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Mild, Metal-Free and Protection-Free Transamidation of N-Acyl-2-piperidones to Amino acids, Amino alcohols and Aliphatic Amines and Esterification of N-Acyl-2-piperidones

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Supporting information for this article is given separately

Abstract

Amides are indispensable building blocks of biological systems, pharmaceuticals, and materials. We report a highly selective method for the synthesis amides via transamidation process. Transamidation of *N*-acyl-2-piperidones with a broad range of amines is demonstrated under exceedingly mild and metal-free reaction condition that relies on the amide bond twist to weaken the amidic resonance. Transamidation proceeds under the neat condition at room temperature, in short reaction times (30-90 min) with good yields. Considerable variation is tolerated with both amine and imide substrates. Of note, amines bearing carboxylic acids (glycine and serine) and hydroxyl groups (dopamine and tyramine) are well tolerated which are otherwise problematic under the metal-catalyzed protocol. Our current method is applicable for transamidation of both alkyl and aryl-*N*-acyl-2-piperidones. The practical value of the method is highlighted by the synthesis of four natural product amide alkaloids in high yields under mild reaction conditions. In the absence of nucleophilic amines, *N*-acyl-2-piperidones undergoes esterification with aliphatic alcohols at elevated temperature. Single crystal X-ray analysis of an *N*-acyl-2-piperidone shows amide bond twist, τ = -20.39° and pyramidalization, χ_N = -11.73°. This weakens the amidic conjugation and might be the factor controlling the reactivity and selectivity of these imides. We envision that the *N*-acyl-2-piperidone scaffold would be useful in the synthesis of pharmaceuticals and materials.

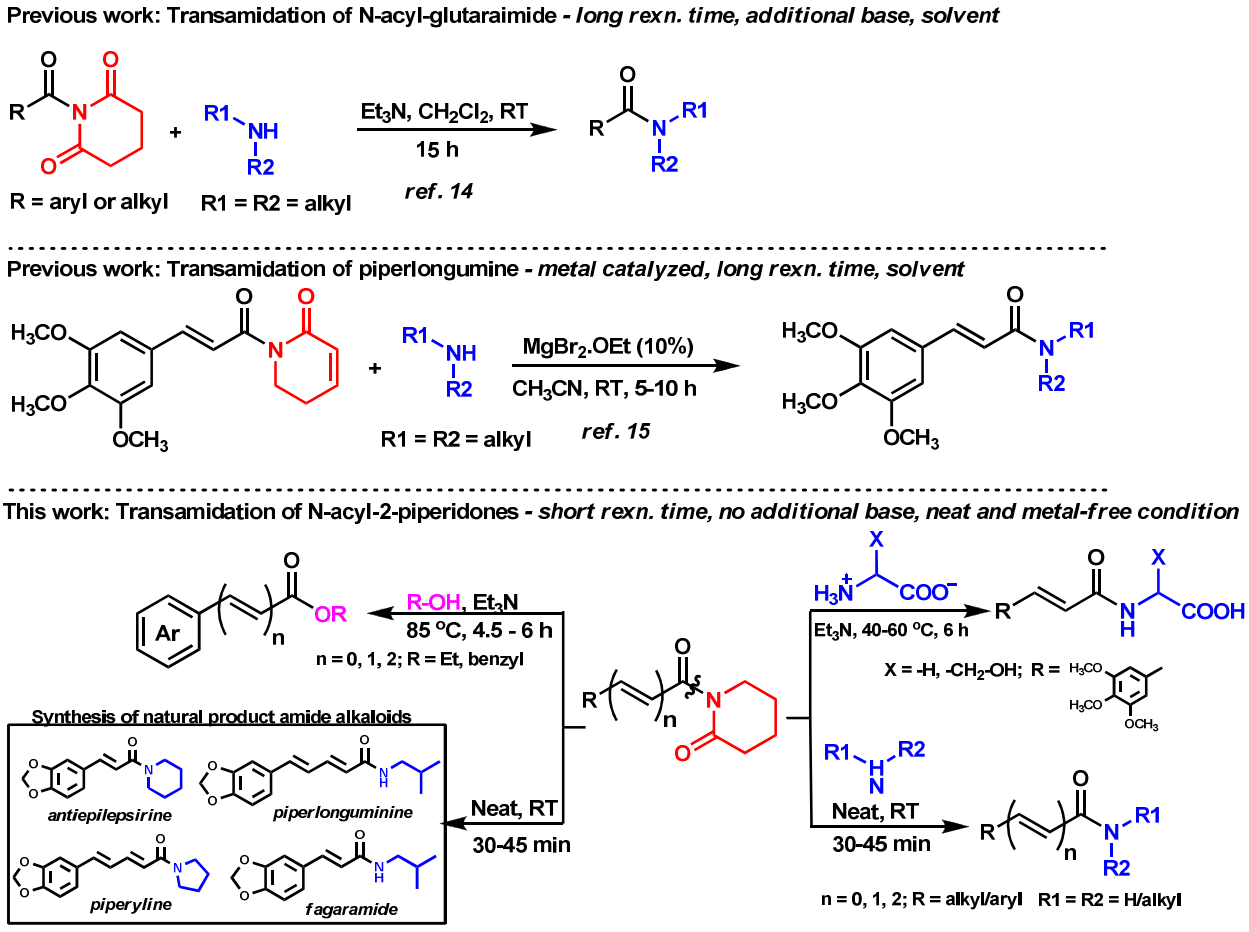
Introduction

Amides are essential constituents of life and building blocks of many drugs, pharmaceutical molecules, agrochemicals, and natural products. It is estimated that 55% of pharmaceutical drugs and 25% of the registered pharmaceuticals contain the amide motif. [1] A recent survey estimates

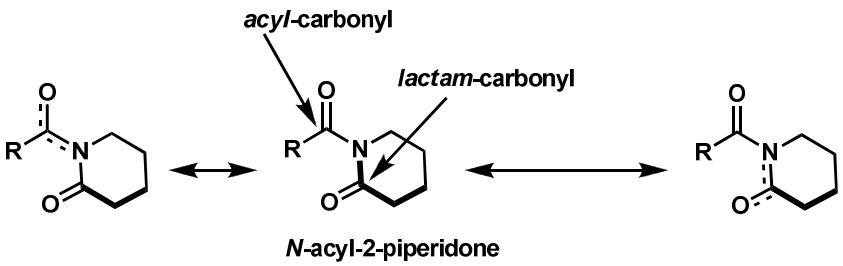
that the formation of the amide bond is one of the most prevalent chemical transformations conducted by industrial organic chemists. Thus the development of new methods for amides will have a major impact on chemical and biological sciences.[1] Typically, amides are prepared by the reaction of amines with activated carboxylic acids, esters, aldehydes, alcohols, hydration of nitriles, hydroamination of alkynes and aminocarbonylation.[2] Alternately, amides can be prepared by transamidation, in which an amine is exchanged with a constituent of amides.[2] The high stability of amide linkages arising out of amidic resonance and comparable energetics of starting materials and products render transamidation a challenging task. Due to this, transamidation requires harsh reaction conditions, high temperature, prolonged reaction times[1] and activating agents in stoichiometric/catalytic amounts.[3] For the past two decades, great efforts have been made in this area to conduct transamidation at relatively milder reaction conditions.[1,4] Though great headway has been achieved with primary amides,[4d,5] it is still elusive with secondary amides[6]. A general strategy that was widely followed is the functionalization of amide nitrogen with electron-withdrawing functional groups typically *tert*-butoxycarbonyl[4a,7] acetyl, benzoyl[8] and lactams[9] to weaken the amidic resonance and enhance the electrophilicity of the amide carbonyl. Also, to create an imbalance in the thermoneutrality of the reactants and the products (by-products will be carbamates or amides rather than competitive amines). In 2016, a breakthrough study was reported by Garg and co-workers[6d] in addition to the above activation strategy, a non-precious metal catalyst was used for the transamidation of secondary amides under mild reaction conditions. The *N*-*tert*-butoxycarbonyl (N-BoC) functionalization weakens the amidic resonance thereby facilitating the N-C metal insertion/transamidation process. Significant progress has been made in the development of this method for amide bond cross-coupling[10] and transamidation.[11] Recently (2018), Szostak et al[4a,b] and Chandrasekaran et al[12] followed the

