Cyclobutylidenecyclopropane: New Synthesis and Use in 1,3-Dipolar Cycloadditions − A Direct Route to Spirocyclopropane-Annulated Azepinone Derivatives[‡]

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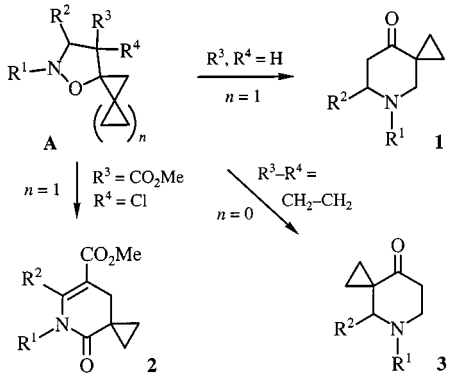
Cyclobutylidenecyclopropane (**7**) was prepared in multigram quantities by a new three-step sequence starting from ethyl cyclobutanecarboxylate (**4**) (39% overall yield). 1,3-Dipolar cycloadditions of phenyl- (**9**), pyridyl- (**10**), and the newly prepared (four steps, 43% overall yield) spirocyclic nitrone **11** onto **7** resulted in the regioselective formation of the corresponding adducts **15**–**17**, with the spirobutane moieties adjacent to the oxygen atom in the oxazolidine rings, in 52, 84, and 48% yields, respectively. Under flash vacuum pyrolysis conditions, the cycloadducts **15**–**17** underwent thermal rearrangement with opening of the four-membered ring, to afford the spirocyclopropanated azepinones **21**–**23** in 32, 30, and 19% yields, respectively. In the case of **17**, the indolizidinone **25** was also isolated (13% yield). Mechanistically this rearrangement is interpreted in terms of a cyclobutylmethyl-to-penten-5-yl radical rearrangement.

Introduction

Highly strained alkenes, such as those containing an exocyclic double bond on a small ring, have attracted the attention of researchers because of their peculiar structural features and reactivities.[1,2] The high strain energies that characterize these molecules confer high reactivities towards many cyclophiles in various addition reactions.[3] In recent years we have shown how highly strained methylenecyclopropanes readily undergo 1,3-dipolar cycloadditions with nitrones, affording spirocyclopropane-isoxazolidines **A** (Scheme 1).[4] The presence of residual strain in such compounds, together with the weak N−O bond adjacent to one of the spirocyclopropane rings, makes further elaboration of these substrates possible by simple thermal treatment, to yield spirocyclopropane-annulated pyridones as the main products.[4] The same overall result can also be achieved more conveniently by performing the 1,3-dipolar cycloaddition at a higher temperature directly.



Scheme 1. Thermal transformations of spirocyclopropane-isoxazolidines **A**

Some of these compounds alkylate DNA,[5] in a manner reminiscent of the activity of natural sesquiterpenes of the illudin[6] and ptaquiloside[7] families. Recently, some of these pyridones have been transformed into octahydro-2-pyrindine derivatives through sequential Wittig−Horner−Emmons olefination and vinylcyclopropane-to-cyclopentene rearrangement.[8] Here we present an extension of the basic methodology to the synthesis of spirocyclopropane-annulated azepinones, based on the cycloaddition of nitrones to cyclobutylidenecyclopropane (**7**), prepared according to a new procedure more convenient than those reported previously.

Results and Discussion

The most practical previous synthesis of cyclobutylidenecyclopropane (**7**) on a preparative scale was by Wittig

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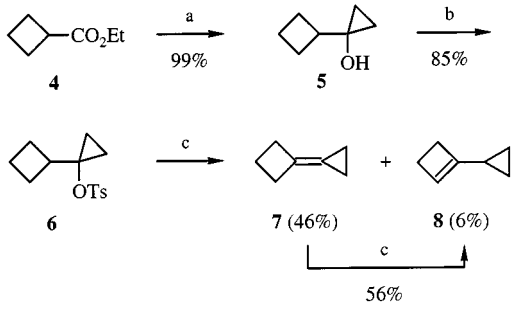
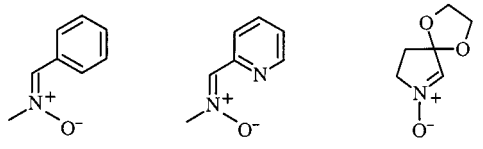
olefination of cyclobutanone with the ylide generated from cyclopropyltriphenylphosphonium bromide.[9] This route, although affording **7** in good yield, suffered from the necessity of using starting materials that were either not readily available or expensive.[10] A new, alternative synthesis of **7** starts from commercially available ethyl cyclobutanecarboxylate (**4**), adopting a strategy previously developed for the synthesis of bicyclopropylidene (Scheme 2).[11]



4 5 6

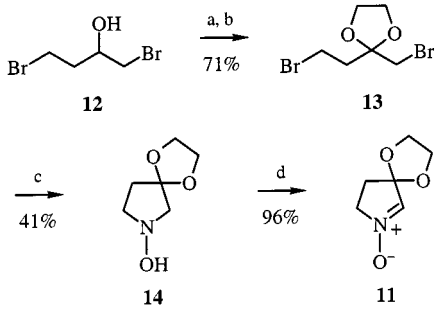
Scheme 2. Preparation of cyclobutylidenecyclopropane: a) EtMgBr, Ti(*i*PrO)$_4$, Et$_2$O, 20 °C, 3 h; b) TsCl, Py, 0−5 °C, 7 d; c) *t*BuOK, DMSO, 20 °C, 2 d

On application of Kulinkovich reaction conditions,[12] the ester **4** was transformed almost quantitatively into 1-cyclobutylcyclopropanol (**5**).[13] The alcohol **5** was converted into its tosylate **6**, which was dehydrotosylated with potassium *tert*-butoxide in DMSO. After 2 d at ambient temperature, a mixture of the methylenecyclopropane **7** and the isomeric 1-cyclopropylcyclobutene (**8**), in a ratio of 8:1, was isolated in 52% yield. Prolonged (2 d) stirring of this mixture of **7** and **8** under these conditions resulted in complete isomerization, and 1-cyclopropylcyclobutene (**8**) was obtained as a single product in 56% yield, or 30% yield from **6**. Cyclobutylidenecyclopropane (**7**) prepared by this route may, however, be used for many synthetic purposes without separation from **8**,[14] and this new method is thus significantly more convenient than those reported previously (cf. ref.[9]).



