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A NEW REACTION OF NITRENE WITH 1H-AZEPINE DERIVATIVES: A FORMATION OF 2,6-DIAZABICYCLO[3.3.0]OCTADIENE AND 2,8-DIAZABICYCLO[3.2.1]OCTADIENE[1]

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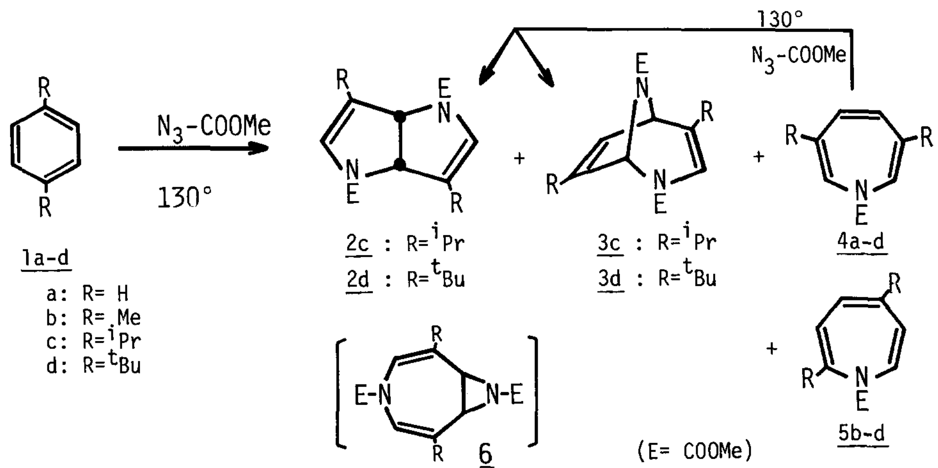
Summary: The formation of two diazabicyclooctadienes (2 and 3) is elucidated by the intermediacy of azahomoazepine.

In the study of heterocyclic conjugated systems, the chemistry of 1H-azepines has been investigated in some detail.[2] Although syntheses of azepines using the nitrene generated from azidoformate were reported by Hafner, Lwowski, Paquette and Photis,[3] the formation of a 1:2 adduct derived from the nitrene and benzene was never described in literature. We wish to report on the formation of two novel heterocyclic compounds (i.e., 2 and 3) which were obtained from the reaction of a nitrene with 1,4-di-tert-butyl- or 1,4-di-isopropylbenzene. The reaction mechanism associated with the formation of these diazabicyclooctadienes is also discussed in this paper.



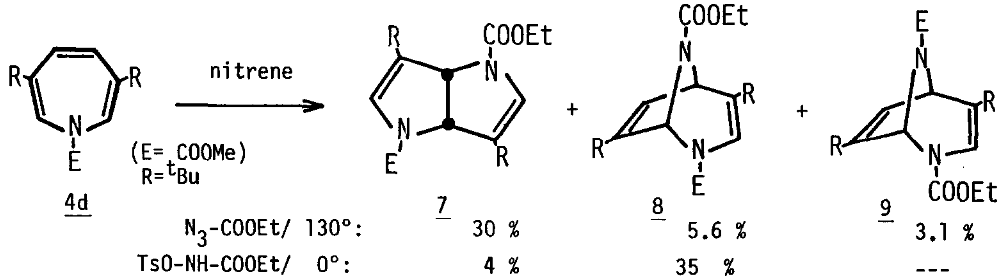
When a half molar equivalent of methyl azidoformate was added to an efficiently stirred vessel containing 1,4-di-tert-butylbenzene (1d) at 130°C, two 1:2-cycloadducts were isolated in 18 and 9 % yield and whose structure were assigned as N,N'-dimethoxycarbonyl-2,6-diazabicyclo[3.3.0]octa-3,7-diene (tetrahydropyrrolopyrrole, 2d)[4] and N,N'-dimethoxycarbonyl-2,8-diazabicyclo-[3.2.1]octa-3,6-diene (3d)[5]. In addition, two azepines were also obtained and their structures were assigned as the 3,6-di-tert-butyl and 2,5-di-tert-butyl derivatives (4d[7], 8 % and 5d[8], 6 %). The NMR spectrum of the major

