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1,4-Conjugate Addition of the Reformatsky Reagent to α-Nitrostyrenes: a New Synthesis of γ-Nitroesters.

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Abstract: α-Nitrostyrenes react with the Reformatsky reagent to yield the corresponding 1,4-addition products. The reaction represents a practical and convenient route to ethyl 3-aryl-4-nitrobutanoates.

3-Aryl-4-nitroaminoacidic systems are important tranquillizing agents.[1] They are usually prepared from the corresponding 3-aryl-4-nitrobutanoates. These latter compounds are available both by Michael addition of nitromethane and ethyl malonate carbanions to suitable cinnamates[2] or to α-nitrostyrenes[3] respectively.

These synthetic approaches prompted us to investigate the possibility of transferring a d_2 carbethoxymethylenic synthon to α-nitrostyrenes by the conjugate addition of the Reformatsky reagent.

Although many reports about the reactivity of the Reformatsky reagent towards both saturated and α,β-unsaturated carbonylic compounds have been reported,[4] the chemistry of such an organometallic reagent with α,β-unsaturated nitroalkenes is still unknown.

We hereby report the results obtained from reaction of α-nitrostyrenes with the Reformatsky reagent. The reaction was checked by using 4-chloro-α-nitrostyrene (**3**) that, when reacted with zinc ethyl bromoacetate, affords ethyl 4-nitro-3-(4'-chlorophenyl)-butanoate (**9**).The main results obtained are showed in Table 1.

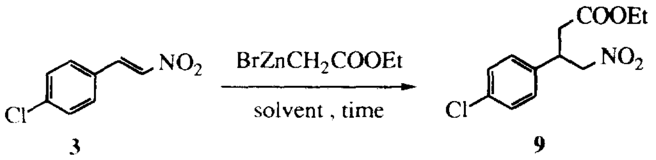
It is noteworthy that the successful course of the 1,4-addition depends strictly on the reaction conditions. As shown, long reaction times are required in order to obtain good substrate conversion (Table 1, run 1 *vs.* runs 2-4); the rise in temperature up to 60°C caused only the drop of the isolated yield of **9** (Table 1, run 3); finally, the use of a mixture of C_6H_6 / THF (3/1, v/v) resulted in the highest yield of **9** (Table 1, run 4).

These reaction conditions (Table 1, run 4) were then applied to other α-nitrostyrenes, in order to verify if the addition of the Reformatsky reagent to such nitrocompounds could represent a general approach to the synthesis of ethyl 4-nitro-3-arylbutanoates (Table 2).

The reported results show that neither electron-withdrawing nor electron-donor aryl substituents influence the successful course of the reaction. In any case only the corresponding γ-nitroester, arising from the Michael-type addition reaction was recovered, even when the electronic withdrawing effect of the nitro group on the aryl substituent of the nitroalkene (Table 2, run 3) might theoretically direct the reaction towards the nucleophilic addition to double bound C_1 or to aromatic C_2 or C_3.[5]

It is noteworthy that ethyl 4-nitro-3-phenylbutanoate (**7**) and ethyl 4-nitro-3-(4'-chlorophenyl)-butanoate (**9**), that are important intermediates in the total synthesis of tranquillizing agents PhGABA[2] and Baclofen™ [3] respectively, were obtained in satisfactory yields.

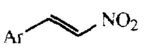
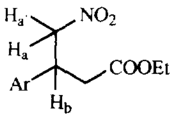
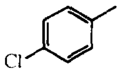
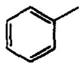
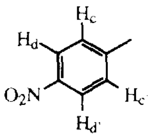
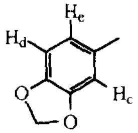
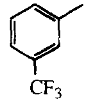
Table 1: *Reaction of 4-Chloro-α-Nitrostyrene* (**3**) *with Zinc Ethyl Bromoacetate.*[a]



