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One-Pot Synthesis of α,β-Unsaturated Esters Promoted by Sodium Hydride

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A new protocol for the synthesis of α,β-unsaturated esters was described with various aldehydes and ethyl acetate in presence of sodium hydride. Advantage of this method is high efficiency, shorter time period and inexpensive.

Key Words: Aldehydes, Ethyl acetate, Sodium hydride, α,β-Unsaturated esters.

INTRODUCTION

The α,β-unsaturated esters are one of the important chemical functionalities that are encountered commonly in organic synthesis[1]. For the preparation of α,β-unsaturated esters various routes have been reported[2]. Most commonly used strategy for the preparation of α,β-unsaturated esters are the Wittig, Reformtsky and Knoevenagel reactions. Major drawback of Wittig reaction is the need for the preparation of intermediates (phosphonium ylides) from the corresponding halogenated reagents[3]. The Reformtsky method involves the reaction of an aldehyde with an acetic ester in presence of sodium or reaction of aldehyde with a halo acetic ester in presence of zinc[4]. In particular these reactions are not suitable for the preparation of α,β-unsaturated esters substituted with halogen, nitro or hydroxy aryl groups. The Knoevenagel condensation for α,β-unsaturated esters, involves two steps *i.e.*, the preparation of the α,β-unsaturated acid followed by its esterification[5]. Other methods involves the use of organometallic catalysts such as $RuCl_2(PPh_3)_3$[6], $ReOCl_3(PPh_3)_3$[7], $Sn(OSO_2CF_3)_2$[3b], and Bu_3Sb[8] to convert aldehydes into α,β-unsaturated esters. Reaction of *ortho* esters with aldehydes can also give α,β-unsaturated esters but requires elevated temperatures and longer times[9]. Ethyl acetate reacts with aromatic benzaldehyde gives ethyl cinnamates by using various bases are previously reported. Those are K_2CO_3[10], NaOEt[11], $InCl_3$/lithium dicyclohexylamine[12], Me_3SiCl/LDA[13], Me_3GeCl/LDA[14], lithium hexamethyldisilazide[15] and phosha tetraazabicyclic compound[16]. Drawbacks of these reactions such as, moderate yields, expensive chemicals, longer reaction time and involving multi step synthesis to produce ethyl cinnamates. Therefore, there is a need to develop a mild and efficient method for the preparation of ethyl cinnamates.

EXPERIMENTAL

All chemicals were purchased from S.D. Fine Chemicals. IR spectra were recorded in $CHCl_3$ on a Shimadzu FTIR-8300 spectrophotometer. The ^1H NMR (300 MHz) and ^{13}C NMR (70 MHz) were run on a Bruker Avance DPX-250 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Chemical shift values are given in δ scale. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus.

Typical experimental procedure: Sodium hydride (11 mmol) was suspended in dry ethyl acetate (5 mL) at 10-15 ºC, was added to a solution of benzaldehyde/substituted benzaldehyde (5 mmol) in dry ethyl acetate (5 mL) slowly during 10 min. The resulting mixture was allowed to reach room temperature and stir for the appropriate time (Table-1). After complete conversion as indicated by TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL) and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford corresponding α,β-unsaturated ester.

Spectral data for selected products: *trans*-Ethylcinnamate (Table-1, entry 1): Colourless oil; IR (neat, cm^{-1}) 3062, 3029, 2982, 1714, 1639, 1579, 1450, 1393, 1367, 1270, 1203, 1176, 1096, 1039; ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, *J* = 7.1 Hz, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 7.33-7.43 (m, 3H), 7.49-7.56 (m, 2H), 7.70 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 62.0, 117.9, 128.0, 129.4, 132.5, 135.9, 147.1, 167.5; MS (EI): m/z 176 (M^+, 37 %), 148 (28), 147 (20), 131 (100), 103 (65), 91 (12), 77 (11), 51 (10).

(*E*)-Ethyl-2-chlorocinnamate (Table-1, entry 2): Viscous pale yellow liquid; IR (neat, cm^{-1}): 2922, 1715, 1633, 1469,

TABLE-1
REACTION OF ALDEHYDES WITH ETHYL ACETATE CATALYZED BY NaH

Entry	Aldehyde (1) R =	Reaction time (min)	Yield* (%)	Purity, GC** (%)
1	C_6H_5	25	93	97
2	2-Cl-C_6H_4	17	92	95
3	3-Cl-C_6H_4	16	87	97
4	4-Cl-C_6H_4	20	76	92
5	2,4-Di Cl-C_6H_3	16	87	97
6	2,4,6-Tri Cl-C_6H_2	16	80	89
7	4-F-C_6H_4	19	78	94
8	4-OCH_3-C_6H_4	25	87	90
9	3-OH,4-OCH_3-C_6H_3	18	92	91
10	2-OH-C_6H_4	26	97	93
11	2-Br,6-OH-C_6H_3	18	90	96
12	2-Cl,6-OH-C_6H_3	22	91	96
13	2-NO_2-C_6H_4	14	86	89
14	4-$N(CH_3)_2$-C_6H_4	30	82	92
15	PhCH=CH	27	82	88

*Isolated yields are given, **Purity based on GC analysis: column OV-1 carrier gas flow H_2/N_2: 25 mL/min, sample size 0.2 mL.

1310, 1268, 1181, 1041, 758; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (1H, d, *J* = 16.12 Hz), 7.62-7.66 (1H, m), 7.36-7.43 (1H, m), 7.27-7.31 (2H, m), 6.44 (1H, d, *J* = 16.12 Hz), 4.28 (2H, q, *J* = 7.1Hz), 1.35 (3H, t, *J* = 7.1Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 140.5, 135.0, 132.5, 131.5, 130.4, 127.8, 127.2, 121.1, 61.1, 14.6; MS (EI): m/z 212 (27, M^{2+}), 210 (82, M^+), 165 (100), 137 (42).

