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Catalysis in Water: Aldol-Type Reaction of Aldehydes and Imines with Ethyl Diazoacetate Catalyzed by Highly Basic Magnesium/Lanthanum Mixed Oxide

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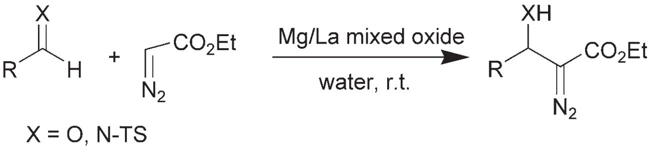
Abstract: Magnesium/lanthanum mixed oxide is an effective heterogeneous catalyst for aldol-type condensation of aldehydes and imines with ethyl diazoacetate (EDA) at room temperature in water to afford corresponding β-hydroxy-α-diazo carbonyl compounds and β-amino-α-diazo carbonyl compounds in good yields. The catalyst is recovered and reused for several cycles with consistent activity.

Keywords: β-amino-α-diazo carbonyl compounds; β-hydroxy-α-diazo carbonyl compounds; heterogeneous catalyst; magnesium/lanthanum mixed oxide; water as solvent

α-Diazo carbonyl compounds[1] are a potential source of amino alcohols and acids. α-Diazo carbonyl compounds are generally prepared by the azido transfer reaction of carbonyl compounds.[2] Condensation of acyldiazomethane to aldehydes and imines also yields α-diazo carbonyl compounds but requires deprotonation of the acyldiazomethane. This is usually carried out by using strong bases, such as butyllithium,[3] lithium diisopropylamide (LDA),[4] sodium hydride,[5] potassium hydroxide,[6] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[7] and quarternary ammonium hydroxide.[8] However, some of the methods require low temperatures and absolutely anhydrous conditions, moreover the use of such strong bases may not be compatible with functional groups in the substrates. Thus, the development of more improved synthetic methods for the preparation of α-diazo carbonyl compounds remains an active research area.

In recent years, there has been increasing emphasis on the use and design of environment-friendly solid catalysts to reduce the amount of toxic waste. The use of a solid catalyst allows easy separation of catalyst from the reaction mixture in large-scale production to conform to the concept of green technology. In a recent review, Sheldon[9] emphasized the point that "the best solvent is no solvent and if a solvent (diluent) is needed then water is preferred. Water is non-toxic, non-flammable, abundantly available and inexpensive" therefore, reactions performed in water are safer and cheaper.

We herein report the synthesis of β-hydroxy-α-diazo carbonyl compounds and β-amino-α-diazo carbonyl compounds by condensation of a wide variety of aldehydes and imines with ethyl diazoacetate using the Mg/La mixed oxide catalyst in water (Scheme 1).

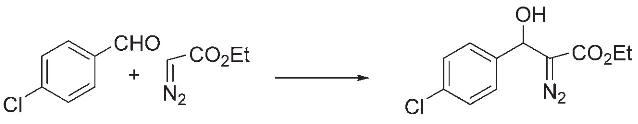


Scheme 1.

To the best of our knowledge, there are no reports on this condensation using a heterogeneous catalyst and water as solvent. The Mg/La mixed oxide catalyst was prepared by the co-precipitation method described earlier.[10] Chemical analysis of the solid gave the composition La_2O_3 29.5%, MgO: 30.1%, K_2O: 3.4%, H_2O: 37%. The catalyst is well characterized by XRD, DTA coupled with mass spectrometry, FTIR and calorimetry. This mixed oxide is macroporous and shows a surface area of 37.6 m^2g^{-1} after calcination at 923 K. Recently, we have efficiently performed transesterifications of diethyl carbonate by alcohols[11] and Michael addition reactions[10] by using this highly basic Mg/La mixed oxide catalyst. We have also used the Mg/La mixed oxide as a support for palladium and performed various C–C bond forming reactions with this palladium/Mg-La mixed oxide catalyst.[12]

In an effort to develop a better catalytic system, various reaction parameters were studied for the preparation of ethyl 3-hydroxy-2-diazo-3-(4-chlorophenyl)-propionate by the reaction of 4-chlorobenzaldehyde with ethyl diazoacetate (EDA) at room temperature and the results are summarized in Table 1.

