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Microwave solvent-free synthesis of nitrocyclohexanols

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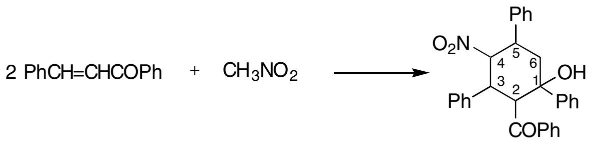
Abstract—New nitrocyclohexanols **3a**–**f** are synthesized by a clean and original method from nitromethane **1** and unsaturated ketones **2a**–**f** in the presence of solid potassium fluoride–alumina under solvent-free conditions coupled with microwave irradiation. The reaction involves a double and diastereoselective Michael addition followed by ring closure. Another diastereomer **3′**, which differs by the configuration of C-4, is obtained in the presence of piperidine and EtOH at room temperature.

1. Introduction

The reactivity of primary nitroalkanes especially nitromethane[1] with electrophilic *gem*-disubstituted alkenes, has been largely studied in our laboratory under solvent-free conditions coupled with microwave irradiation, with supported reagents on various mineral oxides[2–4] in some cases. As part of our program to develop the synthesis of carbocycles after Michael additions in this environmentally benign process, we studied the reaction of nitromethane **1** with alkenes bearing one electron-withdrawing group such as unsaturated α,β-enones **2a**–**f** and we report here our preliminary results.

2. Results and discussion

For example, by mixing nitromethane **1** (0.32 g, 5.2 mmol) and chalcone **2a** (1 g, 4.8 mmol) without solvent in the presence of a mixture, in an unusual ratio, of neutral Alumina 60 Merck (2 g) and a potassium fluoride (3 g)—the molar ratio of KF and Al_2O_3 was carefully optimized—we obtained the new nitrocyclohexanol **3a** (60% yield) after 20 min under microwave irradiation in a monomode reactor Synthewave 402® Prolabo at 90 °C (monitored temperature[5]) reached after 5 min and maintained 15 min (Scheme 1). **3a** Was isolated after cooling to room temperature, addition of boiling acetonitrile, elimination of solids by filtration and acetonitrile evaporation. The reaction is highly diastereoselective: only one isomer (A) was detected by ^{1}H NMR spectroscopy of the crude product. The relative configuration of the carbons of isomer A has been established by X-ray analysis[6,7] (Fig. 1).



2a **1** **3a**

Scheme 1.

The pure product is obtained after crystallization in the appropriate solvent (see Table 1). Classical activation of the reaction in an oil bath with the same temperature profile, does not allow the formation of cyclohexanol. Obviously, this is an evidence for a specific microwave reactivity. If the reaction is realized in EtOH 95% (anhydrous EtOH or diethyl oxide are inefficient), with piperidine in excess (1.5 equiv), after 4 days at room temperature, the ^{1}H NMR spectrum of the crude reaction mixture exhibits signals for four products: the well-known monoadduct **5a** (34%),[10] the bis-adduct **6a** (24%),[8–12] the heteroadduct **4a** (15%) (Scheme 2) and another isomeric cyclohexanol **3′a** (isomer B: 24%

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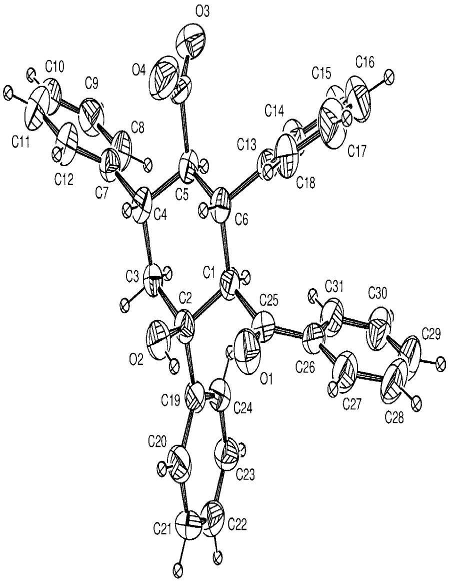
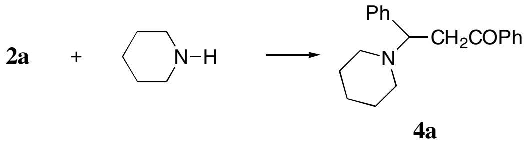


Figure 1. X-ray of 2-benzoyl-4-nitro-1,3,5-triphenyl-cyclohexan-1-ol **3a** (isomer A).

obtained after crystallization in acetone). Its structure was established by X-ray analysis (Fig. 2).[6] Isomers A and B differ by the configuration of carbon-4. Other bases such as triethylamine or potassium *tert*-butoxide were useless.



