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Modified Mg : Al hydrotalcite in the synthesis of oxazolidin-2-ones

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The modified Mg : Al (3 : 1) hydrotalcite has been found to be an efficient catalyst in the conversion of carbamates into oxazolidin-2-ones under mild reaction conditions. A wide variety of oxazolidin-2-ones were obtained with excellent chemical yield.

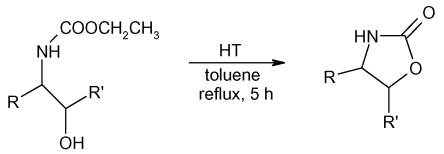
Oxazolidin-2-ones are important compounds in both pharmaceutical[1] and synthetic organic chemistry. They are widely used as chiral auxiliaries in numerous asymmetric syntheses[2] and are applied in the synthesis of a number of valuable natural products, antibiotics, and other compounds with immunosuppressant, antihistaminic, antifungal, antihypertensive, antiallergic, or antibacterial activities.[3]

Numerous synthetic methods have been described in the literature for the preparation of oxazolidin-2-ones such as cyclization of alkyl or aryl carbamates using either acidic[4] or basic[5] catalysts, cyclization of triphenylphosphonium salts[6] or *N*-nitroso compounds,[7] and carbonylation of 2-amino-ethanols using phosgene,[8] diphosgene,[9] triphosgene,[10] urea[11] and cyanates,[12] or oxidative carbonylation of 2-amino-ethanols with selenium[13] or palladium catalysts.[14] The use of these compounds is undesirable because they are often hazardous (*e.g.* phosgene, cyanates), the processes often require very low and very high temperature[15] and lead to the production of a vast amount of toxic wastes. For these reasons, much attention has been paid to the development and use of new, non-toxic catalysts.

Nowadays the use and design of environmental-friendly solid acid and solid base catalysts has become an important research target, which is mainly due to their useful properties like high versatility, easy treatment and work-up, mild experimental conditions, high yield and selectivity, they are inexpensive and often reusable. Hydrotalcites (HT), the anionic layered double hydroxides (LDHs) can be applied as adsorbents, anion-exchangers and basic catalysts. These materials can be described by the formula, $[M(II)_{(1-x)}M(III)_x(OH)_2]^{x+}(A_{x/m}{}^{m-})\cdot nH_2O$, where M(II) is a divalent ion like Mg, Cu, Ni, Co, Mn, Zn; M(III) is a trivalent ion like Al, Fe, Cr, Ga; A is the compensating anion like OH^-, Cl^-, NO_3^-, CO_3^{2-}, SO_4^{2-}, and x is in the range of 0.1–0.33. In general, the activation of HT consists of two steps. First, HT upon thermal treatment at 450–500 °C form a highly active Mg(Al)O mixed oxide that exhibits strong Lewis basicity, which is used for catalyzing various organic reactions.[16,17] In the second step the calcined catalyst is rehydrated which, due to its so-called memory effect, results the restoration of the original HT structure with OH^- groups, giving a Brønsted type catalyst.[18,19] The applicability of the different hydrotalcites, due to the different nature and strength of their basic sites, is largely investigated in various organic synthesis.

In this paper we describe the development of an environmentally friendly, simple and convenient, catalytic method for the cyclization of carbamates with activated hydrotalcite Mg : Al (3 : 1) which gave the expected oxazolidin-2-ones in excellent yields.

We investigated first the cyclization of (2-hydroxy-propyl)-carbamic acid ethyl ester **1b** in the presence of different types of HT catalysts under similar reaction conditions (Scheme 1, Table 1). The applied species were rehydrated, calcined and non-activated Mg : Al 3 : 1 hydrotalcites. The non-activated HT, with carbonate as the compensating anions showed low activity. The calcined HT gave a very poor yield. It seems that the Lewis basic sites (O^{2-}), obtained by the calcination of HT are not efficient in this reaction. For comparison purposes the known solid base $KF/\alpha Al_2O_3$ has also been used. The reaction with $KF/\alpha Al_2O_3$ gave a very good yield, but the use of the quite toxic KF in organic synthesis should be avoided. The results showed that the modified HT, obtained by decarbonylation and rehydration showed the highest activity in this reaction.



