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MIMIRC Reactions of nitromethane with electrophilic alkenes in solvent-free reactions under microwave irradiation

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Abstract—New highly functionalized cyclohexenes **3a**–**h** or **4a**–**i** (after demethoxycarbonylation or deamidation at C-3) are obtained from the reaction of nitromethane **1** with electrophilic alkenes **2a**–**i** RCH=C(CN)(Y) with Y=CO_2R', CN, $CONH_2$ in a solvent-free reaction catalyzed by piperidine at room temperature or under focused microwave irradiation after a few min. The mechanism involves a double Michael addition followed by intramolecular ring closure (MIMIRC reaction). The reaction is diastereoselective (two diastereoisomers only). In some cases, non-cyclized intermediates have been isolated. Stœchiometric amounts of piperidine promote the demethoxycarbonylation of **3**. When Y is an amide group, a first example of chemical deamidation is observed.

1. Introduction

Microwave irradiation (MWI), an elegant protocol for dry organic reactions is actually under extensive progress and has been recently reviewed.[1–7] Solvent-free organic reactions, eventually under microwave irradiation, are one of the main research topics in our laboratory and as part of our program to develop the synthesis of cyclic compounds under these conditions, we have shortly reported[8] a new route to functionalized cyclohexenes **3a**–**g** or **4a**–**g** in a solvent-free reaction catalyzed by piperidine under microwave irradiation from electrophilic alkenes **2a**–**g** activated by cyano and methoxycarbonyl groups and nitromethane **1** (Scheme 1) without the expected, well known, formation of cyclopropane **6a**.

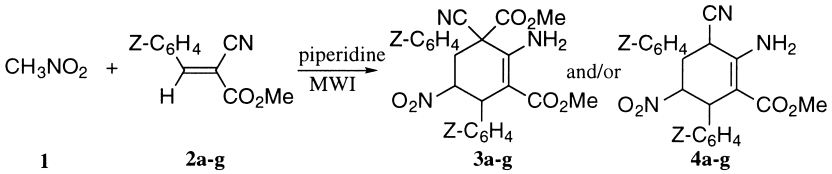
The course of the reaction was strongly depending on the experimental conditions. The optimized results were previously reported[8] and now we describe the study of the various factors which govern the model reaction of nitromethane **1** with methyl benzylidene cyanoacetate **2a** in order to form selectively **3a**, **4a** or **5a** (Scheme 2).

The mechanism of the formation of these different products is outlined in the Scheme 3.[9]

Furthermore, in order to extend these previous studies and to prepare new functionalized cyclohexenes, we decided to use alkenes bearing two cyano groups or one cyano and an amide group. The results are reported and discussed here; a mechanism is proposed, taking into account the diastereoselectivity.

2. Results and discussion

The model reaction of nitromethane **1** with methyl benzylidene cyanoacetate **2a**, catalyzed by piperidine, was carried



1 **2a-g** **3a-g** **4a-g**

Z = H : **a** ; *p*-Cl : **b** ; *p*-MeO : **c** ; *p*-NO_2 : **d** ; *m*-F : **e** ; *o*-F : **f** ; *o*-Br : **g**

Scheme 1.

Keywords: microwave heating; Michael additions; nitrocompounds; cyclohexenes; electrophilic alkenes; solvent-free reactions.

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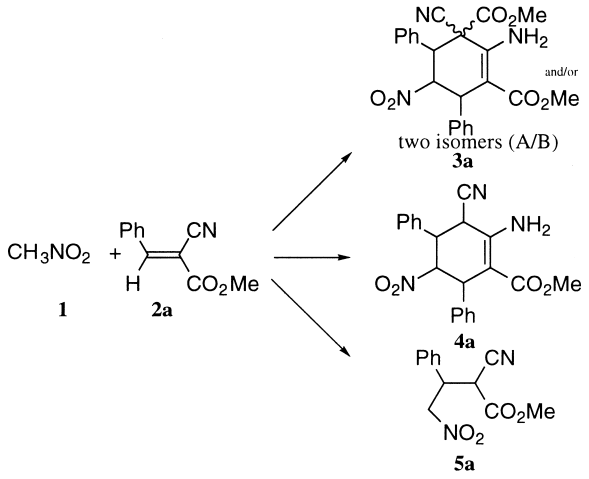
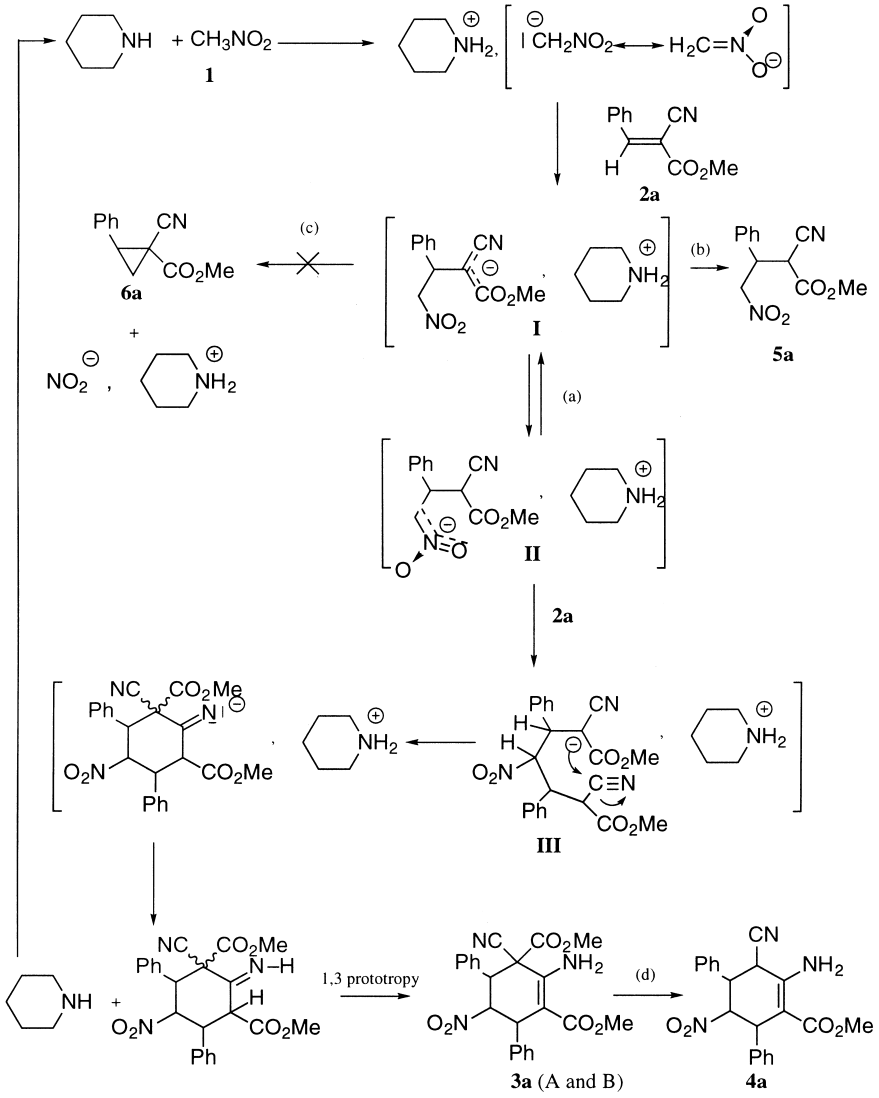


Scheme 2.

out under various conditions in order to study the factors which govern the ratio of the final products **3a**, **4a**, **5a**: presence and nature of a solvent, temperature (final temperature assigned by computer of the PROLABO Synthewave 402®),[10,11] time and amounts of piperidine.

First, we have studied the ratio of nitromethane with respect to the alkene **2a** and piperidine. So, 5 mmol of alkene **2a**, 0.15 mmol of piperidine and different amounts of nitromethane in the range: 0.5, 2, 3, 4 equiv. were mixed and irradiated at a power of 150 W with a temperature of 120°C reached after 3 min and maintained 12 min. The results are reported in Table 1.

In these conditions, the reaction is not complete except in entry 3 where the starting alkene **2a** is no longer detected. If the cyclohexene **3a** is formed, it appears nevertheless that Michael monoadduct **5a**-unknown up to now-is the major product. In fact, nitromethane being reactant and solvent, an



(a) : Michael-Michael addition, Ring Closure (catalytic piperidine)
(b) : Michael monoaddition
(c) : Cyclopropropane ring closure
(d) : Demethoxycarbonylation with stœchiometric amount of piperidine

Scheme 3.

Table 1. Reaction of nitromethane **1** with alkene **2a** catalyzed by piperidine under microwave irradiation: influence of nitromethane amounts

Entry	CH_3NO_2 (equiv.;[a] mmol)	Piperidine (%)[b]	**2a** (%)[c]	**3a** (%)[c]	**5a** (%)[c]
1	0.5; 2.5	6	53	13	34
2	2; 10	1.5	11	5	84
3	3; 15	1	0	10	90
4	4; 20	0.76	10	10	80

[a] Calculated with respect to alkene.
[b] Calculated with respect to nitromethane.
[c] Relative percentages in the crude mixture estimated by ^{1}H NMR. (%) **2a**+(%) **3a**+(%) **5a**=100.

