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The Powerful Effect of *N*-Aryl Substitution in Promoting the Thermal Rearrangement of 5-Spirocyclopropaneisoxazolidines

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Abstract

N-Alkyl 5-spirocyclopropaneisoxazolidines rearrange to tetrahydropyridone derivatives by heating. The presence of a phenyl ring on the nitrogen atom significantly reduces the rearrangement temperature. This effect is enhanced by electron-donating substituents and reduced by electron-withdrawing substituents on the phenyl ring.

Keywords: 1,3-Dipolar Cycloadditions, Thermal Rearrangement, Isoxazolidines, Spiro compounds, Substituent effects

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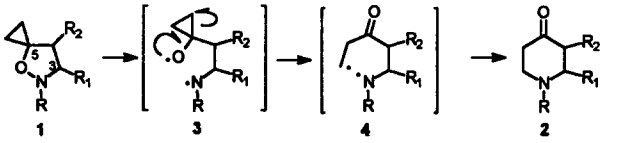
The thermal rearrangement of isoxazolidine-5-spirocyclopropanes **1** has shown its potential for the synthesis of substituted tetrahydropyridones **2**.[1] The rearrangement is usually carried out in solution at 100-160°C for several hours depending on the substrate or by flash vacuum thermolysis (FVT, 400°C, 10^{-2} torr) when volatile compounds are available. Although the method has shown already general adaptability to different substrates, the search for milder conditions to carry out the rearrangement would expand its utility in organic synthesis.

The mechanism of the process, albeit far from being completely understood, involves the homolytic cleavage of the N-O bond which produces the diradical **3** that rapidly evolves to **4**, as **4** is favored by the strain relief at the spiro carbon atom and the strong C-O double bond formation[1f] (Scheme 1).

Scheme 1



Therefore, the cleavage of the N-O bond must be the rate determining step and behaves as a switch to start the whole process. If this is a well established interpretation of the process, much less is known about the factors that influence the N-O bond strain and, therefore, the activation energy. For example, it is not clear why a spirocyclobutane[2] ring or, even more striking, a CO_2Me group on the C-4 of the isoxazolidine ring, should affect

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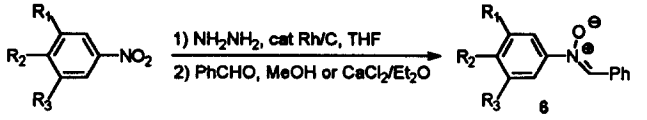
so dramatically the rearrangement temperature.[1g] In both cases, in fact, FVT at 700 and 400°C, respectively, is the only way to obtain rearrangement. As a step towards interpretation of the process, we are able to report that *N*-arylsubstituted 5-spirocyclopropaneisoxazolidines **1** (R = Ar) undergo rearrangement smoothly at room temperature.

We had previously shown that a 2,3-diphenyl-5-spirocyclopropane isoxazolidine must rearrange as fast as it was produced at 60°C, as it was not possible to accumulate and isolate it.[3] We have now repeated the cycloaddition/rearrangement process using a reactive dipolarophile, ethylcyclopropylideneacetate (**5**), together with differently substituted *N*-arylnitrones to see a picture of the effect of the *N*-aryl substituent on the rearrangement step.

The *C,N*-diphenylnitrone (**6a**) and its derivatives **6b-e** were synthesized by condensation of the appropriate phenylhydroxylamine with benzaldehyde (Scheme 2). The phenyl substituted hydroxylamines were obtained by reduction of the corresponding nitro-compounds with hydrazine in the presence of catalytic amounts of Rh/C according to the procedure of Entwistle and Gilkerson,[4] which in our hands proved to be the most efficient for producing these unstable compounds (Scheme 2).

Scheme 2



a: $R_1=R_2=R_3=H$
b: $R_1=R_3=H$ $R_2=OMe$ (94%)
c: $R_1=R_3=H$ $R_2=Me$ (89%)
d: $R_1=R_3=H$ $R_2=CO_2Me$ (72%)
e: $R_1=R_3=CO_2Me$ $R_2=H$ (89%)

The solutions of equimolecular amounts of reagents were monitored by proton NMR. After 24 hrs at r.t. the conversion was only partial in all the examples, but a rather different composition of the reaction mixtures was observed (Scheme 3, Table 1).

