A sustainable approach to amide bond formation via C-O bond cleavage of simple esters in water

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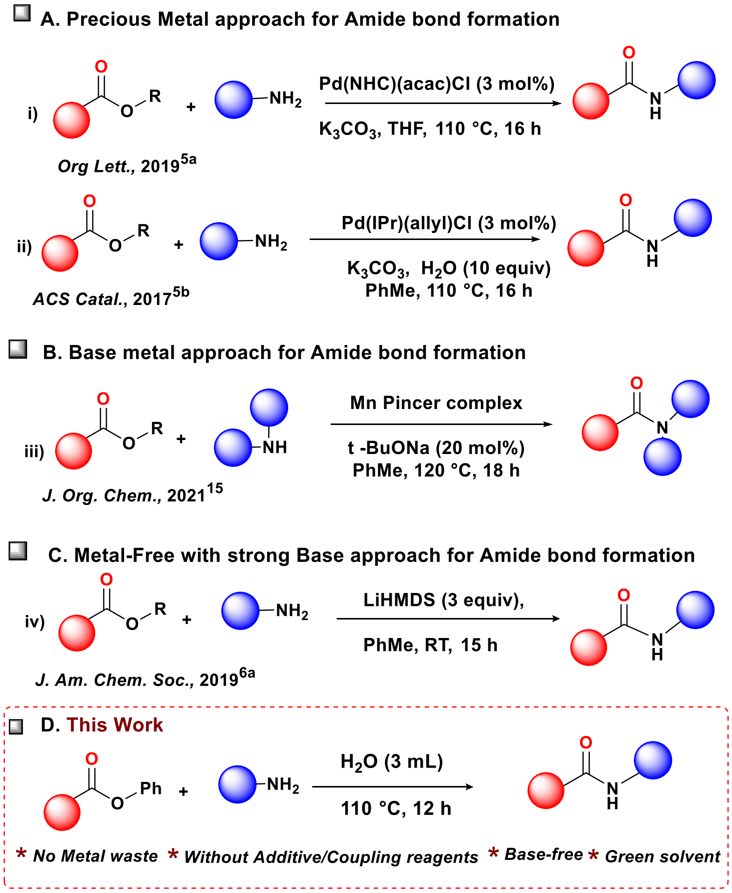
Amides contain the paramount functional group in the field of chemistry as well as biology and they play a unique role in pharmaceutical industries. Amide bond formation is a prevalent reaction using coupling reagents, usually metal catalysts and additives etc. In this context, herein, we developed a simple and efficient synthetic approach for the direct amidation through esters, simply in water, affording the desired products in good to excellent yields. Interestingly, this method features metal-free, additive-free and base-free characteristics, and it also uses water as a green solvent. Therefore, it is a new and eco-friendly way to realize the direct amide bond formation. Applying this methodology, we prepared over 30 different amides including the drug molecule Diethyltoluamide in good yield. Finally, this approach was successfully applied to the gram-scale synthesis of a representative amide product.

