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A New Approach to the Synthesis of Ethyl (4*E*)-Alkenoates

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Abstract—A new approach to the preparation of ethyl (4*E*)-alkenoates was developed on the basis of Fe-catalyzed cross-coupling of ethyl (4*E*)-5-chloropent-4-enoate with the Grignard reagents. The starting ethyl (4*E*)-5-chloropent-4-enoate was obtained by alkylation of malonic ester of (*E*)-1,3-dichloropropene followed by decarbethoxylation.

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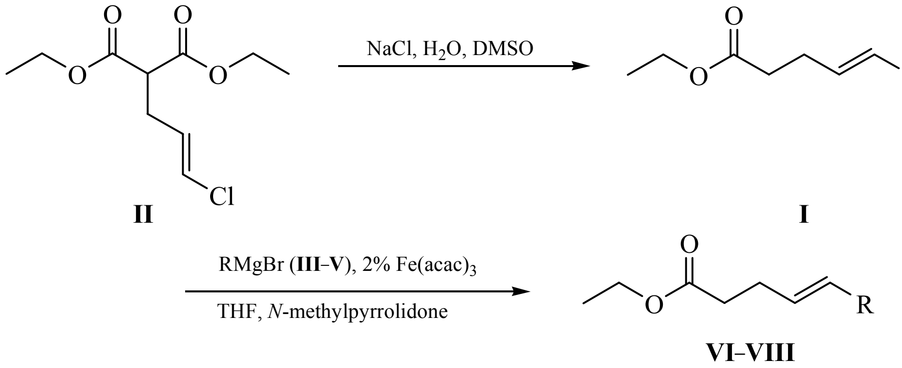
Many (4*E*)-unsaturated alcohols, acids and esters are biologically active; furthermore, they are widely used in organic synthesis [1–6]. These compounds can be obtained starting from acetylenic precursors [7–9], via the Claisen rearrangement [10, 11], the Wittig reaction [12], cyclopropane [13] or dihydropyran ring opening [14], isomerization of (*Z*)-alkenols [15], and homologenization of the corresponding *trans*-precursors [16]. Presently, cross-coupling of vinyl halides with organometallic compounds catalyzed by transition metals (Negishi, Stille, and Kumada reactions) is one of the most efficient methods of (4*E*)-un-saturated compounds preparation [17, 18]. A serious drawback of these methods is the use of vinyl iodides and Pd, Rh, Ru salts or complexes that are expensive and thus limitedly applicable. Therefore, exploration of possibility of similar reactions involving more available vinyl halides and transition metals derivatives (Fe, Co, Ni, Cu, Mn, etc.) in the cross-coupling reactions has become a topical issue [19, 20].

In order to develop a practical method for the synthesis of ethyl (4*E*)-alkenoates, we investigated Fe-catalyzed cross-coupling of some Grignard reagents with ethyl (4*E*)-5-chloropent-4-enoate **I** derived from *trans*-1,3-dichloropropene. The latter is a large-scale side product of propylene chlorination. Due to different boiling points, *cis*- and *trans*-1,3-dichloropropenes can be easily separated by distillation. Highly pure stereoisomers of 1,3-dichloropropene containing two reactive chlorine atoms at vinyl and allyl positions are very promising in view of synthetic applications [21]. In particular, alkylation of malonic ester with (*E*)-1,3-dichloropropene followed by the Krapcho decarbethoxylation of the formed diethyl [(2*E*)-3-chloroprop-2-en-1-yl]propanedioate **II** [22, 23] results in ethyl (4*E*)-5-chloropent-4-enoate **I** with high yield.

Reaction of ethyl (4*E*)-5-chloropent-4-enoate **I** with Grignard reagent (for example, *n*-butylmagnesium bromide **III**, *sec*-butylmagnesium bromide **IV**, or phenylmagnesium bromide **V**) in the presence of catalytic amounts of Fe(acac)$_3$ in a mixture of THF and *N*-methylpyrrolidone at room temperature afforded the corresponding ethyl (4*E*)-non-4-enoate **VI**, ethyl (4*E*)-6-methyloct-4-enoate **VII**, and ethyl (4*E*)-5-phenylpent-4-enoate **VIII** with high yields. Under those reaction conditions, the corresponding tertiary alcohols (products of the Grignard reagent condensation with ester group of I) were not formed. This was evidently due to significantly higher rate of the Fe-catalyzed cross-coupling as compared with nucleophilic addition of alkyl(phenyl)magnesium bromides **III–V** at the carbonyl group. The cross-coupling reaction was highly stereoselective, with retention the substituents configuration at the double bond [the *trans*-isomer of **VI–VIII** > 99%].