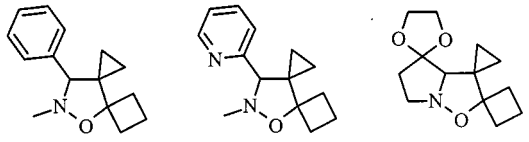
9 10 11

1,3-Dipolar cycloadditions onto **7** were performed with the three model nitrones **9**, **10**, and **11**. Nitrones **9** and **10**[15] were chosen as simple, open-chain nitrones, with **10** affording a higher hydrophilicity in the final product. Nitrone **11**, not known in the literature, was prepared in four steps from commercially available 1,4-dibromobutan-2-ol (**12**) (Scheme 3). Oxidation of **12** and protection of the ketone as an ethylene acetal **13**, followed by cyclizing nucleophilic substitution[16] to yield *N*-hydroxypyrrolidine **14** and subsequent oxidation with mercuric oxide afforded the nitrone **11** in 28% overall yield. The presence of the dioxolane group apparently induces the oxidation to proceed regioselectively, to afford a single regioisomer.[17]



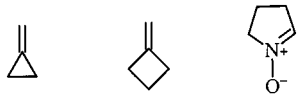
12 13 14 11

Scheme 3. Preparation of the nitrone **11**: a) CrO_3, H_2SO_4, 20 °C, 12 h; b) $(CH_2OH)_2$, Me_3SiCl, 20 °C, 24 h; c) $NH_2OH{\cdot}HCl$, Et_3N, 80 °C, 4 h; d) HgO, CH_2Cl_2, 20 °C, 4 h



15 (47%) **16** (85%) **17** (48%)

The reactions between cyclobutylidenecyclopropane (**7**) and nitrones **9**−**11** provided the isoxazolidines **15**−**17** in moderate to good yields (48−84%). All three reactions proceeded with a high degree of regioselectivity, each affording the corresponding 5-spirocyclobutaneisoxazolidine as a single product. Structure assignment was possible on the basis of the ^{13}C NMR spectra, because all compounds showed a signal typical of the isoxazolidine quaternary carbon atom adjacent to the oxygen atom at δ = 84−85. This signal was assigned to the carbon atom in the cyclobutane ring, because it appeared at least 15 ppm downfield from the analogous carbon signal of a spirocyclopropane group in a corresponding product from bicyclopropylidene.[18] This high regioselectivity is in accordance with results previously observed in 1,3-dipolar cycloadditions to methylenecyclopropane (**18**)[18] and methylenecyclobutane (**19**).[19] While methylenecyclopropane (**18**) yields mixtures of 4- and 5-substituted isoxazolidines, methylenecyclobutane (**19**) exclusively affords 5-spirocyclobutane-isoxazolidines.[19]



18 19 20

To explain observed regioselectivity in a 1,3-dipolar cycloaddition, it is usual to consider the HOMO−LUMO interactions of the dipole and the dipolarophile and the magnitudes of the atomic coefficients at the terminal positions of the reagents.[20] The HOMO and LUMO energies and atomic orbital coefficients for compounds **7**, **18**, **19**, and pyrroline *N*-oxide (**20**) as a model nitrone were calculated by ab initio (up to the STO 6-311G level) and DFT methods (LSDA/VWN/DN level[21]), using the SPARTAN program package.[22] According to these data, however, the

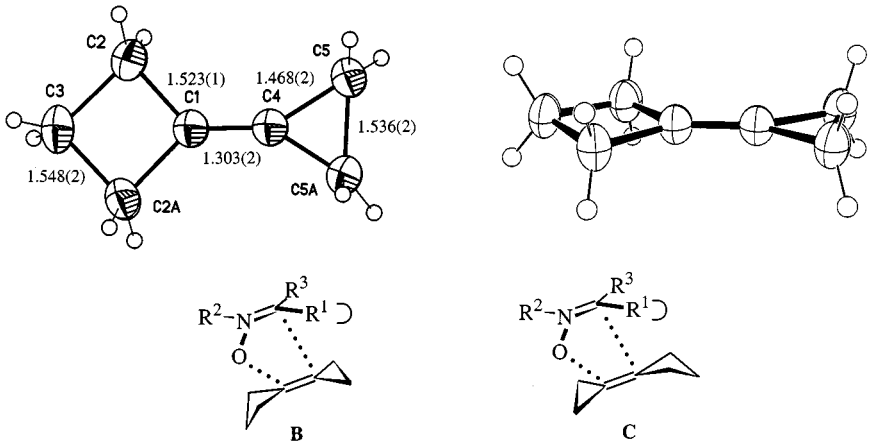
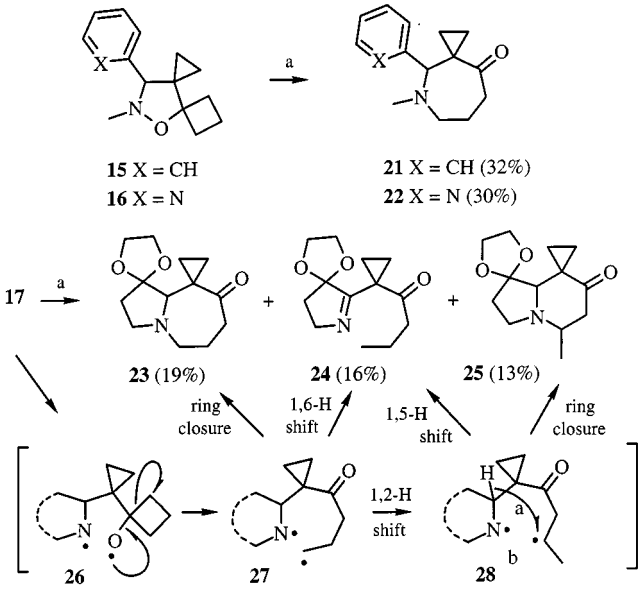


