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A catalyst-free, waste-less ethanol-based solvothermal synthesis of amides

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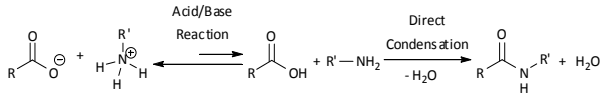
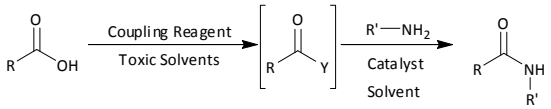
A green one-pot approach based on the solvothermal amidation of carboxylic acids with amines has been developed for the synthesis of diverse aliphatic and aromatic amides. It does not require the use of catalysts or coupling reagents and it occurs in the presence of ethanol that has been proved to have a key role in the process. The proposed strategy is extendable also to biologically active amides and could represent a low-cost and waste-less alternative to the common synthetic pathways.

The amide synthesis represents one of the most useful tools to build molecules of strategic importance in a wide range of applications involving polymers, biologically active compounds and pharmaceutical products. It is therefore not surprising that the synthesis of amides with greener and greener approaches is one of the major goal for organic chemistry[1] due to the fact that the common strategies require problematic solvents,[2] stoichiometric coupling reagents and/or catalysts, thus generating a significant amount of waste.[3] In this framework, the ideal amide synthesis should be the direct condensation of carboxylic acids and amines with release of water by heating, being the atom economy the highest possible. However, this strategy has commonly been considered to be limited by the competitive acid-base reaction that induces the formation of the corresponding ammonium salt[4a] (Scheme 1). In order to improve the yield of the direct thermal amide formation, the removal of water, typically by azeotropic distillation or by using activated molecular sieves, has been proposed. Nevertheless, despite its potentiality (simple, green and waste-less), this method is applicable only to a limited class of liquid substrates with high boiling point, acids with low pK_a value and



Scheme 1 Ideal waste-less, catalyst and solvent free pathway for the amide synthesis.

amines with high nucleophilicity.[4] Moreover, since the formation of charged species is favoured in polar protic media, different non-polar aprotic solvents as toluene, mesitylene and xylene have been explored.[4a,5] In addition, to lower the high activation barrier associated to the direct condensation, different catalysts have been proposed in the literature.[4a,6] As alternative to the thermal treatment, microwaves have been also employed.[7] In spite of the advantages of these methods, to date the most common way to synthesize amides is the activation of the carboxylic acid either by the use of coupling reagents[8] (carbodiimides,[9] boronic acids derivates,[10] phosphoramides,[11] uronium salt[12]) or by the formation of the acyl chloride,[13] followed by the nucleophilic acyl substitution with an amine (Scheme 2). These approaches are of strategic importance because allow to obtain a wide class of amides. However, most of these procedures have the inside drawback of using stoichiometric quantities of coupling reagents and the unfavourable ecological impact of solvents.[2] The eventual presence of a catalyst[14] and the high amount of wastes produced by the reaction make these methodologies complex and expensive. Other authors, in order to overcome the carboxylic acid activation step, proposed esters,[15] aldehydes[16] and alcohols[17] as alternative starting materials,[18] but all of these syntheses often involve expensive catalyst and/or other additives (such as oxidants). In this context, following the general idea of developing green, robust, low-cost and waste-less synthetic



Scheme 2 Amide synthesis involving the carboxylic acid activation.