above *N*-selective amide bond activation/destabilization strategy i.e *N*-BoC or *N*-tosyl functionalization, to achieve transamidation of secondary amides under mild and metal-free conditions. Interestingly, the amide bond in these amides was shown to twisted up to 50-60°.[13] More recently (2018), Szostak and co-workers[14a,b] utilized amide bond twist of *N*-acyl-glutaraimide and achieved transamidation under mild and metal-free conditions (**Scheme 1**). *N*-Acyl-glutaraimide was established to possess high amide bond (85.7°) twist and most reactive amide substrate in transition-metal catalyzed amide N-C bond activation. This amide bond twist weakens the amidic resonance and facilitated nucleophilic addition. Further, the leaving group ability and lower nucleophilicity of glutaraimide are the factors controlling the reactivity of the process. The same group in a recent study reported the most twisted acyclic amides described to date. Benzamide nitrogen was coupled with tosyl and acetyl/Boc groups to achieve the near perpendicularity. They established that these amides readily undergo transamidation and Suzuki coupling.[14c] In 1994, Bertrand and co-workers reported transamidation of acyclic imides promoted by $AlCl_3$.[8] Gowri et al in 2015[15] have shown transamidation of piperlongumine, an imide substrate, with various alkyl amines catalyzed by magnesium bromide etherate at room temperature (**Scheme 1**). Herein, we exploited amide bond twist associated with *N*-acyl-2-piperidones to achieve highly selective transamidation with a broad range of amines under mild and metal-free conditions (**Scheme 2**). Single crystal X-ray analysis shows amide bond twist, τ = -20.39 ° and pyramidalization, χ_N = -11.73. As cited earlier, it is believed that the amide bond twist though less than *N*-acyl-glutaraimide, might weaken the amidic conjugation and facilitated the nucleophilic addition (amines) selectively to N-acyl carbonyl carbon (**Scheme 2**). Further, this was supported by C-N bond metrics (**Figure 1**). The transamidation proceeds at room temperature, under neat condition (when at least one of the reactant is a liquid. Otherwise ethanol was used as

a solvent), no additional base in short reaction times of 30-90 min. The broad applicability of the process was demonstrated with amines bearing carboxylic acids, esters, and hydroxyl groups and alkyl and aryl-*N*-acyl moieties. A competitive transamidation of primary *Vs* secondary amine was conducted to reveal the selectivity pattern. Further, the scope of the methodology was validated with a synthesis of four natural product amide alkaloids under mild condition. Esterification was observed in the absence of primary/secondary amines with aliphatic alcohols ethanol and benzyl alcohol at elevated temperature (85 °C).



Scheme 1. Transamidation protocols reported earlier and present work

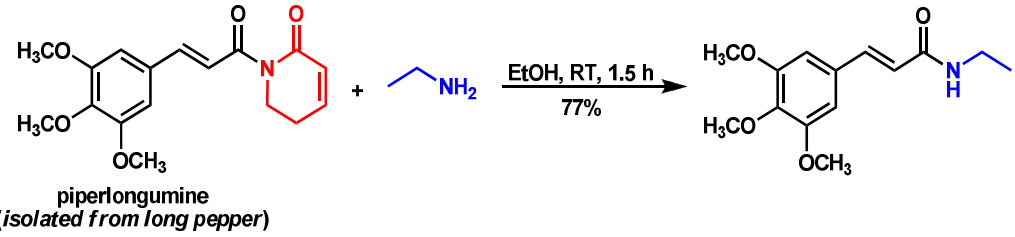


Scheme 2. Amidic conjugation of *N*-acyl-2-piperidones biased towards lactam carbonyl carbon

Results and Discussion

During the course of our investigation for the synthesis of piperlongumine derivatives, we serendipitously obtained transamidation product of piperlongumine. Piperlongumine is a primary constituent of long pepper (*Piper Longum*). It is an amide alkaloid, structured with 3,4,5-trimethoxyl cinnamoyl moiety bonded to 5,6-dihydro-2(1H)-pyridinone (**Scheme 3**).[16] It is a bioactive compound with a broad spectrum of therapeutic activities with a major focus on anticancer activity.[16] Recent studies show piperlongumine selectively kills cancer cells leaving the normal cells unaffected *in vitro* and *in vivo*.[17] This attracts wide interest for piperlongumine and its derivatives for the treatment of various malignancies. The high activity of piperlongumine and our continued interest in pepper based compounds draws our interest in the synthesis of piperlongumine derivatives. We sought to prepare 5,6-dihydro-2(1H)-pyridinone ring for the synthesis of piperlongumine derivatives. Synthetic routes known for the preparation of 5,6-dihydro-2(1H)-pyridinone ring is either lengthy or uses expensive metal catalysts[18]. Hence, we decided to synthesize 5,6-dihydro-2(1H)-pyridinone under metal-free conditions. Among the various methods attempted, we were trying to hydrolyze piperlongumine (isolated from long pepper) with 70% ethylamine to obtain 5,6-dihydro-2(1H)-pyridinone. In one of the earlier reports, 70% ethylamine was used for the deprotection of 5,6-dihydro-2(1H)-pyridinone type molecule.[19] When piperlongumine was reacted with 70% ethylamine at room temperature, it was consumed

within 1.5 hours (**Scheme 3**). Analysis of ^{1}H NMR spectrum of the crude reaction mixture shows no sign of 5,6-dihydro-2(1H)-pyridinone or its ring-opened product. Instead, the formation of transamidation product of piperlongumine with ethylamine, i.e *N*-(3,4,5-trimethoxycinnamoyl)-benzylamine was observed. Several attempts to isolate/find the status of the 5,6-dihydro-2(1H)-pyridinone ring left us clueless. Referring to the literature, we found very few reports for transamidation of imides.[8,14,15] Moreover, these methods require a metal catalyst, activating agents in stoichiometric quantity or excess, long reaction times and used chlorinated solvents, whereas our reaction conditions are exceedingly mild and metal-free. Transamidation proceeds at room temperature, under neat condition (when at least one of the reactant is liquid. Otherwise ethanol was used as a solvent), with no additional base in short reaction time, 30-90 min. These simple conditions imply that there is great potential to develop this method as a valuable synthetic tool for amide synthesis.