Scheme 2.

The Michael reaction is one of the most general methods for C–C bond formation: the addition of nitroalkanes has been largely reviewed.[13] The formation of cyclic compounds from chalcones and nitromethane has no precedent in the literature. We propose the following mechanism (Scheme 3): nitromethane carbanion reacts with chalcone and leads to **5a** after protonation or reacts after prototropy with a second molecule of chalcone to give either **6a** after protonation or cyclohexanol **3a** after intramolecular nucleophilic attack on the carbon of the benzoyl group and subsequent protonation. The formation of isomers A or B depends on the possibility of

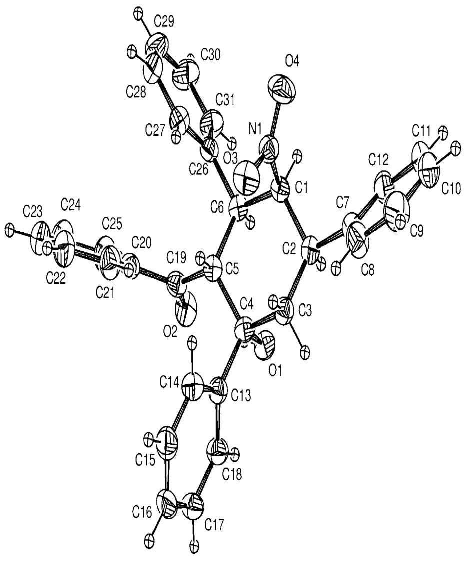


Figure 2. X-ray of 2-benzoyl-4-nitro-1,3,5-triphenyl-cyclohexan-1-ol **3′a** (isomer B).

Table 1. Preparation of nitrocyclohexanols **3a**–**f** on KF/Al_2O_3 under microwave irradiation

α,β-Enone **2**	**3**	Molecular formula	**3a**–**f** Yield (%)[a,b]
PhCH=CHCOPh	**a**	$C_{31}H_{27}NO_4$	65 (EtOH)
PhCH=CHCOMe	**b**	$C_{21}H_{23}NO_4$[c] Calcd 353.162 Found 353.164	55 (Et_2O)
p-MeC_6H_4CH=CHCOPh	**c**	$C_{33}H_{31}NO_4$[d] Calcd 505.225 Found 505.225	45 (EtOH) after 1 h
p-$MeOC_6H_4CH$=CHCOPh	**d**	$C_{33}H_{31}NO_6$[e] Calcd 537.215 Found 537.213	20 (EtOH) after 1 h
p-ClC_6H_4CH=CHCOPh	**e**	$C_{31}H_{25}Cl_2NO_4$[f] Calcd 515.118 Found 515.116	60 (Et_2O)
PhCH=CHCOC_6H_4-*p*-OMe	**f**	$C_{33}H_{31}NO_6$[g] Calcd 507.2171 Found 507.2159	30 (EtOH)

[a] After 30 min at 90 °C under microwave irradiation. No reaction was observed at room temperature.

[b] Pure crystallized product in appropriate solvent.

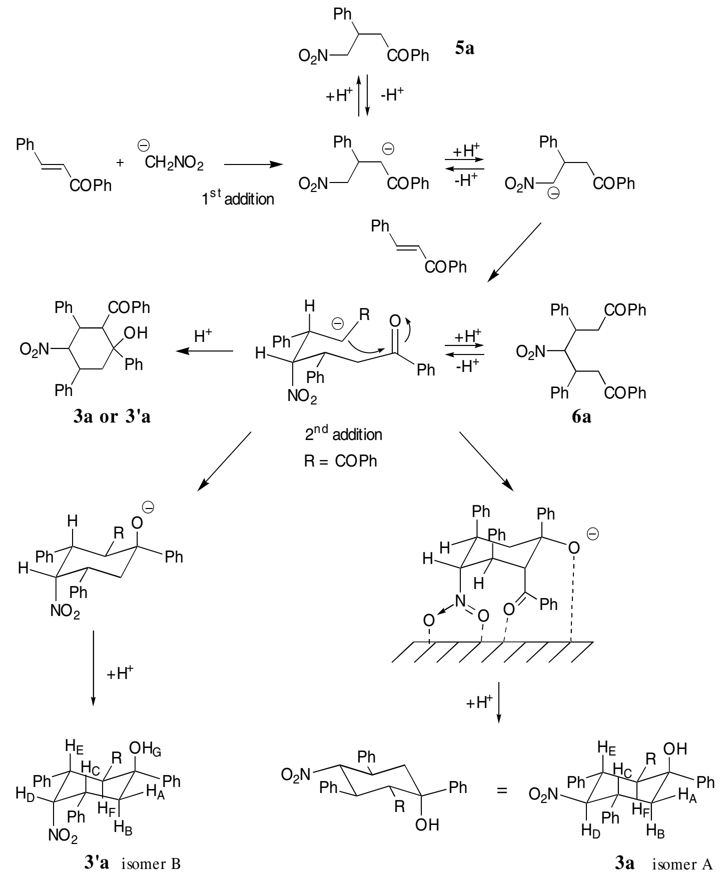
[c] HRMS calcd for $M^{+\cdot}$; Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.15; H, 6.48; N, 4.01.

