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Efficient activity of magnesium–aluminium hydrotalcite in the synthesis of amides†‡

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The synthesis of amides by coupling benzotriazole esters and amines can be achieved conveniently in moderate to excellent yields (50–95%) using a commercial, synthesized, calcined or reconstructed Mg–Al hydrotalcite instead of one of the classic bases (tertiary amines). The experimental results demonstrated that commercial and synthesized hydrotalcite can be quantitatively recovered from the reaction by simple filtration and reused for a number of cycles and that the reconstructed hydrotalcite is the most active form for the amide bond formation. Finally, to test the scope of the protocol for the synthesis of biologically relevant molecules, the total synthesis of Sansalvamide A was carried out.

Introduction

Carboxylic acid amides[1] are an important class of organic compounds of biological, pharmaceutical and industrial importance. Further, 25% of known pharmaceuticals contain in their structures carboxylic acid amides,[2] which play significant roles in biological processes. As a consequence of their biological importance, acylation reactions of carboxylic acids with amines to form amides represent one the most important and commonly employed transformations in organic synthesis.[3] Large scale processes involving acylation reactions are used in the synthesis of products including high-value fine chemicals, such as peptides, polymers, plasticizers, pheromones, fragrances and organocatalysts, which require mild and stringent fabrication protocols.[4] In general, synthetic methods for amide bond formation[5] utilize the acylation of amines with activated carboxylic acids or enzymatic reactions.[1]

Some of those protocols use stoichiometric quantities of bases, principally tertiary amines, which are associated with the generation of high quantities of waste products and expensive end-products.[6] In this context, the development of eco-friendly heterogeneous catalysts that can be used instead of the classic bases[7] has become a major area of research recently. Hydrotalcites (HTs) are one of the materials that have been used to replace the classic bases in the synthesis of fine chemicals and can be easily prepared, handled and recycled. Hydrotalcites $[M^{2+}_{1-x}M^{3+}_{x}(OH)_2]^{x+}[A^{n-}_{x/n}\cdot mH_2O]^{x-}$ are hydrated aluminium–magnesium hydroxides with a lamellar structure, in which the excess of positive charge, originating from the Mg^{2+} to Al^{3+} substitution, is compensated for by carbonate anions in the interlayer space.[8] In these compounds, also known as anionic clays, the layers are built up by the condensation of octahedral MO_6 units ($M = Mg^{2+}$ or Al^{3+}), as in brucite $[Mg(OH)_2]$. Therefore, hydrotalcite has OH groups that are shared by three octahedral cations and point towards the interlayer space.

With these features in mind, and as part of our research program into the use of hydrotalcite in organic reactions[9] we investigated the synthesis of carboxylic acid amides from carboxylic acids and amines in the presence of coupling reagents, replacing the classic tertiary amine bases with hydrotalcites, because of the following advantages: ease of separation of the products, reduction of waste, possible regeneration of the hydrotalcite and low cost. Thus, in the present paper we describe a highly efficient protocol for the synthesis of amides using benzotriazole esters[10] as the activated carboxylic acids[11] in the presence of hydrotalcite, demonstrating the efficiency of these materials by high reaction yields. It is worth noting that recently hydrotalcite supported nano-gold has been reported as an efficient heterogeneous system for the dehydrogenative synthesis of an amide from an alcohol and amine.[12] However, that process involves a catalytic oxidative amidation in the presence of a metal, while this process is a condensation of an amine with a carboxylic acid *via* an active ester. Finally, we used the protocol in the total synthesis of Sansalvamide A to

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demonstrate its synthetic value. Notably, previous works have demonstrated the efficiency of clay[13] and alumina[14] for the elongation of oligopeptide chains in the absence of coupling reagents. However, this report represents the first time that the elongation of a peptide chain has been carried out in the presence of hydrotalcite and coupling reagents.

