

0040-4020(95)00136-0

## A Direct Method for the Synthesis of Polyfunctionalized Unsaturated Carbonyl Derivatives by Michael Addition of Nitroalkanes to Enediones with the Help of DBU.

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Abstract: The Michael addition of several nitroalkanes to dimethyl maleate, (Z)-3-hexene-2,5-dione, Nethyl maleimide, and N-phenyl maleimide, in MeCN or THF, proceeds very efficiently on DBU as base, and furnishes good to high yields of polyfunctionalized unsaturated carbonyl derivatives.

The many synthetic transformations originating from unsaturated carbonyl derivatives have made their preparation an important synthetic problem of long standing interest,<sup>1</sup> so, methods allowing direct formation of polyfunctionalized unsaturated carbonyl derivatives seem to be very important.<sup>2</sup>

Nucleophilic addition of carbanions to electrophilic alkenes activates by one or two electron withdrawing groups (the Michael reaction) is one of the most important tools<sup>3</sup> in organic synthesis for the formation of a new carbon-carbon bond.

As well reported in a recent paper by Makosza and Kwast,<sup>4</sup> the original Michael reaction (Scheme 1) is terminated by protonation of the adduct (path a). When a leaving group  $X^2$  is present at the  $\beta$ -carbon atom of the alkene, elimination of  $X^{2-}$  anion with recovery of the double bond occurs so overall vinylic nucleophilic substitution takes place (path b). On the other hand, when the leaving group is attached to the carbon atom of the nucleophilic reagent, intramolecular  $S_N^2$  substitution occurs with the formation of a cyclopropane ring (path c).

As a part of our continuing efforts to explore the novel utilities of functionalized nitroalkanes in the Michael reaction,<sup>5</sup> we have disclosed that the nitro group may, contemporaneously, behave both as an electron-withdrawing and as a leaving group. In fact (Scheme 2) the conjugate addition of the nitroalkanes 1 to dimethyl maleate 2, in acetonitrile and with DBU as base, gave, directly, the unsaturated esters 4 in high yields (Table I) and in a very short time.<sup>6</sup> The reaction proceeds *via* the *in situ* elimination of nitrous acid, from the adduct 3, induced by the presence of an electron-withdrawing group at the  $\beta$ -position to the nitro function.



During the research to develop this important procedure we found that substrates, different from dimethyl maleate, were also effective and, now we wish to report here further scope and generality of this procedure. The results are reported in Table II.

As shown in Table II, several nitroalkanes underwent clean and remarkably fast formation of unsaturated carbonyl derivatives with a variety of acceptors like (Z)-3-hexene-2,5-dione  $\mathbf{a}$ , N-phenyl maleimide  $\mathbf{b}$ , and N-ethyl maleimide  $\mathbf{c}$ .



We tested different combinations of base and solvent and our results indicated that DBU/MeCN was the most appropriate for the Michael addition of nitroalkanes to (Z)-3-hexene-2,5-dione, while DBU/THF gave better results when N-ethyl or N-phenyl maleimide were used as acceptors.

Short times (0.25-7 h) were required, additionally, the very mild conditions allow high selectivity as supported by the absence of the typical side-reactions (*bis*-additions, polymerizations,  $\beta$ -fission, etc.), and, more interestingly, several functionalities such as hydroxyl group, ketone, ester, ketal, and tetrahydropyranyl were preserved.

Moreover it is important to point out that the products obtained by this method can be regarded as both



Scheme	2

Table	I.
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	R	R'	Yield (%) 4
a	CH <sub>3</sub>	Н	93
b	CH <sub>3</sub> CH <sub>2</sub>	н	91
c	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	н	94
đ	CH <sub>3</sub>	CH <sub>3</sub>	95
e	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	Н	89
f	THPOCH <sub>2</sub>	Н	80
g	CH <sub>3</sub> OCO(CH <sub>2</sub> ) <sub>3</sub>	Н	86
h	CH <sub>3</sub> CH <sub>2</sub>	н	90
i	$CH_3 \xrightarrow{O} (CH_2)_2$	н	90
j	HO(CH <sub>2</sub> ) <sub>4</sub>	Н	70

Entry	Nitroalkane	Acceptor	Product	Yield (%)	Time (h)
5	$\overset{NO_2}{\checkmark}$	2		65	4
6	(J <sub>3</sub> NO <sub>2</sub>	a		70	0.5
7	∕_NO <sub>2</sub>	a		60	1
8		a		96	1
9	(J <sub>4</sub> NO <sub>2</sub>	a		90	0.5
10	CH <sub>3</sub> O <sup>O</sup> (1 <sub>3</sub> NO <sub>2</sub>	2		88	1
11	HO^(73NO2	2	HO (73 HO	85	2
12	O U () 2 NO <sub>2</sub>	a		95	2

Table II

Table II (Contd...)

