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β-Acylvinyl Intermolecular Radical Additions to Double Bonds: Stereoselective Synthesis of Functionalised (*E*)-α,β-Unsaturated Carboxylic Acids

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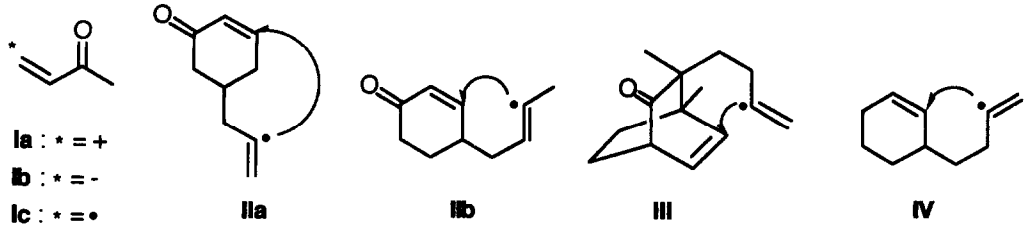
Abstract: The reaction of (*Z*)-3-iodoacrylic acid (**1**) with a substoichiometric amount of tributyltin chloride (1:0.5 molar ratio) and an excess of sodium borohydride (1:4 molar ratio) in the presence of a catalytic amount of AIBN (1:0.18 molar ratio) and an excess of an electrophilic olefin (**2**) in ethanol leads, after treatment with aqueous sodium fluoride, to the expected functionalised (*E*)-α,β-unsaturated carboxylic acids **3** in a stereoselective manner. The probable reaction mechanism involves free radical intermediates.

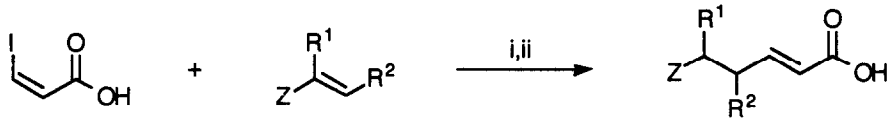
INTRODUCTION

Non-stabilised β-acylvinyl intermediates of the type **I** are of interest because of their ability for providing the α,β-unsaturated acyl functionality[1]. Among them, the corresponding cationic (**Ia**)[2,3] or anionic (**Ib**)[4,5] equivalents have been widely used in synthetic organic chemistry. In contrast, to the best of our knowledge, radicals of the type **Ic** remain unknown[6-8]. Even more, vinylic radicals have been, in general, far less studied than the corresponding sp^3-hybridised ones[6-8]; some typical examples are **II**[9], **III**[10] and **IV**[11], which have been successfully used in the synthesis of polycyclic structures by intramolecular processes. In this paper, and continuing with our interest on functionalised radical intermediates[12], we report the preparation of a β-acylvinyl (homoenolic) radical of the type **Ic**, derived from acrylic acid, and its application to the stereoselective synthesis of functionalised (*E*)-α,β-unsaturated carboxylic acids by an intermolecular process.



RESULTS AND DISCUSSION

The reaction of (*Z*)-3-iodoacrylic acid **1** (easily prepared[13] by addition of lithium iodide to commercially available propiolic acid) with a mixture of a substoichiometric amount of tributyltin chloride (1:0.5 molar ratio) and an excess of sodium borohydride (1:4 molar ratio) in the presence of a catalytic amount of α,α'-azobisisobutyronitrile (AIBN; 1:0.18 molar ratio) followed by addition of an excess of the corresponding electrophilic olefin **2** (1:10 molar ratio) in dry ethanol at temperatures ranging between 0 and 20°C led, after final treatment with sodium fluoride in water, to the corresponding (*E*)-α,β-unsaturated carboxylic acids (**3**) in a stereoselective manner (Scheme 1 and Table 1). Nothing of the other possible (*Z*)-diastereoisomer could be detected in the crude reaction product by 300 MHz ^{1}H NMR. As would be expected, according to the literature data[14], substitution at the β-position in the electrophilic olefin **2** seriously hinders the radical attack (see *infra*) at this centre: thus, the reaction shown in Scheme 1 with methyl crotonoate (**2c**) worked with poor yield (Table 1, entry 3).



