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L-Proline: An Efficient Catalyst for Transamidation of Carboxamides with Amines

Sadu Nageswara Rao, Darapaneni Chandra Mohan, and Subbarayappa Adimurthy*

CSIR-Central Salt & Marine Chemicals Research Institute, G. B. Marg, Bhavnagar-364 002, Gujarat, India

adimurthy@csmcri.org

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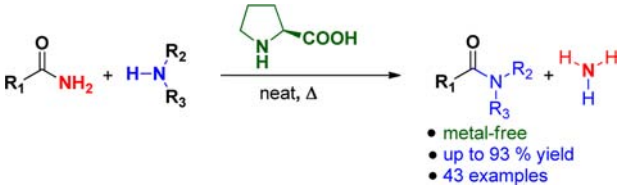
ABSTRACT



In the presence of a catalytic amount of L-proline (10 mol %), transamidations of carboxamides with amines were achieved under solvent-free conditions. The transamidation process is compatible with a wide range of amines.

The amide bond is one of the most important linkages in nature due to its presence in peptides and protein structures and has been well recognized in chemistry and biology.[1] In addition, amides serve as versatile intermediates for the preparation of pharmaceuticals, agrochemicals, polymers, and materials.[2] Traditionally amides have been prepared by the reaction of amines with carboxylic acid derivatives,[3] alcohols,[4] or aldehydes,[5] hydroamination of alkynes,[6] and hydration of nitriles.[7] Alternatively, transamidation is an attractive tool and represents one of the most convenient and straightforward methods for exchanging the constituents of two different amide groups. Transamidation is a distinct biochemical activity[8] associated with several neurodegenerative disorders such as Alzheimer's and Hungtinton's disease.[9]

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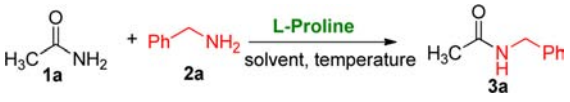
Recently, Stahl,[10] Williams,[11] Myers,[12] Beller,[13] and other groups[14] have developed elegant methods for transamidation. Yet, despite the advances achieved, most of these methods require transition metal[10−13] or lanthanide metal[14a] catalysts to promote this transformation efficiently. Thus, the separation of the metal catalyst from products is a central issue to consider. This separation is of particular importance for the synthesis of pharmaceutical fine chemicals, because of metal residual toxicity in the target compounds. Moreover, transition-metal-catalyzed reactions also generate hazardous waste which is environmentally problematic and hence should be avoided wherever possible. Also, these catalysts are active only in organic solvents. Few reports are available for a completely solvent-free transamidation process.[14c]

Recently, organocatalysis emerged as an area of very rapid growth for chemical synthesis due to environmental-friendliness.[15] Particularly, L-proline has received much attention due to its dual role as a ligand and catalyst.[16] In view of the above perceptions, the development of benign and metal-free transamidation procedures with high yield and selectivity is desirable. In continuation of our efforts to develop green and sustainable methods,[17] herein, we wish to report a general solvent-free L-proline catalyzed transamidation of carboxamides with amines. To the best of our knowledge, this is the first convenient procedure for efficient transamidation using L-proline as the catalyst.

We started our studies on transamidation of acetamide with benzylamine as a model system (Table 1). First, the reaction was performed without a catalyst and solvent; a complete lack of reactivity was observed at 100 °C (Table 1, entry 1). The reaction was carried out in the presence of L-proline as an inexpensive catalyst (10 mol %); it resulted in 14% of transamidation product **3a**, but the conditions were not sufficiently efficient to achieve the desired conversion (Table 1, entry 2). When the reaction was performed in toluene at 100 °C, an 88% conversion was observed (Table 1, entry 3). Further, no improvements were observed when the reaction was carried out in other solvents (Table 1, entries 4−7). To our delight, when the reaction was performed under neat conditions it resulted in >99% conversion (Table 1, entry 8). Transamidation slightly dropped when the catalyst loading was decreased to 5 mol % (Table 1, entry 9). Upon varying the temperature of the reaction between rt and 80 °C, conversion also declined (Table 1, entries 10−12). Transamidation was not efficient with other amino acid catalysts tested (Table 1, entries 13−18).

