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SYNTHESIS AND REACTIVITY OF 1-AZASPIROPENTANES

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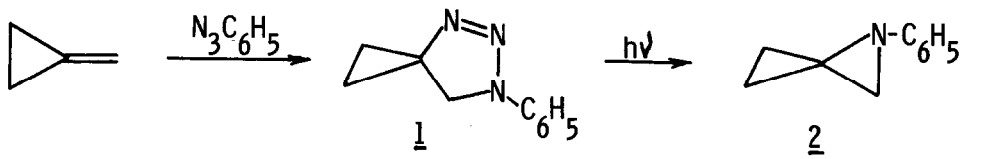
Only recently have heterocyclic analogs of spiropentane been prepared.[2-5] We report herein the preparation and reactivity of N-substituted derivatives of the parent azaspiropentane ring system.

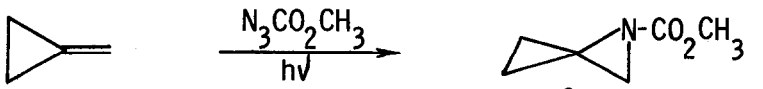
Methylenecyclopropane slowly reacts with phenyl azide in methylene chloride solution at 25° to give a single triazoline, tentatively assigned structure 1, in 68% yield, m.p. 120.5-122.0°; nmr (CCl_4) δ 1.29 (AA'BB', 4H), 3.62 (s, 2H), 7.27 (m, 5H); m/e 173.0947. Irradiation of a



1 2

methylene chloride solution of 1 at 0° with a pyrex filtered mercury arc gives 1-phenyl-1-azaspiro[2.2]pentane, 2 (60%), b.p. 50° (0.1 mm); nmr (CCl_4) δ 1.0 (AA'BB', 4H), 2.68 (s, 2H), 6.9 (m, 5H); m/e 145.0890.

The N-methoxycarbonyl derivative 3 of azaspiropentane is available by direct addition of methoxycarbonylnitrene to methylenecyclopropane. Thus, when a solution of methylazidoformate in methylenecyclopropane is irradiated at 0° with a mercury arc lamp, the azaspiropentane 3 is obtained in 35% yield, b.p. 42-44° (1.5 mm); ir (CCl_4) 1729 cm^{-1}, nmr (CCl_4) δ 1.03 (AA'BB', 4H), 2.57 (s,2H), 3.63 (s, 3H); m/e 127.0635. These reactions provide convenient, potentially general methods for the synthesis of 1-azaspiropentanes.



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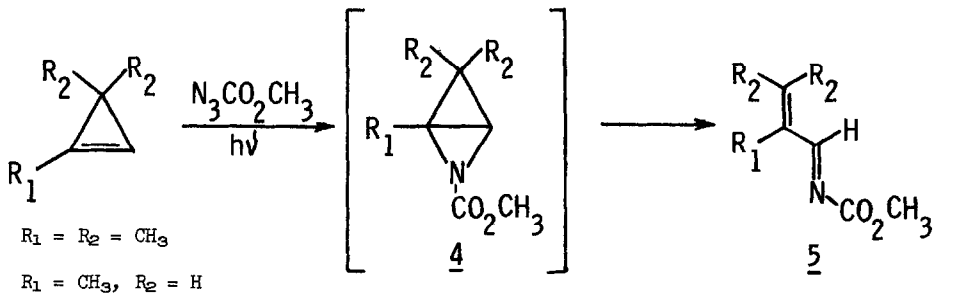
When an analogous nitrene addition to 1,3,3-trimethylcyclopropene was carried out at 0°, the 2-azabicyclobutane 4 was not observed, but the imine 5 was produced in low yield, nmr (CCl_4)

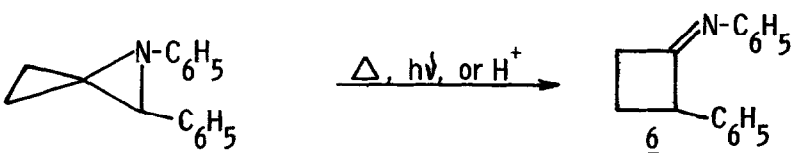


a, $R_1 = R_2 = CH_3$

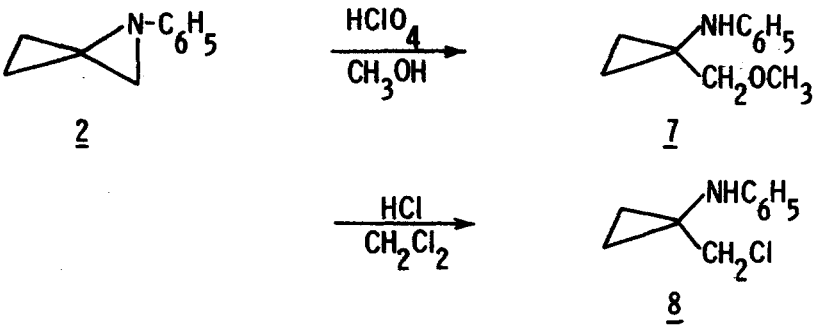
b, $R_1 = CH_3$, $R_2 = H$

δ 1.8-2.2, (m, 9H); 3.83 (s, 3H); 9.04 (s, 1H); ir 1730, 1610 cm^{-1}; m/e 155.0946. Addition to 1-methylcyclopropene proceeds similarly to give 5b.[6] The presumed intermediate 2-azabicyclo-[1.1.0]butane 4, appears to be unstable to thermal ring opening to 5 at low temperature.[7] In contrast to this behavior, the azaspiropentanes 2 and 3 are stable above 100°.[8] Neither 2 nor 3 gives a 1:1 adduct with dimethylacetylenedicarboxylate on heating above 100° or on irradiation. In spite of the fact that spiro[2.2]pentane and bicyclo[1.1.0]butane have almost identical strain energies (ca. 65 kcal/mole),[9] they appear to differ markedly in reactivity toward thermal ring opening[10] as a result of differences in orbital overlap and thermochemistry[8] for the ring opening reactions. The analogous 2-oxaspiropentanes[2,3] are remarkably stable thermally, while 2-oxabicyclobutanes are postulated to be unstable at 0° in peracid oxidations of cyclopropenes.[8,11]