Figure 1. Structure of cyclobutylidenecyclopropane (**7**) in the crystal[23] (the bond lengths and standard deviations are given in Å) and two possible transition structures for the 1,3-dipolar cycloaddition of a nitrone to **7**

observed regioselectivities cannot be justified by more favorable frontier orbital interactions, as demonstrated by the calculated values of ΔE between the frontier orbitals of the alkenes **18**, **19** and the nitrone **20**. Moreover, the polarization of atomic orbitals in the HOMOs and LUMOs of alkenes **7**, **18**, and **19**, although indicating the correct regioselectivity, appears too small to be significant.

The experimentally observed results might be attributable to the greater steric bulk of the planar or slightly puckered cyclobutyl, relative to the cyclopropyl group with its smaller bond angle, which might favor an approach of **7** with its cyclobutyl group towards the sterically less congested oxygen end of the nitrone, as in transition structure **B** in Figure 1. To test this interpretation, the structure of **7** was determined by an X-ray crystal structure analysis (Figure 1).[23] The cyclobutane ring did indeed turn out to be only very slightly puckered, with dihedral angles between the planes defined by C1, C2, C3 and C1, C2A, C3 and between the planes defined by C2, C1, C2A and C2, C3, C2A of 5.3 and 5.4°, respectively. The four carbon atoms C2, C2A, C5, and C5A and C1, C4 of the double bond are almost completely coplanar (the interplanar angle between C2, C1, C2A and C5, C4, C5A is only 2.6°). Nevertheless, the difference in energies between the two different transition states **B** and **C** (Figure 1), but with a planar four-membered ring, related to the two possible regioisomeric products, was computed (at the STO 3G level of theory) as ΔE_a = 1.8 kcal·mol^{-1}. Assuming that the preexponential factors in the Arrhenius equations for both cycloaddition directions are identical, a ΔE_a of 1.8 kcal·mol^{-1} would correspond to rate coefficients ratio of $k_B/k_C \approx 11.4$ at 100 °C (373.15 K).

Thermal rearrangements of the isoxazolidines **15**−**17** could only be effected under conditions much harsher than those used for the corresponding spirocyclopropane-annulated analogs.[18] Upon flash vacuum thermolysis of **15**−**17** at 600 °C and 10^{-3} mbar, the azepinones **21**−**23**[19] were obtained, but accompanied by considerable amounts of decomposition products (Scheme 4).



Scheme 4. Thermal rearrangements of isoxazolidines **15**−**17** and mechanistic interpretation: a) FVT, 600 °C, 10^{-3} mbar

Analysis of the crude reaction mixtures revealed only the expected azepinones **21** and **22** for substances **15** and **16**. The rearrangement process, analogously to that proposed for the cyclopropane-annulated substituted isoxazolidines,[18] starts with the homolytic cleavage of the N−O bond and is followed by the opening of the adjacent small ring in the intermediate diradical **26** to give **27**, which eventually closes to form the seven-membered ring (Scheme 4). Whereas the thermal rearrangement of simple 5-spirocyclobutane-isoxazolidines also resulted in the formation of open-chain products,[18] due to the concomitant shift of one hydrogen atom in the intermediate diradical, the crude reaction mixtures from **15** and **16** did not contain any products of low molecular mass other than **21** and **22**, respectively. This may be attributed to the presence of the spirocyclopro-

pane group, which reduces the rotational freedom of the 1,7-diradical carbon skeleton in **27**, favoring ring-closure, as also observed in previous examples.[4]

However, the crude pyrolysate obtained from compound **17** contained not only the expected azepinone derivative **23** (19%), but also a noncyclized product (16%) identified as the pyrroline derivative **24**, together with the indolizidinone **25** (13%). The indolizidinone **25** was identified from its ^{1}H NMR spectrum, which showed a doublet at δ = 1.21 for the methyl group, and its ^{13}C NMR spectrum, with all signals in agreement with the proposed structure. The formation of these two side products can be explained by assuming an isomerization of the diradical **27** to **28** by means of a 1,2-H shift and a subsequent 1,5-H shift to give **24**, or ring-closure to **25**. Alternatively, **24** might be formed directly from **27** through a 1,6-H shift (Scheme 4). The difference between the reaction mode of compound **17** and that of compounds **15** and **16** must be associated with the presence of the additional rings in the skeleton. These may hamper the closure of the seven-membered ring even more than usual, due to additional geometric restraints in the diradical intermediate. Isomerization processes can therefore compete with the cyclization of the original diradical **27**. This type of radical isomerization of **27**, producing **25**, is unprecedented in the thermal rearrangements of spiroisoxazolidines.[24]

Conclusion

The novel cycloaddition-rearrangement process with cyclobutylidenecyclopropane (**7**) constitutes a straightforward approach, albeit with modest overall yields, to highly substituted azepinones characterized by an α-oxospirocyclopropane moiety. Since this reactive unit has been found to be important for biological activity,[5] or as a starting point for further synthetic elaboration,[8] the overall strategy can now be extended to the introduction of seven-membered rings into more complex heterocyclic structures.

