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New Journal of Chemistry RSCPublishing

ARTICLE

# One Pot domino reaction accessing γ-nitroesters. Synthesis of GABA derivatives.

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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Michael addition of 1,3-dicarbonyl compounds to nitrostyrenes are efficiently promoted by hydrotalcite [Mg-Al] to afford the respective γ-nitrodicarbonyl adducts. Differently, the addition of Meldrum's acid leads to a direct access of γ-nitroesters through a *one pot* domino process. GABA derivatives (+/-)-Phenibut and (+/-)-Baclofen were readily synthesized from the respective nitro adducts.

## 1. Introduction

Layered double hydroxides (LDHs), also known as hydrotalcite-like materials (HT), are a class of anionic clays that are structurally similar to mineral brucite $[Mg(OH)_2]$.[1-4] Some of divalent cations of structure can be replaced by a trivalent ones, resulting in positively charged sheets. This charge is balanced by intercalation of anions into the hydrated interlayer spaces. Thus, magnesium is octahedrally surrounded by six oxygen atoms in hydroxide form, and the octahedral units form an infinite number of sheets by sharing their edges and stacking on top of next sheet.[5-7] The most common divalent metal cations found in HTs are $Mg^{2+}$, $Fe^{2+}$, $Co^{2+}$, $Cu^{2+}$, $Ni^{2+}$, or $Zn^{2+}$ while the trivalent metal cations are typically $Al^{3+}$, $Cr^{3+}$, $Ga^{3+}$, $Mn^{3+}$ or $Fe^{3+}$. Due to this, a number of HTs with different structures and phisicochemical properties can be prepared.[8]

In recent years, much attention has been given to the preparation LDHs with different properties, thus increasing the interest in several areas of industry and scientific research.[9-12] For example, LDHs are used to prevent thermal degradation of PVC polymers[13] or as stabilizing agents of pigments against UV and/or oxygen degradations.[14] In the human health field,[15] the interest on LDH has focused on intercalation of organic molecules into the interlayer spaces.[16] This strategy allowed the use of these materials successfully as delivery carriers for drugs in treatment of diverse diseases.[17]

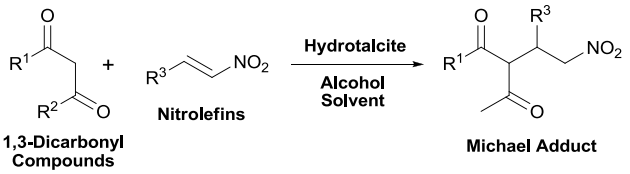
On the other hand, hydrotalcites have been used as solid base catalyst in several organic reactions.[18-20] Although hydrotalcites can be directly used as-synthesized, their application as mixed oxides after calcination[21] or reconstructed form by calcination-hydration (memory effect) process,[22] has resulted in wide use of basic properties of his material.[23]
The use as solid base catalyst includes aldol reactions,[24] Knoevenagel condensations,[25] transesterification reactions,[26] biodiesel production,[27] Baeyer-Villiger oxidations,[28] oxidation of benzyl halides,[29] Friedel-Crafts raction,[30] alkylation of diketones,[31] and epoxidation of olefins.[32] Benzoin condensation,[33] Claisen-Schmidt condensation,[34] hydrosilylation of ketones,[35] Diels-Alder reaction,[36] [3+2] cyclisation,[37] and arylation of amines[38] were carried out successfully under hydrotalcite catalysis. The reactions based on hydrotalcite-Pd hybrids catalysts were also reported in Heck, Suzuki, Sonogashira, and Stille-type couplings.[39-41]

The first example of hydrotalcite-catalysed Michael addition was reported by Choudary and co-workers in 1999.[42] The authors demonstrated the ability of HT[Mg-Al] to promote a selective 1,4-addition of nitroalkanes, malononitriles, diethylmalonates, cyanoacetamides, and thiols to α,β-unsaturated ketones and esters.[43,44] Additionally, terpenoid substrates were also studied as Michael acceptors and served to prepare new derivatives in reactions with malononitriles.[45]

HT supported organic molecules, such as diisopropylamine[46] or the L-proline,[47] were also successfully used for C-C bond formation in Michael adducts. In this last case, optical active derivatives were obtained, but in low enantiomeric excess. Additionally, a synergistic effect was observed on the catalytic performance of HT doped with hydrous Tin IV oxide (HT[Mg-Al-Sn]) in the preparation of 4H-chromenes.[48] It is well established that the basic properties of calcined HTs are increased due to the presence of highly basic mixed oxides. In this context, Kemnitz performed a detailed study on the use of calcined HT[Mg-Al] in Michael addition of 1,3-diketones and β-ketoesters to methyl vinyl ketone, reforcing a superior activity of the calcined material.[49,50] The pyrazolo[1,5-α]pyrimidines are readily accessed through the aza-Michael addition of 5-aminopyrazoles to enaminones. In this case, the authors noted that the HT[Mg-Al] catalyst was superior for the aza-Michael reaction. The high performance of this catalyst was attributed to the co-operative contribution of its acidic and basic sites.[51] Michael 1,4-addition reactions promoted by

HT[Mg-Al] under microwave irradiation,[52] solvent-free[53] conditions, or both[54] were reported as an efficient eco-friendly alternative to the usually used conditions.

As a part of our ongoing research on the synthesis of biologically active molecules of low molecular weight,[55] the goal of the present work was to study the feasibility of using HTs as heterogeneous basic catalysts in the synthesis of γ-nitro dicarbonyl compounds based on Michael-type addition of 1,3-diketones, β-ketoesters and alkyl malonates to β-aryl nitroolefins (Scheme 1).




**Scheme 1.** Synthesis of γ-nitro-dicarbonyl compounds.

## 2. Results and discussion

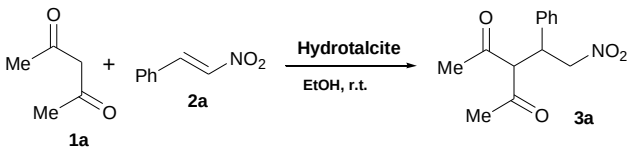
### *2.1 Synthesis of catalyst*

The synthesis of hydrotalcites (HT[Mg-Al]) used as catalyst in this work were performed as ascribed in current literature.[56] The solid was dried in an oven at 100 °C for 6 h. The XRD pattern was compatible with the formation of pure hydrotalcite. A part of this material was submitted to calcination at 600 ºC for 5 h. The XRD pattern, at this time, was compatible with the formation of mixed Mg-Al oxides, called here as $HT_{calc}$.

### *2.2 The catalyst loading*

The investigation about optimum amount of catalyst was made performing the Michael-type addition of acetylacetone (**1a**, 1.1 mmol) to nitrostyrene (**2a**, 1.0 mmol) using different amounts of HT at room temperature in EtOH (2 ml) as the solvent. The results are shown in Table 1.
The first experiment was carried out in absence of the catalyst, for 48 hours and did not lead to isolation of any product (Table 1, entry 1).

**Table 1.** Screening of hydrotalcite catalyst load




| Entry | Hydrotalcite (mg) | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | - | 48 | - |
| 2 | 50 | 12 | 35 |
| 3 | 50 | 24 | 70 |
| 4 | 50 | 48 | 95 |
| 5 | 100 | 8 | 95 |
| 6 | 200 | 8 | 50 |
| 7 | 300 | 8 | 35 |
| 8 | 500 | 8 | 35 |
| 9 | 50[a] | 8 | 97 |
| 10 | 50[a] | 6 | 95 |

[a]Calcined hydrotalcite at 600 ºC, 5 hours.

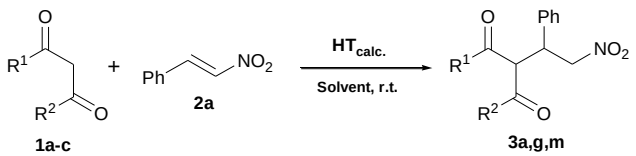
The reaction carried out with 50 mg of catalyst, for 12 hours, afforded the adduct **3a** in 35% yield, thus showing the dependence of catalyst (entry 2). The reaction time also was shown to be important since reactions carried out for 24 and 48 hours at room temperature showed better yields (entries 3 and 4, respectively). The increase of catalyst amount to 100 mg or 200 mg led to superior yields of **3a** (entries 5 and 6, respectively). On the other hand, a decrease of yields was observed with 300 mg or 500 mg of catalyst (entries 7 and 8, respectively). This was attributed to a possible degradation of **5a** in presence of excess of catalyst.

As the basic properties of hydrotalcites are increased by calcination, we investigated the use of calcined HT ($HT_{calc}$) as catalyst. Two experiments were performed employing 50 mg of $HT_{calc}$. In both experiments, high yields of **3a** were observed (entries 9 and 10, respectively) even in a reduced reaction time of 6 hours, confirming the superior activity of the calcined material.

### *2.3 Effect of different solvents*

Once defined the best catalyst and the best loading, best loading, we investigated the reaction profile in different solvents. Although we have performed preliminary studies in EtOH we tried to use non-protic polar solvents such as $CH_2Cl_2$, THF or $CH_3CN$, as well as the non-polar solvent $PhCH_3$. For these reactions of 1,3-dicarbonyl **1a,b,c** (1.1 mmol) and nitrostyrene (1.0 mmol) was used 50 mg of $HT_{calc}$, in 2 ml of indicate solvent at room temperature. The results are shown in Table 2.

**Table 2.** Michael-type addition under different solvents.




| Ent. | 1,3-Dycarbonil Compounds | | Solvent | Time (h) | Adduct 3 | Yield (%) |
|---|---|---|---|---|---|---|
| | R1 | R2 | | | | |
| 1 | Me | Me | $PhCH_3$ | 48 | **3a** | 43 |
| 2 | Me | Me | THF | 24 | **3a** | 75 |
| 3 | Me | Me | $CH_2Cl_2$ | 24 | **3a** | 82 |
| 4 | Me | Me | $CH_3CN$ | 6 | **3a** | 90 |
| 5 | Me | Me | EtOH | 6 | **3a** | 95 |
| 6 | Me | Me | *i*PrOH | 6 | **3a** | 96 |
| 7 | Me | OEt | THF | 24 | **3g** | 68 |
| 8 | Me | OEt | $CH_2Cl_2$ | 24 | **3g** | 80 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 9 | Me | OEt | $CH_3CN$ | 24 | **3g** | 84 |
| 10 | Me | OEt | EtOH | 6 | **3g** | 91 |
| 11 | Me | OEt | *i*PrOH | 6 | **3g** | 73 |
| 12 | OEt | OEt | EtOH | 48 | **3m** | 32 |
| 13 | OEt | OEt | *i*PrOH | 48 | **3m** | 30 |
| 14 | OEt | OEt | EtOH | 12 | **3m** | 88[a] |

[a] Reaction performed at refluxing conditions.

