SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 6, pp. 1117–1123, 2004

Synthesis of β-Keto Esters Promoted by Yttria-Zirconia Based Lewis Acid Catalyst

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ABSTRACT

A variety of aldehydes react with methyl/ethyl diazoacetate in the presence of yttria-zirconia based catalyst to afford the corresponding β-keto esters in excellent yields.

Key Words: Yttria-zirconia based Lewis acid; Heterogeneous catalysis; Aldehyde; Diazoacetate; β-keto esters.

β-Keto esters are multicoupling reagents having electrophilic carbonyl and nucleophilic carbon. They are basic building blocks[1] in the total synthesis of sex pheromones,[2] natural products[3] and are extensively used in

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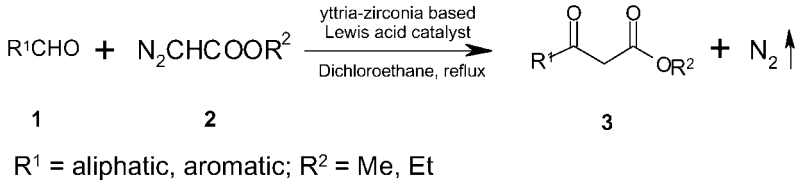
DOI: 10.1081/SCC-120028644 0039-7911 (Print); 1532-2432 (Online)



Scheme 1.

the agrochemical, pharmaceutical and dyestuff industries. Numerous methods have been reported for their preparations.[4] The method involving the condensation of aldehyde with ethyl diazoacetate is short and direct. Apart from the classical Claisen condensation[5] and related reactions,[6] the diazo-mediated protocol is effected either thermally[7] or in the presence of Lewis acids.[8] Solid catalysts have also been used in β-keto esters synthesis.[9]

As a part of our research program aimed at developing new catalyst and subsequent applications to various organic transformations, the yttria-zirconia based Lewis acid was found to be extremely efficient for various transformations.[10] In this report we have explored the efficacy of yttria-zirconia based Lewis acid catalyst in the synthesis of β-keto esters (Sch. 1).

RESULTS AND DISCUSSION

The condensation of aldehydes with methyl/ethyl diazoacetate in the presence of catalytic amount of yttria-zirconia based Lewis acid afforded the corresponding ß-keto esters in good to excellent yields (Table 1). The aliphatic aldehyde reacted faster than aromatic (Table 1, entry 1). The substitution pattern in the aromatic ring has distinctive influence on the rate of reaction. For example, the aromatic aldehyde with electron donating substituents accelerated the reaction (Table 1, entries 4, 9) whereas an electron withdrawing substituent retarded the rate of reaction (Table 1, entries 3, 6), although yields were comparable. The reactions of benzaldehyde with ethyl diazoacetate with varying amounts of yttria-zirconia catalyst were studied which indicated that the optimised amount of catalyst needed for high efficiency was 20 wt%. In the absence of the catalyst there was no reaction up to 48 hr (Table 1, entry 11). The formation of β-keto esters could be visualized through a α-diazo-β-keto ester type of intermediate generated by electrophilic attack on diazoacetate of species formed upon complexation of aldehyde with the acid sites of the catalyst. Loss of nitrogen followed by 1,2-hydride shift is expected to lead to the observed β-keto ester.

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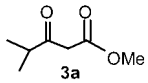
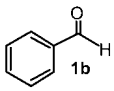
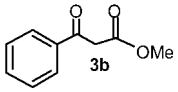
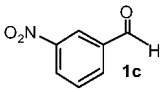
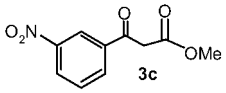
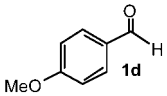
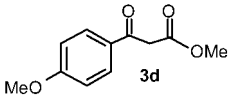
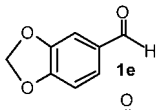
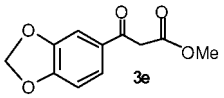
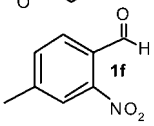
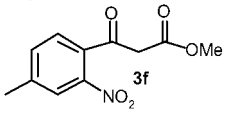
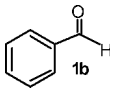
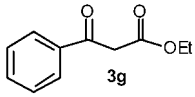
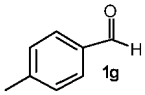
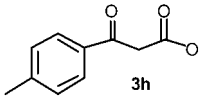
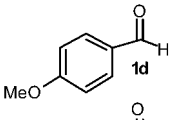
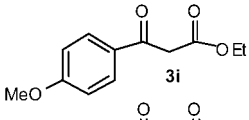
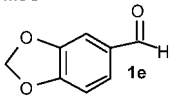
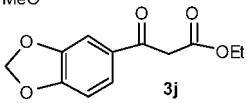
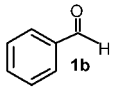
Table 1. Synthesis of β-keto esters via condensation of aldehydes and diazoacetates catalyzed by yttria-zirconia based Lewis acid catalyst.

