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[$6\pi+4\pi$] CYCLOADDITIONS OF 5-AZONIAFULVENE IONS WITH NITRONES AND AZOMETHINE IMINES.

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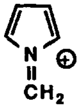
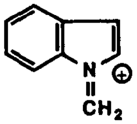
Summary. Nitrones as well as azomethine imines generated by the prototropic route from hydrazones are shown to add readily to the title iminium ions to give pyrrolo-annellated oxadiazine and triazine derivatives.

We recently demonstrated that N-*Mannich* bases of pyrrole and indole are suitable precursors for the 5-azoniafulvene ion 1 and its benzo-annellated analogue 2 respectively [1]. These novel iminium type ions combine structural and functional features that confer promising synthetic potential. Attack of nucleophiles occurs at the *exo*-cyclic carbon atoms, both under orbital and charge control, and restores the pyrrole or indole π-system. This, in turn, can serve as a handle for further transformation; or, in case of cyclization reactions, it can function as a terminator. The ions 1 and 2 are isoelectronic with fulvene and benzofulvene respectively, and hence, they may undergo similar cycloaddition reactions.



1

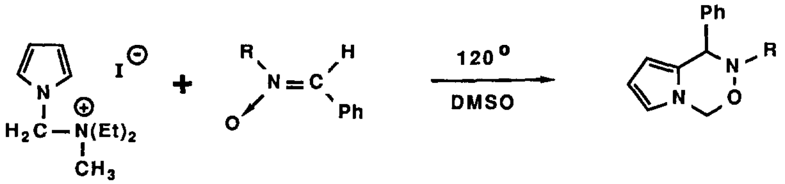


2

Fulvene can react as 6π, 4π, and 2π addend depending upon the nature of the reaction partner. Its periselectivity in cycloadditions has therefore been a favourite topic of frontier MO theory [2]. When allowed to react with 1,3-dipolar reagents with high lying HOMOs, fulvene is reported to behave as a 6π system [3][4]. This prompted us to attempt corresponding cycloadditions with the ions 1 and 2.

In the present communication we wish to report that nitrones and azomethine imines add efficiently to ion 1 in a formal [6π+4π] fashion to give novel pyrrolo-annellated oxadiazine and triazine derivatives respectively. The corresponding reactions of the indole derived ion 2, though feasible, are less efficient, mainly for electronic reasons.

Heating (120 C/4h) of a 0.2 M solution of the quaternary ammonium salt 3 [1] in anhydrous DMSO with 1.5 equiv. of N-methyl-C-phenyl nitrone 4 and 0.1 equiv. of Et_3N gave 2-methyl-1-phenyl-2H-1,4-dihydro-pyrrolo[2,1-d][1,2,5]oxadiazine 5 (m.p. 45-46 C) after the hydrolytic work-up and medium pressure chromatography (silicagel 40-65 μm, hexane-AcOEt 3:1) in 87% yield [5].



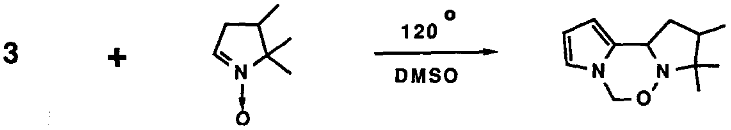
3

4 R = CH_3

6 R = Ph

5 R = CH_3 (87 %)

7 R = Ph (92 %)



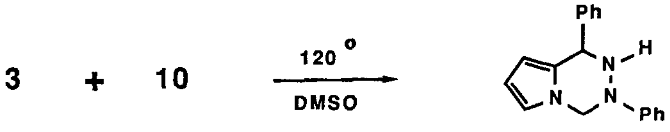
cis / trans = 0.38

8

9 (91 %)

10

10 '

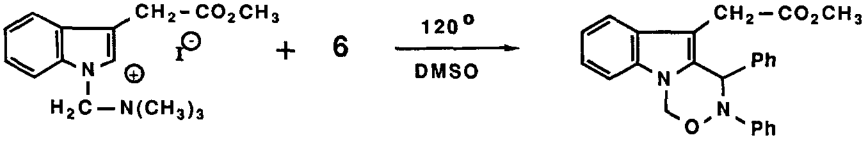


11 (82 %)

