One-pot Wittig reaction for the synthesis of α,β-unsaturated esters using highly basic magnesium/lanthanum mixed oxide

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ABSTRACT

Highly basic Mg/La mixed oxide (Mg/La MO) is an effective heterogeneous base, at room temperature for the one-pot Wittig reaction involving aldehyde, α-halo esters and triphenylphosphine to afford α,β-unsaturated esters in good yields with high *E*-stereoselectivity. Mg/La mixed oxide was recovered quantitatively by simple filtration and reused. The basic properties of Mg/La mixed oxide have been compared to those of nanocrystalline magnesium oxide using the microcalorimetric adsorption of CO_2, and the reactivity for Wittig reactions. Mg/La mixed oxide is a stronger base than magnesium oxide (MgO) but shows a much smaller number of sites. Hammett correlations have been determined for both bases and show that the reaction is base mediated, with values of $\rho = 1.7$ for Mg/La mixed oxide, and 1.1 for nanocrystalline magnesium oxide, and a compensation effect can then be observed.

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1. Introduction

The development of stereoselective methods for the construction of carbon–carbon double bonds represents one of the most challenging aspects in organic synthesis [1]. The Wittig olefination reaction is one of the powerful and versatile tools in organic synthesis for the formation of carbon–carbon double bonds [2], which gained much attention from both mechanistic and synthetic points of view. The most important intermediates for several biologically active molecules [3–5] and fluoro compounds [6–8] have been synthesized through the Wittig reaction. Conventionally Wittig reaction is carried out in three steps, involving preparation of a phosphonium salt, followed by base treatment to give an ylide, and subsequent reaction with carbonyl compounds to give olefinic product.

The most impressive synthetic strategy favored in the Wittig reaction is the replacement of the conventional three step-process with single step one-pot process. Earlier, one-pot Wittig reaction for synthesis of α,β-unsaturated esters was performed directly by the reaction of an aldehyde with methyl bromoacetate using *n*-Bu$_3$P/Zn at 100 °C [9] or catalytic amounts of tributylarsine or dibutyl telluride [10,11] in presence of stoichiometric amounts of triphenyl phosphite and potassium carbonate. Later Huang et al. used PEG-supported telluride [12–14] and modified the process by using sodium bisulfite instead of triphenyl phosphite, which represents a very simple product isolation procedure. Other reports [15–23] include the use of ethyl diazoacetate (EDA) instead of α-bromo esters in the above protocol by using catalytic amounts of iron, ruthenium, or cobalt porphyrin complexes or ruthenium and rhenium complexes in the presence of PPh$_3$, P(OMe)$_3$, P(OEt)$_3$ or other PPh$_2$R ligands. Lebel et al. used rhodium complexes for methylenation of aldehydes in the presence of PPh$_3$ using CH$_2$N$_2$ or TMSCHN$_2$ as the diazo precursors [24]. Very recently we reported one-pot Wittig reaction using nanocrystalline magnesium oxide for the synthesis of α,β-unsaturated esters and nitriles in excellent yields with high *E*-stereoselectivity in the presence of triphenylphosphine under mild conditions [25].

The Wadsworth–Emmons (WWE) reaction is the other widely used alternative method to the Wittig olefination for preparation of α,β-unsaturated esters. Earlier we reported WWE reaction by using the various heterogeneous solid base catalysts such as Mg-Al-hydrotalcite-O-*t*-Bu, NAP MgO and Mg/La mixed oxide [26,27]. This solid has been reported recently to be a strong base and good catalyst for transesterification of diethyl carbonate by alcohols [28] and Michael additions reactions [29]. We have also used this highly basic Mg/La mixed oxide as a support for palladium and performed

various C–C bond formation reactions which activate aryl chlorides at 80 °C [30,31].

2. Experimental

All the chemicals used, were purchased from Aldrich or Fluka and used without further purification. ACME silica gel (100–200 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F254 plates. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods.

Mg/La mixed oxide was prepared by the co-precipitation method at pH = 10 described earlier [28]. The chemical analysis of the solid gave the composition: La_2O_3 29.5%, MgO 30.1%, K_2O 3.4%, H_2O 37%. The solid is well characterized by XRD, DTA coupled with mass spectrometry, and microcalorimetry. This mixed oxide is mesoporous and shows a surface area of $37.6 \, m^2/g$ after calcination at 923 K. Mg/La mixed oxide has been compared to a sample of nanocrystalline magnesium oxide with high surface area ($590 \, m^2 \, g^{-1}$), consisting of nano-crystals prepared by sol gel, which has been described earlier [25].