1:2-cycloadduct 2d shows four singlets at δ 1.12(18H, t-Bu), 3.75(6H, COOMe), 5.41(2H) and 6.30(2H) ppm indicating a highly symmetric structure. The 2,6-diazabicyclo[3.3.0] framework and the 1,5-cis juncture were firmly established by X-ray analysis.[9] In sharp contrast to the NMR spectrum of adduct 2d, the methine and olefinic protons of 3d exibit a complicated pattern. The methyl protons of the ester groups appear at δ 3.67 and 3.80 ppm, where the low field ester signal was split into two peaks (3.76 and 3.84 ppm) at 30°C. This split methyl resonance suggests the existence of rotational isomers which are probably due to the bulkiness of the tert-butyl substituent. In fact, at 68°C, the NMR spectrum of 3d shows simple signals at δ 4.48(d of d, J= 3.0, 1.4 Hz), 5.88(d, J= 3.0 Hz), 6.17(m) and 6.39(broad s) ppm in addition to the tert-butyl protons (1.12 ppm, 18H, s) and the two singlets for the ester groups. The free energy of activation for conversion of the two rotational isomers was estimated to be 17.5 kcal/mole at the coarescence temperature (49°C) by the dynamic NMR method. The structure of 3d was deduced by comparison of the spectral data with those of 2-azabicyclo[3.2.1]octadienes[10] which were previously synthesized by Anastassiou. In accord with the assignment and model inspection, free rotation about the N-C bond at N_2 position will be interfered with by the tert-butyl group at C_7 position.

A set of analogous products (i.e., 2c and 3c)[11], were obtained in 1.7 % and 1.6 % yield when methyl azidoformate was heated with 1,4-diisopropylbenzene at 130°C. Under similar conditions or at high temperatures, benzene, toluene, xylene or tert-butyltoluene gave a mixture of 1H-azepines (4 and 5) in 20-40 % yield. But no 1:2-adduct could be detected in these reaction mixtures.

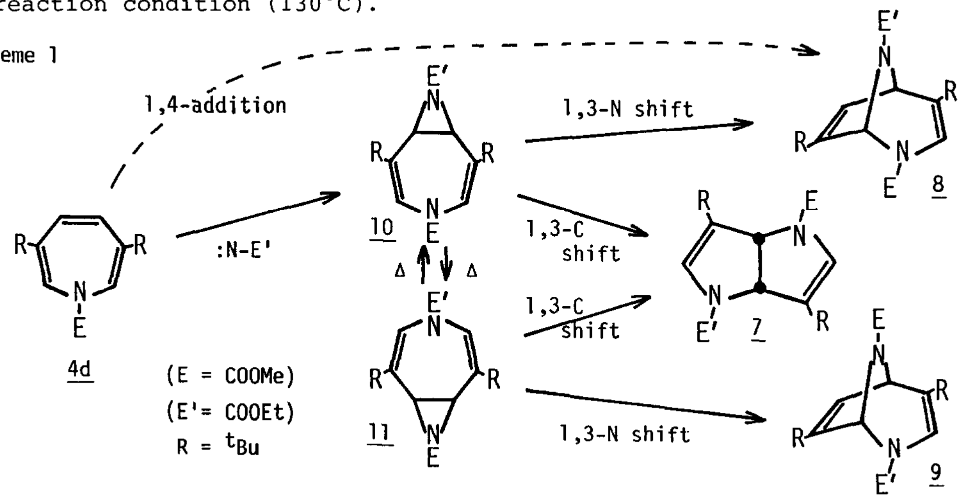
The formation of the 1:2-adducts, 2 and 3, might involve a subsequent addition of nitrene with the 1H-azepine system. It is generally thought, however, that 1H-azepines fail to react with nitrenes. In fact, attempts to detect such an addition of nitrene failed with azepines (4a-b) and (5b-d), where only the starting azepines could be recovered. The 3,6-di-tert-butyl azepine (4d), however, afforded the bicyclo-adducts (2d and 3d) in 25 and 9 % yield when it was heated with one equivalent of methyl azidoformate. The unusual reaction observed with 4d can be rationalized in terms of a steric hindrance between the C_3- and C_6-bulky substituents. This results in activation of the C_4-C_5 double bond for a subsequent addition of nitrene to give azahomoazepine (6) which is the most plausible precursor for structure 2.

The formation of 3 is aslo of interest from a mechanistic view-point since it might be constructed to be an abnormal 1,4-addition product of the nitrene with azepine. In order to elucidate the reaction pathway, a cross experiment was designed using ethoxycarbonyl nitrene. When N-methoxycarbonyl-1H-azepine (4d) was heated with ethyl azidoformate at 130°C, two different 2,8-diazabicyclo[3.2.1]octadienes (8 and 9)[12] were obtained in 5.6 and 3.1 % yields in