Monitoring the formation of adduct 5 by NMR-spectroscopy revealed that the kinetics follow a first order rate law with respect to the quaternary salt 3 [k_1 (DMSO-d6/110 C) = 6.0 $10^{-5}s^{-1}$]. The process is independent of the nitrone concentration. Et_3N, which is not essential for the reaction, was omitted in the kinetic measurements. This finding clearly shows that the rate determining step is the formation of the free azoniafulvene ion 1, which is subsequently intercepted by the nitrone.

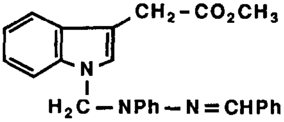
Other nitrones, *e.g.* C,N-diphenyl nitrone **6** or pyrroline-N-oxide **8**, react with 3 in analogous fashion and in equally high yield. For the latter case, modest *stereo*-selectivity with respect to the non-geminal methyl group is observed. The *trans*-stereochemistry is tentatively assigned to the major adduct. However, all the cycloadditions are *regio*-specific, *i.e.* the oxygen atom of the nitrone adds to the *exo*-cyclic carbon atom of the azoniafulvene unit, and C-C bond formation occurs at the α-position of the pyrrole ring.

In principle this [6π+4π] cycloaddition can be extended from nitrones to other 1,3-dipolar reagents. However, the relatively high temperature necessary to produce the free ion 1 from the salt 3 (ca. 120 C), imposes severe restrictions upon the choice of the reaction partner. Nevertheless, azomethine imines, which are accessible under our reaction conditions by the prototropic route from hydrazones [6], add easily to ion 1 to give tetrahydro triazine derivatives. This is shown above for the reaction of 3 with the N-phenylhydrazone of benzaldehyde 10. The latter is known to be in equilibrium with the corresponding diphenyl azomethine imine **10'** [7]. The yield of the cycloadduct 11 again is high (82 %).



12

13 (22%)



14

The indole derived quaternary salt 12 [8], with conditions identical to those chosen for the pyrrole series above, reacts with nitrone **6** to give the cycloadduct **13**. However, the yield is low, *i.e.* 22% of **13** *vz.* 92% of the pyrrole derived **7**. This sharp drop in yield probably reflects the low reactivity of the indolic C(α)-position towards electrophiles and suggests a stepwise ionic mechanism for the cycloaddition process. In this respect, the reaction of the salt **12** with the phenyl hydrazone **10** is even more revealing. It gives the open chained hydrazone **14** in 76% yield, instead of a cycloadduct analogous to the triazine **11**. Clearly, the initial C-N bond formation between the benzazoniafulvene ion and the azomethine imine (or a tautomer thereof) has occurred in the expected way, but the final cyclization step, i.e. the intramolecular aromatic substitution, cannot compete with a premature deprotonation.

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[5] All new compounds gave correct elemental analyses (C,H,N) or high resolution mass spectra, and ^{1}H- and ^{13}C-NMR spectra fully consistent with the structures indicated.

Characteristic of all the new cycloadducts is a sharp [AB] spin pattern for the N-CH_2 group which appears in the ^{1}H-NMR range of δ(ppm) 5.7 ± 0.5

Compound **5**, for instance, has the following NMR data:

^{1}*H-NMR* (200 MHz, $CDCL_3$) δ(ppm): 2.63 (3H,s,CH_3); 4.8 (1H,s,H-C-Ph); 5.5 + 6.15 + 6.6 (3H,pyrrolic [ABC]); 5.56 + 5.88 (2H,[AB],J=8.2,N-CH_2); 7.4 (5H,m,H of Ph).

^{13}*C-NMR* (50 MHz, $CDCL_3$) δ(ppm): 43.64 (CH_3); 71.02 (CH); 78.91 (CH_2); 105.1 (CH); 108.6 (CH); 114.4 (CH); 128.4 (2×CH); 128.5 (CH); 129.3 (2×CH); 130.1 (C) and 138.8 (C).

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