The reactions performed in $PhCH_3$ afforded γ-nitro carbonyl **3a** in 43% yield after 48 hours (Table 2, entry 1). Next, the polar solvents $CH_2Cl_2$, THF and $CH_3CN$ were investigated. In all cases, the adduct **3a** was obtained in reasonable to good yields, up to 75% yield (entries 2, 3 and 4, respectively). We rationalized this influence based on the Dielectric Constant (εr). The best result was achieved using the $CH_3CN$ (εr= 37.5, entry 4) which has the largest value of Dielectric Constant. Lower yields were observed in THF (εr= 7.5) and $CH_2Cl_2$ (εr= 9.1, entries 2, and 3, respectively). Also, reaction times were greater than those carried out in $CH_3CN$. The reactions carried out in $^i$PrOH (εr= 18) showed similar results to EtOH (εr= 24.5, entries 5 and 6, respectively). We believe that the ability of the alcoholic solvents to form hydrogen bonding could activate the reagents accelerating the reaction.

The reactions of β-ketoester **1b** performed in non-protic solvents needed 24 hours (entries 7, 8 and 9, respectively) while those performed in protic solvents were faster (entries 10 and 11, respectively). The EtOH showed to be a superior solvent for these reactions. The adduct **3f** is not symmetric therefore, a mixture of isomers ***syn*-3f** and ***anti*-3f** was produced. The diastereomeric 1:1.2 ratio was determined by relative integrals of methyl hydrogens at $\delta$ 2.30 ppm (major) and $\delta$ 2.05 ppm (minor) in $^1$H-NMR spectrum and was confirmed by Gas Chromatography. The relative configuration of the major diastereomer was not determined (Figure 1).

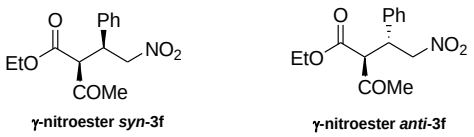


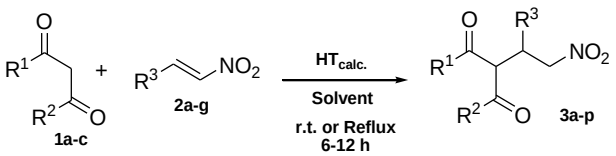

**Figure 1**. Diastereomeric mixture of compound **3f**

The attempt to proceed the reaction with ethyl malonate (**1c**) to nitrostyrene (**2a**) at room temperature proved to be ineffective. Even after longer reaction times, adduct **3m** was produced in low yields (c.a. 30%, entries 12 and 13). New experiments carried out in EtOH under reflux conditions for 12 hours afforded the adduct **3m** in 88% yield. The lower reactivity seems to be associated to the lower acidity of the α-carbonyl hydrogens of malonates. Therefore, the use of reflux conditions might favour the keto/enol equilibrium increasing the nucleophilic of these species.

Once established the best conditions, 1,3-dicarbonyl compounds **1a,b,c** were reacted with different nitroolefins **2a-h** (Table 3). The mixture of 3a with nitroolefin 4b was not totally soluble in EtOH (2.0 ml) and therefore an additional quantity of $CH_3CN$ (0.5 mL) was used to allow the formation of a homogeneous solution (Table 3, entry 2). The nitroolefins **2c-e** showed a similar behavior, requiring the use of a mixture of 2.0 mL of EtOH and 0.5, mL of $CH_3CN$ as solvents of the reaction (entries 3, 4 and 5, respectively). At this new condition was necessary 12 hours of stirring at room temperature to the consumption of starting material (monitored by TLC, entry 2).

The reaction of β-ketoester **1b** with nitroolefins **2a,f,g** in EtOH after 6 hours afforded a mixture of near of 1:1 ratio of two possible diatereoisomers in good yields (entries 6, 7 and 8, respectively). On the other hand, for the reactions with nitroolefins **2c-e**, a mixture of 4:1 EtOH/$CH_3CN$ was used to permit a homogeneous solution. After 12 hours of stirring, the γ-nitroesters **3i-k** were produced in good yields (entries 9, 10 and 11, respectively). The reaction of ethyl malonate (**1c**) with the nitroolefins **2a-d,g** was performed under reflux in EtOH by 12 hours. Although the nitroolefins **2b-d** were poorly soluble in EtOH, the reflux condition turns the reaction mixture clear without needing to use $CH_3CN$ as co-solvent. The Michael adducts **3l-p** were obtained in reasonable to good yields after purification (entries 12-16, respectively).

**Table 3.** Synthesis of γ-nitroesters promoted by calcined hydrotalcite




| Entry | Dicarbonyl | | Nitroolefin | Temperature (°C) | Solvent | Time (h) | Adduct 3 | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | | | | | |
| 1 | Me | Me | $C_6H_5$ | R.T. | EtOH | 6 | **3a** | 95 |
| 2 | Me | Me | 3,4-$(MeO)_2C_6H_3$ | R.T. | EtOH/$CH_3CN$[a] | 12 | **3b** | 75 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3 | Me | Me | 4-F-$C_6H_4$ | R.T. | EtOH/$CH_3CN$[a] | 12 | **3c** | 91 |
| 4 | Me | Me | 4-Cl-$C_6H_4$ | R.T. | EtOH/$CH_3CN$[a] | 12 | **3d** | 88 |
| 5 | Me | Me | 4-Br-$C_6H_4$ | R.T. | EtOH/$CH_3CN$[a] | 12 | **3e** | 90 |
| 6 | Me | OEt | $C_6H_5$ | R.T. | EtOH | 6 | **3f** | 91 |
| 7 | Me | OEt | 4-MeO-$C_6H_4$ | R.T. | EtOH | 6 | **3g** | 85 |
| 8 | Me | OEt | 2-thieny | R.T. | EtOH | 6 | **3h** | 80 |
| 9 | Me | OEt | 4-F-$C_6H_4$ | R.T. | EtOH/$CH_3CN$[a] | 12 | **3i** | 70 |
| 10 | Me | OEt | 4-Cl-$C_6H_4$ | R.T. | EtOH/$CH_3CN$[a] | 12 | **3j** | 70 |
| 11 | Me | OEt | 4-Br-$C_6H_4$ | R.T. | EtOH/$CH_3CN$[a] | 12 | **3k** | 85 |
| 12 | OEt | OEt | $C_6H_5$ | Reflux | EtOH | 12 | **3l** | 88 |
| 13 | OEt | OEt | 3,4-$(MeO)_2C_6H_3$ | Reflux | EtOH | 12 | **3m** | 66 |
| 14 | OEt | OEt | 2-thienyl | Reflux | EtOH | 12 | **3n** | 60 |
| 15 | OEt | OEt | 4-F-$C_6H_4$ | Reflux | EtOH | 12 | **3o** | 60 |
| 16 | OEt | OEt | 4-Cl-$C_6H_4$ | Reflux | EtOH | 12 | **3p** | 80 |

a 4:1 ratio EtOH/$CH_3CN$ (V:V) was used.

### *2.4 A rationale for the bifunctional hydrotalcite catalysis*

The dual acid/base property of HT was earlier reported by various authors.[57-59] Figueras concluded that the high activity of calcined nitroesters probably comes from the synergistic effect of strong Lewis basicity of the oxygen atom of the mixed metal oxide and mild acidity exhibited by the metal centers.[60]

Based on these previous information we envisaged a model where the basic sites on the oxygen atoms can deprotonate the acidic α–hydrogen of 1,3-dicarbonyl compound while the oxygen atom (Lewis basic sites) of both reagents can coordinate to the Lewis acidic sites on the metals (Figure 2, A). The enolate species adds via Michael-type reaction to the activated nitroolefin (Figure 2, B) to afford the desired product γ-nitroester **3**. This mechanism is in agreement with that proposed early by Ivanov based on in situ IR experiments.[6]

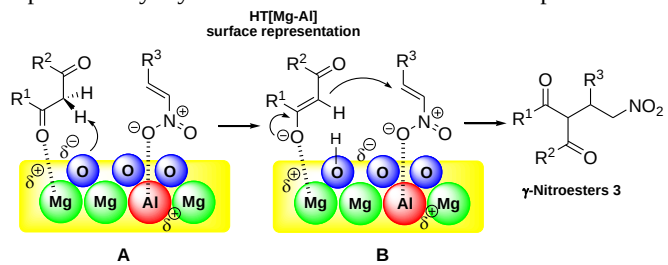
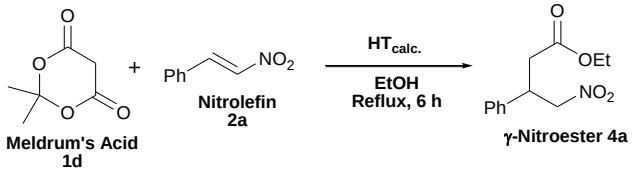



**Figure 2.** Representation of Bifunctional acid/basic catalysis of Hydrotalcites

### *2.5 Addition of Meldrum's acid to nitrostyrenes*

As demonstrated in the previous section, the need of refluxing EtOH in reactions of diethyl malonates (**1c**) could be a consequence of lower acidity of the α–hydrogen (pKa 16.4). We consider the use of Meldrum's acid (**1d**), a cyclic equivalent of **1c**, which is more acid than malonate (pKa 7.3 in DMSO).[62] The first attempt involved the reaction between the Meldrum's acid (**1d**) and nitrostyrene (**2a**) in EtOH at room temperature. The monitoring of the reaction course showed the consumption of the nitrostyrene in about 6 hours. However, a complex mixture of products was observed by $^1$H-NMR analysis. Experiment carried out the in $^i$PrOH furnished similar results. The formation of the complex mixture was attributed to alcoholysis of adduct Meldrum-nitrostyrene initially formed (not isolated). Substitution of alcoholic solvent by dichloromethane permitted the observation of desired adduct in very low yield, c.a. 30 % ($^1$H-NMR analysis). Reflux conditions in EtOH for 6 hours were tested. After carefully purification of the crude mixture in column chromatography was possible to isolate a product which was characterized by spectroscopic methods as being the γ-nitroester **4a** which was isolated in 35% yield (Scheme 2).