Entry	Aldehyde **1**	Diazoacetate **2**	Reaction time (h)	Product[a] **3**	Yield[b] (%)
1	 **1a**	Methyl	10	 **3a**	85
2	 **1b**	Methyl	12	 **3b**	83
3	 **1c**	Methyl	20	 **3c**	85
4	 **1d**	Methyl	12	 **3d**	86
5	 **1e**	Methyl	20	 **3e**	83
6	 **1f**	Methyl	18	 **3f**	80
7	 **1b**	Ethyl	13	 **3g**	80
8	 **1g**	Ethyl	12	 **3h**	85
9	 **1d**	Ethyl	12	 **3i**	75
10	 **1e**	Ethyl	22	 **3j**	80
11	 **1b**	Ethyl	48[c]	No reaction	

[a]Products were characterized by spectroscopic data and comparison with authentic samples.
[b]Yields refer to isolated pure products.
[c]Reaction was performed without catalyst.

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The method described herein is simple and high yielding but more importantly offers easy work-up procedure. The advantages of the present method can be attributed to the preparation of the catalyst and reactivation at 500°C.

EXPERIMENTAL

Solvents were purified and dried by standard procedures before use according to reported procedure; petroleum ether of boiling range 60–80°C was used. The aldehydes were obtained from commercial sources and were purified by distillation/recrystallization before the experiment. Infrared spectra were recorded with ATI MATT-SON RS-1 FT-IR spectrometer. Proton NMR spectra were recorded on Bruker AC-200 machine in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained with Finningen MAT mass spectrometer. The diffractogram of X-ray powder diffraction pattern was recorded on a Rigaku diffractometer model D/Max. IIIVC with Ni-filtered Cu-Kα radiation. FTIR spectrum of pyridine adsorbed on the yttrium-based catalyst was recorded on a Nicolet 60 SXB FTIR spectrometer. TPD profile (ammonia) of the yttrium-based catalyst was recorded on a Sorbstar apparatus. Determination of specific surface area was carried out by BET (Brunner–Emmett–Teller) N_2 adsorption using an Omnisorp 100CX apparatus.

Procedure for the Preparation of Catalyst

The catalyst was prepared by mixing aq. solution of yttrium nitrate and zirconyl nitrate in the mole ratio 16 : 84, followed by addition of aqueous ammonia (28%) with vigorous stirring until a pH of 8.5 reached. The precipitate was washed with deionized water, dried at 110°C for 24 hr. Then the solid was treated with sulfuric acid (4M), dried at 120°C and calcined at 500°C for 3 hr with a heating rate of 2°C min^{-1}. The chemical composition of the final catalyst (determined by XRF technique) was found to be 82.6 mol% Zr, 15.6 mol% Y and 1.8 mol% S. The physicochemical characterization of the catalyst was carried out by titrations, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and N_2 adsorption techniques.

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Typical Experimental Procedure for the Condensation of Diazoacetates with Aldehydes

A solution of aldehyde (5.0 mmol) and diazoacetate (7.5 mmol) in dichloroethane (10 mL) containing yttria-zirconia based Lewis acid catalyst (50 mg; 10% w/w) was refluxed for the indicated length of time (Table 1) under N_2 atmosphere. The catalyst was recovered by filtration and solvent was evaporated under reduced pressure to furnish the crude material. Purification by silica gel column chromatography using pet ether: ethylacetate (9.8 : 0.2) afforded the pure product.

4-Methyl-3-oxopentanoic acid methyl ester (3a): Colorless liquid. IRν_{max}/cm^{-1} (Neat): 1732, 1695, 1456. ^{1}H NMR ($CDCl_3$) δ: 1.3 (d, $J = 6.25$ Hz, 6H), 2.1–2.28 (m, 1H), 3.5 (s, 2H), 3.9 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 16.2, 33.5, 42.1, 50.0, 171.3, 196.0. Anal. calcd. for $C_7H_{12}O_3$: C 58.32, H 8.39%; found: C 58.05, H 8.10%.

3-Oxo-3-phenylpropionic acid methyl ester (3b):[11] Colorless liquid. IRν_{max}/cm^{-1} (Neat): 1735, 1695,1450. ^{1}H NMR ($CDCl_3$) δ: [4.0,5.7,12.3] (s, 2H), 4.1 (s, 3H), 7.8–7.4 (m, 3H), 8.1–7.9 (m, 2H).

3-(3-Nitrophenyl)-3-oxopropionic acid methyl ester (3c): White solid: M.P. 70°C. IRν_{max}/cm^{-1} (Neat): 3310, 1740, 1700, 1595, 1540. ^{1}H NMR ($CDCl_3$) δ: [3.9,5.8,12.6] (s, 2H), 4.1(s, 3H), 7.6–7.3 (m, 2H), 8.1–7.9 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 42.2, 50.0, 89.0 (enolic), 123.5, 128.0, 129.5, 134.5, 138.3, 148.3, 171.0, 196.5. Anal. calcd. for $C_{10}H_9NO_5$: C 53.82, H 4.06, N 6.28%; found: C 53.50, H 3.80, N 5.91%.