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strategies,[19] a new solvothermal method is proposed for the preparation of amides inspired by the ideal reaction involving the unactivated carboxylic acid and the amine. As part of our ongoing interest in the preparation of nanoparticles[20a,b] and investigation of their interaction with the organic molecules,[20c-e] by starting from oleic acid and oleylamine in solvothermal conditions, we stumbled into the identification of *N*-oleyloleamide as capping agent for metal oxide inorganic nanoparticles[20a] (Figure 1**)** The process was then attempted by using oleic acid **1a** and oleylamine **2a**, but in the absence of the metal precursors, leaving all the other parameters unchanged (180°C for 18 hours in absolute ethanol). Surprisingly, we observed the formation of *N*-oleyloleamide **4aa** with high conversion (about 80%). Such promising result, encouraged us to explore the possibility of developing a new and general method for the amides synthesis. To this purpose, a series of experiments have been planned in order to rationalize this result. Oleic acid **1a** and oleylamine **2a** have been used as reference molecules to set up the method, being the most commonly used in the synthesis of metal[21] and metal oxide nanoparticles,[20a,b,d-o] to finely tune their size and shape. In order to optimize the reaction conditions various parameters have been systematically varied, namely, temperature (from 60 to 190 °C see Figure 2a), acid concentration (from 0.2 M to 1.3 M, see Figure 2b), reaction time (from 1 hour to 18 hours, see Figure 2c), autoclave capacity and ethanol purity (absolute and azeotropic). ^{1}H-NMR spectroscopy was the method of choice to monitor the reaction conversion. It has been found that conversion to amide increases with temperature, concentration and reaction time, reaching the highest value at 160°C, 1.05 M acid concentration and 6 hours (Figure 2a-2c). In order to understand the possible mechanism behind the amide formation, oleic acid **1a** has been submitted to the same solvothermal treatment in the absence of the amine **2a**, by using, as usual, absolute ethanol as solvent. These experiments highlighted the formation of the ethyl oleate **3a**: being the conversion to ethyl oleate very similar to the corresponding *N*-oleyloleamide **4aa** (Figure 2d), we might assume that the reaction occurs via an ethyl ester intermediate (Scheme 3 Therefore, it can be concluded that ethanol plays a key role in this process: it is both an ideal green solvent capable to dissolve the reagents, and a fully recoverable or easily removable reagent, being released from the reaction of the ethyl ester with the amine. Finally, the formation of a more reactive carboxylic derivative from the corresponding acid,. facilitates the amine nucleophilic attack leading to the corresponding amide with high conversion and yield Further experiments (see ESI, Table S3) made up starting from ethyl oleate **3a** and oleylamine **2a** in the optimized conditions in the presence of water and/or acetic acid, pointed out the fundamental role of both water and acid during the reaction: acid catalyze the amide formation by protonation of ester while water released from the esterification reaction favor the elimination of the leaving group in the nucleophilic acyl substitution.). The scalability of the process and the possibility to use the azeotropic ethanol-water mixture in place of absolute ethanol and other aliphatic alcohols such as methanol, 2-propanol and pentanol have also been explored (see ESI Table S1). The presence of a certain amount of the

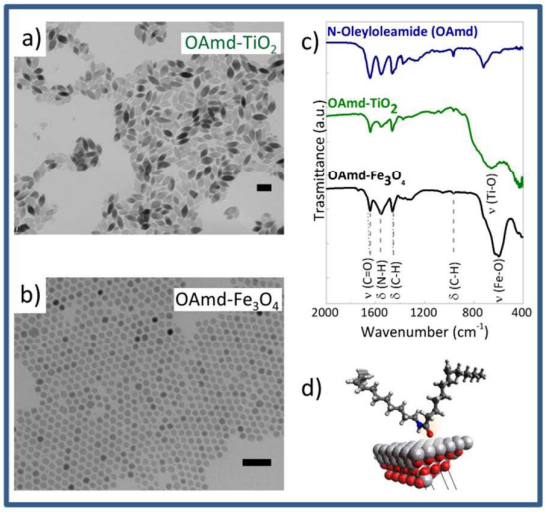

Figure 1 *N*-Oleyloleamide (OAmd) capped titania and magnetite nanoparticles TEM images of (a) titania nanoparticles and (b) magnetite nanoparticles (scale bar: 50 nm); (c) FTIR spectra of titania and magnetite nanoparticles compared with the one of pure N-oleyloleamide; (d) Schematic representation of the amide interaction with the nanoparticles surface.

