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Mg-Al 3:1 hydrotalcite catalyst in the synthesis of cyclopropane carboxylic acid derivatives

Zoltán Finta^a, Zoltán Hell^{a,*}, Daniella Balán^a, Agnieszka Cwik^a,
Sándor Kemény^b, François Figueras^c

^a Department of Organic Chemical Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary

^b Department of Chemical Engineering, Budapest University of Technology and Economics, H-1521 Budapest, Hungary

^c Institut de Recherches sur la Catalyse du CNRS, 2. Avenue Albert Einstein, 69626 Villeurbanne Cedex, France

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Abstract

The non-activated Mg-Al 3:1 hydrotalcite is a suitable basic catalyst both in the intramolecular cyclization reaction of malonic acid allylic esters into bicyclic cyclopropane carboxylic acid lactones and the intermolecular cyclization reaction of dibromoethane and diethyl malonate into cyclopropane dicarboxylic acid diester. The optimal reaction conditions of the intramolecular cyclization were determined using a 2⁴ factorial design. An interesting effect on the diastereoselectivity of the intramolecular cyclization was observed compared with the diastereoselectivity of this cyclization using solid potassium carbonate as base. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Intramolecular cyclization reaction; Cyclopropane carboxylic acid derivatives; Hydrotalcite catalyst

1. Introduction

The use of hydrotalcite-like materials (layered double hydroxides, represented by the formula $[M_{(1-x)}^{2+}M_x^{3+}(\text{OH})_2]^{x+}(\text{A}_{x/m}^{m-}) \cdot n\text{H}_2\text{O}$, where the divalent ion may be Mg^{2+} , Ca^{2+} , Zn^{2+} , Ni^{2+} , the trivalent ion Al^{3+} , Fe^{3+} or Cr^{3+} ; the compensat-

ing anion may be OH^- , Cl^- , NO_3^- , CO_3^{2-} , SO_4^{2-} , and x can take values between 0.25 and 0.33) [1] as catalysts or bases in organic reactions has become an important research target, as these materials have advantageous catalytic properties without requiring special reaction conditions or causing tedious work-up procedures and disadvantageous environmental charges.

Numerous studies on their structure, physical properties and thermal stability have been reported [2–4] and their catalytic activity also was presented e.g. in aldol condensation [4,6], olefin epoxidation [7], isomerization [8], C-alkylation [5] and related reactions. In most of these reactions thermally pre-

* Corresponding author. Tel.: +36-1-463-1414; fax: +36-1-463-3648.

E-mail address: hell@oct.bme.hu (Z. Hell).

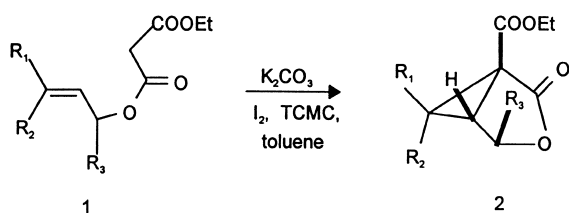


Fig. 1.

treated (above 700 K for some hours) and rehydrated [6] hydrotalcites were used. This treatment increased in the basicity of these materials.

Most of the reactions studied earlier were simple base-catalyzed reactions in which the basic catalyst has a simple but determinant role — providing the basic conditions and/or removing an acidic proton from one of the substrate molecules.

A great number of cyclopropane carboxylic acid derivatives are valuable biologically active compounds. Their syntheses have been intensively studied and a lot of methods were developed, both homogeneous phase and heterogeneous phase reactions were described among them. The latter used solid catalysts or solid bases, in some cases under phase transfer catalytic conditions.

Recently in our laboratories, two phase transfer catalytic methods were described for the synthesis of cyclopropane carboxylic acid derivatives based on solid potassium carbonate as base. One of them started from malonic acid allylic esters **1** yielding bicyclic cyclopropane carboxylic acid lactones **2** in the presence of iodine and a lipophilic quaternary ammonium salt, as phase transfer catalyst in an intramolecular reaction in good yield [9] (Fig. 1). The formation of **2** is a complex, SET-induced reaction with more than 10 elemental steps in which the base can play an important role several times.