Table 2. Reaction of nitromethane with alkene **2a** under microwave irradiation (P=90 W) catalyzed by piperidine: influence of the temperature

Entry	Temperature (°C)[a]	Percent completion[b] (%)	**3a**[c] (%)	**4a**[c] (%)	**3a/4a**[c]
1	60	82	94	6	15.6
2	90	100	80	20	4
3	120	80	81	19	4.25

[a] Maximal temperature assigned by computer on Prolabo Synthewave 402®.
[b] Estimated by ^{1}H NMR of crude reaction mixture.
[c] Relative percentages in the crude mixture estimated by ^{1}H NMR. (%) **3a** +(%) **4a**=100.

Table 3. Reaction of nitromethane with **2a** under microwave irradiation (P=90 W; T=90°C): influence of piperidine amounts

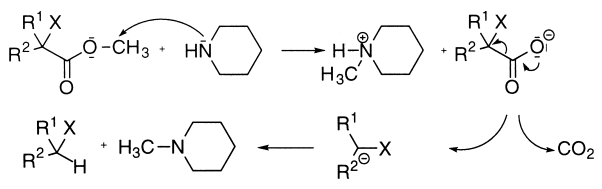
Entry	Piperidine (mL; mmol)	Piperidine (%)[a]	Percent completion[b] (%)	**3a**[c] (%)[a]	**4a**[c] (%)	**3a/4a**
1	0.02; 0.2	13.3	100	80	20	4
2	0.03; 0.3	20	85	82	18	4.55
3	0.05; 0.5	33.3	90	67	23	2.91
4	0.125; 1.25	83.3	100	0	100	0

[a] Calculated with respect to nitromethane.
[b] Estimated by ^{1}H NMR of the crude reaction mixture.
[c] Relative percentages in the crude mixture estimated by ^{1}H NMR. (%) **3a**+(%) **4a**=100.

excess of solvent has for consequence a decrease of the concentration of the alkene and the second Michael addition is less probable. To limit or avoid the formation of **5a**, it is necessary to operate with a stœchiometric quantity of nitromethane.

Then, we have studied the influence of the temperature: so, we decided to run the reaction with nitromethane (1.5 mmol; 1.2 equiv.), alkene **2a** (2.5 mmol; 2 equiv.) and 0.2 mmol of piperidine (13.3% relative to nitromethane) for 7 min (final temperature reached after 3 min and maintained during 4 min) (Table 2).

At 90°C, we observed 100% completion and the cyclohexene **3a** is clearly the major product, the demethoxycarbonylation leading to **4a** being unfavored (entry 2). The ratio **3a/4a** is comparable at 90°C and at 120°C but the percent completion decreased with the temperature. The thermal stability of pure **3a** has been tested by microwave irradiation in the focused Prolabo microwave oven (P=300 W): at 185°C reached after 10 min: no degradation and no demethoxycarbonylation were observed. **3a** remained unchanged after 3 months at room temperature. Furthermore, the irradiation of **3a** in basic medium (ethylamine 30%) after 10 min at 90°C has no influence which means that the cyclization step is irreversible. It is noteworthy that **5a** (Michael monoadduct) is not observed in the reaction mixture under these conditions.



Scheme 4.

Then, we have studied the influence of the amounts of piperidine. In order to reach complete transformation, we have run the reaction at 90°C during 7 min in presence of 2.5 mmol (2 equiv.) of alkene **2a** (Table 2; entry 2); we used a slight excess of nitromethane (1.5 mmol; 1.2 equiv.) with respect to the stœchiometry of the reaction in order to compensate the evaporation in the oven. The results are reported in Table 3.

The results show the correlation between the quantity of piperidine and the amount of demethoxycarbonylation which was complete with 1.25 mmol of piperidine for 2.5 mmol of alkene (entry 4): *N*-methylpiperidine resulting from the demethoxycarbonylation processus was detected by ^{1}H NMR in the crude product[12] (Scheme 4).

Finally, we were interested in the influence of the reaction time at 90°C (final temperature optimized) using 0.2 mmol

Table 4. Reaction of nitromethane with **2a** under microwave irradiation (P=90 W; T=90°C): influence of the reaction time

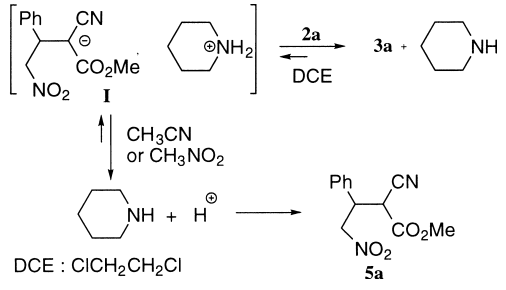
Entry	Time (min)	Percent completion[a] (%)	**3a**[b] (%)	**4a**[b] (%)	**3a/4a**
1	4	90	89	11	8.1
2	7	95	84	16	5.25
3	15	95	79	21	3.76
4	20	100	80	20	4

[a] Calculated by ^{1}H NMR on the crude oil.
[b] Relative percentages (%) **3a**+(%) **4a**=100.

of piperidine, 2.5 mmol of **2a** and 1.5 mmol of nitromethane. The results are reported in Table 4.

The reaction completion reaches 95% after 7 min (entry 2) and we must wait for 20 min to obtain a quantitative reaction (entry 4). We observed a partial demethoxycarbonylation of **3a** which does not change significantly after 15 min. No trace of **5a** was detected.

With the aim to understand the role of the solvent, we ran the reaction in the presence of dichloroethane (apolar) or acetonitrile (polar) which have close boiling points (82 and 83°C), dipolar moments, dielectric permittivity, relative chemical inert and good capacities to dissolve the reactants. The temperature was assigned to 85°C at 90 W, reached in 3 min and maintained 27 min. So, 2.5 mmol of **2a** with a slight excess of nitromethane (1.4 equiv.; 1.75 mmol) in the presence of 17% of piperidine (0.3 mmol) were mixed with 0.25 mL of dichloroethane (the medium becomes heterogeneous with a quantity lower than 0.25 mL). In this last case, the reaction is quantitative but only cyclohexenes **3a** and **4a** are formed (**3a/4a**=77/23). The ratio is unchanged with 1 mL of dichloroethane but the reaction is slower (90% completion): a non-polar solvent lowers the rate of the reaction. Furthermore, the adduct **5a** being not present, it results that the second Michael addition and the subsequent ring closure are faster.



Scheme 5.

The phenomena is different when a large excess of polar nitromethane is used and we observed the formation of the monoadduct **5a**. In the same way, the use of polar acetonitrile (2 equiv. with respect to alkene) leads to comparable results: we notice the presence of **5a** in the crude product (estimated by ^{1}H NMR: (**1a**: 17%; **3a**: 12%; **5a**: 71%). The dipolar aprotic character influence is significant in the reaction pathway. So in apolar aprotic solvent as dichloroethane, the ion pair formed by the cation piperidinium and the carbanion precursor of monoadduct **5a** is intim and the second Michael addition is favored. With nitromethane or acetonitrile, the acid–base equilibrium is displaced towards the protonation of the carbanion leading to **5a** (Scheme 5).

According to these results, we have prepared the cyclohexene **3a** (70% yield, recovering of two diastereoisomers) by mixing without solvent, nitromethane (3 mmol), benzylidene methylcyanoacetate (5 mmol) and piperidine (0.2 mmol, 20 μL) under microwaves (P=90 W; T=90°C reached after 3 min and maintained 8 min). The demethoxycarbonylated cyclohexene **4a**-2 diastereoisomers-was obtained (75% yield of pure product) at 120°C (P=90 W) reached after 3 min and maintained 4 min in presence of 2.5 mmol of piperidine (250 μL) or at room temperature during 120 h (60% yield).