Experimental Section

General Remarks: All operations were carried out under an inert gas. − ^{1}H and ^{13}C NMR spectra were recorded at 200 or 250 MHz (^{1}H) and 50.3 or 62.9 MHz [^{13}C, additional DEPT (Distortionless Enhancement by Polarization Transfer)] with Varian Gemini or Bruker AM 250 spectrometers, respectively, in $CDCl_3$ solution unless otherwise stated; δ in ppm, TMS as internal reference. − IR: Perkin−Elmer 881 spectrophotometer, measured as KBr pellets or as oils between KBr plates. − Mass spectra (EI): QMD 1000 Carlo Erba instrument, by GC or direct inlet (70 eV); (CI): Finnigan MAT 95 spectrometer (70 eV). − Elemental analyses: Perkin−Elmer 240 C or Perkin−Elmer 2400 instruments. − R_f values refer to TLC on 0.25 mm precoated silica gel plates (Merck F_{254}) with the same eluent as used for the separation of the compound by flash column chromatography. − Melting points (m.p.): Büchi 510 capillary melting point apparatus, values uncorrected. − Anhydrous diethyl ether and toluene were obtained by distillation from sodium benzophenone ketyl, pyridine and DMSO from CaH_2. All other chemicals were used as commercially available (Merck, Acrõs, BASF, Bayer, Hoechst, Degussa AG, and Hüls AG). Organic extracts were dried with $MgSO_4$.

1-Cyclobutylcyclopropanol (5): Ethylmagnesium bromide (0.980 mol, 276 mL of a 3.55 M solution in Et_2O) was added over a period of 3 h to a well-stirred solution of ethyl cyclobutanecarboxylate (**4**)[10c] (56.47 g, 0.441 mol) and titanium tetraisopropoxide (26.3 mL, 88.2 mmol, 20 mol %) in anhydrous diethyl ether (200 mL). The temperature was maintained between 20 and 25 °C with a water bath. After the addition was complete, the mixture was stirred for an additional 0.5 h at the same temp. and then cooled to −5 °C. The reaction was quenched by careful addition of ice-cold 10% aqueous sulfuric acid (500 mL) while the temperature was maintained between −5 and 0 °C with an acetone/dry ice bath. The mixture was stirred at 0 °C for an additional 1 h, and the inorganic phase was extracted with Et_2O (100 mL). The combined ethereal phases were washed with saturated $NaHCO_3$ (2 × 200 mL) and brine (200 mL), dried, and concentrated under water-aspirator vacuum at 20 °C to give 48.92 g (99%) of 1-cyclobutylcyclopropanol. Its spectroscopic data are identical to those reported.[12]

1-Cyclobutyl-1-(*p*-tolylsulfonyloxy)cyclopropane (6): *p*-Toluenesulfonyl chloride (87.32 g, 0.458 mol) was added in portions at 0 °C to a solution of the alcohol **5** (48.92 g, 0.436 mol) in anhydrous pyridine (500 mL). The resulting mixture was kept at 5 °C for 7 d, diluted with ice-cold water (1000 mL), and extracted with dichloromethane (3 × 300 mL). The combined organic phases were washed with 5% HCl solution (400 mL), saturated $NaHCO_3$ (2 × 200 mL), and brine (200 mL), dried, and concentrated under reduced pressure to give **6** (98.94 g, 85%) as a light brown solid, which was used without further purification. An analytical sample was purified by column chromatography on silica gel (eluent hexane/Et_2O, 4:1) and then recrystallized from Et_2O, m.p. 46−47 °C, R_f = 0.38. − ^{1}H NMR: δ = 0.74 and 1.04 (m, 4 H, CH_2, cy-Pr), 1.49−1.96 (m, 6 H, CH_2, cy-Bu), 2.43 (s, 3 H, CH_3), 3.08−3.22 (m, 1 H, CH, cy-Bu), 7.30 (d, J = 8.2 Hz, 2 H, C_6H_4), 7.74 (d, J = 8.2 Hz, 2 H, C_6H_4). − ^{13}C NMR: δ = 8.43 (2 CH_2), 17.30 (CH_2), 21.57 (CH_3), 24.93 (2 CH_2), 37.87 (CH), 69.89 (C), 127.31, 129.59 (2 CH), 135.70, 144.29 (C). − MS (EI): *m/z* (%) = 266 (0.1) [M^+], 155 (50) [$C_7H_7O_2S^+$], 139 (14) [$C_7H_7OS^+$], 91 (78) [$C_7H_7^+$], 83 (100) [$C_5H_7O^+$], 65 (17) [$C_5H_5^+$], 55 (94) [$C_5H_7O^+$ − CO]. − $C_{14}H_{18}O_3S$ (266.40): calcd. C 63.13, H 6.81; found C 63.18, H 6.87.