The amide bond formation is an important step in pharmaceutical industries, synthetic polymers, and material products as amide bonds are the most essential constituent in peptide derivatives, natural products and drug designing.[1] Cracking of petroleum products oils, fatty acids, triesters of glycerol, fruits are the sources of esters and thus the methods of conversion of esters into amides becomes significant.[2] Traditionally, most of the pharmaceutical industries follow acid-amine coupling method with over stoichiometric amount of coupling reagents and bases for amide bond formation.[3] Also, in the earlier methods of catalytic synthesis of amides the use of CO gas by amino carbonylation methodology was successfully carried out by Wu and Beller et. al.[4] Another well-known approach in amide bond formation is the C(acyl)-O bond cleavage of esters through catalytic pathway, but using costly metal catalysts,[5] (Figure1, Part A) strong base[6] (Figure 1, Part C), with various additives,[5g, 7] and often non-greener solvents.[8] Sometimes also suitable substituents are required [5g, 7e, 9]for effective conversion. This would also be hazardous tedious processes.[5g, 6e, 10]When the cleavage of esters yields carbonylative and decarbonylative [11] products, the selectivity was reached by the nature of the ligands.[5b, 12] For instance catalyst Ni(IPr)-NHC with N-heterocyclic carbene ligand produced carbonylative product[13] whereas [Ni(dcype)]$^-$ with bis-phosphine ligand produced decarbonylative product.[10a, 14] Other non-noble metals also cleaved the esters of C(acyl)-O bond to produce amides with hybrid ligands such as NHC and nitrogen donors in Mn(pincer)[15] (Figure 1, Part B) and even La(OTf)3 catalysts[16] were employed for the cleavage of ester bonds successfully without extrusion of CO. The transamidation of amides has been studied in catalysis but it requires stoichiometric amount of a strong base.[6a] Moreover the C(acyl)-N bond cleavage of tertiary amides[5a, 8b, 17] is comparatively easier than with secondary amides.[8a, 18]However, the ester bond cleavage may be accomplished in the presence of electron withdrawing substituents.[19] Hence there is a necessity for an environmentally friendly methodology for the industrial synthesis of amides in large quantities. Herein, we report the conversion of simple esters into amides under metal- and base-free conditions using the green solvent water only and avoiding the use/emission of CO, which is an atom economic method leading to environmentally friendly preparation of amides with reduced cost.

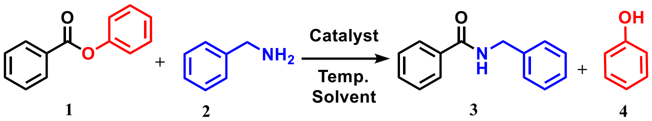
Fig. 1 Different approaches towards C(acyl)-O bond cleavage of esters to amides



Results and Discussion:

At the outset, we have outlined the model scheme for amidation of esters using phenyl benzoate (1) and benzylamine (2) as the ester and amine source respectively (Scheme 1). Initially, we anticipated that the use of heterogeneous catalyst[20] would bring more advantages compared to homogenous catalysts. In this regard, the catalyst can be recycled and reused several times. In this context, the reaction was performed in the presence of recyclable silica materials with and without metal catalyst, namely, Fe-KIT-6, KIT-6 (mesoporous silica nanoparticles10 – 100 µm), SBA-15, (mesoporous silica nanoparticles<150 µm), and mesoporous silica 200-400mesh (25 mg) with water 3 ml at 110 °C furnished amidation product (3) in 82%, 78%, 60%, 80% respectively (Table 1, Entry 1-4).

Table 1 Reaction Optimization



Entry.	Catalyst	Solvent	Yield (%)
1 [a]	Fe KIT-6	Water	82
2 [a]	KIT-6	Water	78
3 [a]	SBA-15	Water	60
4 [a]	Silica	Water	80
5[b]	Catalyst-free	THF	80
6[b]	Catalyst-free	CH_3CN	78
7[b]	**Catalyst-free**	**Water**	**95**
8[b]	Catalyst-free	Ethanol	45
9[b]	Catalyst-free	Methanol	32

[a] conditions: Phenyl benzoate 0.2525 mmol, benzylamine 0.5050 mmol, catalyst 25 mg, solvent 3 mL, 110 °C in oil bath, 12 h, Isolated yields. [b] No catalyst, solvent 3 mL, 110 °C, 12 h, isolated yields.

To examine the importance of solvents we have randomly chosen four solvents among which the non-green solvents like tetrahydrofuran and acetonitrile ended-up with good yield 80% and 78% (Table 1, entry 5 and 6). The green solvents ethanol and methanol showed low yields of 45% and 32% respectively (Table 1, entry 8 and 9). But to our delight the reaction produced good yield with the only use of water. Surprisingly, water afforded the amidation product with high yield of 95% after 12 h (Table 1, entry 7). Exploration of different solvents revealed that the universal solvent-water was optimal. During this investigation, we screened optimal time with a set of reactions on simple ester and benzylamine as a model substrate under different durations (Figure 2). In the row of 3 h, product (3) yield raised, then after 12 h remains constant. Hence, we fixed 12 h as a constant time for every reaction. The effect of temperature was also examined, in the oil bath at 110 °C led the reaction to be completed within 12 h with 95% yield (Table 1). Hence, the optimal condition to achieve maximum yield in the reaction between phenyl benzoate (1) at 110 °C and benzylamine (2) with 3 mL water in an oil bath for a duration of 12 h.

