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# Solid base-catalyzed synthesis of 5-substituted 4,5-dihydroisoxazoles

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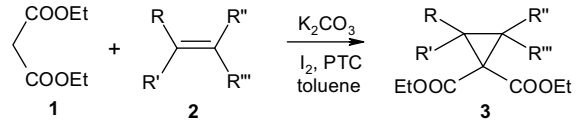
**Abstract**—We present a new synthetic route for the preparation of 5-substituted 4,5-dihydroisoxazole derivatives starting from ethyl nitroacetate and alkenes in the presence of modified Mg:Al 3:1 hydrotalcite.


4,5-Dihydroisoxazoles are an important class of heterocyclic compounds. They can be converted into several useful synthetic units such as β-hydroxy ketones,[1] γ-amino alcohols,[2] α,β-unsaturated oximes,[3] and β-hydroxy nitriles.[4] Moreover, isoxazole derivatives have biological activities and pharmacological properties such as hypoglycemic,[5] antibacterial,[6] or anti-inflammatory.[7]

It is well-known that nitrile oxides undergo [3+2] cycloaddition with olefins to provide isoxazole derivatives.[8] Several methods have been described in the literature for the in situ generation of nitrile oxides. The most popular are Mukaiyama's method using phenyl isocyanate with a catalytic amount of $Et_3N$ for the dehydration of primary nitro compounds[9] and the Huisgen base-induced dehydrohalogenation of hydroximoyl chlorides.[10] However, nitrile oxides are unstable and dimerize readily to form 3,4-diacetyl-1,2,5-oxadiazole 2-oxides (named as furoxans).[11] There are also other methods for the preparation of isoxazole derivatives such as nitrosative cyclization using a DMSO solution of sodium nitrite and *n*-propyl nitrite,[12] reactions of 2,3-disubstituted cyclopropanes with $NOBF_4$,[13] or treatment of isoxazolin-5-ones with olefins.[14]

We have developed a phase transfer catalytic method for the synthesis of cyclopropane carboxylic acid derivatives




**Scheme 1.**

**3** (Scheme 1), which involved the reaction of CH-acids with non-activated olefins **2** in the presence of solid potassium carbonate, a lipophilic quaternary ammonium salt as phase transfer catalyst and iodine.[15]

The reaction is a complex, SET-induced process with more than 10 elemental steps. Starting from malonic acid allylic esters, bicyclic cyclopropane carboxylic acid lactones were formed in a stereoselective intramolecular cyclization in good yield.[16] During our later studies it was found that non-activated Mg:Al 3:1 hydrotalcite (HT) was also a suitable basic catalyst for this intramolecular cyclization reaction even without the phase transfer catalyst.[17]

The hydrotalcites are anionic layered double hydroxides (LDHs). Their structures consist of brucite $Mg(OH)_2$ type octahedral layers in which a part of the M(II) cations are substituted by M(III) cations. The excess positive charge is compensated by different anions such as hydroxyl, carbonate, halogen, nitrate, etc.[18] In general, the activation of HT consists of two steps. First, upon thermal treatment at 450–500 °C, HT forms a highly active Mg(Al)O mixed oxide that exhibits strong Lewis basicity. In the second step the calcined catalyst is

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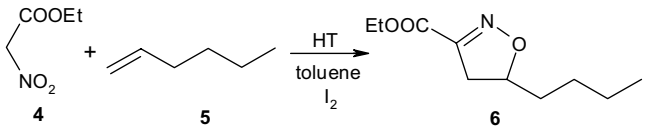
rehydrated which, due to its memory effect, results in the restoration of the original HT structure with $OH^-$ groups, giving a Brønsted type catalyst.[19] We have recently reported, the cyclization of bis-ketonic Mannich bases,[20] investigation of the Henry reaction[21] and the synthesis of oxazolidin-2-ones[22] catalyzed by different types of Mg:Al hydrotalcites.