Run	Solvent	Time (h)	T (°C)	Conversion (%)	**9** (%)[b]
1	THF	24	r.t.	72	48
2	THF	48	r.t.	91	63
3	THF	48	60	90	29
4	C_6H_6/THF[c]	48	r.t.	92	89

a) [3] / [$BrZnCH_2COOEt$] = 1/5, molar ratio b) Isolated yield on the chemically pure product; c) 3/1, v/v

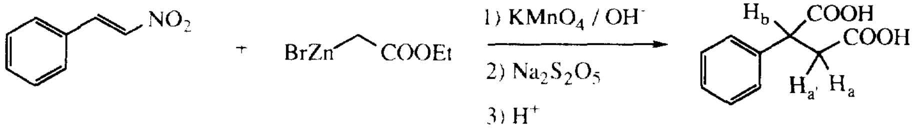
Table 2:[6] *Preparation of Ethyl 4-Nitro-3-Arylbutanoates by the Reaction of α-Nitrostyrenes with the Reformatsky Reagent.*[a]

Run	Ar			Yield (%)[b]
1		**3**	**9**	89
2		**16**	**7**	63
3		**4**	**10**	67
4		**5**	**11**	63
5		**6**	**12**	70

a) Reactions performed in C_6H_6/THF 3/1, v/v, 48 h, r.t. [α-nitrostyrene]/[$BrZnCH_2COOEt$] = 1/5, molar ratio; b) Isolated yield on the chemically pure products.

Taking into account that primary nitroderivatives can be converted, by oxidative Nef reaction,[7] into the corresponding carboxylic acids, we explored the direct conversion of the zinc nitronates into the corresponding 2-arylsuccinic acids. With this aim, zinc nitronate arising from the addition of ethyl zinc bromoacetate to α-nitrostyrene was treated with alkaline $KMnO_4$. After eliminating the exceeding oxidant agent by $Na_2S_2O_5$, the following acidification allowed the recovery of 2-phenylsuccinic acid in satisfactory yield (66 %, Scheme).

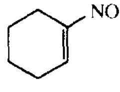
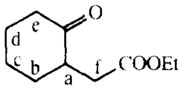
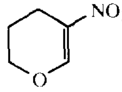
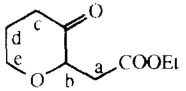
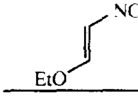
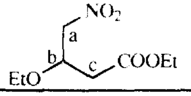
Scheme[6]



This result is valuable for organic synthesis: the preparation of 2-arylsuccinic acids, that are also important intermediates for the synthesis of some anticonvulsive drugs such as N-methyl-3-arylsuccinimides, is performed by a multistep reaction sequence.[8]

On the basis of good results obtained with α-nitrostyrenes, it seemed logical to investigate upon the possibility of extending the methodology to other α-nitroalkenes. The main results obtained in this context are reported in Table 3.

Table 3:[6] *Conjugate Addition of the Reformatsky Reagent to 1-Nitrocyclohexene and β-Nitroenolethers.*[a]

Substrate	Hydrolysis Procedure[b]	Product		Yield (%)[c]
	C		**13**	48[d]
	B		**14**	78
	A		**15**	45 55[e]

a) All the reactions, repeated at least twice, were performed in THF at r. t., if not otherwise stated, by using $[substrate]/[BrZnCH_2COOEt]$ = 1/5, molar ratio; b) see Experimental Section; c) Isolated yield on chemically pure products; d) a 50 % reaction conversion was evaluated (glc); e) the reaction was performed at 0°C.

The experimental findings achieved when 1-nitrocyclohexene was reacted with the Reformatsky reagent pointed out the general behaviour of α-nitroalkenes in the presence of organometallic reagents:[9] in the experimental conditions adopted only a 50 % conversion of the substrate was observed and in the reaction mixture cyclohexyl-2'-one acetate (**13**) along with polymerization by-products were found. Compound **13** was recovered in a low overall yield (48 %).

The reaction of 1-ethoxy-2-nitroethylene[10] with the same reagent in the usual reaction conditions was much faster: within 2 hours no trace of the precursor was detected and in the reaction mixture ethyl 3-ethoxy-4-nitrobutanoate (**15**) along with appreciable amounts of by-products were present. Compound **15** was recovered, after Flash Chromatography purification, in 45 % yield. A higher yield (55 %) of **15** could be obtained performing the reaction at lower temperatures (0 °C, Table 3).

