Switching the Reaction Mode of 4-Methoxycarbonyl-4-chloro-5-spirocyclopropaneisoxazolidines by *N*-Aryl Substitution

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Received 4 May 2010

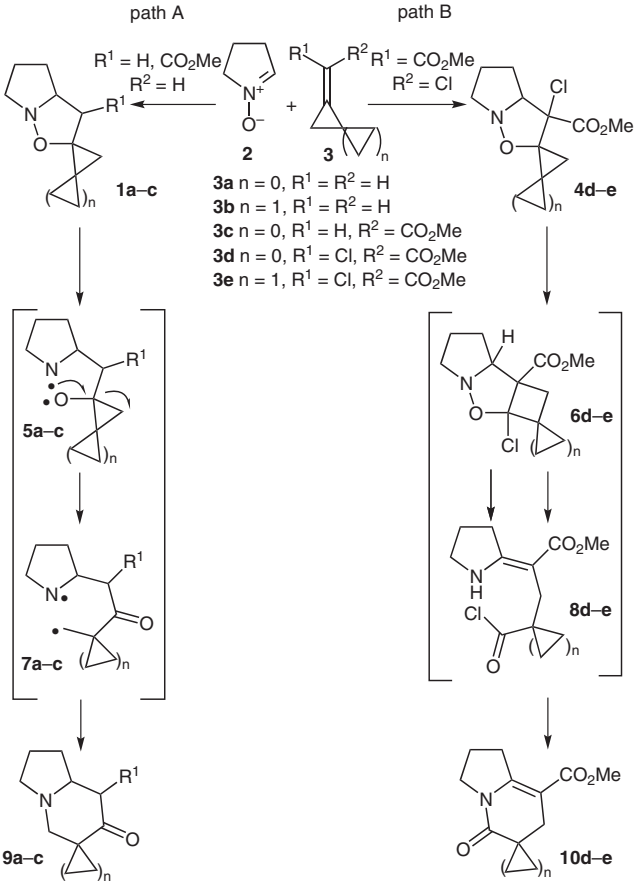
Dedicated to Professor Saverio Florio on the occasion of his 70th birthday

Abstract: 4-Methoxycarbonyl-4-chloro-5-spirocyclopropaneisoxazolidines, easily obtained by in situ cycloadditions of nitrones to methyl 2-chlorocyclopropylideneacetate and 2-chlorospiropentylideneacetate, in contrast to their known thermal rearrangements leading to δ-lactams, undergo rearrangement to their respective tetrahydropyridones, when the nitrone nitrogen is substituted by an aryl moiety.

Key words: 1,3-dipolar cycloadditions, chlorocyclopropylideneacetate, *N*-aryl nitrones, thermal rearrangement, tetrahydropyridones

The thermal rearrangement of 5-spirocyclopropaneisoxazolidines obtained by 1,3-dipolar cycloadditions of nitrones to alkylidenecyclopropanes has proved to be a useful tool for the synthesis of different classes of N-heterocycles[1] and found application in the synthesis of natural products[2] as well as non-natural biologically active compounds.[3] A computational study of the mechanism involved in this transformation[4] has evidenced its dependency on the nature of the substituents present both on the alkylidenecyclopropane and the nitrone counterpart. For example, switching from methylenecyclopropane or cyclopropylideneacetate to 2-chlorocyclopropylideneacetate induced a remarkable change in the reaction conditions and outcome of products as illustrated in Scheme 1.

Methylenecyclopropane (**3a**) reacts with nitrones to afford the corresponding isoxazolidines which easily undergo thermal rearrangement at 100–160 °C (Scheme 1, path A). Cyclopropylideneacetate (**3c**) as well easily gives the corresponding isoxazolidines, but the rearrangement step requires higher temperatures and special techniques (flash vacuum thermolysis, up to 600 °C).[2d] 2-Chlorocyclopropylideneacetate (**3d**)[5] furnishes the expected isoxazolidines, but the rearrangement step afforded a totally different product[6] (Scheme 1, path B). The mechanism of this transformation has been fully rationalized and the reaction conditions (80–100 °C, reaction times from a few hours to days) were optimized to afford enantiopure indolizidine derivatives.[7] The changing behavior of the nitrone counterpart in the reaction, affording different products along the route, was also elucidated. However, in no case was it possible to isolate the product derived from the most common thermal rearrangement (Scheme 1, path A). This was ascribed to two reasons: a) the original observation that introducing a methoxycarbonyl group on C-4 of the isoxazolidine ring retards the thermal rearrangement and lets it occur only at a much higher temperature; b) the presence of a chloromethylenecyclopropane moiety in the substrate offers the product a favorable alternative reaction pathway, that is, the chloromethylcyclopropane to chlorocyclobutane ring-enlargement process.