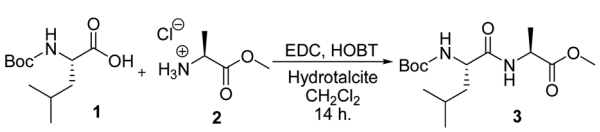
Results and discussion

Initially, we optimized typical reaction parameters including the mole ratio of a commercial hydrotalcite (HTs Aldrich®, $Mg_6Al_2(CO_3)(OH)_{16}\cdot 4H_2O$), temperature and solvents, using *N*-Boc-leucine (1 mmol), L-alanine methyl ester hydrochloride (1 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC; 1.1 mmol) and 1-hydroxybenzotriazole (HOBT; 1.1 mmol) as the model substrates (Scheme 1). Preliminary reactions were carried out to identify the best concentration of hydrotalcite, with CH_2Cl_2 as the solvent at room temperature. Among the various mole ratios of hydrotalcite that we screened, the most effective concentration of hydrotalcite was 250 mg per 1 mmol of *N*-Boc-leucine **1** and 1 mmol of L-alanine methyl ester hydrochloride **2** giving peptide **3** in 95% yield at room temperature. Similar results were obtained when we carried out the reaction using $CHCl_3$, THF and DMF as solvents. It is worth noting that no epimerization products were observed in the ^{1}H NMR spectra and HPLC chromatogram of the crude reaction mixtures (see ESI‡). Additionally, we observed that hydrotalcite can be easily recovered and reused for at least three cycles with significant decreases in yield (1st run 92%; 2nd run 80% and 3rd run 75%). After the third reaction the yield decreased notably by 20%.

At this point, we considered the possibility of using hydrotalcite synthesized by our research group. The principal idea was to study the behavior of synthesized, calcined, and reconstructed hydrotalcites, in the formation of a peptide bond and then to compare these results with those obtained using the commercial hydrotalcite. By heating at a temperature of 500 °C, the hydrotalcite is converted into a homogeneous mixed oxide of Al and Mg with a very small crystal size, high thermal stability and large surface area. The basic property of the mixed oxide comes from the oxygen anions and depends on the Mg–Al ratio[15] in the hydrotalcite precursor as well as the preparation method.[16] We have previously studied both types of basic solid by infrared spectroscopy and demonstrated that there is a variation in the distribution of the carbonate species between the synthesized and calcined samples; the synthesized hydrotalcite had 37% of monodentate carbonates and 63% of the bidentate species. The calcined one had 26% of monodentate carbonates and 74% of the bidentate species.[17] The reconstruction of the layered hydrotalcite, using the so-called memory effect,[18] from the calcined sample by rehydration in a liquid or gas phase generates Brønsted base sites between the new layers, where carbonate anions are substituted by hydroxyl anions. These reconstructed layered materials exhibit different morphologies and textural properties[19] compared with their parent layered double hydroxide materials and often demonstrate higher catalytic activity than the Mg–Al mixed oxides in a variety of reactions such as aldol condensations,[20] Knoevenagel and Claisen–Schmidt condensations,[21] Michael additions,[22] and the transesterification of tributyrin with methanol.[23]

The hydrotalcites investigated in the present study (Mg^{2+}–Al^{3+} in a ratio of $x = 0.33$) were characterized by XRD, FTIR and BET methods. The obtained XRD patterns are shown in Fig. 1. The synthesized hydrotalcite sample exhibited Mg–Al hydrotalcite reflections associated with the layered double hydroxide crystal structure. The maxima correspond to typical diffractions by the (0 0 3) and (0 0 6) planes (Fig. 1, blue line). Calcination of hydrotalcite gives a Mg(Al)O mixed oxide with a periclase-like structure with only two reflections corresponding to the (4 0 0) and (4 4 0) planes (Fig. 1, red line). Rehydration of hydrotalcite in the liquid phase regenerates the layered structure as a consequence of the memory effect (Fig. 1, green line), however it is less crystalline than the synthesized hydrotalcite as can be observed by comparing the intensity of the reflections (Fig. 1).

The adsorption of N_2 (BET method) was used to quantify the surface area and pore size and the results are summarized in Table 1. As shown in Fig. 2 the isotherms of each material closely resemble a type II isotherm; nitrogen uptake monotonically increases with p/p_o values due to sorption in the HT mesopores and the hysteresis loops characteristic of type H III, which describes materials with different adsorption and desorption behaviours that are usually solids consisting of aggregates or agglomerates of particles that form slit-like structures.[24] The synthesized hydrotalcite sample had a low porosity, pore volume and surface area (Table 1, entry 1). The surface area of the calcined hydrotalcite is higher as normally occurs and the reconstructed material obtained from the calcined hydrotalcite has a lower surface area than the calcined hydrotalcite but larger cavities are formed after the structural reconstruction.



Scheme 1 Synthesis of an amide in the presence of hydrotalcite.

