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Tetrahedron Letters 48 (2007) 6121–6123

Tetrahedron Letters

Synthesis of α-diazo-β-hydroxy esters using nanocrystalline MgO

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Received 7 May 2007; revised 19 June 2007; accepted 27 June 2007
Available online 4 July 2007

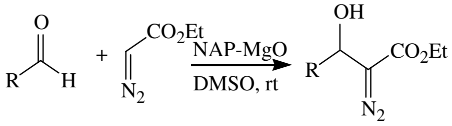
Abstract—Nanocrystalline magnesium oxide (NAP-MgO) has been found to be an effective heterogeneous, solid base catalyst for the direct aldol type reaction of ethyl diazoacetate and various aldehydes to afford the corresponding α-diazo-β-hydroxy esters in excellent yields with high selectivity under mild conditions.

Constructions of carbon–carbon bonds are important reactions that find numerous applications in synthetic organic chemistry. α-Diazo carbonyl compounds are valuable intermediates for the synthesis of amino alcohols and amino acids.[1] Moreover, the carbene species generated from α-diazo carbonyl compounds are widely used in molecular insertion reactions to form new C–C and/or C–heteroatom bonds.[2] Despite their tendency to interconvert into the corresponding β-keto carbonyl compounds, they are useful synthetic intermediates for many natural products.[3] These versatile α-diazo carbonyl compounds are generally prepared by the azido transfer reaction of carbonyl compounds. This can be usually achieved by reaction with a strong base, such as butyllithium, lithium diisopropylamide (LDA), sodium hydride or potassium hydroxide, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and quaternary ammonium hydroxide under controlled conditions.[4] However, some of these methods involve the use of very strong bases or expensive reagents and afford low yields of products. Moreover, the use of strong bases may not be compatible with certain functional groups in the substrates. Therefore, the development of alternative catalysts for the synthesis of β-hydroxy-α-diazo carbonyl compounds is highly desirable.

Although high selectivity for the desired products was achieved, there were many drawbacks under homogeneous conditions including catalyst recovery and waste disposal problems. Industry favours catalytic processes induced by heterogeneous catalysts over homogeneous processes in view of the ease of handling, simple work-up and regenerability. We herein report the use of nanocrystalline magnesium oxide (NAP-MgO) for the synthesis of β-hydroxy-α-diazo-β-hydroxy esters in excellent yields with high selectivity under mild conditions (Scheme 1). Recently, our group developed single-site NAP-MgO for the synthesis of chiral epoxy ketones, chiral nitro alcohols and Michael adducts, chiral β-hydroxy carbonyl compounds, flavanones and α,β-unsaturated esters and nitriles.[5]

Various magnesium oxide crystals [commercial MgO, CM-MgO ($30\,m^2/g$); conventionally prepared MgO, NA-MgO ($252\,m^2/g$); aero gel prepared NAP-MgO ($590\,m^2/g$)] were initially screened in the reaction of 4-chlorobenzaldehyde and ethyl diazoacetate at room temperature. NAP-MgO was found to be more active when compared to the other crystalline forms of MgO (Table 1).

In the process of optimization of the reaction conditions, we explored the use of different solvents. From Table 2, it is evident that DMSO was the best solvent in terms of product yield. Only low yields of products were isolated in the nonpolar solvents DCM and toluene, while moderate yields of products were isolated in MeCN, THF and MeOH.



Scheme 1.

Keywords: NAP-MgO; α-Diazo-β-hydroxy esters; Aldol type reaction; Heterogeneous; Solid base.

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0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.06.141

Table 1. Aldol type reaction 4-chlorobenzaldehyde and ethyl diazoacetate (EDA) with different crystallites of MgO[a]

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	NAP-MgO	DMSO	1	92
2	CP-MgO	DMSO	1	56
3	CM-MgO	DMSO	1	25

[a] Catalyst (50 mg), aldehyde (0.5 mmol), EDA (0.55 mmol), DMSO (2 mL), rt.

[b] Isolated yield.

Table 2. Screening of solvents in the reaction of 4-chlorobenzaldehyde and ethyl diazoacetate using NAP-MgO at room temperature[a]

Entry	Solvent	Time (h)	Yield[b] (%)
1	DMSO	1	92
2	DMF	1	76
3	NMP	1	59
4	MeOH	12	54
5	THF	1	57
6	MeCN	12	38
7	DCM	12	17
8	Toluene	12	37

[a] NAP-MgO (50 mg), aldehyde (0.5 mmol), EDA (0.55 mmol), solvent (2 mL).

[b] Isolated yield.