Much more interesting was finally the course of the reaction of 3-nitro-5,6-dihydro-4H-pyran[11] with ethyl zinc bromoacetate in the usual reaction conditions (Table 3). The analysis (glc) of the reaction mixture indicated a quantitative conversion of the substrate and the formation of expected 1,4-addition product (glc-Mass). Thus, the following work-up was performed in order to promote the solvolytic Nef reaction, taking into account that recently 2-alkyltetrahydropyran-3-ones have been prepared starting from 3-nitro-5,6-dihydro-4H-pyran and Grignard reagents.[12] In order to obtain ethyl tetrahydropyran-(3'-one-2'-yl) acetate (**14**) the reaction mixture was hydrolyzed with 1.2 N HCl and the target molecule (**14**) was the main reaction product (Table 3).

To summarize, the reported results show that: i) The Reformatsky reagent, as well as organoalanes,[13] reacts with α-nitrostyrenes according to a Michael type addition and gives the corresponding 1,4-carbethoxymethylenation products in good yields. The described reactions provide a new and general procedure for the preparation of γ-nitroesters. By this method ethyl 4-nitro-3-phenylbutanoate and ethyl 4-nitro-3-(4'-chlorophenyl)-butanoate, key intermediates in the synthesis of PhGABA and Baclofen™, respectively, have been successfully prepared; ii) The oxidative Nef reaction of zinc nitronate arising from the addition of the Reformatsky reagent to α-nitrostyrene, allows for the preparation of the corresponding 2-phenylsuccinic acid. In this way an interesting one-pot synthesis of 2-arylsuccinic acids, important intermediates in organic synthesis, is suggested; iii) β-nitroenolethers react with the Reformatsky reagent in the same fashion of α-nitrostyrenes. In particular, ethyl tetrahydropyran-(3'-one-2'-yl)-acetate, arising from the addition of the Reformatsky reagent to 3-nitro-5,6-dihydro-4H-pyran[11] followed by acid work-up, might represent an interesting starting point for the preparation of modified carbohydrate derivatives.

Experimental Section

Materials and Instruments

Diethyl ether, benzene and tetrahydrofuran were purified by standard methods and distilled from Na and $LiAlH_4$; ethyl bromoacetate, 3-trifluoromethylbromobenzene and triethyl orthoformate were distilled before use. 4-Chlorobenzaldehyde, 4-nitrobenzaldehyde, 3,4-methylendioxybenzaldehyde and α-nitrostyrene were used without further purification; 1-nitrocyclohexene (Aldrich), 3-nitro-5,6-dihydro-4H-pyran[11] and 1-ethoxy-2-nitroethylene[10] were distilled before use.

Glc analyses (a DB1, 15m x 0.32mm column was used) were performed on a Perkin Elmer 8500 instrument equipped with a flame ionization detector and using He as carrier gas. ^1H and ^{13}C NMR (200 and 50 MHz respectively) spectra were recorded on a Varian Gemini 200 spectrometer; all NMR data were obtained using $CDCl_3$ solutions, if not otherwise stated. Chemical shifts (δ ppm) are referred to tetramethylsilane (TMS) (^1H NMR), or $CDCl_3$ (^{13}C NMR) as internal reference. Mass spectra (m/z, I%) were taken on a Perkin Elmer Q-Mass 910 instrument. All isolated compounds gave satisfactory elemental analyses (± 0.4%). Analytical TLC were performed on silica gel (Merck, SiO_2 60); Flash Chromatographies were carried out on silica gel (Merck, SiO_2 60, 230-400 mesh). All the reactions were carried out in dry apparatus under Argon.