Cyclobutylidenecyclopropane (7) and 1-Cyclopropylcyclobutene (8): The tosylate **6** (88.43 g, 0.332 mol) was added in portions to a solution of potassium *tert*-butoxide (44.66 g, 0.398 mol) in DMSO (0.5 L). The temperature was maintained between 20 and 25 °C with an ice bath, and the resulting solution was then stirred for 24 h under nitrogen in the closed apparatus at ambient temp. After this, all the volatile material was "bulb-to-bulb" distilled into a cold trap under reduced pressure (0.1 Torr), at ambient flask temp. The residue was stirred under the same conditions for an additional 24 h, and the "bulb-to-bulb" distillation procedure was repeated. The combined contents of the cold trap were washed with ice-cold water, saturated NH_4Cl solution, and brine (100 mL each), dried, and distilled directly from $MgSO_4$ under reduced pressure to give a mixture of **7** and **8** (16.15 g, 52%) in a ratio of 8:1, according to the ^{1}H NMR spectrum, b.p. 54−59 °C (110 mbar). The spectroscopic data of **7** and **8** were identical to those reported.[9a,9b]

2-(2-Bromoethyl)-2-(bromomethyl)-1,3-dioxolane (13): A solution of CrO_3 (4.57 g, 45.7 mmol) and 96% H_2SO_4 (8.5 mL) in water (62 mL) was added dropwise with ice-bath cooling to a solution of 1,4-dibromobutan-2-ol (**12**) (3.0 g, 13 mmol) in acetone (150 mL).

The reaction mixture was stirred overnight at ambient temp., then diluted with water (250 mL), and extracted with CH_2Cl_2 (2 × 100 mL). The organic phase was washed with brine, dried with Na_2SO_4, and concentrated to afford crude 1,4-dibromobutan-2-one, which was used without further purification.[25] Trimethylsilyl chloride (0.57 mL, 4.48 mmol) was added under nitrogen to a solution of this ketone (3.37 g, 14.7 mmol) in anhydrous ethylene glycol, and the resulting solution was stirred at ambient temperature for 24 h. The reaction was quenched with a 5% $NaHCO_3$ solution (100 mL) and the mixture was extracted with diethyl ether (2 × 100 mL). The organic phase was washed with brine (50 mL), dried, and concentrated under reduced pressure. The crude product was purified by filtration through a short pad of silica gel, eluting with petroleum ether/diethyl ether (4:1), to afford 2.85 g (71%) of the pure acetal **13** as a colorless oil, R_f = 0.51. − ^{1}H NMR: δ = 2.49−2.36 (m, 2 H, CH_2) 3.46−3.35 (m, 4 H, 2 CH_2Br), 3.94−4.12 (m, 4 H, 2 CH_2O). − IR: ṽ = 2979 cm^{-1}, 1425, 1346, 1290, 1217. − MS (EI): *m*/*z* (%) = 181 (64), 179 (100), 167 (47), 121 (59), 107 (70), 55 (59). − $C_6H_{10}Br_2O_2$ (273.95): calcd. C 26.31, H 3.68; found C 26.45, H 3.85.

1,4-Dioxa-7-azaspiro[4.4]nonan-7-ol (14): A solution of the acetal **13** (1.175 g, 4.29 mmol) and hydroxylamine hydrochloride (0.82 g, 11.8 mmol) in Et_3N (10 mL) was heated under reflux for 4 h under nitrogen. The resulting suspension was then concentrated under reduced pressure, and the residue was thoroughly washed with diethyl ether (100 mL). The ethereal extract was concentrated, and the residue purified by flash column chromatography, eluting with ethyl acetate, to afford 0.256 g (41%) of pyrrolidine **14** as a slightly yellow oil, R_f = 0.28. − ^{1}H NMR: δ = 1.94−2.12 (m, 2 H, CH_2), 3.03−3.15 (m, 4 H, 2 NCH_2), 3.85 (br. s, 4 H, 2 OCH_2). − ^{13}C NMR: δ = 34.8 (CH_2), 57.5, 66.8 (CH_2N), 64.5 (2 CH_2O), 114.8 (C). − IR: ṽ = 2991 cm^{-1}, 1356, 1215, 1090, 1010. − MS (EI): *m*/*z* (%) = 143 (10) [M$^+$ − 2 H], 128 (27), 113 (46), 99 (63), 86 (78), 84 (100), 71 (37). − $C_6H_{11}NO_3$ (145.16): calcd. C 49.65, H 7.64, N 9.65; found C 49.64, H 7.79, N 10.00.

1,4-Dioxa-7-azaspiro[4.4]non-6-ene *N*-Oxide (11): Yellow HgO (5.06 g, 23.4 mmol) was added in one portion to an ice-cooled solution of *N*-hydroxypyrrolidine **14** (0.41 g, 2.8 mmol) in CH_2Cl_2 (12 mL). The resulting suspension was stirred at ambient temp. for 4 h, filtered through a short pad of Celite, and concentrated under reduced pressure. The crude product was purified by filtration through a short pad of silica gel, eluting with ethyl acetate/methanol (10:1), to yield 0.39 g (96%) of nitrone **11** as a colorless solid, R_f = 0.34. − ^{1}H NMR: δ = 2.44−2.52 (m, 2 H, CH_2), 3.97−4.01 (m, 6 H, 2 CH_2O and CH_2N), 6.82 (t, *J* = 2.0 Hz, 1 H, =CH). − ^{13}C NMR: δ = 33.1 (CH_2), 60.6 (NCH_2), 65.3 (2 OCH_2), 113.6 (C), 132.2 (=CH). − IR: ṽ = 2965 cm^{-1}, 1584, 1350, 1309, 1102. − MS (EI): *m*/*z* (%) = 143 (21) [M$^+$], 115 (24) [M$^+$ − C_2H_4], 113 (89) [M$^+$ − NO], 85 (29), 84 (62), 83 (62), 71 (100), 55 (39), 53 (82). − $C_6H_9NO_3$ (143.14): calcd. C 50.34, H 6.34, N 9.78; found C 50.38, H 6.75, N 9.69.

