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THE CYCLOADDITION OF 1-AZIRINES WITH KETENES[1]

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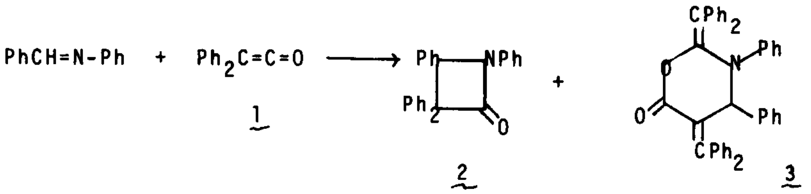
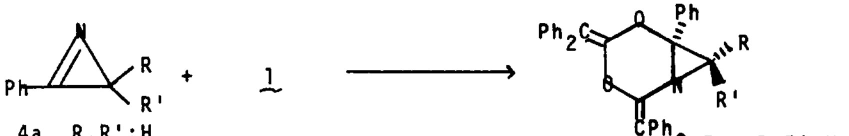
It has recently been shown that azirines can act as 1,3-dipoles in photochemical reactions[2a] or as dienophiles in thermal reactions.[2b, 3c] As part of our continued interest in the chemistry of azirines,[3] we investigated the reaction of 1-azirines with some ketenes. The recent brief report of Woerner, Reimlinger, and Merenyi[4] on the reaction of 2-phenyl-1-azirine (4a) and diphenylketene (1) prompts us to disclose our findings in this area.

In contrast to simple imines which react with ketene 1 to form 1:1 and 1:2 adducts 2 and 3,[5] 1-azirines produce bicyclic 1:2 adducts of type 5 (no carbonyl function) or 1:1 adducts of type 12, depending on the substituent in the azirine ring.

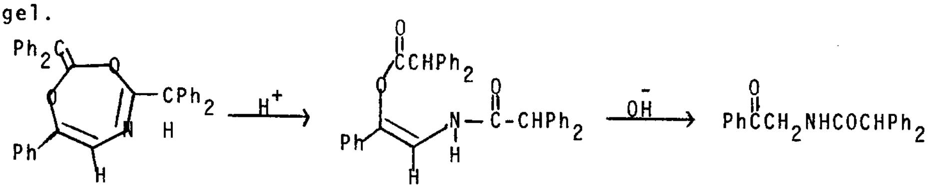




4a, R,R':H
4b, R:H, R':CH_3
4d, R,R':CH_3
4e, R:H, R':Ph

5a, R,R':H
5b,(trans),R:H,R':CH_3
5c,(cis),R:CH_3,R':H
5d, R,R':CH_3

For example, treatment of azirine 4a with 2 (or 1) equivalents of diphenylketene (1) in ether at 25° for 6 hrs. affords adduct 5a in 60% yield. The structure of 5a was established by the following spectral data and chemical reactions. Product 5a gave a parent peak m/e 505 and its infrared spectrum showed enol ether bands at 1670 and 1630 cm^{-1} and no carbonyl absorption. The UV maximum at 262 nm (ε23,000) is consistent with that of the $PhCH=C(OR)_2$ chromophore[6] at 265 nm (ε18,000). The aziridine protons appear as singlets at 7.45 and 7.62τ. Whereas hydrolysis of 5a with aqueous HCl leads to open-chain products exclusively, treatment of a benzene solution of 5a with dry HCl led to rearrangement of the aziridine to dioxazepine 6a. The sensitivity of the fused aziridine 5a to acid is indicated by its conversion to 6a and 7a upon chromatography on neutral alumina or silica gel.


6a 8a 7a

Product 6a showed enolic ether absorptions at 1660 and 1650 cm^{-1} and no carbonyl bands. Its nmr spectrum displayed a multiplet of 25 aromatic protons and two singlets at 3.35 and 5.04τ(1H each), and in the mass spectrum a parent peak at m/e 505.

Reaction of 6a with methanolic HCl gave enol ester 8a, which upon hydrolysis with alcoholic base yielded 7a, and diphenylacetic acid. The structure of 5a is in agreement with that proposed by Woerner and coworkers.[4] Product 5a can be obtained, in 50% yield, from ω-phenyldiazoacetophenone and 4a by heating the reactants in a benzene solution at 60-70° for 30 min., thus obviating the necessity of preparing diphenylketene.

The reaction of 4b with 1 afforded a mixture of trans-cis isomers 5b and 5c (4:1) in 65% yield. The spectral properties of 5b, 5c are consistent with the assigned structures. The evidence for a trans structure for 5b and cis for 5c is based on nmr data in analogy with the nmr chemical shifts of the methyl group and its geminal proton in trans and cis 2-methyl-3-phenylaziridine.[7] Unlike 5a, products 5b, 5c are stable on a silica gel plate, probably due to a steric effect imposed by the methyl group, rendering the N less accessible to acid. Treatment of 5b, 5c with conc. HCl-acetic acid at reflux temperature yielded -aminopropiophenone and diphenylacetic acid, and ozonloysis gave benzophenone.

The trans-cis mixture of 5b and 5c was slowly converted to the less sterically hindered cis isomer 5c by heating in benzene. (See Table I) The isomerization which is faster in methanol than in benzene may proceed via an azomethine ylid.[8]

TABLE I

Thermal Isomerization of 5b to 5c in Refluxing Benzene.