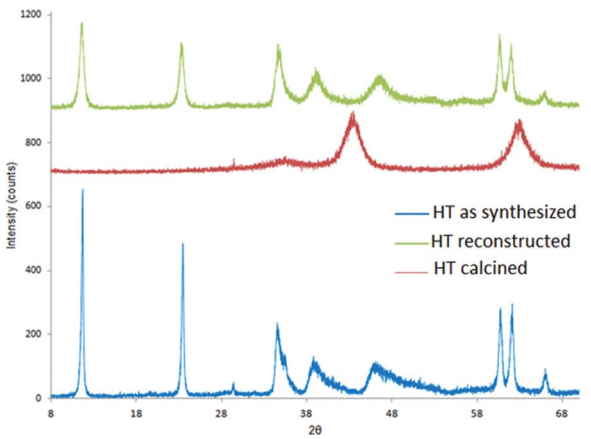


Fig. 1 Powder X-ray diffraction patterns of the hydrotalcites.

Table 1 The nitrogen adsorption–desorption analysis parameters of the materials

Entry	Hydrotalcite	S_{BET} ($m^2\ g^{-1}$)	Pore volume ($cm^3\ g^{-1}$)	Pore size (Å)	d_{003} (Å)
1	Synthesized	44	0.36	165	7.58
2	Calcined	176	0.73	85	—
3	Reconstructed	95	0.53	175	7.64

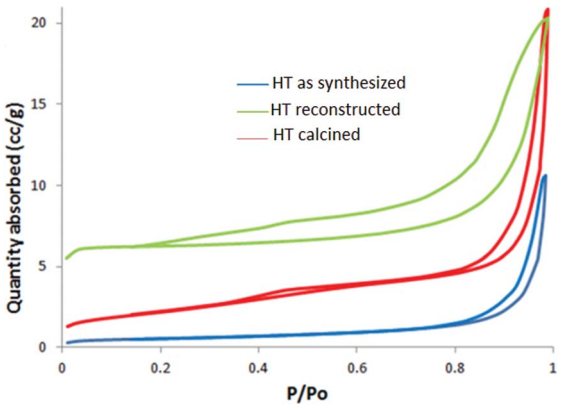


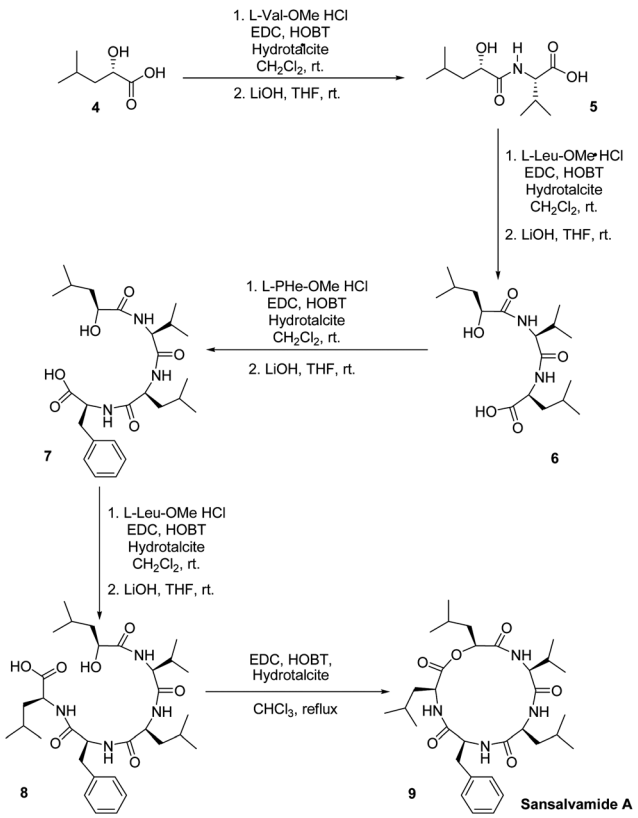
Fig. 2 Nitrogen adsorption–desorption isotherms of the hydrotalcites.