Table 1. Screening reaction parameters for the synthesis of ethyl 3-hydroxy-2-diazo-3-(4-chlorophenyl)-propionate.[a]



Entry	Solvent	Catalyst	Yield [%][b]
1	H_2O	Mg/La mixed oxide	87, 85,[c] 88[d]
2	H_2O	FAP	82
3	H_2O	HAP	67
4	H_2O	KF/Al_2O_3	64
5	H_2O	MgO (Commercial)	54
6	H_2O	LDH-Cl	76
7	H_2O	$LDH-CO_3$	78
8	H_2O:MeOH (1:1)	Mg/La mixed oxide	80
9	CH_3CN	Mg/La mixed oxide	20
10	H_2O:CH_3CN (1:1)	Mg/La mixed oxide	69

[a] *Reaction conditions:* 4-chlorobenzaldehyde (1 mmol), EDA (1.1 mmol), catalyst (0.025 g), solvent (2 mL), reaction time (6 h), room temperature, stirring rate 1500 rpm.

[b] Isolated yields.

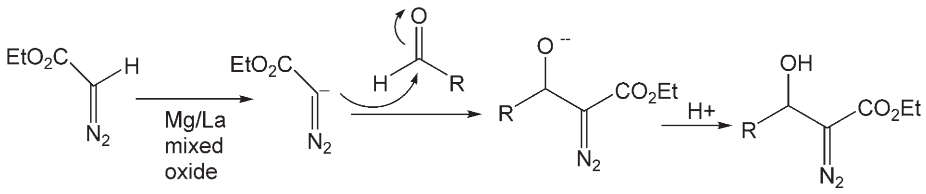
[c] Yield after fourth cycle.

[d] Stirring rate: 2500 rpm.

Various solid base catalysts such as Mg/La mixed oxide, fluorapatite(FAP), hydroxyapatite(HAP), KF/Al_2O_3, commercial MgO, layered double hydroxides-chloride (LDH-Cl) and layered double hydroxides-carbonate (LDH-CO_3) were screened in water and it was found that Mg/La mixed oxide is the most efficient catalyst (Table 1, entry 1). FAP, LDH-Cl and LDH-CO_3 (Table 1, entries 2, 6 and 7) provided moderate yields of ethyl 3-hydroxy-2-diazo-3-(4-chlorophenyl)-propionate whereas HAP, KF/Al_2O_3 and commercial MgO showed poor catalytic activity. The solvent has a pronounced effect in these reactions (Table 1, entries 8–10), in which water provided better yields. This high activity of a solid base in water as solvent is rather surprising since it is well known that, for most solid bases, their catalytic properties appear only after removal of water.[13] The controlled reaction conducted under identical conditions devoid of Mg/La mixed oxide catalyst gave no condensed product, despite prolonged reaction times. Mg/La mixed oxide was recovered quantitatively by simple centrifugation and reused for four cycles with consistent activity (Table 1, entry 1).

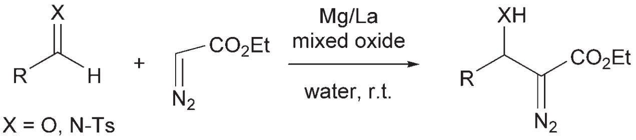
We chose a variety of structurally divergent aldehydes and imines possessing a wide range of functional groups to understand the scope and the generality of the Mg/La mixed oxide catalyzed aldol-type condensation reaction to form β-hydroxy-α-diazo carbonyl compounds and β-amino-α-diazo carbonyl compounds and the results are summarized in Table 2. Among the aromatic, aliphatic and heteroaromatic aldehydes tested, aromatic aldehydes with electron-withdrawing substituents reacted faster than those with electron-donating substituents (Table 2, entries 2–5). Heteroaromatic aldehydes such as pyridine-2-carboxaldehyde, pyridine-4-carboxaldehyde and furfuraldehyde gave good yields of corresponding β-hydroxy-α-diazo-carbonyl compounds (Table 2, entries 6–8), in contrast to quarternary ammonium hydroxide reported earlier which gave poor yields. On the other hand, aliphatic aldehydes such as valeraldehyde, cinnamaldehyde and isovaleraldehyde gave poor yields of the corresponding β-hydroxy-α-diazo carbonyl compounds (Table 2, entries 9–11). It is also worthwhile to note that only the monocondensation product was obtained with a 1,4-dicarboxaldehyde (Table 2, entry 12). Imines such as 2-chloroaldimine and 4-methoxyaldimine were also successfully employed to give the corresponding β-amino-α-diazo carbonyl compounds with moderate yields (Table 2, entries 14 and 15). We have also carried out the reaction with labile substrates like 6-bromopipernal or 6-bromobenzo[1,3]dioxole-5-carbaldehyde and TBDMS-protected aldehyde [3-(*tert*-butyldimethylsilanyloxy)-benzaldehyde]. We obtained good yields of the corresponding β-hydroxy-α-diazo carbonyl compounds and the acetal/TBDMS moieties remained intact (Table 2, entries 16 and 17). The plausible mechanism for the present aldol-type reaction is depicted in Scheme 2.