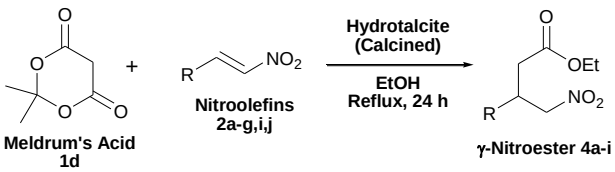



**Scheme 2.** Michael reaction of Meldrum's acid and nitroolefin

The $^{1}$H-NMR spectrum showed a set of signals as a triplet (δ 1.16 ppm, 3H, *J*=7.0 Hz) and a quartet (δ 4.07 ppm, 2H, *J*=7.0 Hz) which were assigned as ethoxy group. The α-carbonyl hydrogens appeared as a doublet at δ 2.75 ppm (2H, *J*=7.6 Hz) and the multiplet around δ 4.00 ppm (m, 1H), was assigned as being the benzylic hydrogen. The two double doublets at δ 4.63 ppm (1H, *J*=12.3 and *J*=7.6 Hz) and δ 4.73 ppm (1H, *J*=12.3 and *J*=7.0 Hz), respectively, were interpreted as the diastereotopic hydrogens attached to the carbon direct bonded to the nitro group. Finally a multiplet in the region between δ 7.20-7.30 ppm with relative integral of 5H was assigned as aromatic hydrogens of the phenyl group. The $^{13}$C-NMR spectrum showed five signals between δ 14.0-80.0 ppm were correlated to the aliphatic carbons. In the aromatic region, were identified four signals between δ 129.0 ppm and 138.2 ppm related to phenyl group. The signal at δ 170.5 ppm was assigned as the C=O carbon of the ester function. A strong absorption sign at δ 1723 cm$^{-1}$ was evidence to an ester carbonyl group.

Due to the low yield achieved in the initial conditions we performed the same reaction under reflux, increasing the time to 24 hours. After isolation of crude mixture and purification by column chromatography, the γ-nitroester **4a** was isolated in 89% yield. To verify the reproducibility, the methodology was extended to a series of reactions between Meldrum's acid (**1d 3d**) and seven other nitroolefins **2b-g,i,j**. The γ-nitroesters **4a-i** were isolated through a simple filtration to remove the hydrotalcite and subsequent purification by column chromatography afforded the products in good yields (85-95%). The results are reported in Table 4.

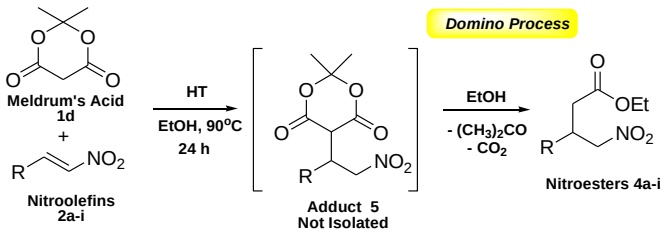
**Table 4.** Direct synthesis of γ-nitro monoesters **4a-i**




| Entry | Nitroolefin R | γ-Nitroester | Yield (%) |
|---|---|---|---|
| 1 | $C_6H_5$ | **4a** | 89 |
| 2 | 3,4-(MeO)$_2$-$C_6H_3$ | **4b** | 82 |
| 3 | 4-F-$C_6H_4$ | **4c** | 96 |
| 4 | 4-Cl-$C_6H_4$ | **4d** | 85 |
| 5 | 4-Br-$C_6H_4$ | **4e** | 88 |
| 6 | 4-(MeO)-$C_6H_4$ | **4f** | 89 |
| 7 | 2-Thienyl | **4g** | 85 |
| 8 | 3,4,5-(MeO)$_3$-$C_6H_2$ | **4h** | 95 |
| 9 | 4-CN-$C_6H_4$ | **4i** | 84 |

*2.6 Mechanistic considerations*

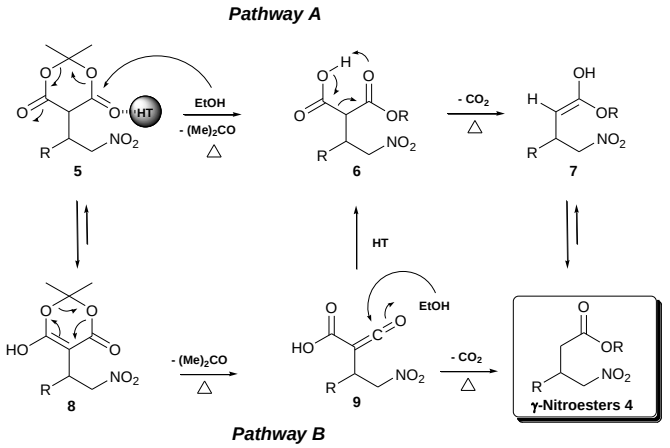
In opposite to the similar reactions of 1,3-dicarbonyl compounds (**1a-c**) and nitroolefins, the use of Meldum's acid (**1d**) did not lead to isolation of γ-nitro dicarbonyl compounds, instead the γ-nitro monoesters were obtained. We rationalized these results based on the low stability of the possible Michael adduct **5** (not isolated, Scheme 3).




**Scheme 3**. β-aryl-γ-nitroesters via domino process promoted by calcined Hydrotalcite

A tentative mechanistic pathway to understand the transformation of probable Michael adduct intermediate **5** into the γ-nitroesters **4** was considered. In the *pathway A*, the opening of the Meldrum's acid moiety with loss of acetone by a conventional partial transesterification in the presence of alcohol, would lead to formation of transient half-ester intermediate **6**. This event could be aided by the HT which would act as a Lewis acid catalyst. Then, the decarboxylation reaction takes place leading to the enol **7** which would equilibrate to the β-aryl-γ-nitroester **4** (Scheme 4).

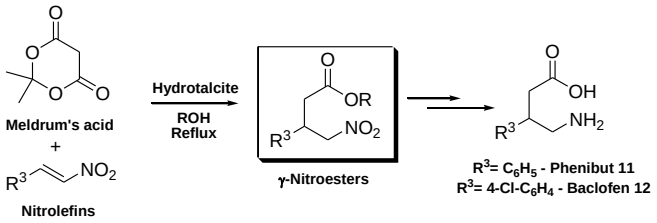
A second possibility - *pathway B* - consider the thermal degradation of intermediary **5** to the formation of ketene derivative **9**,[63] which could be captured by the alcohol also leading to the formation of the half-ester intermediate **7**. Whereas in the pathway A the process of decarboxylation is suggested as a result of a partial transesterification event, on the other hand in the pathway B, the loosing of $CO_2$ at high temperatures, involves the formation of ketene intermediate.




**Scheme 4**. Tentative mechanistic pathways to the trans-esterification/decarboxylation step.

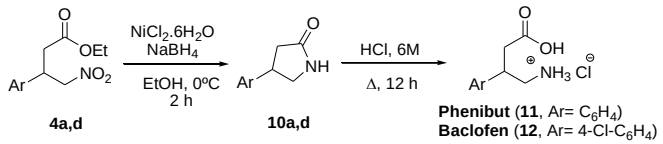
*2.7 Synthesis of (+/-)-Phenibut and (+/-)-Baclofen*

To ensure the utility of the method, the appropriate γ-nitroesters were quickly transformed in the GABA derivatives (+/-)-Phenibut (**11**) and (+/-)-Baclofen (**12**) by additional two steps leading to the products in good yields (Scheme 5).




**Scheme 5**. Synthetic route to Phenibut and Baclofen.

Several synthetic strategies reported for the synthesis of Fenibut (**11**) and Baclofen (**12**) converge to formation of γ-lactams as intermediate.[64-67] These heterocycles can be obtained by intramolecular acyl substitution from the respective γ–aminoesters, from the respective γ–nitroesters precursors. Various methods for the reduction of nitro compounds are described in the literature. Among them, we can consider the use of molecular hydrogen in the presence of nickel Raney,[68] ammonium formate as hydrogen source in the presence of Pd/C,[69] direct reduction with $NaBH_4/NiCl_2.6H_2O$ system,[70,71] and Zn in acidic media,[72] and $LiAlH_4$ as reducing agent.[73] The ammonium formate/Pd/C system had already been adopted in our research group to gain access to aminoindolines with simplicity and high yields.[74] In opposite, this methodology was not effective for the reduction of the γ-nitroester synthesized in this work. Alternatively, the use of $NaBH_4/NiCl_2.6H_2O$ system to reduce γ-nitroesters **4a,d**, according to procedures described in the literature (Scheme 6) was tested.[70] By this methodology, the γ-butyrolactams **10a,d** were isolated as brown oil, in good yields (82-87%).




**Scheme 6.** Synthesis of (+/-)-Baclofen and (+/-)-Phenibut.

The synthesis of γ-amino acids Phenibut (**11**) and Baclofen (1**2**) was achieved by acid hydrolysis of respective lactams without prior purification.[75] By this way, the GABA-derivatives were isolated in yields 88% and 89%, both in the chlorohydrate form.

