The 1,3-Dipolar Cycloaddition of 3-Methylene-*N*-substituted Isoindolones and Nitrones by Classical and Microwave Techniques: Reactivity and Stereochemical Studies

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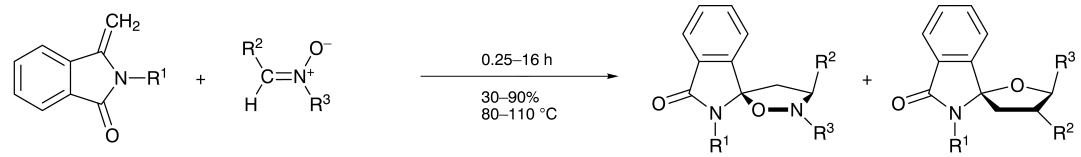
Séverinne Rigolet,[a] Paulo Goncalo,[a] Jean Marie Mélot[a] and Joel Vébrel*[b]

[a]*Laboratoire de Chimie et Electrochimie Moléculaire, Route de Gray, 25030 Besançon Cedex, France*
[b]*IUT Département Chimie, 30 Avenue de l'Observatoire, B.P. 1559, 25009 Besançon Cedex, France*

The regiospecific 1,3-dipolar cycloaddition of various 3-methylene-*N*-substituted isoindolones **1** and nitrones **2** is depicted through a comparative study between classical heating and microwave irradiation; a survey of the relevant stereochemical features is made.

Bicyclic spirocompounds are interesting structures for organic chemists because of their varying practical applications. The ring strain induced by the spiro carbon atom makes these molecules susceptible to undergo rearrangement, either upon heating or by acid–base catalysed treatment, yielding new products. Some of these bicyclic compounds, including some with one lactone- or lactam-ring, are used as weed-killers and plant growth regulators.[1–4] These molecules are synthesised, *inter alia*, through the cycloaddition between heterocycles possessing an exocyclic carbon–carbon double bond and appropriate 1,3-dipoles.



1a R^1 = *p*-$MeOC_6H_4$ **2a** R^2 = PhCO, R^3 = Ph
b R^1 = *p*-MeC_6H_4 **b** R^2 = R^3 = Ph
c R^1 = *p*-NCC_6H_4 **c** R^2 = Ph, R^3 = $PhCH_2$
d R^1 = benzyl

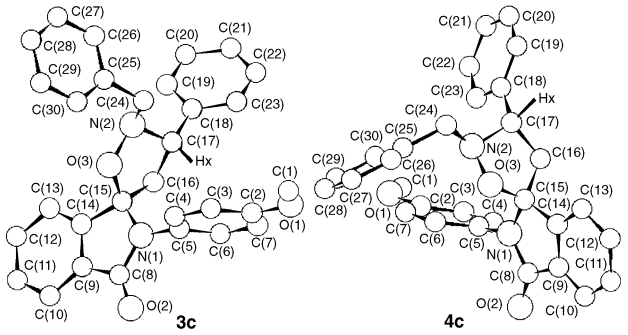
3a–l **4a–l**

Scheme 1

As part of our research,[5] we now report the regiospecific reaction of 2,3-dihydro-3-methylene isoindolones **1** with nitrones **2** (Scheme 1). Good yields of the diastereoisomeric spiro[1*H*-isoindol-1,5′(4′*H*)-isoxazole]-7(6*H*)-ones **3** and **4** are obtained with *N*-aryl nitrones **2a**,**b**; the operating conditions must be carefully chosen, owing to the easy decomposition of a few of the starting materials or spiro adducts upon prolonged heating. Reactions with the *N*-benzyl nitrone **2c** are much slower and give rather poor isolated yields; the reversible character of these latter cycloadditions is worsened by higher temperatures.

To improve both the kinetics and yields, mixtures of **1** and **2** have been subjected to microwave irradiation,[7–10] the spectacular effects of which have been reported for other cycloadditions.[12–15] We noticed, however, that the temperature conditions were not well defined in these works, which used domestic ovens. For our compounds, which are particularly sensitive to overheating, temperature conditions plainly identical to our classical experiments have been achieved by means of a monomode system; based on these preliminary requirements, a rigorous comparison of both techniques becomes feasible (Table 3). Substituted isoindolones **1** and nitrones **2** exhibit a rather weak microwave absorption, which is dependent on their permittivities, and irradiation effects seem, therefore, to be moderate. Nevertheless, reaction rates are raised and, particularly, much better isolated yields are obtained with *N*-benzyl nitrone **2c** in relation to classical heating. Interestingly, microwave irradiation is of no use with other nitrones.

The exact temperatures reached by different mixtures (**1** + **2**) have been measured and are very close to the set temperature of the microwave oven: no significant heterogeneity of these parameters was noticed throughout the reaction vessel. A specific microwave effect does actually exist and can be linked to transient hot spots; this hypothesis cannot be fully asserted at present, on the grounds of the inadequacy of current techniques of local temperature measurements.