The second part of our discussion is focused on the diastereoselectivity of the formation of cyclohexene **3a** and **4a**. Among the 16 possible stereoisomers, only two isomers A and B of **3a** were observed (60/40 calculated from ^{1}H

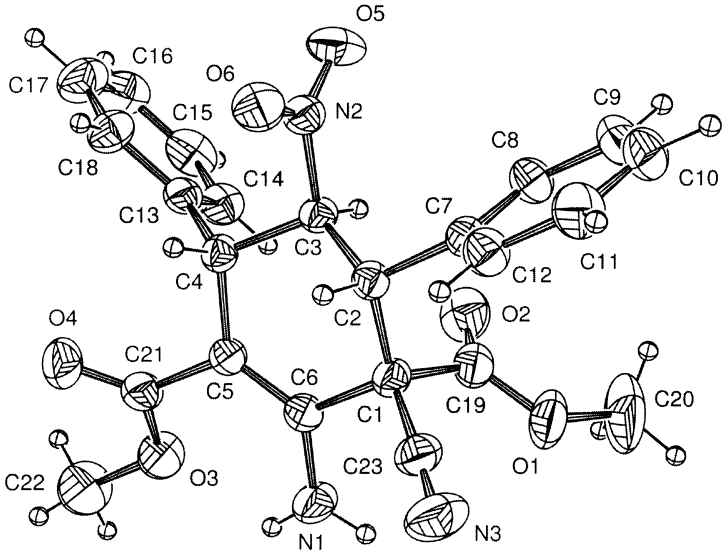
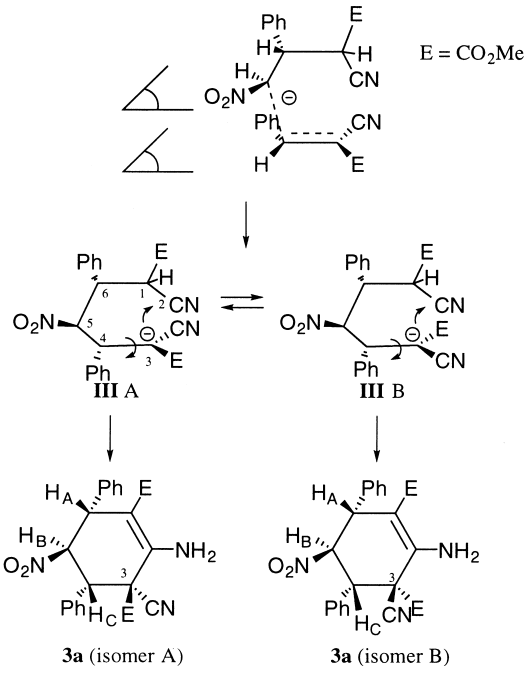


Figure 1. X-Ray structure of 2-Amino-3-cyano-4,6-diphenyl-5-nitro-cyclohex-1-ene-1,3-dimethyldicarboxylate (**3a**: isomer B).



Scheme 6.

NMR integration of the amino group), A and B were obtained after cristallization in diethyl ether (A precipitates first, Ortep diagram already reported).[8] The structures are in agreement with spectroscopic data and confirmed by X-ray analysis: A and B differ by the C-3 configuration. Ortep diagram of isomer **3a** (B) is reported on Fig. 1 (the isomerization takes place on C-1 of the Fig. 1). The C-4, C-5, C-6 of the two isomers have the same relative configuration which is defined after the second Michael addition of carbanion **II** (Scheme 3) upon benzylidene cyanoacetate **2a**. The transition state is more energetically favored when the nitro group is in *trans* position with respect to the vicinal phenyl groups minimizing the destabilizing interactions. The intermediate conformers **III**A and **III**B being in fast equilibrium, the diastereoisomeric excess is low (Scheme 6). The last step is a '6-endo-dig' type cyclization[13] where the carbanion attacks the electrophilic carbon of the nitrile group. The cyclohexene **3a** in the enamine form is obtained after 1,3-sigmatropic hydrogen rearrangement. After demethoxycarbonylation on C-3, two diastereoisomers (60/40) of **4a**–**g** were isolated: $^3J_{CD}$ being similar (see Section 4), their relative configuration was not established.

In conclusion, the cyclohexene formation results from tandem reactions which consist in a double Michael addition followed by intramolecular nucleophilic addition (cyclization): Michael Michael induced ring closure (MIMIRC) mechanism.[14] This point has been evidenced experimentally: indeed, Michael monoadduct **5a** with the alkene **2a** gives **3a** in presence of piperidine (5 μL for 10^{-3} mmol of reactants) at 90°C under microwaves during 8 min.

Although the obtention of cyclohexene **3a** was possible at room temperature (98 h; 60% yield for **3a**), the more convenient microwave heating has been used for the generalization of the synthesis of cyclohexenes **3b**–**g** and **4b**–**g** with various substituents on the aromatic ring. The results are reported in Tables 5 and 6 and in Section 4. The yields are relative to isolated pure products.

Table 5. Preparation of cyclohexenes **3a**–**g** under microwaves and catalyzed by piperidine

Z	3	Molecular formula	Time (min)	**3a**–**g** (%)
H	**a**	$C_{23}H_{21}N_3O_6$	11	70
p-Cl	**b**	$C_{23}H_{19}N_3O_6Cl_2$	15	73
p-OMe	**c**	$C_{25}H_{25}N_3O_8$	25	70
p-NO_2	**d**	$C_{23}H_{19}N_5O_{10}$	20	71
m-F	**e**	$C_{23}H_{19}N_3O_6F_2$	15	75
o-F	**f**	$C_{23}H_{19}N_3O_6Cl_2$	15	75
o-Br	**g**	$C_{23}H_{19}N_3O_6Br_2$	15	75

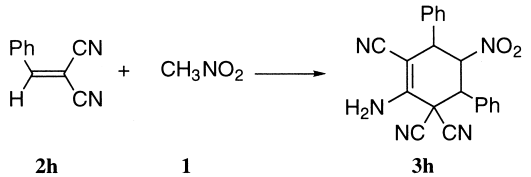
Table 6. Preparation of cyclohexenes **4a**–**g** under microwaves and catalyzed by piperidine

Z	4	Molecular formula	Time (min)	**4a**–**g**[a] %
H	**a**	$C_{21}H_{19}N_3O_4$	11	75
p-Cl	**b**	$C_{21}H_{17}N_3O_4Cl_2$	15	75
p-OMe	**c**	$C_{23}H_{23}N_3O_6$	25	70
m-F	**e**	$C_{21}H_{17}N_3O_4F_2$	15	72
o-F	**f**	$C_{21}H_{17}N_3O_4F_2$	15	70
o-Br	**g**	$C_{21}H_{17}N_3O_4Br_2$	15	75

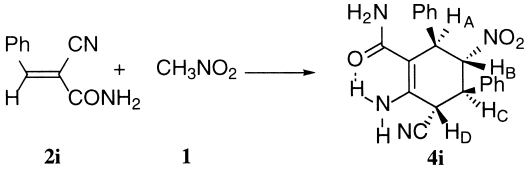
[a] Two diastereoisomers A and B (60/40) are present: coupling constants $^3J_{CD}$ being similar (11.3 and 11.2 Hz, respectively), the relative configuration has not been assigned.

With the aim to functionalize the cyclohexenes with two cyano groups, we have carried out the reaction of benzylidene malononitrile **2h** with nitromethane **1** in presence of piperidine under microwave irradiation (Scheme 7). The cyclohexene **3h** (two isomers)[15] is obtained in 75% yield after 40 min of irradiation at 120°C, chromatography on silicagel and crystallization in CH_2Cl_2/AcOEt: 1/1. Two stereoisomers (50/50) were isolated which differ by the configuration of C-6.

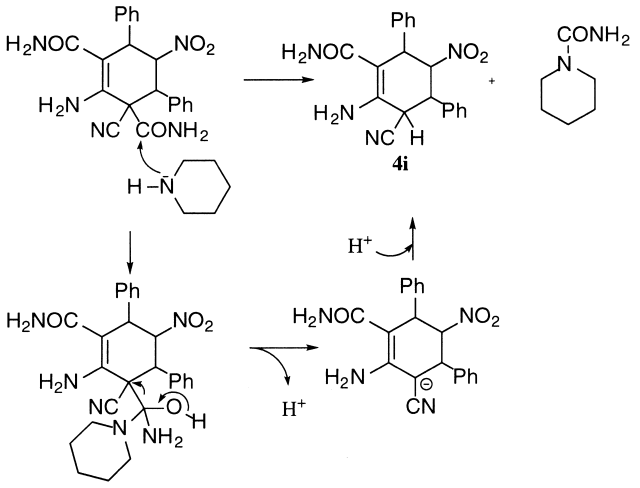
The course of the reaction of benzylidene cyanoacetamide **2i** with nitromethane **1** was different: the cyclohexene **4i** (50% yield after crystallization in ether–methanol; two isomers) obtained after reaction of nitromethane (0.17 g, 1.1 equiv.) with the alkene **2i** (0.9 g, 2 equiv.) and with a piperidine excess (0.54 g, 2.4 equiv.) after 40 min of irradiation at 100°C has got only one amide group on the



Scheme 7.



Scheme 8.



Scheme 9.

carbon C-1 (characterized by NMR, IR, HRMS and elemental analysis)[16] (Scheme 8).

Piperidine carboxamide has been detected in the crude oil by ^{1}H NMR (DMSO *d*-6, 200 MHz) and consequently, we propose the following mechanism for this first example of chemical deamidation (Scheme 9). We postulate that the unisolated cyclohexene bearing two amide groups is involved in a nucleophilic attack on the C-4 by the nitrogen atom of piperidine leading to piperidine carboxamide after deprotonation followed by protonation of the resulting carbanion to give **4i**.

