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Nitroalkanes and ethyl glyoxalate as common precursors for the preparation of both β-keto esters and α,β-unsaturated esters

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Abstract—β-Nitro acrylic esters, obtained by the reaction of nitroalkanes and ethyl glyoxalate, are the key building blocks for the immediate synthesis of both the title compounds. In fact, their treatment with titanium trichloride produce the direct conversion to the β-keto esters, while their reaction with sodium boron hydride gives the one-pot synthesis of α,β-unsaturated esters through formal substitution of the vinylic nitro group with an hydrogen.

Nitroalkanes have proved to be valuable intermediates.[1] Both the activating effect of the nitro group and its facile transformation into various functionalities have extended the importance of nitro compounds in the preparation of complex molecules.[2] Peculiar to aliphatic nitro compounds is the formation of new carbon–carbon single bond, via their nitronate form[3] and, in specific cases, the creation of carbon–carbon double bonds through the elimination of nitrous acid.[4] On the basis of these considerations, we have found that nitroalkanes, combined with ethyl glyoxalate, can be conveniently used as building blocks to produce β-keto esters and α,β-unsaturated esters.

β-Keto esters are multicoupling reagents having an electrophilic carbonyl and a nucleophilic carbon, which makes them a valuable tool for the synthesis of complex molecules. Moreover they are extensively used in the agrochemical, pharmaceutical and dyestuff industries.[5] Apart from the classical Claisen condensation[6] and related reactions,[7] the most direct method for their synthesis involves the condensation of aldehydes with ethyl diazoacetate.[8] The use of methyl 3-nitropropionate, as precursor for the preparation of β-keto esters was also previously reported by our group.[9]

α,β-Unsaturated esters are useful chemical entities which are accessible through condensation reactions involving aldehydes, viz. (i) Knoevenagel condensation of active methylene esters with aldehydes,[10] (ii) condensation of alkyl acetates with aldehydes followed by dehydration,[11] (iii) Reformatsky reaction with aldehydes followed by elimination of the ensuing hydroxy esters,[12] (iv) Wadsworth–Emmons olefination of carbonyl compounds.[13]

Thus, many procedures for the syntheses of both the title compounds have been reported for a long time, but there exist many drawbacks and disadvantages such as the need of drastic conditions, poor yields and low selectivity. In contrast to this, the procedures that we wish to report here give the title compounds in a few steps (Scheme 1), in good yields, and with the possibility to preserve several other functionalities.

The first step of the sequence is a nitroaldol (Henry) reaction between the nitroalkane **1** and ethyl glyoxalate **2**, performed under heterogeneous catalysis, using Amberlyst A-21 as solid base.[14] The reaction proceeds at room temperature, in the presence of just a small amount of solvent (ethyl glyoxalate is commercially available as 50% solution in toluene) and gives the β-nitro alcohols **3** in good yield (70–87%, Table 1). The resulting derivatives **3** were dehydrated to the nitroalkenes **4** (as *E* isomers) by mesylation of the hydroxy group, followed by basic elimination of methanesulfonic acid.[15] The dehydration reaction is very fast (about 1.5 h) and, as reported in Table 1, the yields are good (65–94%)[16]

Keywords: α,β-Unsaturated esters; β-Keto esters; Nitroalkanes; Ethyl glyoxalate; Tandem process.
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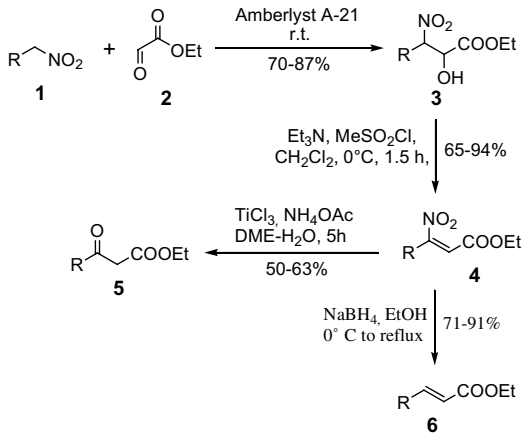
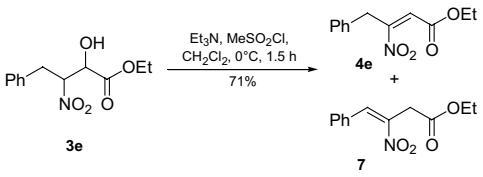


Scheme 1.

