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Direct amidation of carboxylic acids with amines under microwave irradiation using silica gel as a solid support

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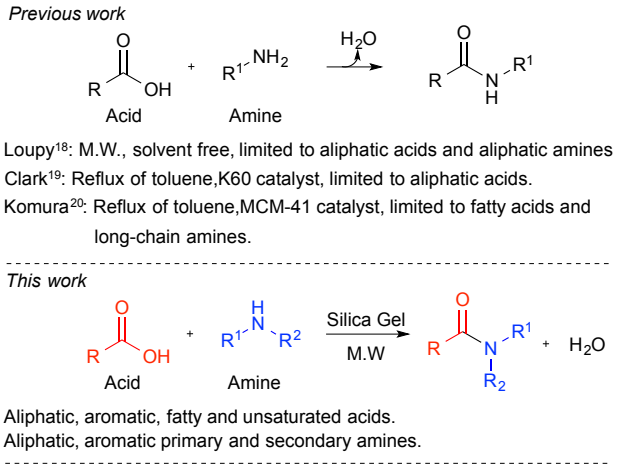
A highly improved and green methodology for the direct amidation of carboxylic acids with amines using silica gel as a solid support and catalyst is described. The scope of this method is exemplified by the use of several aliphatic, aromatic, unsaturated and fatty acids. The reaction is also applied to different primary and secondary amines. Typically, the amines should be aliphatic, but aromatic amines can be used as well, though with lower yields. Several experiments to illustrate the selectivity of this methodology were also carried out with several more functionalized acids and amines. This approach is a substantial improvement over other previously described methods in amide synthesis.

Introduction

Amides are undeniably one of the most important functional groups in organic chemistry; they are present in many naturally occurring molecules, synthetic polymers, peptides, and pharmaceutical agents, among others.[1] Traditionally, amides have been prepared by coupling activated carboxylic acid derivatives and amines,[2] from carboxylic acids using stoichiometric amounts of condensing reagents[3] and more recently by innovative methods such as transamidation,[3c, 4] employing carbamates as the amine source,[5] via *S*-nitrosothiacids,[6] oxidative amidation of aldehydes,[7] very recently via sulfynilamides[8] and amidation of esters,[9] in addition to the more well-known named reactions.[10] Despite all these existing methodologies, new synthetic efforts have been made in order to obtain amides directly from carboxylic acids without using any coupling reagent. The main motivation for the development of new methods is the reduction of waste, leading to a more eco-friendly or green process. The formation of an amide moiety by classical methods is one of the most used procedures in the pharmaceutical industry.[11] However, as acknowledged ten years ago by the ACS, poor atom economy in amide synthesis is one of the most important challenges to overcome in synthetic organic chemistry.[11c]

All of methodologies mentioned above have significant drawbacks, including the generation of by-products or residues, the cost of the coupling reagents and/or the limited scope of substrates. The use of catalytic boron derivatives,[12] other homogeneous[13] or heterogeneous[14] catalysts and/or enzymes[15] has emerged as powerful alternatives to the traditional amidation process. Thus, the thermal amidation of carboxylic acids with amines is a potential complementary procedure to eliminate some of the reported synthetic challenges. This reaction has been neglected for many years principally because of the long reaction times and high temperatures needed.[16] Currently, microwave irradiation has proven to be efficient at reducing the reaction times in many organic transformations.[17] One of the first examples where microwaves have been successfully applied to reduce the reaction time is the esterification reaction of carboxylic acids with alcohols.[18] Our aim was to extend the use of microwaves to the amidation reaction, and we report herein our principal results in this area, which appear very promising as a more general and easier method for amide synthesis than those currently in use.



Scheme 1. Comparison between previous and present work.