Structure and stereochemistry of the prepared compounds was confirmed by gas-liquid chromatography analysis, NMR, and the data of GC-MS analysis. In the ^{1}H NMR spectrum of ethyl (4*E*)-5-phenylpent-4-enoate **VIII**, the value of spin-spin coupling constant of vinyl protons was 15.9 Hz, which corresponded to transoid configuration of the substituents at the double bond. In the ^{13}C NMR spectrum of esters **VI** and **VII**, the allyl C^3-atoms



R = *n*-Bu (**III, VI**); R = *sec*-Bu (**IV, VII**); R = Ph (**V, VIII**).

signals were observed at 27–28 ppm, whereas in the spectrum of its *cis*-analogs they are shifted upfield by ~4–5 ppm [24].

Alkaline hydrolysis or reduction with lithium aluminum hydride of the esters **VI–VIII** performed by the standard procedures gave the corresponding (4*E*)-unsaturated acids or alcohols, respectively.

EXPERIMENTAL

IR spectra were recorded on a Fourier spectrophotometer IRPrestige-21 Shimadzu from thin films. ^{1}H and ^{13}C NMR spectra were registered in $CDCl_3$ on a spectrometer Bruker AM-300 (operating frequencies 300 and 75.47 MHz), internal reference TMS. GC-MS measurements were carried out on an instrument GCMS-QP2010S Shimadzu (EI, 70 eV, range of detected masses 33–500 Da), capillary column HP-1MS (30 m×0.25 mm×0.25 μm), vaporizer temperature 280°C, ion source temperature 200°C, ramp from 50 to 280°C at a rate 10 deg min^{-1}, carrier gas helium (1.1 mL min^{-1}).

Ethyl (4*E*)-5-chloropent-4-enoate (I). A mixture of 2.35 g (0.01 mol) of diethyl [(2*E*)-3-chloroprop-2-en-1-yl]propanedioate **II**, 0.36 g (0.02 mol) of water, 1.17 g (0.02 mol) of NaCl, and 5 mL of DMSO was stirred at reflux during 16 h. Then, 10 mL of water and 10 mL of hexane were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with hexane (2×15 mL). The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. The product was isolated by column chromatography (SiO_2, hexane–diethyl ether, 8 : 1). Yield 1.21 g (74%), oily substance. IR spectrum, ν, cm^{-1}: 2982, 2932, 1732, 1634, 1445, 1373, 1350, 1300, 1240, 1192, 1161, 1096, 1036, 935, 856. ^{1}H NMR spectrum, δ, ppm: 1.26 t (3H, CH_3, *J* 7 Hz), 2.34–2.44 m (4H, $2CH_2$), 4.11 q (2H, CH_2O, *J* 7.1 Hz), 5.86–5.95 m (1H, C^4H), 6.03 d (1H, C^5H, J_{trans} 13.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.04 (CH_3), 26.07 (C^3), 33.34 (C^2), 60.39 (CH_2O), 118.30 (C^5), 131.67 (C^4), 172.27 (C^1). Mass spectrum, *m*/*z* (I_{rel}, %): 127 (86), 117 (27), 99 (100), 91 (24), 89 (40), 88 (31), 75 (27), 53 (46), 43 (15).