Preparation of 3-trifluoromethylbenzaldehyde diethyl acetal. (**1**): A THF solution of 1-bromo-3-trifluoromethylbenzene (0.309 moles) was added to 0.341 gatoms of magnesium turnings, previously washed with dry Et_2O and suspended in 75 ml of dry THF. The mixture was refluxed for 2.5 h. The yield (84 %) and titre (1.19 M) of the Grignard reagent were evaluated by titration. A THF solution of triethyl orthoformate (0.319 moles) was added to the Grignard reagent and, after refluxing (32 h), most of the solvent was removed by distillation, according to a reported procedure for the preparation of *p*.tolualdehyde diethyl acetal.[14] The hydrolysis was performed by pouring the mixture in a saturated solution of NH_4Cl. Organic products were extracted with Et_2O and dried. The distillation of crude products gave 44.5 g (58 % yield) of chemically pure **1**, showing: b.p.: 160°C/150 mmHg; ^1H NMR, 7.80-7.40 [*m*, 4H, $\underline{Ar}$]; 5.55 [*s*, 1H, $-C\underline{H}(OEt)_2$]; 3.57 [*2q*, 4H, J = 7 Hz, $-C\underline{H}_2-CH_3$]; 1.25 [*t*, 6H, J = 7Hz, $-C\underline{H}_3$]; ^{13}C NMR: 140.2, 130.0, 128.6, 125.0, 124.4, 123.6, 123.5, 100.6, 61.1, 15.0; M/e (I%): 247 (M^+ - 1, 0.11), 229 (0.47), 219 (0.25), 203 (88.18), 175 (100), 145 (36.2), 127 (67.2).

Preparation of 3-trifluoromethylbenzaldehyde (**2**): 100 ml of 25 % H_2SO_4 and 44.3 g (0.178 moles) of **1** were refluxed for 4 h. The reaction mixture was then poured into a separating funnel and organic products were repeatedly extracted with CH_2Cl_2, under Argon. After drying the solvent was removed and distillation of the crude product gave 28.6 g (92 % yield) of **2**, showing: b.p.:110-111°C/80 mmHg; ^1H NMR: 10.10 [*s*, 1H, $C\underline{H}O$]; 7.65-8.20 [*m*, 4H, $\underline{Ar}$]; ^{13}C NMR: 190, 136.7, 132.6, 130.7, 130.6, 129.7, 126.4, 120.7; M/e (I %): 174 (M^+, 75.53), 173 (94.15), 155 (22.63), 145 (100), 125 (19.6), 126 (10.00), 107 (4.45), 75 (35.4), 69 (26.0).

Preparation of α–nitrostyrenes (**3-6**):[15] An equimolar, cooled (-5°C) methanolic solution of nitromethane and the suitable aromatic aldehyde was treated with a 10.5 M solution of NaOH ([nitromethane]/[NaOH] = 1/1.05). The reaction mixture was stirred for 40 min and then crushed ice was added until the solid was completely dissolved. The clear solution, mantained at *ca.* 0°C, was dropped into a vigorously stirred solution of 5 M HCl. The solid product, recovered by filtration, washed with water, dried under vacuum, was finally recrystallized. The pure products (yield, solvent used for the recrystallization, m.p.) showed:

4-Chloro-α-nitrostyrene (**3**): (51 %; ethanol; m.p.: 110-111°C);[16] ^1H NMR, 7.95 [*d*, 1H, J = 14 Hz, $Ph\underline{H}C=$]; 7.55-7.40 [*m*, 4H, $\underline{Ar}$]; 7.55 [*d*, 1H, J = 14 Hz, $=C\underline{H}NO_2$]; ^{13}C NMR: 138.3, 137.6, 137.4, 130.2, 129.7, 128.5; M/e (I %): 183 (M^+, 44.36), 148 (32.72), 136 (70.87), 101 (100), 75 (91.76).