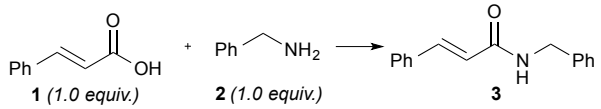
Previous investigations using microwaves in amide synthesis were reviewed recently[19] and include the use of the Ritter reaction[10a] and the amidation of esters.[9b] Furthermore, a previous work reported by Loupy and co-workers[20] showed the first microwave-assisted synthesis of amides from carboxylic acids. Unfortunately, this reaction is restricted to aliphatic acids and primary aliphatic amines, and with only activated aromatic amines being reactive, the method has a very limited substrate scope. Clark and co-workers.[21] recently used a heterogeneous silica-based catalyst for amidation reactions, which demonstrated a better scope but with longer reaction times, the use of azeotropic removal of the water by-product, and the need for very high temperatures to activate the catalyst. Komura and co-workers[22] used a very similar approach employing mesoporous silica MCM-41 with fatty acids and long-chain amines (Scheme 1).

Results and Discussion

These three results reported previously inspired us to explore a combination of techniques avoiding the use of solvent for a more eco-friendly method. The use of silica gel as a solid support for microwave-assisted synthesis has been previously shown to be effective in other reaction types.[23] Hence, we anticipated that the same approach could be applied successfully using chromatographic silica gel and microwave heating as a new approach in amide synthesis.

In our initial studies, an α,β-unsaturated acid and benzylamine was used as a model reaction. Cinnamic acid was chosen because only a few examples exist in the literature where unsaturated acids are used as substrates for direct amidation.[24] This may be a consequence of the two electrophilic sites present, which may participate in competitive Michael reactions.

Table 1. Optimization of the microwave-assisted amidation reaction conditions.



1 *(1.0 equiv.)* **2** *(1.0 equiv.)* **3**

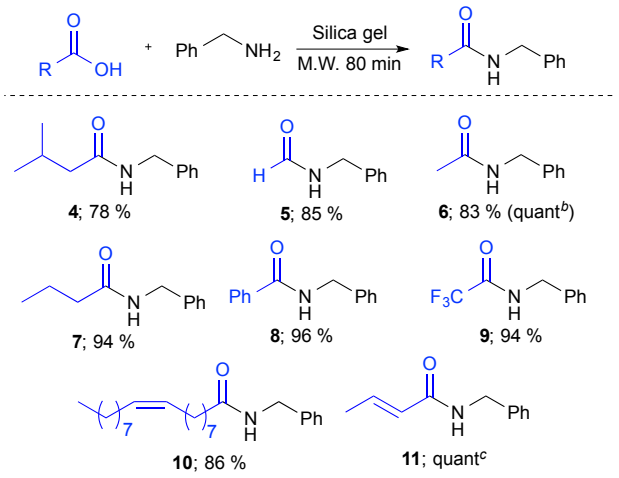
Entry	Conditions	Time	Yield (%)
1	$B(OH)_3$, *p*-xylene reflux[a]	5 h	69
2	20 % w.t silica-gel, *p*-xylene reflux	36 h	50
3	20 % w.t silica-gel, *p*-xylene reflux[a]	3 h	79
4	$FeCl_3$, *p*-xylene reflux	27 h	68
5	Microwave heating solvent free[b]	40 min	73
6	Microwave heating silica gel as support[b]	40 min	94
7	*p*-xylene at reflux[a]	48 h	20

[a.] The reaction was performed with a Dean-Stark trap. [b.]The acid and the amine were heated under microwave irradiation at 130ºC.

Before exploring microwave heating and the use of silica gel, we examined several other systems for comparison to demonstrate the advantages of our approach. Boric acid has been described as an effective catalyst for amidation.[13a] The reaction in the presence of boric acid proceeded smoothly with a 69 % yield (entry 1). Silica gel also proved to be useful (entry 2), and the azeotropic removal of water only moderately increased the obtained yield but diminished the reaction time considerably (entry 3). We decided to use Fe(III) salts as an addition to our previously reported work;[4] however, even though effective, the reaction did not exhibit better yields (entry 4). We were delighted to see that the combination of microwave heating and the use of silica gel as a solid support effectively catalyzed the reaction, affording a much better yield in a shorter reaction time (entry 6) than the reaction in the absence of any catalyst or additive (entry 7). The reaction time is comparable with the reaction performed under solvent-free conditions and microwave heating, but the yield was improved by almost 20 % (entries 5 and 6).