1

2a : R^1=R^2=H, Z=CO_2Me
2b : R^1=Me, R^2=H, Z=CO_2Me
2c : R^1=H, R^2=Me, Z=CO_2Me
2d : R^1=R^2=H, Z=CN
2e : R^1=Me, R^2=H, Z=CN
2f : R^1=R^2=H, Z=$CONMe_2$
2g : R^1Cl, R^2=H, Z=Cl
2h : R^1=Me, R^2=H, Z=CO_2CH_2CH=CH_2

3a-h

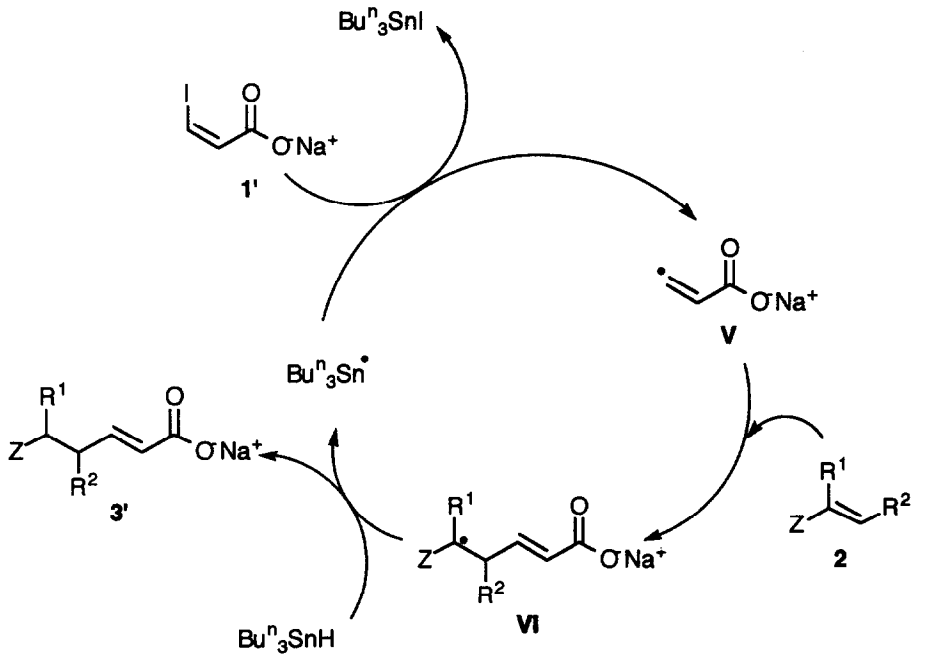
Scheme 1. *Reagents*: i, Bu_3SnCl, $NaBH_4$, AIBN cat., EtOH; ii, NaF, H_2O.

As noted above, and considering that the reaction works only in the presence of AIBN as catalytic initiator, we think that the reaction mechanism involves a free radical intermediate of the type **Ic**. Thus, the *in situ* generated tributyltin hydride (by reaction of tributyltin chloride and sodium borohydride[15]) reacts with the sodium salt **1'** (generated by deprotonation of starting iodoacrylic acid **1** with the excess of sodium borohydride present in the reaction mixture) giving the corresponding radical **V** (and tributyltin iodide), which is added to the electrophilic olefin **2** to yield a new radical **VI**; this last intermediate abstracts a hydrogen from tributyltin hydride to afford the corresponding sodium salt **3'**, precursor of the obtained reaction product **3**, and generating again the tributyltin radical, the whole process being formally catalytic with respect to the tin compound. However, the best results were obtained working with a substoichiometric amount of the starting tributyltin chloride (1:0.5 molar ratio) (Scheme 2).

Table 1. Preparation of Compounds **3**

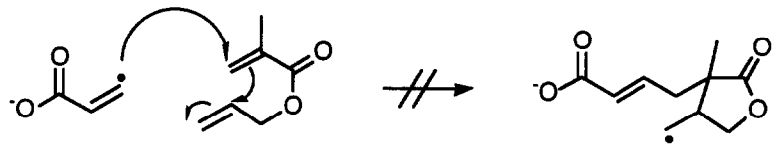
Entry	Starting olefin **2**	Product[a] No.	R^1	R^2	Z	Yield (%)[b]	R_f[c] or mp (°C)[d]
1	**2a**	**3a**	H	H	CO_2Me	48	58-59
2	**2b**	**3b**	Me	H	CO_2Me	74	0.34
3	**2c**	**3c**	H	Me	CO_2Me	11	0.20
4	**2d**	**3d**	H	H	CN	68	69-70
5	**2e**	**3e**	Me	H	CN	88	0.16
6	**2f**	**3f**	H	H	$CONMe_2$	60	0.18
7	**2g**	**3g**	Cl	H	Cl	29	0.37
8	**2h**	**3h**	Me	H	$CO_2CH_2CH{=}CH_2$	48	0.43

[a] All products **3** were >95% pure (GLC and/or 300 MHz ^1H NMR). [b] Isolated yield after flash chromatography (silica gel, hexane/ethyl acetate) based on the starting iodoacrylic acid **1**. [c] Silica gel, hexane/ethyl acetate: 2/1. [d] From hexane/chloroform.