2.1. Typical procedure for the one-pot Wittig reaction for synthesis of α,β-unsaturated esters

Mg/La mixed oxide (0.1 g, calcined at 923 K then stored in a bottle) was added to a mixture of aldehyde (1 mmol), α-halo ester (1 mmol), triphenylphosphine (1 mmol) in 5 mL of DMF and the mixture was stirred at room temperature. After completion of the reaction (as monitored by TLC), the solid was centrifuged, washed with ethyl acetate, water was added to the filtrate, and then the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. The protocol involving addition of water followed by extraction with ethyl acetate is required to remove DMF from the reaction mixture. The solvent was removed under reduced pressure, and crude product was purified by column chromatography on silica gel (100–200 mesh) using ethyl acetate/hexane as an eluent to afford the pure product.
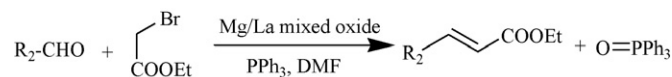
Scheme 1. One-pot Wittig reaction using Mg/La mixed oxide.

3. Results and discussion

We herein report the synthesis of α,β-unsaturated esters via one-pot Wittig reaction involving aldehyde, α-halo esters and triphenylphosphine in good yields with high E-stereoselectivity using highly basic Mg/La mixed oxide (Mg/La MO) (Scheme 1).

In an effort to develop a better system, various reaction parameters were studied for the preparation of ethyl cinnamate by the reaction with benzaldehyde, ethyl bromoacetate and triphenylphosphine at room temperature and the results are summarized in Table 1. The control reaction conducted under identical conditions devoid of Mg/La mixed oxide gave ∼5% of olefinic product. Various heterogeneous solid bases such as Mg/La mixed oxide, fluorapatite (FAP), hydroxyapatite (HAP), KF/Al_2O_3 and homogeneous inorganic bases such as NaOH, K_2CO_3, Cs_2CO_3 and KO^tBu were screened in DMF solvent at room temperature. It was found that Mg/La mixed oxide was the most efficient (Table 1, entry 1). Among homogeneous inorganic bases (1.5 equivalent) NaOH, K_2CO_3, Cs_2CO_3 gave good yields of ethyl cinnamate whereas KO^tBu afforded poor yields with low stereoselectivity (E/Z ratio: 90/10).

The solvent had a pronounced effect in these reactions (Table 1, entries 1–5), in which DMF provided better yields of desired product with excellent stereoselectivity (E/Z ratio: 99/1). When the reaction was conducted in methanol, the olefinated product was obtained in high yields, but with poor stereoselectivity compared to the reaction conducted in DMF. Among other solvents tested acetonitrile, THF and DMSO gave moderate to poor yields of the desired olefinic product with excellent stereoselectivity (Table 1, entry 5).

As reported earlier [9], the reaction between benzaldehyde and α-chloro esters, gave the phosphonium salt in the absence of any catalyst, and the ylide in the presence of MgO. The ylide was also obtained in moderate yield, with high stereoselectivity in longer

Table 1
Screening of reaction parameters for the synthesis of methyl/ethyl cinnamate[a].

Entry	Solvent	X	R	Base	Yield (%)[b]	E/Z[c]
1	DMF	Br	COOEt	Mg/La MO	92 (88), 87[d], 65[e], 91[f]	99/1
2	Methanol	Br	COOEt	Mg/La MO	88	80/20
3	Acetonitrile	Br	COOEt	Mg/La MO	69	98/2
4	THF	Br	COOEt	Mg/La MO	61	99/1
5	DMSO	Br	COOEt	Mg/La MO	85	99/1
6	DMF	Cl	COOMe	Mg/La MO	58[g]	99/1
7	DMF	Cl	COOEt	Mg/La MO	69[g]	98/2
8	DMF	Br	COOEt	NaOH[h]	91	94/4
9	DMF	Br	COOEt	Cs_2CO_3[h]	92	95/5
10	DMF	Br	COOEt	K_2CO_3[h]	90	95/5
11	DMF	Br	COOEt	KO^tBu	40	90/10
12	DMF	Br	COOEt	FAP	Trace	
13	DMF	Br	COOEt	HAP	Trace	
14	DMF	Br	COOEt	KF/Al_2O_3	70	98/2