## 3. Conclusions

In the present work, the use of Hydrotalcite-like compounds as heterogeneous catalyst was efficiently applied for the synthesis of 1,3-dicarbonyl-β-aryl-γ-nitroesters by Michael addition of 1,3-dicarbonyl compounds to nitroolefins in good yields (60-95%). In this process, HT appeared to act as a bifunctional catalyst, behaving as a Bronsted basic/Lewis acid.
Differently, the employment of Meldrum's acid as 1,3-dicarbonyl compound lead to monocarbonyl-γ–nitroesters by domino process involving decarboxylation and loss ketone by the solvent. By this methodology, these important intermediates to synthesis of GABA analogs were obtained in yields 84-96% in a single-step reaction under heterogeneous catalysis of calcined hidrotalcite. The synthesis of γ-nitroesters represent an alternative approach to synthesis of GABA derivatives, Phenibut (**1**) and Baclofen (**2**), which were prepared from the γ-nitroesters **6**a and **6d**, in 88% and 89% overall yield, respectively.

## 4. Experimental section

*4.1 General details*

All solvents for routine isolation of products and chromatography were reagent grade. Flash chromatography was performed using silica gel (230-400 mesh). All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (60F-254) visualizing with UV light or iodine. $^1$H NMR and $^{13}$C NMR spectra were recorded either on a 300 MHz; 75 MHz or 400 MHz; 100 MHz spectrometers, respectively. Chemical shifts (δ) are reported in ppm relative to TMS (tetramethylsilane). The multiplicity of signals is expressed as *s* (singlet); *d* (doublet); *dd* (double doublet); *t* (triplet); *q* (quartet) and *m* (multiplet) and the coupling constant $^3J$ expressed in hertz (Hz). IR spectra were recorded on a Varian 640-IR spectrometer and are expressed in $cm^{-1}$ in the range of 4000-400 $cm^{-1}$. Melting points were measured on Olympus BX41 microscopy equipped with Mettler-Toledo FP82HT hotplate. The MS system used was a quadrupole time-of-flight instrument (UltrOTOF-Q, Bruker Daltonics, Billerica, MA, U.S.A), equipped with an ESI positive ion source. The analyses were performed with the mass spectrometer in full scan mode. The following settings were applied throughout the analyses: capillary voltage 3.900 V; dry gas temperature 150 °C; dry gas flow 4 $Lh^{-1}$; nebulizer gas nitrogen.

*4.2 Synthesis of catalyst*
The hydrotalcite (HT, Mg/Al ratio 3:1) catalyst was synthesized as follows: in an aqueous solution (50 mL) containing $Mg(NO_3)_2.6H_2O$ (0.09 mol) and $Al(NO_3)_3.9H_2O$ (0.03 mol) was added slowly (2 h) to a second solution (100 mL) containing $NaHCO_3$ (0.25 mol) under vigorous stirring at 80 °C, remaining the stirring for 2 h at same temperature. The precipitate formed was filtered and washed with deionized water until the pH of the filtrate was 7. The solid was dried in an oven at 600 °C for 6 h. The XRD pattern shows the presence of pure hydrotalcite, with lattice parameters corresponding to those reported in the literature.[56]

*4.3 Synthesis of γ-nitroesters **3a-k***
A mixture of 1,3-dicarbonyl compound **1a,b** (1 mmol), nitrostyrene **2a-i** (1.1 mmol) and hydrotalcite (50 mg) in ethanol (2 mL) was stirred at room temperature for 6 h. The reaction mixture was filtered through celite and the solvent evaporated in vacuum to give the crude product, which was purified by column chromatography (hexane/EtOAc) to give the compounds **3a-k**.

*4.3.1 3-(2-nitro-1-phenylethyl)pentane-2,4-dione (**3a**):*[76] Pale yellow solid; yield 95%; m.p. 110-112 ºC; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.37-7.27 (m, 3H), 7.20-7.17 (m, 2H), 4.65-4.62 (m, 2H), 4.40-4.21 (m, 2H), 2.30 (s, 3H), 1.94 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 201.7, 200.9, 135.9, 129.3, 128.5, 127.9, 78.1, 70.7, 42.7, 30.4, 29.5; IR $\nu_{max}$ (ATR): 3008, 2961, 2915, 2853, 1730, 1700, 1541, 1494, 1457, 1438, 1409, 1357, 1261,



1135, 1091, 1025, 955, 859, 704 $cm^{-1}$; MS (70 eV) m/z: 203 (0.75), 159 (27), 43 (100).

*4.3.2 3-[1-(3,4-dimethoxyphenyl)-2-nitroethyl]pentane-2,4-dione (**3b**):* Orange solid; yield 75%; m.p. 168-170 °C; $^1H$ NMR (300 MHz, $CDCl_3$): δ 6.75-6.59 (m, 3H), 4.59-4.48 (m, 2H), 4.29 (d, 1H, *J*=12 Hz), 4.16-4.06 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.23 (s, 3H); 1.89 (s, 3H), $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 201.8, 201.1, 149.3, 149.0, 128.1, 119.9, 111.5, 111.1, 78.4, 70.8, 55.9, 55.8, 42.4, 30.4, 29.4; IR $\nu_{max}$ (ATR): 3031, 2969, 2915, 2853, 1724, 1685, 1586, 1543, 1517, 1463, 1421, 1360, 1291, 1260, 1141, 1019, 958, 859, 813, 763 $cm^{-1}$; MS (70 eV) m/z: 309 (M+, 8), 219 (43), 164 (29), 43 (100); Elemental Analysis: Calculated for $C_{15}H_{19}NO_5$: C, 58.25; H, 6.19; N, 4.53% Found: C, 58.23; H, 6.17; N, 4.55%.

*4.3.3 3-[1-(4-fluorophenyl)-2-nitroethyl]-pentane-2,4-dione (**3c**):*[78] Pale yellow solid; yield 88%; m.p. 104-106 °C; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.21-7.17 (m, 2H), 7.07-7.01 (m, 2H), 4.62 (d, 2H, *J*=6.4 Hz), 4.37- 4.22 (m, 2H), 2.31 (s, 3H), 1.98 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 201.4, 200.7, 162.5 (d, *J*=247.5 Hz), 131.8 (d, *J*=3.0 Hz), 129.7 (d, *J*=8.2 Hz), 116.3 (d, *J*=21 Hz), 78.1, 70.7, 42.0, 30.3, 29.6; IR $\nu_{max}$ (ATR): 3015, 2969, 2923, 2853, 1731, 1692, 1602, 1546, 1508, 1441, 1418, 1354, 1272, 1227, 1163, 1137, 1096, 953, 829, 736 $cm^{-1}$, MS (70 eV) m/z: 221 (0.39), 179 (14), 177 (18), 43 (100).

*4.3.4 3-[1-(4-chlorophenyl)-2-nitroethyl]-pentane-2,4-dione (**3d**):*[77] Pale yellow solid; yield 90%; m.p. 125-127 °C, $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H), 7.15-7.12 (m, 2H), 4.62-4.60 (m, 2H), 4.36-4.19 (m, 2H), 2.30 (s, 3H), 1.98 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 201.3, 200.5, 134.5, 129.5, 129.3, 77.9, 70.5, 42.1, 30.4, 29.6; IR $\nu_{max}$ (ATR): 3023, 2961, 2915, 1739, 1692, 1596, 1538, 1484, 1415, 1361, 1260, 1141, 1094, 1011, 953, 845, 820, 743, 722 $cm^{-1}$; MS (70 eV) m/z: 237 (0.43), 194 (15), 192 (13), 43 (100).

*4.3.5 3-[1-(4-bromophenyl)-2-nitroethyl]pentane-2,4-dione(**3e**):*[76] Pale yellow solid; yield 80%; m.p. 137-139 ºC; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.48-7.45 (m, 2H), 7.09-7.06 (m, 2H), 4.62-4.59 (m, 2H), 4.35-4.18 (m, 2H), 2.30 (s, 3H), 1.98 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 201.3, 200.5, 135.0, 132.4, 129.6, 122.6, 77.8, 70.4, 42.2, 30.4, 29.7; IR $\nu_{max}$ (ATR): 3023, 2969, 2915, 2846, 1731, 1685, 1545, 1486, 1442, 1409, 1355, 1270, 1169, 1132, 1074, 1007, 953, 815, 767, 706, 646 $cm^{-1}$; MS (70 eV) m/z: 281 (0.37); 239 (12); 43 (100).

*4.3.6 Ethyl 2-acetyl-4-nitro-3-phenylbutanoate (**3f**):*[76] Pale yellow solid; yield 91%; m.p. 74-75 ºC. $^1H$ NMR (300 MHz, CDCl3): δ 7.35-7.19 (m, 5H), 4.89-4.70 (m, 2H), 4.28-4.17 (m, 1.87 H), 4.12 (d, 0.58 H, *J*=10.0 Hz), 4.03 (d, 0.42 H, *J*=10.0 Hz), 3.96 (q, 1.13 H, *J*=7.0 Hz), 2.30 (s, 1.76 H), 2.05 (s, 1.24 H), 1.28 (t, 1.24 H, *J*=7.0 Hz,), 1.00 (t, 1.76 H *J*=7.0 Hz); $^{13}C$ NMR (75 MHz, CDCl3): δ 201.2, 200.4, 167.5, 166.8, 136.4, 136.3, 129.0, 128.8, 128.3, 128.2, 127.9, 127.8, 77.9, 77.7, 61.9, 61.6, 42.5, 42.2, 30.2, 30.0, 13.9, 13.6; IR νmax (ATR): 2985, 2923, 1735, 1710, 1558, 1456, 1427, 1384, 1367, 1273, 1238, 1178, 1144, 1092, 1024, 949, 852, 763, 701, 626 $cm^{-1}$; MS (70 eV) m/z: 233 (0.63), 189 (19), 145 (23), 104 (11), 43 (100).

*4.3.7 Ethyl 2-acetyl-3-(4-methoxyphenyl)-4-nitrobutanoate (**3g**):*[79] Brownish oil; yield 85%; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.12 (d, 2H, *J*=8.8 Hz), 6.83 (d, 2H, *J*=8.8 Hz), 4.86-4.65 (m, 2H), 4.23 (q, 1H, *J*=7.0 Hz), 4.17-4.12 (m, 1H), 4.07 (d, 0.5H, *J*=10.0 Hz), 4.01-3.94 (m, 1.5H), 3.76 (s, 3H), 2.29 (s, 1.50H), 2.05 (s, 1.50H), 1.28 (t, 1.50, *J*=7.3 Hz), 1.03 (t, 1.5H, *J*=7.3 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 201.2, 200.4, 167.5, 166.8, 159.3, 129.0, 128.1, 127.9, 114.4, 114.2, 78.2, 78.0, 62.1, 61.8, 61.7, 55.1, 41.9, 41.6, 30.2, 29.9, 13.9, 13.6, IR $\nu_{max}$ (ATR): 2969, 2923, 2830, 1742, 1712, 1612, 1552, 1506, 1466, 1436, 1373, 1360, 1254, 1181, 1029, 833, 733, 643 $cm^{-1}$; MS (70 eV) m/z: 219 (33), 189 (35), 175 (45), 134 (41), 43 (100).