Table 1. Optimization of Reaction Conditions for **3a**[a]



entry	catalyst (mol %)	solvent	temp (°C)	yield (%)[b]
1	–	–	100	0
2	L-proline (10)	H_2O	100	14
3	L-proline (10)	toluene	100	88
4	L-proline (10)	DMF	100	19
5	L-proline (10)	DMSO	100	65
6	L-proline (10)	EtOH	100	36
7	L-proline (10)	*i*PrOH	100	60
8	**L-proline (10)**	–	**100**	**99**
9	L-proline (5)	–	100	96
10	L-proline (10)	–	80	81
11	L-proline (10)	–	60	30
12	L-proline (10)	–	rt	9
13	L-lysine (10)	–	100	90
14	L-histidine (10)	–	100	87
15	L-leucine (10)	–	100	74
16	L-glutamic acid (10)	–	100	77
17	L-alanine (10)	–	100	82
18	L-glycine (10)	–	100	88

[a] Conditions: **1a** (10 mmol), **2a** (10 mmol), and L-proline (10 mol %) in a sealed tube at 100 °C for 36 h, unless otherwise stated. [b] Determined by GC-MS.

Under these optimized conditions (Table 1, entry 8), the transamidation of acetamide with various amines was examined (Scheme 1). The results in Scheme 1 demonstrate that the reaction has a high degree of functional group tolerance. Benzlyamines with electron-rich and -deficient (*p*/*m*/*o*) substituents were reacted smoothly and produced corresponding transamidation products in good to excellent yields (**3b**−**3h**). The less nucleophilic anilines, *p*-methyl aniline and *m*-chloroaniline, provided good to moderate yields (**3i**−**3k**). This may be due to the delocalization of the nitrogen lone pair of electrons on the aromatic ring, which is apparent according to the literature.[14b] Notably, alkyl

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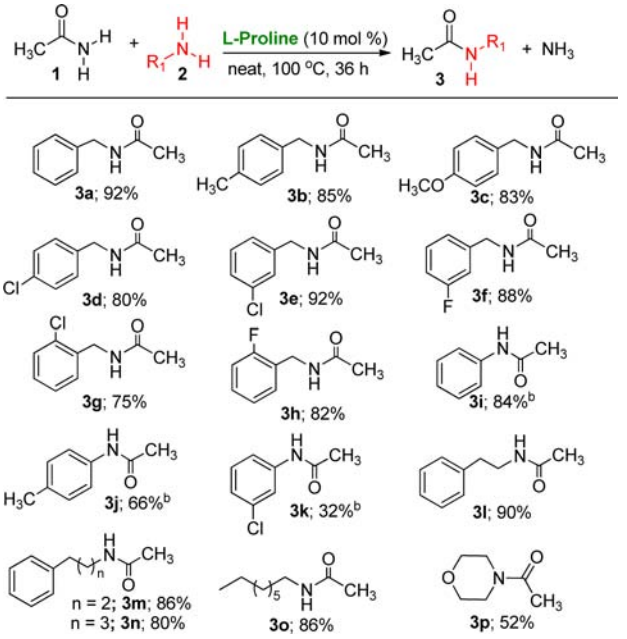
aromatic, aliphatic, and secondary amines proceeded smoothly (**3l**–**3p**) under these conditions.