Entry	Nitroalkane	Acceptor	Product	Yield (%)	Time (h)
13	NO2	a		85	7
14		a		56	3
15		Ь	N-Ph O	70	0.25
16	()3 NO2	b	O N-Ph O	56	0.25
17	()4 NO2	b	O Vi4 N-Ph	55	0.25
18	∽ <sub>NO2</sub>	b	O N-Ph O	55	0.25
19	$CH_3O$ $()_3 NO_2$	b	CH <sub>3</sub> O CH	80	2
20	HO $(7_3 NO_2)$	b	HO (73 N-Ph	56	2
21		b	O N-Ph	50	0.75

Table II (	Contd	)
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Entry	Nitroalkane	Acceptor	Product	Yield (%)	Time (h)
22	U (T2 NO2	b	N-Ph	73	3
23		c	N-Et	77	0.5
24	()4 NO2	c	N-Et	88	3
25	$CH_3O (7_3 NO_2)$	c	CH <sub>3</sub> O <sup>O</sup> (7 <sub>3</sub> ) <sup>O</sup> N-Et	90	3
26	HO (73 NO2	c	HO (73 N-Et	87	3
27		c	N-Et	88	1
28		c	O N-Et	80	0.25
29	↓NO2	c	N-Et	70	0.25
30	∕ <sub>NO2</sub>	с	N-Et	63	0.5

 $\alpha$ ,  $\beta$ - and  $\beta$ ,  $\gamma$ -unsaturated carbonyl derivatives.

In conclusion this procedure offers a new direct, chemoselective, good to high yielding and alternative<sup>7</sup> procedure for the synthesis of polyfunctionalized unsaturated carbonyl compounds.

## Experimental

General: All the reactions were monitored by TLC and gas chromatographic analyses, performed on a Carlo Erba Fractovap 4160 using a capillary column of duran glass (0.32 mm x 25 mt), stationary phase OV1 (film thickness 0.4-0.45 nm). All <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub>, at 200 MHz on a Varian Gemini 200. Chemical shifts are expressed in ppm downfield from tetramethylsilane. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. All the products were purified by flash chromatography<sup>8</sup> on Merck silica gel (0.040-0.063 mm), using appropriate mixtures of EtOAc/cyclohexane as eluents.

Synthesis of Unsaturated Carbonyl Derivatives. General Procedure: DBU (1.52 g, 10 mmol) was added, at room temperature to a solution of nitroalkane (10 mmol) and enedione a-c (10 mmol) in MeCN (50 ml) or THF (when N-substituted maleimides were used as acceptors, 50 ml). After stirring for the right time (see Table II) at the same temperature, silica gel (Merck 0.04-0.063 mm, 2-3 g) was added and the solution was then evaporated. The residue, consisting of crude silica gel, was flash chomatographed, using a suitable ratio of EtOAc/cyclohexane as eluent.

5: IR (film): v = 1710, 1680 and 1645 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.74$  (3H, s), 1.97 (3H, s), 2.15 (3H, s), 2.3 (3H, s), 3.44 (2H, s).

**6:** IR (film):  $\nu = 1710$ , 1660 and 1640 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 0.9$  (3H, t, J = 7.1Hz), 1.2-1.53 (4H, m), 2.1-2.3 (2H, m), 2.2 (3H, s), 2.3 (3H, s), 3.42 (2H, s), 6.85 (1H, t, J = 7.3Hz).

7: IR (film):  $\nu = 1700$ , 1660 and 1630 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.87$  (3H, d, J = 10.4Hz), 2.2 (3H, s), 2.34 (3H, s), 3.43 (2H, s), 6.9 (1H, q, J = 10.4Hz).

