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Condensation of carboxylic acids with amines using the Boc_2O/DMAP system under solvent-free conditions†

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The present study describes the use of the di-*tert*-butyl dicarbonate (Boc_2O)/4-(*N*,*N*-dimethylamino)pyridine (DMAP) system for the amidation of carboxylic acids under neat conditions without heating. A set of carboxylic acids was explored, such as non-steroidal anti-inflammatory drugs (NSAIDs), fatty acids and protected prolines in the presence of aromatic, benzylic and aliphatic amines as nucleophilic partners. The scope of this easy approach was extended to the preparation of thirty-two diverse carboxylic amides, which were recovered with isolated yields varying from moderate to excellent. To increase the value of this protocol, a scalable chemoselective amidation of oleic acid with ethanolamine was successfully established. The corresponding fatty carboxylic amide, *N*-oleoylethanolamide (OEA), was recovered with 73% yield. This study highlights the potency of the use of mixed anhydrides formed *in situ* and the pursuit of the reaction profile reveals sequential steps rather than a one-pot process.

Introduction

Carboxylic amides play an important role as building blocks for the synthesis of peptides, proteins and antibiotics.[1–3] A statistical analysis of medicinal chemistry databases revealed that the amide group was present in 24% of the 200 most prescribed drugs in 2016, and in 60% of the drugs approved in 2017.[4] Further, they are used as synthetic intermediates in the manufacture of polymers, detergents, lubricants, food additives and other products.[5–9]

There are myriad reported synthetic routes for carboxylic amides, each one adapted for a specific substrate under appropriate conditions.[10–13] The organocatalytic and organometallic approaches for the elaboration of amide bonds *via* functionalization of hydrocarbons have attracted great interest, both academic and industrial.[14–16]

However, several amidation methods have been developed under metal-free conditions, using aldehydes,[17–20] ketones,[21] oximes,[22,23] alcohols,[24] nitriles,[25,26] acids and derivatives,[27–29] amines and their derivatives,[30–32] halogenated aryls,[33] alkenes,[34,35] and alkynes.[36,37]

The classical described approaches for amide synthesis are commonly founded on the coupling of amines and carboxylic acid derivatives. The most popular used coupling reagents are carbodiimides,[38] benzotriazoles,[39,40] chlorofomates,[41–43] and immonium[44–47] or phosphonium salts.[48–51] Unfortunately, those reagents present several disadvantages, such as toxic or corrosive by-products, in some cases affecting the overall isolated yields because of the difficulty and the cost of the final product purification. Thus, the development of novel environmentally benign pathways are desired; for example, exploiting biocatalysis for the direct condensation of carboxylic acids and amines *via* the *in situ* activation of carboxylic acids by formation of an acyl-enzyme intermediate constitutes an alternative approach.[52–59]

To date, few methods have been reported using a mixed anhydride for the amidation reaction.[60–62] The first one, reported by Vaughan and Osato, was dedicated to the synthesis of peptides and showed that *N*-substituted amino acids react easily with an aqueous solution of a salt or an ester of a second amino acid to give the corresponding peptide derivatives.[63] Meanwhile, Pozdnev applied a new protocol for the preparation of peptide derivatives using a di-alkyl dicarbonate/pyridine (such as 4-(*N*,*N*-dimethylamino)pyridine (DMAP)) system in dioxane.[64,65] This pathway furnished the desired peptides with good isolated yields after a standard work-up. As valuable reaction waste, carbon dioxide and the *tert*-butanol were also produced.[66–68] However, for environmental and sustainability reasons, the reduction or/and the switching of conventional solvents for other safer options has become a priority.[69–72]

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The present work falls within our investigations, with the main objective being the development of sustainable methodologies for the synthesis of valuable building blocks.[73–75] Along these lines, herein, we describe an easy and low-waste synthesis of a set of secondary amides using the Boc_2O/DMAP system under neat conditions. Several parameters that may significantly impact the amidation rates were scrutinized, such as temperature, as well as amounts of DMAP and Boc_2O. Since the mechanism of this reaction was not clear, an attempt towards its explanation was also made.