Table 2 Synthesis of Sansalvamide A

Entry	Product	Hydrotalcite (mg)	Yield[a] (%)
1	Dipeptide **5**	Commercial	90
		Synthesized	90
		Calcined	92
		Reconstructed	95
2	Tripeptide **6**	Commercial	91
		Synthesized	92
		Calcined	95
		Reconstructed	95
3	Tetrapeptide **7**	Commercial	88
		Synthesized	86
		Calcined	90
		Reconstructed	90
4	Pentapeptide **8**	Commercial	90
		Synthesized	90
		Calcined	92
		Reconstructed	95
5	Macrolactone[b] **9**	Commercial	65
		Synthesized	60
		Calcined	65
		Reconstructed	65

[a] Yield of isolated product after chromatographic purification. Yield of isolated product after the two reaction steps. [b] *Reagents and conditions* for the macrolactonization reaction: ω-hydroxy acid **8** (1 mmol), EDC (1.1 mmol), HOBT (1.1 mmol), $CHCl_3$ (50 mL), reflux, 18 h.

In order to compare the efficiency of these hydrotalcites in the amide bond formation, catalyst screening was carried out using different concentrations of the hydrotalcite: synthesized, calcined and reconstructed (see ESI‡). The synthesized hydrotalcite and commercial hydrotalcite exhibited similar behaviours. The calcined hydrotalcite is less active than the reconstructed hydrotalcite. However, these hydrotalcites are more active than the synthesized hydrotalcite and the commercial hydrotalcite (HTs Aldrich®). These results confirm previous observations reported in the literature about the higher catalytic activity of reconstructed hydrotalcite in organic reactions.[18,23] The synthesized hydrotalcite was recovered and reused in at least three cycles with significant decreases in yield (1st run 80%; 2nd run 75% and 3rd run 60%). Unfortunately, attempts to reuse the reconstructed hydrotalcite have not been successful.



Scheme 2 Synthesis of Sansalvamide A.

To determine whether our methodology is useful for the synthesis of complex molecules, we synthesized Sansalvamide A (**9**), which is a cyclic pentadepsipeptide isolated from the mycelium of a fungus of the genus *Fusarium*, which is collected from the surface of the seagrass *Halodule wrightii* that is found on San Salvador Island in the Bahamas. This cyclic depsipeptide has an IC_{50} value of 27.4 mg mL^{-1} against the National Cancer Institute's 60-cell-line panel and an *in vitro* IC_{50} value of 9.8 mg mL^{-1} toward HCT-116 colon carcinoma cells.[25] Furthermore, it is an inhibitor of virus-encoded type-1 topoisomerase, which is likely to be necessary for the replication of the *Molluscum contagiosum* virus (MCV).[26] With this stimulating biological background and the complications in obtaining Sansalvamide A from natural sources, Silverman's[27] and McAlpine's[28] groups have focused on synthesizing Sansalvamide analogues and evaluating their antitumor activities. In the same context, Jiang[29] has developed a ionic-liquid-supported total synthesis of this peptide analogue. Herein, the total synthesis of this cyclic

pentadepsipeptide is described in solution. The enlargement of the chain from 2-hydroxy-4-methylpentanoic acid **4**,[30] was carried out by using the corresponding amino acid methyl ester hydrochlorides, EDC, HOBT and commercial, synthetic, calcined or reconstructed hydrotalcite as the base. Thus, the residues of Val, Leu, Phe, and Leu were present in the ω-hydroxy acid **8** (Scheme 2). Finally, the macrolactonization of the ω-hydroxy acid **8** was carried out under conditions previously reported by our group.[9] In the four coupling reactions (Table 2, entries 1–4) and macrolactonization to obtain Sansalvamide A (Table 2, entry 5), the behaviour of the hydrotalcites was similar to that described above. Again, the reconstructed hydrotalcite was more active than the other hydrotalcites. The final product **9** had a mp of 143–145 °C (ref. 25, mp 143–152 °C) and an $[\alpha]_D$ of −116 (*c* 0.001 in MeOH) (ref. 25, $[\alpha]_D$ −115 (*c* 0.001 in MeOH)). From these results, we consider that hydrotalcites can be very useful for the elongation of peptide chains.

Conclusions

In summary, the present study demonstrates the capacity of hydrotalcite to replace typical tertiary amine bases in the synthesis of amides. Compared with the traditional protocol, this method possesses at least four advantages: (i) the hydrotalcite can be easily removed from the reaction mixture, (ii) reduction of waste, (iii) possibility for the reuse of the hydrotalcite and (iv) low cost of the process. In addition, this study demonstrates that hydrotalcite reconstructed using the memory effect is the most active form for this amide bond formation. Finally, considering the biological importance of peptides, the use of hydrotalcites in the elongation of oligopeptide chains introduces an attractive alternative for their synthesis.

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