During the course of our studies toward the catalytic application of hydrotalcites, we became interested in examination of the reaction between ethyl nitroacetate **4** and 1-hexene **5**. The bases tested in this reaction were activated and non-activated Mg:Al 3:1 hydrotalcite as well as the commercially available Mg:Al 2:1 HT. The reactions were carried out in toluene at 110 °C in the presence of iodine, which was necessary for the formation of cyclopropane derivatives.[15,17] To our surprise, none of the expected cyclopropane derivative was formed. The $^1$H NMR spectrum showed two double doublets at $\delta$ 2.83 ppm ($J_1 = 8.7$ Hz and $J_2 = 17.4$ Hz) and 3.23 ppm ($J_1 = 10.8$ Hz and $J_2 = 17.4$ Hz) with the same intensity. The $^{13}$C NMR spectrum showed a signal at 158.2 ppm. Based on these data, the formation of a 5-substituted 4,5-dihydro-3-isoxazole ring (Scheme 2) was evident.[23] The IR spectrum confirmed the presence of the C=N bond (1585 $cm^{-1}$).

When rehydrated Mg:Al 3:1 HT was used, which is a strong Brønsted base, ethyl 5-butyl-4,5-dihydro-3-isoxazole carboxylate **6** was obtained in 65% yield.[24] The non-activated HT with carbonate as the compensating anion failed to give any product, only unchanged starting material was recovered. With calcined HT, prepared by heating at 450 °C for 8 h giving a mixed oxide of Mg and Al, only very small amounts of the product were observed (Table 1, entry 2). An increase in the amount of iodine did not increase the yield.

On replacing rehydrated Mg:Al 3:1 HT by potassium carbonate under the same reaction conditions, ethyl 5-butyl-4,5-dihydro-3-isoxazole carboxylate **6** was also obtained but in only a small amount. The other product detected in this reaction was diethyl 1,2-dinitro-ethane-1,2-dicarboxylate **7**, which is the dimerization product of ethyl nitroacetate. This kind of dimer is a known product in the reaction of CH-acids in the presence of iodine under basic conditions.[25,26] Increasing the reaction time led to a considerable increase in the yield of **6** and **7** (Table 1, entry 6). The two compounds can be separated easily; while **6** is soluble in toluene, **7** precipitates onto the surface of potassium carbonate. Treatment of the solid with acetone yielded pure **7**. Other bases (e.g., KF on alumina, DBU, and triethylamine) gave no product.




4 5 6

**Scheme 2.**

**Table 1.** Results of the preparation of ethyl 5-butyl-4,5-dihydro-3-isoxazole carboxylate **6** with various catalysts[a]

| Entry | Catalyst | Reaction time (h) | Yield (%) |
|---|---|---|---|
| 1[a] | Rehydrated Mg:Al 3:1 HT[20] | 7 | 65[c] |
| 2[a] | Calcined Mg:Al 3:1 HT | 7 | <5[c] |
| 3[a] | Non-activated Mg:Al 3:1 HT | 9 | — |
| 4[a] | Non-activated Mg:Al 2:1 HT | 9 | — |
| 5[b] | $K_2CO_3$ | 3 | 11 (12)[d] |
| 6[b] | $K_2CO_3$ | 15 | 30 (33)[d] |

[a] Reaction conditions: ethyl nitroacetate 0.13 g (1 mmol), hexene 0.09 g (1.1 mmol), catalyst 0.15 g, catalytic amount of iodine, toluene (5 ml), 60 °C.
[b] Reaction conditions: ethyl nitroacetate 0.4 g (3 mmol), hexene 0.25 g (3 mmol), $K_2CO_3$ 0.66 g, iodine 0.6 g, toluene (10 ml), one drop of TCMC, 60 °C.
[c] Determined by $^1$H NMR.
[d] Isolated yield, the values in parentheses refer to the yield of **7**.

We next investigated the reactivity of a variety of olefins with ethyl nitroacetate in the presence of rehydrated Mg:Al 3:1 HT. The corresponding 4,5-dihydroisoxazole derivatives were obtained in all cases (Table 2).

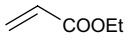
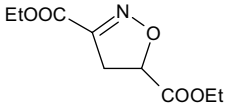
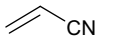
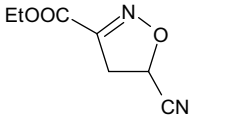
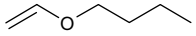
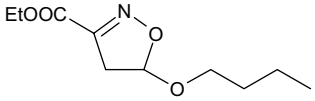
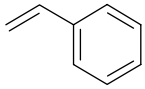
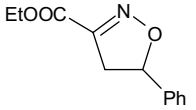
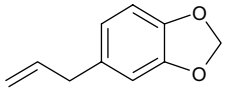
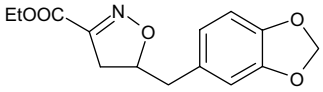
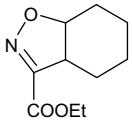
The identity of the products was confirmed by $^1$H NMR and $^{13}$C NMR spectroscopic analysis. The results are summarized in Table 2.