With these promising results, we decided to further explore the scope of this method by investigating a variety of different acids.

Table 2. Reaction of benzylamine with different acids.[a]



[a.] All reactions were performed with 1.5 mmol of acid and 1.5 mmol of amine supported on 1.0 g of silica gel 60 and irradiated for 4 cycles of 20 min at 130ºC. [b.] The reaction was performed using malonic acid. [c.] The reaction was performed using 1.95 mmol of acid and 1.5 mmol of amine.

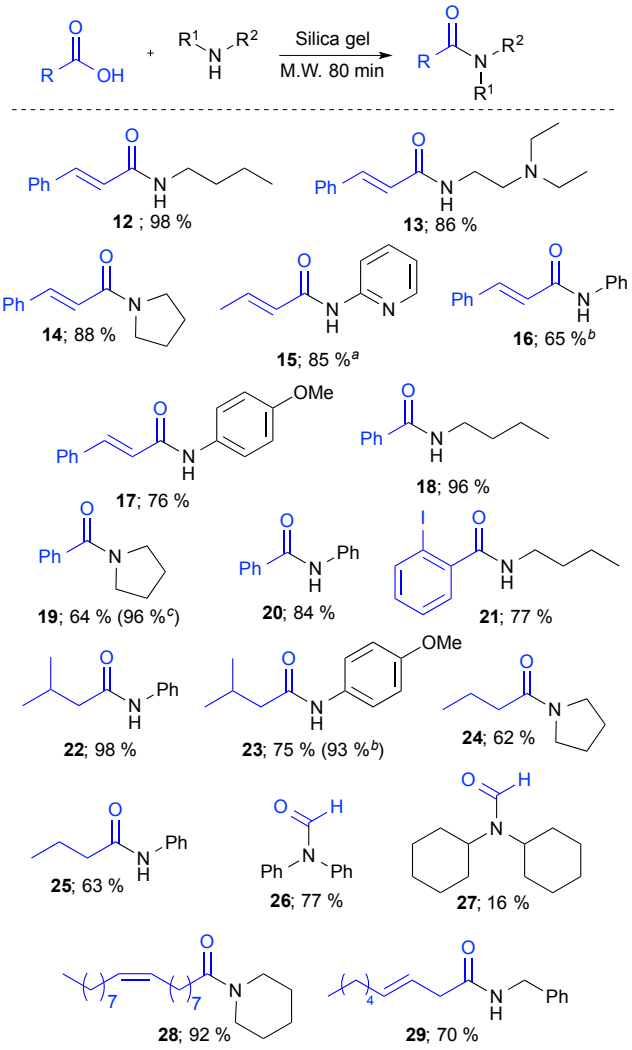
Table 2 shows that in terms of acid compatibility, the reaction is quite general. Saturated aliphatic acids reacted very well (products **4**-**7**), and even small acids such as formic and acetic acid still afforded good yields (products **5** and **6**). Benzoic acid was used as a representative example of aromatic acids and proved to work much better than expected. In fact, looking in detail at all previous direct amidation protocols, aromatic acids generally give the lowest yields. However, in our case, the combination of benzoic acid with the primary aliphatic amines worked very well to obtain product **8** (see below) with excellent yields. Highly acidic trifluoroacetic acid showed good reactivity and to the best of our knowledge is the first example of direct trifluoroacetylation with a free acid (product **9**). Long-chain acids also worked as expected and afforded the desired product **10** in good yield. Surprisingly, using malonic acid did not produce double or single amidation; instead, product **6** (acetylation product) was the only isolated product, even when a large excess of amine was used. We believe that the product is

formed after the decarboxylation of the first formed monoamide. Other unsaturated acids such as crotonic acid are also active, and the product was obtained in quantitative yield (product **11**).