Scheme 3

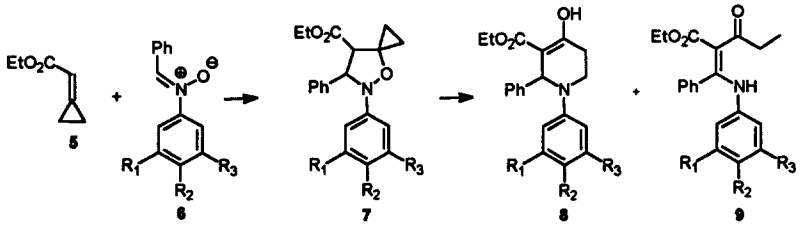


Table 1 Composition of the reaction mixtures after 24h at r.t.

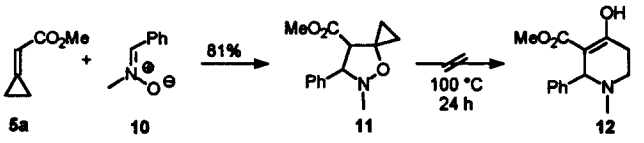
Entry	R_1	R_2	R_3	conversion (%)[a]	molar ratio[a]		
					dipolarophile **5**	adducts **7**	products **8-9**
a	H	H	H	72	1	1.1	1.5
b	H	OMe	H	38	1	-	0.6
c	H	Me	H	45	1	-	0.8
d	H	CO_2Me	H	40	1	0.7	-
e	CO_2Me	H	CO_2Me	52	1	1.1	< 0.1

a) Calculated by integration of ^{1}H-NMR diagnostic signals.

The experimental data show that the rate of the rearrangement process is strongly affected by the electronic nature of the *N*-phenyl substituent. While the rate of the two steps of the cycloaddition/rearrangement process with the unsubstituted nitrone are comparable (Table 1, entry a), the presence of an EDG on the *para* position of the phenyl ring strongly enhances the rearrangement rate with the result that it was not possible to detect the presence of the intermediate cycloadducts **7** at r.t. (Table 1, entries b,c). The cycloaddition is therefore the rate determining step of the process with EDG substituted *N*-aryl nitrones. Finally the introduction of one or two EWGs on the phenyl ring strongly reduces the rate of the rearrangement step hence only very little amounts of the final products were produced at r.t.(Table 1, entries d,e).

By comparison, the analogues with an *N*-methyl substituted isoxazolidine **11** show good thermal stability as they were recovered unchanged after 24 hrs at 100°C in toluene (Scheme 4).

Scheme 4



The reaction in entries **a-c** reached completion after 7 days at r.t., while adducts **7d,e** were still present in the reaction mixtures after 21 days and the rearrangements were completed by heating at 60°C for 4.5 hrs. The products were purified and partially separated by chromatography on silica gel in order to assign their structure. In all cases the pyridone derivatives **8a-e** were obtained in their enolic form and in modest yield (**8a**, 22%; **8b**, 35%; **8c**, 36%; **8d**, 34%; **8e**, 22%). The assignment of the structure was based on the presence of the enolic proton resonance (δ 13.5-13.2 ppm) and the singlet of the benzylic proton (δ 5.9-5.4 ppm) in their ^{1}H-NMR spectra.[5] Small amounts of the ring opened rearrangement products **9** (generally arising from the diradical intermediate **4** by a 1,5-hydrogen shift[1]) were also obtained (**9a**, 9%; **9b**, 13%; **9c**, 8%; **9e**, 2%) except in the case of *p*-methoxycarbonyl derivative **9d**. The structures of **9** were easily deduced by the presence of an ethyl group in ^{1}H-NMR spectra and the α,β-unsatured carbonyl resonance (δ 199.6-199.4 ppm) in ^{13}C-NMR spectra.[5,6]