Ethyl (4*E*)-non-4-enoate (VI). A solution of *n*-buthylmagnesium bromide **III** in THF (1 mol/L, 1.35 mL, 1.35 mmol) was added to a solution of 0.2 g (1.23 mmol) of ethyl (4*E*)-5-chloropent-4-enoate **I** and 8.7 mg (0.0245 mmol) of $Fe(acac)_3$ in a mixture of 1.2 mL of THF and 1.1 mL of *N*-methylpyrrolidone (dropwise, during 5 min, under argon atmosphere, at 0°C). The reaction mixture was stirred during 30 min at room temperature. Then, 5 mL of 5% HCl and 5 mL of hexane were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with hexane (3×5 mL). The combined organic layers were washed with saturated solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated. The product was isolated by column chromatography (SiO_2, hexane–diethyl ether, 8 : 1). Yield 0.184 g (81%), oily substance. IR spectrum, ν, cm^{-1}: 2957, 2926, 2872, 1738, 1464, 1447, 1371, 1250, 1163, 1042, 968. ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, C^9H_3, *J* 7.1 Hz), 1.23–1.34 m (7H, $C\underline{H}_3CH_2O$, $2CH_2$), 1.97 q (2H, CH_2, *J* 6.5 Hz), 2.26–2.37 m (4H, $2CH_2$), 4.13 q (2H, $CH_3C\underline{H}_2O$, *J* 7.1 Hz), 5.36–5.46 m (2H, C^4H, C^5H). ^{13}C NMR spectrum, δ_C, ppm: 13.82 (C^9), 14.15 ($\underline{C}H_3CH_2O$), 22.03 (C^8), 27.87 (C^3), 31.52 (C^7), 32.09 (C^6), 34.35 (C^2), 60.10 ($CH_3\underline{C}H_2O$), 127.84 (C^5), 131.70 (C^4), 173.19 (C^1). Mass spectrum, *m*/*z* (I_{rel}, %): 138 (44), 97 (28), 96 (100), 95 (38), 88 (64), 84 (17), 81 (40), 71 (35), 70 (38), 69 (37), 68 (22), 67 (45), 61 (27), 60 (27), 55 (89), 54 (40), 43 (36), 41 (64).

Ethyl (4*E*)-6-methyloct-4-enoate (VII) was prepared similarly from ethyl (4*E*)-5-chloropent-4-enoate **I** and *sec*-butylmagnesium bromide **IV**. Yield 0.165 g (73%), oily substance. IR spectrum, ν, cm^{-1}: 2963, 2930, 2874, 1738, 1456, 1373, 1250, 1175, 972. ^{1}H NMR spectrum, δ, ppm: 0.83 t (3H, C^8H_3, *J* 7.3 Hz), 0.94 d (3H, $C^6HC\underline{H}_3$, *J* 6.8 Hz), 1.22–1.30 m (5H, $C\underline{H}_3CH_2O$, C^7H_2), 1.92–2.00 m (1H, $C^6\underline{H}CH_3$), 2.30–2.38 m (4H, $2CH_2$,), 4.12 q (2H, $CH_3C\underline{H}_2O$, *J* 7.1 Hz), 5.31–5.37 m (2H, C^4H, C^5H). ^{13}C NMR spectrum, δ_C, ppm: 11.66 (C^8), 14.21 ($\underline{C}H_3CH_2O$), 20.26 ($C^6H\underline{C}H_3$), 27.93 (C^3), 29.67 (C^7), 34.52 (C^2), 38.30 (C^6), 60.16 ($CH_3\underline{C}H_2O$), 126.25 (C^4), 137.48 (C^5), 173.28 (C^1). Mass spectrum, *m*/*z* (I_{rel}, %): 110 (24), 109 (15), 97 (17), 96 (78), 95 (16), 81 (88), 69 (17), 67 (36), 57 (15), 55 (73), 53 (29), 43 (36), 42 (20), 41 (100).

Ethyl (4*E*)-5-phenylpent-4-enoate (VIII) was prepared similarly from ethyl (4*E*)-5-chloropent-4-enoate **I** and phenylmagnesium bromide **V**. Yield 0.178 g (71%), oily substance. IR spectrum, ν, cm^{-1}: 3026, 2980, 1734, 1481, 1447, 1371, 1252, 1179, 1159, 1036, 964. ^{1}H NMR spectrum, δ, ppm: 1.24 t (3H, CH_3, *J* 7 Hz), 2.44–2.55 m (4H, $2CH_2$), 4.14 q (2H, $CH_3C\underline{H}_2O$, *J* 7 Hz), 6.20 d. t (1H, C^4H, J_{trans} 15.9, 6.7 Hz), 6.42 d (1H, C^5H, J_{trans} 15.9 Hz), 7.19–7.32 m (5H, CH_{Ar}). ^{13}C NMR spectrum, δ_C, ppm: 14.17 ($\underline{C}H_3CH_2O$), 28.21 (C^3), 33.94 (C^2), 60.31 ($CH_3\underline{C}H_2O$), 125.95 ($2CH_{Ar}$), 127.04 (CH_{Ar}), 128.41 ($2CH_{Ar}$), 128.66 (C^5), 130.84 (C^4), 137.28 (C_{Ar}), 172.92 (C^1). Mass spectrum, *m*/*z* (I_{rel}, %): 204 (21) [M^+], 133 (11), 131 (16), 130 (100), 129 (53), 128 (11), 117 (63), 116 (15), 115 (52), 91 (30).

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