1,3-Dipolar Cycloadditions of Nitrones 9−11 to Cyclopropylidenecyclobutane (7). − General Procedure (GP) 1: A solution of the respective nitrone (2−6 mmol) and cyclobutylidenecyclopropane (**7**) (1.5−1.7 equiv.) in toluene (5 mL) was heated in a sealed vial at 100 °C for 6 d. The solution was concentrated under reduced pressure, and the crude product was purified by flash column chromatography.

9-Methyl-10-phenyl-8-oxa-9-azadispiro[2.0.3.3]decane (15): Compounds **9** (0.811 g, 6 mmol) and **7** (0.846 g, 9 mmol) gave 0.717 g (52%) of **15** as a slightly yellow oil, R_f (CH_2Cl_2) = 0.42. − ^{1}H NMR: δ = 0.10−0.22 (m, 1 H, cy-Pr), 0.36−0.41 (m, 1 H, cy-Pr), 0.53−0.61 (m, 1 H, cy-Pr), 0.84−0.98 (m, 1 H, cy-Pr), 1.33−1.44 (m, 1 H, cy-Bu), 1.83−2.01 (m, 1 H, cy-Bu), 2.04−2.22 (m, 2 H, cy-Bu), 2.22−2.43 (m, 2 H, cy-Bu), 2.76 (s, 3 H, CH_3), 3.60 (s, 1 H, CH), 7.23−7.31 (m, 5 H, C_6H_5). − ^{13}C NMR: δ = 6.6, 6.8 (CH_2, cy-Pr), 13.5, 32.1, 33.7 (CH_2, cy-Bu), 37.6 (C, cy-Pr), 44.4 (CH_3), 78.4 (CH), 84.4 (C, cy-Bu), 127.6, 128.0 (2 CH), 128.5 (CH), 137.1 (C). − IR: ṽ = 3069 cm^{-1}, 2992, 2962, 1428, 1356, 1297, 1220, 1139. − MS (EI): *m*/*z* (%) = 229 (49) [M$^+$], 201 (100) [M$^+$ − C_2H_4], 158 (32), 118 (25), 91 (18), 77 (9) [$C_6H_5^+$]. − $C_{15}H_{19}NO$ (229.31): calcd. C 78.57, H 8.35, N 6.11; found C 78.75, H 8.34, N 6.20.

9-Methyl-10-(2-pyridyl)-8-oxa-9-azadispiro[2.0.3.3]decane (16): Compounds **10** (0.816 g, 6 mmol) and **7** (0.846 g, 9 mmol) gave 1.16 g (84%) of **16** as a slightly yellow oil, R_f (CH_2Cl_2) = 0.33. − ^{1}H NMR: δ = 0.03−0.14 (m, 1 H, cy-Pr), 0.45−0.54 (m, 1 H, cy-Pr), 0.62−0.73 (m, 1 H, cy-Pr), 0.77−0.84 (m, 1 H, cy-Pr), 1.22−1.31 (m, 1 H, cy-Bu), 1.76−1.88 (m, 1 H, cy-Bu), 1.91−2.00 (m, 2 H, cy-Bu), 2.10−2.31 (m, 2 H, cy-Bu), 2.75 (s, 3 H, CH_3), 3.81 (s, 1 H, CH), 7.16 (t, *J* = 6.1 Hz, 1 H, C_5H_4N), 7.43 (d, *J* = 7.5 Hz, 1 H, C_5H_4N), 7.60 (t, *J* = 7.6 Hz, 1 H, C_5H_4N), 8.41 (d, *J* = 7.4 Hz, 1 H, C_5H_4N). − ^{13}C NMR: δ = 5.8, 7.5 (CH_2, cy-Pr), 13.6, 32.5, 33.3 (CH_2, cy-Bu), 37.2 (C, cy-Pr), 45.3 (CH_3), 78.7 (CH), 84.8 (C, cy-Bu), 122.3, 122.9, 136.4, 148.5 (CH, C_5H_4N), 158.6 (C). − IR: ṽ = 3074 cm^{-1}, 2991, 1684, 1433, 1263, 1137. − MS (CI): *m*/*z* (%) = 248 (1) [M + NH_4^+], 245 (6) [M$^+$ + 15], 231 (100) [M + H$^+$]. − $C_{14}H_{18}N_2O$ (230.31): calcd. C 73.02, H 7.88, N 12.16; found C 72.66, H 7.89, N 12.39.

Dispiro Compound 17: Compounds **11** (0.38 g, 2.6 mmol) and **7** (0.414 g, 4.4 mmol) gave 0.296 g (48%) of **17** as a slightly yellow oil, R_f (CH_2Cl_2/CH_3OH 15:1) = 0.37. − ^{1}H NMR: δ = 0.51−0.59 (m, 1 H, cy-Pr), 0.64−0.92 (m, 2 H, cy-Pr), 0.96−1.03 (m, 1 H, cy-Pr), 1.11−1.29 (m, 1 H, cy-Bu), 1.55−1.97 (m, 3 H, cy-Bu), 2.11−2.34 (m, 4 H, cy-Bu + CH_2), 3.12 (s, 1 H, CH), 3.15−3.37 (m, 2 H, CH_2N), 3.75−3.98 (m, 4 H, 2 CH_2O). − ^{13}C NMR: δ = 4.5, 9.5 (CH_2, cy-Pr), 13.0, 32.5, 33.9 (CH_2, cy-Bu), 32.8 (C, cy-Pr), 35.2 (CH_2), 53.9 (CH_3), 63.9, 65.4 (CH_2O), 77.5 (CH), 85.2 (C, cy-Bu), 117.0 (C). − IR: ṽ = 2992 cm^{-1}, 2950, 1430, 1305, 1263. − MS (EI): *m*/*z* (%) = 122 (26), 109 (37), 99 (82), 94 (42), 86 (100), 84 (58), 80 (52), 67 (41), 55 (52). − $C_{13}H_{19}NO_3$ (237.30): calcd. C 65.80, H 8.07, N 5.90; found C 66.12, H 7.89, N 5.95.