Scheme 2

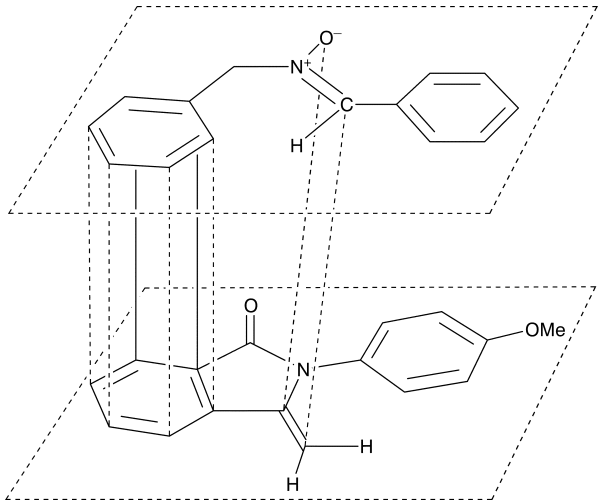
*To receive any correspondence.

Table 3 Reaction of methyleneisoindolones **1** and nitrone **2c** under both classical heating and microwave irradiation (110 °C, 4 h)

Entry	3-Methylene isoindolone **1**	Nitrone **2**	Adduct **3** + **4**	Classical heating[a] Reaction rate[c] (% isolated yield)	Microwave irradiation[b] Reaction rate[c] (% isolated yield)
2	**1a**	**2c**	**3c** + **4c**	45 (20)	80 (50)
4	**1b**	**2c**	**3f** + **4f**	55 (27)[d]	75 (61)[d]
6	**1c**	**2c**	**3i** + **4i**	20 (12)[e]	37 (30)[e]
8	**1d**	**2c**	**3l** + **4l**	45 (16)	65 (40)

[a]Yields of pure **3**+**4** unless indicated otherwise. [b]Non-optimised reproducible yields. [c]Evaluated by ^{1}H NMR. [d]Yields of pure **3f**. [e]Based on **2c** (**1c** not detectable).

The cycloadducts **3** and **4** have been fully identified by ^{1}H and ^{13}C NMR; X-ray crystallography clarifies their exact stereochemistry and, in particular, justifies the chemical shifts of the H_x atom of the isoxazolidine ring (Scheme 2). The slight stereoselectivity observed for cycloadditions proceeding from the *N*-benzyl nitrone **2c** (35–60% de) might be linked to secondary π–π interactions[23,24] between aromatic nuclei of both dipolar and dipolarophilic species in the course of one of the two possible transition states. This hypothesis is not fully asserted, but it is noteworthy that such weak interactions are conspicuously absent in the case of the nitrones (*N*-aryl or simple *N*-alkyl) that do not react with any stereoselectivity (Scheme 4).



Scheme 4

Crystallographic Studies of **3c** *and* **4c**.—The X-ray structures were obtained with an Enraf Nonius CAD4 diffractometer; radiation: graphite filtered Mo-Kα; $\lambda = 0.71073$ Å; $\mu = 0.786$ cm^{-1}. All scans used the θ–2θ technique.

The structures were solved with the MolEN 90 program.[33] Molecules were drawn with the ORTEP program.[34] Atomic scattering factors were taken from the literature.[35]

3c and **4c**: $C_{30}H_{26}N_2O_3$, $M_r = 462.6$. **3c**: triclinic system, $P\bar{1}$ space group; $a = 6.890(4)$ Å, $b = 9.994(2)$ Å, $c = 18.763(3)$ Å; $\alpha = 76.08(2)^\circ$, $\beta = 79.87(3)^\circ$, $\gamma = 71.55(3)^\circ$; $V = 1182(1)$ Å^3; $Z = 2$; $d_{calc} = 1.299$ g cm^{-3}. Number of independent reflections: 4528; 1731 reflections with $I > 3\sigma(I)$; $2^\circ < 2\theta < 50^\circ$. The refinement converges to $R(F) = 0.054$; $Rw(F) = 0.057$. The weighting scheme is given by $w = 4Fo^2/[\sigma^2(I) + (0.04\ Fo^2)^2]$.

4c: Triclinic system; $P\bar{1}$ space group; $a = 10.47(1)$ Å, $b = 14.614(2)$ Å, $c = 16.653(3)$ Å. $\alpha = 81.66(2)^\circ$, $\beta = 81.25(3)^\circ$, $\gamma = 85.99(3)^\circ$; $V = 2488(1)$ Å^3; $Z = 4$; $d_{calc} = 1.235$ g cm^{-3}. Number of independent reflections: 8240; with $I > 3\sigma(I)$: 2726. The refinement converges to $R(F) = 0.056$; $Rw(F) = 0.069$; weight factor = 0.070.

The standard deviations in **3c** and **4c** are a very good fit (0.006–0.010 Å on the bond length and 0.3–0.7° on the bond angles).

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Techniques used: ^{1}H and ^{13}C NMR, IR, X-ray diffractometry, differential thermal analysis

References: 35

Schemes: 4

Table 1: Differential thermal analysis of 1:1 mixtures of **1a–d** and **2a–c**

Table 2: Reaction of 3-methyleneisoindolones **1** and nitrones **2**

Tables 6–8: ^{1}H and ^{13}C NMR spectroscopic data for compounds **3** and **4**

Tables 9–14: X-ray diffractometry data for **3c** and **4c**

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