Results and discussion

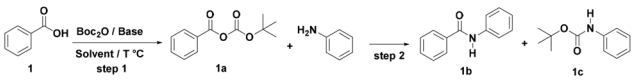
Several parameters may impact on the efficiency of the amidation of carboxylic acids. Both the nature and amount of the chosen base control the reaction chemoselectivity.

Optimization of reaction conditions

Initially, we proceeded with the amidation of benzoic acid **1** with a weakly nucleophilic aromatic primary amine: aniline. It should be noted that the use of a base catalyst that does not allow the formation of the mixed anhydride **1a** promotes the formation of the by-product **1c** in detriment of the desired amide **1b** (Scheme 1).

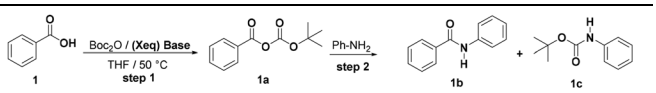
The amidation of benzoic acid **1** took place in two steps. In the first one, the Boc_2O was activated in the presence of a catalytic amount of the appropriate organic base, in 1 mL of tetrahydrofuran (THF) at 50 °C, to furnish the mixed anhydride **1a**. This step was confirmed by the appearance of air bubbles. Once this phenomenon disappeared, the amine was introduced to the reaction mixture. Again, the formation of the amide **1b** was noted by the appearance of air bubbles. The evolution of the reaction was checked *via* TLC (petroleum ether/ethyl acetate: 8/2 v/v). The obtained results are summarized in Table 1.

As is well shown in Table 1, the amidation rates were strictly dependent on the used base. The introduction of 0.2 equivalents of triethylamine (NEt_3) as a catalyst mainly leads to the formation of protected amine **1c** with 70% isolated yield (entry 1). It is to be underlined that no mixed anhydride **1b** formation was observed in the first step in this case. When the reaction was catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) or diisopropylethyl amine (DIPEA), two products were formed (**1c** and **1b**) in different proportions, but in favor of the desired amide, with isolated yields of 67% and 55%, respectively (entries 2 & 3). Better results were recorded when using *N*,*N*-dimethylaminopyridine (DMAP), where the amide **1b** was recovered with 72% yield (entry 4). Interestingly, reducing the amount of the latter catalyst to 0.1 equivalents



Scheme 1 Synthesis of *N*-phenylbenzamide **1b**.

Table 1 Impact of the nature and amount of base on the amidation of **1**



Entry[a]	Base (*x* equiv.)	Time (min)	Yield[b] (%) (**1b**/**1c**)
1	NEt_3 (0.2)	180	–/70
2	DABCO (0.2)	120	67/20
3	DIPEA (0.2)	120	55/36
4	**DMAP** (0.2)	45	**72/14**
5	**DMAP** (**0.1**)	60	**85/05**
6	DMAP (0.3)	30	72/20

[a] 1 mmol of benzoic acid **1**, 1 mmol of aniline and 1.1 mmol of Boc_2O, in 2 mL of THF at 50 °C. [b] Chemical isolated yield after standard aqueous work-up followed by crystallization.

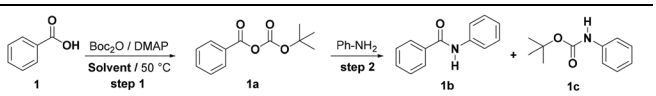
enhances the amidation selectivity, in favor the amide **1b**, whilst a decrease in the selectivity was observed when increasing the amount of DMAP to 0.3 equivalents (entry 5 *versus* 6).

The nature of the solvent was also examined. Five organic solvents with different polarities (solvent polarity or hydrophobicity log *P*: the partition coefficient of the employed solvent between water and octanol in a two-phase system) were chosen: tetrahydrofuran, acetonitrile, dichloromethane, *tert*-butyl methyl ether (TBME) and heptane. The obtained results are given in Table 2.

An important impact of the used solvent on the amidation selectivity was observed. No or very low selectivity was noted when the reactions were performed in CH_3CN, CH_2Cl_2, TBME and heptane (entries 2–5). The best selectivity was recorded in THF and under solvent-free conditions; the amide **1b** was recovered quantitatively with isolated yields of 85%–89% within one hour of stirring (entries 1 & 6). A trace amount of the by-product **1c** was recovered under neat conditions; this result affirms the inhibition of the competitive amidation under those conditions.

