4 mL) at 0-10 °C, carboxylic acids (**1a-g**) (0.004 mmol) and EDC.HCl (0.004 mmol) were added and the mixture was stirred. After 30 min, aromatic amines (**2a-d**) (0.004 mmol) were added to the reaction mixture at cooled condition. Reaction progress was monitored by TLC using ethyl acetate:hexane (3:7) as solvents. Then, after 8 h of stirring at room temperature (30 °C), reaction mass was poured on crushed ice. Thus obtained crude products were filtered and crystallized.

Spectroscopic data of the representative compounds

N'-Benzoyl 4-methyl benzohydrazide (3a): White solid 80%, IR (KBr, ν cm⁻¹) Characteristic absorptions: 3632 (N-H stretching), 3050 (Ar-H stretching), 2928 (C-H stretching), 1655 (C=O stretching); ¹H NMR (400 MHz, DMSO-*d*₆, δ ppm): 10.96 (s, 2H, NH), 8.48 (d, 1H, ArH, *J* = 2.0 Hz), 8.33 (d, 1H, ArH, *J* = 2.2 Hz), 8.24 (d, 1H, ArH, *J* = 9.0 Hz), 8.05-7.97 (m, 2H, ArH), 7.65 (t, 1H, ArH, *J* = 7.3 Hz), 7.58 (t, 2H, ArH, *J* = 7.4 Hz), 2.50 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO): 166.4, 166.3, 144.0, 141.6, 133.7, 131.5, 132.4, 128.6, 127.9, 127.5, 123.4, 122.7, 122.1, 118.3, 23.5 HRMS (C₁₅H₁₄N₂O₂) [M+H]: 254.0638 found 254.0650.

N'-Benzoyl nicotinamidehydrazide (3o): Yellow solid 70%, IR (KBr, ν cm⁻¹) Characteristic absorptions: 3642 (N-H stretching), 3057 (Ar-H stretching), 2930 (C-H stretching), 1668 (C=O

stretching); ¹H NMR (400 MHz, DMSO-*d*₆, δ ppm): 10.43 (s, 2H, NH), 9.10 (s, 1H, ArH), 8.76 (d, 1H, ArH, *J* = 4.1 Hz), 8.29 (d, 1H, ArH, *J* = 7.9 Hz), 7.77 (d, 2H, ArH, *J* = 7.9 Hz), 7.57 (dd, 1H, ArH, *J* = 7.6, 5.0 Hz), 7.37 (t, 2H, ArH, *J* = 7.9 Hz), 7.13 (t, 1H, ArH, *J* = 7.4 Hz). ¹³C NMR (100 MHz, DMSO): δ 164.1, 164.5, 152.2 (2C), 148.7 (2C), 138.8, 135.5, 130.7, 128.7, 124.1, 123.6, 120.4 HRMS (C₁₃H₁₁N₃O₂) [M+H]: 241.0871 found 241.0880

N-phenylbenzamide (3p): Yellow solid 74%, IR (KBr, ν cm⁻¹) Characteristic absorptions: 3598 (N-H stretching), 3046 (Ar-H stretching), 2912 (C-H stretching), 1656 (C=O stretching); ¹H-NMR (400 MHz, DMSO-*d*₆, δ ppm): 7.90-7.88 (m, 2H, ArH), 7.67-7.65 (m, 2H, ArH), 7.59-7.56 (m, 1H, ArH), 7.53-7.50 (m, 2H, ArH), 7.41-7.38 (m, 2H ArH), 7.18 (t, 1H, ArH, *J*=7.4 Hz) ¹³C NMR (100 MHz, DMSO-*d*₆, δ ppm): 165.9, 138.2, 135.3, 132.1, 129.3, 129.0, 127.2, 124.8, 120.4 HRMS (C₁₃H₁₂NO) [M+H]: 198.0914, found 198.0912.

