New route to functionalized cyclohexenes from nitromethane and electrophilic alkenes without solvent under focused microwave irradiation

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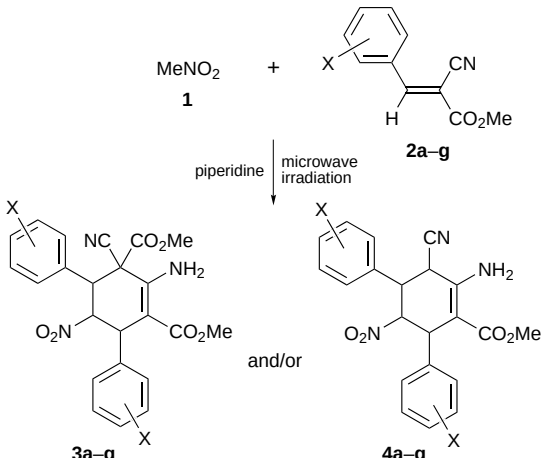
Nitromethane reacts *via* a diastereoselective double Michael addition with electrophilic alkenes activated by cyano and methoxycarbonyl groups [$XC_6H_4CH{=}C(CN)CO_2Me$] in the presence of catalytic amounts of piperidine under solvent-free conditions coupled with focused microwave irradiation to afford new, highly functionalized cyclohexenes; no cyclopropane formation is observed.

Organic synthesis in dry media coupled with microwave irradiation is currently a matter of increasing interest.[1–3] Microwave-assisted organic reactions in the presence or absence of solvents have recently been reviewed.[4] In the course of our studies related to the catalytic effect of piperidine towards condensations[5–7] under microwave irradiation (MWI), we report a novel reaction of nitromethane **1** with some electrophilic alkenes **2a–g**,† which leads to highly functionalized cyclohexenes **3a–g**‡ and/or **4a–g**‡ after demethoxycarbonylation of **3** (Scheme 1). Nitroalkanes and electrophilic alkenes are known to give cyclopropanes, although in the case of nitromethane, the yields are rather poor.[8–10]

The simple mixture of **1** and **2**, without solvent in the presence of adjusted amounts of piperidine, afforded **3** or **4** at room temperature (for example **3a** was obtained in 60% yield after 98 h, with 12 mol% piperidine with respect to the alkene) or in a few minutes under focused microwave irradiation in a Synthewave 402 Prolabo[11] at 90 °C (monitored temperature[12]) (see Tables 1 and 2). The reaction is highly diastereoselective: only two isomers were detected in the crude product by ^1H NMR spectroscopy. The relative configuration of the major isomer has been established by X-ray analysis (Fig. 1).[13] However, the relative configuration of the minor isomer has not yet been established.

In order to check the effect of the focused microwave irradiation, we performed the following experiments for the



Scheme 1

Table 1 Microwave synthesis of **3a–g**

	Irradiation time/min	Yield (%)[a]	Molecular formula
3a	11	70	$C_{23}H_{21}N_3O_6$
3b	15	73	$C_{23}H_{19}N_3O_6Cl_2$
3c	25	70	$C_{25}H_{25}N_3O_8$
3d	20	71	$C_{23}H_{19}N_5O_{10}$
3e	15	75	$C_{23}H_{19}N_3O_6F_2$
3f	15	75	$C_{23}H_{19}N_3O_6F_2$
3g	15	75	$C_{23}H_{19}N_3O_6Br_2$

[a] Pure isolated product after column chromatography on silica gel (eluent CH_2Cl_2) and then crystallization from diethyl ether.

Table 2 Microwave synthesis of **4a–g**

	Irradiation time/min	Yield (%)[a]	Molecular formula
4a	11	75	$C_{21}H_{19}N_3O_4$
4b	15	75	$C_{21}H_{17}N_3O_4Cl_2$
4c	25	70	$C_{23}H_{23}N_3O_6$
4e	15	72	$C_{21}H_{17}N_3O_4F_2$
4f	15	70	$C_{21}H_{17}N_3O_4F_2$
4g	15	75	$C_{21}H_{17}N_3O_4Br_2$

[a] Pure isolated product after column chromatography on silica gel (eluent CH_2Cl_2) and then crystallization from diethyl ether.