The next step to show reaction generality was to explore different amines. We decided not to use a specific acid in order to illustrate that many combinations are possible. Table 3 shows the results obtained for the amide synthesis using a variety of carboxylic acids with aliphatic, aromatic primary and secondary amines.

The reaction between unsaturated acids and aliphatic primary amines (products **12** and **13**) was successful with the products obtained in excellent yield, even when a more functionalized amine (product **13**) was used.

Table 3. Amidation of carboxylic acids with amines.



[a] The reaction was performed using 1.95 mmol of acid and 1.5 mmol of amine. [b] The reaction was performed using freshly distilled aniline and making 4 additions of 0.3 equivalents each one, after each irradiation. [c] based on the recovered starting material.

The unsaturated acids also reacted with secondary (product **14**) and heteroaromatic (product **15**) amines, with very good results.

It should be noted that all reactions performed using crotonic acid were prepared using a small excess of acid (1.3 equiv.); otherwise, the Michael addition product on the amide resulted, as observed by ^{1}H NMR of the crude product. However, the acid excess was enough to avoid the Michael product formation, and simple amides were the only observed product after treatment.

The unsaturated acids also reacted with aromatic primary amines (products **16** and **17**). The reaction between aniline and cinnamic acid is slower than the reactions of the same acid with other amines; this causes partial oxidation of aniline and consequently low yields. We decided to use freshly distilled aniline and make its addition in portions of 0.3 equivalents after each microwave irradiation. Using this slight modification we were able to obtain product **16** in good yield. Nevertheless, inactivated amines such as *o*-nitroaniline did not react, and the starting material was recovered even when the temperature or reaction time was increased. As mentioned above, the use of aromatic acids in direct amidation processes has always been a drawback. In our case, benzoic acid reacted very well with aliphatic primary amines (products **8** and **18**), with secondary amines (product **19**) and with aromatic amines (product **20**). However, in this case, the reaction with inactivated aromatic primary amines (*p*-nitroaniline) was unsuccessful. Ortho-substituted benzoic acid is also reactive despite its more hindered environment (product **21**).

It has to be noted that products **15** and **17** are successful examples where both solid reagents were used.

Isovaleric acid showed very good reactivity with aniline (product **22**) and *p*-methoxyaniline (product **23**). Other aliphatic saturated acids were also active with secondary (product **24**) and aromatic (product **25**) amines. All acids discussed previously showed no reactivity with hindered secondary amines; nevertheless, the use of formic acid in combination with the secondary amine diphenylamine afforded the desired amide in good yield (product **26**). Surprisingly, the use of dicyclohexylamine only allowed us to isolate the desired amide in low yield (product **27**). Fatty acids and secondary amines are also a reactive couple (product **28**); in addition, long β,γ-unsaturated acids proved to be active (product **29**), although the conjugated isomer was isolated in 15 % yield.

As mentioned above, amide synthesis is one of the most used reactions in organic chemistry laboratories in both academia and industry. One of the principal reasons for the widespread use of amidation is the synthesis of peptides. In our case, the reaction of several acids with amino acid (glycine and phenylalanine) methyl esters did not afford the desired amide. On the other hand, free amino acids were completely unreactive. We also tried *N*-protection with an acetyl group and with BOC. Unfortunately, in those cases, only mixtures of unidentified polar products were obtained.

