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π-Facial diastereoselection in the cycloaddition of nitrile oxides to arylmethylenespiropyrroline derivatives

Francesco Risitano,[a,*] Giovanni Grassi,[a] Francesco Foti[a] and Archimede Rotondo[b]

[a]*Dipartimento di Chimica Organica e Biologica, Università, Vill. S. Agata, I-98166 Messina, Italy*
[b]*Dipartimento di Chimica Inorganica, Analitica e Struttura Molecolare, Università, Vill. S. Agata, I-98166 Messina, Italy*

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Abstract—Rigid and sterically congested spirocompounds **1**, derived from arylmethyleneisoxazol-5-ones and in situ prepared pyridinium ylides, induced complete diastereofacial selection in site and regiospecific cycloaddition reactions with nitrile oxides.

1. Introduction

While the ability of nitrile oxides to attack exocyclic C═C bonds has been well documented,[1] their addition to the unsaturated C═N bond of either aromatic or non aromatic *N*-heterocycles, with five or six membered rings, has only recently been investigated.[2,3] In particular, using variously substituted azoles or azines, this reaction has been shown to be site-selective, with preferential attack by nitrile oxide on the C═N bond. In most cases, the resulting fused oxadiazoline moiety undergoes a rearrangement,[4] and finally evolves into azolone[2a] or azinone[3] adducts.

In this regard, we recently synthesized arylmethylene spirocompounds (*E*)-1 obtained as single ($5R^*$, $6R^*$)-diasteromers from arylmethyleneisoxazol-5-ones and pyridinium ylide prepared in situ.[5]

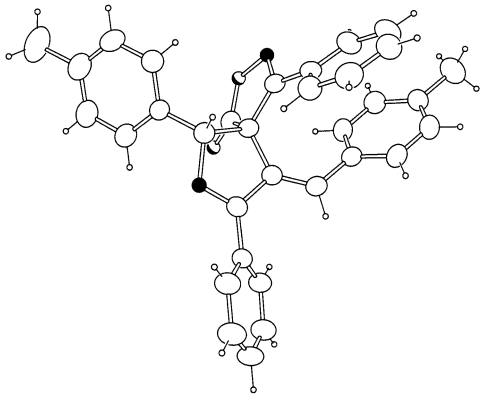
Structural characterization by X-ray analysis,[6] showed considerable steric congestion in these derivatives **1** (Fig. 1).

Therefore, bearing in mind the intriguing dipolarophile activity displayed by sterically strained compounds, such as nobornene,[7] these unusual spiro derivatives **1**, which contain two potential dipolarophile sites (endocyclic C8–N7 and exocyclic C9–CAr double bonds) (Scheme 1), seemed to be very interesting substrates because of their structural rigidity and strong steric strain.

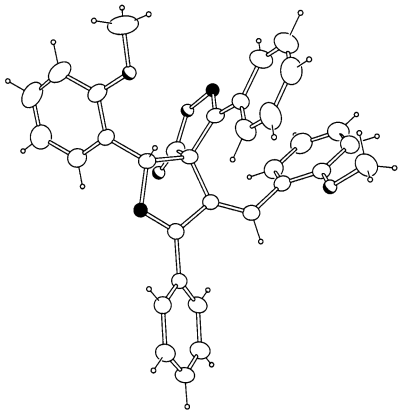
This paper presents the results of cycloaddition reactions between spiro compounds **1** and nitrile oxides which show that the reactivity of the C═N moiety of these dipolarophiles is greater than that of the exocyclic C═C bond.

2. Results and discussion

The cycloaddition reaction was performed in $CHCl_3$, at room temperature for approximately 1 h, using equimolecular



1b



1f

Figure 1. View of **1b** and **1f** at the state solid by X-ray diffraction.

Keywords: sterically congested molecules; regiospecificity; fused spirans.
* Corresponding author. Tel.: +39-0906765512; fax: +390-90-393897; e-mail: frisitan@isengard.unime.it

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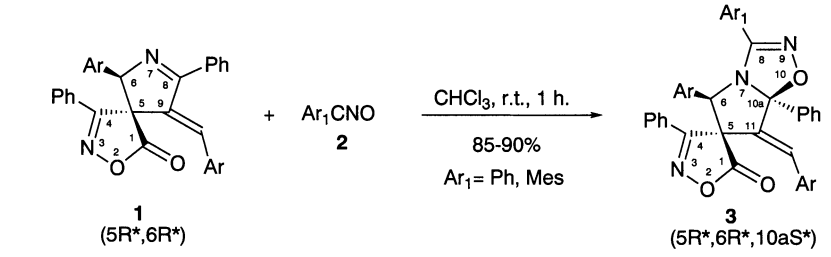