[a] Benzaldehyde (1 mmol), α-halo ester (1 mmol), PPh_3 (1 mmol), base (0.1 g), DMF (4 mL) at room temperature.
[b] Yield based on ^1H NMR, yield in parenthesis refers to isolated yield.
[c] The ratio of E:Z isomers was determined by ^1H NMR spectroscopy and GCMS of the crude reaction mixture.
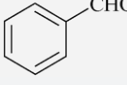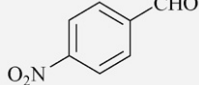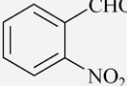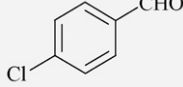[d] Yield after first recycle.
[e] Yield after second recycle.
[f] Yield after third recycle (solid base pretreated at 250 °C for 2 h under N_2 atmosphere).
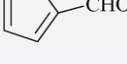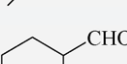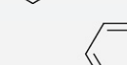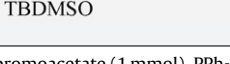[g] Reaction was continued until 24 h.
[h] 1.5 equiv. of base was used.
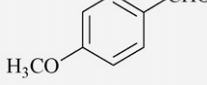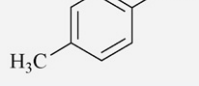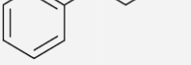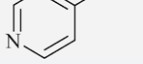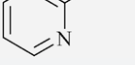
Table 2
Wittig reaction of different aldehydes with ethyl bromoacetate using Mg/La mixed oxide[a].

$R_2\text{-CHO} + \overset{Br}{\underset{COOEt}{\diagup}} \xrightarrow[\text{PPh}_3, \text{DMF}]{\text{Mg/La mixed oxide}} R_2\diagup\diagdown\text{COOEt} + O=PPh_3$

Entry	R₂-CHO	Time (h)	Yield (%)[b]	E/Z[c]
1		14	92 (88)	99/1
2		1	99 (92)	99/1
3		5	96	94/6
4		10	85	99/1
5		18	58 (53)	99/1
6		18	49	99/1
7		14	95	98/2
8		10	94 (90)	96/4
9		10	95	98/2
10		10	93	98/2
11		14	93	99/1
12		14	76	99/2
13		14	56	99/1

[a] Benzaldehyde (1 mmol), ethyl bromoacetate (1 mmol), PPh₃ (1 mmol), Mg/La MO (0.1 g), DMF (4 mL) at room temperature.
[b] Yield based on ¹H NMR, yield in parenthesis refers to isolated yield.
[c] The ratio of E:Z isomers was determined by ¹H NMR spectroscopy and GCMS of the crude reaction mixture.
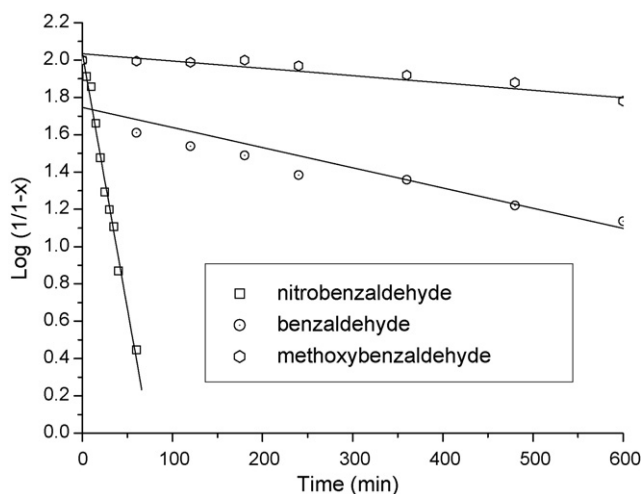
Fig. 1. Plot of the fisrt order kinetic equation as a function of time for three benzaldehydes.