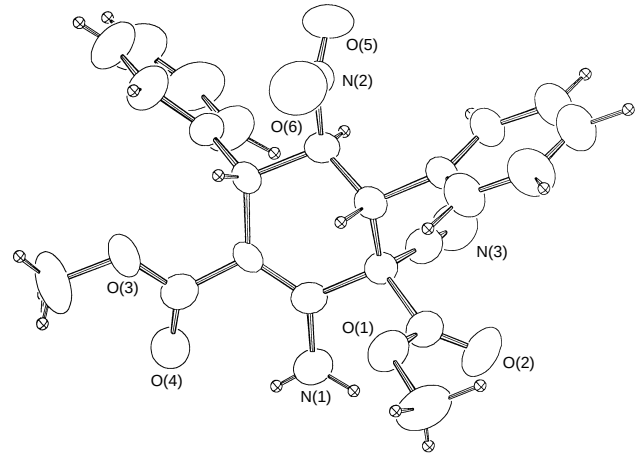
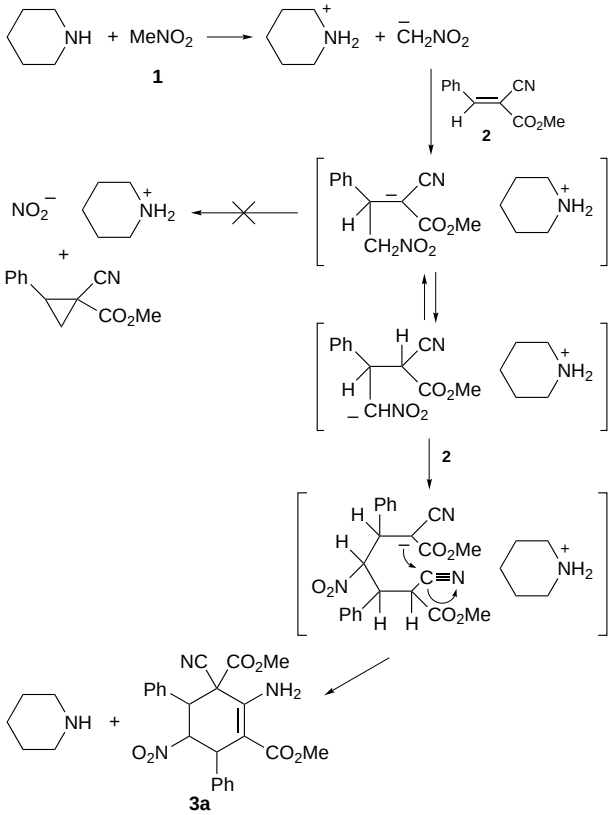


Fig. 1 ORTEP diagram of **3a**



Scheme 2

synthesis of **3a**. (i) The reaction mixture was irradiated at 750 W in a domestic oven (Philips M602) for the same time (11 min, 97 °C measured at the end), and gave 5% of **3a** (estimated by ^{1}H NMR spectroscopy). (ii) The same reaction mixture was placed in an oil bath at 90 °C for the same time (11 min), but the reaction only went to 60% completion; the low yield of **3a** (27%) is due to competition from the Michael monoadduct. After 20 min this yield remained unchanged.

Cyclohexene formation can be explained by the mechanism presented in Scheme 2. After a double Michael addition, the ring closure occurs *via* nucleophilic attack on the nitrile group by the carbanion and regeneration of piperidine in a catalytic cycle. A stoichiometric amount of piperidine promotes the demethoxycarbonylation of **3** to **4** by a mechanism already described by Carrié.[14]

This cyclohexene synthesis, previously unreported in the literature, is a simple, clean, economical and environmentally benign process which can be performed either at room temperature over a rather long reaction time or under focused microwave irradiation in a short time with better yields.

The extension of this reaction to other electrophilic alkenes (dicyano and cyano amide) is under investigation.

Footnotes and References

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† *Typical procedure*: A mixture of alkene (5 mmol), nitromethane (0.18 g, 3 mmol) and piperidine (20 μl, 0.2 mmol for **3a** and 250 μl, 2.5 mmol for **4a**) was placed in a quartz tube (diameter 37 mm) and introduced into a Synthewave 402 Prolabo microwave reactor (2.45 GHz) fitted with a rotational system, adjustable power within the range 20–300 W and a wave guide (monomode T_{01}) (ref. 11). Microwave irradiation was carried out at 90 °C (ref. 12) (obtained after 3 min and then maintained for 8 min). Other irradiation times are given in Tables 1 and 2. The mixture was cooled to room temperature and the crude residue was characterized by ^{1}H NMR spectroscopy. Pure product was isolated after chromatography on silica gel (eluent CH_2Cl_2) and slow crystallization from diethyl ether.