N-phenyl-2-phenylacetamide (3u): Yellow solid 75%, IR (KBr, ν cm⁻¹) Characteristic absorptions: 3596 (N-H stretching), 3056 (Ar-H stretching), 2920 (C-H stretching), 1668 (C=O stretching); ¹H-NMR (400 MHz, DMSO-*d*₆, δ ppm): 10.42 (s, 2H, NH), 7.95 (dd, 1H, ArH, *J* = 8.2, 1.2 Hz), 7.76-7.66 (m, 2H, ArH), 7.41-7.31 (m, 5H, ArH), 7.29-7.23 (m, 1H, ArH), 3.71 (s, 2H, CH₂). ¹³C NMR (100 MHz, DMSO): δ 169.3, 142.0, 135.0, 134.0, 131.3, 129.3, 128.4, 126.7, 125.1, 125.0, 124.9, 42.7 HRMS (C₁₄H₁₃NO) [M+H]: 211.2621, found 257.2620

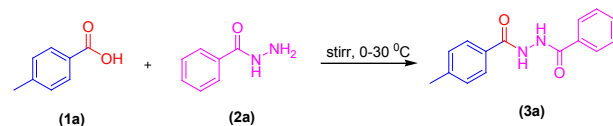
N-(4-methoxyphenyl)benzamide (3t): Yellow solid 80%, IR (KBr, ν cm⁻¹) Characteristic absorptions: 3567 (N-H stretching), 3058 (Ar-H stretching), 2954 (C-H stretching), 1670 (C=O stretching); ¹H-NMR (400 MHz, DMSO-*d*₆, δ ppm): 10.11 (s, 2H, NH), 7.96 - 7.93 (m, 2H, ArH), 7.70-7.66 (m, 2H, ArH), 7.59-7.50 (m, 3H, ArH), 6.95-6.91 (m, 2H, ArH), 3.75 (s,

3H, -OCH₃). ¹³C NMR (100 MHz, DMSO): δ 165.1, 155.5, 135.0, 132.2, 131.3, 128.3, 127.5, 122.0, 113.7, 55.2. HRMS (C₁₄H₁₄NO₂) [M+H]: 228.1020, found 228.1017.

3.Result and Discussion

Synthesis

Initially, the reaction between 4-methyl carboxylic acid **1a** and phenyl acid hydrazide **2a** was chosen as a model reaction to investigate the catalytic conditions to realize the goal. We first tried several catalytic systems for model reaction that have been known as active for the direct amidation.²⁶ Various carbodiimides, Dicyclohexyl carbodiimide (DCC)/DMAP, *N,N*-Diisopropyl carbodiimide (DIC)/HOBt and 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride EDC.HCl/HOBt in DMF however, none of these provided the desired product in significant amounts. (**Table 1, entries 1–3**).



Scheme 1: Standard model reaction for the synthesis of *N'*-Benzoyl 4-methyl benzohydrazide (**3a**)

Considering the significance of PEG-400 and its hydroxyl groups, efforts were directed towards the use of PEG-400 as green reaction media with carbodiimides. Hence the above model reaction was performed in PEG-400 using DCC/DMAP, DIC/HOBt, EDC.HCl/HOBt, DCC, DIC and EDC.HCl as coupling reagents separately at 0-30 °C. Interestingly, clear improvement was obtained in product yields of the model reaction when, carried in PEG-400 (**Table 1, entries 4-9**). Remarkably, good conversions of

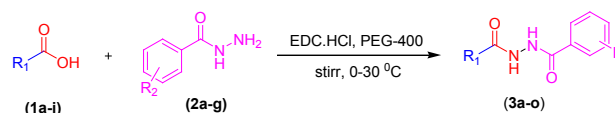
85% yield were observed within 8 h after the introduction of PEG-400 in EDC.HCl (**Table 1, entries 9**). When, DCC and DIC has been used singly and with additives in PEG-400, the titled products were obtained in 58-65% yields in 8 h (**Table 1, entries 4, 5, 7, 8**). DCC and DIC are less efficient than EDC.HCl giving low yields of the titled products in PEG-400 because of formation of water insoluble urea. EDC.HCl forms the water soluble urea which can be easily removed during the workup and this makes the catalyst advantageous over the DCC and DIC in PEG-400.

Inspired from these observations, we optimize the effect of different PEGs on the coupling reaction. The model reaction was executed using EDC.HCl in PEG-300, PEG-600, as solvent and obtained *N'*-Benzoyl 4-methyl benzohydrazide **3a** with 79 and 75 % yield within 8 h at 0-30 °C respectively (**Table 1, entries 10-11**). We have also carried model reaction using EDC.HCl and catalytic amount of solid PEGs like PEG-1000 and PEG-6000 in DMF and obtained desired product with 67 and 69 % yields respectively (**Table 1, entries 12-13**). Predictably, PEG-400 is excellent medium for carrying coupling reaction using EDC.HCl. (**Table 1, entry 8**). When the model reaction was carried out in PEG-400 in the absence of carbodiimide EDC.HCl there was no reaction (**Table 1, entry 14**).

