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Synthesis and Cycloaddition Reactions of *N*-Methylcyclobutylideneamine *N*-Oxide

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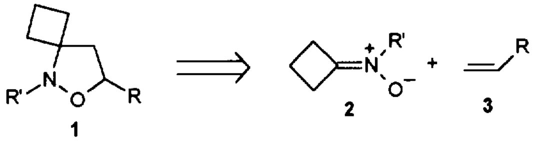
Abstract: Reaction of cyclobutanone with methylhydroxylamine gives *N*-methylcyclobutylideneamine *N*-oxide (**2**), which spontaneously dimerizes. Cycloadditions of the *in situ* generated 4-membered exocyclic nitrone **2** with reactive dipolarophiles afford the corresponding cycloadducts.

During the last two decades the nitrone cycloaddition to alkenes has emerged as one of the most versatile methods for the construction of complex nitrogen heterocycles by manipulation of the primary saturated isoxazole cycloadducts.[1,2] In this context, our research group has developed an original protocol for the synthesis of 4-pyridones and 4-azepinones based on the thermal rearrangement of isoxazole derivatives possessing strained small size rings in the 5-position.[3] These cycloadducts are in turn easily available by cycloaddition of nitrones to methylenecyclopropanes[4] or -butanes.[5]

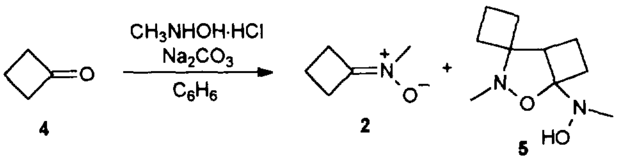
For a further extension of these studies, we were interested in obtaining strained 3-spiroannulated isoxazolidines such as 3-spirocyclobutane isoxazolidines **1**. These compounds might be accessed most obviously by 1,3-dipolar cycloaddition of cyclobutanone-derived nitrones **2**, according to Scheme 1. However, only rare examples of four membered exocyclic nitrones have been reported in the literature,[6-8] mostly obtained by oxidation of the corresponding imines,[7] or serendipitously,[8] and always being heavily substituted at the four membered ring. Moreover, no cycloaddition reaction of a cyclobutylideneamine *N*-oxide have been reported so far, to the best of our knowledge. In this paper we report on the synthesis and the chemical behaviour of the ring-unsubstituted *N*-methylcyclobutylideneamine *N*-oxide (**2**, R' = Me), including the first examples of cycloaddition reactions of four membered exocyclic nitrones.



Scheme 1

Simple exocyclic nitrones, such as those derived from cyclopentanone, cyclohexanone and cycloheptanone, have been obtained by condensation of the parent ketones with *N*-methylhydroxylamine since long time.[9] They have been reported to be very hygroscopic and quite unstable, easily undergoing hydrolysis to the corresponding ketones.[9,10] However, they have been employed in 1,3-dipolar cycloadditions only relatively recently.[10-12] In these isolated examples, five- to seven-membered exocyclic nitrones have shown a moderate reactivity, especially in intermolecular cycloadditions,[10,11] while slightly more satisfying results have been achieved in the intramolecular version.[12]

Several attempts were made aimed to the synthesis of nitrone **2** (R' = Me) by reaction of cyclobutanone (**4**) with methylhydroxylamine hydrochloride in the presence of a base. The use of sodium carbonate in benzene was satisfying, but the reaction gave always two products in different proportions depending on the temperature and reaction time (Scheme 2).



	2	2 : 5	5
r.t., 5 h	37%	>50 : 1	
r.t., 24 h		2.5 : 1	
r.t., 72 h		1.2 : 1	
80 °C, 6 h		1 : 10	78%

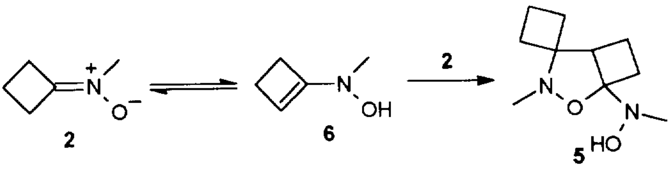
Scheme 2

The two products were assigned as the desired nitrone **2** and its dimer **5** on the basis of their spectral data. The nitrone **2** gave a singlet at 149.4 ppm for the C=N carbon atom in the ^{13}C NMR spectrum and a peak at 1663 cm^{-1} in the IR spectrum, consistent with an absorption due to the C=N double bond in a four-membered exocyclic nitrone. Moreover, the ^1H NMR spectrum of **2** displayed the signal for N-Me at 3.31 ppm as a quintet, due to homoallylic coupling constants (J = 1.6 Hz) with the methylene groups α to nitrogen, as already reported for other ketonitrones.[13]