Thermal Rearrangement of Adducts 15−17. − General Procedure (GP) 2: The respective adducts **15**−**17** (0.5−1 mmol) were heated at 100−120 °C under vacuum (10^{-3} mbar), and the vapors allowed to pass through a quartz tube preheated to 600 °C by a furnace (heating path length ca. 15 cm). The vapors were collected in a liquid nitrogen cooled trap, as red-yellow oils. The crude reaction mixture was separated by flash column chromatography.

5-Methyl-4-phenyl-5-azaspiro[2.6]nonan-9-one (21): Compound **15** (96 mg, 0.42 mmol) gave 31 mg (32%) of **21** as a slightly yellow oil, R_f (CH_2Cl_2) = 0.37. − ^{1}H NMR: δ = 0.71−0.79 (m, 1 H, cy-Pr), 1.25−1.37 (m, 2 H, cy-Pr), 1.44−1.53 (m, 1 H, cy-Pr), 2.05−2.22 (m, 1 H, CH_2), 2.51−2.60 (m, 1 H, CH_2), 2.62 (s, 3 H, CH_3), 2.72−2.81 (m, 2 H, CH_2), 2.84−2.95 (m, 1 H, CH_2N), 3.15−3.23 (m, 1 H, CH_2N), 3.83 (s, 1 H, CH), 7.21−7.48 (m, 5 H, C_6H_5). − ^{13}C NMR: δ = 16.1, 20.2 (CH_2, cy-Pr), 21.7, 41.9, 50.7 (CH_2), 31.2 (C, cy-Pr), 43.0 (CH_3), 69.9 (CH), 127.2, 128.2 (2 CH), 128.5 (CH), 140.8, 213.1 (C). − IR: ṽ = 3054 cm^{-1}, 2987, 1676, 1422. − MS (EI): *m*/*z* (%) = 229 (45) [M$^+$], 160 (45), 152 (62) [M$^+$ − C_6H_5], 132 (82), 118 (69), 86 (81), 84 (100), 77 (54) [$C_6H_5^+$], 51 (86). − $C_{15}H_{19}NO$ (229.32): calcd. C 78.56, H 8.35, N 6.11; found C 78.66, H 8.08, N 6.36.

5-Methyl-4-(2-pyridyl)-5-azaspiro[2.6]nonan-9-one (22): Compound **16** (230 mg, 1 mmol) gave 69 mg (30%) of **22** as a slightly yellow oil, R_f (CH_2Cl_2/MeOH 40:1) = 0.26. − ^{1}H NMR: δ = 0.63−0.67 (m, 1 H, cy-Pr), 0.70−0.74 (m, 1 H, cy-Pr), 1.18−1.23 (m, 1 H, cy-Pr), 1.42−1.46 (m, 1 H, cy-Pr), 1.55−1.62 (m, 1 H, CH_2), 2.11−2.19 (m, 1 H, CH_2), 2.57 (s, 3 H, CH_3), 2.81 (t, J = 6.8 Hz, 2 H, CH_2), 2.90 (dt, J = 3.8, 4.5 Hz, 1 H, CH_2N), 3.06−3.12 (m, 1 H, CH_2N), 3.88 (s, 1 H, CHN), 7.14−7.16 (m, 1 H, C_5H_4N), 7.47 (d, J = 7.8 Hz, 1 H, C_5H_4N), 7.64 (td, J = 1.8, 7.8 Hz, 1 H, C_5H_4N), 8.54−8.56 (m, 1 H, C_5H_4N). − ^{13}C NMR: δ = 15.6, 21.0 (CH_2, cy-Pr), 32.2 (C, cy-Pr), 42.6 (CH_3), 21.3, 42.9, 50.1 (CH_2), 72.5 (CH), 122.5, 123.7, 136.6, 149.1 (CH), 160.5, 212.1 (C). − IR: $\tilde{\nu}$ = 3058 cm^{-1}, 2992, 2941, 1673, 1432. − MS (EI): *m/z* (%) = 230 (4) [M^+], 202 (12) [$M^+ - C_2H_4$], 174 (69) [$M^+ - CO - C_2H_4$], 152 (31), 132 (51), 117 (16), 93 (16), 86 (63), 84 (100), 79 (15), 78 (24) [$C_5H_4N^+$], 70 (63). − MS (HR-EI): 230.1419 ($C_{14}H_{18}N_2O$, calcd. 230.1419).

Thermal Rearrangement of Adduct 17: Compound **17** (80 mg, 0.34 mmol) gave 15 mg (19%) of **23**, 13 mg (16%) of **24**, and 10 mg (13%) of **25** as slightly yellow oils.