In conclusion, we have developed a simple and efficient method for the preparation of β-hydroxy-α-diazo carbonyl compounds and β-amino-α-diazo carbonyl compounds by the condensation of aldehydes and imines with ethyl diazoacetate using Mg/La mixed oxide as a heterogeneous catalyst in water at room temperature. The catalyst can be readily recovered and reused. This methodology illustrates the fact



Scheme 2.

Table 2. Mg/La mixed oxide catalyzed aldol-type reaction of aldehydes and imines with EDA.[a]

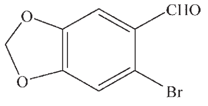


Entry	R in Substrate	X	Time [h]	Yield [%][b]
1	C_6H_5	O	7	85
2	4-Cl-C_6H_4	O	6	87
3	4-CN-C_6H_4	O	7	82
4	4-NO_2-C_6H_4	O	8	92
5	4-Me-C_6H_4	O	10	76
6	2-pyridyl	O	10	84
7	4-pyridyl	O	10	78
8	2-Furfuryl	O	10	78
9	$CH_3(CH_2)_3$	O	18	67
10	$C_6H_4(CH)_2$	O	24	52
11	*i*-$CH_2CH(CH_3)_2$	O	18	72
12	4-CHO-C_6H_4	O	18	93
13	3-Br-C_6H_4	O	12	75
14	2-Cl-C_6H_4	N-Ts	12	71
15	4-MeO-C_6H_4	N-Ts	12	69
16	6-Bromopipernal[c]	O	10	72
17	3-TBDMS-OC_6H_4	O	12	85

[a] *Reaction conditions:* aldehyde/imine (1 mmol), EDA (1.1 mmol), Mg/La mixed oxide catalyst (0.025 g), water (2 mL), room temperature.

[b] Isolated yields.

[c]



that solid bases can also be operated in water, and may find widespread use in organic synthesis for the preparation of β-hydroxy-α-diazo carbonyl compounds and β-amino-α-diazo carbonyl compounds.

Experimental Section

Typical Procedure for Preparation of Ethyl 3-Hydroxy-2-diazo-3-(4-chlorophenyl)-propionate

Mg/La mixed oxide (0.025 g) was added to a mixture of 4-chlorobenzaldehyde (1 mmol), EDA (1.1 mmol) in water (2 mL) and stirred at room temperature. After completion of reaction (as monitored by TLC), the catalyst was centrifuged, washed with ethyl acetate and the centrifugate was treated with ethyl acetate (10 mL) and stirred vigorously. The resultant organic layer was separated and the aqueous layer was again extracted with ethyl acetate (5 mL). The combined organic layer was concentrated to give the crude ethyl 3-hydroxy-2-diazo-3-(4-chlorophenyl)-propionate. Column chromatography was performed using silica gel (100–200 mesh) to afford pure ethyl-3-hydroxy-2-diazo-3-(4-chlorophenyl)-propionate as an oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 7.1$ Hz, 3H), 3.73 (br s, 1H), 4.23 (q, $J = 7.1$ Hz, 2H), 5.82 (s, 1H), 7.25–7.36 (m, 4H); MS: $m/z = 254$ (M^+).

Supporting-Information

Characterization of all compounds with scanned ^{1}H NMR spectra are available in the Supporting Information

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