For further optimization of the reaction conditions, the influences of the activating reagent amount (Boc_2O) and the

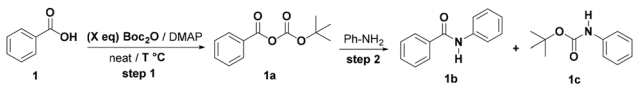
Table 2 Influence of the nature of the solvent on the amidation of **1**



Entry[a]	Solvent (log *P*)[b]	Time (min)	Yield[c] (%) (**1b**/**1c**)
1	THF (0.4)	60	85/05
2	CH_3CN (0.17)	60	51/37
3	CH_2Cl_2 (1.01)	60	43/46
4	TBME (0.96)	120	54/39
5	Heptane (3.42)	120	55/46
6	—	60	**89/08**

[a] 1 mmol of benzoic acid **1**, 1 mmol of aniline, 1.1 mmol of Boc_2O and 0.1 mml of DMAP in 2 mL of solvent at 50 °C. [b] 2 mL of organic solvent. [c] Isolated yield after standard aqueous work-up followed by crystallization.

Table 3 Influence of the temperature and the Boc_2O amount on the amidation of **1**

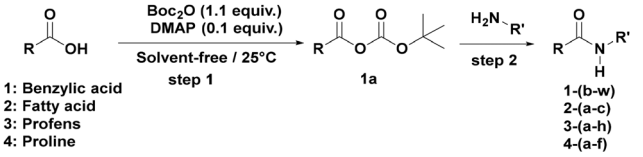


Entry[a]	Boc_2O (*x* equiv.)[b]	Temperature (°C)	Yield[c] (%) (**1b**/**1c**)
1	**1.1**	**25**	**94**/—
2	1.1	50	89/08
3	1.1	75	80/10
4	0.5	25	34/—
5	2.0	25	28/62

[a] 1 mmol of benzoic acid **1**, 1 mmol of aniline and 0.1 mmol of DMAP. [b] Stirring under neat conditions for 60 min. [c] Isolated yield after standard aqueous work-up followed by crystallization.

temperature were also investigated. The results are summarized in Table 3.

Heating was not considered as an impactful parameter for this reaction, neither for the reactivity nor for the selectivity (entry 1 *versus* 2 & 3). The best result in terms of reactivity and selectivity was recorded at room temperature in the presence of 1.1 equivalents of the activating reagent, where the desired amide **1b** was recovered with 94% overall yield (entry 1). A decrease in the amount of Boc_2O led to an inversion of the selectivity, in favor of the carbamate **1c** (entry 5).



Scheme 2 Synthesis of a set of amides under the optimized conditions.

Scope of the amidation reaction using the Boc_2O/DMAP system

With the optimal conditions in hand, the scope of the amidation using the Boc_2O/DMAP system was determined using various structures of carboxylic acids and amines (Scheme 2).

The amidation was carried out on 1 mmol of carboxylic acid. Firstly, 1.1 equivalents of di-*tert*-butyl dicarbonate (Boc_2O) and 0.1 equivalents of dimethylaminopyridine (DMAP) were added. After thirty minutes of stirring at room temperature, 1 equivalent of an amine was introduced to the reaction mixture. The advancement of the reaction was checked *via* TLC analyses. The structures of all products were confirmed by ^1H and ^{13}C NMR analyses.

Amidation of aromatic acids depends not only on their structures but also on the steric and electronic effects of the partner amine. The isolated chemical yields of the prepared amides varied between 20% and 90% (Fig. 1).

The amidation of benzoic acid **1** using anilines, as weakly nucleophilic amines, with different electron-withdrawing or electron-donating substituents in the *meta*, *ortho* and *para*-positions ($-CH_3$, $-CF_3$, $-NO_2$, OCH_3) smoothly afforded the corresponding carboxamides **1d**, **1e**, **1f**, **1g**, **1h** & **1i** with satisfactory yields (70% < yield < 80%). There is no remarkable influence of electronic effects from the substituted anilines on the amidation rates compared to amide **1b** (90% yield). However, using 1-(3-aminophenyl)ethanone led to the formation of the corresponding amide **1j** with a moderate yield of 56%. The same results were observed when benzylamine and methylbenzylamine were used as amine partners. The corresponding amides **1k** and **1l** were recovered with 73% and 74% yields, respectively.