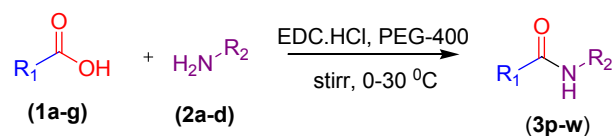
With the optimal conditions in hand, appropriate concentration of the PEG-400 was investigated. Model reaction was tested with different concentrations of PEG-400 such as 0.2-2 mL and 4-6 mL (**Table 2**). This study revealed that the product was formed in poor to excellent yields. As the concentration of PEG-400 increased from 0.2 to 6 mL yield of the desired product also increased from 56-85 %. This indicates that 4 mL of PEG-400 is enough to carry out the reaction efficiently.

With the optimal conditions in hands, the

reaction was explored using various carboxylic acids, acidhydrazides and amines (**Scheme 2** and **3**). To explore the scope of the carboxylic acid partner, benzoic, heterocyclic and benzylic carboxylic acids were reacted with acid hydrazides, and substituted amines. *N*'-Benzoyl benzohydrazide (**3a-o**) and *N*-phenylbenzamide (**3p-w**) derivatives were obtained in 70–89% yields at room temperature (**Table 3**).



Scheme 2: Synthesis of *N*'-Benzoyl substituted benzohydrazide (**3a-o**)



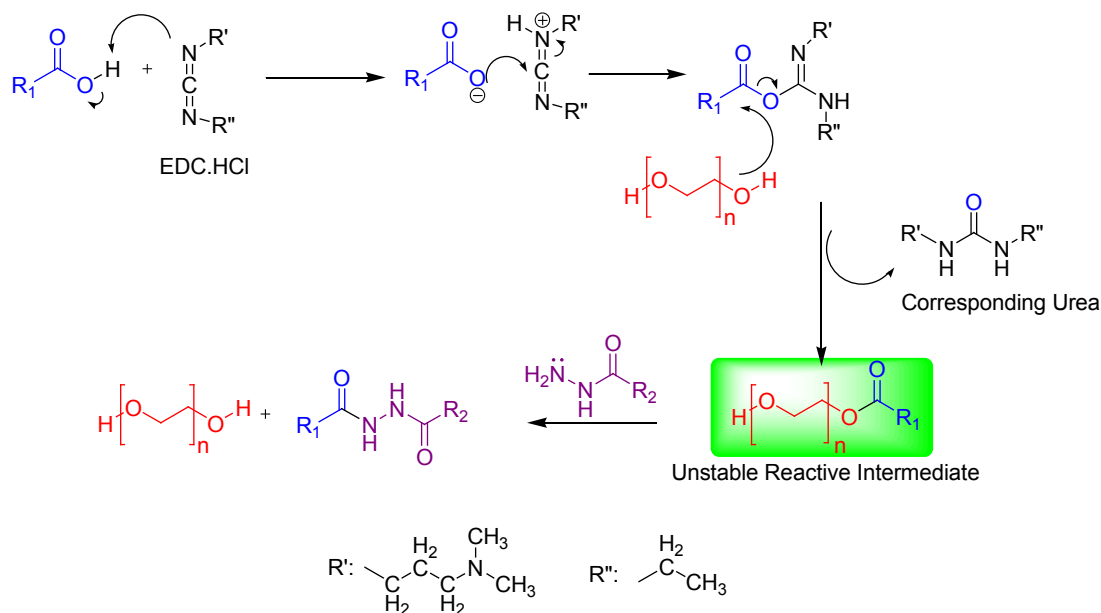
Scheme 3: Synthesis of substituted *N*-phenylbenzamides (**3p-w**)

A plausible mechanism for the efficient formation of carboxamide using EDC.HCl and PEG-400 would be as follows:

The rate acceleration for the formation of carboxamide has been found to be enhanced due to the dual nature of the PEG-400, i.e. as a catalyst and medium. PEG-400 might be helping to create a high initial concentration of the reactants in solvation at room temperature.