To examine the scope of transamidation, a variety of benzylic, aromatic, aliphatic, propargylic, heteroaromatic, and secondary amines were reacted with other amides (Scheme 2). In general, the transamidation of benzamide with benzyl amines (electron-neutral, -rich, -deficient), aliphatic, alkyl aromatic, and cyclic secondary amines gave corresponding transamidation products in good to moderate yields (**5a**–**5i**). Similarly, transamidation of formamide with a variety of amines including morpholine, propargylic amine, 2-aminopyridine, piperidine, and cyclic secondary amines also gave good to moderate yields (**5j**–**5r**). However, the present method is not suitable for acyclic secondary (dibenzyl and diisopropyl) amines. Further, it should be noted that transamidation products **5m**, **5n**, and **5p**–**5r** were obtained from corresponding amines at rt. The change of temperature may be due to the high electrophilicity of formamide.

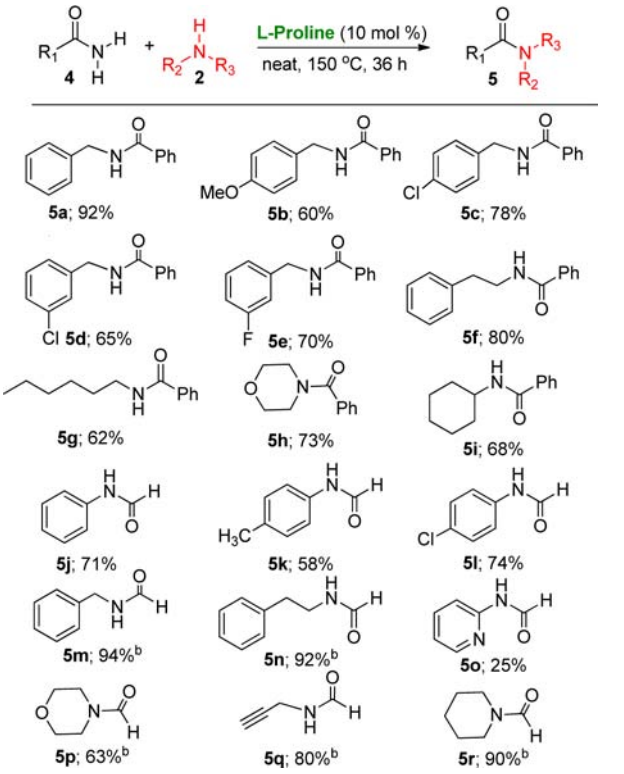
Finally, the L-proline catalyzed transamidation of phthalimide was examined with various primary amines (Table 2). All primary amines reacted smoothly to provide corresponding N-substituted phthalimides in good to excellent yields. The tansamidation of phthalimide can be assumed to be similar to what has been proposed by Nguyen et al.[14b] To our delight, we found this transformation to be very general for a wide range of amines. Transamidation of the secondary and tertiary amides resulted in low to moderate yields, compared to primary amides (Scheme 3).

Scheme 1. Transamidation of Acetamide with Various Amines[a]



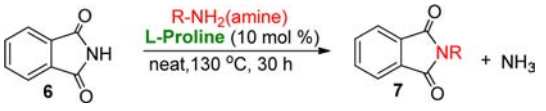
[a] Conditions unless otherwise stated: **1a** (10 mmol), **2** (10 mmol), L-proline (10 mol %) in a sealed tube at 100 °C for 36 h, isolated yield. [b] Reactions carried out at 150 °C.

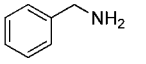
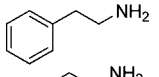
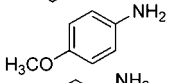
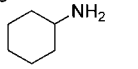
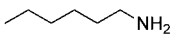
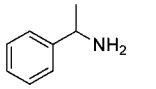
Scheme 2. Expanded Substrate Scope of Transamidation Method[a]



[a] Conditions unless otherwise stated: **4** (10 mmol), **2** (10 mmol), and L-proline (10 mol %) in a sealed tube at 150 °C, 36 h; isolated yield. [b] Reactions carried out at rt (27 °C).

