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Michael Addition of Nitroalkanes to Dimethyl Maleate with DBU. A New Direct Method for the Synthesis of Polyfunctionalized α,β-Unsaturated Esters.

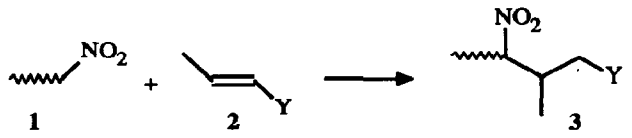
Roberto Ballini,* and Alessandro Rinaldi

Dipartimento di Scienze Chimiche dell'Università, Via S. Agostino n.1, I-62032 Camerino, Italy.

Abstract: Michael addition of nitroalkanes to dimethyl maleate, in acetonitrile and with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base affords, directly, polyfunctionalized α,β-unsaturated esters, *via* elimination of nitrous acid.

Methods allowing direct formation of polyfunctionalized α,β-unsaturated esters are of importance to organic synthesis.[1] The resultant compounds can be functionalized further by Michael or Diels-Alder reactions in order to furnish polyfunctionalized molecules of considerable use, especially in the synthesis of natural products.[2]

The conjugate addition of nitroalkanes **1** is a very important reaction and has been studied extensively[3] under several conditions and with different electron-deficient olefins **2**, affording the nitro-adducts **3** (Scheme 1).



1 2 3

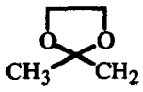
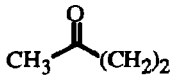
Y= SOR, SO_2R, CN, NO_2, COR, CHO, COOR

Scheme 1

Aliphatic nitro compounds can be considered as versatile building blocks and intermediates[4] and, in special cases, if electron-withdrawing groups exist at the β-position of the nitro function, elimination of nitrous acid takes place readily to give olefins in good yields,[5,6] however in the Michael adducts **3** the electron-withdrawing groups are in γ-position so, in spite of the numerous examples described, there are not reports of direct elimination of nitrous acid.

In the course of investigations of the reactivity of nitroalkanes, we have discovered that Michael addition of the latter **4** to dimethyl maleate **5**, in acetonitrile and with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base, gave, directly, the α,β-unsaturated esters **7** in high yields and in very short time (15 min.) (Scheme 2).

Table I. Yields of α,β-Unsaturated Esters (7) Prepared.

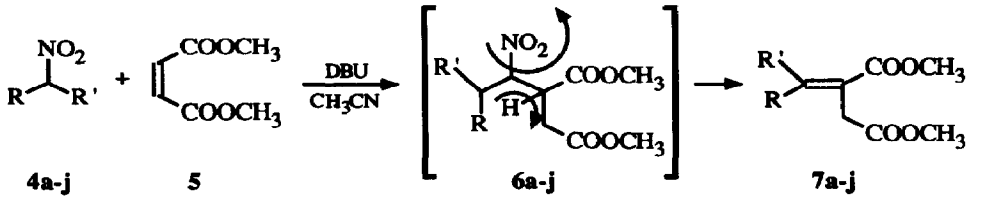
	R	R'	Yield (%)[a] 7
a	CH_3	H	93
b	CH_3CH_2	H	91
c	$CH_3(CH_2)_3$	H	94
d	CH_3	CH_3	95
e	$(CH_3)_2CHCH_2$	H	89
f	$THPOCH_2$	H	80
g	$CH_3OCO(CH_2)_3$	H	86
h		H	90
i		H	90
j	$HO(CH_2)_4$	H	70

[a] Yields are based on nitroalkanes and refer to pure and isolated products, fully characterized by their analytical data.[8]

The reaction proceeds *via* the adduct **6** in which the *in situ* elimination of nitrous acid takes place induced by the presence of an electron-withdrawing group at the β-position to the nitro function.

The very mild conditions allow high selectivity as supported by the absence of the typical side-reactions (*bis*-additions, polymerizations, β-fission, etc.), and, more interestingly, several functionalities such as hydroxy group, ketone, ester, ketal, and tetrahydropyranyl are preserved (Table I).

In optimizing the reaction conditions, we tested other different combinations of base (basic alumina,[3a] Amberlyst A21,[3b] and triethylamine[3d]) and solvent (Et_2O, dichloromethane). Our results indicated that DBU/acetonitrile were the most appropriate.



4a-j **5** **6a-j** **7a-j**

Scheme 2

In conclusion, the present methodology represents a new direct, chemoselective, high yielding and alternative[7] procedure for the synthesis of polyfunctionalized α,β-unsaturated esters.

The study of new potentiality of this method is now in progress in our laboratory.