On the other hand, the use of a less nucleophilic amine than aniline, namely tosylamine, afforded *N*-tosylbenzamide **1n** with a moderate yield in the region of 20%. Along the same lines, the steric hindrance of the used amine drastically decreases the amidation rate, wherein amide **1s** was moderately produced (30% yield).

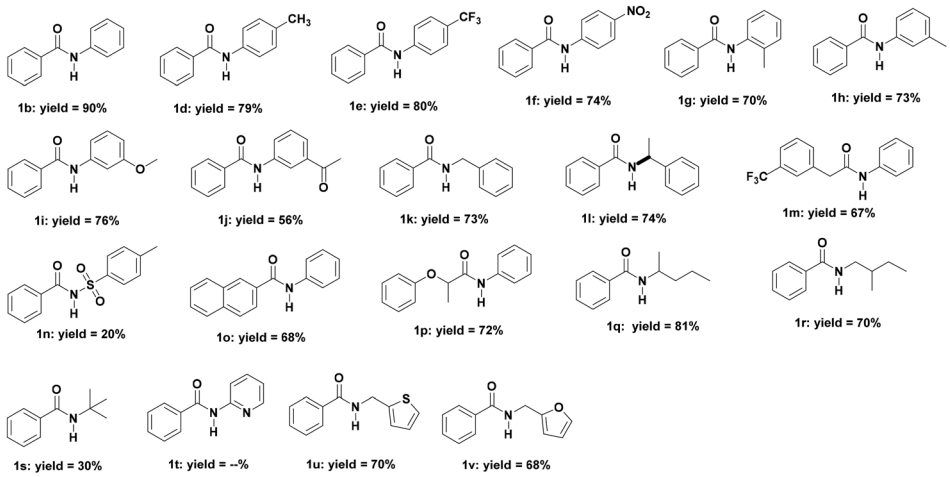


Fig. 1 Substrate scope of the reaction with aromatic acids.

When aliphatic amines, secondary and primary, were used, the amidation reaction proceeded smoothly and the corresponding amides (**1q** & **1r**) were obtained with good yields, 81% and 70% respectively.

Furthermore, the transformation of naphthoic, trifluoromethylphenyl acetic and phenoxypropionic acids into their corresponding amides was performed without any notable difficulty. The corresponding carboxamides **1o**, **1m** and **1p** were obtained with acceptable yields (67% < yield < 72%).

The study of various heterocyclic amines showed interesting trends. Thiophene and furan provided amides **1u** and **1v** with yields of 70% and 68%, respectively. Surprisingly, 2-pyridinamine completely inhibited the amidation reaction.

Fatty-acid amides are known as organo-gelling agents.[76–78] They have potential for gelating organic solvents at low mass concentrations. Also, they are referenced as being used as rheology additives, in particular in coating, molding, mastic or sealing compositions, or cosmetic compositions.[79]

Owing to their importance, we have proceeded to apply the optimized conditions of the amidation to synthesize some of those amides (Fig. 2).

The amidation of decanoic acid using aniline under our conditions afforded the fatty amide **2a** with a moderate yield of 55%. Meanwhile, the use of benzylamine instead aniline notably decreases the amidation rate, and amide **2b** was recovered with 73% yield. Furthermore, increasing the alkyl chain length, in the case of myristic acid, afforded the corresponding amide **2c** with a good yield of 80%.

For further increasing the value of the amidation reaction, we have envisaged exploring it for the amidation of some arylpropionic acids, known as non-steroidal anti-inflammatory drugs (NSAIDs), commonly used for the treatment of pain and edema and representing the choice treatment for various inflammatory diseases.[80]

Naproxen, flurbiprofen, ketoprofen and ibuprofen were investigated using substituted anilines and benzylamine (Fig. 3).