While 1,2-diphenyl-1-azaspiro[2.2]pentane rearranges to 6 thermally, photochemically or with acid catalysis,[5] and oxaspiropentanes readily rearrange to cyclobutanones;[2,3] the azaspiropentanes 2 and 3 are stable in the gas phase at elevated temperatures[8] and they do not rearrange to cyclobutanone derivatives with acid catalysts. Instead, they undergo S_N2-like openings to cyclopropane derivatives on treatment with strong protic acids. Like the acid catalyzed ring

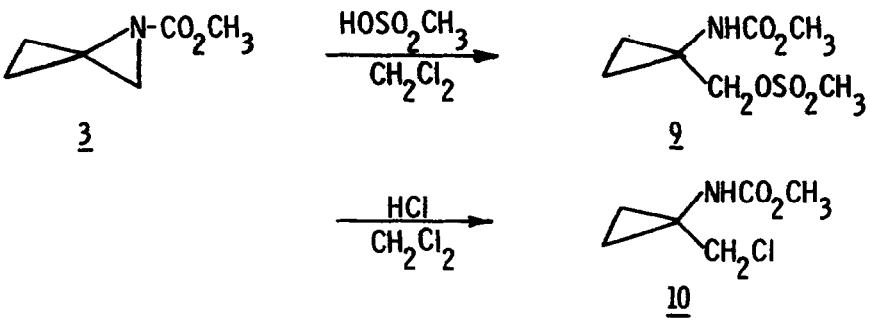


openings of oxaspiropentane, the ring opening always leads to nucleophilic attack at the less hindered primary carbon site.[3] For example, treatment of 2 with sulfuric acid in methanol leads to the amino ether 7 (74%), b.p. 70° (0.01 mm); nmr (CCl_4) δ 0.77 (s, 4H); 3.25 (s, 3H); 3.62 (s, 2H); 4.30 (s, 1H); 7.0 (m, 5H); m/e 177.1155.



2 7 8

Addition of anhydrous hydrogen chloride to 2 in methylene chloride quantitatively gives the chloride 8; nmr (CCl_4) δ 0.95 (m, 4H); 3.72 (s, 3H); 7.0 (m, 5H); m/e 181.0657. Addition of hydrogen chloride to 3 likewise gives a quantitative yield of an unrearranged adduct 10, m.p. 73.0-74.5°; ir (CCl_4) 3430, 1735 cm^{-1}; nmr (CCl_4) δ 0.92 (broad s, 4H), 3.64 (s, 2H), 3.66 (s, 3H), 5.72 (broad s, 1H); m/e 163.0395. Similarly, 3 reacts with methanesulfonic acid



3 9 10

in methylene chloride to produce an adduct 9 (63%), m.p. 90° (dec.); ir ($CHCl_3$) 3430, 1725 cm^{-1}; nmr (CCl_4) δ 0.96 (s, 4H), 3.04 (s, 3H), 3.58 (s, 3H), 4.27 (s, 2H); 5.42 (broad s, 1H). Both aziridines 2 and 3 are stable, however, to lithium iodide in refluxing methylene chloride. Oxaspiropentanes react readily with sulfonic acids and lithium salts to give cyclobutanones,[3] but with hydrogen chloride in methylene chloride solution they give stable epichlorohydrins analogous to the azaspiropentane products 8 and 10.

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7. The possibility that 5 might have been formed by ring opening of a dipolar intermediate in a stepwise nitrene addition rather than via 4 appears unlikely since 3 is formed without rearrangement and because the direction of aziridine ring opening to give 5 is not consistent with a polar intermediate. Similarly, opening of the epoxide rings in oxabicyclobutanes give large amounts of products inconsistent with cleavage to the more stable carbonium ion (ref. 11).

8. In the gas phase, 2 rearranges with a half-life of ca. 10 min. at 160° while 3 decomposes at 190° in 1 hr. Professor J. K. Crandall has observed formation of a cyclobutanone derivative from 2 analogous to 6 above 275° (J. K. Crandall and W. W. Conover, private communication). We also observe this product in the gas phase at 160°. Oxaspiropentane rearranges to cyclobutanone much more readily with acid and on heating in solution, but the gas phase rearrangement to cyclobutanone is slower with $t_{\frac{1}{2}} \approx 70$ min. at 230° (see ref. 3). In analogous hydrocarbon reactions, spiropentane rearranges to methylenecyclobutane (with Ea = 57.6 kcal/mole, ref. 10), while bicyclobutane gives 1,3-butadiene (with Ea = 40.6 kcal/mole, ref. 10) on heating. The apparent thermal instabilities of azabicyclobutanes and oxabicyclobutanes (Ea ≤ 18 kcal/mole) relative to the analogous hydrocarbons may be the result of thermochemical differences; see for example L. E. Friedrich and G. B. Schuster, J. Amer. Chem. Soc., 93, 4603 (1971). Note that for spiropentane ΔH°= -14.2 kcal, but for bicyclobutane ΔH°=-25.2 kcal.

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