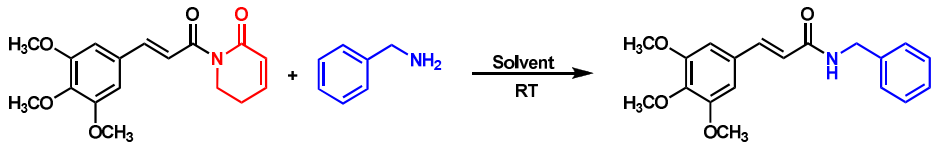


Scheme 3. Transamidation of piperlongumine with ethylamine

Solvent optimization studies

Effect of solvents on this reaction was evaluated with solvents outlined in **table 1.** Benzylamine was taken as the standard amine substrate. Yields and reactions time revealed that neat conditions (**Table 1**, entry 5) are the best if at least one of the reactant is liquid. Otherwise, ethanol was found to be the most optimal solvent (**Table 1**, entry 1).

Table 1. Solvent optimization studies



S. No	Solvent	Time (h)	Yield (%)
1[a]	EtOH	1.5	74
2[a]	DCM	24	63
3[a]	DMSO	1.5	67
4[a]	DMF	1.5	65
5[b]	Neat	45 min	76

[a]Piperlongumine (50 mg, 1 equiv.), amine (3 equiv.). [b]Piperlongumine (50 mg, 1 equiv.), amine (5 equiv.).

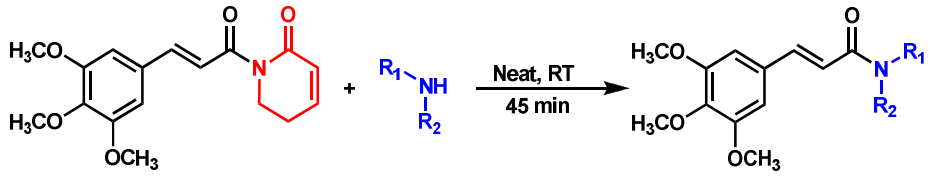
Transamidation of piperlongumine with various amines

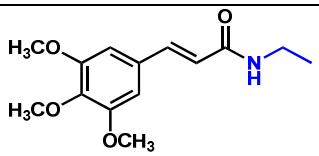
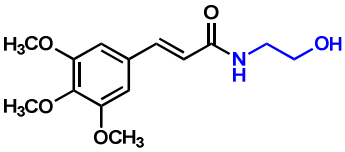
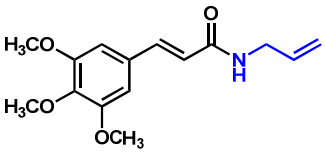
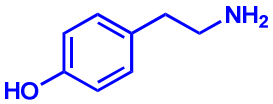
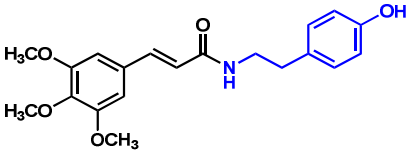
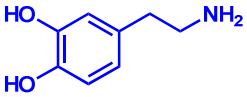
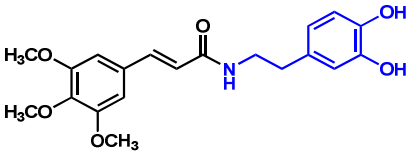
Under the optimized reaction condition, the scope of our initial finding was expanded to a broad range of amines outlined in **table 2**. Transamidation proceeds smoothly with ethyl and allylamine and now, the time required for completion is just half of the reaction time of ethanol condition (compare **Table 2**, entry 1 and **Scheme 3**) and almost same yield was observed, 76%. We were pleased to find that even amines bearing a hydroxyl group(s) such as ethanolamine, dopamine, and tyramine were well suited for the transamidation process. Of note, only the amine group participated in the nucleophilic addition. The hydroxyl groups remained unaffected and did not interfere with the transamidation process (**Table 2**, entry 2, 4 and 5). The corresponding amides were formed in moderate yields of 71, 62 and 54% respectively (**Table 2**, entry 2, 4 & 5). The dopamine coupled amide was evaluated as an efflux pump inhibitor.[20] Tyramine and dopamine were commercially available as hydrochloride salts they were neutralized with trimethylamine

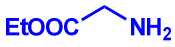
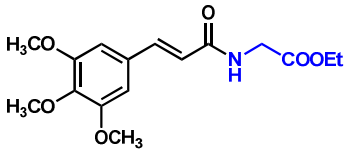
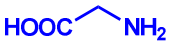
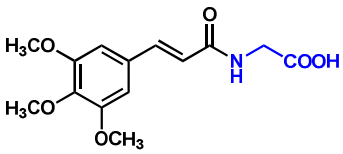
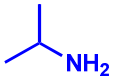
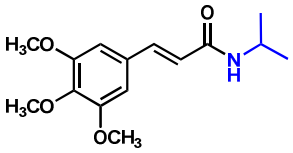
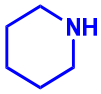
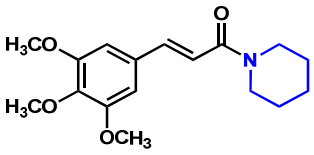
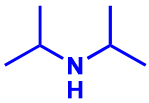
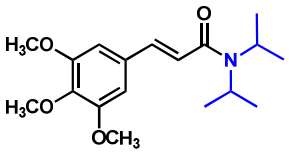
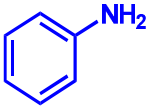
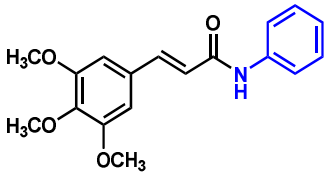
prior to use. Transamidation of tyramine and dopamine was conducted in ethanol, trace amount (~5%) of formation of ethyl ester of piperlongumine was observed as a by-product in both cases. The obtained results show that the process is highly selective for *N*-nucleophile than *O*-nucleophile. Transamidation proceeds smoothly with ethyl glycinate, and the secondary amine, piperidine. The reaction completed within 45 min and the corresponding amides were formed in good yields of 78 and 71% respectively (**Table 2**, entry 6 and 9). Glycine ethyl ester is commercially available as the hydrochloride salt. It was neutralized with trimethylamine prior to use. Transamidation of sterically demanding amine, isopropylamine was found to be a little slower, it takes 1.5 hours for the completion of the reaction (**Table 2**, entry 8). We then examined the challenging amine substrate, free amino acid, glycine. The zwitterionic glycine was initially neutralized with trimethylamine and then reacted with piperlongumine in trimethylamine/ethanol solvent. We were delighted to find that in both cases, glycine underwent transamidation. However, it required longer reaction times. It requires 6 h stirring at 40 °C with trimethylamine and with ethanol it took 16 h at 40 °C for the completion of the reaction (**Table 2**, entry 7). The corresponding transamidated product formed in good yields of 70 and 62% respectively. The reaction that uses ethanol solvent, lead to the formation of minor amount (~10%) of ethyl ester of piperlongumine as a by-product. To the best of our knowledge, this is the first report of transamidation of free amino acid. We determined that sterically hindered di-isopropyl amine was unreactive under the reaction conditions (**Table 2**, entry 10). Extending the reaction time up to 24 hours at room temperature or heating at 85 °C for 24 hours was also not fruitful. Only the starting materials were recovered. We envisaged that increasing the bulkiness around amines would decrease the reactivity which can be exploited for selective transamidation of less sterically-hindered amine in the presence of sterically-demanding amines. Similarly, aromatic amine, aniline

was also found to be unreactive under the reaction conditions (**Table 2**, entry 11). Only the starting materials were recovered. This inactivity can be exploited for selective transamidation of alkylamine in the presence of an aromatic amine.