A proposed mechanism of the process is summarized in **Scheme 4**. The present synthetic sequence was initiated by proton transfer from the carboxylic acid to the weakly basic nitrogen on the carbodiimide to give an ion pair. Addition of the resulting carboxylate anion forms the *O*-acylisourea. The *O*-acylisourea can also rearrange by intramolecular acyl transfer to give the *N*-acylurea, which is an irreversible pathway that does not lead to desired amide. The use of auxiliary nucleophiles is a common practice to reduce *N*-acylurea formation.²⁷

Hydroxy groups of PEG-400 act as nucleophile and might be reacting with *O*-acylisourea. The resulting unstable reactive intermediate (activated ester) then coupled with the acid hydrazide/amine and there is formation of carboxamide.¹



Scheme 4: Plausible mechanistic formation of the titled compounds

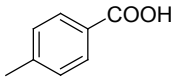
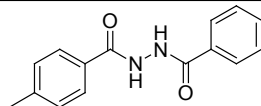
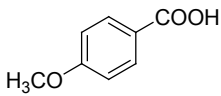
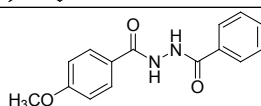
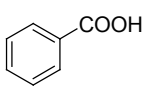
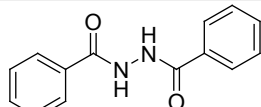
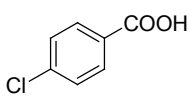
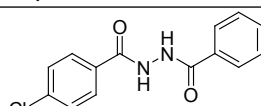
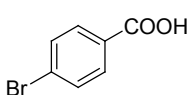
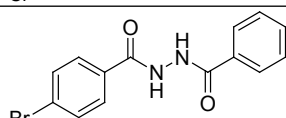
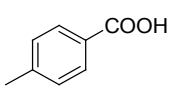
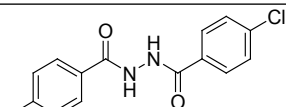
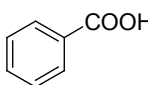
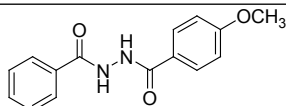
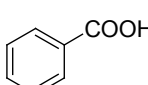
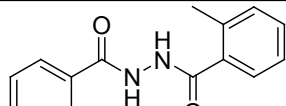
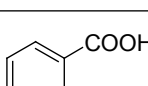
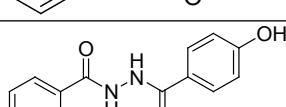
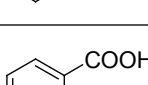
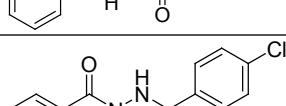
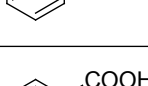
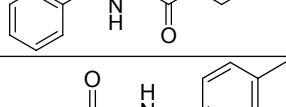
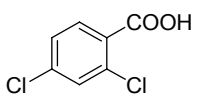
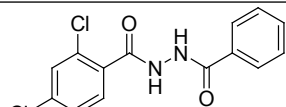
Table 1
Screening of catalyst and solvents

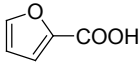
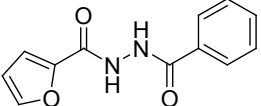
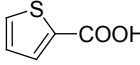
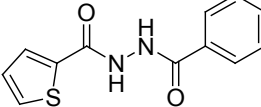
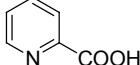
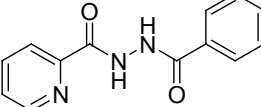
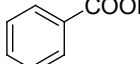
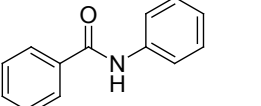
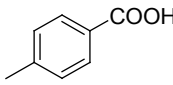
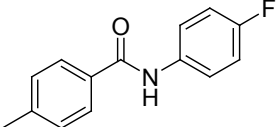
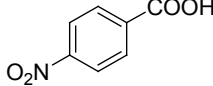
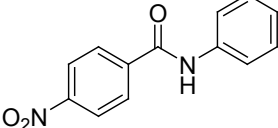
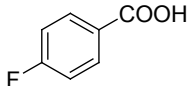
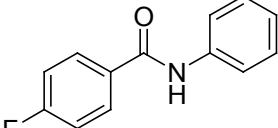
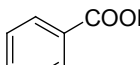
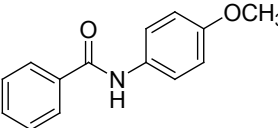
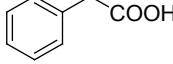
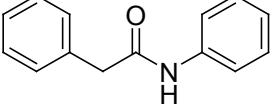
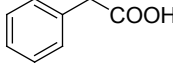
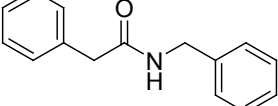
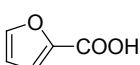
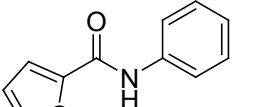
Sr. No.	Catalyst	Additives	Solvents (5 mL)	Time (h)	Yield ^a (%)
1	DCC	DMAP	DMF	20	49
2	DIC	HOBt	DMF	20	48
3	EDC.HCl	HOBt	DMF	20	52
4	DCC	DMAP	PEG-400	8	60
5	DIC	HOBt	PEG-400	8	62
6	EDC.HCl	HOBt	PEG-400	8	83
7	DCC	PEG-400	PEG-400	8	58
8	DIC	PEG-400	PEG-400	8	65
9	EDC.HCl	PEG-400	PEG-400	8	84
10	EDC.HCl	PEG-300	PEG-300	8	79
11	EDC.HCl	PEG-600	PEG-600	8	75
12	EDC.HCl	PEG-1000	DMF	8	67
13	EDC.HCl	PEG-6000	DMF	8	69
14	-	-	PEG-400	-	-
Reaction conditions: 4-Methylbenzoic acid (1a) (0.0036 mmol), benzohydrazide (2a) (0.0036 mmol), EDC.HCl (0.0036 mmol), stirred at 0-30 °C ^a Isolated yields					

