690 **RESEARCH PAPER** VOL. 38 NOVEMBER, 690–691 JOURNAL OF CHEMICAL RESEARCH 2014

An efficient aldol-type reaction of ethyl diazoacetate with aldehydes promoted by MgI$_2$ etherate

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The first example of the preparation of α-diazo-β-hydroxy esters by the aldol-type condensation of aldehydes with ethyl diazoacetate using Et$_3$N as base in the presence of magnesium iodide etherate [MgI$_2$.(Et$_2$O)$_n$] has been achieved in good to excellent yields at room temperature in CH$_2$Cl$_2$ in 15–30 min.

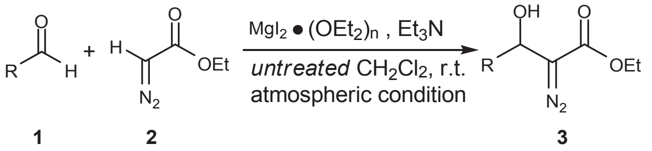
Keywords: aldehyde, ethyl diazoacetate, α-diazo-β-hydroxy esters, magnesium iodide etherate

The chemistry of α-diazocarbonyl compounds has received considerable attention because of the diverse range of synthetically useful transformations that these compounds can undergo.[1] In particular, α-diazocarbonyl compounds are considered to be a potential source of amino alcohols and acids. The application of α-diazo-β-hydroxy esters has been extensively explored because these compounds are involved in many organic transformations.[2–4] Among the diverse synthetic routes available to access α-diazo-β-hydroxy esters, one attractive method is the condensation of diazoacetate to aldehydes catalysed by Lewis acids.[5,6] In addition to these methods, α-diazo-β-hydroxy esters can also be obtained by reactions of diazoacetate with aldehydes through nucleophilic addition in the presence of a strong base, such as butyllithium,[7,8] lithium diisopropylamide (LDA),[9–11] sodium hydride,[12] potassium hydroxide,[13–15] 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU),[16] quaternary ammonium hydroxide,[17] potassium *t*-butoxide (KO^{t}Bu).[18] Although the anionic species thus generated can efficiently add to carbonyl compounds, some of these methods clearly require strongly basic reagents and anhydrous conditions.

In a previous paper, we have demonstrated that MgI$_2$.(Et$_2$O)$_n$, a mild Lewis acid efficiently promoted the direct aldol addition of methyl ketones to aromatic aldehydes.[19] We now report an efficient and facile method for the synthesis of α-diazo-β-hydroxy esters by the coupling of aldehydes with ethyl diazoacetate (EDA) promoted by MgI$_2$.(Et$_2$O)$_n$ in the presence of Et$_3$N at room temperature under atmospheric conditions.

Results and discussion

To optimise the reaction (Scheme 1), we chose benzaldehyde (**1a** R=Ph) as a model substrate and we determined the yield of product (**3a** R=Ph) using various amounts of MgI$_2$.(Et$_2$O)$_n$ and Et$_3$N and 1.2 equiv. EDA in CH$_2$Cl$_2$ at room temperature. As shown in Table 1, without MgI$_2$.(Et$_2$O)$_n$ or Et$_3$N, the reaction could not be carried out (entries 1 and 2). With increasing amounts of MgI$_2$.(Et$_2$O)$_n$, the yield of aldol product ethyl 2-diazo-3-hydroxy-3-phenylpropanoate successively was improved (entries 3–9). This yield was optimised to 95% by using 1.0 equiv. of MgI$_2$.(Et$_2$O)$_n$ and 2.0 equiv. of Et$_3$N (entry 10).



Scheme 1

Of various untreated solvents screened, an excellent yield was obtained in non-coordinating reaction media CH$_2$Cl$_2$. Moderate yields (83%) were provided in toluene. The reaction was very sluggish in the coordinative polar solvents such as Et$_2$O, MeCN and THF. The reactions did not take place in more polar solvents, such as DMF, dioxane and MeOH. To examine the halide anion effect, halogen analogues of MgI$_2$ etherate were compared under parallel reaction conditions (1.0 equiv. of promoters). MgCl$_2$ etherate was almost inactive and MgBr$_2$ etherate was less effective in terms of substrate conversion and yield.

With the best optimal conditions in hand, a variety of different aldehydes, including aliphatic, aromatic, and heteroaromatic aldehydes were subjected to this reaction and the results are summarised in Table 2. There was no need to exclude moisture and oxygen from the reaction system. As shown in Table 2, MgI$_2$ etherate-Et$_3$N promoted aldol coupling of ethyl diazoacetate (EDA) with aromatic aldehydes in good to excellent yields in a very short period. Moreover aromatic aldehydes bearing either electron-donating or electron-withdrawing groups in the aromatic ring reacted smoothly to afford the desired aldol adducts in very good to excellent yields (Table 2, entries 1–8).