4-Nitro-α-nitrostyrene (**4**): (59 %; aceton; m.p.: 210-211°C);[17] ^1H NMR, 8.32 [*dd*, 2H, J = 7, J = 2 Hz, H_d, $H_{d'}$]; 8.25 [*d*, 1H, J = 13.6 Hz, $-C\underline{H}=CHNO_2$]; 7.64 [*d*, 1 H, J = 13.6 Hz, $-CH=C\underline{H}NO_2$]; 7.74 [*dd*,, 2 H, J = 7, J = 2 Hz, H_c, $H_{c'}$]; ^{13}C NMR (C_2D_6CO): 150.34, 141.48, 137.78, 136.92, 131.34, 124.94; M/e (I %): 194 (M^+, 70.35), 147 (72.29), 118 (42.43), 102 (100), 89 (84.72), 76 (73.18), 63 (54.7), 50 (58.46), 46 (62.83).

3,4-Methylenedioxy-α-nitrostyrene (**5**): (60 %; chloroform; m.p.: 166-168°C);[18] ^1H NMR: 7.90: [*d*, 1H, J = 13.6 Hz, $-C\underline{H}=CHNO_2$]; 7.42 [*d*, 1H, J = 13.6 Hz, $-CH=C\underline{H}NO_2$]; 7.07 [*dd*, 1 H, $J_{e,d}$ = 8, $J_{e,c}$ = 1.7 Hz, H_e]; 6.98 [d, 1 H, $J_{c,e}$ = 1.7 Hz, H_c]; 6.85 [*d*,1H, J = 8 Hz, H_d]; 6.20 [*s*, 2H, $-O-C\underline{H}_2-O-$]; ^{13}C NMR: 151.4, 148.9, 138.8, 135.7, 126.3, 124.5, 109.1, 107.2, 102.0; M/e (I%): 193 (M^+, 91.5), 146 (100), 89 (86.65), 63 (78.27).

3-Trifluoromethyl-α-nitrostyrene (**6**): (78 %; hexane; m.p.: 74-76 °C); ^1H NMR: 8.05 [*d*, 1H, J = 13.7 Hz, $-C\underline{H}=CH-NO_2$], 7.85-7.55 [*m*, 4H, $\underline{Ar}$]; 7.63 [*d*, 1 H, J = 13.7 Hz, $-CH=C\underline{H}NO_2$]; ^{13}C NMR: 138.48, 137.18, 131.97, 130.94, 130.04, 128.44, 128.14, 125.67, 125.59; M/e (I %): 217 (M^+, 23.8), 198 (17.58), 170 (31.38), 159 (40.60), 151 (100), 75 (38.75).

Reactions of α-nitroalkenes with the Reformatsky reagent: A 2 M solution of ethyl bromoacetate in C_6H_6/THF (3/1, v/v) was added dropwise to an equimolar quantity of previously activated zinc;[19] the mixture was stirred until room temperature was reached. A solution (benzene was used for **3-6**, **16** and THF was employed in any other case) of the suitable α-nitroalkene was added to the Reformatsky reagent ([Reformatsky reagent]/[α-nitroalkene] = 5/1). The mixture was stirred until the highest conversion was achieved (glc). The final hydrolysis was performed pouring the reaction mixture into a flask containing: **A**) a solution of 0.2 N HCl; **B**) 1.2 N HCl / THF (4/1, v/v); **C**) 6 N HCl. The oxidative Nef reaction (procedure **D**) was accomplished by transferring through a sintered glass filter the reaction mixture into a flask containing a cold (0°C), vigorously stirred 0.2 N NaOH solution and adding $KMn0_4$ portionwise (10 g); after 6 h the exceeding oxidant agent was destroyed by adding $Na_2S_2O_5$ and the resulting mixture was extracted with Et_2O and finally acidified with 20 % H_2SO_4.