‡ *Selected data* for **3a**: 70%; δ_H (300 MHz, $CDCl_3$) (major isomer) 3.36 (s, 3 H, CO_2CH_3), 3.72 (s, 3 H, $C{=}CCO_2CH_3$), 4.28 (d, 1 H, C_5-H, *J* 12.7), 4.52 (d, 1 H, C^3-H, *J* 9.6), 5.30 (dd, 1 H, C^4-H, *J* 12.7, 9.6), 6.26 (s, 2 H, NH_2), 7.15–7.34 (m, 10 H, C_6H_5); δ_C (75 MHz, $CDCl_3$) 47.65 (dm, C^3, *J* 135.3), 48.16 (dm, C^5, *J* 138.4), 51.16 (q, CCO_2CH_3, *J* 147.2), 54.81 (q, $C{=}CCO_2CH_3$, *J* 149.7), 55.90 (td, $C{=}CCO_2CH_3$), 91.55 (dt, C^4, *J* 151.7, 6.9), 97.44 (m, $C{=}CCO_2CH_3$), 115.16 (d, *C*N, *J* 9.9), 126.9–144 (m, 12 C arom), 145.35 (m, CNH_2), 164.89 (dq, CCO_2CH_3, *J* 4.1, 2.4), 168.37 (m, $C{=}CCO_2CH_3$); HRMS: Calc for [$M^{+\cdot} - HNO_2$]: 388.142. Found: 388.142. Found: C, 63.57; H, 4.88; N, 9.72. $C_{23}H_{21}N_3O_6$ requires C, 63.44; H, 4.86; N, 9.65%. For **4a**: 75%; δ_H (300 MHz, DMSO) (major isomer) 3.46 (s, 3 H,OCH_3), 3.71 (dd, 1 H, C^5-H, *J* 11.4, 12), 4.07 (dd, 1 H, C^6-H, *J* 11.4, 2.4), 4.24 (dd, 1 H, C^3-H, *J* 10.3, 2.4), 5.55 (dd, 1 H, C^4-H, *J* 10.3, 12), 6.22 (s, 2 H, NH_2), 7.19–7.38 (m, C_6H_5); δ_C (75 MHz, DMSO) 46.79 (dm, C^3, *J* 136), 47.41 (dm, C^5, *J* 133), 51.75 (dm, C^6, *J* 135), 52.4 (q, OCH_3, *J* 147.5), 74.75 (m, CNH_2), 91.67 (dt, C^4, *J* 156.5), 118.4 (s, CN), 127.23–139.61 (m, 12 C arom), 153.14 (m, CCO_2CH_3), 169.6 (m, CO_2CH_3); HRMS: Calc. for [$M^{+\cdot} - HNO_2$]: 330.1368. Found: 330.137. Found: C, 66.99; H, 5.17; N, 11.15. $C_{21}H_{19}N_3O_4$ requires C, 66.83; H, 5.07; N, 11.13%.

All products were fully characterized by ^{1}H and ^{13}C NMR and mass spectroscopy and elemental analysis.

§ *Crystal data* for **3a** (ref. 13): $C_{23}H_{21}N_3O_6$: *M* = 435.44, monoclinic, $P2_1/c$, *a* = 14.962(2), *b* = 10.028(2), *c* = 14.725(9) Å, β = 91.96(3)°, *V* = 2208(2) Å^{-3}, *Z* = 4, D_x = 1.310 Mg m^{-3}, λ(Mo-Kα) = 0.70926, μ = 0.899 cm^{-1}, *F*(000) = 912, *T* = 294 K, final *R* = 0.032 for 1812 observations and 373 parameters. Structure solved by direct methods and refined by the full-matrix least-squares technique to *R* = 0.032 for 1812 observations and 373 parameters. CCDC 182/536.

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Received in Liverpool, UK, 25th February 1997; Revised manuscript received, 17th June 1997; 7/04241H