Table 2. Transamidation of piperlongumine with various amines



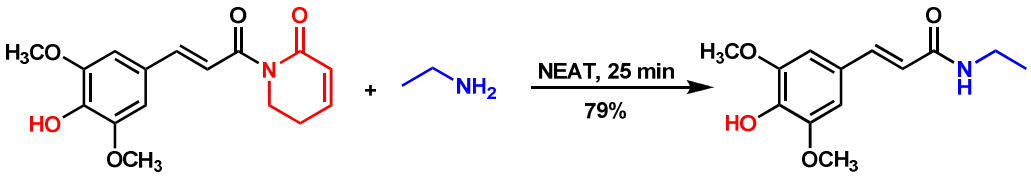
S.No	Amine	Product	Yield (%)
1[a]			76
2[a]			71
3[a]			76
4[b]			62
5[b]			54

6[b]			78
7[c,d]			62, 70
8[e]			69
9[a]			71
10[a]			No reaction
11[a]			No reaction

[a]Piperlongumine (50 mg, 1 equiv.), amine (5 equiv.), 45 min. [b](i)hydrochloride salt of amine (3 equiv.), EtOH (0.8 mL), Et_3N (3 equiv.), 30 min, RT, (ii) piperlongumine (50 mg, 1 equiv), 1.5 h, RT. [c](i) Zwitterionic glycine (3 equiv.), H_2O (22 µL), EtOH (0.8 mL), Et_3N (3 equiv.), 30 min, RT (ii) piperlongumine (50 mg, 1 equiv.), 40 °C, 16 h. [d]Piperlongumine (50 mg, 1 equiv.), zwitterionic glycine (3 equiv.), Et_3N (10 equiv.), H_2O (22 µL), 40 °C, 6 h. [e]Piperlongumine (50 mg, 1 equiv.), amine (5 equiv.), 1.5 h, RT.

Transamidation of hydroxyl piperlongumine

Another important observation of the reaction scope is that the hydroxyl group on the imide substrate was also well tolerated. *p*-Hydroxy piperlongumine was found to undergo transamidation with ethylamine at room temperature. The transamidation completed within 25 min. The phenolic -OH did not interfere with the transamidation process. The corresponding amide formed in a good yield of 79% (**Scheme 4**). This finding corroborated that the process is highly selective for the *N*-nucleophile than the *O*-nucleophile. *p*-Hydroxy piperlongumine was synthesized from piperlongumine (*ESI*) by monodemethylation.



p-Hydroxy piperlongumine

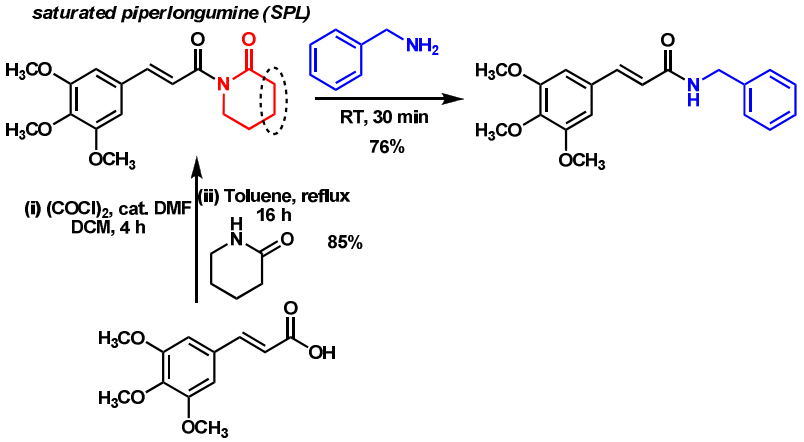
Scheme 4. Transamidation of *p*-hydroxy piperlongumine with ethylamine

Transamidation of saturated piperlongumine (SPL) with various amines

To expand the substrate scope, we evaluated the applicability of piperlongumine with the saturated 2-piperidone ring as the imide substrate. Accordingly, we synthesized piperlongumine with saturated piperidone ring[21] (SPL, **Scheme 5**) and subjected to the transamidation process. The molecular structure of saturated piperlongumine (SPL) was unambiguously established by single crystal X-ray analysis (**Figure 1**). The two carbonyl groups were almost anti-periplanar and their torsion angle was found to be 153.80° (O5-N1-C9-O4). The bond distance between the amide nitrogen and the carbonyl carbons (N1-C9 = 1.413 Å, N1-C10= 1.386 Å, N1-C14 = 1.48 Å, C10-O5 = 1.213 Å, C9-O4 = 1.215 Å) indicates that amidic resonance is more prominent towards ring carbonyl carbon (**Figure 1**). The amide bond twist (τ) and pyramidalization (χ_N) were calculated to, -20.39° and = -11.73° respectively.[22]

In the initial study, we examined the transamidation of saturated piperlongumine (SPL) with benzylamine under neat conditions at room temperature. We were delighted to find that transamidation proceeded smoothly and even faster than piperlongumine. The transamidation completed with 30 min and the corresponding amide product formed in 76% yield (**Table 3**, entry 1). We were able to isolate the by-product, 2-piperidone in 38% yield. To examine the scope, saturated piperlongumine (SPL) was reacted with a broad range of amines to afford pharmaceutically valuable amides in good yields. Transamidation accommodates simple alky amines, ethyl, and allylamine, amines bearing hydroxyl group like ethanolamine, sterically demanding isopropylamine and the secondary amine, piperidine. The reaction completed within 30 min with primary amines and 45 min with sterically demanding isopropylamine and piperidine. The corresponding transamidation products were formed in good yields of 70%, 74%, 71%, 69% and 74% respectively (**Table 3,** entry 2-6). We then evaluated the challenging amine substrates, amino acids such as glycine, and serine. Notably, the transamidation was carried out keeping carboxylic acid groups and hydroxyl groups remain unprotected. We were pleased to find that transamidation proceeds smoothly with both the amino acids and yielded the corresponding amides in good yields 70 and 60% respectively (**Table 3**, entry 7 and 8). Glycine/serine was initially neutralized with trimethylamine prior to transamidation process. To the amino acid, SPL in triethylamine was added and stirred for 6 h at 40 °C for glycine and 60 °C for serine. The corresponding amide products were formed in good yields (**Table 3**, entry 7 and 8). Since these amide products are previously not known, they could be evaluated as piperlongumine derivatives for biological applications. Similarly, transamidation proceeded smoothly with a neuromodulator, tyramine, and neurotransmitter, dopamine (**Table 3**, entry 9 and 10). Yielded the corresponding amides in good to moderate yield, 64 and 54% respectively. Di-isopropylamine and aniline were

ineffective under our reaction conditions (**Table 3**, entry 11 and 12). Only the starting materials were recovered, which should prove useful in selective transamidation of this class of imides with aliphatic amines in the presence of less nucleophilic aromatic and sterically demanding amines.