Organic products were repeatedly extracted with Et_2O and the organic phase was washed with brine and then dried. The solvent was removed and crude products were purified by Flash Chromatography. Chemically pure **7-15** (hydrolysis procedure, conversion, yield, Flash Chromatography eluent or recrystallization solvent) showed:

Ethyl 3-phenyl-4-nitrobutanoate (**7**): (**A**; 92 %; 58 %; benzene / tetrahydrofuran = 96/4, v/v); ^{1}H NMR, 7.40-7.20 [*m*, 5H, $\underline{Ar}$]; 4.74 e 4.63 [2*dd*, 2H, $J_{aa'}$ = 12.54, J_{ab} = 7.78, $J_{a'b}$ = 7.16 Hz, $-C\underline{H}_2-NO_2$]; 4.20-3.90 [*m*, 1H, $>C\underline{H}-Ph$]; 4.08 [*q*, 2 H, J = 7.5 Hz, $CH_3-C\underline{H}_2-O-$]; 2.75 [*d*, 2H, J = 7.5 Hz, $-C\underline{H}_2-COOEt$]; 1.15 [*t*, 3H, J = 7.5 Hz, $-C\underline{H}_3-CH_2-O-$]; ^{13}C NMR: 170.56, 138.33, 128.8, 128.7, 127.33, 79.4, 60.8, 40.2, 37.8, 14.02; M/e (I %): 190 (M^+ - 47, 100), 145 (26.21), 117 (99.28), 118 (94.93), 104 (50.81), 131 (7.22), 91 (71.30), 78 (28.43).

2-Phenylsuccinic acid (**8**): (**D**; 100 %; 66 %; pentane; m. p.: 167°C);[20] ^{1}H NMR (C_2D_6CO), 8.90 [*bs*, 2H, $-COO\underline{H}$]; 7.30 [*m*, 5H, $\underline{Ar}$]; 4.08 [*dd*, 1H, J_{ba} = 10.17, $J_{ba'}$ = 5.09 Hz, $Ph-C\underline{H}-COOH$]; 3.15 [*dd*, 1H, $J_{aa'}$ = 17, J_{ab} = 10.13 Hz, H_a]; 2.66 [*dd*, 1H, $J_{a'a}$ = 17, $J_{a'b}$ = 5.09 Hz, $H_{a'}$]; ^{13}C NMR: 174.35, 172.91, 139.68, 129.54, 128.72, 128.19, 47.83, 38.08.[21]

Ethyl 3-(4-chlorophenyl)-butanoate (**9**): (**A**; 89 %; 89 %; benzene / tetrahydrofuran = 98 /2, v/v); ^{1}H NMR, 7.40-7.10 [*m*, 4H, $\underline{Ar}$]; 4.72 e 4.60 [2*dd*, 2H, $J_{aa'}$ = 12.6, J_{ab} = 8, $J_{a'b}$ = 6.9 Hz, $-C\underline{H}_2-NO_2$]; 4.15-3.90 [*m*, 3H, J = 7.5 Hz, $-O-C\underline{H}_2-CH_3$; $>C\underline{H}-Ar$]; 2.75 [2*d*, 2H, J = 7.5 Hz, $-OCO-C\underline{H}_2-$]; 1.15 [*t*, 3H, J = 7.5 Hz, $-O-CH_2-C\underline{H}_3$]; ^{13}C NMR: 170.3, 136.8, 133.8, 129.2, 129.0, 79.1, 60.9, 39.6, 37.5, 14.0; M/e (I %): 271 (M^+, 0.33), 224 (81.11), 179 (24.06), 152 (92.59), 183 (13.20), 138 (39.09), 103 (25.72), 91 (7.80), 31 (100).

Ethyl 3-(4'-nitrophenyl)-4-butanoate (**10**): (**A**; 100 %; 67 %; hexane / ethyl acetate = 60/40, v/v); ^{1}H NMR, 8.20 [*dd*, 2H, J_{dc} = 9, $J_{dc'}$ = 2 Hz, H_d, $H_{d'}$]; 7.45 [*dd*, 2H, J_{cd} = 9, $J_{d'c}$ = 2 Hz, H_c, $H_{c'}$]; 4.82 e 4.69 [2*dd*, 2H, $J_{aa'}$ = 13, J_{ab} = 8.3, $J_{a'b}$ = 6.56 Hz, $-C\underline{H}_2NO_2$]; 4.24-4.00 [*m*, 1H, H_b]; 4.10 [*q*, , 2 H, J = 7.1 Hz, $-COO-C\underline{H}_2-CH_3$]; 2.80 [*dd*, 2H, J = 7.1 Hz, $-C\underline{H}_2-COOEt$]; 1.20 [*t*, 3H, J = 7.1 Hz, $-COO-CH_2-C\underline{H}_3$]; ^{13}C NMR: 169.9, 147.6, 145.8, 128.5, 124.2, 78.6, 61.2, 39.8, 37.3, 14.0; M/e (I %): 235 (M^+ - 47 , 25.93), 207 (11.56), 194 (11.08), 190 (15.58), 166 (29.99), 163 (33.25), 149 (8.91), 116 (100), 103 (2.53), 91 (52.01), 77 (51.58).