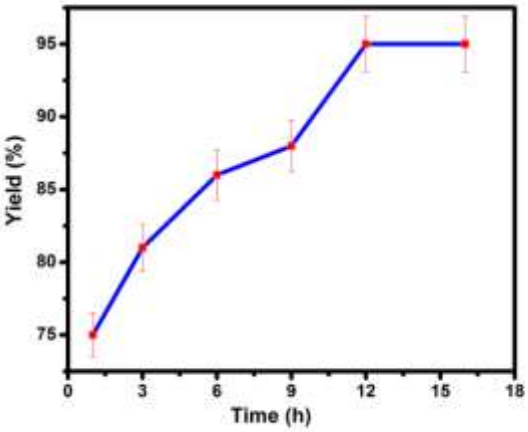
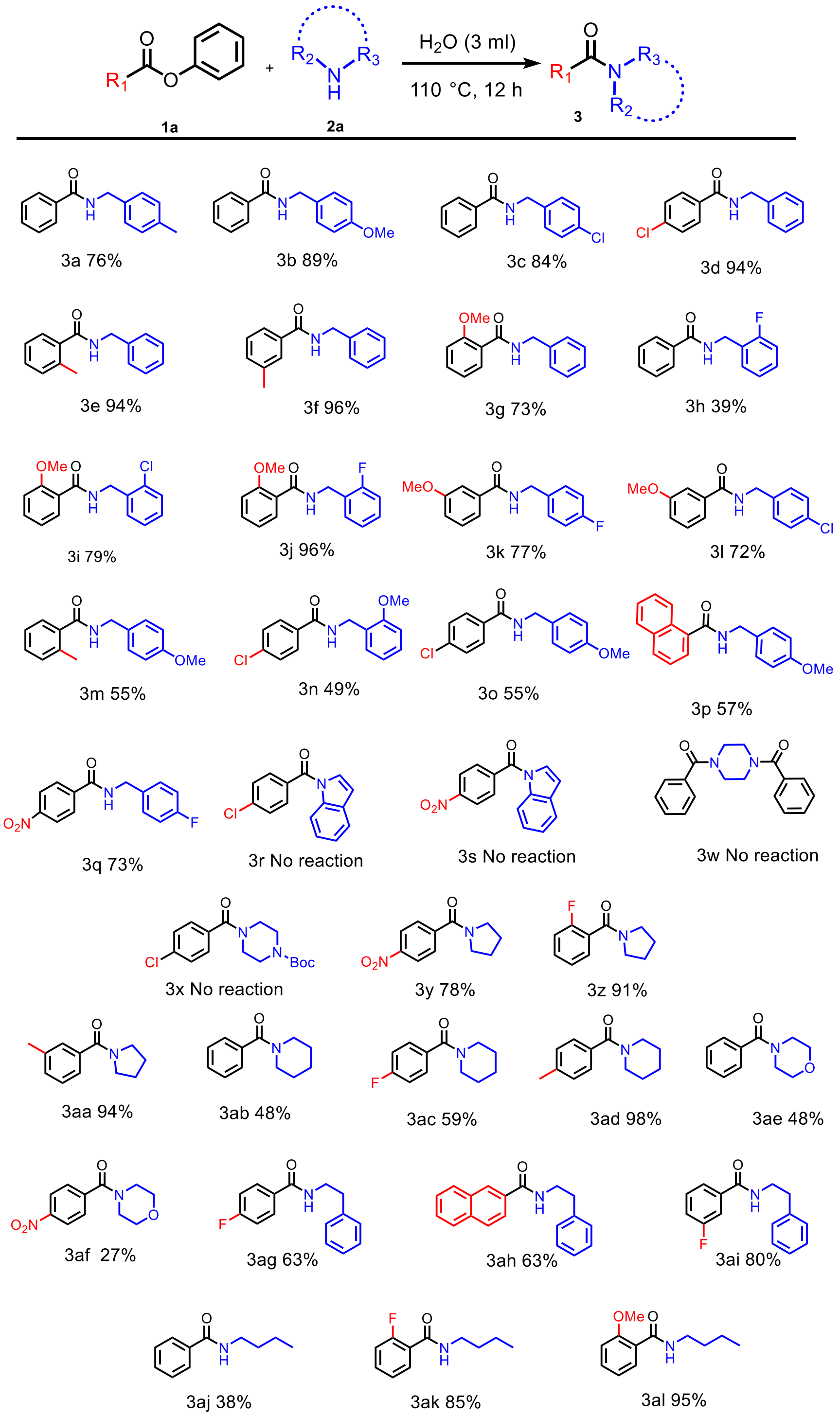