Scheme 2.

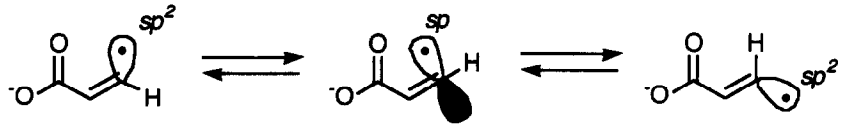
According to the proposed mechanism we tried a sequential ("cascade") cyclisation[16] using an electrophilic olefin such as allyl methacrylate (**2h**). In this case, instead of the sequential addition (**V+2h→VII**) shown in Scheme 3, we obtained product **3h**, in which the allylic rest remained unchanged (Table 1, entry 8). This result is in agreement with previous attempts of 5-exo radical cyclisations, which are unfavourable due to the ester geometry[16,17].



V **2h** **VII**

Scheme 3.

Finally, a short comment should be made about the observed (*E*)-stereochemistry in products **3** ($J_{HC=CH}$=15.6±0.1 Hz): as it is commonly accepted, vinyl radicals can exist in two bent forms **VIII** and **IX** (sp^2-hybridised) in equilibrium with a linear one **X** (*sp*-hybridised)[18], the inversion barrier being very low[19]. So, In general, there is no correlation betweeen precursor and product stereochemistry. In our case, the stereochemistry of the final product **3** is governed just by its own stability, obtaining the most thermodynamically stable (*E*)-product (Scheme 4).



VIII **X** **IX**

Scheme 4.

In conclusion, the methodology described herein represents a reasonable alternative to intermediates of the type **Ia** and **Ib**, above all to the last one (β-acylvinyl anion) in Michael-type condensations with electrophilic olefins. An important feature of this reaction is its total stereoselectivity giving only the (*E*)-products **3**.

EXPERIMENTAL PART

General.- For general information see reference 12a. High resolution mass spectra were measured at the University of Zaragoza in the corresponding service. Starting iodoacrylic acid **1** was prepared as described[13]. All other reagents used in this study were commercially available (Aldrich, Fluka) and were used as received.

Preparation of Compounds **3**. *General Procedure.*- To a mixture of (*Z*)-iodoacrylic acid (**1**; 0.20 g, 1.0 mmol), sodium borohydride (0.15 g, 4.0 mmol), AIBN (0.03 g, 0.18 mmol) and the corresponding olefin **2** (10.0 mmol) in dry ethanol (8 ml) was dropwise added a solution of tributyltin chloride (0.16 g, 0.5 mmol) in dry ethanol (2 ml) over a period of 10 min at 0°C. The reaction mixture was then stirred allowing the temperature to rise to 20°C overnight (*ca.* 12 h). Then, a saturated aqueous sodium fluoride solution (5 ml) was added to the resulting mixture, the precipitate was removed by filtration and the filtrate evaporated (15 Torr). The obtained residue was treated with ethyl acetate and successively washed with a saturated aqueous solution of sodium carbonate and 3 N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr). The resulting residue was purified by flash chromatography (silica gel, hexane/ethyl acetate) and/or recrystallised (see Table 1) to yield pure products **3**. Yields and mp's or R_f values are given in Table 1;

analytical, physical and spectroscopic data follow.

(E)-5-Methoxycarbonyl-2-pentenoic Acid (**3a**)[20]: ν_{max} (KBr) 3600-2700 (CO_2H), 1700-1670 cm^{-1} (C=O); δ_H 2.43-2.51 [4H, m, $(CH_2)_2$], 3.62 (3H, s, OCH_3), 5.80 (1H, dt, *J*=15.7, 1.5, CH=C*H*CO_2H), 7.0 (1H, dt, *J*=15.7, 6.3, C*H*=$CHCO_2H$), 10.4 (1H, s, CO_2H); δ_C 27.2 ($CH_2CH_2CO_2CH_3$), 32.0 ($CH_2CO_2CH_3$), 51.8 (CH_3), 121.5 (CH=*C*HCO_2H), 149.4 (*C*H=$CHCO_2H$), 171.8 (CO_2H), 172.6 (CO_2CH_3); *m/z* 158 (M^+, 0.1%), 140 (25), 127 (16), 126 (21), 109 (20), 108 (100), 81 (36), 80 (16), 53 (20), 43 (19).