Scheme 5. Synthesis and transamidation of saturated piperlongumine (SPL)

Single crystal X-ray structure of saturated piperlongumine (SPL)

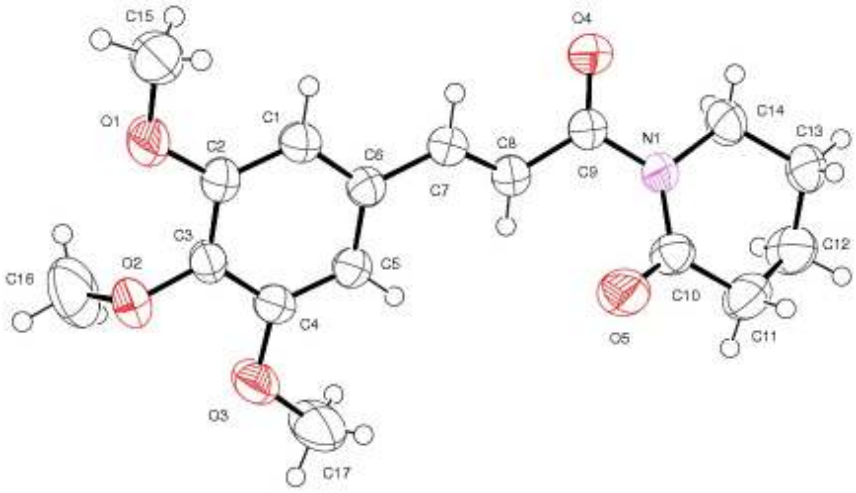
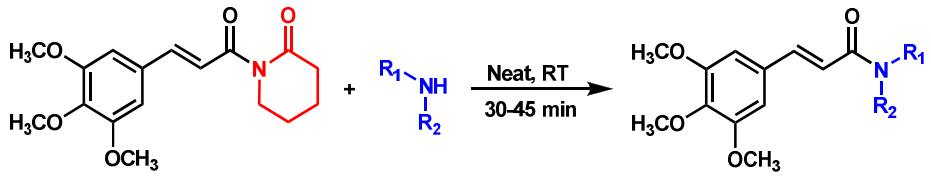
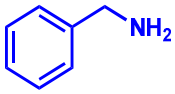
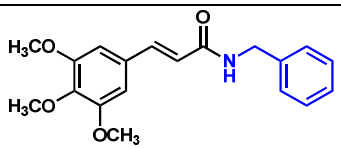
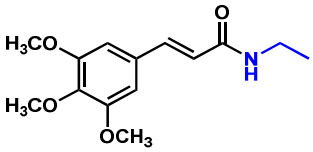
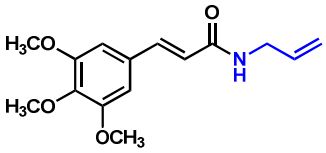
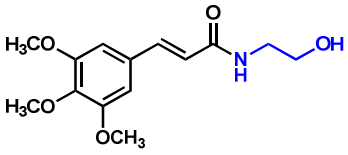
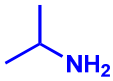
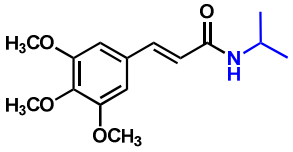
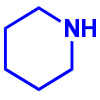
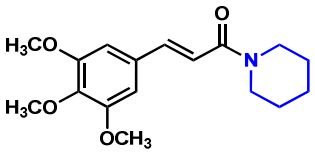
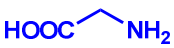
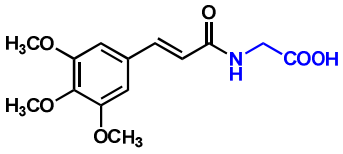
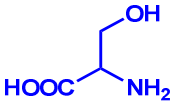
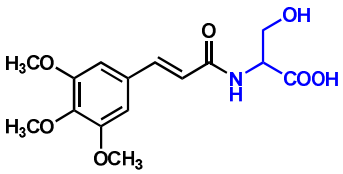
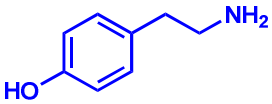
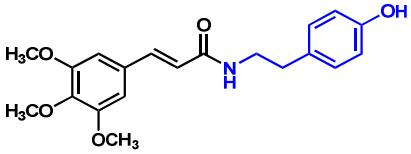
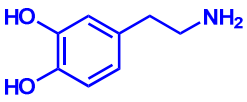
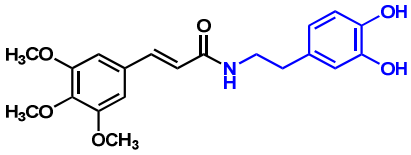
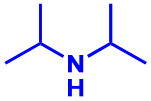
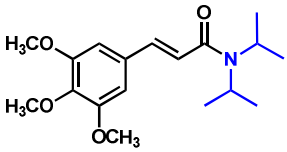
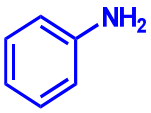
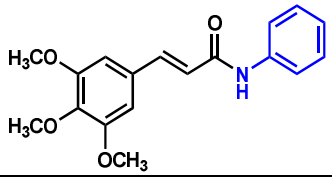


Figure 1. ORTEP diagram of piperlongumine with saturated 2-piperidone ring. Bond distance: N1-C9 = 1.413 Å, N1-C10= 1.386 Å, N1-C14 = 1.48 Å, C10-O5 = 1.213 Å, C9-O4 = 1.215 Å Torsion angle (O5-N1-C9-O4) = 153.80°, amide bond twist, τ = -20.39° and pyramidalization, χ_N = -11.73°, $\tau + \chi_N$ = 32.12 °.

Table 3. Transamidation of saturated piperlongumine with various amines



S.No	Amine	Product	Yield (%)
1[a]			76
2[a]			70
3[a]			74
4[a]			71
5[b]			69
6[b]			74
7[c]			70

8[d]			60
9[e]			64
10[e]			54
11[a]			No reaction
12[a]			No reaction

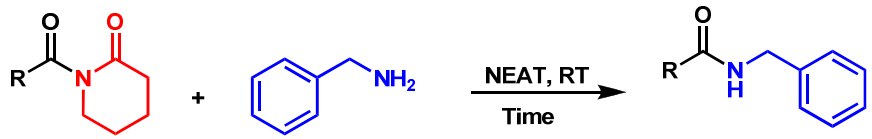
[a]Saturated piperlongumine (100 mg, 1 equiv.), amine (5 equiv.), 30 min, RT. [b]Saturated piperlongumine (100 mg, 1 equiv.), amine (5 equiv.), 45 min, RT. [c]Saturated piperlongumine (100 mg, 1 equiv.), glycine (3 equiv.), Et_3N (10 equiv., 0.4 mL), H_2O (44 µL), 40 °C, 6 h. [d]Saturated piperlongumine (100 mg, 1 equiv.), glycine (3 equiv.), Et_3N (10 equiv., 0.4 mL), H_2O (44 µL), 60 °C, 6 h. [e](i) hydrochloride salt of amine (3 equiv.), EtOH (1.6 mL), Et_3N (3 equiv.), 30 min, RT, (ii) Saturated piperlongumine (100 mg, 1 equiv.), 1.5 h, RT.