The synthesized amidoprofens (**3a–3h**) were obtained with isolated yields varying between 47% and 80%. The lowest yields were recorded with ketoprofen and flurbiprofen with *p*-MeO-aniline and benzylamine. This fact may be due to the steric hindrance of those carboxylic acids. However, the best yields were noted with ibuprofen with aniline and *p*-CF_3-aniline.

Finally, we have applied this protocol for the synthesis of proline amide derivatives. These compounds are usually used as catalysts in asymmetric synthesis, such as asymmetric aldolisation,[81–83] the Mannich reaction[84,85] and the Robinson

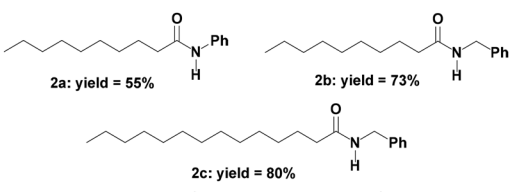


Fig. 2 Substrate scope of the reaction with fatty acids.

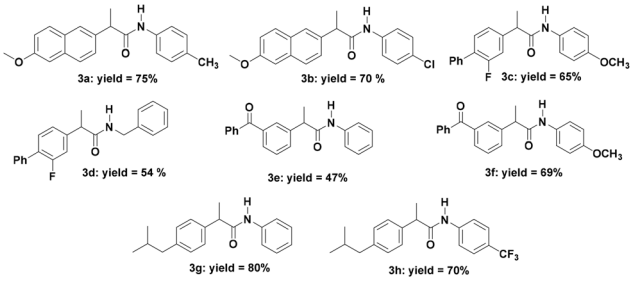


Fig. 3 Substrate scope of the reaction with profens.

reaction.[86] Also, they are used as ligands coordinated to transition metals for enantioselective reduction.[87,88] (Scheme 3).

The amidation of L-Boc-proline was carried out smoothly using aliphatic and aromatic amines. The corresponding amides were obtained with isolated yields ranging from 40 to 73% after deprotection of the proline, depending on the steric and electronic effects of the substituents of the aniline.

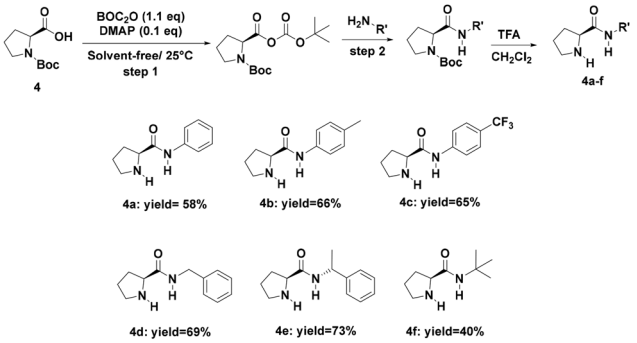
Explanation and discussion of the plausible mechanisms

The condensation of benzoic acid **1** and aniline was carried out following two approaches. The first one was considered as a "**one pot**" reaction, where all reagents were added simultaneously, and the second one was "**sequential**", involving the reaction of Boc_2O and the carboxylic acid in the presence of a catalytic amount of DMAP, followed by the introduction of the aniline.

The TLC analyses of the first approach revealed the formation of two by-products instead the desired amide. The obtained products were separated and characterized by the usual spectroscopic analyses (IR, ^{1}H NMR and ^{13}C NMR). Those products were identified as *tert*-butyl phenylcarbamate **7** and 1,3-diphenylurea **8**.

On the other hand, by monitoring the profile of the "sequential" approach *via* TLC, two products were isolated and characterized *via* the usual spectroscopic analyses (IR, ^{1}H NMR and ^{13}C NMR). These products were identified as the mixed anhydride **1a** and *tert*-butyl benzoate (tBB) (Fig. 4).

In order to explain the formation of the carbamate and the urea instead of the desired amide during the "one pot"



Scheme 3 Synthesis of proline amide derivatives.

