Wadsworth–Emmons reactions catalyzed by nanocrystalline MgO

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Abstract

Wadsworth–Emmons reactions between different aldehydes including aliphatic, aromatic, cyclic and heterocyclic with various phosphonates affords α,β-unsaturated nitriles and esters under mild conditions without the formation of by-products such as Michael or Knoevenagel products using a nanocrystalline MgO catalyst.
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1. Introduction

Wadsworth–Emmons reaction (WE) belongs to a class of C–C bond formation reactions, which finds wide applications in the fine chemical industry for the manufacture of perfumes, fragrances, analgesics, insecticides, carotenoids, pheromones, pharmaceuticals and prostaglandins [1–6]. In general these reactions are effected under homogeneous conditions using various strong soluble bases such as KOH, Ba(OH)$_2$, BuLi, K$_2$CO$_3$, 18 crown-6, KOtBu and NaOEt in stoichiometric quantities [7–11]. Industry favors the use of heterogeneous catalysts in view of its simple work up and recycling. In the direction of heterogenization, commercially available MgO, ZnO, KF/alumina [12–14] in stoichiometric amounts and mixed oxides of lanthanum and magnesium [15], hydrotalcite supported *tert*-butoxide [16] and silica gel in the presence of base [17], catalysts have been employed successfully. Recently, nanomaterials have become potential candidates for wide and divergent applications that include biomedicals, pharmaceuticals and catalysis. Recently, we reported the synthesis of chiral epoxy ketones using nanocrystalline MgO, since these materials have basic sites in high density [18].
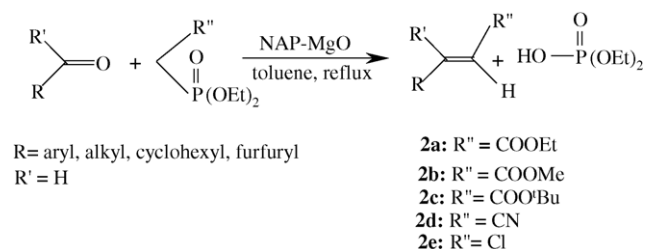
Herein we report the use of recyclable nanocrystalline magnesium oxide for the WE reaction to afford α,β-unsaturated esters, nitriles with excellent yields under mild conditions without the formation of by-products (Scheme 1).

2. Experimental

A mixture of carbonyl compound (1 mmol), phosphonate (1 mmol), NAP-MgO (0.075 g) was stirred in a 50-ml round-bottomed flask containing 5 ml of toluene. The stirring was continued at reflux temperature to effect the condensation reaction of the carbonyl compound with phosphonate until completion of the reaction, as monitored by thin-layer chromatography (TLC). After completion of the reaction, the catalyst was centrifuged, water was added to the supernatant solution, and the final product of the reaction was extracted with ethyl acetate. The protocol involving addition of water followed by extraction with ethyl acetate is required to separate the by-product (EtO)$_2$P(O) OH. The solvent was removed in vacuo, and the crude product was purified by column chromatography using ethyl acetate/hexane (2/8) as an eluent. NA-MgO and NAP-MgO catalysts were purchased from NanoScale Materials Inc., Manhattan, KS, USA. The catalyst was recycled three times without loss

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R= aryl, alkyl, cyclohexyl, furfuryl
R' = H

2a: R" = COOEt
2b: R" = COOMe
2c: R" = COO^{t}Bu
2d: R" = CN
2e: R" = Cl

Scheme 1. WE reaction between various benzaldehydes and phosphonates catalyzed by NAP-MgO.

of activity after activating at 250 °C for 1 h under nitrogen flow.

3. Results and discussion

Various magnesium oxide crystals [commercial MgO, CM-MgO (30 m^2/g); conventionally prepared MgO, NA-MgO (252 m^2/g); aerogel prepared MgO, NAP-MgO (590 m^2/g)] were evaluated in the WE reaction between benzaldehyde and triethylphosphonoacetate to understand the relation between structure and reactivity. All these MgO crystals catalyze the WE reaction with quantitative yields. However NAP-MgO shows higher reactivity over NA-MgO and CM-MgO (Table 1). Pleased with these results and to widen the scope, NAP-MgO was tested in WE reaction of further aromatic, aliphatic, cyclic and heterocyclic aldehydes with phosphonates. As expected the rate of the reaction is faster with benzaldehyde carrying electron-withdrawing groups than the reactants bearing electron-donating groups (Table 2). When the benzaldehyde is substituted either with an electron-withdrawing group or donating group at the 2-position the rate of the reaction is slow (Table 2). The scope of the reaction is also extended to various phosphonates including methyl, ethyl, *t*-butyl, cyano- and chloro-substituted ones. In all cases, yields are quantitative with high *E:Z* ratios of 99:1 under optimized conditions, whereas the diethylcyanomethylphosphonate gives *E:Z* ratio from 89:11 to 66:34. The increase in *Z* isomer is due to the lesser steric requirement of the linear cyano group. The catalyst was recycled three times without loss of activity (Table 1). Before reuse the catalyst is activated by heating at 250 °C under nitrogen flow for 1 h.