The other method started from dihaloalkanes and malonic acid esters **3** and yielded the simple cyclo-

propane dicarboxylic acid diesters **5**, in refluxing toluene, also in good yield [10] (Fig. 2).

The aim of this work was to investigate the effect of the non-calcined Mg-Al 3:1 hydrotalcite (HT) in these phase transfer reactions.

2. Experimental

2.1. Synthesis of hydrotalcite

Hydrotalcite was prepared according to the method described in [7]. The workup procedure was modified; the solid substance obtained in the reaction was filtered out, then washed with hot distilled water and dried at 393 K for 10 h.

2.2. Intramolecular cyclization of malonic acid allylic esters **1** (general method)

To a stirred mixture of hydrotalcite (0.5 g), iodine (0.57 g), one drop of TCMC (Aliquat® 336, tri-caprylmethyl ammonium chloride, in some cases) in toluene (10 ml), ester **1** (1 mmol) in toluene (2 ml) was added dropwise at 393 K (bath temperature). Then the mixture was stirred until the complete consumption of the ester, which was checked by TLC (Merck Kieselgel 60 F₂₅₄ plate, eluent: hexane:acetone 4:1, typical reaction time 4 h). The mixture was cooled, the solid filtered off, the filtrate was washed with aqueous sodium thiosulfate solution and with water, dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was analyzed by ¹H NMR spectroscopy. In the factorial design the amount of the base and the iodine as well as the reaction temperature was varied. The diastereomeric composition of the products was determined also by ¹H

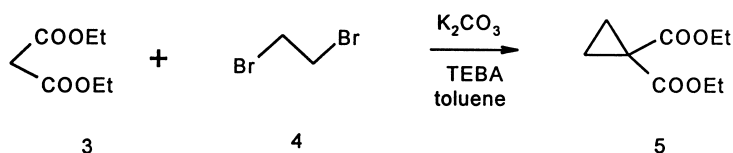


Fig. 2.

NMR spectroscopy according to the method described [11].

2.3. Reaction of cyclopropanedicarboxylic acid diethyl ester with 1,2-dibromoethane

A mixture of malonic ester (1.6 g, 0.01 mol), 1,2-dibromoethane (4 g, 0.021 mol), hydrotalcite (2 g) and iodine (0.3 g) in toluene (10 ml) was stirred at 373 K for 10 h. Then the solid was filtered out, the filtrate was washed with sodium thiosulfate solution and with water, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The residue was distilled, bp 383 K/20 mmHg (lit. 384–388 K/20 mmHg [12]). ^1H NMR data are identical with those reported in [13].

3. Results and discussion

3.1. Catalytic effect of hydrotalcite in the intramolecular reaction

The intramolecular cyclization of malonic acid allylic esters **1** required 2 moles of solid potassium carbonate, 2 moles of iodine for the good conversion. The quaternary ammonium salt frequently used was Aliquat® 336 (TCMC). Recent experiments showed that weaker solid bases such as hydrocarbonates were insufficient in this reaction. Stronger bases e.g. solid potassium *t*-butoxide or sodium methylate as well as bases in homogeneous phase (pyridine, DBU, sodium methylate in DMSO) failed to produce any product, only decomposition of the starting ester were observed in some cases [9].

Replacing potassium carbonate with HT we could observe that HT showed excellent activity under the reaction conditions used. Although hydrotalcites are known to diminish their activity in the presence of halogens, in this case the great amount of iodine in the reaction mixture did not cause any decrease in the reaction rate. The products were obtained in good to excellent yield in a fast reaction. Surprisingly, there was no significant change in the yield when the phase transfer catalyst was omitted from the reaction mixture. It seems that the special lamellar structure of HT is sufficient and suitable for the deprotonation

of the malonic acid methylene group, which is the first step of the reaction. The anion thus formed can stay between the layers where the conditions are suitable for the further reaction steps. This is supported by the fact that the HT structure was necessary because solid MgO, Al₂O₃ or the physical mixture of both did not result in any reaction.