[d] HRMS calcd for $M^{+\cdot}$.

[e] HRMS calcd for $M^{+\cdot}$; Anal. Calcd for $C_{33}H_{31}NO_6$: C, 73.73; H, 5.81; N, 2.61. Found: C, 73.36; H, 5.77; N, 2.67.

[f] HRMS calcd for $M^{+\cdot}$−NO; Anal. Calcd for $C_{31}H_{25}Cl_2NO_4$: C, 68.14; H, 4.61; N, 2.56. Found: C, 67.98; H, 4.55; N, 2.60.

[g] HRMS calcd for $M^{+\cdot}$−NO.



Scheme 3.

adsorption of polar groups on the solid KF/Al_2O_3 (Scheme 3).

With the aim to study the influence of the carbonyl substitution, we have realized the reaction of nitromethane with benzalacetone **2b** in analogous conditions (90 °C, 30 min; **2b**: 10 mmol; **1**: 10.8 mmol; KF/Al_2O_3: 2.9 g/2 g). The isolated pure product **3b** (isomer A: Fig. 3) after crystallization in ether is 55%. In the same way, the reaction of **2f** leads after 30 min to the corresponding nitrocyclohexanol **3f** (isolated product: 30%). The substitution of the aromatic ring by an electron-donating group (Me, OMe) or an electron-withdrawing group (Cl) has for consequence a decrease of the reactivity with Me or MeO (**3c**, **3d**, **3f**) (Scheme 4). Table 1 gives our preliminary results. The various chalcones were prepared using our previously reported methods.[14]

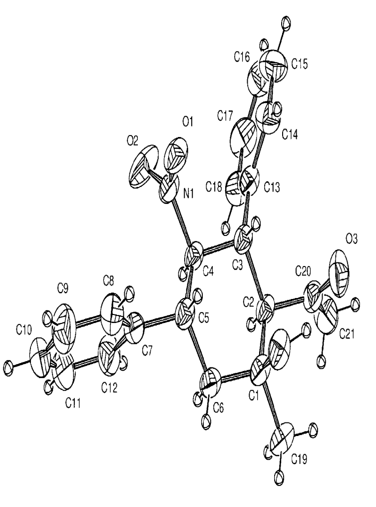
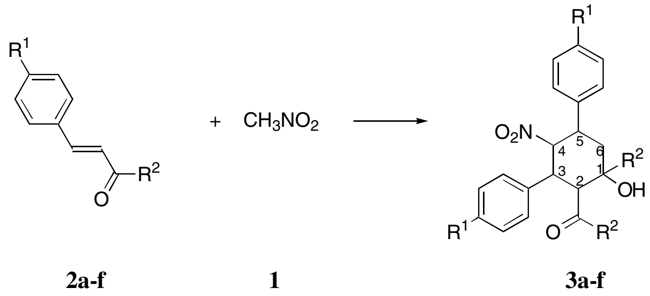


Figure 3. X-ray of 2-acetyl-4-nitro-1-methyl-3,5-diphenyl-cyclohexan-1-ol **3b** (isomer A).



2a-f **1** **3a-f**

R^1 = H, *p*-Me, *p*-OMe, *p*-Cl

R^2 = Ph, *p*-MeO-C_6H_4, Me

Scheme 4.