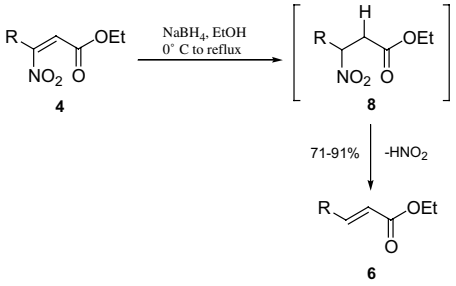
even in the presence of other functional groups such as ketone, ketal, ester and heteroaromatic systems.

The dehydration of the nitroalcohol **3e** (Scheme 2) provides the expected nitroalkene **4e**, together with its isomer **7**, in a 1:1 ratio.

β-Nitro acrylic esters **4** are key building blocks for the immediate synthesis of both the title compounds. Thus, treatment of a 1,2-dimethoxyethane (DME)/water solution of **4a**–**i** (or **7**) with titanium trichloride, in the presence of ammonium acetate,[1e,17] gives the direct conversion to the β-keto esters **5** in satisfactory yield (50–63%).[18] The method also tolerates several functionalities such as esters, carbonyls, ketals and heteroaromatic structures. Finally, in order to verify the possibility of forming the α,β-unsaturated esters **6**, we selected a representative number of nitroalkenes **4**, as their precursors, and found that this conversion can be directly performed through a tandem Michael addition–elimination process promoted by $NaBH_4$ in methanol (Scheme 3).[19]



Scheme 2.



Scheme 3.

In fact, the sodium borohydride first acts as a reducing agent, converting nitroalkenes **4** into nitroalkanes **8** then, under reflux, causes nitrous acid elimination, aided by its behaviour as base and by the presence of an acidic hydrogen in α-position to the carbonyl. The conversion **4** to **6** appears as a formal substitution of a vinylic nitro group with a hydrogen.

The conjugated esters **6** are obtained in high yield (71–91%) with complete diastereoselectivity since just the *E*-isomers are produced.

In conclusion, we reported two new, mild and convenient approaches for the synthesis of the title compounds, starting from aliphatic nitro compounds and ethyl glyoxalate as common precursors. It is important to point out that the procedures tolerate different functionalities such as ethers, acetals, heteroaromatic systems, ketones and chiral protected alcohols.

Table 1. Compounds **3**, **4**, **5** and **6** prepared

Entry	R	Yield (%)[a] of **3** (reaction time, h)	Yield (%)[a] of **4**	Yield (%)[a] of **5**	Yield (%)[a] of **6**
A	CH_3CH_2	75 (18)	85	55	
b	$CH_3(CH_2)_2$	70 (16)	87	61	85
c	$CH_3(CH_2)_3$	76 (16)	86	59	91
d	$CH_3(CH_2)_4$	71 (17)	91	60	
e	$C_6H_5CH_2$	82 (17)	71	63	
f	$(CH_2)_2CO_2CH_3$	79 (19)	70	56	71
g	$CH_3CO(CH_2)_2$	77 (20)	69	58	
h		73 (19)	87	50	73[b]
i	$CH_3C(OCH_2CH_2O)(CH_2)_2$	78 (20)	73	54	
j		80 (18)	94[c]		76
k	$AcO(CH_2)_3$	78 (19)	65		71
l	C_6H_5	87 (21)	71[c]		87

[a] Yield of pure, isolated products.
[b] The compound **6h** is obtained as the β,γ-unsaturated ester.
[c] Obtained as a mixture of *E*/*Z* isomers (ratio 6:4 for **4j** and 7.2:2.5 for **4l**).