3.2. Determination of the optimal reaction conditions

A 2⁴ factorial design [14] was performed to determine the optimal reaction conditions. This involved 16 experiments at the points of the hypercube plus two central points. The reaction chosen for this examination is represented in Fig. 3.

In this case, both the starting ester **1a** and the product **2a** have simple ^1H NMR spectra. Thus, the progress in the conversion can be followed easily by the spectra of the reaction mixture. The signals used for the determination were: the singlet of the methylene CH₂ at 3.46 ppm for **1a**, and the singlet of the proton at the annelation point at 2.83 ppm for **2a**. The parameters examined were: the amount of the iodine, the amount of HT, the reaction temperature and use of phase transfer catalyst. The design is presented in Table 1. The four factors were chosen as: z_{I_2} , the amount of iodine (mmol) calculated to 1 mmol of starting ester **1a**; z_B , the amount of HT (mg) calculated to 1 mmol of **1a**; z_T , the reaction temperature (bath temperature, K); z_{Cat} , the presence of the phase transfer catalyst (yes/no).

The calculation of the main effects and the two-way and three-way interactions was performed by the software STATISTICA for Windows [15]. The degrees of freedom for the test of significance were 2, one from the two repetitions at the center and one from the neglected 1*2*3*4 interaction. The supposed linear model was adequate (curvature was not

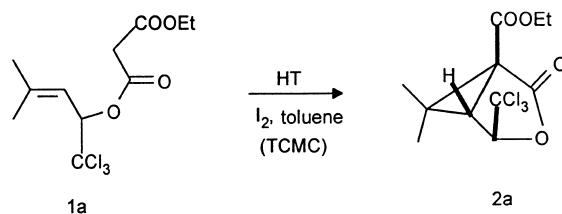


Fig. 3.

Table 1
Parameter settings of the 2^4 factorial design

<i>i</i>	Natural units				Coded factor levels				Conversion (%)
	z_{I_2}	z_B	z_T	$z_{Cat.}$	x_{I_2}	x_B	x_T	$x_{Cat.}$	<i>y</i>
1	1.75	0.30	353	No	-1	-1	-1	-1	75.8
2	2.25	0.30	353	No	1	-1	-1	-1	80.0
3	1.75	0.50	353	No	-1	1	-1	-1	95.0
4	2.25	0.50	353	No	1	1	-1	-1	84.0
5	1.75	0.30	393	No	-1	-1	1	-1	62.8
6	2.25	0.30	393	No	1	-1	1	-1	62.0
7	1.75	0.50	393	No	-1	1	1	-1	90.4
8	2.25	0.50	393	No	1	1	1	-1	95.0
9	1.75	0.30	353	Yes	-1	-1	-1	1	31.5
10	2.25	0.30	353	Yes	1	-1	-1	1	48.6
11	1.75	0.50	353	Yes	-1	1	-1	1	75.6
12	2.25	0.50	353	Yes	1	1	-1	1	81.0
13	1.75	0.30	393	Yes	-1	-1	1	1	65.6
14	2.25	0.30	393	Yes	1	-1	1	1	59.5
15	1.75	0.50	393	Yes	-1	1	1	1	95.0
16	2.25	0.50	393	Yes	1	1	1	1	93.5
17	2.00	0.40	373	Yes	0	0	0	1	72.6
18	2.00	0.40	373	Yes	0	0	0	1	69.7

significant) and the response surface with the significant parameters can be written as follows:

$$y = 74.7 + 14.0x_B + 3.3x_T - 5.9x_{Cat.} + 3.5x_B x_{Cat.} + 6.3x_T x_{Cat.} + 2.3x_{I_2} x_B x_T - 2.5x_{I_2} x_T x_{Cat.} - 3.2x_B x_T x_{Cat.}$$

Beyond the mathematical expression, this model gives the following information.