Fig. 2. Effect of the substituent X on the rate of substituted benzaldehydes using Mg/La mixed oxide, and by nanoparticles of MgO.

reaction times compared to ethyl bromoacetate, which might be due to the difference in electronegativity between chlorine and bromine. This formation of ylide corresponds to an elimination of HBr, which surprisingly does not inhibit the activity for further steps, in spite of the very small number of basic sites on the solid (about 0.03 meq g^{-1}). Indeed, Mg/La mixed oxide could be recovered quantitatively by simple centrifugation and reused several times (Table 1, entry 1). This suggests that in organic media HBr is not readily adsorbed at the surface. We propose that it is neutralised by DMF, which is a basic solvent, and indeed the best one for this process.

We chose a variety of structurally divergent aldehydes possessing a wide range of functional groups to understand the scope and the generality of the Mg/La mixed oxide for one-pot Wittig reaction with ethyl bromoacetate and the results are summarized in Table 2. Among the various aromatic aldehydes tested, the rate of the reaction is faster with benzaldehydes having electron-withdrawing groups such as 4-nitrobenzaldehyde, 2-nitrobenzaldehyde and 4-chlorobenzaldehyde (Table 2, entries 2–4) compared to the substrates bearing an electron-donating group such as *p*-anisaldehyde and *p*-tolualdehyde (Table 2, entries 5 and 6). All the substituted benzaldehydes gave high stereoselective olefinic product (E/Z: 99/1) except 2-nitrobenzaldehyde which show little difference in stereoselectivity (6% of Z isomer or E/Z: 94/6) which might be due to an *ortho*-steric effect.

Highly conjugated aromatics like cinnamaldehyde, heteroaromatic aldehydes such as 2-pyridinecarboxaldehyde, 4-pyridinecarboxaldehyde, 2-furaldehyde and aliphatic aldehydes namely cyclohexylcarboxaldehyde, isovaleraldehyde afforded good yields of the corresponding α,β-unsaturated esters with high stereoselectivity (Table 2, entries 7–12). Labile substrates like TBDMS-protected aldehyde namely 3-(tert-butyl-dimethyl-silanyloxy)-benzaldehyde underwent smooth reaction to give the corresponding α,β-unsaturated esters with TBDMS moieties untouched (Table 2, entry 13).

A quantitative analysis of the kinetics was done using benzaldehyde, nitro- and methoxy-benzaldehyde. The reaction obeys a first order rate law, represented by the equation:

$$\log(1 - x) = -k_a t$$

where k_a is the first order rate constant, x the fractional conversion of benzaldehyde, and t the reaction time. The plot is linear over a large range of conversions, as shown in Fig. 1. The rate constant k_a is obtained from the slope of the line. This rate constant is related
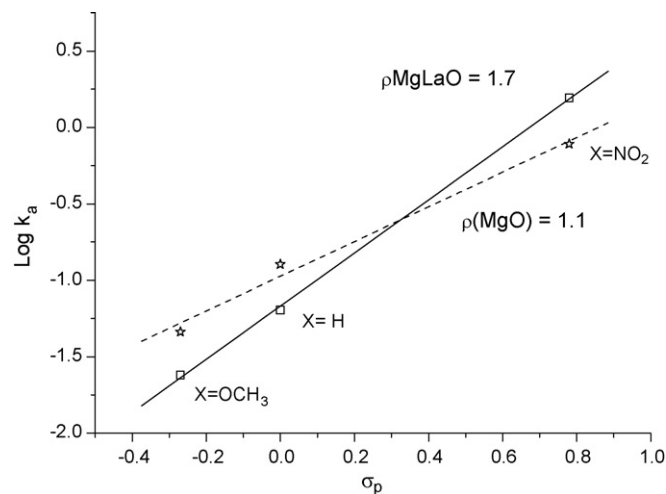
to the mechanism and can be used to study the electronic effect of substituents. A good Hammett correlation is obtained (correlation coefficient = 0.999), using σ_p values to measure the effect of substituents (Fig. 2). The positive slope proves that the reaction is base mediated. The slope of the linear plot, ρ, is related to the charge on the intermediate complex. A high value is observed, $\rho = 1.7$, showing a high charge on this intermediate complex. By comparison, values of 2.8 have been reported for the reaction of benzaldehyde with benzylidenetriphenylphosphoranes in THF, catalysed by sodium hexamethyldisilazide [32]. This high charge is consistent with the known high basicity of Mg/La mixed oxide. This reactions proceeds then by formation of a carbanion, by attack of the acetate at a basic site, which is the active site, the carbanion being stabilised at an acid site.