Fig. 2 Time Optimization

Under these optimal conditions, we turned our attention to the scope of esters and amines that can participate in this reaction (Scheme 1). Benzyl amine bearing electron donating groups gives 76% yield (Scheme 1, 3a) on the other hand, electron withdrawing groups in their para position gives 89%,84% yields (Scheme 1, 3b & 3c). On varying the aryl esters with electron withdrawing and donating groups, the corresponding amide yield was not affected (Scheme 1, 3d to 3g). Mostly, in benzyl amine derivative substitutents in para position resulted in high yield when compared to ortho or meta position (Scheme 1, 3b to 3g). Later we introduced halogenated derivatives in amines in ortho and para positions which were converted effectively into amides with 39% to 96% yield (Scheme 1, 3h to 3l). Surprisingly we obtained moderate yields when methoxy groups were introduced in amines with 49% to 57% of yield (Scheme 1,3m to 3p).

Scheme 1 Substrate scope for amidation of ester

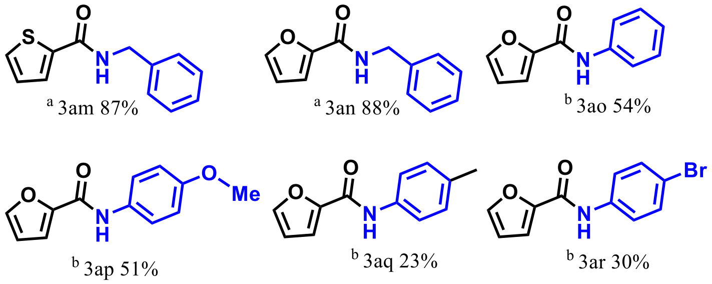


3a 76%
3b 89%
3c 84%
3d 94%
3e 94%
3f 96%
3g 73%
3h 39%
3i 79%
3j 96%
3k 77%
3l 72%
3m 55%
3n 49%
3o 55%
3p 57%
3q 73%
3r No reaction
3s No reaction
3w No reaction
3x No reaction
3y 78%
3z 91%
3aa 94%
3ab 48%
3ac 59%
3ad 98%
3ae 48%
3af 27%
3ag 63%
3ah 63%
3ai 80%
3aj 38%
3ak 85%
3al 95%

Conditions: Ester (1 eqv.), amine (2 eqv.), solvent 3 mL, 110 °C, 12 h.

In the case of electron withdrawing substituents in both aryl groups we obtained very good yield of 73% of product (Scheme 1, 3q). No reaction was observed between aryl ester (1) with piperazine, n-Boc piperazine and Indole (Scheme 1, 3r to 3x). Surprisingly, Water plays a similar role in amidation of various esters with cyclic secondary amines which resulted in excellent yield of corresponding amides. Several substituted esters underwent the aminolysis with Pyrrolidine, Piperidine, Morpholine, to the corresponding amides with good to excellent yields (Scheme 1, 3y in 78%, 3z in 91%, 3aa in 94%, 3ab in 48%, 3ac in 59%, and 3ad in 98% isolated yield).Notably, the morpholine and phenethylamine showed moderate reactivity with various esters (Scheme 1, 3ae) in 48%, (3af) in 27%. Particularly, when the alkyl chain of the amine was lengthened, the activated ester was converted smoothly into the corresponding amides with good yield (3ag, 3ah) of 63% & (3ai) of 80% yield. Interestingly, we achieved positive result with primary amine namely n-butylamine (3aj) in 38%, (3ak) in 85% & (3al) in 95%.