*4.3.8 Ethyl 2-acetyl-4-nitro-3-(thiophen-2-yl)butanoate (**3h**):* Brownish oil; yield 95%; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.23-7.18 (m, 1H), 6.94-6.91 (m, 2H), 4.86-4.80 (m, 2H), 4.59-4.48 (m, 1H), 4.24 (q, 1.03 H, *J*=7.0 Hz); 4.17 (d, 0.49 H, *J*=8.8 Hz), 4.12-4.05 (m, 1.48 H), 2.31 (s, 1.58 H), 2.17 (s, 1.42 H), 1.28 (t, 1.42, *J*=7.0 Hz), 1.13 (t, 1.58 H, *J*=7.0 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 201.0, 200.1, 167.2, 166.6, 138.7, 127.1, 127.0, 126.8, 126.5, 125.4, 125.3, 78.2, 78.1, 62.4, 62.1, 37.9, 37.7, 30.2, 13.9, 13.7; IR $\nu_{max}$ (ATR): 2923, 2838, 1740, 1720, 1553, 1460, 1376, 1260, 1144, 1096, 909, 845, 800, 713 $cm^{-1}$; MS (70 eV) m/z 269(11); 268(21); 195(100); 177(27); 167(53); 151(32); 110(50); 97(10); 79(7); 65(8); Elemental Analysis: Calculated for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91% Found: C, 50.63; H, 5.42; N, 4.92%.

*4.3.9 Ethyl 2-acetyl-3-(4-fluorophenyl)-4-nitrobutanoate (**3i**):*[80] Yellowish oil; yield 71%; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.23-7.18 (m, 2H), 7.04-6.98 (m, 2H), 4.89-4.66 (m, 2H), 4.28-4.17 (m, 2H), 4.08 (d, 0.55H, *J*=10.0 Hz); 4.01-3.94 (m, 1.45 H), 2.30 (s, 1.69 H), 2.08 (s, 1.31 H); 1.28 (t, 1.31 H, *J*=7.0 Hz); 1.03 (t, 1.69 H, *J*=7.0 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 200.8, 200.0, 167.3, 166.6, 163.7 (d, *J*=247.5 Hz); 132.1 (d, *J*=3.0 Hz); 129.6 (t, *J*=7.5 Hz), 116.0 (d, *J*=17.2 Hz), 115.7 (d, *J*=16.5 Hz), 77.8, 77.6, 62.2, 62.0, 61.9, 61.6, 41.7, 41.5, 30.1, 29.8, 13.8, 13.6; IR $\nu_{max}$ (ATR): 2993, 2915, 1739, 1715, 1608, 1555, 1510, 1430, 1368, 1167, 1100, 1020, 836, 739, 711, 625 $cm^{-1}$, MS (70 eV) m/z: 251 (0.4), 207 (20), 163 (20), 122 (14), 43 (100).

*4.3.10 Ethyl 2-acetyl-3-(4-chlorophenyl)-4-nitrobutanoate (**3j**):*[77] Yellowish oil; yield 85%; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.30 (d, 2H, *J*=8.2 Hz), 7.16 (d, 2H, *J*=8.2 Hz), 4.88-4.67 (m, 2H), 4.27-4.16 (m, 2H), 4.08 (d, 0.55 H, *J*=10.0 Hz), 4.00-3.96 (m, 1.45 H), 2.31(s, 1.69 H), 2.09 (s, 1.31 H), 1.29 (t, 1.3 1H, *J*=7.0 Hz), 1.05 (t, 1.69 H, *J*=7.0 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 200.7, 199.9, 167.2, 166.6, 134.9, 134.2, 129.4, 129.3, 129.2, 129.0, 77.6, 77.4, 62.3, 62.1, 61.7, 61.5, 41.7, 41.6, 30.2, 29.9, 13.9, 13.6; IR $\nu_{max}$ (ATR): 2993, 2923, 1734, 1717, 1551, 1486, 1432, 1412, 1374, 1245, 1178, 1093, 1011, 821, 716, 665 $cm^{-1}$; MS (70 eV) m/z: 267 (0.6), 223 (16), 179 (11), 138 (8), 43 (100).

*4.3.11 Ethyl 2-acetyl-3-(4-bromophenyl)-4-nitrobutanoate (**3k**):* Yellowish oil; yield 70%; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.45 (d, 2H, *J*=8.3 Hz), 7.10 (d, 2H, *J*=8.3 Hz), 4.88-4.67 (m, 2H), 4.27-3.96 (m, 4H), 2.30 (s, 1.65 H); 2.09 (s, 1.35H), 1.28 (t, 1.35 H, *J*=7.3 Hz), 1.05 (t, 1.65 H, *J*=7.3 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 200.7, 199.9, 167.2, 166.5, 135.5, 135.4, 132.2, 132.0, 129.6, 129.5, 122.3, 122.2, 77.5, 77.4, 62.3, 62.1, 61.6, 61.4, 41.8, 41.6, 30.2, 29.9, 13.9, 13.6, IR $\nu_{max}$ (ATR): 2985, 2907, 1739, 1716, 1552, 1487, 1368, 1246, 1177, 1142, 1008, 821, 717, 650 $cm^{-1}$; MS (70 eV) m/z: 240 (5); 238 (5);

182 (3); 159 (3); 128 (1); 115 (6); 102 (4); 91 (2); 77 (5); 63 (2); 43 (100); Elemental Analysis: Calculated for $C_{14}H_{16}BrNO_5$: C, 46.95; H, 4.50; N, 3.91% Found: C, 46.96; H, 4.64; N, 3.99%.

*4.4 Synthesis of γ-nitroesters **3l-p***

A mixture of ethyl malonate **1c** (1 mmol), nitrostyrene **2a-d,g** (1.1 mmol) and hydrotalcite (50 mg) in ethanol (2 mL) was stirred at reflux by 12 h. After this period, the reaction mixture was filtered through celite and the solvent evaporated in vacuo to give the crude product, which was purified by column chromatography (hexane/EtOAc) to give the compounds **3l-p**.

*4.4.1 Diethyl (2-nitro-1-phenylethyl)-propanedioate (**3l**):*[76] Orange solid; yield 80%; m.p. 62-64 ºC; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.34-7.22 (m, 5H), 4.93 (dd, 1H, *J*=12.9 and 5.3 Hz), 4.85 (dd, 1H, *J*=12.9 and 8.8 Hz), 4.27-4.18 (m, 3H), 4.00 (q, 2H, *J*=7.0 Hz), 3.82 (d, 1H, *J*=9.4 Hz,), 1.25 (t, 3H, *J*=7.0 Hz,), 1.03 (t, 3H, *J*=7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 167.3, 166.7, 136.1, 128.7, 128.1, 127.9, 77.5, 62.0, 61.7, 54.8, 42.8, 13.8, 13.5; IR $\nu_{max}$ (ATR): 2993, 2900, 1724, 1545, 1494, 1434, 1366, 1287, 1230, 1196, 1094, 1034, 1016, 860, 766, 705 cm$^{-1}$. MS (70 eV) m/z: 263 (18), 218 (13), 189 (100), 104 (45).

*4.4.2 Diethyl [1-(3,4-dimethoxyphenyl)-2-nitroethyl]-propanedioate (**3m**):* Orange solid; yield 68%; m.p. 85-87 ºC; $^1$H NMR (300 MHz, $CDCl_3$): δ 6.72-6.67 (m, 3H), 4.86-4.73 (m, 2H), 4.23-4.01 (m, 3H), 3.96 (q, 2H, *J*=7.0 Hz), 3.79 (s, 3H), 3.77 (s, 3H), 3.75 (d, 1H, *J*=9.4 Hz,), 1.20 (t, 3H, *J*=7.0 Hz), 1.02 (t, 3H, *J*=7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 167.4, 166.8, 149.0, 148.8, 128.5, 120.0, 111.3, 111.2, 77.8, 62.0, 61.8, 55.8, 55.7, 55.0, 42.6, 13.9, 13.8; IR $\nu_{max}$ (ATR): 2993, 2938, 1726, 1591, 1551, 1520, 1469, 1439, 1378, 1297, 1264, 1237, 1166, 1142, 1095, 1078, 1020, 872, 804, 767, 642 cm$^{-1}$; MS (70 eV) m/z: 369 (M+, 31) 322 (41) 249 (100), 164 (90); Elemental Analysis: Calculated for $C_{17}H_{23}NO_8$: C, 55.28; H, 6.28; N, 3.79% Found: C, 55.25; H, 6.19; N, 3.79%.

*4.4.3 Diethyl [2-nitro-1-(thiophen-2-yl)ethyl]-propanedioate (**3n**):*[81] Brownish oil; yield 75%; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, 1H, *J*=4.7 Hz), 6.89-6.84 (m, 2H), 4.91-4.76 (m, 2H), 4.52-4.45 (m, 1H), 4.20-4.01 (m, 4H), 3.87 (d, 1H, *J*=8.2 Hz), 1.27 (t, 3H, *J*=7.0 Hz), 1.16 (t, 3H, *J*=7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 167.1, 166.6, 138.4, 126.9, 126.8, 125.6, 125.4, 78.0, 62.2, 62.1, 55.6, 55.4, 38.4, 13.8, 13.7; IR $\nu_{max}$ (ATR): 2923, 2838, 1726, 1557, 1466, 1436, 1372, 1259, 1180, 1150, 1093, 1025, 852, 796, 701, 600 cm$^{-1}$. MS (70 eV) m/z: 269 (11), 268 (21), 195 (100), 177 (27), 167 (53), 151 (32), 110 (50), 97 (10), 79 (7), 65 (8).