Typical conditions for these reactions are the following: To a solution of nitroalkane **4** (10 mmol) and dimethyl maleate **5** (1.44 g, 10 mmol) in acetonitrile (40 ml), was added DBU (1.52 g, 10 mmol) at room temperature. After stirring for 15 min. and evaporation of the solvent, the crude product was purified by distillation or flash chromatography, affording the pure **7**.[8]

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8. All compounds were characterized by spectroscopic methods: **7a**: ν_{max} neat/cm^{-1} 1650, 1710 and 1735; ^{1}H NMR δ ($CDCl_3$) 1.82 (3H, d, *J* 7.1Hz, CH_3), 3.38 (2H, s, CH_2), 3.68 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 7.1 (1H, q, *J* 7.1Hz, CH=C). **7b**: ν_{max} neat/cm^{-1} 1645, 1712 and 1735; ^{1}H NMR δ ($CDCl_3$) 1.08 (3H, t, *J* 7.5Hz, CH_3), 2.2 (2H, m, *J* 7.5Hz, CH_3CH_2), 3.38 (2H, s, CH_2), 3.68 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 6.95 (1H, t, *J* 7.5Hz, CH=C). **7c**: ν_{max} neat/cm^{-1} 1645, 1712 and 1735; ^{1}H NMR δ ($CDCl_3$) 0.92 (3H, t, *J* 7.1Hz, CH_3), 1.4 (4H, m), 2.2 (2H, m), 3.35 (2H, s, CH_2COOCH_3), 3.68 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 6.97 (1H, t, *J* 7.6Hz), CH=C).**7d**: ν_{max} neat/cm^{-1} 1650, 1710 and 1737; ^{1}H NMR δ ($CDCl_3$) 1.87 (3H, s, CH_3), 2.13 (3H, s, CH_3), 3.38 (2H, s, CH_2), 3.68 (3H, s, OCH_3), 3.73 (3H, s, OCH_3). **7e**: ν_{max} neat/cm^{-1} 1640, 1710 and 1735; ^{1}H NMR δ ($CDCl_3$) 0.92 (6H, d, *J* 6.7Hz, $(CH_3)_2CH$), 1.8 (1H, m, *J* 6.7Hz, CH), 2.1 (2H, t, *J* 7.2Hz), 3.38 (2H, s, CH_2COOCH_3), 3.68 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 7.0 (1H, t, *J* 7.6Hz, CH=C). **7f**: ν_{max} neat/cm^{-1} 1645, 1712 and 1735; ^{1}H NMR δ ($CDCl_3$) 1.45-1.92 (6H, m), 3.42 (2H, s, CH_2COOCH_3), 3.45-3.6 (2H, m,CH_2O), 3.68 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.12-4.45 (2H, m, CH_2O), 4.65 (1H, m, CH), 7.08 (1H, t, *J* 7.7Hz, CH=C). **7g**: ν_{max} neat/cm^{-1} 1653, 1715, 1730 and 1735; ^{1}H NMR δ ($CDCl_3$) 1.8 (2H, m, *J* 7.2Hz), 2.25 (2H, m), 2.43 (2H, t, *J* 7.5Hz, $CH_2CH_2COOCH_3$), 3.38 (2H, s, CH_2COOCH_3), 3.67 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 6.93 (1H, t, *J* 7.6Hz, CH=C). **7h**: ν_{max} neat/cm^{-1} 1645, 1712 and 1735; ^{1}H NMR δ ($CDCl_3$) 1.35 (3H, s, CH_3), 2.55 (2H, d, *J* 7.7Hz, CH_2CH), 3.38 (2H, s, CH_2COOCH_3), 3.68 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.95 (4H, m, $(CH_2)_2$), 7.02 (1H, t, *J* 7.7Hz, CH=C). **7i**: ν_{max} neat/cm^{-1} 1650, 1715 and 1735; ^{1}H NMR δ ($CDCl_3$) 2.15 (3H, s, CH_3), 2.45 (2H, m), 2.62 (2H, m), 3.39 (2H, s, CH_2COOCH_3), 3.68 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 6.9 (1H, t, *J* 7.6Hz, CH=C). **7j**: ν_{max} neat/cm^{-1} 1640, 1705, 1730 and 3400; ^{1}H NMR δ ($CDCl_3$) 1.45-1.9 (4H, m), 2.12-2.28 (2H, m, CH_2CH_2CH=C), 3.35 (2H, s, CH_2COOCH_3), 3.6-3.7 (2H, m, CH_2O), 3.68 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 6.95 (1H, t, *J* 7.6Hz, CH=C).

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