(E)-5-Methoxycarbonyl-2-hexenoic Acid (**3b**): ν_{max} (film) 3600-2700 (CO_2H), 1690-1670 cm^{-1} (C=O); δ_H 1.13 (3H, d, *J*=6.9, CHCH_3), 2.26-2.35 (1H, m, CH), 2.49-2.61 (2H, m, CH_2), 3.62 (3H, s, OCH_3), 5.80 (1H, dt, *J*=15.6, 1.3, CH=C*H*CO_2H), 6.94 (1H, dt, *J*=15.6, 6.9, C*H*=$CHCO_2H$), 10.41 (1H, s, CO_2H); δ_C 16.8 (CH_3CH), 35.8 (CH_2), 39.0 (CH), 51.8 (OCH_3), 122.6 (CH=*C*HCO_2H), 148.4 (*C*H=$CHCO_2H$), 171.7 (CO_2H), 175.7 (CO_2CH_3); *m/z* 172 (M^+, 3%), 141 (27), 140 (19), 122 (100), 113 (38), 112 (33), 111 (21), 97 (71), 95 (80), 91 (37), 71 (17), 69 (27), 68 (18), 67 (71), 59 (39), 57 (31), 55 (26), 53 (16), 45 (30), 43 (27), 41 (67) (Found: M^+, 172.073655. $C_8H_{12}O_4$ requires M, 172.073559).

(E)-5-Methoxycarbonyl-4-methyl-2-pentenoic Acid (**3c**)[21]: ν_{max} (film) 3620-2720 (CO_2H), 1680-1640 cm^{-1} (C=O); δ_H 1.07 (3H, d, *J*=6.8, CHCH_3), 2.29 (1H, dd, *J*=15.5, 7.0, C*H*HCO_2CH_3), 2.39 (1H, dd, *J*=15.5, 7.0, CH*H*CO_2CH_3), 2.81-2.85 (1H, m, CH), 3.62 (3H, s, OCH_3), 5.77 (1H, dd, *J*=15.7, 1.3, CH=C*H*CO_2H), 6.96 (1H, dd, *J*=15.7, 7.1, C*H*=$CHCO_2H$), 9.57 (1H, s, CO_2H); δ_C 18.9 (CH_3CH), 33.1 (CH), 39.9 ($CH_2CO_2CH_3$), 51.7 (OCH_3), 119.5 (CH=*C*HCO_2H), 154.7 (*C*H=$CHCO_2H$), 171.6 (CO_2H), 172.1 (CO_2CH_3); *m/z* 172 (M^+, 0.5%), 151 (28), 141 (20), 126 (20), 123 (32), 122 (100), 111 (22), 99 (23), 98 (20), 97 (29.5), 95 (51), 94 (68), 59 (32), 55 (21), 53 (26), 43 (39), 41 (30).

(E)-5-Cyano-2-pentenoic Acid (**3d**)[22]: ν_{max} (KBr) 3620-2760 (CO_2H), 2200 (CN), 1660 cm^{-1} (C=O); δ_H 2.44-2.59 [4H, m, $(CH_2)_2$], 5.90 (1H, dt, *J*=15.6, 1.3, CH=C*H*CO_2H), 6.96 (1H, dt, *J*=15.6, 6.3, C*H*=$CHCO_2H$), 10.54 (1H, s, CO_2H); δ_C 16.0 (CH_2CN), 27.7 (CH_2CH_2CN), 118.2 (CH=*C*HCO_2H), 123.2 (CN), 146.0 (*C*H=$CHCO_2H$), 170.9 (CO_2H); *m/z* 125 (M^+, 0.2%), 108 (23), 107 (67), 97 (18), 85 (20), 81 (16), 80 (100), 79 (40), 57 (21), 53 (57), 52 (22), 51 (17), 45 (28), 41 (26).