Ar	Ph	*p*-MeC$_6$H$_4$	*p*-MeOC$_6$H$_4$	*p*-ClC$_6$H$_4$	*o*-MeC$_6$H$_4$	*o*-MeOC$_6$H$_4$	*m*-MeC$_6$H$_4$	*m*-MeOC$_6$H$_4$
	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**

Scheme 1.

quantities of nitrile oxides and spiro compounds **1**. Employing benzonitrile oxide **2** (Ar_1=Ph), the cycloaddition gives only the fused cyclic adducts **3** in high yield (85–90%). Thus, under these conditions, cycloadducts **3** are stable and the oxadiazoline moiety is preserved. Surprisingly, the reaction took place only with spiro compounds **1a–d**. The remaining spirocompounds **1e–h** did not show any reactivity, and the starting materials were recovered unchanged together with 3,4-diphenylfuroxane, derived from the dimerisation of benzonitrile oxide.

The structures of adducts **3** were deduced from analytical and spectroscopic data (Section 4). Elemental analysis shows that only one benzonitrile oxide molecule participates in the reaction, while IR and ^{1}H NMR data support the benzonitrile oxide attack on the pyrroline C–N double bond. In particular, the unchanged isoxazolone carbonyl stretching in the IR spectra and only one new ^{1}H NMR resonance in the region between 4.50 and 6.00 ppm prove that both the isoxazolone and arylmethylene moieties of the starting spiro system **1** remain unaltered. On the other hand, the higher frequency (about 1 ppm) of the arylamino proton indicates saturation of the C=N bond and the chemical shift of the Ar_1 protons is consistent with a phenyl system on a carbon bonded to two electronegative heteroatoms.

In agreement with previous results obtained from nitrile oxide cycloaddition to conjugated 1-azadiene systems,[8] the assigned regiochemistry was that expected from frontier molecular orbital (FMO) theory, considering LUMO (1,3-dipole)/HOMO (dipolarophile) interaction.[9]

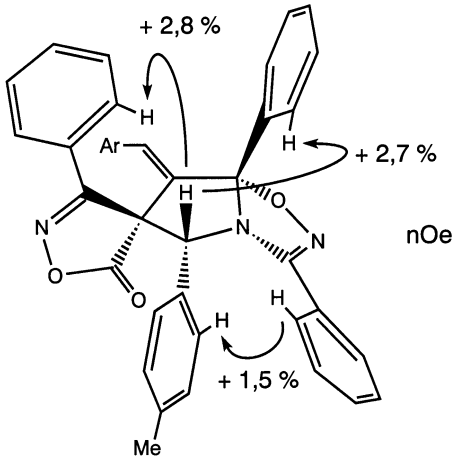

Figure 2. Stereochemical assignments of **3b**.

The stereochemical features of compound **3b** (Fig. 2) were established by NOED experiments after complete assignment of proton resonances by conventional 2D techniques.

Thus, the isolated cycloadduct **3** is formed exclusively by *anti* addition with respect to the isoxazolone C-phenyl group and it is precisely this group which, as a consequence of its close spatial proximity to the C=N double bond, controls the complete diastereofacial selectivity observed in this cycloaddition reaction.

The above described nitrile oxide cycloaddition also makes it possible to minimize steric interactions among substituents of the fused system **3**. However, when Ar is bulkier (with *ortho* or *meta*-substituents), the peri interaction between this system and the phenyl of the nitrile oxide can be sufficient to stop the reaction. It is very probable that for this reason no reaction was observed with the spiro compounds **1e–h**. To further confirm this, cycloaddition of mesitylnitrile oxide **2** (Ar_1=Mesityl)[10] to the spiro compounds **1a–d** was attempted. As expected, no reaction was observed and the starting materials were recovered unaltered even after a week of reaction in refluxing benzene or chloroform.

3. Conclusion

In conclusion, the failure of cycloadditions to the exocyclic C=C is rationalized on the basis of considerable steric congestion at the arylmethylene site; while the reaction failures in cases **1e–h** can be explained by steric hindrance of the *meta* and *ortho* substituents on the C4-Ar group (Fig. 1). Thus cycloaddition of the nitrile oxide to spiro-derivatives **1a–d** proceeded with complete stereofacial discrimination and readily generated a new chiral center with (*S*) configuration. Assuming that other chiral carbon configurations remain unchanged during the reaction, the cycloadducts have the (5*R*,6*R*,10a*S*) configuration.

