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Catalyst-free amidation of aldehyde with amine under mild conditions

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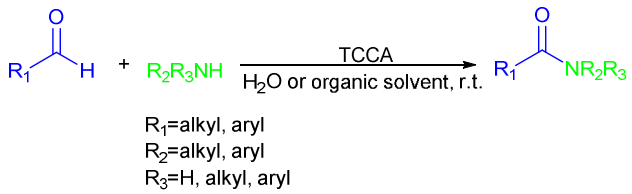
A high efficient, catalyst-free and one-pot procedure for direct synthesis of amides from aldehydes and amines under mild conditions has been developed. Both aliphatic and aromatic aldehydes with primary or secondary amines are successfully converted to the corresponding amides, and reactions can proceed in either aqueous or organic media.

Amide units exist in a variety of natural products, bio-pharmaceuticals, polymers and materials[1], which has been proved to have important applications in a wide range of fields such as dyes, plastics, chemical reagents, organic synthesis,[2] pharmaceuticals, agrochemicals and polymer synthesis.[3] Therefore, the formation of the amide bond is one of the most used transformations in pharmaceutical chemistry.[4] Over the past few decades, a plethora of approaches for the formation of amide compounds have been explored and addressed. Among of them, some innovative processes mainly include the direct synthesis of amides from alkynes,[5] thioesrers[6] or azides,[7] the condensation reaction of carboxylic acids with amines catalysed by borane[8] or boric acid ester,[9] amidation of alcohols with amines in the presence of ruthenium catalyst,[10] amidation of esters with amines assisted by sodium methoxide catalysis,[11] acyl chlorides with the amines applying zinc powder and ice acetic acid as reducing agent,[12] cross-coupling reaction of activating aldehydes with amines promoted by the copper catalyst,[13] and the generation of amides from α-bromo nitro compounds with amines.[14] Nevertheless, the majority of these developed approaches for amide synthesis are related to the intermediate utilization of carboxylic acids or activated carboxylic acid derivatives. Usually harsh reaction conditions, expensive metal or transition metal catalyst is required, and which also have difficulties in product isolations. These addressed methods mentioned above usually suffer from low yields and not environmentally benign.[15] Therefore, the development of novel amide formation methodologies especially green processes is still challenging.

The oxidative amidation of aldehydes and amines constitutes one of the most efficient and direct routes to construct amide bonds. Primary or secondary amines have been successfully installed in the corresponding substrates via cross-coupling reaction or oxidative amination, whereas aldehydes as active organic compounds in direct and catalyst-free amide formation have been less studied. In most conditions, reactions usually proceed under harsh reaction conditions[16] for that purpose, and heavy or transition metal catalyst(s) are usually involved to assist the reactions[17]. The employment of heavy or transition metal catalysis is usually considered as being not environmental friendly. All the deficiencies mentioned above promote us to continuously explore efficient and catalyst-free processes for industrial applications that can meet some principles of green chemistry.

Herein, we present a catalyst-free protocol employing trichloroisocyanuric acid (TCCA), with which, aldehydes (aliphatic or aromatic) and amines (primary- or secondary- amine) can be proceeded in both aqueous solution and organic solvent at ambient temperature smoothly and efficiently to form the desired amides, no catalyst and harsh reaction conditions were required for that purpose. During reaction, trichloroisocyanuric acid can react with aldehyde and amine to rapid formation of desired product amide (**Scheme 1**).

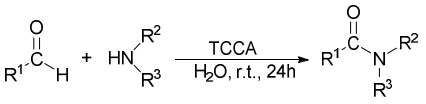


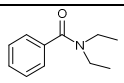
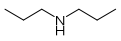
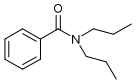
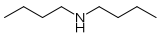
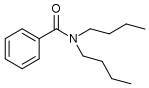
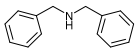
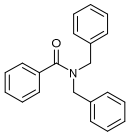
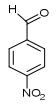
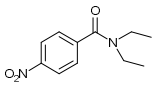
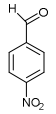
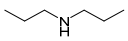
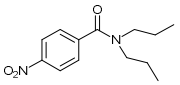
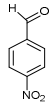
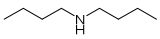
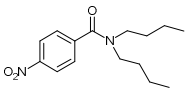
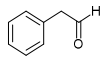
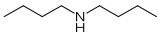
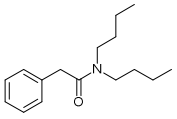
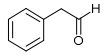
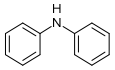
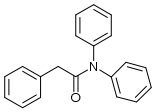
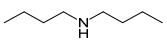
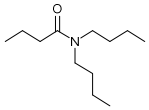
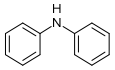
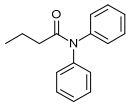
Scheme 1 Cascade reaction for direct formation of amide from aldehyde and amine

