Conjugated Addition Reactions of Nitroalkanes with Electrophilic Alkenes in Aqueous Media

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The Michael reaction of various nitroalkanes **1** with electrophilic alkenes **2** can be performed in NaOH (0.025−0.1 M), without any organic solvent. In many cases the presence of cetyltrimethylammonium chloride (CTACl), as cationic surfactant, produces better results. Good yields of the products **3** are obtained even with hindered, and functionalized starting materials.

Nucleophilic addition of carbanions to electrophilic alkenes activated by an electron-withdrawing group (the Michael reaction) is one of the most important procedures[1] in organic synthesis for the formation of a new carbon−carbon bond.

In this context the use of primary and secondary nitroalkanes as carbanions is a valuable tool considering that the nitro group can be further transformed into various functionalities.[2] As routine procedures, this reaction is performed in the presence of different organic bases in homogeneous solutions[3] or, alternatively, under heterogeneous catalysis.[4]

Increasingly demanding environmental legislation, public and corporate pressure and resulting drive towards clean technology in the chemical industry, with the emphasis on reduction of waste at source, will require increasing attention on the use of less toxic and environmentally compatible materials in the design of new synthetic methods.[5]

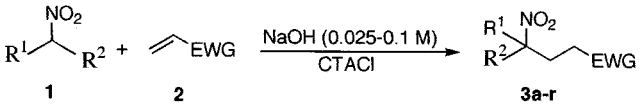
Established chemical processes that are often based on technology developed in the first half of the 20th century, may no longer be acceptable in these environmentally conscious days.[6]

For this purpose, in recent years, there has been increasing interest in the use of water as an attractive medium for many organic reactions.[7][8] Moreover, the aqueous medium allows the right control of pH, while the solubility of most reagents in water is not an obstacle to the reactivity which, on the contrary, is often improved.[9]

We have reported in a recent communication[10] that nitroalkanes can be efficiently reacted with α,β-unsaturated ketones in an aqueous media using a solution of sodium hydroxide. Under these conditions nitroalkanes easily react with a variety of conjugated enones in very short reaction times.

Electron-deficient alkenes,[1] such as α,β-unsaturated esters, nitriles, sulphones are less active than the corresponding ketones in the Michael reaction with nitroalkanes. In fact strong basic conditions,[3k] long reaction times,[3a][3l][3m] a large excess of nitroalkane,[4d] or the help of ultrasound[4e] are required.

The need to accomplish this important synthetic transformations under milder conditions and with less toxic and environmentally compatible materials has led us to develop this procedure of Michael reaction in aqueous media (Scheme 1, Table 1).



1 **2** **3a-r**

1−3	R^1	R^2	EWG
a	H	CH_3	CO_2Me
b	H	C_2H_5	CO_2Me
c	H	$CH_3(CH_2)_3$	CO_2Me
d	CH_3	CH_3	CO_2Me
e	H	C_6H_5	CO_2Me
f	H	$CH_3CHOH(CH_2)_2$	CO_2Me
g	H	CH_3	CN
h	H	C_2H_5	CN
i	CH_3	CH_3	CN
j	H	$CH_3(CH_2)_4$	CN
k		$-(CH_2)_5-$	CN
l	H	CH_3	SO_2Ph
m	H	C_2H_5	SO_2Ph
n	H	$CH_3(CH_2)_4$	SO_2Ph
o	CH_3	CH_3	SO_2Ph
p	H	C_6H_5	SO_2Ph
q	H	$CH_3CO(CH_2)_2$	SO_2Ph
r	H	$CH_3O_2C(CH_2)_2$	SO_2Ph

Our procedure is performed using a solution of sodium hydroxide 0.025−0.1 M (see Table 1) in the presence of catalytic amount of cetyltrimethylammonium chloride (CTACl) as cationic surfactant. We tested different concentrations of base but 0.025 M NaOH gave the best results. For the compounds **3a**, **b**, **d** 0.1 M NaOH produced higher yields, as soon as the absence of CTACl sometime gave higher yields (entry **3a−c**, **l**, **m**, **p**).