We have shown that our method is more general, more versatile and less expensive than other existing procedures. In addition, this method fulfils at least six out of the twelve principles of green chemistry.[25] They are 1) prevention, 2) atom economy, 3) less hazardous chemical synthesis, 5) safer solvents and

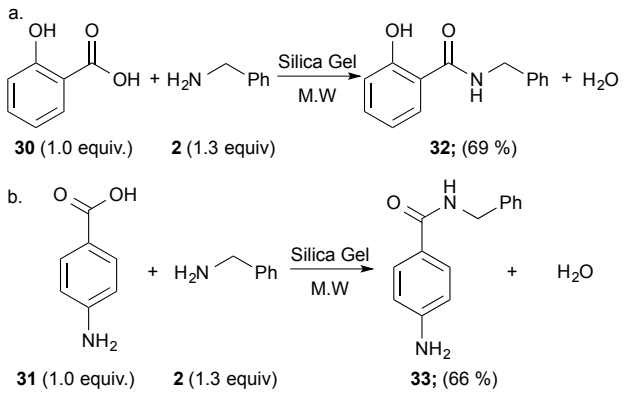
auxiliaries, 8) reduced derivatives and 12) inherently safer chemistry for accident prevention. In addition, two additional principles can be considered: 6) design for energy efficiency and 9) catalysis. The energy efficiency of microwave synthesis has been recently analyzed and discussed by Moseley and Kappe.[26] The authors concluded, and we agree, that each reaction has to be evaluated before automatically labelled as "green" in terms of energy use. We are at present evaluating the energy efficiency of this method compared with the other methods previously described. Nevertheless, more recently, Török and co-workers[27] demonstrated that solid-supported reactions under microwave irradiation are generally more energy efficient than those using conventional heating.

Concerning the ninth principle, which suggests the use of a catalyst, it is evident that silica gel has an additional effect and that microwaves are not the only factor responsible for these results (Table 1, entries 5 and 6). We strongly believe that this effect does not result from the heat transfer of the solid support alone but instead that there is a catalytic effect, as reinforced by entries 2 and 3 in Table 1, where the use of catalytic amounts of silica improves the yield in comparison to the use of conventional heating of the reagents without any additive or catalyst (entry 7). To provide further evidence to support our hypothesis, we are currently working on a mechanistic proposal. In conclusion, 6 out of the 12 principles of green chemistry are fulfilled using our approach for amide synthesis, with the potential for another 2 principles to be satisfied, pending future results.

The last factor we evaluated in this study was selectivity. To this end, we conducted a series of experiments that are listed below.

The first experiment was the evaluation of carboxylic acids with two electrophilic sites. For this experiment, we chose chloroacetic and oxoacetic acid to study in independent experiments with benzylamine. Unfortunately, both experiments were unsuccessful, and the desired amides were not observed. Only mixtures of polar inseparable products were obtained.

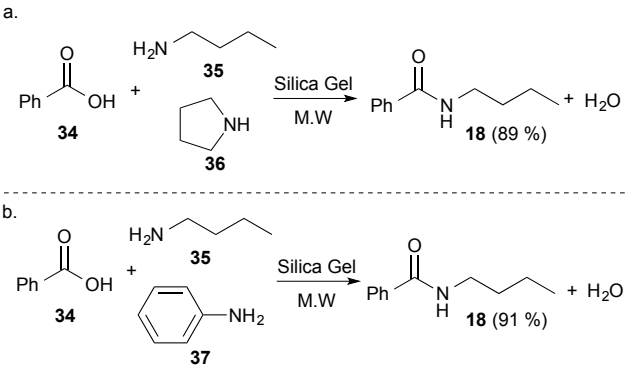
Following from these results, we were interested in the evaluation of the reactivity of carboxylic acids containing a nucleophilic site. The chosen compounds were salicylic acid **30** and *p*-aminobenzoic acid **31**. Each of these two compounds may react with itself to produce esters or amides, respectively. To avoid or minimize this possibility, we used 1.3 equivalents of amine (Scheme 2). The reaction of salicylic acid with benzylamine (Scheme 2a) afforded the desired amide **32** in 69 % yield as the only observed product. On the other hand, the reaction with aminobenzoic acid produced a slightly lower yield (66 %) of amide **33**. These results are very encouraging, showing the versatility of our method.



Scheme 2. Reactions of carboxylic acids containing a nucleophilic site.