8: IR (film):  $\nu = 1710$ , 1660 and 1615 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 0.95$  (6H, d, J = 6.6Hz), 1.68-1.9 (1H, m), 2.1 (2H, dd, J = 7 and 7Hz), 2.2 (3H, s), 2.35 (3H, s), 3.42 (2H, s), 6.85 (1H, t, J = 7.3Hz).

**9:** IR (film):  $\nu = 1715$ , 1660 and 1640 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 0.92$  (3H, t, J = 6.6Hz), 1.22-1.56 (6H, m), 2.12-2.26 (2H, m), 2.17 (3H, s), 2.34 (3H, s), 3.41 (2H, s), 6.84 (1H, t, J = 7.3Hz).

**10:** IR (film):  $\nu = 1725$ , 1715, 1660 and 1635 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.73$ -1.9 (2H, m), 2.2 (3H, s), 2.21-2.32 (2H, m), 2.33 (3H, s), 2.36 (2H, t, J = 7.2Hz), 3.42 (2H, s), 3.68 (3H, s), 6.8 (1H, t, J = 7.3 Hz).

11: IR (film):  $\nu = 3430$ , 1700, 1650 and 1620 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.56-1.68$  (4H, m), 2.18-2.29 (2H, m), 2.2 (3H, s), 2.34 (3H, s), 3.41 (2H, s), 3.62-3.73 (2H, m), 6.85 (1H, t, J = 7.3Hz).

**12:** IR (film):  $\nu = 1700$ , 1655 and 1625 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.18$  (3H, s), 2.2 (3H, s), 2.3 (3H, s), 2.4-2.5 (2H, m), 2.65 (2H, t, J = 7Hz), 3.45 (2H, s), 6.79 (1H, t, J = 7.3Hz).

**13:** IR (film):  $\nu = 1710$ , 1675 and 1615 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.53-1.7$  (6H, m), 2.07-2.15 (2H, m), 2.17 (3H, s), 2.33 (3H, s), 2.34-2.4 (2H, m), 3.42 (2H, s).

14: IR (film): v = 1715, 1665 and 1640 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.5$ -1.91 (6H, m), 2.2 (3H, s), 2.39 (3H, s), 3.45 (2H, s), 3.48-3.6 (2H, m), 4.18 (1H, dd, J = 14.9 and 6HZ), 4.45 (1H, dd, J = 14.9 and 5.42Hz), 4.6-4.7 (1H, m), 6.92 (1H, t, J = 5.7Hz).

**15:** IR (KBr): v = 1750, 1695, 1650 and 1620 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.95$  (3H, s), 2.39 (3H, t, J = 1.7Hz), 3.37-3.42 (2H, m), 7.24-7.52 (5H, m).

**16:** IR (KBr):  $\nu = 1760$ , 1695, 1665 and 1640 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 0.95$  (3H, t, J = 7Hz), 1.24-1.55 (4H, m), 2.19-2.33 (2H, m), 3.39-3.42 (2H, m), 6.96 (1H, tt, J = 7.7 and 2.4Hz), 7.28-7.53 (5H, m).

**17:** IR (KBr):  $\nu = 1760$ , 1695, 1660 and 1630 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 0.88-0.98$  (3H, m), 1.24-1.62 (6H, m), 2.18-2.32 (2H, m), 3.4 (2H, m), 6.96 (1H, tt, J = 7.7 and 2.4Hz), 7.3-7.54 (5H, m).

**18:** IR (KBr):  $\nu = 1760$ , 1695, 1665 and 1635 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.91$  (3H, dt, J = 7.2 and 1.6Hz), 3.36-3.41 (2H, m), 7.0 (1H, qt, J = 7.2 and 2.4Hz), 7.28-7.52 (5H, m).

**19:** IR (KBr):  $\nu = 1775$ , 1700, 1665 and 1645 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.8$ -1.9 (2H, m), 2.24-2.46 (4H, m), 3.39-3.44 (2H, m), 3.7 (3H, s), 6.92 (1H, tt, J = 7.7 and 2.4Hz), 7.3-7.58 (5H, m).

**20:** IR (KBr):  $\nu = 3360$ , 1760, 1695, 1665 and 1645 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.4$ -1.72 (4H, m), 1.98-2.16 (2H, m), 3.39-3.46 (2H, m), 3.62-3.79 (2H, m), 6.96 (1H, tt, J = 7.7 and 2.52Hz), 7.3-7.6 (5H, m).