3. Conclusion

We have described in this paper an original synthesis of new highly functionalized cyclohexenes from the reaction of nitromethane with electrophilic alkenes RCH=C(CN)(Y) with Y=CO_2R', CN, $CONH_2$ in a solvent-free reaction catalyzed by piperidine at room temperature or under focused microwave irradiation after a few minutes. According to the experimental conditions, it is possible to obtain selectively a cyclohexene **3** or **4** (after demethoxycarbonylation or deamidation in presence of stœchiometric amounts of piperidine) or the up to now unknown Michael monoadduct **5** (non-cyclized intermediate). The mechanism involves a double Michael addition followed by intramolecular ring closure (MIMIRC reaction). The reaction is diastereoselective (two diastereoisomers only). When Y is an amide group, a first example of chemical deamidation is observed.

Coupling dry media and focused microwave irradiation appears to be a useful tool to promote organic reactions by clean, economical and environmentally benign process.

4. Experimental

4.1. General methods

Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a PERKIN-ELMER 1420 spectrometer. ^{1}H NMR spectra were recorded on BRUKER ARX 200 (200 MHz), BRUKER AC 300 P (300 MHz) spectrometers and ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a VARIAN MAT 311 at a ionizing potential of 70 eV in the Centre de Mesures Physiques de l'Ouest (CRMPO, Rennes). Elemental analyses were performed at the Laboratoire Central de Microanalyses-CNRS (Lyon). For preparative column chromatography, silica gel 60 Merck (230–240 Mesh ASTM) was used. Reactions under microwave irradiation were performed in a PROLABO Synthewave 402® (2.45 GHz) microwave reactor with a single focused system.[10,11] All solvents and reagents were purchased from Acros Organics and Aldrich Chimie and used without further purification unless otherwise stated.

Electrophilic alkenes **2a–i** were readily prepared by literature methods.[17,18]

4.2. General procedure for the preparation of cyclohexenes 3 and 4

Nitromethane in small excess, piperidine, freshly distilled on molecular sieves, in catalytic amounts and the alkene (5 mmol) were placed in a quartz tube (diameter: 37 mm), introduced into Synthewave 402® reactor fitted with rotational system, adjustable power within the range 20–300 W and a wave guide (monomode T_{01}). The temperature consign is programmed with the computer of the oven. Irradiation time, temperature, amount of piperidine and nitromethane are optimized according to the alkene. After cooling to room temperature, the crude product is extracted with CH_2Cl_2, the solvent is removed under vacuum and the product analyzed by ^{1}H NMR. Two isomers A and B (60/40) were isolated after chromatography on silica gel (eluent CH_2Cl_2 unless otherwise stated) and slow crystallization from diethyl ether or appropriated solvent.

4.2.1. 2-Amino-3-cyano-4,6-diphenyl-5-nitro-cyclohex-1-ene-1,3-dimethyldicarboxylate (3a: two isomers A and B; A/B=60/40). From nitromethane (0.18 g, 3 mmol), benzylidene methylcyanoacetate **2a** (0.94 g, 5 mmol) and piperidine (20 μL, 0.2 mmol) at 90 W (90°C) during 11 min (90°C reached after 3 min), **3a** was isolated in 70% yield after chromatography on silica gel (eluent CH_2Cl_2, R_f=0.50) and slow crystallisation from diethyl ether. The spectroscopic and crystal data for **3a** (major isomer A) were reported in Ref. 8.

4.2.2.1. Data of isomer B (40%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.37 (s, 3H, CO_2CH_3), 3.75 (s, 3H, C=C–CO_2CH_3), 4.08 (d, 1H, CH_C, $^3J_{BC}$=12.6 Hz); 4.43 (d, 1H, CH_A, $^3J_{AB}$=9.4 Hz); 5.82 (dd, 1H, CH_B, $^3J_{BC}$=12.6 Hz, $^3J_{AB}$=9.4 Hz); 6.36 (s, 2H, NH_2), 7.15–7.34 (m, 10H arom.). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 46.95 (dm, C^6–H_A, ^1J=134.6 Hz); 49.19 (dm, C^4–H_C, ^1J=138.4 Hz); 51.16 (q, C–CO_2CH_3, ^1J=147.2 Hz); 54.70 (q, C=C–CO_2CH_3, ^1J=149.6 Hz); 56.43 (m, *C*–CN); 89.69 (dt, C^5–H_B,

^1J=156 Hz, ^3J=6.8 Hz); 98.47 (m, C=C^1–CO_2CH_3); 115.59 (d, *C*N, ^3J=3.7 Hz); 126.87–144.20 (A and B) (m, 12C arom.); 146.49 (m, C^2–NH_2); 165.32 (dq as quintet, C–*C*O_2CH_3, ^3J=3.9 Hz); 168.41 (m, C=C–*C*O_2CH_3). IR (nujol) 1740, 1750 cm^{-1}. HRMS calcd for $C_{23}H_{21}N_3O_6$: 435.435, found $M^{+\cdot}-HNO_2$: 388.142. Anal. calcd for $C_{23}H_{21}N_3O_6$: C, 63.44; H, 4.86; N, 9.65. Found: C, 63.57; H, 4.88; N, 9.72.

4.2.1.2. X-Ray crystallographic analysis data for 3a (minor isomer B). $C_{23}H_{21}N_3O_6$: M=435.44, triclinic, P-1, a=10.802(2), b= 10.807(2), c=10.881(8) Å, α=80.74(3)°, β=67.36(3)°, δ=69.47(1)°, V=1097 (1) $Å^{-3}$, Z=2, D_x=1.318 Mg m^{-3}, λ (Mo Kα)=0.70926, μ=0.905 cm^{-1}, F(000)=456, T= 294 K, final R=0.039 for 2185 observations and 352 parameters.

The sample (0.35×0.35×0.40 mm^3) is studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized Mo Kα radiation. The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection (2θmax=50°, scan $\omega/2\theta$=1, t_{max}=60 s, range *HKL*: *H* 0.12 *K* 12.12 *L* 12.12, intensity controls without appreciable decay (0.3%) gives 4071 reflections from which 2185 were independent (R_{int}= 0.015) with $I > 3\sigma(I)$.

After Lorenz and polarization corrections the structure was solved with SIR-92 which reveals the non-hydrogen atoms of the structure. After isotropic (R=0.092), then anisotropic refinement (R=0.078), all the hydrogen atoms may be found with a Fourier Difference (between 0.61 and 0.21 e $Å^{-3}$). The whole structure was refined by the full-matrix least-square techniques (use of F magnitude; x, y, z, β_{ij} for C, N and O atoms, x, y, z, for H atoms; 352 variables and 2185 observations; $w = 1/\sigma(F_o)2 = [\sigma 2(I) + (0.04F_o^2)^2]^{-1/2}$) with the resulting R=0.040, R_w=0.039 and S_w=0.62 (residual $\Delta\rho \leq 0.19$ e $Å^{-3}$).

Atomic scattering factors are from International Tables for X-ray Crystallography (1974).[19] All the calculations were performed on a Silicon Graphics Indy computer with the MOLEN package.[20]

Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre under the number CCDC 177998 and may be obtained free of charge from the Director (deposit@ccdc.cam.ac.uk).

4.2.2. 2-Amino-4,6-di(4-chlorophenyl)-5-cyano-5-nitro-cyclohex-1-ene-1,3-dimethyldicarboxylate (3b: two isomers A and B). From nitromethane (0.18 g, 3 mmol), 4-chlorobenzylidene methylcyanoacetate (1.11 g, 5 mmol) and piperidine (40 μL, 0.4 mmol) at 90 W (90°C) during 15 min, **3b** was isolated in 75% yield after chromatography on silica gel (eluent: CH_2Cl_2, R_f=0.50). Data of forms A and B: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.41 (A and B) (s, 3H, CO_2CH_3), 3.80 (A and B) (s, 3H, C=C–CO_2CH_3), 4.03 (B) and 4.27 (A) (d, 1H, C–H_C, $^3J_{BC}$=12.7 Hz); 4.40 (B) and 4.50 (A) (d, 1H, C–H_A, $^3J_{AB}$=9.4, 9.7 Hz)); 5.74 (B) and 5.18 (A) (dd, 1H, C–H_B, $^3J_{AB}$=9.4, 9.7 Hz, $^3J_{BC}$=12.7 Hz); 6.41 (B) and 6.31 (A) (s, 2H, NH_2), 7.08–7.32 (m, 8H arom.). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 46.21 (B) and 46.93 (A) (dm, *C*–H_A, ^1J=135.5 Hz); 47.36 (A) and 48.46 (B) (dm, *C*–H_C, ^1J=140.4, 138.0 Hz); 51.28 (B) and 51.31 (A) (q, C–CO_2CH_3, ^1J=147.6 Hz); 54.91 (B) and 55.42 (A) (m, *C*–CN); 55.65 (A and B) (q, C=C–CO_2CH_3, ^1J=150 Hz); 89.32 (B) and 91.21 (A) (dt, *C*–H_B, ^1J=156, 151.4 Hz, ^2J=6.7 Hz); 96.74 (A) and 97.54 (B) (m, C=*C*–CO_2CH_3); 114.85 (A) and 115.21 (B) (d, *C*N, ^3J=8.5, 4 Hz); 128.17–139.89 (A and B) (m, 12C arom.); 145.50 (B) and 146.43 (A) (m, *C*–NH_2); 164.50 (A) and 165.14 (B) (m, C–*C*O_2CH_3); 168.05 and 168.07 (A and B) (m, C=C–*C*O_2CH_3).; IR (nujol) 3420, 3300, 2190, 1720 cm^{-1}; HRMS calcd for $C_{23}H_{18}N_2O_4Cl_2$: $M^{+\cdot}$–HNO_2 456.064, found 456.064. Anal. calcd for $C_{23}H_{19}N_3O_6Cl_2$: C, 54.77; H, 3.80; N, 8.33. Found: C, 55.21; H, 3.87; N, 8.46.