1 **2**

Scheme 1

The enhanced catalytic activity of this catalyst is attributed to the presence of OH groups, generated during rehydration of the thermally activated hydrotalcite, forming Brønsted basic sites. The synthetic applications of rehydrated hydrotalcite have been recently reported *e.g.* in aldol,[18] Knoevenagel[20] and Michael reactions.[21]

We explored the effect of solvent on the reaction yield. As shown in Fig. 1, toluene proved to be the most efficient among the solvents tested. In ethanol the conversion after 5 h was only 8%, while in dioxane it was 16%.

Fig. 2 shows the conversion of (2-hydroxy-propyl)-carbamic acid ethyl ester **1b** in toluene at 20 °C, 80 °C and 110 °C in the presence of rehydrated HT. Since the yield of the oxazolidin-2-one increased dramatically at 110 °C and reached 89% after 5 h while in the reaction at room temperature (20 °C) and at 80 °C after 5 h only 9% and 25% conversion was observed, respectively,

Table 1 Comparison of modified Mg : Al (3 : 1) hydrotalcite with several heterogeneous catalysts in the synthesis of 5-methyl-oxazolidin-2-one **2b**[a]

Entry	Solid catalyst	Yield (%)[b]
1	Rehydrated Mg : Al HT	88
2	Calcined Mg : Al HT	20
3	Non-activated Mg : Al HT	48
4	$KF/\alpha Al_2O_3$	82

[a] General conditions: carbamate 5 mmol, catalyst 0.13 g, toluene (10 ml), 110 °C, 5 h. [b] Determined by ^1H NMR.

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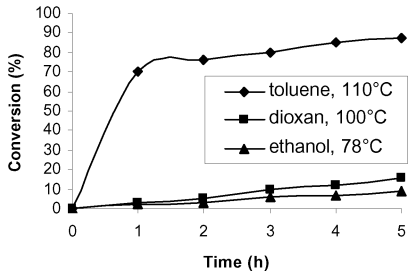


Fig. 1 Conversion of (2-hydroxy-propyl)-carbamic acid ethyl ester **2b** in different solvents.

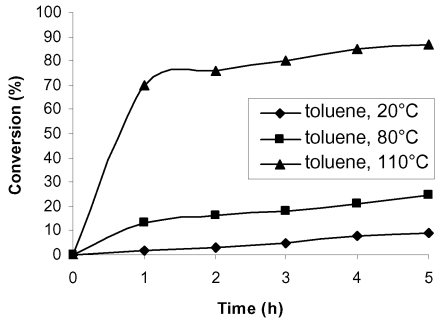


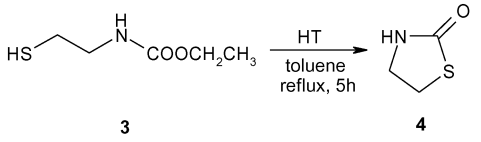
Fig. 2 Time course of the yield of 5-methyl-oxazolidin-2-one **2b** over modified Mg : Al (3 : 1) hydrotalcite in toluene at various temperatures.

it seems that in this case there is mostly the reaction temperature which determines the yield and the nature of the solvent is less important.

Next we investigated the cyclization of a wide range of alkyl or aryl substituted carbamates **1a–f** (Scheme 1). The reactions were carried out in the presence of a catalytic amount of HT in boiling toluene for 5 h. The appropriate oxazolidinones **2a–f** were obtained with excellent yields, as represented in Table 2. The overall yields were above 80%.

In the reaction of optically active carbamates **1d,e,f** the corresponding oxazolidin-2-ones **2d,e,f** were formed stereospecifically. The optical purity was determined by comparing the optical rotation of the products with the literature value.