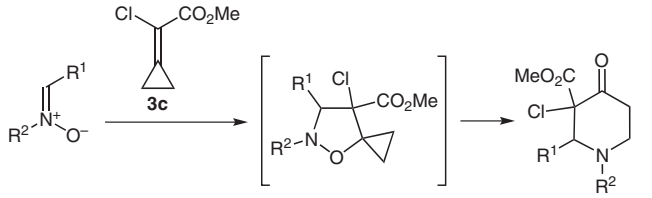
Scheme 1

SYNLETT 2010, No. 13, pp 1939–1942
Advanced online publication: 09.07.2010
DOI: 10.1055/s-0030-1258136; Art ID: G15210ST

If it was possible to lower the energy barrier of the thermal rearrangement (path A), the latter would be favored over the sequence involving a ring enlargement (Scheme 1, path B). Such a possibility was conceivable, as according to an earlier observation the use of *N*-aryl-substituted open chain nitrones with **3c** allowed the rearrangement of the corresponding isoxazolidines to occur at room temperature.[8] This experimental observation was later rationalized by a computational study showing a lower activation energy (about 11 kcal/mol) for the initial formation of the 1,5-diradical intermediate, when an aromatic substituent is present on the nitrogen of the isoxazolidine ring.[4] The use of *N*-arylnitrones allows the synthesis of *N*-aryltetrahydropyridones in a multicomponent domino process starting from nitrones and alkylidenecyclopropanes. In this communication, we wish to report the results of a study concerning the cycloaddition reactions of 2-chlorocyclopropylideneacetate (**3d**) and (*Z*)-2-chlorospiropentylideneacetate (*Z*)-**3e**[9] with *N*-arylnitrones that support the hypothesis.

The cycloaddition of *C*,*N*-diphenyl nitrone (**11a**) to methyl 2-chlorocyclopropylideneacetate (**3c**) and subsequent rearrangement proceeded at room temperature and was complete within five days to afford exclusively the tetrahydropyridone derivative **13a** in 40% yield as a single diastereomer (Table 1, entry 1).[10]

Table 1 Cycloaddition of *N*-Arylnitrones **11** to Methyl 2-Chlorocyclopropylideneacetate (**3c**) with Ensuing Rearrangement

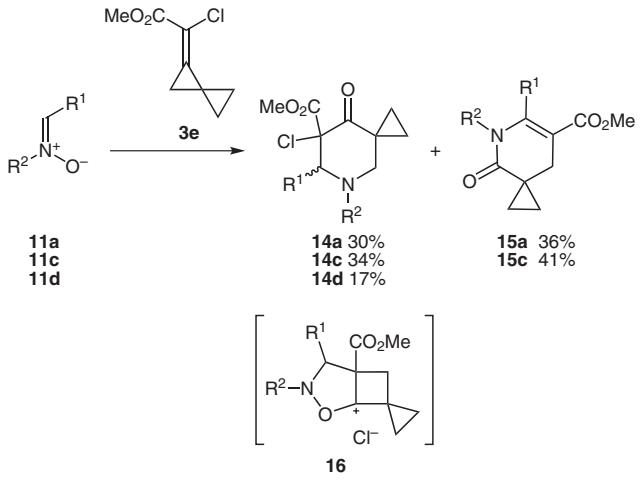


11a–d **12** **13a–d**

Entry	Nitrone	Reaction conditions	Yield (%)	Product
1	**11a** $R^1 = R^2 =$ Ph	r.t., 5 d	40	**13a**
2	**11a** $R^1 = R^2 =$ Ph	60 °C, 5 h	40	**13a**
3	**11b** R^1 = Ph, R^2 = 4-$MeOC_6H_4$	80 °C, 2 h	45	**13b**
4	**11c** R^1 = Fu, R^2 = Ph	80 °C, 12 h	38	**13c**
5	**11d** R^1 = Fu, R^2 = 4-$MeOC_6H_4$	80 °C, 5 h	40	**13d**

As the nitrone **11a** decomposes to a large extent, two equivalents had to be employed, and in spite of that, the product **13a** was obtained only in a moderate yield. An increase of the reaction temperature (60–80 °C, using $CHCl_3$ or 1,2-dichloroethane as solvent) reduced sensibly the reaction time to several hours, but did not improve the product yield. The intermediate isoxazolidine **12a** could be, tentatively, detected as a transient product in the reaction mixture by NMR, but could not be isolated. The product **13a** was easily identified on the basis of its ^{1}H NMR spectrum showing no high-field signals of the cyclopropane ring, but a singlet (δ = 5.94 ppm) for the R^1CHN proton. The ^{13}C NMR spectrum revealed the presence of a regular carbonyl (δ = 197.7 ppm), which is not a lactam group. The mass spectrum confirmed the presence of a chlorine atom in the structure. Neither the corresponding cyclobutane derivative of type **6** nor the lactam of type **10** were detected in the crude reaction mixture. The relative configuration of the formed diastereomer **13a** could only tentatively be assigned, lacking information of the structure of the isoxazolidine precursor, on the basis of previous results of the cycloaddition of an *N*-Me,*C*-Ph-nitrone to **3c**.[6b] Therefore, the undefined designation of the configuration is preferred at this level of the study.