4.2.3. 2-Amino-3-cyano-4,6-di(4-methoxyphenyl)-5-nitro-cyclo-hex-1-ene-1,3-dimethyldicarboxylate (3c: two isomers A and B). From nitromethane (0.22 g, 3.7 mmol), 4-methoxybenzylidene methyl cyanoacetate (1.09 g, 5 mmol) and piperidine (100 μL, 1 mmol) at 90 W (60°C) during 25 min, **3c** was isolated with 70% yield after chromatography on silica gel (eluent: CH_2Cl_2, R_f=0.50). Data of forms A and B: ^{1}H NMR (DMSO *d*-6, 200 MHz) δ 3.29–3.41 (A and B) (s, 3H, CO_2CH_3), 3.66–3.87 (A and B) (s, 9H, C=C–CO_2CH_3 and –C_6H_4–OCH_3);4.11 (A) (d, 1H, C–H_C, $^3J_{CB=}$12.5 Hz); 4.29–4.49 (A and B) (m, 1H, C–H_A); 5.13–5.24 (A and B) (dd, 1H, C–H_B, $^3J_{BC}$=12.5 Hz, $^3J_{AB}$=9.8 Hz); 7.48 (s, 2H, NH_2), 6.93–7.26 (m, 8H arom.). ^{13}C NMR (DMSO *d*-6, 75 MHz) δ: 46.85 and 47.44 (B and A) (dm, *C*H_A, ^1J=136 Hz); 48.20 and 48.64 (B and A) (m, *C*H_C, ^1J=136 Hz); 51.48 and 51.65 (B and A) (q, NC–C–CO_2CH_3, ^1J=147 Hz); 55.42, 55.85 and 55.96 (q, O*C*H_3, ^1J=147 Hz); 56.78 (A and B) (m, *C*–CN); 91.48 and 92.83 (B and A) (dm, *C*–NO_2, ^1J=151 Hz); 95.06 and 96.05 (A and B) (m, =C–CO_2Me); 144.85 and 115.08 (B and A) (m, *C*N); 116.58–160.81 (A and B) (m, 12 C arom.); 165.12 and 166.27 (A and B) (m, NC–C–*C*=O); 168.86 (A and B) (m, *C*=O). IR (nujol) 2190, 1730, 1530 cm^{-1}; HRMS calcd for $C_{25}H_{25}N_3O_8$: 495.161, found $M^{+\cdot}$: 495.168. Anal. calcd for $C_{25}H_{25}N_3O_8$: C, 60.60; H, 5.08; N, 8.48. Found: C, 60.69; H, 5.13; N, 8.18.

4.2.4. 2-Amino-3-cyano-5-nitro-4,6-di(4-nitrophenyl)-cyclo-hex-1-ene-1,3-dimethyldicarboxylate (3d: two isomers A and B). From nitromethane (0.24 g, 4 mmol), 4-nitrobenzylidene methyl cyanoacetate (5 mmol) and piperidine (50 μL, 0.5 mmol) at 90 W (75°C) during 20 min, **3d** was isolated in 70% yield after chromatography on silica gel (eluent: CH_2Cl_2, R_f=0.50). Data of forms A and B: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.41 (s, 3H, CO_2CH_3), 3.86 (A) (s, 3H, C=C–CO_2CH_3), 4.22 (B) and 4.48 (A) (d, 1H, CH_C, $^3J_{CB}$=12.6, 12.7 Hz); 4.56 (B) and (A), (d, 1H, CH_A, $^3J_{AB}$=9.3, 9.7 Hz); 5.24 (A) and 5.87 (B), (dd, 1H, CH_B, $^3J_{BC}$=12.7, 12.6 Hz, $^3J_{AB}$=9.7, 9.3 Hz); 6.50 (A) and 6.60 (B), (s, 2H, NH_2), 7.27–7.62 (m, 4H, C_6H_4), 8.12–8.38 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.7 (A and B) (dm, *C*–H_A, ^1J=136.7 Hz); 48.3 (A and B) (dm, *C*–H_C, ^1J=140 Hz); 51.7 (A and B) (q, C–CO_2CH_3, ^1J=147.3 Hz); 56.0 (A and B) (q, C=C–CO_2CH_3, ^1J=140.8 Hz); 55.7 (A and B) (m, *C*–CN); 90.6 (A and B) (m, *C*–H_B, ^1J= 153.3 Hz); 93.5 (A and B) (m, C=*C*–CO_2CH_3); 115.7 (A

and B) (d, *C*N, ^3J=9.7 Hz); 125–151 (A and B) (m, 13 C, C_6H_4 and *C*–NH_2); 164.8 (A and B) (m, C–*C*O_2CH_3); 168.3 (A and B) (m, C=C–*C*O_2CH_3). IR (nujol): 1735, 2220 cm^{-1}. HRMS calcd for $C_{23}H_{19}N_4O_8$: M−NO_2 479.120, found 479.120. Anal. calcd for $C_{23}H_{19}N_5O_{10}$: C, 52.57; H, 3.64; N, 13.33. Found: C, 52.58; H, 3.78; N, 13.17.

4.2.5. 2-Amino-3-cyano-5-nitro-4,6-di(3-fluorophenyl)-cyclo-hex-1-ene-1,3-dimethyldicarboxylate (3e: two isomers A and B). From nitromethane (0.16 g, 2.7 mmol), 3-fluorobenzylidene methylcyanoacetate (5 mmol) and piperidine (30 μL, 0.3 mmol) at 90 W (75°C) during 15 min, **3e** was isolated in 75% yield after chromatography on silica gel (eluent: CH_2Cl_2, R_f=0.50). Mp: 242°C. Data of forms A and B: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.41 (A and B) (s, 3H, C–CO_2CH_3); 3.81 (A and B) (s, 3H, =C–CO_2CH_3); 4.06 (B) and 4.28 (A) (d, 1H, CH_C, $^3J_{CB}$=12.7 Hz); 4.43 (B) and 4.52 (A) (d, 1H, C–H_A, $^3J_{AB}$=9.3, 9.7 Hz); 5.22 (A) and 5.77 (B) (dd, 1H, C–H_B, $^3J_{BA}$=9.7, 9.3 Hz, $^3J_{BC}$=12.7 Hz); 6.33 (A) and 6.45 (B) (s, 2H, NH_2); 6.93–7.36 (m, C_6H_4). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.20 (A and B) (dm, *C*–H_A, ^1J=139.1 Hz); 41.16 (A and B) (dm, *C*–H_C, ^1J=143.4 Hz); 51.20 (A and B) (q, C–CO_2CH_3, ^1J=147.2 Hz); 54.89 (A and B) (q, C=C–CO_2CH_3, ^1J=149.7 Hz); 55.28 (A and B) (m, *C*–CN); 87.98, 89.59 (A and B) (m, *C*–H_B, ^1J=152.8 Hz); 96.50 (A) and 97.30 (B) (m, C=*C*–CO_2CH_3); 115.12, 115.32 (A and B) (d, *C*N, ^3J=9.5 Hz); 114.80–131.70, 158.10, 162.95 (A and B) (m, 12C arom.); 146.73 (A and B) (d, *C*–NH_2, ^3J=3.3 Hz); 164.68 (A and B) (m, C–*C*O_2CH_3); 168.02 (A and B) (m, C=C–*C*O_2CH_3). IR (nujol) 1745, 3300, 3420 cm^{-1}. HRMS calcd for $C_{23}H_{18}N_2O_4F_2$: $M^{+\cdot}$−HNO_2 424.123, found 424.119. Anal. calcd for $C_{23}H_{19}N_3O_6F_2$: C, 58.60; H, 4.06; N, 8.91. Found: C, 58.98; H, 4.03; N, 9.00.