Furthermore, the synthesis of 2-thiazolidinone **4** from (2-mercapto-ethyl)-carbamic acid ethyl ester **3** was also successfully performed under similar conditions (Scheme 2) in 50% yield.



3 4

Scheme 2

In the reaction of [(1*R*,2*R*)-2-hydroxy-1-hydroxymethyl-2-(4-nitro-phenyl)-ethyl]-carbamic acid ethyl ester under the same conditions we obtained the mixture of **6** and **7** in a 4 : 1 ratio (Scheme 3).

The two products were separated by simple recrystallization from ethyl acetate. Compound **6** has been known only in the racemic form.[22] Compound **7** has not been described in the literature yet. The structural identity of this compound was determined by ^{1}H and ^{13}C NMR analysis, furthermore by a single crystal X-ray structural study.

Table 2 Conversion of carbamates to oxazolidin-2-ones with activated hydrotalcite Mg : Al (3 : 1)

2	R	R′	Yield (%)[a]
a	H	H	83
b	H	(±)-CH_3	89 (86)[b]
c	(±)-C_2H_5	H	95
d	(*S*)-C_2H_5	H	96
e	(*R*)-Ph	H	91
f	(*S*)-$PhCH_2$	H	91

[a] Based on ^{1}H NMR. [b] Recycled hydrotalcite.

There are two chemically the same but crystallographically independent molecules in the asymmetric unit (Fig. 3) organised by a pseudo inversion centre that can be found between the 2-oxazolidinone moieties of the molecules. Inversion symmetry cannot be realised because the absolute configuration of both molecules are the same: C71, C81, and C72, C82 are all *R*. Flack *x* parameter[24] is −0.14(17). The distance between the atoms concerned by least-squares fitting of the 17 heavy atoms of the independent molecules is 0.2(4). The participating atoms in the strong N–H···O and O–H···O type intermolecular interactions of the two molecules are accordingly the same (N11–H11N···O22 1.97 Å 170°; N12–H12N···O21 2.23 Å 145°; O31–H31O···O21 2.07 Å 154°; O32–H32O···O22 1.96 Å 160°), while weak C–H···O secondary interactions are different (C21–H21···O31 2.43 Å 136°; C22–H22···O41 2.53 Å 131°; C61–H61···O42 2.56 Å 167°; C71–H71···O32 2.44 Å 145°; C82–H82···O21 2.48 Å 143°).

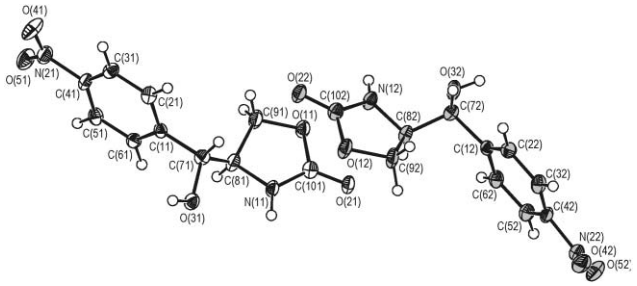
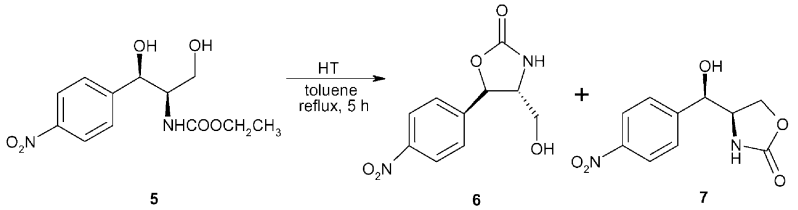


Fig. 3 ORTEP diagram[23] at 50% probability level showing the two crystallographically independent molecules in the asymmetric unit (residues are identified by the last number of the label). Residue 1 is presented in white, residue 2 with gray octant shaded heavy atoms.

The reuseability of the catalyst was studied through the reaction of (2-hydroxy-propyl)-carbamic acid ethyl ester **2b**. The catalyst was recovered from the reaction mixture by simple filtration, then it was successfully reused without significant loss of activity after washing it with toluene and being heated for 1 h at 120 °C (see Table 2, **2b**).