(*E*)-Ethyl-4-chlorocinnamate (Table-1, entry 4): Light yellow oil; IR (neat, cm^{-1}): 2965, 1709, 1640, 1512, 1475, 1310, 1268, 1181, 1041, 908; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.1 Hz, 3H), 4.32 (q, *J* = 7.1 Hz, 2H), 6.51 (d, *J* = 16.0 Hz, 1H), 7.37 (m, 2H), 7.46 (m, 2H), 7.60 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 141.1, 137.3, 132.3, 128.1, 129.1, 120.1, 60.0, 14.9; MS (EI): m/z 210 (M^+, 100 %), 165 (48 %), 102 (25 %).

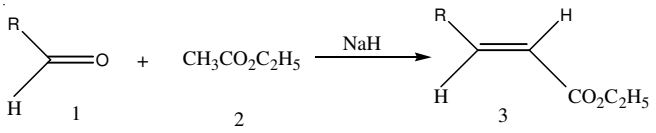
(*E*)-Ethyl-2-methoxycinnamate (Table-1, entry 8): Colourless oil; IR (neat, cm^{-1}) 2975, 1716, 1641, 1512, 1453, 1310, 1248, 1181, 1041, 921; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 3H), 3.91 (s, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 6.41 (d, *J* = 16.0 Hz, 1H), 7.44 (m, 2H), 6.96 (m, 2H), 7.60 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 162.6, 145.7, 130.3, 127.4, 116.4, 113.9, 61.4, 56.3, 14.0; MS (EI): m/z 206 (M^+, 100 %), 161 (25 %).

3-(4-Dimethylaminophenyl)-(*E*)-propenoic acid ethyl ester (Table-1, entry 14): Yellow solid; m.p. 74-76 ºC; IR (neat, cm^{-1}): 3072, 3033, 1701, 1601, 1579, 1496, 1450, 1393, 1367, 1268, 1206, 1169, 1096; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39 (t, *J* = 7.2 Hz, 3H), 3.07 (s, 6H), 4.29 (q, *J* = 7.2 Hz, 2H), 6.20 (d, *J* = 15.9 Hz, 1H), 6.67 (m, 2H), 7.39 (m, 2H), 7.69 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.9, 150.1, 142.3, 127.7, 124.4, 114.7, 112.0, 60.1, 40.2, 15.4; MS (EI): m/z 219 (M^+, 100 %), 174 (45 %), 146 (20 %).

Ethyl-(2*E*,4*E*)-5-phenyl-2,4-pentadienoate (Table-1, entry 15): Yellowish oil; IR (neat, cm^{-1}): 2982, 1708, 1626, 1525, 1432, 1330, 1246, 1195, 1039, 962; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.1 Hz, 3 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 6.03 (d, *J* = 15.2 Hz, 1 H), 6.86 (d, *J* = 4.8 Hz, 1 H), 7.38-7.30 (m, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 145.2, 139.1, 136.3, 129.5, 128.2, 127.1, 126.0, 120.9, 60.2, 14.4; MS (EI): m/z 202 (M^+, 20), 157 (22), 129 (100), 77 (12).

RESULTS AND DISCUSSION

The present method gave excellent results and proved to be a direct method for the synthesis of α,β-unsaturated esters than those described in the literature. Herein we report a simple and rapid one-pot synthesis of α,β-unsaturated esters using NaH as catalyst (**Scheme-I**). Various aldehydes were treated with ethyl acetate at lower temperatures in presence of NaH, thus obtained α,β-unsaturated esters had a purity > 88 % (GC). To our best of knowledge there has not been any literature, reporting the direct conversion of aldehyde to α,β-unsaturated ester using NaH.



R = aryl, α,β-unsaturated aldehydes

Scheme-I: Synthesis of α,β-unsaturated esters

It has been seen that both the electron rich as well as electron deficient aldehydes reacted effectively under these reaction conditions with an overall yield between 76-97 % irrespective of the nature of aldehyde. The aromatic aldehyde with electron withdrawing groups such as chloro, fluoro and nitro (Table-1, entries 2-7 and 13) faster rates than those with donating groups. This reaction can be more efficiently carried out using various aromatic and α,β-unsaturated aldehydes to give respective esters, Table-1, entries 6, 11 and 12 which have not been reported previously by other methods. The derived α,β-unsaturated esters are obtained in acceptably high purities and can be used for further subsequent transformations without any purification. The products obtained were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectrometry and also compared with authentic samples. Calcium hydride fails to produce α,β-unsaturated esters in similar reaction conditions. Acetophenones and their substituted compounds had no reaction under identical conditions. In the absence of catalyst the reaction failed to give the desired product even after a longer reaction time.

The advantage of this procedure includes mild condition, shorter reaction time, easy work-up, no additional solvent usage and no purification was required. This reaction proceeds to give exclusively (*E*)-isomer and no significant side reactions were observed.

Encouraged by these results, we subjected various aromatic, α,β-unsaturated aldehydes for conversion to α,β-unsaturated esters using NaH and the results are presented in Table-1.

In conclusion, we have presented a novel and efficient sodium hydride catalyzed condensation of ethyl acetate with various aldehydes to generate α,β-unsaturated esters with good yields. The above method may find utility as an alternative to the currently available procedures for the preparation of these compounds, which can be further used to prepare various pharmaceutical ingredients[17].

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