4.2.6. 2-Amino-3-cyano-5-nitro-4,6-di(2-fluorophenyl)-cyclo-hex-1-ene-1,3-dimethyldicarboxylate (3f: two isomers A and B). From nitromethane (0.16 g, 2.7 mmol), 2-fluorobenzylidene methylcyanoacetate (5 mmol) and piperidine (30 μL, 0.3 mmol) at 90 W (75°C) during 15 min, **3f** was isolated in 75% yield after chromatography on silica gel (eluent: CH_2Cl_2, R_f=0.50). Mp: 202°C. Data of forms A and B: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.41 (A and B) (s, 3H, C–CO_2CH_3); 3.78 (A and B) (s, 3H, =C–CO_2CH_3); 4.82–4.97 (A and B) (m, 1H, C–H_C); 5.36 (A and B) (m, 1H, C–H_A); 5.79 (A and B) (m, 1H, C–H_B); 6.32 (A) and 6.99 (B) (s, 2H, NH_2); 6.93–7.36 (A and B) (m, 8H arom.). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 39.25 (A and B) (dm, *C*–H_A, ^1J=136 Hz); 41.11 (A and B) (dm, *C*–H_A, ^1J=136 Hz); 51.20 (A) and 51.28 (B) (q, C–CO_2CH_3, ^1J=147.5 Hz); 54.90 (A) (q, C=C–CO_2CH_3, ^1J=149.5 Hz); 55.28 (A) (s, *C*–CN); 87.99 (B) and 89.62 (A) (dm, *C*–H_B, ^1J=148.5 Hz); 96.54 (A) and 97.43 (B) (d, C=*C*–CO_2CH_3, ^2J=8 Hz); 115.5 (A and B) (s, *C*N); 114.79–162.95 (A) (m, 12C arom.); 146.71 (A) (m, *C*–NH_2); 164.69 (A) (m, C–*C*O_2CH_3); 168.03 (A) (m, C=C–*C*O_2CH_3). IR (nujol): 1730, 3280, 3440 cm^{-1}. HRMS calcd for $C_{23}H_{18}N_2O_4F_2$: $M^{+\cdot}$−HNO_2 424.123, found: 424.117 Anal. calcd for $C_{23}H_{19}N_3O_6F_2$: C, 58.60; H, 4.06; N, 8.91. Found: C, 58.50; H, 4.18; N, 8.85.

4.2.7. 2-Amino-3-cyano-5-nitro-4,6-di(2-bromophenyl)-cyclo-hex-1-ene-1,3-dimethyldicarboxylate (3g: two isomers A and B). From nitromethane (0.18 g, 3 mmol), 2-bromobenzylidene methylcyanoacetate (5 mmol) and piperidine (50 μL, 0.5 mmol) at 90 W (65°C) during 15 min, **3g** was isolated in 75% yield after chromatography on silica gel (eluent: CH_2Cl_2, R_f=0.50). Mp>250°C. Data of forms A and B: ^{1}H NMR (DMSO *d*-6, 300 MHz) δ: 3.31 (A and B) (s, 3H, C–CO_2CH_3); 3.72 (A and B) (s, 3H, =C–CO_2CH_3); 4.66 (B) and 4.74 (A) (d, 1H, C–H_C, d, $^3J_{CB}$=12.3 Hz); 5.07 (d, 1H, C–H_A, $^3J_{AB}$=9.6 Hz); 5.39–5.50 (A and B) (dd, 1H, C–H_B, $^3J_{BC}$=12.3 Hz, $^3J_{BA}$=9.6 Hz); 7.17–7.87 (m, 10H, 8H arom. and NH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 44.96 (dm, *C*–H_A, ^1J=141.3 Hz); 45.55 (dm, *C*–H_C, ^1J=139.7 Hz); 50.68 (q, C–CO_2CH_3, ^1J=147.1 Hz); 54.10 (m, *C*–CN); 54.77 (q, C=C–CO_2CH_3, ^1J=150.0 Hz); 90.18 (dm, *C*–H_B, ^1J=154.6 Hz); 93.51 (m, C=*C*–CO_2CH_3); 115.27 (d, *C*N, ^3J=9.6 Hz); 124.49–141.22 (m, 12C arom, C_6H_4); 148.58 (m, *C*–NH_2); 163.48 (m, C–*C*O_2CH_3); 167.47 (m, C=C–*C*O_2CH_3). IR (nujol): 1550, 1730, 1740, 3420 cm^{-1}. HRMS calcd for $C_{23}H_{18}N_2O_4Br_2$: $M^{+\cdot}$−HNO_2: 543.963, found 543.960. Anal. calcd for $C_{23}H_{19}N_3O_6Br_2$: C, 46.57; H, 3.23; N, 7.08. Found: C, 46.76; H, 3.06; N, 6.98.

4.2.8. 2-Amino-5-nitro-4,6-diphenylcyclo-hex-1-ene-1,3,3-tricarbonitrile (3h: two isomers A and B, 50/50).[15] From nitromethane (0.26 g, 4.33 mmol), benzylidene malononitrile (5 mmol) and piperidine (30 μL, 0.3 mmol) at 90 W (120°C) during 40 min, **3h** was isolated in 75% yield after chromatography on silica gel (eluent: CH_2Cl_2/AcOEt: 1/1, R_f=0.50) and slow crystallization in ether/pentane (95/5). Mp=133°C. Data of forms A and B: ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 4.38 (A) and 4.48 (B) (d, 1H, C–H_C, $^3J_{CB}$=12.7, 10.2 Hz); 4.76 (A) and 4, 81 (B) (d, 1H, C–H_A, $^3J_{AB}$=6.5, 12.2 Hz); 5.61 (B) and 6.22 (A) (dd, 1H, C–H_B, $^3J_{BC}$=12.2, 12.7 Hz, $^3J_{BA}$=10.2, 6.5 Hz); 6.87 (B) and 6.91 (A) (s, 2H, NH_2); 7.35–7.69 (A) (m, 10H arom.). ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 43.90 (B) and 44.14 (A) (m, *C*$(CN)_2$); 44.74 (A) and 48.40 (B) (dm, *C*–H_C, ^1J=140 Hz); 45.28 (A) and 49.76 (B) (dm, *C*–H_A, ^1J=140 Hz); 79.74 (A) and 80.80 (B) (m, *C*–NH_2, ^3J=3.8 Hz); 84.23 (A and B) (dt, *C*–H_B, ^1J=152 Hz, ^2J=6.7 Hz); 112.22 (A and B) (d, C–*C*N, ^3J=9.5 Hz); 112.57 (A and B) (d, C–*C*N, ^3J=3.8 Hz); 116.81 (B) and 117.45 (A) (d, =C–*C*N, ^3J=3.6 Hz); 129.16–138.37 (A and B) (m, 12C arom.); 145.76 (A) and 146.11 (B) (m, =*C*–CN). IR (nujol): 1540, 2200 cm^{-1}. HRMS calcd for $C_{21}H_{15}N_5O_2$: 369.122, found $M^{+\cdot}$: 369.122. Anal. calcd for $C_{21}H_{15}N_5O_2$: C, 68.28; H, 4.09; N, 18.96. Found: C, 67.83; H, 4.13; N, 18.75.

4.2.9. 2-Amino-3-cyano-5-nitro-4,6-diphenyl-cyclohex-1-ene-methylcarboxylate (4a). From nitromethane (0.18 g, 3 mmol), benzylidene methylcyanoacetate **2a** (0.94 g, 5 mmol) and piperidine (250 μL, 2.5 mmol) at 90 W (90°C) during 11 min (90°C reached after 3 min), **4a** was isolated in 75% yield after chromatography on silica gel (eluent CH_2Cl_2, R_f=0.25) and slow crystallization from ether. Mp>250°C. Data of forms A (major) and B (minor): ^{1}H NMR (DMSO *d*-6, 300 MHz,) δ: 3.46 (A) and 3.48 (B) (s, 3H, O–CH_3); 3.71 (A and B) (dd, 1H, C–H_C, $^3J_{CD}$=11.4, 10 Hz, $^3J_{CB}$=12, 10 Hz); 4.07 (A) and

4.17 (B) (dd, 1H, C–H_D, $^3J_{DC}$=11.4, 10 Hz, $^5J_{DA}$=2.4 Hz); 4.17 (B) and 4.24 (A) (dd, 1H, C–H_A, $^3J_{AB}$=10.3, 10 Hz, $^5J_{AD}$=2.4 Hz); 5.55 (A) and 5.65 (B) (dd, 1H, C–H_B, $^3J_{BA}$=10.3, 10 Hz, $^3J_{BC}$=12, 10 Hz); 6.22 (A) and 6.49 (B) (s, 2H, NH_2); 7.19–7.39 (A and B) (m, 8H arom.). ^{13}C NMR (DMSO *d*-6, 75 MHz) δ: 43.85 (B) and 46.79 (A) (dm, *C*–H, ^1J=136 Hz); 47.16 (B) and 47.41 (A) (dm, *C*–H_C, ^1J=133 Hz); 50.85 (B) and 51.75 (A) (dm, *C*–H, ^1J=135 Hz); 52.31 (B) and 52.40 (A) (q, O–*C*H_3, ^1J=147.5 Hz); 74.68 (B) and 74.75 (A) (m, *C*–NH_2); 89.40 (B) and 91.67 (A) (dm, *C*–H_B, ^1J=156.5 Hz); 118.40 (A) and 118.60 (B) (s, *C*N); 127.23–139.61 (A and B) (m, 12C arom.); 153.14 (A) and 153.28 (B) (m, *C*–CO_2CH_3); 169.61 (A) and 170.38 (B) (m, *C*O_2CH_3). IR (nujol): 1725, 2190 cm^{-1}. HRMS calcd for $C_{21}H_{18}N_2O_2$: $M^{+\cdot}-HNO_2$ 330.137, found 330.137 Anal. calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.99; H, 5.17; N, 11.15.