The study has shown that the effect of an *N*-aryl substituent on the rearrangement of 5-spirocyclopropaneisoxazolidines is quite effective. The acceleration caused by *N*-aryl substituents suggests that a polarization of the N-O bond in the Transition State of the rearrangement (Figure 1) must be important. This polarization must produce an electronic deficiency at the nitrogen atom. The formation of a polar intermediate however, can be excluded by the absence of a solvent effect on the process. An aromatic ring on nitrogen is able to stabilize this electronic deficiency, thus accelerating the N-O bond cleavage. A *para* electron-donating substituent must increase even more the stabilization, as was demonstrated by the strong acceleration of the rearrangement step. Conversely, an electron-withdrawing substituent acts in exactly the opposite way, almost eliminating the effect of the aromatic ring on nitrogen.

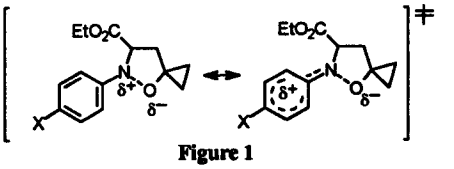


Figure 1

The results of this study will be of high utility for further applications of our cycloaddition/rearrangement methodology in organic synthesis.

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References and notes

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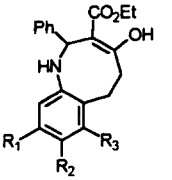
5. **General procedure:** Cycloaddition/rearrangement reaction: Equimolar amounts of nitrone **6** and ethylcyclopropylideneacetate **5** (0.4-0,5 mmol) in 0.5 mL $CDCl_3$ were maintained at r.t. for 7 days (entries a-c) or for 21 days and then heated at 60°C for 4h (entries d,e). The solvent was removed under reduced pressure and the products were separated by column chromatography on silica gel using mixtures of petrol ether(40-60) and ethyl acetate as eluent. Spectral data of **8a** and **9a** as representative for the **a-e** series; **8a:** ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 12.20 (s, 1H), 7.35-6.76 (m, 10H), 5.69 (s, 1H), 4.15 (q, J=7.3 Hz, 2H), 3.50 (dd, J=13.9; 7.3 Hz, 1H), 3.24 (ddd, J=13.9, 10.9, 4.8 Hz, 1H), 2.80-2.56 (m, 1H), 2.26 (dd, J=15.0; 4.0 Hz, 1H), 1.11 (t, J=7.3 Hz, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 172.2 s, 171.1 s, 149.4 s, 141.7 s, 129.2 d (2C), 127.9 d (2C), 127.9 d (2C), 127.0 d, 119.4 d, 116.6 d (2C), 99.5 s, 60.4 t, 57.4 d, 39.8 t, 27.0 t, 14.0 q; MS *m/z* (%): 323 (M^+, 48), 250 (19), 246 (32), 200 (100), 104 (41); IR(CDCl3): 3080, 3040, 2990, 2940, 1649, 1616, 1598, 1492, 1365, 1301, 1260, 1233, 1216 cm^{-1}; **9a:** ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.31-6.84 (m, 8H), 6.69 (d, J=7.7 Hz, 2H), 3.72 (q, J=7.3 Hz, 2H), 2.74 (q, J=7.3 Hz, 2H), 1.16 (t, J=7.3 Hz, 3H), 0.73 (t, J=7.3 Hz, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 199.6 s, 169.7 s, 162.7 s, 138.5 s, 134.3 s, 129.4 d, 128.7 d (2C), 128.5 d (2C), 128.4 d (2C), 125.0 (d), 124.2 d (2C), 106.8 s, 60.4 t, 33.8 t, 13.4 q, 9.0 q; MS *m/z* (%): 276 (29), 262 (15), 248 (100), 165 (17); IR ($CDCl_3$): 3080, 2990, 2950, 1695, 1590, 1555, 1252, 1194 cm^{-1}.
6. In all cases the formation of small quantities of the isomer **13** were also observed. The benzoazocinones **13**, must arise via a different reaction of the diradical **4**[3] and appear to be particularly unstable as the ratio of **13** to **8** decreased steadily in the course of the reaction. The products **13** are characterized in their ^{1}H-NMR spectra by a singlet at 4.6-4.7 ppm due to the resonance of the benzylic proton.



13