In order to identify suitable reaction conditions for the catalyst-free, one-pot cascade and direct route for amide formation from aldehydes and amines, both organic solvent and aqueous solution, varified temperatures, and ratios of substrates (benzaldehyde: diethylamine, benzaldehyde: TCCA) were evaluated by employing benzaldehyde and diethylamine as the model substrates. In most conditions, the desired product *N, N*-diethylbenzamide could be obtained in moderate to excellent yields. The results were summarized in **Table S1.** It was indicated that both the substrate TCCA loading and the ratio of substrate benzaldehyde over diethylamine have effects on product formation and yields. When TCCA was loaded 40 (mol)% of benzaldehyde, and the ratio of benzaldehyde/diethylamine was 1:3 or 1:3.5, the product yield was achieved up to 95% (Entry 5,6, Table **S1**) , a higher or a lower ratio of substrate benzaldehyde/diethylamine made no positive contributions to the formation yield (Entry 1-4 and 7-9, **Table S1**). Therefore in future reactions, all the ratios of applied aldehydes over amines should be kept at 1:3 or 1:3.5, for meeting one of the principles of green chemistry, lower concentration of substrate is better and welcomed when the same yield could be provided. And in future reactions, the ratio of substrate benzaldehyde over diethylamine will surely be chosen at 1:3. Also, the loading amount of TCCA was examined, among of the tried examples, when TCCA's loading was from 17% to 57%, the highest yields 95% was achieved, and when the loading was 40%, a higher or lower loading of TCCA could not make any positive contribution to product yield, and therefore in the following reactions, 40 (mol) % of TCCA is chosen to apply (Entry 5, 10-17, **Table S1**). A higher

temperature was also attempted to check whether there were some improvements in the formation yield of product *N, N*-diethylbenzamide, to our disappointed, poor yields were obtained, and the higher in temperature the worse in product yield was obtained. The product yields varied from 92% when conducted at 25°C to 74% at 50°C, whereas a worse yield (trace amount) was provided when reaction was carried out at 75°C, nothing could be detected when reaction was performed at an even higher temperature 90°C (Entry 5, 18-20, **Table S1**). Therefore in future reactions, all reactions will be proceeded at 25°C.

Table 1 Synthesis of amides from various aldehydes and Secondary amines [a]



Entry	Aldehyde	Amine	Product	Yield[b] (%)	References
1				96 (73[c])	[18]
2				94(77[c])	[19]
3				95(40[c])	[20]
4				76	[21]
5				88	[22]
6				83	[23]
7				90	[24]
8				97	[25]
9				66	[26]
10				63	[27]
11				91	[28]

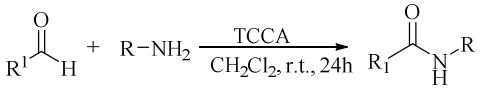
[a] Reactions were performed on a 6 mL sale employing H_2O as the solvent at room temperature, conditions: aldehyde 0.5mmol, TCCA 0.2 mmol, secondary amines 1.5 mmol, and DMSO 0.1 mL, reaction time 24h, unless otherwise stated, all reactions were proceeded in H_2O. [b] Yields were determined by HPLC analysis equipped with a Vertex column at the wavelength of 254 nm. [c] Dichloromethane as the solvent.

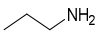
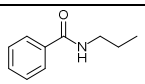
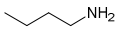
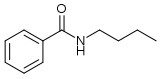
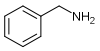
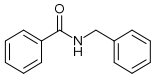
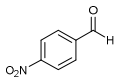
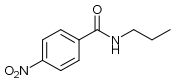
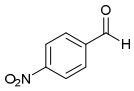
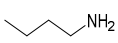
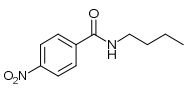
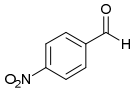
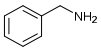
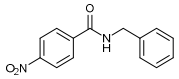
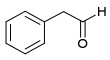
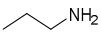
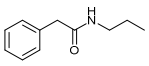
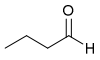
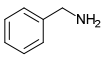
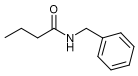
To explore whether the reaction media has some effects on the transformation yield, three organic solvents dichloromethane, methanol, and acetonitrile were then evaluated, it was indicated that compared with those reactions in aqueous solution, reactions that proceeding in organic solvent were provided worse yields, therefore, H_2O is more suitable compared with the above three organic solvents and was chosen. Generally, organic solvent makes the applied substrate aldehyde more soluble, usually aldehyde has poor solubility in aqueous solution compared with which in organic phase, as a consequence, DMSO is

introduced to the reaction solution (aqueous solution) for purpose of a possible better solubility of aldehyde, to our delight, a slight higher yield of 96% was obtained, which proved that reactions benefit from the addition of DMSO, thus in future reactions for those reactions proceed in aqueous solution, it is suggested that an addition of DMSO is necessary for improvement in product conversion (Entry 5, **Table S1**). Triethyl amine (TEA) is also introduced to the reaction solution (organic solution) to bind byproduct HCl for possible higher conversions in product formation. However, results indicated that there was only a slight improvement in the product yields. Therefore, the addation of TEA is not required in future reactions that proceeded in organic solution (Entry 24-26, **Table S1**).