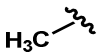
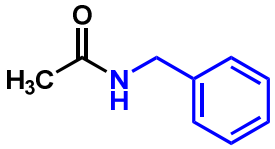
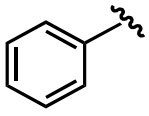
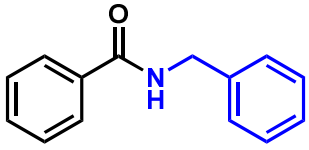
Transamidation of different N-acyl-2-piperidones with benzylamines

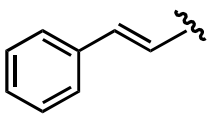
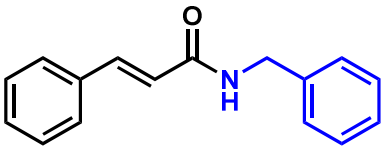
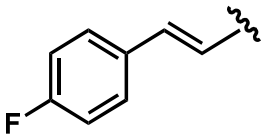
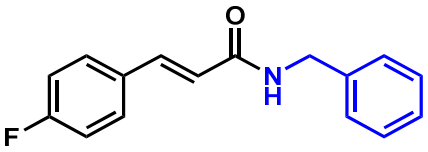
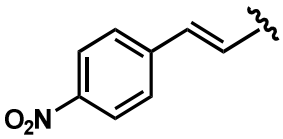
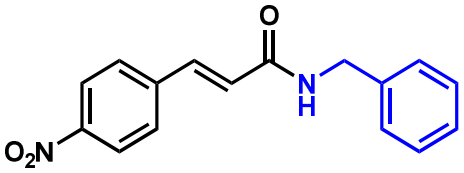
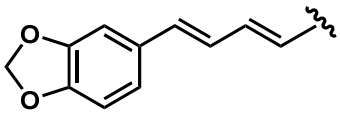
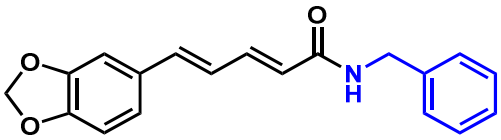
We next focused on the scope of *N*-acyl-2-piperidones that can participate in this protocol. Accordingly, *N*-acetyl, *N*-benzoyl, *N*-cinnamoyl, and *N*-piperoyl-2-piperidone (**Table 4**) were synthesized[21] and evaluated for transamidation. *N*-Acyl-2-piperidones and benzylamine were

reacted at room temperature under neat conditions. We determined that both alkyl and aryl *N*-acyl-2-piperidones underwent transamidation smoothly and the reaction completed within 30-45 min (**Table 4**, entry 1-6). The corresponding amides were formed in good yields. Notably, fluorine substituent often encountered as a medicinally relevant scaffold, and electrophilic nitro substituent posed no difficulty (**Table 4**, entry 4, 5). In fact, the higher yield was observed with electrophilic substituents (-F and -NO_2) (**Table 4**, entry 4, 5). The most probable reason is that these substituents increase the electrophilicity of the acyl carbonyl carbon. Interestingly, transamidation proceeds faster with *N*-piperoyl-2-piperidone (**Table 4**, entry 6), the reaction completed within 30 min. This is the first report of transamidation of di-conjugated amides. Yields and reaction times (**Table 4**, compare entry 2, 3 and 6) suggest that increasing the conjugation to *N*-acyl-2-piperidone may be beneficial for the transamidation process. The enhanced reactivity may be due to reduced steric hindrance around the acyl carbonyl carbon.

Table 4. Transamidation of various imides with benzylamine



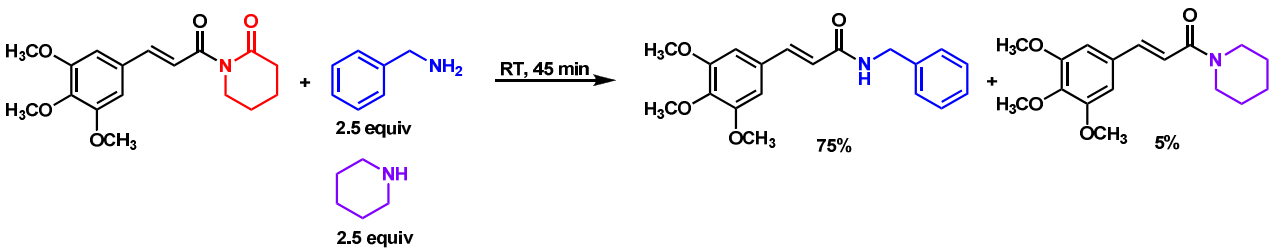
S.No	R	Time (min)	Product	Yield (%)
1[a]		45		79
2[a]		45		69

3[a]		45		72
4[a]		45		81
5[a]		45		82
6[a]		30		77

[a]*N*-Acyl-2-piperidone (100 mg, 1 equiv.), benzylamine (5 equiv.), 45 min.

The selectivity of transamidation process: Primary Vs Secondary amines

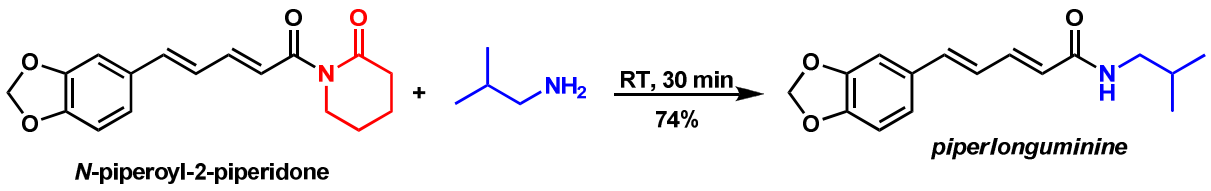
To establish selectivity of the transamidation process for primary and secondary amine, SPL was reacted with a mixture of an equal amount of benzylamine and piperidine (**Scheme 6**). Interestingly, benzylamine underwent faster transamidation than piperidine, yielding the benzylamide as the major product at 75% yield and piperidine exchanged amide as the minor product in 5% yield. This is contrary to the consideration of the relative basicity of primary and secondary amines.[14] This reversal of reactivity is attributed to higher steric hindrance associated with secondary amines.[6b] The above factor should be advantageous for selective transamidation of this class of imides with sterically less demanding primary amines in the presence of a sterically hindered secondary amines.



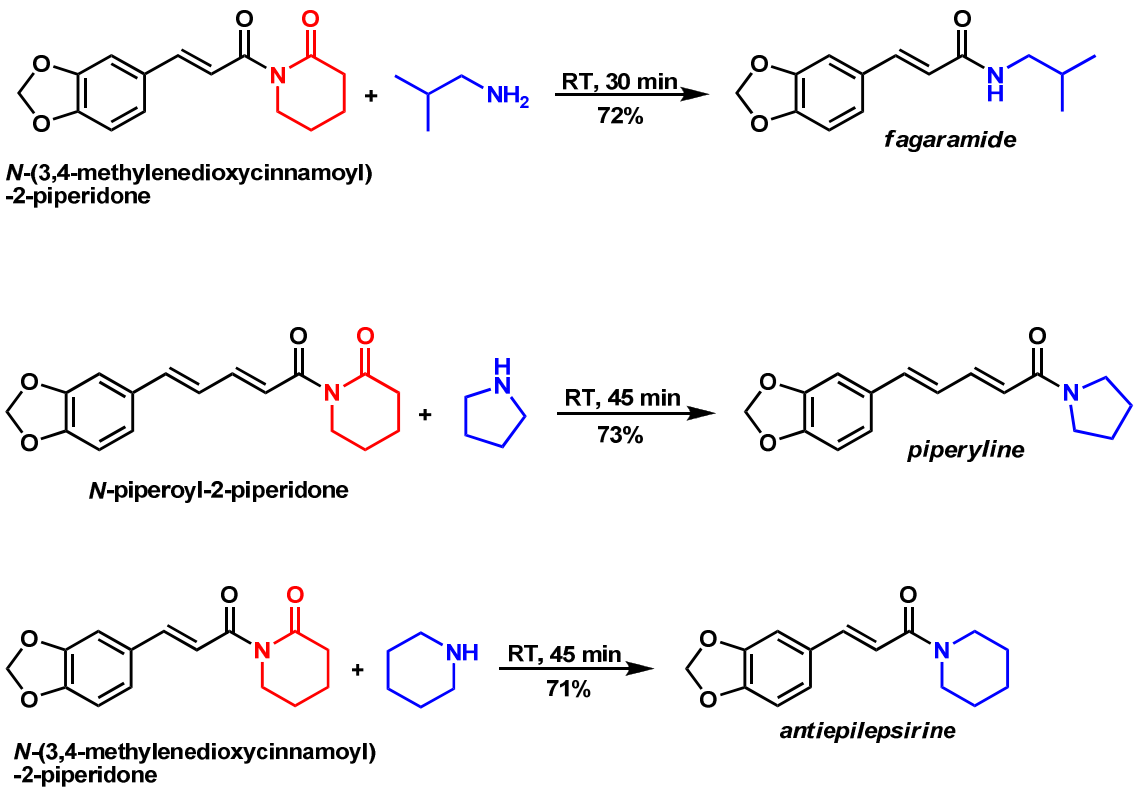
Scheme 6. Selectivity study of transamidation protocol: Primary *Vs* secondary amines.