Under these conditions both primary and secondary nitroalkanes easily react with a variety of electrophilic al-

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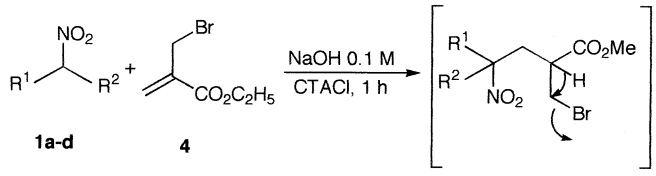
Table 1. Preparation of nitroderivatives **3**

Product **3**	Yield [%]	bp [°C/Torr] or mp [°C]	NaOH	CTACl	Reaction time [h]
a	80	86/1 (89−90/2)[12]	0.1	No	1
b	80	92/1 (97−98/2)[12]	0.1	No	1
c	58	Oil	0.025	No	2
d	54	Oil	0.1	Yes	8
e	59	Oil	0.025	Yes	2
f	55	Oil	0.025	Yes	3
g	50	Oil	0.025	Yes	1
h	57	Oil	0.025	Yes	1
i	74	Oil	0.025	Yes	2
j	61	Oil	0.025	Yes	1
k	78	39−42	0.025	Yes	4
l	70	54−55	0.025	No	2
m	58	58−60	0.025	No	2
n	61	35−37	0.025	Yes	1
o	56	Oil	0.025	Yes	1
p	90	89−91	0.025	No	2
q	50	71−72	0.025	Yes	2
r	51	Oil	0.025	Yes	1

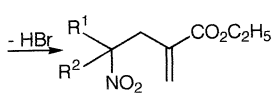
kenes (α,β-unsaturated ketones, esters, sulphones, and nitriles), and the need of diluted solution of base prevents polymerisations or polyadditions often observed during this reaction.

Satisfactory to good yields were obtained in short reaction times (1−8 h), additionally, the very mild reaction conditions allow the preservation of functionalities like ketones, hydroxyl, and ester.

An important extension of this procedure is the efficient tandem conjugated addition−elimination (HBr) observed when nitroalkanes **1a−d** react with **4** (Scheme 2). The obtained α,β-unsaturated esters **5a−d** (55−72% yield) are of special interest because they can be simultaneously employed as electrophiles (Michael addition) and/or as nucleophiles at carbon bearing the nitro group (entry **5a−c**), moreover, the presence of the latter functionality facilitates several other conversions, due to the high versatility of this group (Scheme 2).[2]



1a-d **4**



5a-d

1−5	R^1	R^2
a	H	CH_3
b	H	C_2H_5
c	H	$CH_3(CH_2)_3$
d	CH_3	CH_3

In conclusion, since our method can be applied to a variety of combinations of nitroalkanes and electrophilic alkenes, we consider this procedure an attractive general option of the conventional methods due to its evident economical and ecological advantages.

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Experimental Section

All the reactions were monitored by TLC and gas-chromatographic analyses, performed with a Carlo Erba Fractovap 4160 using a capillary column of duran glass (0.32 mm × 25 mt), stationary phase OV1 (film thickness 0.4−0.45 nm). − All ^{1}H-NMR spectra were recorded in $CDCl_3$, at 200 MHz with a Varian Gemini 200. Chemical shifts are expressed in ppm downfield from tetramethylsilane. − IR spectra were recorded with a Perkin-Elmer 257 spectrometer. − All the products were purified, when necessary, by flash chromatography on Merck silica gel with EtOAc/cyclohexane as eluent, or by distillation. − Elementary analyses were performed using a C,H,N,S Analyzer Model 185 from Hewlett-Packard. − The compound **4** has been prepared as previously reported.[11]