The nitrone **2** and the dimer **5** could be isolated in 37% and 78% yield, respectively, by flash column chromatography of the crude reaction mixtures prepared under different conditions (Scheme 2). Indeed, after 5 h at room temperature, the nitrone **2** was the only product revealed by a ^1H NMR spectrum of the mixture, while the dimer was predominant by refluxing the reaction mixture. The isolated nitrone **2** showed a high tendency to dimerize to **5**, which also formed during the chromatographic separation.

The formation of structurally related dimers has been observed for other *C*-alkyl nitrones and has been ascribed to the presence of a tautomeric equilibrium between nitrone and ene-hydroxylamine forms.[1,2] The dimer **5** then presumably arises from 1,3-dipolar cycloaddition of the nitrone **2** to the activated double bond of its tautomer **6** (Scheme 3).

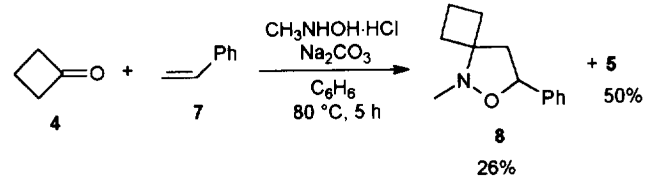
The structural assignment as **5** to the product was based on the proton signal on C4 of the isoxazolidine ring which resonates at 3.14 ppm (dd) in the NMR spectrum, and on the carbon signal of C5 resonating at 98.1 ppm, according with an aminal carbon atom. The regiochemical outcome of the reaction is the one expected on the basis of the known directing effect of electron-donor substituents in the alkene for nitrone cycloadditions.[1,2]



Scheme 3

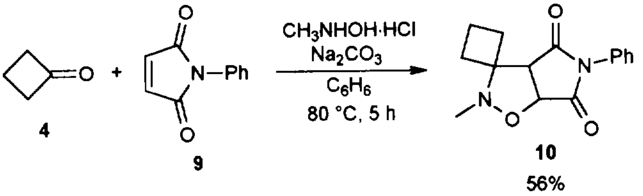
The nitrone **2** exhibited a distinct behaviour with respect to its higher homologues. Indeed, it appeared stable enough towards hydrolysis,[9] allowing its purification from silica gel. On the other hand, its thermal instability has no precedent among exocyclic nitrones,[9-12] for which dimers analogous to **5** have never been reported. This peculiarity is even more surprising in consideration of the unfavorable equilibrium for the formation of the highly strained tautomer **6** with the endo double bond. However, the related tautomeric equilibrium presumably exists also for the higher homologous exocyclic nitrones, since these undergo an α-hydroxylation reaction;[14] this is believed to occur via the tautomeric enehydroxylamine.

The behaviour of nitrone **2** towards dipolarophiles is related to its competing dimerization. An attempt to make preformed **2** react with styrene (**7**) predominantly led to formation of the dimer. It has been found advantageous to carry out the reaction of styrene (**7**) with **2** generated *in situ* in refluxing benzene. Under these conditions, a 1:1 mixture of the expected cycloadduct **8** and the dimer **5** was obtained (Scheme 4).



Scheme 4

Modified procedures did not succeed to give higher yields of **8**; even slow addition of cyclobutanone by a syringe pump to the mixture of the other reagents afforded essentially the same ratio of products. In order to prevent dimerization, **5** was heated at reflux in xylene in the presence of an excess of styrene, since reversibility in the formation of dimers of type **5** has been observed.[2,15] However, the dimer was recovered quantitatively, showing that cycloreversion is not operative in this case, at least not at temperatures below 135 °C.