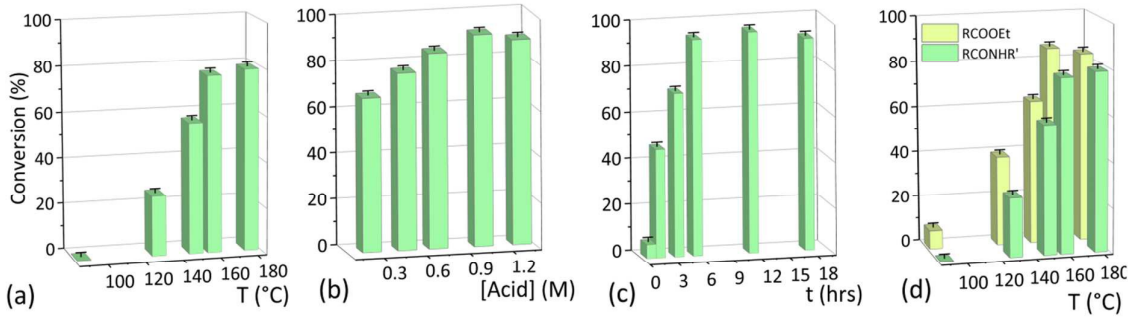

Figure 2 Conversion (determined by ^{1}H-NMR) as a function of (a) temperature ([**1a**] = 0.5M; **1a/2a** = 0.83, t = 18hrs); (b) acid concentration (**1a/2a** = 0.83; T = 160°C, t = 18hrs); (c) time ([**1a**] = 1.05 M; **1a/2a** = 0.83, T = 160°C). (d) Conversion to ester compared with conversion to amide for a set of experiments at different temperatures in the absence of amine with [**1a**] = 0.5M; t = 18hrs. See ESI Table S1 and Table S2 for further details.

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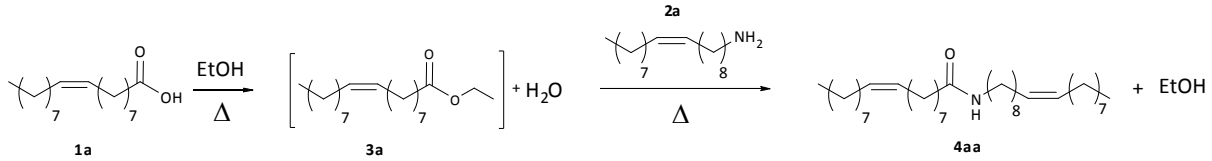

Scheme 3 Proposed mechanism for *N*-oleyloleamide **4aa** synthesis involving the ester **3a** as intermediate.

corresponding ester in all the crude mixtures obtained by using other alcohols confirms that the mechanism involved ester as intermediate (Scheme 3).The use of an autoclave four times bigger, keeping the full to empty volume ratio (0.21) unchanged, as well as the use of 96% ethanol did not influence the conversion to amide, pointing out the possibility to make this approach cheaper and easily scalable (from 7g to 27g of amide).

In order to evaluate the versatility of the optimized procedure, different aliphatic and aromatic carboxylic acids (**1a-j**) and amines (**2a-q**) have been explored, and the results are summarized in Table 1. It is important to note that, in all the analysed crude reaction of the selected substrates, a certain amount of ethyl ester was evidenced by ^{1}H-NMR allowing to generalize the mechanism proposed for the reference molecules. First, oleic acid **1a** was subjected to reaction with different aliphatic primary amines **2a-e** affording the corresponding *N*-alkylamides **4aa**-**4ae** with good to excellent yields (entries 1-5). **1a** was also reacted with the enatiomerically enriched (+)-1-phenylethanamine (ee 98%) affording the corresponding amide **4af** in excellent yields and with preservation of the stereochemical identity (98% ee). Reaction of **1a** with secondary amines pyrrolidine **2g** and dibenzylamine **2h**, leads to the corresponding compounds **4ag** and **4ah** respectively in 92% and 40% yield (entries 7 e 8), while the one with aniline **2i** gives **4ai** with 50% yield (entry 9). This reduced reactivity were also observed when *p*-toluidine **2j,** *p*-cloro **2k** and *p*-bromo **2l** aniline were used in this investigation (entries 10-12) probably due to the reduced reactivity of the aromatic amine.[7a] Reactions of **1a** with aniline derivatives bearing an electron withdrawing groups such as *p*-cyanoaniline **2m**, were inconsistent and the starting materials were recovered unchanged after 6 hours reaction (entry 13). Oleic acid also reacts with liquor ammonia **2n** and the corresponding oleamide **4an** was obtained in high conversion (76%) but moderate yield (35%) without further optimization (entry 14). In the case of the adduct **4ag** (entry 7), ^{1}H NMR signal for the alkenyl protons at 5.30 ppm clearly indicates the *trans*-geometry of the double bond, while in all of the other cases (entries 1-6, 8-14) the *cis*-geometry of the starting reagent was preserved. Identification of double bond isomerisation was possible on the basis on the fine structure of the multiplet, whose *J*-couplings pattern was shown for both *cis*- and *trans*-9-octadecenoic acids, in the work by Williamson *et al.*[22]