Table 2. Selected spectroscopic data of nitro derivatives **3**

Product **3**	IR (film) $\tilde{\nu}$ [cm^{-1}]	^{1}H NMR ($CDCl_3$/TMS) δ, *J* [Hz]
a	1720, 1535	1.55 (d, 3 H, *J* = 6.6), 2.0−2.45 (m, 4 H), 3.7 (s, 3 H), 4.55−4.75 (m, 1 H).
b	1730, 1535	0.97 (t, 3 H, *J* = 7.4), 1.75−2.43 (n, 6 H), 3.7 (s, 3 H), 4.4−4.55 (m, 1 H)
c	1730, 1535	0.89 (t, 3 H, *J* = 7.2), 1.2−1.4 (m, 4 H), 1.6−2.3 (m, 4 H), 2.31−2.4 (m, 2 H), 3.68 (s, 3 H), 4.55 (m, 1 H, *J* = 4.7)
d	1730, 1530	1.6 (s, 6 H), 2.2−2.4 (m, 4 H), 3.68 (s, 3 H)
e	1730, 1535	2.3−2.9 (m, 4 H), 3.7 (s, 3 H), 5.5−5.6 (m, 1 H), 7.4−7.5 (m, 5 H)
f	3380, 1720, 1535	1.2 (d, 3 H, *J* = 6.1), 1.4−1.58 (m, 4 H), 1.8−2.4 (m, 6 H), 3.68 (s, 3 H), 3.73−3.85 (m, 1 H)
g	2220, 1535	1.65 (d, 3 H, *J* = 6.7), 1.95−2.57 (m, 4 H), 4.6−4.8 (m, 1 H)
h	2220, 1535	1.0 (t, 3 H, *J* = 7.4), 1.75−2.55 (m, 6 H), 4.45−4.6 (m, 1 H)
i	2220, 1535	1.7 (s, 6 H), 2.28−2.7 (m, 4 H)
j	2220, 1535	0.8−1.0 (m, 3 H), 1.2−1.65 (m, 6 H), 1.0−2.6 (m, 6 H), 4.5−4.65 (m, 1 H)
k	2220, 1535	1.25−1.8 (m, 10 H), 2.18−2.55 (m, 4 H)
l	1530, 1360, 1135	1.59 (d, 3 H, *J* = 6.8), 2.15−2.5 (m, 2 H), 3.15 (t, 2 H, *J* = 7.7), 4.65−4.8 (m, 1 H), 7.5−7.8 (m, 3 H)
m	1530, 1360, 1137	0.9−1.0 (m, 3 H), 1.7−2.5 (m, 4 H), 3.1 (t, 2 H, *J* = 7.7), 4.5−4.75 (m, 1 H), 7.5−7.75 (m, 3 H), 7.85−7.96 (m, 2 H)
n	1530, 1360, 1135	0.8−0.93 (m, 3 H), 1.2−1.4 (m, 6 H), 1.6−2.1 (m, 2 H), 2.2−2.45 (m, 2 H), 3.1 (t, 2 H, *J* = 7.7), 4.52−4.76 (m, 1 H), 7.5−7.75 (m, 3 H), 7.85−7.96 (m, 2 H)
o	1530, 1360, 1135	1.6 (s, 6 H), 2.25−2.4 (m, 2 H), 3.05−3.15 (m, 2 H), 7.5−7.75 (m, 3 H), 7.85−7.96 (m, 2 H)
p	1530, 1360, 1135	2.5−2.95 (m, 2 H), 3.05−3.15 (m, 2 H), 5.65 (t, 1 H, *J* = 7.6), 7.3−7.5 (m, 5 H), 7.55−7.75 (m, 2 H)
q	1700, 1530, 1360, 1135	2.0−2.18 (m + s, 5 H), 2.2−2.42 (m, 2 H), 2.44−2.54 (m, 2 H), 3.0−3.2 (m, 2 H), 4.6−4.7 (m, 1 H), 7.58−7.73 (m, 3 H), 7.88−7.9 (m, 2 H)
r	1720, 1530, 1360, 1135	2.0−2.5 (m, 6 H), 3.13 (t, 2 H, *J* = 7.7), 3.68 (s, 3 H), 4.6−4.8 (m, 1 H), 7.53−7.7 (m, 3 H), 7.85−7.95 (m, 2 H)

Michael Addition of Nitroalkanes (**1**) *to Electrophilic Alkenes* (**2**). – *General Procedure:* Nitroalkane (45 mmol) and the alkene **2** (30 mmol) were added to a solution of 0.025 M NaOH (0.1 M for entry **3a**, **b**, **d**; 70 ml). Then, cetyltrimethylammonium chloride (CTACl, 3 mmol; without CTACl for entry **3a–c**, **l**, **m**, **p**) was added at room temperature and the resulting mixture was stirred, at the same temperature, for the appropriate time (TLC, GC, see Table 1), then saturated with NaCl and extracted with Et_2O (4 × 25 ml). The organic phase was dried ($MgSO_4$), concentrated, and the crude product, when necessary, was purified by flash chromatography (EtOAc/cyclohexane, 2:8) or by distillation giving the pure product **3** (Tables 2 and 3).