The same reaction conditions were applied to the reactions of **3c** with other nitrones **11b–d** only varying the reaction time according to TLC monitoring. All the new compounds were isolated in comparable yields, and easily identified by their characteristic NMR spectra as evidenced for compound **13a**. In no case was it possible to isolate from the crude reaction mixture any product evolving by the ring-enlargement process of path B (Scheme 1) leading to lactams. *N*-*p*-Methoxyphenyl-substituted nitrones gave only slightly better yields in shorter reaction times, as would be expected for a lower activation energy required with this substituent in the cleavage of the N–O bond (about 3 kcal/mol less than the *N*-Ph derivatives).[4]



Scheme 2

The transformation was then extended to methyl (*Z*)-2-chlorospiropentylideneacetate (*Z*)-**3e**. Its reactions with nitrones **11a** and **11c** were carried out in 1,2-dichloroethane at 80 °C for 3.5 hours, and in this case gave the tetrahydropyridones **14a** and **14c**, respectively, as mixtures of diastereomers (designated as **14ax**,**ay** and **14cx**,**cy**),[11] along with the δ-lactams **15a** and **15c** in good overall yields (Scheme 2).[11] The structural assignment of compounds **14a**,**c** and **15a**,**c** was made on the basis of diagnostic ^{1}H NMR signals for each of them. For example, compounds **14a** showed an AB line pattern centered at δ = 3.65 and 3.20 ppm for diastereomers **14ax** and **14ay**, respectively,[11] for the methylene group near the nitrogen

atom, and showed a diagnostic isotopic pattern in the mass spectrum due to the presence of the chlorine atom. In contrast, compound **15a** showed the methylene signal at much higher field (δ = 1.2 ppm), and the mass spectrum confirmed the absence of a chlorine atom. The lactams **15a**,**c** must derive from the initial adducts of **11a**,**c** to **3e** via chlorocyclobutane-annelated intermediates of type **6**. This reaction mode can compete with the one leading to **14a**,**c** because the additional spirocyclopropane moiety brought in with **3e** may significantly stabilize (by up to about 15 kcal/mol)[12] the transient intimate ion pair intermediate **16** (Scheme 2) in the chloromethylcyclopropane to chlorocyclobutane ring-enlargement process.

The 4-MeOC$_6$H$_4$-substituted nitrone **11d** with **3e** gave exclusively the tetrahydropyridones **14d**, albeit in poor yield. Once more the result confirms the effect of electron-donating groups on the *N*-aryl substituent that reduces the activation energy for the N–O cleavage.[4]

In conclusion, it was demonstrated that the reaction mode of 3-methoxycarbonyl-3-chloro-5-spirocyclopropaneisoxazolidines, the products of 1,3-dipolar cycloadditions of nitrones to 2-chlorocyclopropylideneacetate, which undergo an efficient ring enlargment to δ-lactams, can be driven to an alternative rearrangement leading to tetrahydropyridones by switching the N-substituent of the nitrone from an alkyl to an aryl group. In this case a two-component domino process affords the tetrahydropyridones in which the isoxazolidines are only nonisolable intermediates.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are spectroscopic and analytical data of compounds **13b**,**c**,**d**, **14cx**,**cy**, and **15c**.

Acknowledgment

The authors thank the Ministry of University and Research (Rome) for partial financial support. I.O. acknowledges a Sokrates student exchange fellowship from the Georg-August-Universität Göttingen (Germany).