In summary the results show that the cyclization of carbamates in the presence of activated Mg : Al (3 : 1) hydrotalcite is an efficient, environmentally friendly synthesis of oxazolidin-2-ones. Several advantages, such as high catalytic activity, simply



5 6 7

Scheme 3

work-up, reuseability of the catalyst avoiding the problem of disposing of concentrated basic solutions, use of harmless reagents, can make this procedure a useful and attractive alternative of synthesis of oxazolidin-2-ones.†

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Notes and references

† **General procedure for the preparation of oxazolidin-2-ones.** The carbamates **1** were synthesized by alkoxycarbonylation of the corresponding aminoalcohols with EtO_2CCl using the method reported by Wu and Shen.[5e] Thus, 5 ml (50 mmol) EtO_2CCl was dropped into an ice-mixture of 50 mmol aminoalcohol and 25 g (0.25 mol) $KHCO_3$ in 40 ml water under vigorous stirring. After the addition was complete, the cooling bath was removed. The reaction mixture was stirred at rt for 1.5 h, then it was extracted with EtOAc (4 × 25 ml). The combined organic phases were washed with brine and water, dried over anhydrous magnesium sulfate then the solvent was removed to give the pure carbamate **1**.
Selected data of **(2-hydroxy-propyl)-carbamic acid ethyl ester** (**1b**): 4.12 g (57%) white oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.16 (t, $J = 7.5$, 3H), 1.27 (t, $J = 9$ Hz, 3H), 2.99–3.19 (m, 2H), 3.91–3.98 (m, 1H), 4.10 (q, $J = 10.5$ Hz, 2H), 5.58 (bs, 1H).
[(1*R*,2*R*)-2-Hydroxy-1-hydroxymethyl-2-(4-nitro-phenyl)-ethyl]-carbamic acid ethyl ester (**5**): 7.37 g (81%) light-yellow solid, mp: 107 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.18 (t, $J = 7.2$ Hz, 3H), 3.54–3.57 (m, 1H), 3.72–3.75 (m, 2H), 3.83–3.86 (m, 2H), 3.91 (q, $J = 7$ Hz, 2H), 0.89 (bs, 1H), 5.08 (bs, 1H), 7.63 (d, $J = 8.5$ Hz, 2H), 8.18 (d, $J = 8.5$ Hz, 2H).
In a typical condensation reaction, hydrotalcite (0.13 g) was added to the mixture of carbamate (5 mmol) and toluene (10 ml) under argon. The mixture was stirred at 110 °C for 5 h. Then the catalyst was filtered out, washed with toluene and the filtrate was evaporated. The residue, if necessary, was purified by column chromatography or recrystallized to give the corresponding oxazolidin-2-ones. The known products were characterized by comparing the ^{1}H NMR, IR spectroscopy, optical rotations and melting points data with those reported in the literature. The spectral and physical data of the known compounds were identical with those reported in the literature.
Selected data of 5-methyl-oxazolidin-2-one (**2b**): oil, IR (neat) 3320, 1740, 1260 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.44 (d, $J = 6$ Hz, 3H), 3.20 (t, $J = 7.5$ Hz, 1H), 3.71 (t, $J = 8$ Hz, 1H), 4.77–4.80 (m, 1H), 6.52 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 20.6, 47.0, 72.8, 159.8.
Spectral data of new compounds:
(4*R*,5*R*)-5-(4-Nitrophenyl)-4-hydroxymethyl-1,3-oxazolidin-2-one (**6**): light-yellow solid, mp: 120 °C, IR (KBr): 3335, 1746, 1550, 1315, cm^{-1}; ^{1}H NMR (300 MHz, methanol-d_4) δ (ppm): 3.78 (s, 2H), 4.29–4.31 (m, 1H), 5.6 (d, $J = 4.2$ Hz, 1H), 7.66 (dd, $J_1 = 3$ Hz, $J_2 = 7.2$ Hz, 2H), 8.29 (dd, $J_1 = 1.8$ Hz, $J_2 = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, methanol-d_4) δ (ppm): 59.1, 67.8, 74.4, 124.5, 128.9, 149.1, 149.4, 159.5. $[\alpha]_D^{25} = +1.46$ ($c = 1$, MeOH). $C_{10}H_{10}N_2O_5$ Anal. Calcd. C 50.42, H 4.2, N 11.76, Found C 50.02, H 3.98, N 11.54%.
4*R*-(1*R*-Hydroxy-(4-nitrophenyl)-methyl)-1,3-oxazolidin-2-one (**7**): white solid, mp: 175–177 °C, IR (KBr): 3335, 1746, 1550, 1315, cm^{-1}; ^{1}H NMR (300 MHz, methanol-d_4) δ (ppm): 4.15–4.19 (m, 2H), 4.31–4.35 (m, 1H), 4.81–4.89 (m, 1H), 7.66–7.70 (m, 2H), 8.25 (dd, $J_1 = 1.8$ Hz, $J_2 = 7.8$ Hz, 2H); ^{13}C NMR (75 MHz, methanol-d_4) δ (ppm): 59.1, 63.8, 80.1, 124.5, 127.7, 148.1, 149.5, 159.8. $[\alpha]_D^{25} = +8.25$ ($c = 1$, MeOH). $C_{10}H_{10}N_2O_5$ Anal. Calcd. C 50.42, H 4.2, N 11.76, Found C 50.18, H 3.96, N 11.52%.
Single crystal X-ray diffraction of compound (7). Single crystals of (**7**) were grown from the mixture of toluene and acetone, and were recrystallized from toluene by controlled solvent evaporation technique at room temperature. Crystal data: $C_{10}H_{10}N_2O_5$, Fwt.: 238.20, size: 0.75 × 0.67 × 0.52 mm, crystal system: monoclinic, space group $P2_1$, $a = 5.600(1)$ Å, $b = 24.290(2)$ Å, $c = 7.740(1)$ Å, $\alpha = \gamma = 90.00°$, $\beta = 96.240(4)°$, $V = 1046.6(2)$ Å^3, $T = 93(2)$ K, $Z = 4$, $F(000) = 496$, $D_x = 1.512$ Mg m^{-3}, $\mu = 1.059$ mm^{-1}. A crystal of prism shape was mounted on a glass fibre. Cell parameters were determined by least-squares of 3150 reflections in the range of $3.6378 \leq \theta \leq 72.1250°$. Intensity data were collected on a Rigaku R-AXIS RAPID image plate diffractometer[25] (graphite monochromator; Cu-Kα radiation, $\lambda = 1.54178$ Å at 93(2) K in the range $3.64 \leq \theta \leq 71.78°$. A total of 19078 reflections were collected of which 3716 were unique [$R_{int} = 0.0989$, $R_\sigma = 0.0906$]; 3290 reflections were more intense than $2\sigma(I)$. Completeness to $2\theta = 0.951$. Numerical absorption correction was applied. The structure was solved by direct methods.[26] Neutral atomic scattering factors and anomalous scattering factors were taken from the International Tables for X-ray Crystallography.[27] Anisotropic full-matrix least-squares refinement[28] on F^2 for all non-hydrogen atoms yielded $R_1 = 0.0452$ and $wR_2 = 0.0867$ for 3290 [$I > 2\sigma(I)$] and $R_1 = 0.0478$ and $wR_2 = 0.0885$ for all (3716) intensity data, goodness-of-fit = 0.909; the maximum and mean shift/esd 0.000 and 0.000). Number of parameters is 335. The maximum and minimum residual electron density in the final difference map was 0.200 and −0.246 e Å^{-3}. Hydrogen atomic positions were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. CCDC reference number 258502. See http://www.rsc.org/suppdata/ob/b4/b418848a/ for crystallographic data in .cif or other electronic format.

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