Then, other aliphatic acids (C_8-C_{12}) were reacted with *n*-butylamine leading to the corresponding amides **4bb**-**4cb** (entries 15-16) with high conversions (99%) and yields (78-98%). Again, phenylacetic acid **1d** was reacted with *n*-butylamine **2b** yielding the corresponding *N*-*n*-butyl-2-phenyl-acetamide **4db** with 90% yield (entry 17). Finally, the reactivity of benzoic acid **1e** and its derivatives **1f**-**1i** have been evaluated (entries 18-23). Acid **1e** reacted with benzylamine **2e** affording **4ee** with 59% yield (entry 18), and with *n*-butylamine **2b** giving the corresponding amides **4eb** with acceptable yields (41%) (entries 19). Amine **2b** also reacted with acids **1f** and **1g** (entry 20-21) yielding the corresponding **4fb** and **4gb** with 50% and 22% yield, respectively. As expected, electron-withdrawing group on the aromatic ring facilitated the formation of the amide compound (entry 20), whereas electron-donating group caused a drop of the yield (entry 21). *para*-Substituted benzoic acids (**1h** and **1i**) were also evaluated as substrates. Specifically *p*-NH_2 benzoic acid **1h** reacted with *N*,*N*'-dimethylethylenediamine **2o** affording the amide **4ho** in 78% yield (entry 22). These results can be explained by assuming that the *p*-NH_2 functionalization in the aromatic ring could be protonated during the amide synthesis, causing a reduction of the electron donor effect of this substituent. Moreover, no polycondensation products or polymeric adducts were observed. Unlikely, reaction of *p*-hydroxybenzoic acid **1i** with **2o** was ineffective and the corresponding amide **4io** was isolated in traces and accompanied by unidentified oxidation reaction products (entry 23).

The synthesis was also successfully applied to biologically active amides such as ethanolamides,[23] (lauryl ethanolamide LEA, and palmitoyl etanolamide PEA) and procainamide[24]achieving good (59%) to excellent (92%) conversion (Scheme 4).

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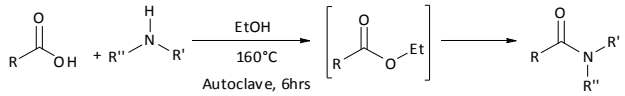
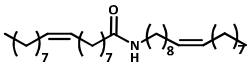
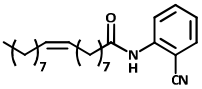
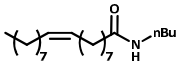
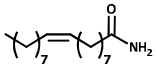
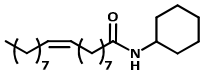
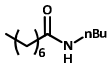
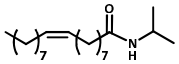
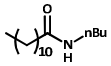
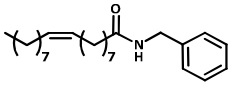
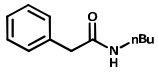
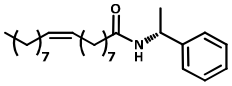
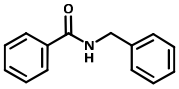
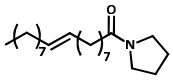
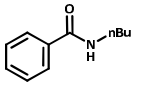
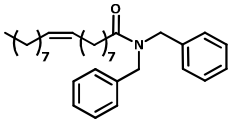
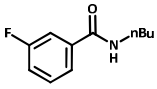
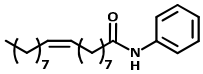
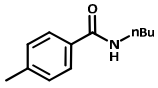
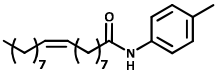
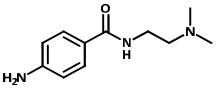
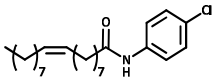
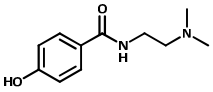
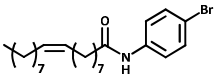
Table 1 *Synthesis of amides **4aa-4io**: reaction scope*[a,b]