**21:** IR (KBr):  $\nu = 1780$ , 1705, 1680 and 1650 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.43$  (3H, s), 2.58-2.67 (2H, d, J = 8.0Hz), 3.42-3.5 (2H, m), 3.98-4.06 (4H, m), 7.01 (1H, tt, J = 7.8 and 2.4Hz), 7.3-7.58 (5H, m).

**22:** IR (KBr):  $\nu = 1765$ , 1695, 1665 and 1630 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.2$  (3H, s), 2.43-2.6 (2H, m), 2.68-2.79 (2H, t, J = 6.9Hz), 3.5-3.59 (2H, m), 6.81 (1H, tt, J = 7.6 and 2.4Hz), 7.3-7.55 (5H, m).

**23:** IR (KBr):  $\nu = 1750$ , 1690 and 1650 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.14-1.23$  (3H, t, J = 7.2Hz), 1.88 (3H, s), 2.35 (3H, t, J = 1.6Hz), 3.15-3.22 (2H, m), 3.6 (2H, q, J = 7.2Hz).

**24:** IR (film):  $\nu = 1765$ , 1700, 1675 and 1625 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 0.9$  (3H, t, J = 6.6Hz), 1.2 (3H, t, J = 7.2Hz), 1.26-1.6 (6H, m), 2.11-2.28 (2H, m), 3.18-3.21 (2H, m), 3.63 (2H, q, J = 7.2Hz), 6.82 (1H, tt, J = 7.7 and 2.4 Hz).

**25:** IR (film):  $\nu = 1765$ , 1725, 1700 and 1665 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.2$  (3H, t, J = 7.2Hz), 1.76-1.93 (2H, m), 2.18-2.31 (2H, m), 2.37 (2H, t, J = 7.2Hz), 3.19-3.23 (2H, m), 3.63 (2H, q, J = 7.2Hz), 3.69 (3H, s), 6.77 (1H, tt, J = 7.65 and 2.38Hz).

**26:** IR (film):  $\nu = 3480$ , 1760, 1695 and 1670 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.2$  (3H, t, J = 7.2Hz), 1.56-1.7 (4H, m), 2.19-2.33 (2H, m), 3.2-3.24 (2H, m), 3.58-3.69 (4H, m), 6.81 (1H, tt, J = 7.7 and 2.4Hz).

27: IR (film):  $\nu = 1765$ , 1700, 1675 and 1625 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.2$  (3H, t, J = 7.2Hz), 1.39 (3H, s), 2.54 (2H, d, J = 7.8Hz), 3.22-3.28 (2H, m), 3.6 (2H, q, J = 7.2Hz), 3.93-4.01 (4H, m), 6.87 (1H, tt, J = 7.8 and 2.4Hz).

**28:** IR (KBr):  $\nu = 1755,1705, 1690$  and 1645 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.19$  (3H, t, J = 7.2Hz), 1.59-1.65 (6H, m), 2.14-2.24 (2H, m), 3.0-3.1 (2H, m), 3.2 (2H, s), 3.6 (2H, q, J = 7.2Hz).

**29:** IR (film):  $\nu = 1760$ , 1695, 1670 and 1635 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 0.96$  (6H, d, J = 6.8Hz), 1.2 (3H, t, J = 7.2Hz), 1.72-1.94 (1H, m), 2.03-2.13 (2H, m), 3.17-3.21 (2H, m), 3.65 (2H, q, J = 7.2Hz), 6.84 (1H, tt, J = 7.8 and 2.4Hz).

**30**: IR (film): v = 1765, 1705, 1675 and 1645 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.2$  (3H, t, J = 7.2Hz), 1.87 (3H, dt, J = 7.2 and 1.5Hz), 3.19-3.23 (2H, m), 3.64 (2H, q, J = 7.2Hz), 6.88 (1H, qt, J = 7.2 and 2.4Hz).

Acknowledgement: We thank the Consiglio Nazionale delle Ricerche (C.N.R.)-Italy and Ministero dell'Università e della Ricerca Scientifica e Tecnologica MURST)-Italy for financial support.

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(Received in UK 30 January 1995; accepted 9 February 1995)