4.2.10. 2-Amino-3-cyano-5-nitro-4,6-di (4-chlorophenyl)-cyclohex-1-ene-methylcarboxylate (4b). From nitromethane (0.18 g, 3 mmol), benzylidene methylcyanoacetate **2a** (0.94 g, 5 mmol) and piperidine (250 μL, 2.5 mmol) at 90 W (80°C) during 15 min (80°C reached after 3 min), **4b** was isolated in 75% yield after chromatography on silica gel (eluent CH_2Cl_2, R_f=0.20) and slow crystallization from ether. Mp=244°C. Data of forms A (major) and B (minor): ^{1}H NMR (DMSO *d*-6, 300 MHz,) δ: 3.39 (B) and 3.49 (A) (s, 3H, O–CH_3); 3.71 (B) and 3.72 (A) (dd, 1H, C–H_C, $^3J_{CB}$=11.6 Hz, $^3J_{CD}$=11.6 Hz); 4.02 (A and B) (dd, 1H, C–H_D, $^3J_{CD}$=11.6 Hz, $^5J_{DA}$=2.2 Hz); 4.18–4.31 (A and B) (dd, 1H, C–H_A, $^3J_{AB}$=10.4 Hz, $^5J_{AD}$=2.2 Hz); 5.58 (A and B) (dd, 1H, C–H_B, $^3J_{BA}$=10.4 Hz, $^3J_{BC}$=11.6 Hz); 6.33 (A) and 6.58 (B) (s, 2H, NH_2); 7.36–7.52 (A and B) (m, 8H arom.). ^{13}C NMR (DMSO *d*-6, 75 MHz) δ: 45.95 (A and B) (dm, *C*–H_C, ^1J=137 Hz); 46.61 (A and B) (dm, *C*–H_D, ^1J=140.5 Hz); 51.53 (A and B) (dm, *C*–H_A, ^1J=135 Hz); 52.50 (A and B) (q, O–*C*H_3, ^1J=148.5 Hz); 74.05 (B) and 74.16 (A) (m, *C*–NH_2); 89.08 (A) and 91.22 (A) (d, *C*–H_B, ^1J=157 Hz); 118.31 (A) and 118.48 (B) (s, *C*N); 128.7–137.5 (A and B) (m, 12C arom.); 153.14 (A) and 153.35 (B) (m, *C*–CO_2CH_3); 169.35 (A) and 170.22 (B) (m, *C*O_2CH_3). IR (nujol): 1540, 1720, 2195 cm^{-1}. HRMS calcd for $C_{21}H_{16}N_2O_2Cl_2$: $M^{+\cdot}-HNO_2$: 398.059, found 398.059. Anal. calcd for $C_{21}H_{17}N_3O_4Cl_2$: C, 56.51; H, 3.84; N, 9.41. Found: C, 55.92; H, 3.87; N, 9.09.

4.2.11. 2-Amino-3-cyano-5-nitro-4,6-di(4-methoxyphenyl)-cyclohex-1-ene-methylcarboxylate (4c). From nitromethane (0.22 g, 3.67 mmol), benzylidene methylcyanoacetate **2a** (0.94 g, 5 mmol) and piperidine (275 μL, 2.75 mmol) at 90 W (60°C) during 25 min (60°C reached after 3 min), **4c** was isolated in 70% yield after chromatography on silica gel (eluent CH_2Cl_2, R_f=0.20) and slow crystallization from ether. Mp>250°C. Data of forms A (major) and B (minor): ^{1}H NMR (DMSO *d*-6, 300 MHz,) δ: 3.48 (A and B) (s, 3H, CO_2CH_3); 3.60 (A and B) (dd as t, 1H, C–H_C, $^3J_{CD}$=$^3J_{CB}$=11.5 Hz); 3.70 and 3.74 (A and B) (s, 3H, $C_6H_4OCH_3$); 3.99 (A and B) (dm, 1H, C–H_D, $^3J_{CD}$=11.5 Hz); 4.13 (dm, 1H, C–H_A, $^3J_{AB}$=9.65 Hz); 5.43 (A) and 5.6 (B) (dd, 1H, C–H_B, $^3J_{BA}$=9.65 Hz, $^3J_{BC}$=11.5 Hz); 6.15 (A) and 6.38 (B) (s, 2H, NH_2); 6.84–6.92 and 7.21–7.28 (A and B) (m, 8H arom.). ^{13}C NMR (DMSO *d*-6, 75 MHz) δ: 43.31 (B) and 46.03 (A) (dm, *C*–H_C, ^1J=137.7 Hz); 46.42 (B) and 46.68 (A) (dm, *C*–H_A, ^1J=132 Hz); 50.92 (B) and 51.81 (A) (dm, *C*–H_D, ^1J=136 Hz); 52.35 (B) and 52.44 (A) (q, CO_2CH_3, ^1J=148 Hz); 54.90 (A) (q, C_6H_4–O*C*H_3, ^1J=144.20 Hz); 75.17 (B) and 75.30 (A) (m, *C*–NH_2); 89.82 (B) and 92.05 (A) (dm, *C*–H_B, ^1J=155.80 Hz); 118.43 (A) and 118.63 (B) (s, *C*N); 127.8–130.2 (A) (m, 12C arom.); 152.95 (A) and 153.14 (B) (m, =*C*–CO_2CH_3); 158.9 (A) and 158.97 (B) (m, =*C*–OMe); 169.71 (A) and 170.52 (B) (m, *C*O_2CH_3). IR (nujol): 3460, 3360, 2180, 1730, 1530 cm^{-1}. HRMS calcd for $C_{23}H_{22}N_2O_4$: $M^{+\cdot}-HNO_2$: 390.158, found 390.160. Anal. calcd for $C_{23}H_{23}N_3O_6$: C, 63.15; H, 5.30; N, 9.60; found C, 62.68; H, 5.29; N, 9.31.

4.2.12. 2-Amino-3-cyano-5-nitro-4,6-di(3-fluorophenyl)-cyclohex-1-ene-methylcarboxylate (4e). From nitromethane (0.16 g, 2.67 mmol), benzylidene methylcyanoacetate **2a** (0.94 g, 5 mmol) and piperidine (250 μL, 2.5 mmol) at 90 W (75°C) during 15 min (75°C reached after 3 min), **4e** was isolated in 72% yield after chromatography on silica gel (eluent CH_2Cl_2, R_f=0.20) and slow crystallization from ether. Mp=246°C. Data of forms A (major) and B (minor): ^{1}H NMR ($CDCl_3$, 200 MHz,) δ: 3.71 (B) and 3.73 (A) (s, 3H, CO_2CH_3); 3.79 (A) and 4.03 (B) (dd, 1H, C–H_D, $^3J_{DC}$=11.3, 11.5 Hz, $^5J_{DA}$=2.20 Hz); 4.09 (A) and 4.22 (B) (dd, 1H, C–H_C, $^3J_{CB}$=12.0, 11.20 Hz, $^3J_{CD}$=11.3, 11.5 Hz); 4.29 (A) and 4.50 (B) (dd, 1H, C–H_A, $^3J_{AB}$=10.3, 10.4 Hz, $^5J_{AD}$=2.2 Hz); 4.80 (A) and 5.36 (B) (dd, 1H, C–H_B, $^3J_{BA}$=10.3, 10.4 Hz, $^3J_{BC}$=12, 11.20 Hz); 4.87 (B) and 4.94 (A) (s, 2H, NH_2); 6.93–7.38 (A) (m, 8H arom.). ^{13}C NMR (DMSO *d*-6, 75 MHz) δ: 46.09 (A and B) (dm, *C*–H_C, ^1J=138.0 Hz); 46.80 (A and B) (dm, *C*–H_D, ^1J=132.5 Hz); 51.57 (A and B) (dm, *C*–H_A, ^1J=132.5 Hz); 52.49 (A and B) (q, O–*C*H_3, ^1J=148.5 Hz); 73.98 (A and B) (m, *C*–NH_2); 88.80 (B) and 91.07 (A) (dm, *C*–H_B, ^1J=156 Hz); 114.40–163.76 (A and B) (m, 10C arom.); 118.27 (A and B) (s, *C*N); 153.11 (A and B) (m, =*C*–CO_2CH_3); 162.07 (A and B) (dm, =*C*–F, $^1J_{CF}$=244 Hz); 169.32 (A) and 170.16 (B) (m, *C*O_2CH_3). IR (nujol): 2200, 3310, 3460 cm^{-1}. HRMS calcd for $C_{21}H_{17}N_3O_4F_2$: 413.1187; found $M^{+\cdot}$ 413.116. Anal. calcd for $C_{21}H_{17}N_3O_4F_2$: C, 61.02; H, 4.14; N, 10.16; found C, 61.55; H, 4.14; N, 10.09.