Table 3. Microanalyses of nitroderivatives **3**

3	Empirical Formula	Molec. mass	Calcd. C	H	N	S	Found C	H	N	S
a	$C_6H_{11}NO_4$	161.2	44.72	6.88	8.69	–	44.87	6.75	8.77	–
b	$C_7H_{13}NO_4$	175.2	47.99	7.47	7.99	–	48.19	7.55	7.86	–
c	$C_9H_{17}NO_4$	203.1	53.19	8.43	6.89	–	53.30	8.36	6.99	–
d	$C_7H_{13}NO_4$	175.2	47.99	7.47	7.99	–	48.10	7.57	7.90	–
e	$C_{11}H_{13}NO_4$	223.1	59.18	5.87	6.27	–	59.07	5.96	6.13	–
f	$C_{10}H_{19}NO_5$	233.1	51.49	8.21	6.00	–	51.55	8.13	5.89	–
g	$C_5H_8N_2O_2$	128.1	46.87	6.29	21.86	–	46.94	6.18	21.97	–
h	$C_6H_{10}N_2O_2$	142.1	50.69	7.09	19.70	–	50.77	6.98	19.58	–
i	$C_6H_{10}N_2O_2$	142.1	50.69	7.09	19.70	–	50.53	7.18	10.77	–
j	$C_9H_{16}N_2O_2$	184.1	58.67	8.75	17.37	–	58.78	8.66	17.48	–
k	$C_9H_{14}N_2O_2$	182.1	59.32	7.74	17.56	–	59.24	7.88	17.44	–
l	$C_{10}H_{13}NO_4S$	243.1	49.47	5.38	5.75	13.18	49.44	5.27	5.78	13.09
m	$C_{11}H_{15}NO_4S$	257.1	51.35	5.87	5.44	12.46	51.20	5.99	5.37	12.33
n	$C_{14}H_{21}NO_4S$	299.1	56.17	7.07	4.68	10.71	56.01	7.15	4.77	10.59
o	$C_{11}H_{15}NO_4S$	257.1	51.35	5.86	5.44	12.46	51.39	5.77	5.51	12.37
p	$C_{15}H_{15}NO_4S$	305.4	59.00	4.95	4.58	10.50	58.88	5.04	4.66	10.57
q	$C_{13}H_{17}NO_5S$	299.3	52.16	5.72	4.68	10.71	52.09	5.79	4.60	10.59
r	$C_{13}H_{17}NO_6S$	315.3	55.10	6.05	4.94	11.31	55.01	5.99	5.02	11.38

General Procedure for the Michael Addition of Nitroalkanes (**1a–d**) *to Electrophilic Alkenes* (**4**): Nitroalkane **1a–d** (12 mmol) and the alkene **4** (10 mmol) were added to a solution of NaOH (0.1 M, 20 ml). Then, cetyltrimethylammonium chloride (CTACl, 1 mmol) was added at room temperature and the resulting mixture was stirred, at the same temperature, for 2 h, then saturated with NaCl and extracted with Et_2O (4 × 15 ml). The organic phase was dried ($MgSO_4$), concentrated, and the crude product was purified by flash chromatography (EtOAc/cyclohexane, 2:8) giving the pure product **5a–d**.

5a: Oil (72% yield). – IR (film): $\tilde{\nu}$ = 1710 cm^{-1}, 1630, 1545. – ^1H NMR ($CDCl_3$): δ = 1.3 (t, 3 H, *J* = 7.2 Hz), 1.58 (d, 3 H, *J* = 7.1 Hz), 2.7–2.95 (m, 2 H), 4.22 (q, 2 H, *J* = 7.2 Hz), 4.75–5.00 (m, 1 H), 5.68 (s, 1 H), 6.28 (s, 1 H). – $C_8H_{13}NO_4$ (187.1): calcd. C 51.33, H 6.99, N 7.48; found C 51.22, H 7.07, N 7.35.

5b: Oil (71% yield). – IR (film): $\tilde{\nu}$ = 1710 cm^{-1}, 1630, 1530. – ^1H NMR ($CDCl_3$): δ = 0.98 (t, 3 H, *J* = 7.3 Hz), 1.31 (t, 3 H, *J* = 7.1 Hz), 1.72–2.12 (m, 2 H), 2.81 (d, 2 H, *J* = 5.2 Hz), 4.22 (q, 2 H, *J* = 7.1 Hz), 4.6–4.78 (m, 1 H), 5.65 (m, 1 H), 6.23 (m, 1 H). – $C_9H_{15}NO_4$ (201.1): calcd. C 53.72, H 7.51, N, 6.96; found C 53.88, H 6.88, N 7.05.

5c: Oil (61% yield). – IR (film): $\tilde{\nu}$ = 1705 cm^{-1}, 1625, 1545. – ^1H NMR ($CDCl_3$): δ = 0.8–2.2 (m, 12 H), 2.72–2.98 (m, 2 H), 4.15–4.32 (m, 2 H), 4.7–4.9 (m, 1 H), 5.8 (s, 1 H), 6.4 (s, 1 H). – $C_{11}H_{19}NO_4$ (229.1): calcd. C 57.62, H 8.35, N 6.11; found C 57.89, H 8.48, N 6.00.

5d: Oil (55% yield). – IR (film): $\tilde{\nu}$ = 1710 cm^{-1}, 1625, 1535. – ^1H NMR ($CDCl_3$): δ = 1.3 (t, 3 H, *J* = 7.1 Hz), 1.58 (s, 6 H), 3.0 (s, 2 H), 4.2 (q, 2 H, *J* = 7.1 Hz), 5.58 (s, 1 H), 6.3 (s, 1 H). – $C_9H_{15}NO_4$ (201.1): calcd. C 53.72, H 7.51, N 6.96; found C 53.61, H 7.64, N 6.87.

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