Spiro Compound 23: R_f (ethyl acetate/petroleum ether, 1:1) = 0.23. − ^{1}H NMR: δ = 0.66−0.73 (m, 1 H, cy-Pr), 0.99−1.07 (m, 1 H, cy-Pr), 1.12−1.28 (m, 1 H, cy-Pr), 1.34−1.47 (m, 1 H, cy-Pr), 1.83−1.99 (m, 4 H, 2 CH_2), 2.52−2.65 (m, 2 H, CH_2), 2.76 (s, 1 H, NCH), 2.69−2.86 (m, 2 H, CH_2N), 3.00−3.12 (m, 2 H, CH_2N), 3.82−3.96 (m, 4 H, 2 CH_2O). − ^{13}C NMR: δ = 9.8, 17.6 (CH_2, cy-Pr), 31.8 (C, cy-Pr), 23.9, 35.4, 40.8, 50.8, 52.6, 63.9, 65.2 (CH_2), 71.1 (CHN), 116.5, 211.3 (C). − IR: $\tilde{\nu}$ = 2993 cm^{-1}, 2979, 1686. − MS (EI): *m/z* (%) = 237 (40) [M^+], 165 (38) [$M^+ - C_3H_4O_2$], 151 (100) [$M^+ - C_4H_6O_2$], 137 (50) [$M^+ - C_3H_4O_2 - C_2H_4$], 122 (39), 109 (75), 85 (71). − MS (HR-EI): 237.1364 ($C_{13}H_{19}NO_3$, calcd. 237.1361).

1-[1-(1,4-Dioxa-7-azaspiro[4.4]non-6-en-6-yl)cyclopropyl]butan-1-one (24): R_f (ethyl acetate/petroleum ether, 1:1) = 0.51. − ^{1}H NMR: δ = 0.87 (t, J = 7.5 Hz, 3 H, CH_3), 0.84−0.94 (m, 1 H, cy-Pr), 1.22−1.34 (m, 3 H, cy-Pr), 1.52−1.63 (m, 2 H, CH_2), 2.11 (t, J = 6.6 Hz, 2 H, CH_2), 2.59 (t, J = 7.4 Hz, 2 H, CH_2), 3.88 (t, J = 6.6 Hz, 2 H, CH_2N), 3.94 (m, 4 H, 2 CH_2O). − ^{13}C NMR: δ = 17.4 (CH_3), 14.6 (2 CH_2, cy-Pr), 29.7 (C, cy-Pr), 13.7, 35.5, 43.0, 55.7 (CH_2), 65.7 (2 CH_2), 117.7, 174.6, 206.9 (C). − IR: $\tilde{\nu}$ = 2964 cm^{-1}, 1697, 1639. − $C_{13}H_{19}NO_3$ (237.29) calcd. C 65.80, H 8.07, N 5.90; found C 65.62, H 8.25, N 5.54.

Spiro Compound 25: R_f (ethyl acetate/petroleum ether, 1:1) = 0.23. − ^{1}H NMR: δ = 0.79−0.81 (m, 1 H, cy-Pr), 0.99−1.03 (m, 1 H, cy-Pr), 1.21 (d, J = 6.7 Hz, 3 H, CH_3), 1.23−1.26 (m, 1 H, cy-Pr), 1.29−1.33 (m, 1 H, cy-Pr), 1.87−1.96 (m, 2 H, CH_2), 2.19 (dd, J = 2.4, 17.5 Hz, 1 H, CH_2), 2.56 (dd, J = 12.2, 17.5 Hz, 1 H, CH_2), 2.72−2.75 (m, 1 H, CH_2N), 2.98 (s, 1 H, CHN), 2.99−3.04 (m, 1 H, CH_2N), 3.33−3.40 (m, 1 H, CH), 3.82−3.97 (m, 4 H, 2 CH_2O). − ^{13}C NMR: δ = 10.4, 17.7 (CH_2, cy-Pr), 19.0 (CH_3), 30.1 (C, cy-Pr), 52.2, 69.3 (CH), 35.1, 43.2, 44.8 (CH_2), 65.2 (2 CH_2), 115.5, 209.0 (C). − IR: $\tilde{\nu}$ = 2928 cm^{-1}, 1699, 1384. − $C_{13}H_{19}NO_3$ (237.29) calcd. C 65.80, H 8.07, N 5.90; found C 66.02, H 8.34, N 5.95.

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[23] **Crystal Structure Determination of 7:** The crystal of cyclobutylidenecyclopropane (**7**) was grown in situ at 195 K with the Optical Heating and Crystallization Device (OHCD), using a miniature zone melting procedure with focused IR laser light [R. Boese, M. Nussbaumer, in: *Organic Crystal Chemistry* (Ed.: D. W. Jones), Oxford University Press, Oxford, **1994**, pp. 20−37]. The device was mounted on a Nicolet R3m/V four-circle diffractometer, and the crystal formation detected using graphite-monochromated Mo-K_α radiation. Correction for the cylindrical shape of the crystals (0.3 mm diameter) was applied for **7**. The structure solutions and refinements on F^2 were performed with the Bruker AXS SHELXTL program suite (Version 5.10). The hydrogen atoms were located in difference Fourier maps and refined as riding groups with the 1.2-fold isotropic displacement parameter of the corresponding C atom. C_7H_{10} (94.15), monoclinic, a = 4.0933(8), b = 9.5034(18), c = 7.5436(15) Å, β = 91.876(5)°, V = 293.29(10) Å^3, Z = 2, space group $P2_1/m$, T = 183(2) K, ρ = 1.066 g cm^{-3}, $F(000)$ = 104, μ = 0.059 mm^{-1}, intensities measured: 742 (3.45° ≤ θ ≤ 28.22°), independent: 526 (R_{int} = 0.0091), observed: 468 [F_o = 4σ(F)], 38 parameters refined, $R1$ = 0.0471, $wR2$ (final [I > 2σ(I)]) = 0.1322, Goof = 1.083, maximum residual electron density 0.203 and −0.187 e Å^{-3}. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited as supplementary publication no. CCDC-162633 with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
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