4. Experimental

Melting points: Reichert–Kofler hot-stage microscope. Microanalyses: Carlo Erba EA 1102. IR: Nicolet FT-IR

Impact 400D spectrometer. ^{1}H- and ^{13}C NMR spectra. Bruker ARX 300, tetramethylsilane as internal reference. Arylhydroximic acid chlorides (Ar_1=Ph[11] and Mesityl[10]) and spiroderivatives **2**[5] were prepared according to literature procedures.

4.1. General procedure for the cycloaddition

To a stirred solution of **1** (0.01 mol) in chloroform (50 ml) was added a solution of benzhydroximoyl chloride (0.01 mol) in chloroform (20 ml) at room temperature followed by dropwise addition of triethylamine (0.02 mol). After stirring for 1 h at room temperature, the triethylamine hydrochloride was removed by filtration and the solvent evaporated at reduced pressure to give the crude product **3**, which was purified by crystallization (methanol).

4.1.1. Compound 3a. Yield: 90%; white solid; mp 202–203°C; [Found: C, 79.78; H, 4.82; N, 7.52. $C_{38}H_{27}N_3O_3$ requires C, 79.56; H, 4.74; N, 7.33%]; $\nu_{C=O}$ (Nujol) 1781 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Hz, rt): δ=5.07 (s, 1H, ArC*H*), 6.84–8.22 (m, 26H, Ar*H* and ArC*H*=C); ^{13}C NMR ($CDCl_3$, 75 Hz, rt): δ=64.4, 74.8, 111.7, 124.7, 126.4, 126.6, 127.4, 127.6, 127.7, 128.1, 128.2, 128.4, 128.7, 129.2, 129.3, 129.4, 131.1, 131.9, 133.6, 133.9, 137.2, 138.8, 140.2, 161.4, 163.5, 175.3.

4.1.2. Compound 3b. Yield: 90%; white solid; mp 149–150°C; [Found: C, 79.96; H, 5.27; N, 7.13. $C_{40}H_{31}N_3O_3$ requires C, 79.85; H, 5.19; N, 6.98%]; $\nu_{C=O}$ (Nujol) 1793 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Hz, rt): δ=2.22 (s, 3H, *Me*), 2.26 (s, 3H, *Me*), 5.03 (s, 1H, ArC*H*), 6.75–8.20 (m, 24H, Ar*H* and ArC*H*=C); ^{13}C NMR ($CDCl_3$, 75 Hz, rt): δ=21.2, 21.3, 64.5, 74.8, 111.9, 126.5, 126.7, 127.5, 127.7, 127.9, 128.2, 128.4, 128.7, 128.8, 128.9, 129.1, 129.2, 130.6, 131.1, 131.9, 137.3, 137.8, 138.1, 139.5, 140.4, 161.3, 163.8, 175.3.

4.1.3. Compound 3c. Yield: 88%; white solid; mp 103–104°C; [Found: C, 76.05; H, 4.84; N, 6.71. $C_{40}H_{31}N_3O_5$ requires C, 75.81; H, 4.93; N, 6.63%]; $\nu_{C=O}$ (Nujol) 1787 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Hz, rt): δ=3.70 (s, 3H, *Me*), 3.74 (s, 3H, *Me*), 5.00 (s, 1H, ArC*H*), 6.72–8.20 (m 24H, Ar*H* and ArC*H*=C)); ^{13}C NMR ($CDCl_3$, 75 Hz, rt): δ=55.2, 55.3, 64.6, 74.9, 111.7, 113.9, 114.1, 126.5, 126.3, 127.4, 127.7, 127.8, 127.9, 128.0, 128.6, 128.8, 128.9, 129.1, 129.2, 129.3, 130.7, 131.1, 131.9, 137.4, 137.9, 138.2, 139.5, 161.3, 163.9, 175.4.

4.1.4. Compound 3d. Yield: 85%; white solid; mp 129–130°C; [Found: C, 71.25; H, 4.05; N, 6.73. $C_{38}H_{25}N_3O_3Cl_2$ requires C, 71.03; H, 3.92; N, 6.54%]; $\nu_{C=O}$ (Nujol) 1796 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Hz, rt): δ=5.03 (s, 1H, ArC*H*), 6.75–8.17 (m, 24H, Ar*H* and ArC*H*=C); ^{13}C NMR ($CDCl_3$, 75 Hz, rt): δ=64.1, 74.1, 111.6, 113.9, 126.5, 127.5, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.2, 129.3, 129.4, 131.3, 136.1, 139.2, 158.1, 161.2, 163.3, 174.9.

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