- The amount of the iodine does not influence the chemical yield, a very good conversion can be achieved with equimolar amount of iodine, too, while the reaction with potassium carbonate required 2 mol of iodine.
- The amount of the base is the key factor which is recommendable to be high, good conversion is achieved with 0.50 g mmol starting ester.
- Higher conversion can be achieved at higher temperature (at 393 K) but there is a strong interaction between the temperature and the presence of the catalyst. High temperature is more advantageous if phase transfer catalyst (PTC) is present, while without PTC the lower temperature gives higher conversion. If the substrate is sensitive to the high

temperature, high conversion can be also achieved at 353 K but without phase transfer catalyst.

- The two- and three-way interactions are mainly canceled out, except the 3×4 interaction which suggests the choice either of higher temperature with PTC or lower temperature without PTC.

The dependence between the yield of the reaction and the reaction temperature in the presence or absence of PTC is well demonstrated in Fig. 4.

Fig. 4 shows that in the presence of PTC (left diagram) on a given level of the base the conversion depends strongly on the reaction temperature and increased with increasing temperature, while in the absence of PTC this dependence is small (right diagram).

The goodness of this model is verified by the examination of two sets of parameter setting out of the area of the plain. The first setting is $x_{I_2} = -4$, $x_B = 1$, $x_T = 1$ and $x_{Cat.} = -1$, the calculated conversion from these parameters is 65%, while the observed one is 72%. The other setting is $x_{I_2} = -2$, $x_B = 1$, $x_T = 1$ and $x_{Cat.} = 1$; calculated conversion is 87%, observed 94%. Taking into account the

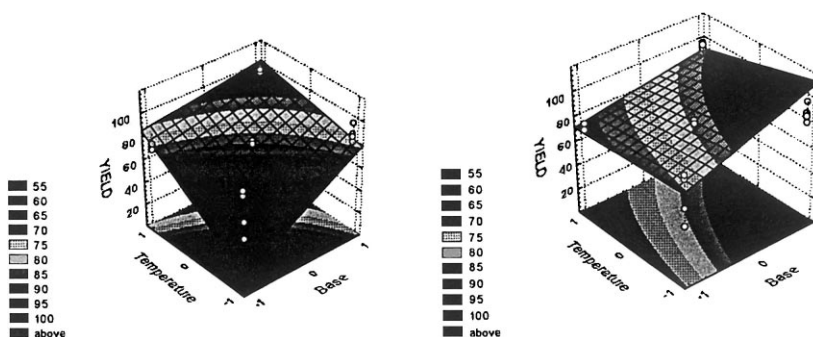


Fig. 4.

accuracy of a NMR measuring in both cases the theoretical and the calculated values are in good agreement.

This model and its conclusions refer to the reaction **1a** → **2a** but taking into account that the mechanism of the cyclization of other related compounds can be considered the same these results can be accepted as general conclusions of this type of reaction. Based on this statement one can state the following: hydrotalcite is a suitable basic catalyst for the intramolecular cyclization reaction of malonic acid allylic esters in the presence of iodine. better than potassium carbonate, and using hydrotalcite the amount of iodine required for the conversion of 90% or higher can be reduced significantly. In addition, there is no need for the presence of phase transfer catalyst.

3.3. Effect of hydrotalcite on the diastereoselectivity of the cyclization

The intramolecular cyclization reaction of esters **1** is diastereoselective, the two rings are always *cis*-

fused and the R_3 group is exclusively in the *exo* position (see Fig. 5). If R_1 and R_2 are different, a new chiral carbon atom appears at the cyclopropane C(2) position. Recently it was shown that in these cases two diastereomers were formed and their ratio depended on the nature of the R_1 , R_2 and R_3 groups, and the reaction temperature [11].

We examined the effect of hydrotalcite on the diastereoselectivity of the cyclization of cinnamyl derivatives **1b-d** (Fig. 5). The reactions were carried out at 393 K with the optimal HT–ester ratio obtained in the factorial design. Surprisingly, there was a significant difference in the diastereoselective composition of the product obtained in the reaction with or without phase transfer catalyst. The results are summarized in Table 2.