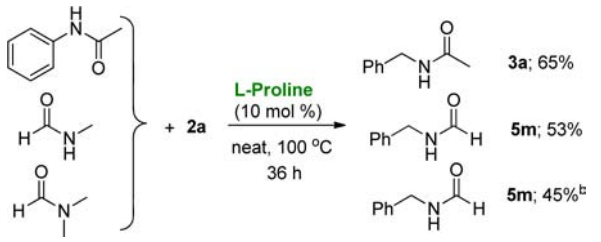
Table 2. L-Proline Catalyzed Transamidation of Phthalimide with Amines[a]



entry	amine	product	yield (%)[b]
1		**7a**	91
2		**7b**	93
3		**7c**	54
4		**7d**	90
5		**7e**	91
6		**7f**	80

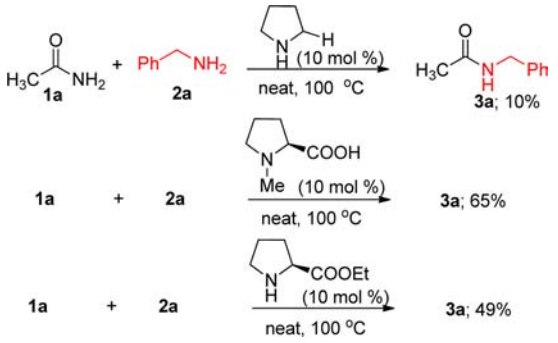
[a] Conditions: **6** (10 mmol), amine (10 mmol), in a sealed tube. [b] Isolated yield.

Scheme 3. Transamidation of 2° and 3° Amides[a]



[a] Conditions unless otherwise stated: amide (10 mmol) and **2a** (10 mmol) in a sealed tube; isolated yield. [b] 150 °C.

Scheme 4. Experiments for Mechanistic Studies[a]

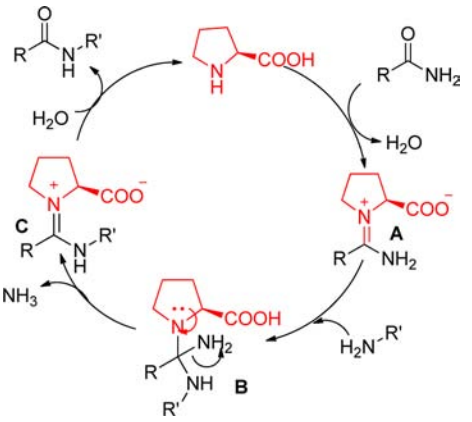


[a] Conditions: **1a** (10 mmol) and **2a** (10 mmol) in a sealed tube, 36 h; isolated yield.

To gain insight into the reaction mechanism, we performed some additional experiments (Scheme 4). To check the effect of both the carboxylic and N−H group of L-proline, the reactions were performed using pyrrolidine as well as the *N*-methyl and ethyl ester of L-proline as catalysts. However, the latter two catalysts showed some activity but were not efficient. These studies indicate that both free N−H and −COOH groups of L-proline are essential for efficient transamidation.

Based on experimental observations and literature reports[18] a plausible reaction mechanism for an L-proline catalyzed transamidation is proposed (Scheme 5). We assume that L-proline reacts with an amide to form

Scheme 5



intermediate **A**,[19] which further undergoes nucleophilic addition with an amine to generate tetrahedral intermediate **B**. Subsequently, elimination of ammonia results in another intermediate, **C**. Finally its hydrolysis provides the transamidation product.

In summary, we have developed a novel L-proline-catalyzed transamidation process that can be selectively transaminated in an efficient manner. Compared to previously known transamidation catalysts, L-proline is inexpensive, is readily available, and can be used conveniently. A wide range of benzylic, aromatic, aliphatic, propargylic, and heteroaromatic amines can be effectively used to produce corresponding transamidation products in good to excellent yields.

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Supporting Information Available. Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.