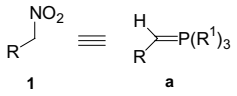


Figure 1.

These transformations are a further illustration of the great versatility of the nitroalkanes in organic synthesis, and it is important of note that in the synthetic sequence for the preparation of the α,β-unsaturated esters **6** (**1** + **2** to **6**), nitro compounds **1** can be regarded as the synthetic equivalents of ylids **a** (Wittig or Wittig–Horner reagents, Fig. 1), but with the great advantage of the easier availability of a large variety of nitroalkanes compared with the availability of the ylids.

Acknowledgements

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16. Although the synthesis of the nitroalkenes **4**, by condensation of **1** with **2**, has been previously reported, Shin, C.; Yonezawa, Y.; Narukawa, H.; Nanjo, K.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3595 the method needs of a large excess of nitroalkanes, and give moderate overall yields.
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18. Sample procedure (Table 1, product **5e**): To a stirred solution of 1,2-dimethoxyethane, (21.5 mL) and distilled water (15.5 mL) were added 15% $TiCl_3$ solution (10.4 mL, 12.13 mmol) and ammonium acetate (5.627 g, 73 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. A solution of nitroalkene **4e** (0.47 g, 2 mmol) in 2 mL of 1,2-dimethoxyethane was added to the reaction mixture at 0 °C and stirring was continued at room temperature for an additional 5 h. The reaction was quenched with 2 N HCl, then extracted with dicloromethane (4 × 30 mL) and dried over Na_2SO_4 dry. Finally the organic solution was filtrated and concentrated under vacuum to give the crude product that was purified by fast flash chromatography (hexane–ethyl acetate) allowing 0.3 g (71%) of the pure compound **5e**: oil; IR (neat): ν = 1716, 1741 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.27 (t, 3H, J = 7.3 Hz), 3.45, (s, 2H), 3.84 (s, 2H), 4.17 (q, 2H, J = 7.0 Hz), 7.20–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 14.2, 48.4, 50.1, 61.5 127.4, 129.0, 129.7, 133.2, 167.4, 200.2; EI-MS (70 ev) *m/z*: 39, 41, 43, 55, 65, 69, 77, 87, 91 (100), 115, 118, 131, 206; Anal. Calcd for $C_{12}H_{14}O_3$ (206.24) C, 69.89; H, 6.84. Found C, 70.08; H, 7.01.
19. Sample procedure (Table 1, compound **6k**): To an ethanolic solution (14 mL) of β-nitro acrylic ester **4k** (0.490 g, 2 mmol) maintained at 0 °C, was slowly added $NaBH_4$ (4.4 mmol). The reaction mixture was first stirred at 0 °C for 15 min, then refluxed for 45 min. The reaction mixture was quenched with 1 N HCl (12 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried on Na_2SO_4, evaporated and the crude product purified by flash chromatography (hexane–ethyl acetate) giving 0.284 g (71%) of the pure compound **6k**: oil; IR (neat): ν = 1243, 1722, 1739 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.21 (t, 3H, J = 7.0 Hz), 1.77–1.93 (m, 2H), 2.00 (s, 3H), 2.24 (dq, 2H, J = 7.0, 1.5 Hz), 4.06–4.20 (m, 4H), 5.80 (dt, 1H, J = 15.6, 1.5 Hz), 6.90 (dt, 1H, J = 15.6, 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 14.4, 21.0, 27.1, 28.7, 60.6, 63.6, 122.16, 147.7, 166.6, 171.1; EI-MS (70 ev) *m/z*: 29, 43, 55, 71 (100), 87, 113, 130, 158; Anal. Calcd for $C_{10}H_{16}O_4$ (200.23) C, 59.99; H, 8.05. Found C, 60.21; H, 7.81.