Having studied more functionalized acids, we were interested in investigating the reaction selectivity. To this end, we can speculate from the results shown in Table 3 that primary aliphatic amines are the preferred substrate in this methodology. We were therefore interested in what would happen when two different amines are present in the reaction medium.

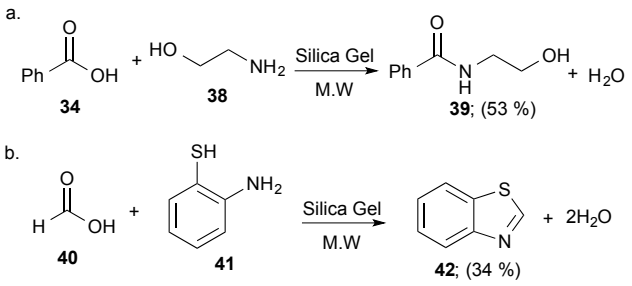
To explore this scenario, we conducted two experiments. In the first experiment, a primary **35** and a secondary amine **36** were used (Scheme 3a). As expected, the amide formation occurred only with the primary amine **18** (89%).



Scheme 3. Selectivity between amines.

The second test (Scheme 3b) demonstrates the competition between aromatic and aliphatic amines. In this experiment, 1.0 equivalent of *n*-butylamine **35** and 1.0 equivalent of aniline **37** were mixed with 1.0 equivalent of benzoic acid **34** and supported in 1.0 g of silica gel. After irradiation for 3 periods of 20 min, only amide **18** was isolated in very good yield (91 %), showing that the reaction is completely selective to primary aliphatic amines.

Lastly, to complete our evaluation of the selectivity in this reaction, the use of amines with an additional nucleophilic site was explored. To this end, we used ethanolamine **38** and aminothiophenol **40**.



Scheme 4. Reaction of benzoic acid and binucleophilic amines.

Scheme 4a depicts the reaction between benzoic acid **34** and ethanolamine **38.** As expected, the more nucleophilic nitrogen was preferred over the oxygen, and consequently, the amide **39** was the only isolated product with acceptable yield (53 %). This result was also observed by Orru and co-workers using microwave heating, but at higher temperatures.[24]

When the competition is between the sulfur and nitrogen, the only isolated product was benzothiazole **42** in low yield (34 %). We strongly believe that the amide formation is the first step of this reaction sequence, followed by the rapid dehydration of the amide as described previously[4], as no traces of amide were observed by ^{1}H NMR even after stopping the reaction at low conversion. On the other hand two control experiments were carried out using thiophenol and formic or acetic acid, in both cases no traces of thioester was observed. Accordingly, we can conclude that the reaction is completely selective towards nitrogen when other nucleophilic atoms (oxygen or sulfur) are present in the amine. Nevertheless, *o*-substituted aromatic amines are less reactive compared with unsubstituted or *p*-substituted anilines.

Experimental

General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 400 MHz spectrometer. The chemical shifts are expressed in parts per million (ppm) referenced to TMS. The data are reported as follows: δ, chemical shift; multiplicity (recorded as br, broad; s, singlet; d, doublet; t, triplet; q, quadruplet; quint, quintuplet and m, multiplet), coupling constants (J in Hertz, Hz) and integration. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same instrument at 101 MHz. The chemical shifts are expressed in parts per million (ppm), referenced to TMS. Infrared spectra (IR) are reported in terms of absorption frequency (v, cm-1) using KBr. Mass spectrometry (MS) was performed in electron impact (EI; 70 eV) mode. Mass spectra are reported as m/z. High-resolution mass spectrometry (HRMS) was performed on a Q-TOF LC/MS instrument.

Typical procedure for amide synthesis

Amine (1.5 mmol) and carboxylic acid (1.5 mmol) were dissolved in ethyl acetate (15 ml) before silica gel 60 230-400 mesh (1.0 g) was added. The solvent was then removed under reduced pressure, and the reaction mixture was transferred to a microwave tube. The mixture was then placed in a CEM microwave reactor and subjected to 20 min cycles using a power of 200 W, maintaining a constant temperature of 130 °C, and a hold time of 2 min. The reaction mixture was then allowed to cool to room temperature, sonicated for 20 min with 30 ml of ethyl acetate, and filtered, and the silica was washed with another 30 ml of ethyl acetate. The organic phase was washed with a saturated solution of $NaHCO_3$ and HCl (10 %), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to obtain the pure product. In some cases, flash chromatography was needed, as indicated in the characterization data.