A variety of different aromatic aldehydes, containing electron-withdrawing or donating groups and heterocyclic aldehydes, were subjected to this reaction and the results are summarized in Tables 3 and 4.[6] As expected the rate of reaction was high for the aldehydes possessing electron-withdrawing groups compared with the aldehydes bearing electron-donating groups. Excellent yields were obtained with aromatic aldehydes bearing an electron-withdrawing group at the *para* position (Table 3, entries 2–4) and high yields were afforded with *ortho*- and *meta*-substituted aromatic aldehydes (Table 3, entries 7–9). Aromatic aldehydes bearing electron-donating groups afforded high yields of the desired products albeit in longer reaction times. 2-Naphthaldehyde and alicyclic cyclohexane carboxaldehyde afforded excellent yields of α-diazo-β-hydroxy esters in short reaction times (Table 3, entries 13 and 14). Excellent yields were also obtained in the reactions of *N*-heterocyclic aldehydes (Table 4, entries 1–3).

Table 3. Direct aldol type reaction of various aldehydes and ethyl diazoacetate using NAP-MgO[a]

Entry	Substrate (R)	Time (h)	Yield[b] (%)
1	C_6H_5	2	78
2	4-Cl–C_6H_4	1	92
3	4-CN–C_6H_4	1	98, 93[c]
4	4-CF_3–C_6H_4	0.5	98
5	4-F-C_6H_4	2	83
6	4-NO_2–C_6H_4	2	65
7	2-Cl–C_6H_4	2	81
8	2-NO_2–C_6H_4	2	93
9	3-NO_2–C_6H_4	2	93
10	4-Br–C_6H_4	2	72
11	4-OMe–C_6H_4	6	50
12	4-CH_3–C_cH_4	6	92
13	2-Naphthyl	3	83
14	Cyclohexyl	6	91
15	6-Bromo piperonyl	3	80

[a] NAP-MgO (50 mg), aldehyde (0.5 mmol), EDA (0.55 mmol), DMSO (2 mL), rt.

[b] Isolated yield.

[c] Yield after third cycle.

Table 4. Direct aldol type reaction of heterocyclic aldehydes and ethyl diazoacetate using NAP-MgO[a]

Entry	Substrate (R)	Time (h)	Yield[b] (%)
1	4-Pyridyl	1	96
2	3-Pyridyl	1	96
3	2-Pyridyl	1	98
4	2-Furfuryl	6	61
5	2-Thiophenyl	6	63

[a] NAP-MgO (50 mg), aldehyde (0.5 mmol), EDA (0.55 mmol), DMSO (2 mL), rt.

[b] Isolated yield.

After completion of the reaction (monitored by TLC), the reaction mixture was centrifuged to separate the catalyst and washed several times with ethyl acetate, ether and air-dried. The recovered catalyst was recycled three times without loss of activity after activation at 250 °C for 1 h under a flow of nitrogen.

In conclusion, we have shown that NAP-MgO is a highly active, reusable catalyst for the synthesis of β-hydroxy-α-diazo carbonyl compounds. Thus nanocrystalline MgO with its definite shape, size and accessible OH groups, and higher density of Mg^+ at the edges/corners shows high activity in the synthesis of β-hydroxy-α-diazo carbonyl compounds.

Acknowledgements

We wish to thank the CSIR for financial support under the Task Force Project CMM-0005. L.C. thanks the CSIR, India, and T.R. thanks the UGC for providing a senior research fellowship.

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6. *A typical procedure*: To a dried 25 mL round-bottomed flask charged with NAP-MgO (50 mg) was added DMSO (2 mL) followed by aldehyde (0.5 mmol) and EDA (0.55 mmol) at room temperature. The reaction was monitored by TLC. After completion of the reaction, the catalyst was separated by centrifuging the reaction mixture and the supernatant solution was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the crude product. Column chromatography of the crude on silica gel (60–120 mesh) using a mixture of ethyl acetate and hexane in varying proportions as eluent, gave the corresponding β-hydroxy-α-diazo ester. All the products (except for that in Table 3, entry 15) are known compounds, which were identified by IR, ^{1}H NMR and mass spectroscopic data.[4] Spectroscopic and analytical data of the new compound (Table 3, entry 15): Yellow oil. Yield: 0.137 g (80%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (1H, s), 6.97 (1H, s), 5.99 (1H, s), 5.91–5.92 (d, $J = 3.0$ Hz, 1H), 4.26 (q, $J = 7.5$ Hz, 2H), 3.8 (1H, br s), 1.3 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.64, 61.47, 68.83, 102.18, 107.92, 112.24, 112.98, 131.40, 147.94, 148.37, 166.64; IR (neat): 3427, 2980, 2902, 2096, 1671 cm^{-1}; Mass (ESI): m/z 364 $(M+Na)^+$; HRMS (ESI-MS): exact mass calcd for $C_{12}H_{11}N_2O_5$ NaBr, 364.9749; found, 364.9743.