In all cases the reactions were regioselective and led to the formation of the 5-substituted isoxazolines exclusively, as suggested by the lowfield values of the CH signal around $\delta$ 4.0–5.0 ppm.[28] The reaction of cyclohexene (Table 2, entry 6) with ethyl nitroacetate furnished the desired bicyclic product, albeit in low yield.

In our reactions we did not detect furoxans. This might be a quasi high dilution effect due to nitrile oxide formation happening on the solid surface. However, this by-product would have been formed exclusively from the nitrile oxide, so as its presence was undetectable, we might also suppose that in the presence of hydrotalcites the reaction goes via another intermediate. When iodine was omitted from the reaction mixture no reaction occurred. During the investigation of the mechanism of the cyclopropanation reaction, we showed the participation of iodomalonic esters and their reaction in a SET-induced process.[15] Since ethyl nitroacetate is a strong CH-acid, we can assume an analogous mechanism for this cyclization. The absence of the cyclopropane as a product can be explained by tautomerism of ethyl nitroacetate into the *aci* form, which might induce one oxygen to participate in ring formation.

In conclusion, rehydrated Mg:Al 3:1 hydrotalcite is a suitable catalyst for the cyclization of ethyl nitroacetate and olefins into 4,5-dihydroisoxazole derivatives. In contrast to most described methods, this new reaction may not be a 1,3-dipolar cycloaddition, but rather a complex, SET-induced radical process similar to the formation of cyclopropane carboxylic acid derivatives.[15]

**Table 2.** Reaction between ethyl nitroacetate **4** and various alkenes in the presence of rehydrated Mg:Al 3:1 HT[a]

| Entry | Olefin | Reaction time (h) | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  | 25 |  | 24[c] |
| 2 |  | 20 |  | 21[c] |
| 3 |  | 20 |  | 51[27] |
| 4 |  | 20 |  | 52[c] |
| 5 |  | 20 |  | 55[c] |
| 6 |  | 25 |  | 30[c] |

[a] Reaction conditions: ethyl nitroacetate 0.13 g (1 mmol), alkene (1.1 mmol), catalyst 0.15 g, catalytic amount of iodine, toluene (5 ml), 110 °C.
[b] Determined by $^1$H NMR.
[c] Known products were characterized by comparing the $^1$H NMR, $^{13}$C NMR and IR data with those reported in the literature.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24. Selected data of ethyl 5-butyl-4,5-dihydro-3-isoxazole carboxylate (**6**): light-yellow oil, 0.13 g (0.65 mmol). IR (neat): 1698, 1585 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.92 (t, 3H, $J = 7.3$ Hz), 1.20–1.45 (m, 7H), 1.51–1.64 (m, 1H), 1.72–1.82 (m, 1H), 2.83 (dd, 1H, $J = 8.7$ Hz, $J = 17.4$ Hz, $CH_2$), 3.23 (dd, 1H, $J = 10.8$ Hz, $J = 17.4$ Hz, $CH_2$), 4.33 (q, 2H, $J = 7.3$ Hz), 4.72–4.85 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 158.2, 151.5, 84.4, 62.2, 38.5, 34.9, 27.4, 22.5. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.30; H, 8.54; N, 7.03. Found: C, 60.12; H, 8.37; N, 6.94.
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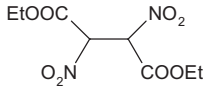
26. Selected physical data of **7**: mp >220 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.23 (t, 6H, $J = 7$ Hz), 3.59–3.62 (m, 2H), 4.13 (q, 4H, $J = 14.5$ Hz).




**7**

27. Spectral data of ethyl 5-butoxy-4,5-dihydro-3-isoxazole carboxylate: yellow oil, 0.11 g (0.51 mmol), IR (neat): 1719, 1587 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.90 (t, 3H, $J = 7$ Hz), 1.15–1.45 (m, 7H), 1.50–1.62 (m, 2H), 3.21–3.37 (m, 1H), 3.43–3.66 (m, 1H), 4.32 (q, 2H, $J = 7.1$ Hz), 4.58–4.71 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 163.5, 162.0, 88.2, 62.6, 41.4, 35.2, 31.9, 20.0. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.81; H, 7.91; N, 6.51. Found: C, 55.67; H, 7.79; N, 6.44.

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