Scheme 5

Less reactive dipolarophiles failed to give any cycloaddition product, as did more sterically demanding and electron-donor substituted ones, such as norbornene and dihydropyran. In these cases, the competitive dimerization prevailed and only **5** was obtained. On the contrary, the use of a more reactive, electron-withdrawing substituted dipolarophile, i.e. *N*-phenylmaleimide (**9**), prevented dimer formation and the cycloadduct **10** was produced in good yield, comparable with those obtained in cycloadditions of 5- and 6-membered exocyclic nitrones (Scheme 5).[10,11]

In conclusion, the synthesis of *N*-methylcyclobutylideneamine *N*-oxide and its unexpected dimerization have been reported. Cycloaddition of reactive dipolarophiles, able to compete favorably with dimerization, has been proven viable.

EXPERIMENTAL

All reagents are commercially available and were purchased from Aldrich, Fluka, or Acros and used without further purification. R_f values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}) by eluting with the same eluent used for the chromatographic separation of the compound. Melting points were measured with a Büchi 510 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 spectrometer (^1H, 200 MHz; ^{13}C, 50 MHz); notations s, d, t, q, quint, m, and br indicate singlet, doublet, triplet, quartet, quintet, multiplet, and broad, respectively. IR spectra were recorded with a Perkin-Elmer 881 spectrophotometer. Mass spectra (MS) were recorded on a QMD 1000 Carlo Erba instrument by GC inlet (EI, 70 eV). Microanalyses were measured with a Perkin-Elmer 240 C instrument.

N-Methylcyclobutylideneamine N-Oxide (2).

Cyclobutanone (**4**, 300 µL, 280 mg, 4.0 mmol), *N*-methylhydroxylamine hydrochloride (250 mg, 2.9 mmol) and anhydrous Na_2CO_3 (1.0 g, 9.4 mmol) reacted in dry benzene (10 mL) at r.t. under magnetic stirring for 5 h. The reaction mixture was filtered over Celite, concentrated, and purified by flash column chromatography. After elution of the dimer **5** with CH_2Cl_2/CH_3OH 25:1, the nitrone **2** (108 mg, 1.09 mmol, 37%) was collected as a colorless liquid on eluting with CH_3OH.

^1H NMR: δ 3.31 (quint, J = 1.6 Hz, 3 H), 2.97-2.80 (m, 4 H), 1.88 (quint, J = 7.7 Hz, 2 H); ^{13}C NMR: δ 149.4 (s), 44.7 (q), 31.2 (t), 29.8 (t), 12.4 (t); IR ($CDCl_3$): 2970, 1663, 1300, 1151 cm^{-1}.

Spiro[cyclobutane-1,4'-1-N-hydroxymethylamino-3-methyl-2-oxa-3-azabicyclo[3.2.0]heptane] (5).

Cyclobutanone (**4**, 75 µL, 70 mg, 1.0 mmol), *N*-methylhydroxylamine hydrochloride (100 mg, 1.2 mmol) and anhydrous Na_2CO_3 (530 mg, 5 mmol) were heated to reflux in dry benzene (3 mL) with magnetic stirring for 6 h. Filtration over Celite and removal of the solvent under reduced pressure afforded a 10:1 mixture of dimer **5** and nitrone **2**. Flash column chromatography, eluent CH_2Cl_2/CH_3OH 25:1, gave the pure dimer **5** (R_f = 0.23, 77 mg, 0.39 mmol, 78%) as a colorless liquid.

^{1}H NMR: δ 5.33 (br s, 1 H), 3.14 (dd, *J* = 9.2, 5.3 Hz, 1 H), 2.71 (s, 3 H), 2.60 (s, 3 H), 2.39-2.08 (m, 3 H), 2.02-1.74 (m, 3 H), 1.68-1.50 (m, 4 H); ^{13}C NMR: δ 98.1 (s), 68.2 (s), 53.9 (d), 39.4 (q), 37.3 (q), 29.6 (t), 25.9 (t, 2 C), 13.7 (t), 13.1 (t); IR ($CDCl_3$): 3579, 3444, 3230, 2989, 2965, 2889, 1464, 1442, 1362, 1319, 1301, 1272, 1250, 1220, 1137, 1113 cm^{-1}; MS: *m/z* 198 (M$^+$, 10%), 181 (39), 170 (24), 153 (100), 152 (34), 124 (46), 110 (47), 108 (39), 100 (53), 96 (35), 82 (50), 68 (64), 56 (60), 55 (99), 42 (86), 41 (63), 39 (56). Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.37; H, 9.23; N, 14.05.