The results obtained using nanoparticles of MgO are also reported in Fig. 2, and show a much lower ρ constant, 1.1 instead of 1.7. This lower value is indicative of a lower charge on the intermediate complex, consistent with the lower basicity of MgO compared to Mg/La MO (Fig. 3).

The basic properties of Mg/La mixed oxide have been compared to those of nanocrystalline magnesium oxide using the microcalorimetric adsorption of CO_2. Fig. 3 presents the isotherms of adsorption and Fig. 4 the variation of the differential heat of
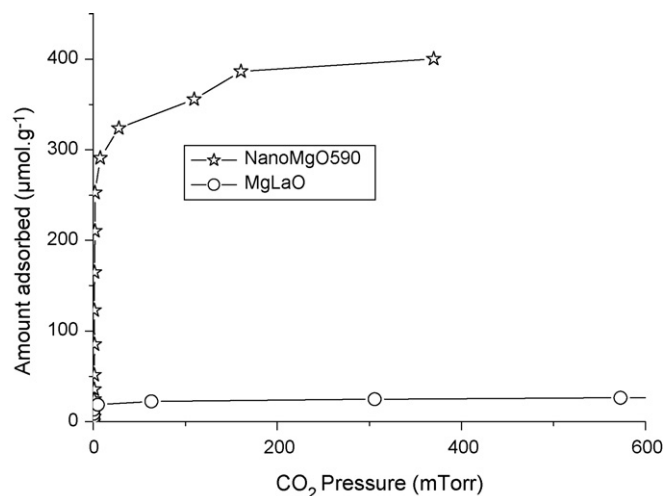

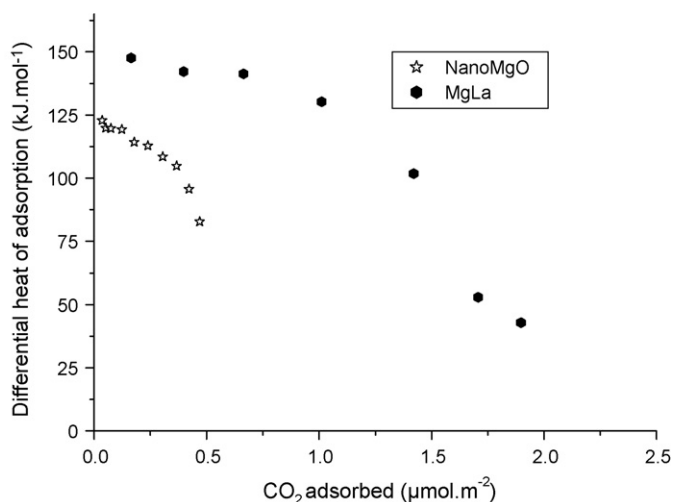**Fig. 3.** Isotherms of CO_2 adsorption on MgO and Mg/La MO.

Fig. 4. Differential heats of CO_2 adsorption on MgO and Mg/La MO.

adsorption as a function of coverage. The comparison of several experiments shows a reproducibility of about 95%, with a higher uncertainty at high coverage, due to the very long time required to reach equilibrium. At low coverages a higher basic strength is observed for Mg/La mixed oxide, with a higher heat of adsorption. However, due to the higher surface area of MgO, the specific number of sites is $300 \,\mu\text{mol}\,\text{g}^{-1}$ for the nanocrystalline MgO, compared to 20–$30 \,\mu\text{mol}\,\text{g}^{-1}$ for the mixed oxide. The turnover number frequency, or activity per active site, for the reaction of benzaldehyde, is then $4 \times 10^4 \,\text{h}^{-1}$ for MgO, and $30 \times 10^4 \,\text{h}^{-1}$ for Mg/La MO. When compared by unit weight, a reverse result is observed since the large surface area of MgO ($590 \,\text{m}^2 \,\text{g}^{-1}$) and the consequent large number of sites, compensate the lower basic strength.

4. Conclusions

In conclusion, we have developed a simple and efficient method for the preparation of α,β-unsaturated esters *via* one-pot Wittig reaction involving aldehyde, α-halo esters and triphenylphosphine to afford α,β-unsaturated esters in good yields with high *E*-stereoselectivity using Mg/La mixed oxide. The solid can be readily recovered and reused.

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