addition to 2,6-diazabicyclo[3.3.0]octadiene (7[12], 30 %). The formation of the 8-methoxycarbonyl derivative (9) suggests that its immediate precursor is azahomoazepine (11) which is produced by a Cope rearrangement of 10. We consider that the major product (7) originates from a 1,3-carbon migration of both azahomoazepines (10) and (11), and that the two minor products (8 and 9) are generated by a competitive 1,3-nitrogen migration of the same precursors. When a different nitrene source (i.e. ethyl N-toluenesulfonyloxyurethane) was treated with 2d in the presence of base at 0°C, none of the 8-methoxycarbonyl derivative (9) could be detected.[13] Under these conditions, compound 8 was obtained as the major product in 35 % yield in addition to 7 (4 %). It would be seen that the Cope rearrangement does not occur at 0°C and that the 1,3-nitrogen migration reaction leading to 8 occurs preferentially at the low temperature used. The reaction pathways are summarized in Scheme 1. The direct 1,4-addition reaction of the nitrene with the 1H-azepine can be eliminated. The preference for formation of 8 relative to 9 probably reflects the relative rates of 1,3-carbon migration and Cope rearrangement from precursor 10 under the reaction condition (130°C).[14]

Scheme 1



In summary, the work described here has uncovered a degenerate Cope rearrangement of an azahomoazepine as well as a new method for preparing several novel heterocyclic compounds. Further studies dealing with these diazabicyclooctadienes will be published elsewhere.

References and Notes

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3. K. Hafner and C. Konig, Angew. Chem., 75, 89 (1963); W. Lwowski, T.J. Maricich, and T.W. Mattingly Jr., J. Am. Chem. Soc., 85, 1200 (1963); L.A. Paquette, D.E. Kuhla, J.H. Barrett, and R.J. Haluska, J. Org. Chem., 34, 2866 (1969); J.M. Photis, J. Heterocyclic Chem., 8, 1249 (1971).
4. Compound 2d[6]: colorless prisms, mp 116-7°C; IR(oil) 1710, 1640 cm^{-1}; UV(cyclohexane) λmax= 223 nm (ε 25,450).
5. Compound 3d[6]: pale yellow oil; IR(oil) 1720, 1635 cm^{-1}; UV(cyclohexane) λmax= 248 nm (ε 5,010).
6. All new compounds gave satisfactory elemental analyses and Mass spectra.
7. Azepine 4d[6]: pale yellow oil; IR(oil) 1720, 1655, 1625 cm^{-1}; NMR(CCl_4) δ 1.09(18H, s), 3.66(3H, s), 5.79(2H, broad s), 6.29(2H, s); UV(cyclohexane) λmax= 212 (ε 19,500), 233 (sh, 4,570), 285 nm (sh, 390).
8. Azepine 5d[6]: colorless needles, mp 56-57°C; IR(KBr) 1716, 1623 cm^{-1}; NMR(CCl_4) δ 1.12(9H, t-Bu), 1.17(9H, t-Bu), 3.49(COOMe). 5.8-6.3(4H, m); UV(cyclohexane) λmax= 208 (ε 14,130), 245 nm (sh, 3,800).
9. The detail of this result will be reported elsewhere; T.Kabuto and T.Mukai.
10. A.G. Anastassiou, J. Am. Chem. Soc., 90, 1527 (1968).
11. Compound 2c[6]: colorless prisms, mp 103-104°C; IR(KBr) 1718, 1659 cm^{-1}; NMR($CDCl_3$) δ 1.0-1.3(12H, m), 2.37(2H, m), 3.74(6H, s), 5.41(2H, s), 6.26 (2H, broad s); UV(cyclohexane) λmax= 226 nm (ε 23,280).
    Compound 3c[6]: pale yellow oil; IR(oil) 1723, 1642 cm^{-1}; NMR($CDCl_3$) δ 1.06 (6H, d, J= 7.0 Hz), 1.11(6H, splitted d, J= 7.0 Hz), 2.37(2H, broad spt, J= 7.0 Hz), 3.68(3H, s), 3.79(3H, splitted s), 4.73(1H, m), 5.80(1H, m), 6.1-6.3(2H, m); UV(cyclohexane) λmax= 221 (sh, ε 6,360), 248 nm (5,040).
12. Compound 7[6]: colorless fine needles, mp 77-78°C; IR(KBr) 1715, 1655, 1643 cm^{-1}; NMR($CDCl_3$) δ 1.15(18H, s), 1.31(3H, t, J= 6.6 Hz), 3.75(3H, s), 4.21 (2H, q, J= 6.6 Hz), 5.53(2H, s), 6.31(2H, broad s); UV(cyclohexane) λmax= 224.5 nm (ε 22,660).
    Products 8 and 9 could not be separated. The product ratio was determined by analysis of its 200 MHz NMR spectrum.
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14. Compounds 8 and 9 afforded 7 on heating at 230°C for 6 hr. No reaction was observed at 130°C indicating that the interconversions did not occur under the reaction conditions.

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