A heteroaromatic aldehyde, 2-thiophenealdehyde, was a good substrate as well (entry 9). An α,β-unsaturated aldehyde, cinnamaldehyde, reacted with EDA to afford the aldol adduct in excellent yield without any decomposition or polymerisation

Table 1 Optimisation of the reaction conditions for formation of ethyl 2-diazo-3-hydroxy-3-phenylpropanoate **3a** (R=Ph) by reaction of benzaldehyde **1a** (R=Ph) with ethyl diazoacetate (EDA) **2** for various times and under several sets of conditions (Scheme 1)[a]

Entry	MgI$_2$.(Et$_2$O)$_n$/ mol%[b]	Et$_3$N/mol%[b]	Time/h	Yield of **3a** (R=Ph)/%[c]
1	100	0	12	0
2	0	200	12	0
3	15	200	8	40
4	30	200	8	62
5	50	150	8	60
6	50	200	3	71
7	60	200	3	78
8	70	200	2	84
9	80	200	1	90
10	100	200	0.25	95
11	100	300	0.33	94

[a] Reaction conditions: to a solution of benzaldehyde **1a** (R=Ph) (1 mmol) and EDA (1.2 mmol) in untreated CH$_2$Cl$_2$ (5 mL) was added MgI$_2$.(OEt$_2$)$_n$ and Et$_3$N and the mixture stirred for various times.

[b] Relative to benzaldehyde.

[c] Isolated yields after silica gel column chromatographic purification.

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Table 2 Yields of ethyl 2-diazo-3-hydroxy-3-aryl/alkylpropanoates **3a–l** by reaction of the corresponding aldehydes **1** with ethyl diazoacetate (EDA) **2** using Et_3N as base in the presence of magnesium iodide etherate [$MgI_2.(Et_2O)_n$] for various times (Scheme 1)[a]

Entry	R	t/min	Product	Yields of **3a–l**/%[b]
1	C_6H_5	15	**3a**	95
2	4-$MeOC_6H_4$	15	**3b**	92
3	2-MeC_6H_4	20	**3c**	93
4	4-ClC_6H_4	20	**3d**	94
5	4-FC_6H_4	20	**3e**	93
6	4-$NO_2C_6H_4$	25	**3f**	97
7	4-$CF_3C_6H_4$	15	**3g**	96
8	1-Naphthyl	15	**3h**	93
9	2-Thienyl	15	**3i**	93
10	*trans*-PhCH=CH	30	**3j**	89
11	Cyclohexyl	15	**3k**	90
12	*t*-Bu	15	**3l**	88

[a] Reaction conditions: To a solution of aldehyde **1** (R = various) (1 mmol) and EDA (1.2 mmol) in untreated CH_2Cl_2 (5 mL) was added $MgI_2.(OEt_2)_n$ (1 mmol) and Et_3N (2 mmol) and the mixture stirred for various times.

[b] Isolated yields after silica gel column chromatographic purification.

(entry 10). In addition to aromatic aldehydes, aliphatic aldehydes also reacted efficiently under the same conditions (entries 11 and 12). Note that the addition to the more sterically hindered aldehyde, *t*-butyl aldehyde, gave the product in good yield (88%). However, ketones did not react, even prolonging the reaction time.

In conclusion, we have demonstrated the unique reactivity of MgI_2 etherate in the aldol coupling of aldehydes with EDA. This magnesium-promoted aldol addition is mild, efficient and operationally simple. Further investigation on the reactivity of MgI_2 etherate in other C–C bond constructing reactions is underway.

Experimental

All reagents were obtained from commercial suppliers, and were used without further purification unless otherwise indicated. Silica gel for column chromatography was purchased from Qingdao Haiyang Chemical Co., Ltd. Melting points were determined using a Büchi B-540 capillary melting-point apparatus. ^1H NMR spectra were recorded with a Bruker Avance instrument at 500 MHz in $CdCl_3$ with tetramethylsilane as the internal standard.

MgI_2 etherate-promoted aldol reaction; general procedure

Freshly prepared MgI_2 etherate[20] was added to a stirred solution of aldehyde (1.0 mmol), EDA (127 mg, 1.2 mmol) and Et_3N (121 mg, 1.2 mmol) in CH_2Cl_2 (5 mL) (1.0 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 15–30 min and quenched with saturated aqueous Na_2SO_3. Extractive workup with ether and chromatographic purification of the crude product on silica gel gave the desired aldol adduct.

Ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (**3a**):[17] Pale yellowish oil; δ_H 1.31 (t, J = 7.2 Hz, 3H), 3.26 (br s, 1H), 4.29 (q, J = 7.2 Hz, 2H), 5.93 (d, J = 2.5 Hz, 1H), 7.28–7.45 (m, 5H).

Ethyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)propanoate (**3b**):[17] Yellowish oil; δ_H 1.33 (t, J = 7.3 Hz, 3H), 3.00 (br s, 1H), 3.83 (s, 3H), 4.29 (q, J = 7.3 Hz, 2H), 5.88 (s, 1H), 6.93 (d, J = 7.0 Hz, 2H), 7.36 (d, J = 7.0 Hz, 2H).

Ethyl 2-diazo-3-hydroxy-3-(o-tolyl)propanoate (**3c**):[16] Pale yellowish oil; δ_H 1.29 (t, J = 7.1 Hz, 3H), 3.75 (br s, 1H), 3.84 (s, 3H), 4.25 (q, J = 7.1 Hz, 2H), 5.96 (d, J = 4.8 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 7.00 (m, 1H), 7.31 (m, 1H), 7.47 (d, J = 7.3 Hz, 1H).

Ethyl 3-(4-chlorophenyl)-2-diazo-3-hydroxypropanoate (**3d**):[17] Pale yellowish oil; δ_H 1.29 (t, J = 7.1 Hz, 3H), 3.69 (br s, 1H), 4.25 (q, J = 7.1 Hz, 2H), 5.87 (s, 1H), 7.34–7.38 (m, 4H).

Ethyl 2-diazo-3-(4-fluorophenyl)-3-hydroxypropanoate (**3e**):[17] Yellowish oil; δ_H 1.29 (t, J = 7.1 Hz, 3H), 3.52 (br s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 5.89 (d, J = 1.25 Hz, 1H), 7.06–7.09 (m, 2H), 7.40–7.43 (m, 2H).

Ethyl 2-diazo-3-hydroxy-3-(4-nitrophenyl)propanoate (**3f**):[17] Yellowish oil; δ_H 1.28 (t, J = 7.1 Hz, 3H), 3.90 (br s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 5.99 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 8.21–8.24 (m, 2H).

Ethyl 2-diazo-3-hydroxy-3-(4-(trifluoromethyl)phenyl)propanoate (**3g**): Pale yellowish solid, m.p. 52.3–53.1 °C (lit.[21] 51–53 °C). δ_H 1.29 (t, J = 7.2 Hz, 3H), 3.65 (br s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 5.96 (s, 1H), 7.56 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H).

Ethyl 2-diazo-3-hydroxy-3-(naphthalen-1-yl)propanoate (**3h**):[21] Pale yellowish oil; δ_H 1.33 (t, J = 7.2 Hz, 3H), 3.72 (br s, 1H), 4.32 (q, J = 7.2 Hz, 2H), 6.64 (s, 1H), 7.50–7.56 (m, 3H), 7.83–7.95 (m, 4H).

Ethyl 2-diazo-3-hydroxy-3-(thiophen-2-yl)propanoate (**3i**):[22] Yellowish oil; δ_H 1.31 (t, J = 7.2 Hz, 3H), 3.39 (br s, 1H), 4.29 (q, J = 7.2 Hz, 2H), 6.12 (s, 1H), 7.02 (d, J = 3.9 Hz, 1H), 7.03–7.07 (m, 1H), 7.31 (d, J = 3.9 Hz).

(E)-Ethyl 2-diazo-3-hydroxy-5-phenylpent-4-enoate (**3j**):[17] Yellowish oil. δ_H 1.32 (t, J = 7.1 Hz, 3H), 2.87 (br s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 5.46 (d, J = 5.3 Hz, 1H), 6.28 (dd, J = 5.6, 16.0 Hz, 1H), 6.82 (d, J = 15.6 Hz, 1H), 7.29–7.42 (m, 5H).

Ethyl 3-cyclohexyl-2-diazo-3-hydroxypropanoate (**3k**):[17] Pale yellowish oil; δ_H 0.92–1.31 (m, 8H), 1.45–1.80 (m, 5H), 2.0 (d, J = 12 Hz, 1H), 3.23 (br s, 1H), 4.19 (q, J = 7.02 Hz, 2H), 4.26 (d, J = 9.34 Hz, 1H).

Ethyl 2-diazo-3-hydroxy-4,4-dimethylpentanoate (**3l**):[21] Pale yellowish oil. δ_H 0.97 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 2.94 (br s, 1H), 4.19–4.23 (m, 3H).

We are grateful to the National Natural Science Foundation of China (No. 21372203 and 21272076).

Received 24 September 2014; accepted 23 October 2014
Paper 1402914 doi: 10.3184/174751914X14145853961149

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