*4.4.4 Diethyl [1-(4-fluorophenyl)-2-nitroethyl]-propanedioate (**3o**):*[81] Yellowish oil; yield 75%; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.27-7.20 (m, 2H), 7.05-6.97 (m, 2H), 4.92 (dd, 1H, *J*=12.9 and 4.7 Hz), 4.82 (dd, 1H, *J*=12.9 and 9.4 Hz), 4.28-4.18 (m, 3H), 4.02 (q, 2H, *J*=7.0 Hz), 3.78 (d, 1H, *J*=9.4 Hz), 1.27 (t, 3H, *J*=7.0 Hz), 1.07 (t, 3H, *J*=7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 167.2, 166.6, 162.4,(d, *J*=246 Hz), 131.9 (d, *J*=3.7 Hz), 129.7 (d, *J*=8.2 Hz), 115.9 (d, *J*=21 Hz), 77.6, 62.2, 61.9, 54.9, 42.2, 13.9, 13.7; IR $\nu_{max}$ (ATR): 2923, 2846, 1727, 1606, 1554, 1508, 1463, 1437, 1373, 1229, 1150, 1098, 1018, 842, 747 cm$^{-1}$. MS (70 eV) m/z 327 (M+, 1), 281 (16), 207 (100), 122 (57).

*4.4.5 Diethyl [1-(4-chlorophenyl)-2-nitroethyl]-propanedioate (**3p**):*[81] Yellowish oil; yield 80%; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.32-7.29 (m, 2H), 7.21-7.18 (m, 2H), 4.94 (dd, 1H, *J*=12.9 and 4.7 Hz), 4.83 (dd, 1H, *J*=12.9 e 9.4 Hz), 4.28-4.18 (m, 3H), 4.03 (q, 2H, *J*=7.0 Hz), 3.78 (d, 1H, *J*=9.4 Hz,), 1.27 (t, 3H, *J*=7.0 Hz,), 1.08 (t, 3H, *J*=7.0 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 167.2, 166.6, 134.7, 134.3, 129.4, 129.1, 77.4, 62.2, 62.0, 54.7, 42.3, 13.9, 13.8. IR $\nu_{max}$ (ATR): 2977, 2923, 1729, 1552, 1487, 1371, 1256m 1176, 1090, 1010, 826, 700, 650 cm$^{-1}$. MS (70 eV) m/z: 343 (M+; 1), 297 (15), 223 (100), 138 (40).

*4.5 Synthesis of γ-nitroesters **4a-i***

A mixture of Meldrum's acid **1d** (1 mmol), nitrostyrene **2b-g,i,j** (1.1 mmol) and hydrotalcite (50 mg) in ethanol (2 mL) was stirred under reflux by 24 h. After this period, the reaction mixture was filtered through celite and the solvent evaporated in vacuo to afford the crude product, which was purified by column chromatography (hexane/EtOAc) to give the compounds **4a-i**.

*4.5.1 Ethyl 4-nitro-3-phenylbutanoate (**4a**):*[82] Brownish oil; yield 95%; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.21-7.36 (m, 5H), 4.73 (dd, 1H, *J*= 12.3 and 7.0 Hz), 4.63 (dd, 1H, *J*=12.3 and 7.6 Hz), 3.93-4.11 (m, 3H), 2.75 (d, 2H, *J*=7.6 Hz,), 1.16 (t, 3H, *J*=7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.5, 138.2, 128.9, 127.9, 127.3, 79.4; 60.8, 40.1, 13.9, 37.7; IR $\nu_{max}$ (ATR): 3031, 2985, 1723, 1547, 1453, 1430, 1376, 1224, 1168, 852, 767, 734, 698 cm$^{-1}$. MS (70 eV) m/z: 237 (M+; 1), 190 (51), 145 (31), 118 (100), 117 (89), 104 (44).

*4.5.2 Ethyl 3-(3,4-dimethoxyphenyl)-4-nitrobutanoate (**4b**):* Brown oil; yield 82%; $^1$H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, 3H, *J*=7.2 Hz), 2.74 (d, 2H, *J*= 7.8 Hz), 3.85 (s, 3H), 3.87 (s, 3H), 3.93 (m, 1H), 4.09 (q, 2H, *J*= 6.9 Hz), 4.61 (dd, 1H, *J*=12.4 and 7.5 Hz), 4.70 (dd, 1H, *J*= 12.3 and 7.2 Hz), 6.72-6.83 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 170.7, 149.1, 148.6, 130.6, 119.2, 111.4, 110.6, 79.7, 60.9, 55.9, 55.8, 39.9, 37.9, 14.1; IR $\nu_{max}$ (ATR): 2969, 2833, 1718, 1597, 1545, 1500, 1470, 1432, 1364, 1251, 1176, 1018, 829, 694 cm$^{-1}$; HRMS: Calculated for: [$C_{14}H_{19}NO_6$+Na] 320.1110; Found 320.1115.

*4.5.3 Ethyl 3-(4-fluorophenyl)-4-nitrobutanoate (**4c**):* Brownish oil; yield 96%; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.19-7.24 (m, 2H); 6.99-7.05 (m, 2H), 4.72 (dd, 1H, *J*=12.3 and 7.0 Hz,), 4.61 (dd, 1H, *J*=12.3 and 8.2 Hz), 4.08 (q, 2H, *J*=7.0 Hz), 3.93-4.03 (m, 1H), 2.77 (dd, 1H, *J*=15.8 and 7.0 Hz), 2.70 (dd, 1H, *J*=15.8 and 7.6 Hz); 1.17 (t, 3H, *J*=7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.4, 162.2 (d, *J*=246,6 Hz), 133.9 (d, *J*=4.4 Hz), 129.0 (d, *J*=7.7 Hz), 115.9 (d, *J*=22.1 Hz), 60.9, 79.3, 39.5, 37.7, 14.0; IR $\nu_{max}$ (ATR): 2985, 2931, 1725, 1599, 1552, 1508, 1429, 1370, 1228, 1161, 1098, 1019, 830, 781, 768, 720, 702 cm$^{-1}$. HRMS: Calculated for: [$C_{12}H_{14}FNO_4$-$HNO_2$] 208.0900; Found 208.0921.

*4.5.4 Ethyl 3-(4-chlorophenyl)-4-nitrobutanoate (**4d**):*[82] Brownish oil; yield 85%; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, 2H, *J*=8.2 Hz); 7.18 (d, 2H, *J*=8.2 Hz), 4.60 (dd, 1H, *J*=12.9 and 8.2 Hz), 4.72 (dd, 1H, *J*=12.9 and 7.0 Hz); 4.07 (q, 2H, *J*=7.0 Hz), 4.01-3.91 (m, 1H), 2.76 (dd, 1H, *J*=16.4 and 7.0 Hz), 2.70 (dd, 1H, *J*=16.4 and 7.6 Hz), 1.17 (t, 3H, *J*=7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.3, 136.7, 133.8, 129.2, 128.7, 79.1, 60.9, 39.5, 37.5, 14.0; IR $\nu_{max}$ (ATR): 2923, 2915, 1724, 1538, 1484, 1368, 1182, 1097, 1012, 826, 734, 717 cm$^{-1}$.

*4.5.5 Ethyl 3-(4-bromophenyl)-4-nitrobutanoate (**4e**):* Brownish oil; yield 88%; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, 2H,



*J*=8.2 Hz); 7.12 (d, 2H, *J*=8.2 Hz), 4.72 (dd, 1H, *J*=12.3 and 6.5 Hz), 4.61 (dd, 1H, *J*=12.3 and 8.2 Hz), 4.08 (q, 2H, *J*=7.0 Hz), 4.00-3.91 (m, 1H), 2.76 (dd, 1H, *J*=15.8 and 7.0 Hz), 2.70 (dd, 1H, *J*=15.8 and 7.6 Hz), 1.18 (t, 3H, *J*=7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.3; 137.3, 132.2, 129.1, 122.0, 79.1, 61.0, 39.7, 37.5, 14.0; IR $\nu_{max}$ (ATR): 2984, 1726, 1545, 1485, 1357, 1161, 1070, 1010, 829, 726, 715 cm$^{-1}$; HRMS: Calculated for: [$C_{12}H_{14}BrNO_4$-$HNO_2$] 268.0099; Found 268.0105.

*4.5.6 Ethyl 3-(4-methoxyphenyl)-4-nitrobutanoate (**4f**):* Brown oil; yield 89%; $^1$H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, 3H, *J*=7.2 Hz), 2.74 (dd, 2H, *J*=7.5 and 2.1 Hz), 3.80 (s, 3H), 3.90-4.00 (m, 1H), 4.11 (q, 2H, *J*=7.2 Hz), 4.61 (dd, 1H, *J*=12.4 and 8.1 Hz), 4.72 (dd, 1H, *J*=12.4 and 6.9 Hz), 6.87 (d, 2H, *J*=9.0 Hz), 7.16 (d, 2H, *J*=8.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 170.7, 159.1, 130.1, 128.4, 114.3, 79.7, 60.9, 55.2, 39.5, 37.9, 14.1; IR $\nu_{max}$ (ATR): 2969, 2833, 1718, 1597, 1545, 1500, 1470, 1432, 1364, 1251, 1176, 1018, 829, 694 cm$^{-1}$; HRMS: Calculated for: [$C_{13}H_{17}NO_5$+Na] 290.1004; Found 290.0999.

*4.5.7 Ethyl 4-nitro-3-(thien-2-yl)-butanoate (**4g**):*[83] Brownish oil; yield 85%; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.20-7.22 (m, 1H), 6.95-6.93 (m, 2H), 4.76 (dd, 1H, *J*=12.9 and 6.5 Hz), 4.65 (dd, 1H, *J*=12.9 and 7.6 Hz), 4.35-4.35 (m, 1H), 4.12 (q, 2H, *J*=7.0 Hz), 2.81 (d, 2H, *J*=7.0 Hz), 1.21 (t, 3H, *J*=7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.3, 141.0, 127.1, 125.5, 124.9, 79.6, 61.1, 38.5, 35.6, 14.0; IR $\nu_{max}$ (ATR): 3108, 2985, 1708, 1545, 1432, 1382, 1203, 1176, 1024, 853, 701 cm$^{-1}$. MS (70 eV) m/z: 243 (M+, 1), 196 (66), 151 (15), 124 (100), 110 (47).