Synthesis of natural product amide alkaloids

The practical value of the method was highlighted by the synthesis of four pharmaceutically important natural product amides, (i) *Antiepilepsirine* an antiepileptic drug[23] and TRPV1 agonist;[24] (ii) *Piperlonguminine* an anti-tumor and anti-inflammatory agent;[25] (iii) *Piperyline* an antifungal[26a] and antibacterial agent;[26b] and (iv) *Fagaramide* which is an antidepressant[27] and antifungal agent,[26a] in high yields at mild reaction conditions. These amides were prepared at room temperature, under solvent-free condition, in short reaction times of 30-45 min, no additional base and needed no purification by column chromatography. The *N*-piperoyl-2-piperidone was reacted with isobutylamine/pyrrolidine to obtain Piperlonguminine/Piperyline in good yields of 74% and 73% respectively (**Scheme 7**). Similarly, *N*-(3,4-methylenedioxy cinnamoyl)-2-piperidone was reacted with isobutylamine/piperidine to obtain Fagaramide/Antiepilepsirine in good yields of 72% and 71% respectively (**Scheme 7**).



N-piperoyl-2-piperidone

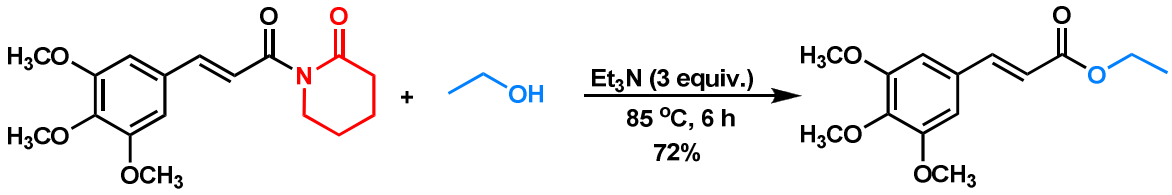


Scheme 7. Synthesis of natural product amide alkaloids via present transamidation protocol

Esterification of different imides with aliphatic alcohols

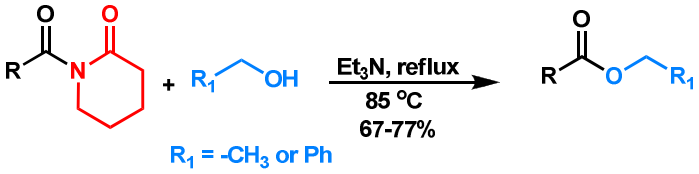
Recently, Szostak and co-works recently (2018) demonstrated esterification of transient *N*-BoC activated amide with aromatic and aliphatic alcohols. Also, they have showcased thioesterification reaction under the same reaction conditions.[28] To expand the scope of our methodology for the synthesis of esters, *N*-acyl-2-piperidone was reacted with *O*-nucleophile in the absence of nucleophilic amines. Our studies commenced by surveying the reaction of SPL with ethanol in the presence of trimethylamine at room temperature. There was no reaction, hence, the reaction mixture was heated to reflux for 6 h, starting materials were completely consumed. Analysis of the reaction products shows the formation of expected ester, 3,4,5-trimethoxy ethyl cinnamate in good yield, 72% (**Scheme 8**). Similarly, the other *N*-acyl-2-piperidones outlined in **Table 5** were reacted with ethanol/benzyl alcohol. All the *N*-acyl-2-piperidones underwent esterification and

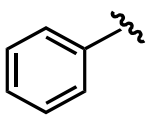
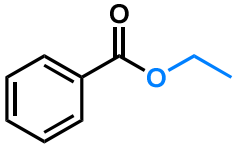
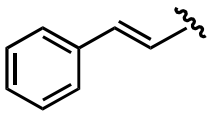
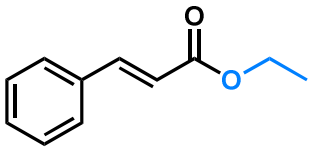
yielded the corresponding esters in good yields, 67-77% (**Table 5**). It is noticed that reactivity for esterification increased with increasing the number of alkene double bond (compare time and yield of benzoyl, cinnamoyl and piperoyl imides). As mentioned earlier, the increased reactivity could be due to decreased steric hindrance around the acyl carbonyl carbon. This highlights the broad scope of the present methodology for the synthesis of both amides and esters from this class of imides by simply changing the reaction conditions.

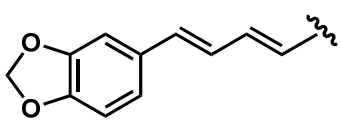
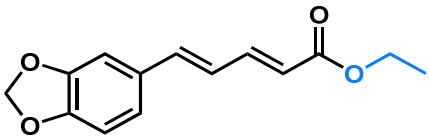
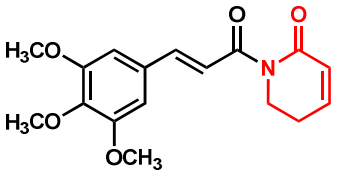
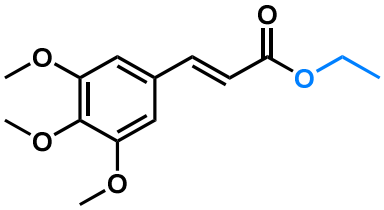
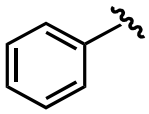
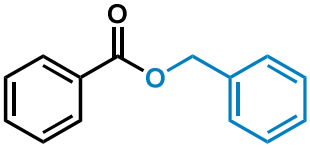
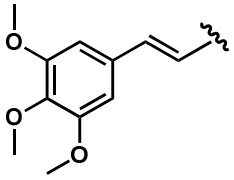
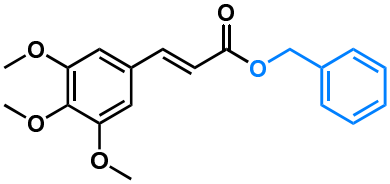
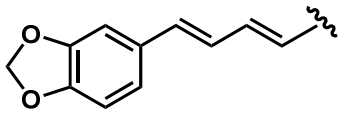
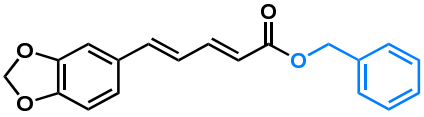
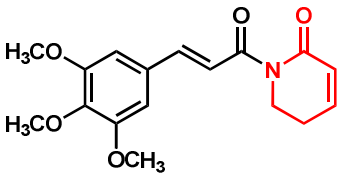
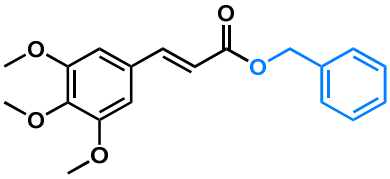


Scheme 8. Esterification of saturated piperlongumine

Table 5. Esterification of different imides with ethanol.