3. Conclusion

In conclusion, we have set up a new diastereoselective synthetic process for the formation of original nitrocyclohexanols by means of tandem Michael additions and intramolecular cyclization using neat nitromethane and α,β-enones supported on KF/Al_2O_3 surface, in solvent-free conditions coupled with microwave irradiation. Furthermore, in the framework of the 5th RTDP 'Competitive and Sustainable Growth', we are actually measuring the dielectric constants ε' and ε'' under microwave irradiation with the active collaboration of Microondes Energie Systèmes (MES) in Paris.[15a] We are also studying these reactions in Liverpool[15b] by means of a free electron laser, which produces 8.47 GHz microwaves. We will fully report later about this.

This work is an another example of organic synthesis in the area of Green Chemistry.[16,17]

Crystallographic data (excluding structure factors) for the structures **3a**, **3′a** and **3b** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 211264–211266. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4. Spectral data of compounds

For example, selected data for **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (dd, 1H, CH_a, $^2J = 14$ Hz, $^3J = 3.5$ Hz), 2.51 (td, 1H, CH_b, $^2J = 14$ Hz, $^4J = 2.5$ Hz), 4.06 (m, 1H, CH_c), 4.13–4.23 (m, 2H, CH_d and CH_e), 4.49 (d, 1H, CH_f, $J = 11.1$ Hz), 5.39 (d, 1H, OH_g, $^4J = 2.5$ Hz), 6.68–7.56 (m, 20H, $4C_6H_5$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.39 (dm, C-5, $J = 131.5$), 45.86 (tm, C-6), 48.11 (dm, C-3), 56.76 (dm, C-2), 75.43 (tm, C-4), 145.96 (s, C-1), 125.8–129.5 (m, $4C_6H_5$), 203.66 or 207.23 (s, C=O). Crystal data: $C_{31}H_{27}NO_4$, CH_3CN: $M_r = 518.62$, monoclinic, $P2_1/c$, $a = 10.809(2)$, $b = 11.109(2)$, $c = 23.599(9)$ Å, $\beta = 99.71(4)°$, $V = 2793(2)$ Å^{-3}, $Z = 4$, $D_X = 1.233$ Mg m^{-3}, $\lambda(\mathrm{MoK}\alpha) = 0.71073$ Å, $\mu = 0.758$ cm^{-1}, $F(000) = 1096$, $T = 293$ K. Sample (0.25 * 0.15 * 0.13 mm) studied on an automatic diffractometer CAD4 ENRAF-NONIUS. Whole structure refined with SHELXL97:[6b] 353 variables and 1953 observations: $R = 0.087$, $R_W = 0.198$ and $S_W = 0.9244$ ($\Delta\rho = 0.28$ e Å^3). For **3′a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.11 (dd, 1H, CH_a, $^2J = 14$ Hz, $^3J = 4$ Hz), 3.34 (td, 1H, CH_b, $^2J = 14$ Hz, $^4J = 2.5$ Hz), 4.12–4.20 (m, 2H, CH_c and CH_e), 5.07 (d, 1H, OH_g, $^4J = 2.5$ Hz), 5.13 (t, 1H, CH_d, $^3J = 4$ Hz), 5.45 (d, 1H, CH_f, $^3J = 12.3$ Hz), 7.0–7.65 (m, 20H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.12 (dm, C-5), 41.33 (tm, C-6), 46.52 (dm, C-3), 48.71 (dm, C-2), 75.33 (tm, C-4), 145.37 (s, C-1), 124.9–138.5 (m, $4C_6H_5$), 203.66 or 207.23 (s, C=O). Crystal data: $C_{31}H_{27}NO_4$: $M_r = 477.54$, monoclinic, $P2_1/c$, $a = 17.554(9)$, $b = 6.234(4)$, $c = 22.628(9)$ Å, $\beta = 70.16(4)$, $\gamma = 94.54(4)°$, $V = 2468(2)$ Å^{-3}, $Z = 4$, $D_X = 1.285$ Mg m^{-3}, $\lambda(\mathrm{MoK}\alpha) = 0.71073$ Å, $\mu = 0.85$ cm^{-1}, $F(000) = 1008$, $T = 293$ K. Sample (0.42 * 0.26 * 0.22 mm) studied on an automatic diffractometer CAD4.[6a] Whole structure refined with SHELXL97:[6b] 407 variables and 5563 observations: $R = 0.0425$, $R_W = 0.0954$ and $S_W = 1.012$ ($\Delta\rho \leqslant 0.22$ e Å^{-3}).

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