Characterization of representative products

***N*-Benzyl-3-phenyl-acrylamide (3)**

Following the general procedure, the compound was isolated and analysis of the sample indicated 94 % yield (335 mg). mp: 107 °C (Lit.[28] 106-107 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66 (d, J = 15.6 Hz, 1H), 7.25-7.48 (m, 10H), 6.43 (d, J = 15.7 Hz, 1H), 6.15 (s, 1H), 4.55 (d, J = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 165.8, 141.4, 138.2, 134.8, 129.7, 128.8, 128.7, 127.9, 127.7, 127.6, 120.5, 43.9. IR: 3267, 3028, 1652, 1616, 1543 cm^{-1}. MS (EI): 237 $[M]^+$ (44), 131 (100), 103 (79), 91 (21), 77 (39).

***N*-Benzyl-2,2,2-trifluoro-acetamide (9)**

Following the general procedure, the compound was isolated and analysis of the sample indicated 94 % yield (286 mg). mp: 69 °C (Lit.[29] 70-71 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48 – 7.21 (m, 5H), 6.65 (s, 1H), 4.47 – 4.58 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 157.2 (q, J_{C-F}=37.3 Hz), 135.9, 129.1, 128.3, 128.0, 115.9 (q, J_{C-F}=287.9 Hz), 44.0. IR: 3302, 3109, 1702, 1560 cm^{-1}. MS (EI): 203 $[M]^+$ (52), 134 (28), 91 (100).

***N*-Butyl-2-iodo-benzamide (21)**

Following the general procedure, the compound was isolated and analysis of the sample indicated 77 % yield (350 mg). mp: 90-92 °C (Lit.[30] 94-96 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85 (d, J = 7.8 Hz, 1H), 7.36 (dd, J = 5.4, 1.8 Hz, 2H), 7.06-7.09 (m, 1H), 3.42 - 3.47 (m, 2H), 1.67 – 1.56 (m, 2H), 1.44 (dd, J = 15.2, 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.3, 142.6, 139.8, 130.9, 128.2, 128.1, 92.4, 39.8, 31.4, 20.2, 13.7. IR: 3275, 2947, 2865, 1637, 1547 cm^{-1}. MS (EI): 303 $[M]^+$ (11), 261 (31), 231 (100), 203 (23), 105 (22), 76 (42).

Conclusions

In conclusion, we have developed a versatile, simple, general and green method for the direct amidation of carboxylic acids with amines. The selectivity of this methodology was proved using several examples, and it constitutes one of the more efficient and simple methods for amide synthesis described to date. The most significant advantages are the use of inexpensive chromatographic silica gel without any special treatment or activation and the use of microwave heating.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data and copies of all ^{1}H NMR and ^{13}C NMR spectra]. See DOI: 10.1039/b000000x/

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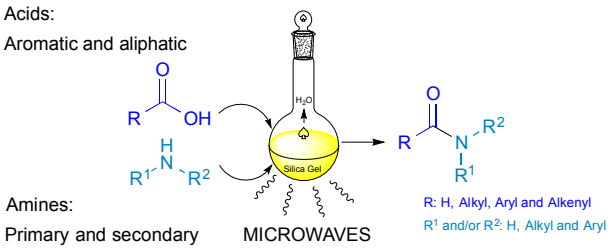

32 examples, up to quantitative yield

A highly improved methodology for the direct amidation of carboxylic acids with amines using silica gel as a solid support and catalyst is described. Several examples using aliphatic, aromatic, unsaturated and fatty acids combined with primary and secondary amines are shown.