After getting the optimized reaction conditions, a series of cascade reactions were carried out by employing a wide range of aldehydes and secondary amines, and the results were summarized in **Table 1**. All reactions were proceeded in aqueous solution smoothly and efficiently to generate the desired product amides in moderate to excellent yields of up to 97%. It is indicated that when substrate's acid moiety bearing an aromatic ring, while the amine motif is aliphatic, most of the product amides could be obtained with yields of >83%, and up to 97% (Entry 1-3, 5-8, **Table 1**), and if both of the acid moiety and

Table 2 Synthesis of amides from aldehydes and primary amines [a]



Entry	Aldehyde	Amine	Product	Yield [b] (%)	Ref.
1				68	[29]
2				59	[30]
3				61	[31]
4				82	[32]
5				95	[33]
6				94	[34]
7				95	[35]
8				97	[36]

[a] Reactions were carried out on a 6 mL sale employing dichlorometane (CH_2Cl_2) as the solvent at room temperature, conditions: aldehyde 0.5 mmol, TCCA 0.2 mmol, primary amines 1.5 mmol, reaction time 24h, unless otherwise stated, all reactions were proceeded in CH_2Cl_2. [b] Yields were determined by GC analysis equipped with an Agilent DB-624 column.

amine moiety bearing an aromatic ring, the product amides could be provided in moderate to good yields (Entry 4, 9, **Table 1**). The same rule is also suitable for those whose both moieties containing aliphatic chains. For instance, propionic aldehyde (acid moiety) and dibutylamine (amine moiety) were conducted in the reaction resulting product *N,N*-dibutylbutyramide in a yield of 63% (Entry 10, **Table 1**), and for substrate 2-phenylacetaldehyde and diphenylamine, the product is obtained in a moderate yield of 66% (Entry 9, **Table 1**)

For purpose of exploring the scope of substrate, a pair of substrate benzaldehyde and primary amine, 1-propanamine were thus subjected with the optimized conditions optimized for aldehyde and secondary amine for possible amidation of aldehydes and primary amines, to our disappointed, no product was detected in the samples taken interval during reaction, indicated that the transformation to product *N*-propylbenzamide from substrate benzaldehyde and primary amine 1-propanamine was not successful in aqueous solution. Further investigations were attempted by performing reactions in organic solvent CH_2Cl_2, and the desired product *N*-propylbenzamide was provided in 68% yield (Entry 1, **Table 2**). Consequently, a variety of aldehydes and primary amines were then applied in CH_2Cl_2. Most of the corresponding products were obtained with excellent yields of up to 97%. The results were summarized in **Table 2**. It is indicated that electron-withdrawing substituent on aromatic rings has positive effects on the transformations, for instance, when aldehyde moiety containing nitro group on aromatic ring, the final products were generated with excellent yields of up to 97% (Entry 4-6, **Table 2**), and for those with no electron-withdrawing substituted group(s), poor to moderate

yields were obtained (Entry 1-3, **Table 2**).

In summary, we have, to the best of our knowledge, for the first time, developed a catalyst-free and one-pot process for direct amidation of aldehydes with primary and secondary amines to form the corresponding amides. The reactions are easy-operated and no harsh reaction conditions are required for such purpose. Reactions can proceed efficiently in either aqueous solution or organic solvent for aldehydes with secondary and primary amines, respectively. A wide variety of aldehydes can successfully react with both primary and secondary amines to the formation the corresponding amides. These reactions represent a green methodology for direct preparation of amide, and have potential applications in large-scale preparations especially for industrial purpose.

Experimental

To a solvent of 4 mL, aldehyde of 0.5 mmol together with 0.1mL DMSO were introduced and well dissolved. TCCA of 0.2 mmol were added into the previous solution and stirred. Amine of 1.5 mmol dissolved in 2mL solvent was dropwised into the solution and incubated overnight. After reaction, pH value of the solution was made at 8.0, which was extracted with ethyl acetate three times (3x5ml). The organic solution was isolated and combined together, distilled under reduced pressure to afford residues, chromatographed to afford pure product amides

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/
‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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