3-(4-Methoxyphenyl)-3-oxopropionic acid methyl ester (3d): Colorless liquid. IRν_{max}/cm^{-1} (Neat): 3300, 1725, 1695,1590. ^{1}H NMR ($CDCl_3$) δ: 3.7 (s, 3H) 3.8 (s, 3H), [4.1,5.5,12.6] (s, 2H), 7.8–6.9 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 42.1, 50.1, 56.2, 114.0, 129.7, 166.5, 171.5, 196.5. Anal. calcd. for $C_{11}H_{12}O_4$: C 63.45, H 5.81%; found: C 63.01, H 5.51%.

3-(3,4-Methylenedioxyphenyl)-3-oxopropionic acid methyl ester (3e): Colorless liquid. IRν_{max}/cm^{-1} (Neat): 3300, 1727, 1698, 1593. ^{1}H NMR ($CDCl_3$) δ: [4.0, 5.6, 12.6] (s, 2H), 4.1(s, 3H), 6.05 (s, 2H), 6.95 (d, $J = 7$ Hz, 1H), 7.45 (d, $J = 7$ Hz, 1H), 7.6–7.55 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 42.1, 50.1, 91.3, 115.2, 121.5, 131.0, 147.5, 152.0, 171.0, 196.5. Anal. calcd. for $C_{11}H_{10}O_5$: C 59.46, H 4.54%; found: C 59.21, H 4.24%.

3-(2-Nitro-4-methylphenyl)-3-oxopropionic acid methyl ester (3f): White solid: M.P. 110°C. IRν_{max}/cm^{-1} (Neat): 3300, 1746, 1698, 1557, 1447. ^{1}H NMR ($CDCl_3$) δ: 2.6 (s, 3H), [3.9, 5.7, 12.3] (s, 2H), 4.1 (s, 3H), 7.2 (s, 1H), 8.0 (d, $J = 7$ Hz, 1H), 8.4 (d, $J = 7$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 19.9, 41.2, 50.1, 124.2, 129.3, 129.5, 135.5, 143.0, 171.0, 196.5. Anal. calcd. for $C_{11}H_{11}NO_5$: C 55.70, H 4.67, N 5.90% found: C 55.25, H 4.35, N 5.55%.

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3-Phenyl-3-oxopropionic acid ethyl ester (3g):[9a] Colorless liquid. IRν_{max}/cm^{-1} (Neat): 3345, 1738, 1695, 1592, 1447. ^{1}H NMR ($CDCl_3$) δ: 1.18–1.3 (m, 3H), [3.9, 5.7, 12.3] (s, 2H), 4.1–4.2 (m, 2H), 7.4–7.8 (m, 3H), 8.0–8.1 (m, 2H).

3-(4-Methylphenyl)-3-oxopropionic acid ethyl ester (3h):[9a] Colorless liquid. IRν_{max}/cm^{-1} (Neat): 3300, 1740, 1700, 1560, 1450. ^{1}H NMR ($CDCl_3$) δ: 1.15–1.28 (m, 3H), 2.4 (s, 3H), [4.0, 5.7, 12.5] (s, 2H), 4.1–4.2 (m, 2H), 7.2–7.8 (m, 4H).

3-(4-Methoxyphenyl)-3-oxopropionic acid ethyl ester (3i):[9a] Colorless liquid. IRν_{max}/cm^{-1} (Neat): 3300, 1725, 1698, 1557, 1447. ^{1}H NMR ($CDCl_3$) δ: 1.1–1.22 (m, 3H), 3.8 (s, 3H), [4.0, 5.7, 12.6] (s, 2H), 4.1–4.2 (m, 2H), 7.0–7.5 (m, 4H).

3-(3,4-Methylenedioxyphenyl)-3-oxopropionic acid ethyl ester (3j):[9a] Solid: M.P. 40°C (lit. 41°C).[9a] IRν_{max}/cm^{-1} (Neat): 1740, 1685, 1640, 1447. ^{1}H NMR ($CDCl_3$) δ: 1.22 (t, $J = 7.4$ Hz, 3H), [4.0, 5.65, 12.6] (s, 2H), 4.2 (q, $J = 7.4$ Hz, 2H), 6.1 (s, 2H), 6.95 (d, $J = 7$ Hz, 1H), 7.4 (d, $J = 7$ Hz, 1H), 7.5–7.6 (m, 1H).

ACKNOWLEDGEMENTS

RKP thanks CSIR, New Delhi for award of senior research fellowship. We are grateful to Dr. M. K. Gurjar, Head, Organic Chemistry: Technology Division for his constant encouragement and support. This is NCL communication No. 6653.

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Received in India September 30, 2003

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