Table 2
Effect of the amount of PEG-400 on the synthesis of *N*'-Benzoyl 4-methyl benzohydrazide (**3a**)

Sr. No.	PEG-400 (mL)	Solvent	Yields ^a (%)
1	0.2, 0.4, 0.6, 0.8	DMF	56, 59, 67, 69
2	2	DMF	74
3	4	-	85
4	6	-	84
Reaction conditions: 4-Methylbenzoic acid (1a) (0.0036 mmol), benzohydrazide (2a) (0.0036 mmol), EDC.HCl (0.0036 mmol), stirred for 8 h at 0-30 °C ^a Isolated yields			

Table 3
Physical data of *N*'-Benzoyl substituted benzohydrazide (**3a-o**) and *N*-substituted phenylbenzamides (**3p-w**)

Entry	R ₁	R ₂	Product	Yield ^a (%)	Melting Point (°C) ^b
1		-H	3a 	80	226-228
2		-H	3b 	82	180-182
3		-H	3c 	81	236-238
4		-H	3d 	83	214-216
5		-H	3e 	76	217-220
6		4-Cl	3f 	89	212-216
7		4-OCH ₃	3g 	75	175-176
8		2-CH ₃	3h 	71	156-158
9		4-OH	3i 	84	232-234
10		4-Cl	3j 	87	208-210
11		4-CH ₃	3k 	76	213-215
12		-H	3l 	72	218-220

13		-H	3m		75	216-220
14		-H	3n		71	242-243
15		-H	3o		70	190-192
16		C ₆ H ₅	3p		74	162-164
17		4-F C ₆ H ₅	3q		78	185-186
18		C ₆ H ₅	3r		72	211-212
19		C ₆ H ₅	3s		78	181-182
20		4-OCH ₃ C ₆ H ₅	3t		80	178-180
21		C ₆ H ₅	3u		75	115-116
22		C ₆ H ₅ CH ₂ ⁻	3v		72	118-120
23		C ₆ H ₅	3w		71	131-132

Reaction conditions: Carboxylic acids (**1a-j**) (0.004 mmol), Acid hydrazides (**2a-g**) (0.004 mmol), amines (**2a-d**) (0.004 mmol), EDC.HCl (0.004 mmol), PEG-400 (4 mL) stirred for 8 h at 0-30 °C

^aIsolated yields

^bMelting points, ¹H NMR and ¹³C NMR are in good agreement with those reported in the literature.²⁸

4. Conclusion

In conclusion, for the first time we have explored a unique combination of carbodiimide and PEG-400 for clean and efficient synthesis of carboxamide derivatives. The use of inexpensive additive i.e. PEG-400, operational simplicity and good yields of products at room temperature are the key features of this methodology. This protocol provides an opportunity to avoid organic solvents and requires no further purification of the desired product compared to the traditional reaction system. We believe that this synthetic approach provides a better scope for the synthesis of carboxamide analogues and will be a more practical alternative to the other existing methods.

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