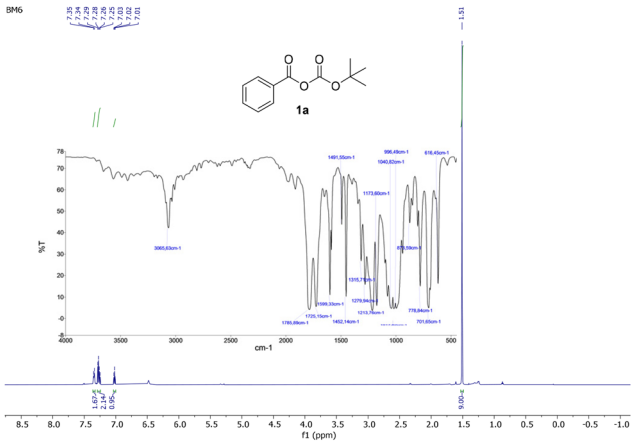


Fig. 4 ^{1}H NMR and infrared spectra of the mixed anhydride **1a**.

approach, two additional experiments were performed. In the first one, we reacted aniline and Boc_2O in the presence of DMAP, whereas the aniline was switched with benzoic acid in the second reaction (Fig. 5).

The monitoring of both reactions by TLC reveals that the carbamate was formed spontaneously during the first reaction within 5 min. In comparison, the mixed anhydride appeared after 30 min of stirring. Scheme 4 illustrates the plausible mechanism of the "one pot" approach.

All the above attempts and experiments allow us to develop a catalytic cycle for the sequential amidation of carboxylic acids (Scheme 5). It involves a very reactive intermediate (**A**) produced during the decarboxylation of Boc_2O in the presence of DMAP as a catalyst. The interaction of the substrate with this intermediate furnishes the mixed anhydride (**B**). The nucleophilic attack of *t*-butanol on the anhydride (**B**) affords the corresponding *t*-butyl ester (**C**). The addition of an amine during this step promotes the formation of the desired amide (**D**) *via* decarboxylation of the mixed anhydride (**B**) and substitution of the *t*-butyl moiety of the ester (**C**).

Scalable synthesis of *N*-oleoylethanolamide

N-Oleoylethanolamide (OEA) is a natural analog of an endogenous cannabinoid, anandamide (arachidonoylethanolamide), which does not activate cannabinoid receptors.[89] It is known for its several biological activities, such as the modulation of feeding and energy homeostasis by binding to peroxisome proliferator-activated receptor-α (PPAR-α),[90] sleep inducing properties[91] and treatment of obesity and cancer.[92]

Owing to its bioactivities and in order to increase the value of our easy amidation methodology, we have decided to perform scalable chemoselective amidation of *N*-oleic acid with ethanolamine for the preparation of this potential target (Scheme 6).

We have used the optimal conditions of the amidation for performing the condensation of 10 mmol of oleic acid (2820 mg) and we have recovered 2390 mg of the fatty amide (73% chemical yield).

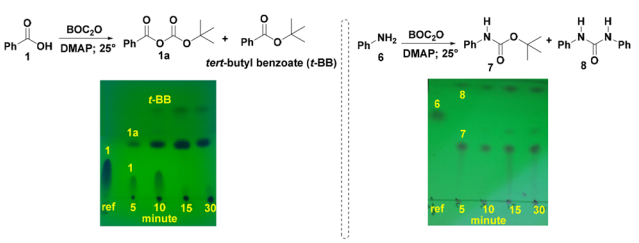
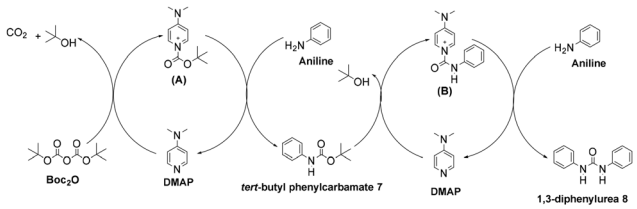
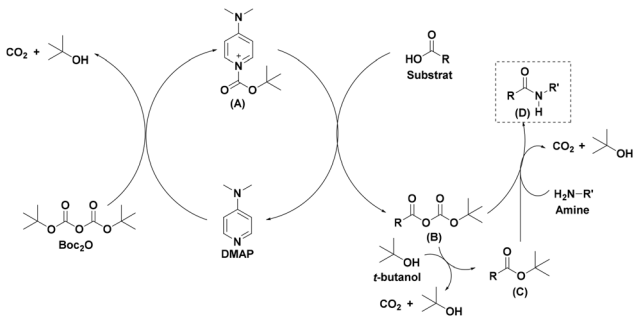


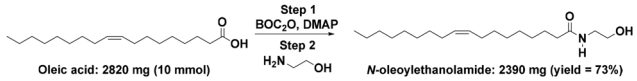
Fig. 5 Comparative analysis of the "one-pot" method and the "sequential" method.