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(10) A solution of **3d** (37.0 mg, 0.252 mmol, 1 equiv) and **11a** (100 mg, 0.505 mmol, 2 equiv) in $CHCl_3$ (1 mL) was left at r.t. for 5 d. After concentration in vacuo, the crude material was purified by flash column chromatography (silica gel, eluent Et_2O–PE = 1:5) to afford compound **13a** (35 mg, 0.102 mmol, 40%) as a yellow oil (R_f = 0.13).
Methyl 3-Chloro-1-phenyl-4-oxo-2-phenyl-piperidine-3-carboxylate (13a)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.81–3.00 (m, 1 H, CH_2), 3.02–3.23 (m, 2 H, CH_2), 3.31–3.43 (m, 1 H, CH_2), 3.94 (s, 3 H, CO_2CH_3), 5.94 (s, 1 H, CH), 6.80–6.89 (m, 2 H, PhH), 6.92–7.05 (m, 4 H, PhH), 7.05–7.36 (m, 4 H, PhH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 39.9 (t), 41.5 (t), 54.0 (q, OCH_3), 72.1 (d, CHN), 73.1 (s, CCl), 119.0 (d, 2 C, Ph), 121.8 (d, Ph), 127.8 (d, 2 C, Ph), 128.0 (d, Ph), 128.4 (d, 2 C, Ph), 128.9 (d, 2 C, Ph), 131.3 (s, Ph), 149.0 (s, NPh), 167.4 (s, CO_2Me), 197.7 (s, C=O). Anal. Calcd for $C_{19}H_{18}ClNO_3$: N, 4.07; C, 66.38; H, 5.28. Found: N, 4.32; C, 66.20; H, 5.66.

(11) **Representative Procedure**
A solution of **3e** (44.0 mg, 0.254 mmol, 1 equiv) and **11a** (100 mg, 0.507 mmol, 2 equiv) in DCE (1 mL) was heated at 80 °C for 3.5 h. After concentration in vacuo, the crude material was purified by flash column chromatography (silica gel, eluent Et_2O–PE = 1:5) to afford **14a** (28 mg, 0.076 mmol, 30%) as a brown oil (R_f = 0.29) and **15a** (30 mg, 0.090 mmol, 36%) brown oil (R_f = 0.18).
Methyl 7-Chloro-6-phenyl-8-oxo-5-phenyl-5-azaspiro[2.5]octane-7-carboxylate (14a): mixture of two diastereomers.
Diastereomer **14ax**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.95 (m, 1 H, *c*-PrH), 1.15–1.22 (m, 1 H, *c*-PrH), 1.70–1.73 (m, 2 H, *c*-PrH), 3.40 (d, ^2J = 12.0 Hz, 1 H, CH_2), 3.50 (s, 3 H, OCH_3), 3.89 (d, ^2J = 12.0 Hz, 1 H, CH_2), 5.40 (s, 1 H, CH), 6.76–7.43 (m, 10 H, Ph).
Diastereomer **14ay**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.95 (m, 1 H, *c*-PrH), 1.15–1.22 (m, 1 H, *c*-PrH), 1.47–1.51 (m, 1 H, *c*-PrH), 1.90–1.95 (m, 1 H, *c*-PrH), 3.10 (dd, ^2J = 12.0 Hz, ^4J = 0.8 Hz, 1 H, CH_2), 3.33 (dd, ^2J = 12.0 Hz, ^4J = 0.8 Hz, 1 H, CH_2), 3.88 (s, 3 H, OCH_3), 5.91 (d, J = 0.8 Hz, 1 H, CH), 7.60–7.43 (m, 10 H, PhH).
Diastereomers **14ax**,**ay**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8, 20.7, 22.1, 24.9, 26.9, 28.5, 49.9, 51.0, 52.9, 53.8, 71.5, 72.8, 115.1, 116.7, 119.4, 120.6, 122.4, 124.7, 127.7, 127.9, 128.1, 128.2, 128.3, 128.8, 128.9, 129.2, 132.5, 136.2, 148.7, 162.9, 167.2, 198.4. Anal. Calcd for $C_{21}H_{20}ClNO_3$: N, 3.79; C, 68.20; H, 5.45. Found: N, 4.20; C, 68.13; H, 5.77.

Methyl 6-Phenyl-4-oxo-5-phenyl-5-azaspiro[2.5]oct-6-ene-7-carboxylate (15a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.42–0.59 (m, 2 H, CH_2), 0.93–1.09 (m, 2 H, CH_2), 1.21–1.30 (m, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 7.08–7.50 (m, 10 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1 (t), 20.8 (t, 2 C, *c*-Pr), 21.4 (s, *c*-Pr), 52.7 (q, OCH_3), 76.9 (s, *C*CO_2Me), 126.5 (d, Ph), 127.2 (d, Ph), 127.7 (d, Ph), 128.5 (d, Ph), 129.2 (d, Ph), 129.5 (d, Ph), 134.7 (s, Ph), 140.9 (s, NPh), 146.4 (s, CPh), 163.2 (s, CO_2Me), 175.7 (s, C=O). Anal. Calcd for $C_{21}H_{19}NO_3$: N, 4.20; C, 75.66; H, 5.74. Found: N, 4.38; C, 75.26; H, 6.01.

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