Ethyl 3-(3',4'-methylenedioxyphenyl)-4-nitrobutanoate (**11**): (**A**; 100 %; 63 %; hexane / ethyl acetate = 70/30, v/v); ^{1}H NMR, 6.72 [*m*, 3H, $\underline{\text{Ar}}$]; 5.95 [*s*, 2H, -O-C$\underline{\text{H}}_2$-O-]; 4.69 e 4.57 [*2dd*, 2H, J$_{aa'}$ = 12.45, J$_{ab}$ = 8, J$_{a'b}$ =7 Hz, -C$\underline{\text{H}}_2$-NO$_2$]; 4.10 [*q*, 2H, J = 7.1 Hz, -COO-C$\underline{\text{H}}_2$-]; 3.90 [*quint*, 1H, J = 7.45 Hz, Hb]; 2.70 [*d*, 2H, J = 7.3 Hz, -C$\underline{\text{H}}_2$-COOEt]; 1.20 [*t*, 3H, J = 7.1 Hz, -COO-CH$_2$-C$\underline{\text{H}}_3$]; ^{13}C NMR: 170.50, 148.15, 131.99, 120.74, 113.02, 108.67, 107.60, 101.23, 79.64, 60.91, 40.06, 37.96, 14.07; M/e (I %): 281 (M$^+$, 14.31), 234 (63.91), 189 (16.34), 175 (5.61), 162 (100), 148 (61.49), 131 (44.04), 103 (58.10), 89 (40.53).

Ethyl 3-(3'-trifluoromethylphenyl)-4-nitrobutanoate (**12**): (**A**; 100 %; 67 %; benzene / tetrahydrofuran = 97/3, v/v); ^{1}H NMR, 7.50 [*m*, 4H, $\underline{\text{Ar}}$]; 4.78 e 4.67 [*2dd*, 2H, J$_{aa'}$ = 12.9, J$_{ab}$ = 8, J$_{a'b}$ = 6.8 Hz, -C$\underline{\text{H}}_2$-NO$_2$]; 4.14-4.03 [*m*, 1H, >C$\underline{\text{H}}$-CH$_2$-COOEt]; 4.08 [*q* , 2H, J = 7.1 Hz, -COO-C$\underline{\text{H}}_2$-CH$_3$]; 2.78 [*2d*, 2H, J = 7.69 Hz, -C$\underline{\text{H}}_2$-COOEt]; 1.17 [*t*, 3H, J = 7 Hz, C$\underline{\text{H}}_3$-CH$_2$-OOC-]; ^{13}C NMR: 170.13, 139.57, 130.91, 129.57, 124.89 (2 C atoms), 124.27, 124.12, 78.89, 61.05, 40.00, 37.58, 13.92; M/e (I %): 286 (M$^+$ - 19, 8.43), 258 (37.57), 213 (23.63), 186 (100), 172 (76.41), 165 (55.08), 151 (40.65), 145 (30.43), 117 (83.40), 77 (37.59).