Spiro[cyclobutane-1,3'-2-methyl-5-phenyltetrahydroisoxazole] ***(8)***.

Cyclobutanone (**4**, 75 µL, 70 mg, 1.0 mmol) and styrene (**7**, 208 mg, 2.0 mmol) were added to a suspension of *N*-methylhydroxylamine hydrochloride (100 mg, 1.2 mmol) and anhydrous Na_2CO_3 (530 mg, 5 mmol) in dry benzene (3 mL). The mixture was heated to reflux with magnetic stirring for 5 h, then filtered over Celite and concentrated. Flash chromatography of the crude material, eluent CH_2Cl_2/CH_3OH 25:1, gave the dimer **5** (R_f = 0.22, 50 mg, 0.25 mmol, 50%) and the cycloadduct **8** (R_f = 0.38, 52 mg, 0.26 mmol, 26%), as a colorless liquid.

^{1}H NMR: δ 7.40-7.20 (m, 5 H), 5.10 (t, *J* = 7.4 Hz, 1 H), 2.77 (dd, *J* = 12.3, 7.9 Hz, 1 H), 2.65 (s, 3 H), 2.36 (dd, *J* = 12.2, 7.6 Hz, 1 H), 2.37-2.23 (m, 2 H), 2.03-1.90 (m, 2 H), 1.81-1.71 (m, 2 H); ^{13}C NMR: δ 141.7 (s), 128.2 (d, 2 C), 127.3 (d), 126.0 (d, 2 C), 78.1 (d), 68.5 (s), 47.7 (t), 39.2 (q), 31.3 (br t, 2 C), 13.9 (t); IR ($CDCl_3$): 3067, 3031, 2988, 2884, 1712, 1604, 1492, 1449, 1365, 1279 cm^{-1}; MS: *m/z* 203 (M$^+$, 15%), 202 (12), 175 (100), 174 (91), 158 (46), 129 (69), 128 (37), 117 (54), 98 (38), 77 (29). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.47; H, 8.66; N, 7.00.

Spiro[cyclobutane-1,3'-2-methyl-5-phenylhexahydropyrrolo[3,4-d]isoxazol-4,6-dione] ***(10)***.

Cyclobutanone (**4**, 150 µL, 140 mg, 2.0 mmol) was added to a suspension of *N*-phenylmaleimide (**9**, 346 mg, 2.0 mmol), *N*-methylhydroxylamine hydrochloride (200 mg, 2.4 mmol) and anhydrous Na_2CO_3 (1 g, 9.4 mmol) in dry benzene (7 mL). The mixture was heated to reflux with magnetic stirring for 5 h, then filtered over Celite, and concentrated. Flash chromatography of the crude material, eluent CH_2Cl_2, gave the cycloadduct **10** (R_f = 0.15, 305 mg, 1.12 mmol, 56%) as a colorless solid. Mp 153-154 °C (CCl_4/CH_2Cl_2).

^{1}H NMR: δ 7.51-7.28 (m, 5 H), 4.82 (d, *J* = 7.4 Hz, 1 H), 3.58 (d, *J* = 7.4 Hz, 1 H), 2.75 (s, 3 H), 2.75 (m, 1 H), 2.55 (m, 1 H), 2.04-1.83 (m, 4 H); ^{13}C NMR: δ 174.3 (s), 173.6 (s), 131.4 (s), 129.1 (d, 2 C), 128.7 (d), 126.3 (d, 2 C), 74.7 (d), 70.6 (s), 56.6 (d), 36.6 (br q), 26.8 (br t), 25.9 (t), 13.6 (t); IR ($CHCl_3$): 3007, 1719, 1379, 1180 cm^{-1}; MS: *m/z* = 272 (M$^+$, 0.7%), 245 (13), 244 (100), 173 (10), 119 (15), 97 (27), 91 (11), 82 (16), 77 (11), 71 (10), 68 (18), 57 (16), 55 (37), 54 (23). Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.89; H, 6.16; N, 10.37.

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