1 2 3 4

Entry		Formula	Conversion[b] (%)	Yield[c] (%)	Entry		Formula	Conversion[b] (%)	Yield[c] (%)
1	**4aa**		94	88	13	**4am**		0	0
2	**4ab**		99	86	14	**4an**		76	35
3	**4ac**		79	76	15	**4bb**		99	78
4	**4ad**		86	80	16	**4cb**		99	>98
5	**4ae**		93	87	17	**4db**		99	90
6	**4af**		91	82	18	**4ee**		60	59
7	**4ag**		99	92	19	**4eb**		45	41
8	**4ah**		41	40	20	**4fb**		54	50
9	**4ai**		64	50	21	**4gb**		26	22
10	**4aj**		34	33	22	**4ho**		79	78
11	**4ak**		25	21	23	**4io**		3	(Traces[d])
12	**4al**		24	22					

[a]Reactions were carried out in a 85 mL autoclave with carboxylic acids **1a-j** (0.025 mol, 1M), amines **2a-o** (0.030 mol, 1.2 M), absolute ethanol to lead the final volume to 15mL, at 160°C for 6 hours in absolute ethanol. [b]Determined by ^{1}H-NMR. [c]Determined by weight after purification. [d]Compound **4io** isolated in traces after crystallization

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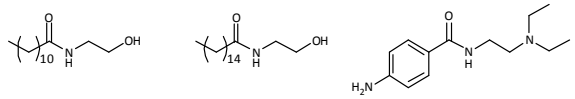

Scheme 4 *Synthesis of biologically active compounds* ***4cp****,* ***4jp*** *and* ***4hq****.*

Conclusions

In this work, we have developed a straightforward ethanol-mediated solvothermal amidation of carboxylic acids that provide a rapid access to several *N*-substituted amides. In a sealed reactor, ethanol reacts with the unactivated acid forming the ethyl ester, which is easily subjected to nucleophilic amine attack affording the corresponding amide in good to excellent yield. Being ethanol either a reactant and the solvent, and being water and ethanol the only by-products of the overall reaction, this practical approach assures the highest atom economy avoiding all the typical drawbacks of the common strategies reported in the literature. This green and scalable (up to about 30 grams in the present work) procedure has been extended to biologically active molecules, as procainamide and ethanolamides, opening a new prospective both in the amide synthesis field and in the development of a new class of biocompatible capping agents for inorganic nanoparticles.

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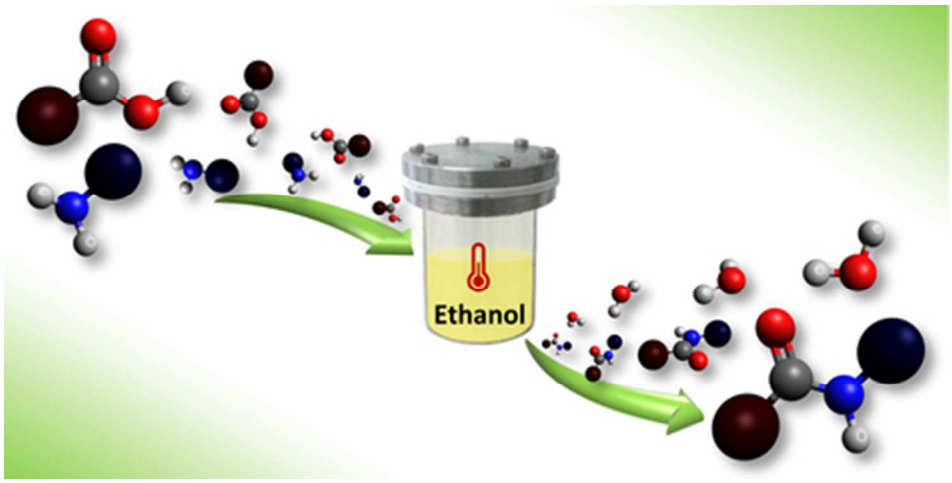

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