Ethyl cyclohexyl-(2'-one)-acetate (**13**): (**C**; 47 %; 48 %; hexane / ethyl acetate = 70/30, v/v);^{1}H NMR,[22] 4.15 [*q*, 2H, J = 7.13 Hz, -COO-C$\underline{\text{H}}_2$-CH$_3$]; 2.82 [*m*, 3H, H$_a$, H$_f$]; 2.40 [*m*, 2H, H$_e$]; 2.15 [*m*, 2H, H$_b$]; 1.77 [*m*, 4H, H$_c$, H$_d$]; 1.25 [*t*, 3H, J = 7.4 Hz, -COO-CH$_2$-C$\underline{\text{H}}_3$]; ^{13}C NMR: 210.95, 172.58, 60.42, 47.14, 41.82, 34.47, 33.88, 27.79, 25.22, 14.20; M/e (I %): 184 (M$^+$, 11.57), 139 (71.08), 138 (100), 110 (27.84), 97 (39.07), 55 (70.14), 41 (57.46).

Ethyl (tetrahydropyran-3'-one-2'-yl)-acetate (**14**): (**B**; 93 %; 78 %; hexane / ethyl acetate = 55/45, v/v); ^{1}H NMR,[23] 4.27 [*dd*, 1H, J$_{ba}$ = 4.9 Hz, J$_{ba'}$ = 6.8 Hz, H$_b$]; 4.16 [*q*, 2H, J = 7.1 Hz, -COO-C$\underline{\text{H}}_2$-CH$_3$]; 4.14-4.03 [*m*, 2H, H$_e$, H$_{e'}$]; 3.80 [*ddd*, 1H, J$_{e'e}$ = 10.7, J$_{e'd}$ = 3.4, J$_{e'd'}$ = 3.7 Hz, H$_{e'}$]; 2.87 [*dd*, 1H, J$_{aa'}$ = 16.5, J$_{ab}$ = 4.9 Hz, H$_a$]; 2.64 [*dd*, 1H, J$_{a'a}$ = 16.5, J$_{a'b}$ = 6.8 Hz, H$_{a'}$]; 2.71-2.40 [*m*, 2H, H$_c$, H$_{c'}$]; 2.30-2.00 [*m*, 2H, H$_d$, H$_{d'}$]; 1.25 [*t*, 3H, J = 7.1 Hz, -COO-CH$_2$-CH$_3$]; ^{13}C NMR: 206.8, 170.7, 79.9, 66.2, 60.7, 37.5, 35.3, 26.0, 14.0; M/e (I %): 186 (M$^+$, 5.57), 141 (31.07), 140 (49.18), 112 (59.68), 99 (18.44), 71 (100), 43 (93.85).

Ethyl 3-ethoxy-4-nitrobutanoate (**15**): (**A**; 100 %; 44 %; hexane / ethyl acetate = 63/37, v/v).^{1}H NMR,[24] 4.55 [*2d*, 2H, J$_{ab}$ = 5.1, J$_{a'b}$ = 6.3 Hz, H$_a$, H$_{a'}$] ;4.45 [*m*, 1H, H$_b$]; 4.17 [*q*, 2H, J = 7.2 Hz, CH$_3$-C$\underline{\text{H}}_2$-OOC-]; 3.60 [*m*, 2H, CH$_3$-C$\underline{\text{H}}_2$-O-CH<]; 2.69 e 2.58 [*2dd*, 2H, J$_{cc'}$ = 16.1, J$_{cb}$ = 5.8, J$_{c'b}$ = 6.5 Hz, H$_c$, H$_{c'}$]; 1.37 [*t*, 3H, J = 7.1 Hz, C$\underline{\text{H}}_3$-CH$_2$-OOC-]; 1.15 [*t*, 3H, J = 7.0 Hz, C$\underline{\text{H}}_3$-CH$_2$-O-CH<]; ^{13}C NMR: 169.96, 78.13, 72.72, 66.10, 60.99, 37.03, 15.13, 14.09; M/e (I %): 160 (M$^+$ - 45, 6.52), 145 (1.23), 132 (7.91), 118 (13.10), 103 (11.48), 85 (63.53), 71 (22.53), 31 (100).

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24 Chemical shift attribution was performed by ^{1}H NMR COSY spectroscopy; the following cross peaks were found (4.45, 2.65); (4.17, 1.25); (3.60, 1.15).

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