Table 1
Wadsworth–Emmons reaction between benzaldehyde and triethylphosphonoacetate with various catalysts

Catalyst	Time (h)	Yield (%)[a]
NAP-MgO	18, 18[b]	97, 97[b]
NA-MgO	36	95
CM-MgO	48	90
Sil-NAP-MgO	36	90
Sil-NA-MgO	50	90

[a] Isolated yield.
[b] Third cycle.

Table 2
Wadsworth–Emmons reaction of different carbonyl compounds with various phosphonates catalyzed by NAP-MgO

Aldehyde	Phosphonate	Time (h)	Yield (%)[a]	*E:Z*[b]
C_6H_5	2a	18	97	99:1
4-ClC_6H_4	2a	16	96	99:1
4-$NO_2C_6H_4$	2a	16	98	99:1
2-ClC_6H_4	2a	18	81	98:2
2-$NO_2C_6H_4$	2a	18	83	96:4
4-MeC_6H_4	2a	21	76	99:1
4-$OMeC_6H_4$	2a	22	69	99:1
C_4H_3O	2a	20	78	99:1
C_6H_{13}	2a	18	86	99:1
C_9H_{19}	2a	19	83	99:1
—cC_6H_{11}	2a	17	85	99:1
2-$C_{10}H_7$	2a	18	63	99:1
t-$C_6H_5CH{=}CH$	2a	18	86	99:1
C_6H_5	2b	18	96	99:1
4-ClC_6H_4	2b	17	98	99:1
4-$NO_2C_6H_4$	2b	17	98	99:1
4-MeC_6H_4	2b	21	76	99:1
4-$OMeC_6H_4$	2b	22	71	99:1
C_4H_3O	2b	18	73	99:1
C_6H_{13}	2b	19	86	99:1
—cC_6H_{11}	2b	19	83	99:1
C_6H_5	2c	19	89	99:1
C_6H_5	2d	17	97	77:23
4-ClC_6H_4	2d	17	96	71:29
4-$NO_2C_6H_4$	2d	16	97	66:34
4-MeC_6H_4	2d	21	83	89:11
4-$OMeC_6H_4$	2d	21	78	83:17
C_4H_3O	2d	18	94	81:19
C_6H_{13}	2d	19	82	74:26
—cC_6H_{11}	2d	19	76	69:31
2-$C_{10}H_7$	2d	20	78	79:21
C_6H_5	2e	19	87	99:1

[a] Isolated yield.
[b] Based on ^1H NMR.

To understand the relation between structure and reactivity, it is important to know the structure and nature of the reactive sites of NAP-MgO. NAP-MgO has a three-dimensional polyhedral structure, with the presence of high surface concentrations of edge/corner and various exposed crystal planes (such as 0 0 2, 0 0 1, 1 1 1). This leads to inherently high surface reactivity per unit area. Thus, NAP-MgO indeed displayed the highest activity compared to NA-MgO and CM-MgO. Besides this, the NAP-MgO has Lewis acid site Mg^{2+}, Lewis basic sites O^{2-} and O^-, lattice bound and isolated Bronsted hydroxyls, and anionic and cationic vacancies [19]. WE reactions are known to be driven by base catalysts [9] and accordingly the surface −OH and O^{2-} of these oxide crystals are expected to trigger these reactions. To examine the role of −OH, the Sil-NA-MgO and Sil-NAP-MgO [20], devoid of free −OH groups were tested in WE reactions. It is found that the silylated MgO samples need longer reaction times than the corresponding MgO samples in WE reaction (Table 1). NAP-MgO is having polyhedral structure and NA-MgO is having hexagonal platelets with same average concentration of −OH groups [20–22]. A possible rationale for the

display of higher reactivity to unsaturated esters, nitriles by NAP-MgO is that the −OH groups present on the edge and corner sites on NAP-MgO are more isolated and accessible for the reactants. NAP-MgO has single crystallite polyhedral structure, which is having the presence of high surface concentrations of edge/corner and various exposed crystal planes (such as 0 0 2, 0 0 1, 1 1 1), leads to inherently high surface reactivity per unit area. Thus, NAP-MgO indeed displayed the highest activity compared to NA-MgO and CM-MgO [23].

4. Conclusion

To conclude, we have shown that the NAP-MgO is a highly active reusable catalyst in the WE reaction under mild conditions without any side reactions such as Knoevenagel and Michael. Thus nanocrystalline MgO with its definite shape, size, and accessible −OH groups, higher density of Mg^+ at the edges/corner shows higher activity in the synthesis of unsaturated esters, nitriles.

Acknowledgement

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