S.No	R	Time (h)	Product	Yield (%)
1[a]		8		69
2[a]		8		70

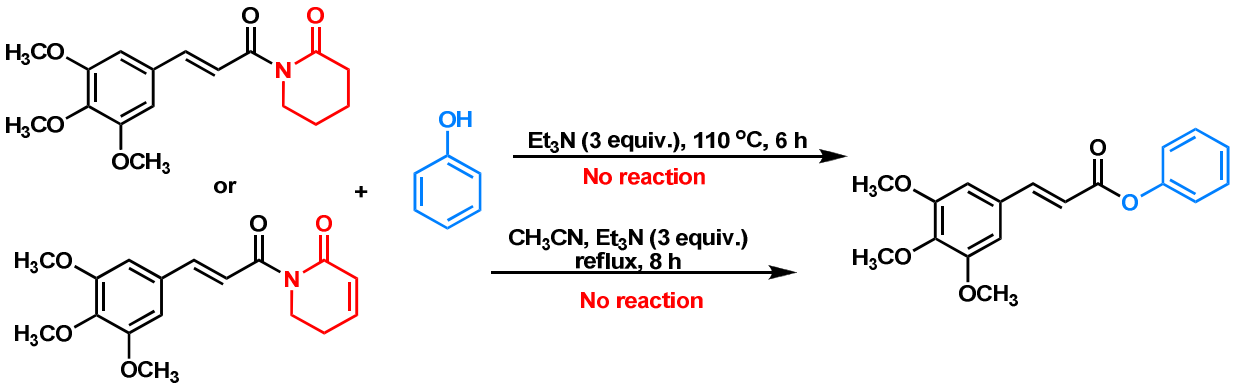
3[a]		4.5		67
4[a]		6		67
5[a]		8		70
6[a]		8		74
7[a]		7		77
8[a]		8		71

[a]*N*-Acyl-2-piperidone (100 mg, 1 equiv.), Ethanol or benzyl alcohol (1.5-2.5 mL), Et_3N (3 equiv.).

Esterification of different imides with phenol

Attempts to esterify *N*-acyl-2-piperidones, SPL and piperlongumine with aromatic alcohol, phenol under the aforementioned conditions were not fruitful (**Scheme 9**). SPL/PL was reacted with phenol in the presence of triethylamine at room temperature, at 85 °C and at 110 °C. There was no

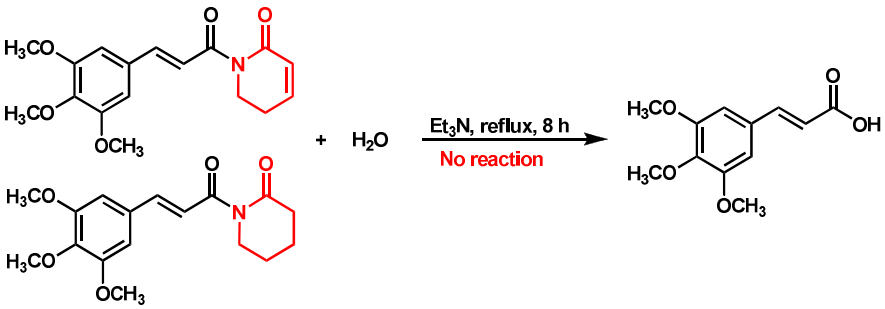
reaction, only the starting materials were retrieved. The same observation was noticed when the reaction was conducted in acetonitrile at reflux conditions for 8 h.



Scheme 9. Attempted esterification of piperlongumine and saturated piperlongumine with phenol

Determination of stability of piperlongumine and saturated piperlongumine under the hydrolytic condition

We next evaluated the stability of the imides, piperlongumine, and SPL under hydrolytic conditions. An aqueous solution of piperlongumine/SPL was heated under reflux in the presence of trimethylamine for 8 h. There was no noticeable hydrolytic cleavage observed in both cases. Only the starting material was recovered (**Scheme 10**). These results indicate that the imides are robust and that they can be prepared in large quantities for further chemical transformations.



Scheme 10. Hydrolysis of piperlongumine and saturated piperlongumine.

In essence, our results support the applicability of aliphatic *N*-nucleophilic and *O*-nucleophilic addition to the weakened amide bond, arising out of the amide twist, however under selective reaction conditions *viz N*-nucleophilic addition at room temperature and *O*-nucleophilic addition at a higher temperature in the absence of nucleophilic amines.

Conclusions

A simple protocol for the synthesis of amides is developed based on the transamidation process. Transamidation of *N*-acyl-2-piperidones with amines is achieved under mild and metal-free conditions. Transamidation proceeds at room temperature, under neat condition (in the case of solid reactants, EtOH was used as solvent), in short reaction time of 30-90 min, no additional base with good to moderate yields. Amide bond twist associated with *N*-acyl-2-piperidones was exploited for the transamidation of amines. Considerable variation is tolerated with regard to both imide and amine substitutions. Of note, amines bearing carboxylic acid, ester and hydroxyl groups that would be problematic under metal-catalyzed protocols, are tolerated under the reaction condition. Transamidation of both alkyl and aryl *N*-acyl-2-piperidones was demonstrated. Transamidation was found to be ineffective with less nucleophilic amines, anilines and biased towards less sterically demanding alkyl amines, which should be useful for selective transamidation in the presence of aromatic and sterically demanding alkyl amines. The practical value of the methodology was highlighted by the synthesis of four pharmaceutically important amide alkaloids, antiepilepsirine**,** piperlonguminine, piperyline and fagaramide in good yields under mild reaction conditions, in short reaction time, 30-45 min and no purification by column chromatography. In the absence of nucleophilic amines, *N*-acyl-2-piperidones underwent esterification with aliphatic alcohols at elevated temperature (85 °C). Furthermore, *N*-acyl-2-

piperidones are easier to synthesize and robust under the reaction conditions and they could be prepared in large quantities for general applications in metal-free transformations. Thus, the transamidation protocol developed herein for the synthesis of amides have broad substrate scope, yet involves simple reaction conditions, will be of great interest in organic synthesis, polymers, natural products, pharmaceuticals, and material sciences.

Experimental Section

The full experimental data related to this article are given in the supplementary file. It includes synthetic procedure, ^{1}H NMR, and ^{13}C NMR spectra of transamidation products and their precursors. CIF data of **SPL** was deposited in Cambridge Crystallographic Data Centre (CCDC) and its CCDC numbers: 1899117. The data is available free of charge at http://www.ccdc.cam.ac.uk

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Keywords: Transamidation, Piperlongumine, Piperidones, Amide alkaloid, Amide bond twist.

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