Scheme 4 Plausible mechanism of the "one-pot" method.



Scheme 5 Plausible mechanism of the "sequential" method.



Scheme 6 Synthesis of *N*-oleoylethanolamide.

Conclusion

In summary, we have developed an efficient amidation of a spectrum of carboxylic acids with various amines, aliphatic and aromatic, in the presence of Boc_2O as an activating agent and DMAP as a catalyst. This reaction was performed without heating under neat conditions. The mechanistic study allows us to highlight the *in situ* formation of a mixed anhydride as the key step of the described methodology. The latter presents numerous advantages, notably the preparation of valuable carboxylic amides under neat conditions within a short time, easy purification and satisfactory chemical yields, as well reproducibility and scalability. The carboxylic amides of non-steroidal

anti-inflammatory drugs, fatty acids and L-proline amides were smoothly obtained with moderate to excellent isolated yields. A scalable chemoselective application of this amidation allows one to easily obtain the *N*-oleoylethanolamide.

Experimental section

General information

All reagents purchased from Aldrich were used as received. All used solvents are of PA quality. The carboxylic acids and amines are commercially available.

NMR spectra were recorded on Bruker or Jeol spectrometers (250 MHz, 300 MHz or 600 MHz for ^{1}H and 62.9 MHz or 75 MHz for ^{13}C) and calibrated using residual deuterated solvent as an internal reference (peak at 7.26 ppm in ^{1}H NMR and 3 peaks at 77 ppm in ^{13}C NMR in the case of $CDCl_3$ and a peak at 2.5 ppm in ^{1}H NMR and multiplet at 38–40 ppm in ^{13}C NMR for DMSO). The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br: broad signal, and dd = double-doublet. Chemical shifts were expressed in ppm and coupling constants (J) in Hz. The Fourier-transform infrared spectroscopy spectrum was obtained using a Shimadzu Spectrometer (FTIR 8700, Japan) with the KBr pellet method. The spectra were registered in the spectral range from 400 to 4000 cm^{-1} with a resolution of 4 cm^{-1}. Melting points were measured using a Büchi Melting Point B-545.

Reactions were monitored using TLC on silica gel 60 F_{254} plates, type MERCK 5179, 250 mesh.

Condensation of carboxylic acids and amines using the Boc_2O/DMAP system. To 1 mmol of carboxylic acid, 1.1 equivalents of di-*tert*-butyl dicarbonate (Boc_2O) and 0.1 equivalents of dimethylaminopyridine (DMAP) were added. After 30 min of stirring at room temperature, 1 equivalent of an amine was introduced to the reaction mixture. The advancement of the reaction was checked *via* TLC analyses. The produced amides were recovered after standard aqueous treatment followed by crystallization. The structures of all products were confirmed by ^{1}H and ^{13}C NMR analyses (complete experimental data and NMR spectra have been provided in the ESI†).

Deprotection of proline amides 4a–f. To remove the protecting group from the proline amides, 30% trifluoroacetic acid (TFA) in dichloromethane was employed. After 2 hours, the solvent was evaporated. The resulting product was then neutralized with sodium carbonate and extracted with an organic solvent (ethyl acetate). The organic phase was washed, dried, and concentrated. The pure compound was finally obtained by purification on a silica gel column, followed by recrystallization.

Author contributions

The manuscript was written through contributions from all authors. M.B. performed the experimental work and developed the methodology, carried out formal analyses, visualized the results, interpreted the results and wrote the article. M.K.M. participated in a part of the experimental work and contributed to interpreting and analyzing the results, as well as correcting the first version of the article. O.R. contributed to the discussion and the correction of the final version of this paper. All authors have read and agreed to the published version of the manuscript.

Data availability

The data underlying this study are available in the article and its ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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