Heating time:	0 hr	5 hr	21 hr	50 hr	23 hr[a]
% 5b:	66	45	30	23	10
% 5c:	34	55	71	77	90

(a) in refluxing methanol.

The formation of 5 to the exclusion of lactones of type 3 is probably accountable by the greater reactivity of an azirinium ion as compared to an imminium ion causing regioselective ring closure of 9 through the more electronegative O rather than through C.

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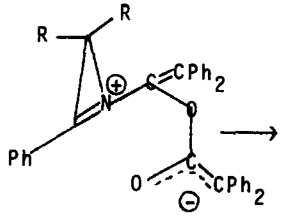
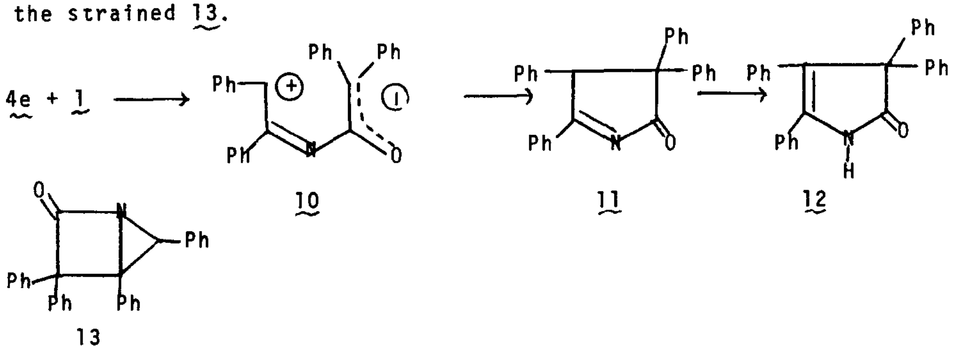


Unlike azirines 4a-d, 4e reacted with 1 to give 12, a 1:1 adduct, in low yield. The reaction is conceived to proceed through intermediates 10 and 11,[9] rather than through the strained 13.



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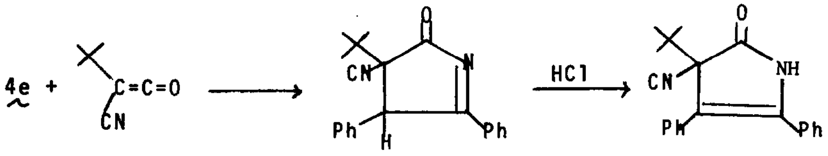
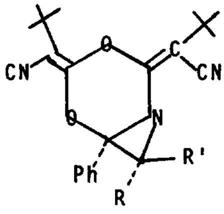
Evidence in support of the above postulate is the isolation of intermediate 15 from the reaction of 4e and t-butylcyanoketene (14).[10] Acid treatment of 15 gave 16.

Reaction of 4a-d with ketene 14 yielded fused aziridines 17 as single isomers (by nmr), which suggests a high degree of selectivity during bond formation between



15 16



17a, R,R':H
17b, R:CH_3, R':H
17d, R, R':CH_3

the azirine and the ketene as well as in the ring closure.[11]

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References

1. (a) Presented in past before the Symposium on Small Ring Heterocycles, 162nd ACS National Meeting, Washington, D.C., September 14, 1971; (b) Cycloadditions VII. For previous paper in series see R.M. Cory and A. Hassner, Tetrahedron Letters, in press.

2. (a) A. Padwa and J. Smolanoff, J. Amer. Chem. Soc., 93, 549 (1971); (b) V. Nair, Tetrahedron Letters, 4831 (1971).

3. (a) A. Hassner and F.W. Fowler, J. Amer. Chem. Soc., 90, 2869 (1968); (b) ibid. 90, 2875 (1968); (c) D.J. Anderson and A. Hassner, J. Amer. Chem. Soc., 93, 4339 (1971).

4. F.P. Woerner, H. Reimlinger and R. Merenyi, Ber., 104, 2786 (1971).

5. (a) R. Huisgen, B.A. Davis and M. Morikam, Angew. Chem. Internat. Ed., 7, 826 (1968); (b) F. Duran and L. Ghosez, Tetrahedron Letters, 245 (1970); (c) J.C. Martin, K.C. Brannock, R.D. Burpitt, P.G. Gott and V.A. Hoyle, Jr., J. Org. Chem., 36, 2211 (1971).

6. J.E. Baldwin and L.E. Walker, J. Org. Chem., 31, 3985 (1966).

7. (a) M.Y. Shandale, M.D. Solomon and E.S. Waight, Jr., J. Chem. Soc., 892 (1965); (b) K. Kotera, T. Okada and S. Miyazaka, Tetrahedron Letters, 5677 (1968); (c) S.J. Brois, J. Org. Chem., 27, 3532 (1962); (d) A. Hassner, G.J. Matthews and F.W. Fowler, J. Amer. Chem. Soc., 91, 5046 (1969).

8. R. Huisgen and H. Maeder, J. Amer. Chem. Soc., 93, 1777 (1971).

9. Ring opening of the azirinium ion intermediate is facilitated by the presence of the phenyl substituent at C-3 which stabilizes the positive charge in 10; hence, ring closure of 10 to 11 occurs before a second molecule of ketene can react as in the formation of 9.

10. H.W. Moore and W. Weyler, Jr., J. Amer. Chem. Soc., 93, 2812 (1971).

11. All compounds gave satisfactory elemental analysis (±0.3%) and consistent spectral data.