When phase transfer catalyst was present the results obtained were similar to those we had obtained earlier in the reaction with solid potassium carbonate [11]. In the absence of phase transfer catalyst the amount of the *exo* isomer increased in all the three cases examined. The extent of this increase depended on the size of the R_3 substituent, a considerable

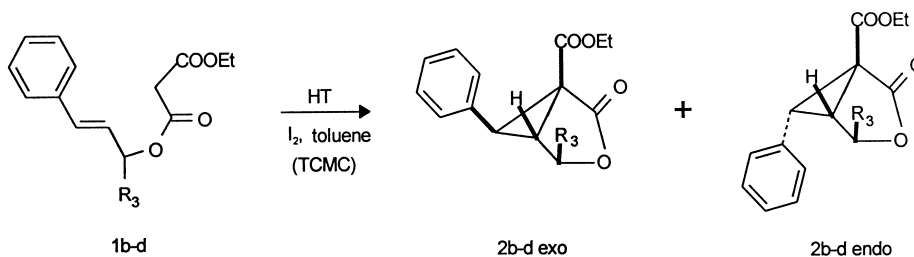


Fig. 5.

Table 2
Diastereomeric composition of the bicyclic cyclopropanes **2b-d**^a

Conditions	Exo:endo ratio		
	2b (R ₃ = H)	2c (R ₃ = CH ₃)	(R ₃ = C ₆ H ₅)
Reaction in the presence of K ₂ CO ₃ ^b	60:40	62:38	65:35
Reaction in the presence of HT with PTC	62:38	63:37	64:36
Reaction in the presence of HT without PTC	80:20	70:30	72:28

^a Determined by ¹H NMR according to [11].

^b Data taken from [11].

effect was observed in case of hydrogen, while this effect was small but appreciable in case of the methyl or phenyl group. As both potassium carbonate and HT gave the same result in the presence of PTC, but HT produced increasing in the amount of the exo isomer in the products obtained in the presence or absence of PTC, one can conclude that the effect of HT is more than using another base in the reaction. A possible interpretation of its effect can be the following; in the presence of PTC the catalyst facilitates moving the intermediate deprotonated malonic ester anion [11] away from the surface of the base, thus the further reaction steps can occur in the solvent phase where the 'normal' stereochemical control operates. Whereas without PTC the reaction occurs between the layers of the hydrotalcite, where the rotation of the different parts of the intermediate is hindered so the formation of the sterically more favorable exo isomer would be the dominant.

3.4. Reaction of diethyl malonate and 1,2-dibromoethane in the presence of HT

The reaction of diethyl malonate with 1,2-dibromoethane in the presence of solid potassium carbonate and TEBA as phase transfer catalyst in toluene resulted in the cyclopropane dicarboxylic acid ester **5** in good yield. When potassium carbonate was replaced by HT surprisingly there was no reaction observed. Addition of 10 mol% of iodine to the reaction mixture resulted in the formation of the desired ester **5** in 87% yield. From the ¹H NMR spectra some amount of the bromoethyl-substituted malonic ester could also be detected. Upon replacing dibromoethane by 1,2-dichloroethane a dramatic decrease in the yield was observed. The addition of anhydrous sodium iodide instead of the iodine was

also unsuccessful. This suggests that the role of the iodine is not only a simple halogen exchange, probably, similar to the intramolecular reaction, the cyclization occurs via the iodomalonic ester intermediate. Verifying this hypothesis, we reacted diethyl malonate with iodine in the presence of HT according to the method described in [16] for potassium carbonate. We could isolate the expected diethyl iodomalonate from the reaction mixture in good yield.

4. Conclusion

The thermally non-activated Mg-Al 3:1 hydrotalcite is a suitable and efficient basic catalyst for the intra- and intermolecular cyclization of malonic acid derivatives and olefins into cyclopropane carboxylic acid derivatives. Compared to the reaction in the presence of solid potassium carbonate the intramolecular cyclization required less amount of iodine for a good conversion. Also good conversion was observed in the absence of phase transfer catalyst, too. In one case the diastereoselectivity of the reaction was considerably changed. The large amount of iodine did not influence the catalytic properties of hydrotalcite. Even the intermolecular cyclization failed to produce any cyclopropane in the absence of iodine.

Acknowledgements

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