4.2.13. 2-Amino-3-cyano-5-nitro-4,6-di(2-fluorophenyl)-cyclohex-1-ene-methylcarboxylate (4f). Experimental conditions are the same for **4e** and **4f**; yield:70%. Mp>250°C. Data of forms A (major) and B (minor): ^{1}H NMR ($CDCl_3$, 300 MHz,) δ: 3.70 (A) and 3.71 (B) (s, 3H, O–CH_3); 3.83 (A) and 4.02 (B) (dd, 1H, C–H_D, $^3J_{DC}$=11.5, 11.2 Hz, $^5J_{DA}$=2.40 Hz); 4.09 (A) and 4.21 (B) (dd as t, 1H, C–H_C, $^3J_{CB}$=$^3J_{CD}$=11.5, 11.2 Hz); 4.30 (A) and 4.50 (B) (dd, 1H, C–H_A, $^3J_{AB}$=10.3, 11.2 Hz, $^5J_{AD}$=2.4 Hz); 4.87 (A and B) (dd, 1H, C–H_B, $^3J_{BC}$=11.5, 11.2 Hz, $^3J_{BA}$=10.3, 11.2 Hz); 4.87 (A) and 5.36 (B) (s, 2H, NH_2); 7.21–7.38 (A) (m, 8H arom.). ^{13}C NMR (DMSO *d*-6, 75 MHz) δ: 49.09 (B) and 50.94 (A) (dm, *C*–H_A, *C*–H_C, *C*–H_D, ^1J=135.5 Hz); 52.43 (B) and 52.55 (A) (q, O–*C*H_3, ^1J=148 Hz); 73.41 (A) and 73.66 (B) (m, *C*–NH_2); 89.27 (A and B) (dm, *C*–H_B, ^1J=156.6 Hz); 115.39–130.48 (A and B) (m, 10C arom.); 118.11 (A) and 118.35 (B) (s, *C*N); 153.26 (A and B) (m, *C*–CO_2Me); 160.23 and 160.05 (A and B) (dm, =*C*–F arom., $^1J_{CF}$=274.7 Hz); 169.03 (A) and

169.60 (B) (m, CO_2CH_3). IR (nujol): 1540, 1720, 2195 cm^{-1}. HRMS calcd for $C_{21}H_{17}N_3O_4F_2$: 413.118; found $M^{+\cdot}$ 413.116.

4.2.14. 2-Amino-3-cyano-5-nitro-4,6-di(2-bromophenyl)-cyclohex-1-ene-methylcarboxylate (4g). From nitromethane (0.18 g, 3 mmol), benzylidene methylcyanoacetate **2a** (0.94 g, 5 mmol) and piperidine (250 μL, 2.5 mmol) at 90 W (80°C) during 18 min (80°C reached after 3 min), **4g** was isolated in 75% yield after chromatography on silica gel (eluent CH_2Cl_2, R_f=0.20) and slow crystallization from ether. Mp>250°C. Data of forms A (major) and B (minor): ^1H NMR ($CDCl_3$, 300 MHz,) δ: 4.01 (A) and 4.13 (B) (s, 3H, O–CH_3); 4.32 (B) and 4.57 (A) (d, 1H, C–H_A, $^3J_{AB}$=10.0, 6.3 Hz); 5.14 (A and B) (s, 2H, NH_2); 5.34 (B) and 5.68 (A) (dd, 1H, C–H_B, $^3J_{AB}$=10, 6.3 Hz, $^3J_{BC}$=12.2, 12.6 Hz); 7.11–7.57 (A and B) (m, 8H arom.). ^{13}C NMR (DMSO *d*-6, 75 MHz) δ: 42.96 (B) and 44.75 (A) (dm, *C*–H_D, ^1J=138.9 Hz); 44.90 (B) and 45.10 (A) (dm, *C*–H_C, ^1J=140 Hz); 47.90 (B) and 51.86 (A) (dm, *C*–H_A, ^1J=140 Hz); 52.55 (A and B) (q, CO_2CH_3, ^1J=148.2 Hz); 73.53 (A) and 74.24 (B) (m, *C*–NH_2); 87.60 (B) and 89.81 (A) (dm, *C*–H_B, ^1J=156.6 Hz); 117.90 (A and B) (s, *C*N); 124.14–138.71 (m, 12C arom.); 152.77 (B) and 153.44 (A) (m, *C*–CO_2CH_3); 168.92 (A) and 169.66 (B) (m, CO_2CH_3). IR (nujol): 1540, 1715, 2190 cm^{-1}. HRMS calcd for $C_{21}H_{16}N_2O_2Br_2$: $M^{+\cdot}-HNO_2$ 485.958, found 485.951. Anal. calcd for $C_{21}H_{17}N_3O_4Br_2$: C, 47.13; H, 3.20; N, 7.85. Found C, 47.37; H, 3.34; N, 7.84.

4.2.15. 2-Amino-3-cyano-5-nitro-4,6-diphenyl-cyclo-hex-1-ene-carboxamide (4i).[16] From nitromethane (0.35 g, 5.83 mmol), benzylidene cyanoacetamide (1.81 g, 12 mmol) and piperidine (1.08 g, 13 mmol) at 90 W (100°C) during 42 min, **4i** was isolated in 50% yield and crystallization in ether/methanol (1/1); ^1H NMR (DMSO *d*-6, 300 MHz) δ: 3.70 (d, 1H, C–H_A, $^3J_{AB}$=11.0 Hz); 3.90 (dd as t, 1H, C–H_C, $^3J_{CB}$=$^3J_{CD}$=11.0 Hz); 4.18 (d, 1H, C–H_D, $^3J_{CD}$=11.0 Hz); 5.54 (dd as t, 1H, C–H_B, $^3J_{BA}$=$^3J_{BC}$= 11.0 Hz); 5.84 (s, 2H, NH_2); 5.84 (s, 1H, NH_2) and 7.65 (1H, NH_2); 7.16–7.66 (m, 8H arom.). ^{13}C NMR (DMSO *d*-6, 75 MHz) δ: 46.61 (dm, *C*–H_D, ^1J=138.5 Hz); 46.67 (dm, *C*–H_C, ^1J=138.5 Hz); 52.32 (dm, *C*–H_A, ^1J= 148.5 Hz); 74.74 (m, *C*–NH_2); 92.03 (d, *C*–H_B, ^1J= 155.5 Hz); 118.5 (s, *C*N); 127.78–138.44 (m, 12C arom.); 153.12 and 154.53 (m, *C*–CO_2CH_3); 169.56 (m, CO_2CH_3). IR (nujol): 1530, 2195 cm^{-1}. HRMS calcd for $C_{20}H_{19}N_4O_3$: 362.138; found $M^{+\cdot}$: 362.137.

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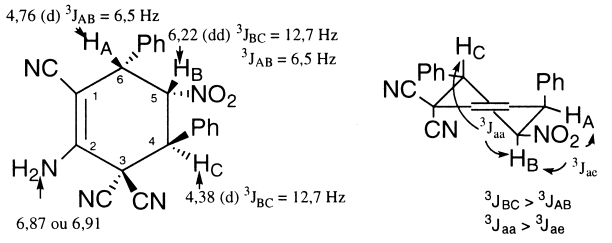
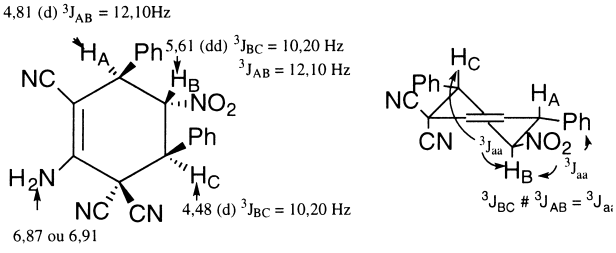
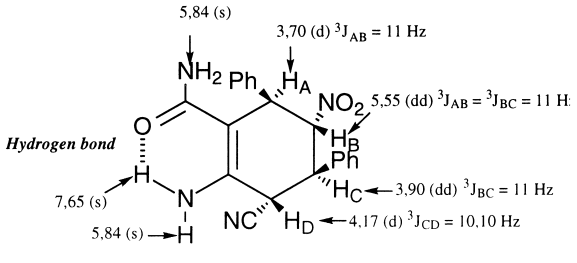
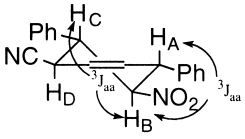




16. $^3J_{CD}$, $^3J_{BC}$, $^3J_{AB}$ being comparable, the relative configuration of isomers A and B of **4i** was not etablished.





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