*4.5.8 Ethyl 4-nitro-3-(3,4,5-trimethoxyphenyl)-butanoate (**4h**):* Orange solid; yield 95%; m.p. 91-93 ºC. $^1$H NMR (300 MHz, $CDCl_3$): δ 6.43 (s, 2H), 4.61-4.79 (m, 3H), 4.11 (q, 2H, *J*=7.0 Hz); 3.85 (s, 6H), 3.82 (s, 3H), 2.75 (d, 2H, *J*=7.6); 1.20 (t, 3H, *J*=7.0 Hz,); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.5, 153.4, 137.5, 133.9, 104.3, 104.2, 79.3, 60.9, 60.6, 56.1, 56.0, 40.4, 37.7, 14.0; IR $\nu_{max}$ (ATR): 2946, 2830, 1724, 1591, 1545, 1462, 1421, 1396, 1353, 1319, 1270, 1251, 1217, 1176, 1129, 995, 905, 841, 773, 731 cm$^{-1}$. HRMS Calculated for: [$C_{15}H_{21}NO_7$+Na] 350.1216; Found 350.1224.

*4.5.9 Ethyl 3-(4-cyanophenyl)-4-nitrobutanoate (**4i**):* Yellow pale oil; yield 84%; $^1$H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, 3H, *J*=7.2 Hz), 2.77 (m, 2H), 4.04-4.14 (m, 3H), 4.66 (dd, 1H, *J*=12.7 and 8.7 Hz), 4.78 (dd, 1H, *J*=12.9 and 6.6 Hz), 7.38 (d, 2H, *J*=8.4 Hz), 7.66 (d, 2H, *J*=8.4 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$):δ 169.9, 164.9, 143.6, 128.3, 118.2, 112.1, 78.6, 61.2, 40.0, 37.2, 14.0; IR $\nu_{max}$ (ATR): 2982, 2934, 2230, 1729, 1610, 1548, 1378, 1226, 1158, 1090, 1018, 842, 784, 763, 718, 694 cm$^{-1}$.; HRMS: Calculated for: [$C_{13}H_{14}N_2O_4$+Na] 285.0851; Found 285.0847.

*4.6 Experiment of Recycling of $HT_{calc}$. Catalyst*:
Due the small size of HT particles, it can't be isolated by a simple filtration. Due to this, the crude mixture of an ordinary reaction was diluted in 5ml of ethanol and was centrifuged for several minutes. The liquid fase was removed by decantation. A 5 ml volume of ethanol was added and mixed with the remained solid HT and centrifugation process takes place; this process was repeated by 1 time. The HT was isolated and dried at 100ºC for 12 hours. Next the HT was resubmitted to the calcination's process at 600ºC for 5 hours. This calcined material was reused in a standard experiment with nitrostyrene (**2a**) and Meldrum's acid (**1d**) as described before. The compound **4a** was obtained in 90% yield, confirming the activity of the catalyst.

*4.7 General procedure for the synthesis of lactams **10a** and **10d***[70]
In a round bottom flask were added the nitroesters **4a,d** (1 mmol) and $NiCl_2.6H_2O$ (10 mmol) dissolved in 5 mL ethanol. The mixture was submitted to magnetic stirring in an ice bath, followed by addition of $NaBH_4$ (10 mmol), remaining the stirring for 2 h in 0 °C. After, 20 mL of $NH_4Cl$ were addicted in the flask and extracted with $CHCl_3$ (3 x 20 mL). The organic phases were combined, dried with $MgSO_4$ anhydrous, filtered through celite and evaporated under vacuum.

*4.7.1 4-(4-phenyl)pyrrolidin-2-one (**10a**):*[84] Brownish oil; yield 88%; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.25-7.37 (m, 5H), 6.90 (s, 1H), 3.82-3.64 (m, 2H), 3.43 (dd, 1H, *J*=9.4 and 7.0 Hz), 2.74 (dd, 1H, *J*=16.9 and 8.8 Hz), 2.51 (dd, 1H, *J*=16.9 and 8.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 177.8, 142.6, 128.8, 127.0, 126.7, 49.5, 40.2, 37.9; IR $\nu_{max}$ (ATR): 3240, 2923, 2861, 1669, 1496, 1442, 1356, 1255, 1051, 742, 688, 627 cm$^{-1}$; MS (70 eV) m/z 161 (M+, 42%); 143 (1); 117 (5); 104 (100).

*4.7.2 4-(4-chlorophenyl)pyrrolidin-2-one (**10d**):*[84] Brownish oil; yield 89%; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 2H, *J*=7.0 Hz); 7.19 (d, 2H, *J*=7.0 Hz), 3.82-3.62 (m, 2H), 6.52 (s, 1H), 3.39 (t, 1H, *J*=7.6 Hz), 2.74 (dd, 1H, *J*=16.9 and 8.8 Hz), 2.45 (dd, 1H, *J*=16.9 and 8.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 177.8; 140.8, 133.2, 129.3, 128.4, 49.7, 39.9, 29.9; IR $\nu_{max}$ (ATR): 3194, 2923, 2840, 1673, 1485, 1259, 1089, 1006, 824, 718, 666 cm$^{-1}$.

*4.8 General procedure for synthesis of Phenibut and Baclofen.*[85]
In a round bottom flask was added the lactam **10a,d** (0.4 mmol) and 10 mL of HCl (6M). The mixture was stirred under reflux by 12 h. Evaporation under vacuum leads to the γ-amino acids **11** and 1**2**.

*4.8.1 (+/-)-3-carboxy-2-phenylpropan-1-aminium chloride (Phenibut, **11**):*[84] Orange solid; yield 88%; m.p 188-190 ºC; $^1$H NMR (300 MHz, $D_2O$): δ 7.26-7.36 (m, 4H); 7.33 (d, 2H, *J*=8.8 Hz), 3.30-3.10 (m, 3H), 2.75 (dd, 1H, *J*=15.8 and 5.3 Hz), 2.65 (dd, 1H, *J*=15.8 and 8.8 Hz); $^{13}$C NMR (75 MHz, $D_2O$) δ 177.9, 140.8, 131.8, 130.8, 130.3, 46.3, 42.4, 40.7; IR $\nu_{max}$ (ATR): 2930, 1711, 1590, 1515, 1485, 1402, 1259, 1199, 1146, 972, 860, 761, 701 cm$^{-1}$.

*4.8.2 (+/-)-3-carboxy-2-(4-chlorophenyl)propan-1-aminium chloride (Baclofen, **12**):*[85] Orange solid; yield 89%; m.p. 198-200 ºC; $^1$H NMR (300 MHz, $D_2O$): δ 7.43 (d, 2H, *J*=8.8 Hz), 7.33 (d, 2H, *J*=8.8 Hz), 3.48-3.20 (m, 3H), 2.86 (dd, 1H, *J*=16.4 and 5.9 Hz), 2.73 (dd, 1H, *J*=16.4 and 8.8 Hz), $^{13}$C NMR (75 MHz, $D_2O$) δ 175.5; 137.1, 133.5, 129.6, 129.42, 43.8, 39.6, 38.4; IR $\nu_{max}$ (ATR): 2885, 1711, 1590, 1560, 1493, 1410, 1395, 1245, 1194, 1139, 970, 813, 760, 706 cm$^{-1}$.

## Acknowledgements

The authors would like to thanks to FAPERGS, CAPES and CNPq by financial support and fellowships (F.F.N., C.RM.D., CAPES and D.Z.V., CNPq). Prof. Luiz Alberto Beraldo, Jacqueline Nakau Mendonça and Prof. Norberto Peporine

Lopes from Pharmaceuticals Science Faculty of Ribeirão Preto are acknowledged by providing the HRMS analysis.