(E)-5-Cyano-2-hexenoic Acid (**3e**): ν_{max} (film) 3600-2700 (CO_2H), 2200 (CN), 1680 cm^{-1} (C=O); δ_H 1.30 (3H, d, *J*=7.0, CH_3), 2.43 (1H, dd, *J*=14.4, 6.5, C*H*H), 2.51 (1H, dd, *J*=14.4, 6.5, C*H*H), 2.75 (1H, sextet, *J*=6.9, CH), 5.93 (1H, d, *J*=15.7, CH=C*H*CO_2H), 6.95 (1H, dt, *J*=15.7, 7.2, C*H*=$CHCO_2H$), 10.24 (1H, s, CO_2H); δ_C 17.5 (CH_3), 24.5 (CH), 35.9 (CH_2), 121.5 (CH=*C*HCO_2H), 124.3 (CN), 145.0 (*C*H=$CHCO_2H$), 170.8 (CO_2H); *m/z* 139 (M^+, 0.2%), 121 (29), 94 (30), 85 (100), 68 (17), 67 (20), 57 (36), 55 (17), 45 (17), 41 (20) (Found: M^+, 139.063735. $C_7H_9NO_2$ requires M, 139.063329).

(E)-6-Dimethylamino-6-oxo-2-hexenoic Acid (**3f**)[21]: ν_{max} (film) 3620-2400 (CO_2H), 1700 (C=O), 1640 cm^{-1} (N-C=O); δ_H 2.41-2.55 [4H, m, $(CH_2)_2$], 2.90, 2.96 (6H, 2s, 2xCH_3), 5.79 (1H, dt, *J*=15.6, 1.5, CH=C*H*CO_2H), 7.01 (1H, dt, *J*=15.6, 6.6, C*H*=$CHCO_2H$), 10.21 (1H, s, CO_2H); δ_C 27.5 (CH_2CH=CH), 31.3 (CH_2CO), 35.7, 37.2 (2xCH_3), 121.5 (CH=*C*HCO_2H), 149.9 (*C*H=$CHCO_2H$), 170.8 (CON), 171.7 (CO_2H); *m/z* 153 (M^+-H_2O, 14%), 121 (8), 119 (6), 57 (38), 55 (10), 42 (9), 41 (100).

(E)-5,5-Dichloro-2-pentenoic Acid (**3g**)[21]: ν_{max} (film) 3380-2820 (CO_2H), 1680 cm^{-1} (C=O); δ_H 3.03-3.11 (2H, m, CH_2), 5.78 (1H, t, *J*=5.7, CH), 5.95 (1H, dt, *J*=15.6, 1.3, CH=C*H*CO_2H), 6.99 (1H, dt, *J*=15.6, 7.2, (C*H*=$CHCO_2H$), 8.5 (1H, s, CO_2H); δ_C 45.4 (CH_2), 70.2 ($CHCl_2$), 125.4 (CH=*C*HCO_2H), 143.0 (*C*H=$CHCO_2H$), 170.8 (CO_2H); *m/z* 135 (M^+-Cl, 31%), 133 (92), 97 (100), 85 (35), 83 (37), 79 (28), 68 (29), 53 (27), 51 (38), 45 (29), 43 (51), 41 (21).

(E)-5-Allyloxycarbonyl-2-pentenoic Acid (**3h**)[21]: ν_{max} (film) 3440-2520 (CO_2H), 1720-1690 cm^{-1} (C=O); δ_H 1.15 (3H, d, *J*=6.8, CH_3), 2.26-2.36 (1H, m, CH), 2.50-2.65 (2H, m, CH_2CH), 4.52 (2H, dd, *J*=5.6, 1.2, OCH_2), 5.17 (1H, dd, *J*=10.4, 1.1, CH=C*H*H), 5.24 (1H, dq, *J*=17.3, 1.2, CH=CH*H*), 5.80 (1H, dt,

J=15.5, 1.0, CH=C*H*CO_2H), 5.87 (1H, ddt, *J*=17.3, 10.4, 5.6, C*H*=CH_2), 6.93 (1H, dt, *J*=15.5, 7.0, C*H*=CHCO_2H), 10.68 (1H, s, CO_2H); δ_C 16.8 (CH_3CH), 35.9 (CH_2), 38.4 (CH), 65.3 (OCH_2), 118.4 (CH=CH_2), 122.6 (CH=CHCO_2H), 131.9 (*C*H=CH_2), 148.5 (*C*H=CHCO_2H), 171.6 (CO_2H), 174.8 (CO_2CH_2); *m/z* 113 (M^+-$CO_2CH_2CH=CH_2$, 4%), 67 (13), 57 (19), 55 (16), 45 (48), 41 (100).

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