Scheme 2 Heteroaromatic esters:

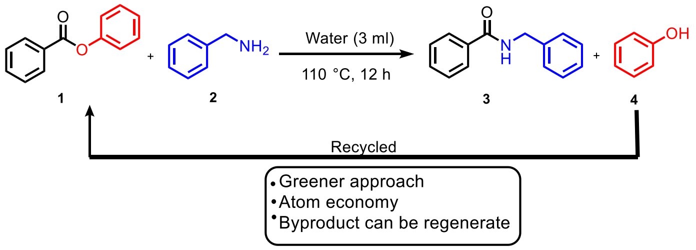


[a] 3am 87%
[a] 3an 88%
[b] 3ao 54%
[b] 3ap 51%
[b] 3aq 23%
[b] 3ar 30%

Conditions: [a] Ester (1 eqv.), amine (1.2 eqv.) , solvent 3 mL, 110 °C, 12 h.[b] amine (2 eqv.).

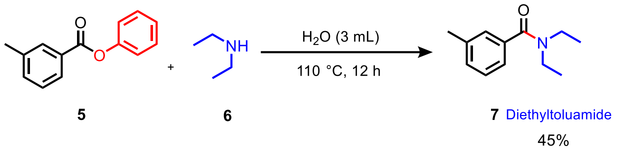
Also, we introduced heteroaromatic esters as carbonylating sources, (Scheme 2) initially we chose phenyl thiophene-2-carboxylate reacts with benzylamine which gives 3am in 87% and phenyl furan-2-carboxylate 3an in 88%. Interestingly, less nucleophilic nature of aromatic amines also we tried, such as aniline reacts with phenyl furan-2-carboxylate coupled successfully and gives moderate yield (3ao) 54%, followed by substituted p-anisidine (3ap) gives 52% yield, p-toluidine (3aq) gives 23%, p-bromo aniline reacts modestly with phenyl furan-2-carboxylate and gives (3ar) 30% yield.

Scheme 3 Identification of side product reaction



In order to prove the environment friendly of the proposed methodology the corresponding side product phenol (4) was recovered pure to give 60-70% yield which could be used further in the preparation of ester derivatives (Scheme 3). Significantly we prepared the drug, Diethyltoluamide which is an insect repellent by following the proposed optimized protocol (Scheme 4). Aminolysis of meta-methyl phenyl benzoate (5) with diethylamine (6) was carried out to give amide (7) with moderate yield of 45%.

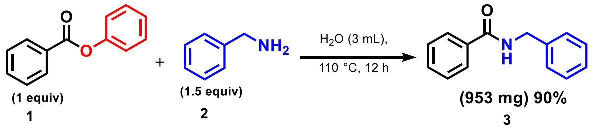
Scheme 4 Synthesis of Diethyltoluamide



Gram Scale:

Finally, we assessed the gram scale procedure (scheme 5) with a mixture of Phenyl benzoate (1), 1 g (1 equiv.), Benzylamine (2), 810 mg (1.5 equiv.) which was stirred in the presence of H2O at 110 °C for 12 h to afford the formation of 953 mg of benzyl benzamide (3) with 90% yield.

Scheme 5 Gram scale synthesis



Conclusion

In Summary, we have succeeded in finding a metal-free, base /additive- free amidation protocol under aqueous conditions. This report explores the importance of water as an Eco-friendly benign solvent. Based on the substrate scope and gram scale experiment, combination of aromatic esters derivatives of phenol and aliphatic amines showed good activity under the standard protocol. To the best of knowledge this is the first report on ester Acyl(C-O) bond cleavage to amide with catalyst-free, base-free and additive- free and green solvent such as water.

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Author Contributions

NR: methodology, writing, editing. KK: methodology, writing. SJ: methodology. MS: editing. PHD: co-supervision, editing, review & supervision. CBB: conceptualization, editing, supervision, project administration.

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