1. B. F. Sels, D. E. De Vos, P. A. Jacobs, *Catal. Rev*., 2001, **43**, 443.
2. X. Lei, F. Zhang, L. Yang, X. Guo, Y. Tian, S. Fu, F. Li, D. G. Evans, X. Duan, *Am. Inst. Chem. Eng.*, 2007, **53**, 932.
3. J. J. Bravo-Suárez, *Quimica Nova*, 2004, **27**, 601.
4. K. Kaneda, T. Mitsudome, T. Mizugaki, K. Jitsukawa, *Molecules*, 2010, **15**, 8988.
5. F. Cavani, F. Trifiro, A. Vaccari, *Catal. Today*, 1991, **11**, 173.
6. A. I. Khan, D. O'Hare, *J. Mater. Chem.* 2002, **12**, 3191.
7. A. de Roy, C. Forano, J. Besse, In *Layered Double Hydroxides: Present and Future;* V. Rives, Ed.; Nova Science Publishers, New York, 2001; pp 1-39.
8. F. Li, X. Duan, *Struct. Bonding*, 2006, **119**, 193.
9. D. G. Evans, X. Duan, *Chem. Commun.*, 2006, **5**, 485.
10. X. Guo, F. Zhang, D. G. Evans, X. Duan, *Chem Commun.*, 2010, **46**, 5197.
11. G. G. C. Arizaga, K. G. Satyanarayana, F. Wypych, *Solid State Ionics*, 2007, **178**, 1143.
12. P. Nalawade, B. Aware, V. J. Kadam, R. S. Hirlekar, *J. Sci. Ind. Res.*, 2009, **68**, 267.
13. A. Vaccari, *Appl. Clay Sci.*, 1999, **14**, 161.
14. K. Zlatanova, P. Markovsky, I. Spassova, G. Danev, *Opt. Mater.*, 1996, **5**, 279.
15. C. Del Hoyo, *Appl. Clay Sci.*, 2007, **36**, 103.
16. J. H. Choy, *J. Phys. Chem. Solids*, 2004, **65**, 373.
17. S. Y. Kwak, Y. J. Jeong, J. S. Park, J. H. Choy, *Solid State Ionics*, 2002, **151**, 229.
18. Y. Ono, *J. Catal.*, 2003, **216**, 406.
19. D. Tichit, B. Coq, *Cattech*, 2003, **7**, 206.
20. F. Figueras, *Top. Catal.*, 2004, **29**, 189.
21. G. Negrón, N. Guerra, L. Lomas, R. Gaviño, J. Cárdenas, *Arkivoc*, 2003, **11**, 179.
22. K. Ebitani, K. Motokura, K. Mori, T. Mizugaki, K. Kaneda, *J. Org. Chem.*, 2006, **71**, 5440.
23. M. J. Climent, A. Corma, S. Iborra, K. Epping, A. Velty, *J. Catal.*, 2004, **225**, 316.
24. J. Cerveny, J. Splıchalova, P. Kacer, F. Kovanda, M. Kuzma, L. Cerveny, *J. Mol. Catal. A: Chem.*, 2008, **285**, 150.
25. K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Tetrahedron Lett.*, 2005, **46**, 5507.
26. F. Mei, E. C. G. Li, A. Zhanga, *React. Kinet. Catal. Lett.*, 2008, **93**, 101.
27. N. Barakos, S. Pasias, N. Papayannakos, *Biores. Technol.*, 2008, **99**, 5037.
28. J. R. Ruiz, C. Jimenez-Sanchidrian, R. Llamas, *Tetrahedron*, 2006, **62**, 11697.
29. S. W. Kshirsagar, N. R. Patil, S. D. Samant, *Tetrahedron Lett.*, 2008, **49**, 1160.
30. V. R. Choudhary, R. Jha, P. A. Choudhari, *J. Chem. Sci.*, 2005, **117**, 635.
31. C. Cativiela, F. Figueras, J. I. Garcia, J. A. Mayoral, M. M. Zurbano, *Synth. Commun.*, 1995, **25**, 1745.
32. K. Yamaguchi, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Org. Chem.*, 2000, **65**, 6897.
33. X. Xie, K. Yan, J. Li, Z. Wang, *Catal. Commun.*, 2008, **9**, 1128.
34. A. Dubey, *Green Chem.*, 2007, **9**, 424.
35. M. L. Kantam, S. Laha, J. Yadav, P. R. Likhar, B. Sreedhar, S. Jha, S. Bhargava, M. Udayakiran, B. Jagadeesh, *Org. Lett.*, 2008, **10**, 2979.
36. A. Lemos, J. P. Lourenço, *Tetrahedron Lett.*, 2009, **50**, 1311.
37. A. Cwik, Z. Hell, A. Fuchsb, D. Halmaia, *Tetrahedron Lett*., 2005, **46**, 6563.
38. V. H. Jadhav, D. K. Dumbre, V. B. Phapale, H. B. Borate, R. D. Wakharkar, *Catal. Commun.*, 2007, **8**, 65.
39. B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.*, 2002, **124**, 14127.
40. M. Kantam, P. Srinivas, K. B. S. Kumar, R. Trivedi, *Catal. Commun*., 2007, **8**, 991.
41. C. Jimenez-Sanchidrian, M. Mora, J. R. Ruiz, *Catal. Commun*., 2006, **7**, 1025.
42. B. M. Choudary, M. L. Kantam, C. R. V. Reddy, K. K. Rao, F. Figueras, *J. Mol. Catal. A: Chem.*, 1999, **146**, 279.
43. B. M. Choudary, M. L. Kantam, B. Kavita, C. V. Reddy, F. Figueras, *Tetrahedron*, 2000, **56**, 9357.
44. B M. Choudary, M. L. Kantam,; V. Neeraja, K. K. Rao, F. Figueras, L. Delmottec, *Green Chem.*, 2001, **3**, 257.
45. T. M. Khomenko, K. P. Volcho, A. V. Toktarev, G. V. Echevskii, N. F. Salakhutdinov, V. A. Barkhash, *Russ. J. Org. Chem.*, 2005, **41**, 838.
46. M. L. Kantam, A. Ravindra, C. V. Reddy, B. Sreedhar, B. M. Choudary, *Adv. Synth. Catal.*, 2006, **348**, 569.
47. S. Vijaikumar, A. Dhakshinamoorthy, K. Pitchumani, *Appl. Catal. A: Gen.*, 2008, **340**, 25.
48. U. Costantino, M. Curini, F. Montanari, M. Nocchetti, O. Rosati, *Micropor. Mesopor. Mat.*, 2008, **107**, 16.
49. H. A. Prescott, Z-J. Li, E. Kemnitz, A. Trunschke, J. Deutsch, H. Lieske, A. Auroux, *J. Catal.*, 2005, **234**, 119.
50. B. Veldurthy, J. M. Clacens, F. Figueras, *Adv. Synth. Catal.*, 2005, **347**, 767.
51. M. Mokhtara, T. S. Saleha, S. N. Basahela, *J. Mol. Catal. A: Chem.*, 2012, **353**, 122.
52. M. D. Surpur, S. Kshirsagar, S. D. Samant, *Tetrahedron Lett.*, 2009, **50**, 719.
53. S. W. Kshirsagar, N. R. Patil, S. D. Samant, *Tetrahedron Lett.*, 2010, **51**, 2924.
54. S. Vijaikumar, K. Pitchumani, *Indian J. Chem.*, 2010, **49**, 469.
55. a) D. Russowsky, C. L. Petzhold, A. C. A. Borges, J. P. B. Loppes, M. A. Ceschi, E. Konrath, C. Battastini, P. S. Lunardi, C. Gonçalves, *Eur. J. Med. Chem.*, 2013, **62**, 556; b) M. Rodrigues, J. B. Cantos, C. R. M. D'Oca, K. L. Soares, T. S. Coelho, L. A. Piovesan, D. Russowsky, P. A. Silva, M. G. M. D'Oca, *Bioorg. Med. Chem.*, 2013, **21**, 6910; c) F. Figueiró, F. B. Mendes, P. F. Corbelini, F. Janarelli, E.H.F. Jandrey, D. Russowsky, V.L. Eifler-Lima, A.M.O. Battastini, *Anticancer Research* 2014, **34**, 1837. d) R.F.S Canto, A. Bernardi, A.M.O. Battastini, D. Russowsky, V.L. Eifler-Lima, *J. Braz. Chem. Soc.* 2011, **22**, 1379.
56. D. Wang, X. Zhang, W. Wei, Y. Sun, *Catal. Commun.*, 2012, **28**, 159
57. T. J. Pinnavaia, M. Chibwe, V. R. L. Constantino, S. K. Yun, *Appl. Clay Sci.*, 1995, **10**, 117.
58. K. Yamaguchi, K. Ebitani, T. Yoshida, H. Yoshida, K. Kaneda, *J. Am. Chem. Soc.* 1999, **121**, 4526.
59. D. Tichit, D. Lutic, B. Coq, R. Durand, R. Teissier, *J. Catal.*, 2003, **219**, 167.
60. P. S. Kumbhar, J. Sanchez-Valente, J. Lopez, F. Figueras, *Chem. Commun.*, 1998, 535.



61. V. A. Ivanov, J. Bachelier, F. Audry, J. C. Lavalley, *J. Mol. Catal.*, 1994, **91**, 45.
62. E. M. Arnett, S. L. Maroldo, S. L. Shilling, J. A. Harrelson, *J. Am. Chem. Soc.*, 1984, **106**, 6759.
63. L. George, R. N. Veedu, H. Sheibani, A. A. Taherpour, R. Flammang, C. Wentrup, *J. Org. Chem.*, 2007, **72**, 1399.
64. Z. Chen, Z. Chen, Y. Jiang, W. Hu, *Tetrahedron*, 2005, **61**, 1579.
65. A. S. Paraskar, A. Sudalai, *Tetrahedron*, 2006, **62**, 4907.
66. S. Spiess, C. Berthold, R. Weihofen, G. Helmchen, *Org. Biomol. Chem.*, 2007, **5**, 2357.
67. A. Lebedev, *Chem. Heterocycl. Compd.*, 2007, **43**, 673.
68. G. Bartoli, G. Di Antonio, S. Giuli, E. Marcantoni, M. Marcolini, M. Paoletti, *Synthesis*, 2008, **2**, 320.
69. R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed*., 2005, **44**, 6576.
70. P. S. Hynes, P. A. Stupple, D. J. Dixon, *Org. Lett.*, 2008, **10**, 1389.
71. J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem. Int. Ed*., 2008, **47**, 4016.
72. Y. Sui, L. Liu, J. L. Zhao, D. Wang, Y. J. Chen, *Tetrahedron*, 2007, **63**, 5173.
73. M. Bandini, A. Garelli, M. Rovinetti, S. Tommasi, A. Umani-Ronchi, *Chirality*, 2005, **17**, 522.
74. C. S. Schwalm, M. A. Ceschi, D. Russowsky, *J. Braz. Chem. Soc.*, 2011, **22**, 623.
75. M-Y. Chang, P-P. Sun, S-T. Chen, N-C. Chang, *Tetrahedron Lett.*, 2003, **44**, 5271.
76. I. Zenz, H. Mayr, *J. Org. Chem.*, 2011, **76**, 9370.
77. R. Ballini, R. Maggi, A. Palmieri, G. Sartori, *Synthesis*, 2007, **19**, 3017.
78. X. Jiang, Y. Zhang, X. Liu, G. Zhang, L. Lai, L. Wu, J. Zhang, R. Wang, *J. Org. Chem.*, 2009, **74**, 5562.
79. G. Srihari, M. M. Murthy, *Synth. Commun*. 2009, **39**, 896.
80. R. Manzano, J. M. Andrés, R. Pedrosa, *Synlett*, 2011, **15**, 2203.
81. S. Hajra, Sk M. Aziz, R. Maji, *RSC Advances*, 2013, **3**, 10185.
82. R. Menicagli, S. Samaritani, *Tetrahedron*, 1996, **52**, 1425.
83. P. Berthelot, C. Vaccher, N. Flouquet, M. Debaert, M. Luyckx, C. Brunet, *J. Med. Chem.*, 1991, **34**, 2557.
84. F. Felluga, V. Gombac, G. Pitacco, E. Valentim, *Tetrahedron: Asymmetry*, 2005, **16**, 1341.
85. E. J. Corey, F. Y. Zhang, *Org. Lett.*, 2000, **2**, 4257.