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An Unusual Rearrangement of Isoxazoles to 2-Alkenoylpyrroles or 1-Azafulvenes

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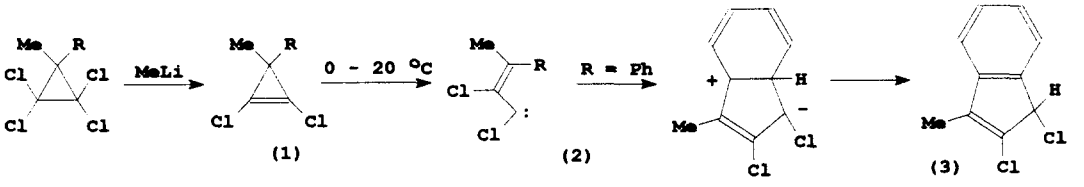
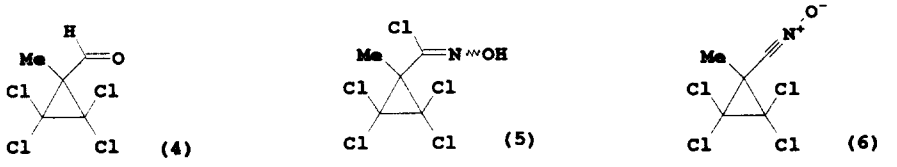
Abstract: Intramolecular interaction of vinylcarbenes derived from 1,2-dichlorocyclopropenes with isoxazoles or bicyclic isoxazolines can lead to a rearrangement with the formation of 1-azafulvenes or derived 2-alkenoylpyrroles. © 1997 Published by Elsevier Science Ltd.

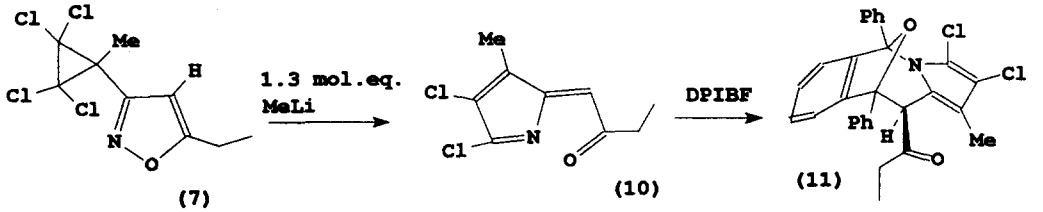
We reported some time ago that, although 3,3-dialkyl-1,2-dichlorocyclopropenes (**1**) are often stable for a considerable period on standing in either ether or chloroform at ambient temperature, they react rapidly in the presence of an added alkene to give products apparently derived by ring-opening to a 1,2-dichlorovinylcarbene (**2**) and trapping of this by the alkene.[1-6] In the case of unsymmetrically 3,3-disubstituted compounds, there was a high degree of stereocontrol in the ring-opening. We have also briefly reported that 3-methyl-3-phenyl-1,2-dichlorocyclopropene (**1**, R = Ph), derived by dechlorination of the corresponding tetrachlorocyclopropane by reaction with methyllithium, cannot be isolated and under the reaction conditions rearranges to a dichloro-indene (**3**) in good yield.[7] We now report that a number of tetrachlorocyclopropanes bearing an isoxazole or bicyclic isoxazoline at C-3 also lead directly to apparent products of intramolecular trapping of a vinylcarbene of type (**2**) derived from a dichlorocyclopropene on reaction with methyllithium at 0 - 20 °C.



The aldehyde (**4**), readily available from chloretone,[8] was converted into the corresponding oxime and N-chloro-oxime (**5**) by standard methods;[9] reaction of this with triethylamine in ether generated the nitrile oxide (**6**) which could be trapped either by an added terminal alkyne such as but-1-yne to give (**7**)[10] or an added cyclopropene such as 1-butylcyclopropene or 3-methyl-3-phenylcyclopropene to give (**8**)[11] or (**9**) respectively.

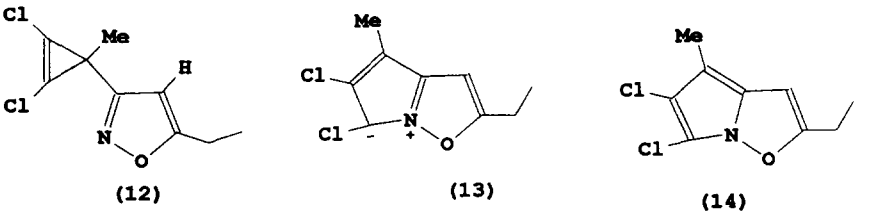


Reaction of the tetrachloride (7) with 1.3 mol.equiv. of MeLi at 0 - 20 °C for 15 m followed by quenching with water at 0 °C led to the methylenepyrrole (10)[12] which could be trapped in 40 % yield as the [6+4]-cycloadduct (11) with diphenylisobenzofuran: [13]



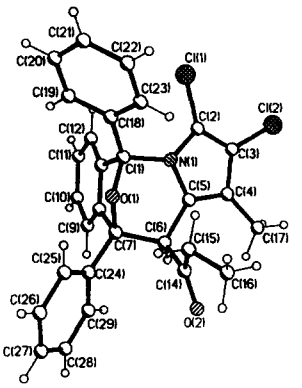
(7) (10) (11)

The structure of compound (11) was confirmed by X-ray crystallography on a single crystal,[14] and is shown in Fig. 1. The formation of (10) may be explained in terms of an initial 1,2-dechlorination to produce the cyclopropene (12) followed by ring-opening of this to the corresponding vinylcarbene which cyclises to (13) and (14);* fragmentation would then generate the observed azafulvene:



(12) (13) (14)

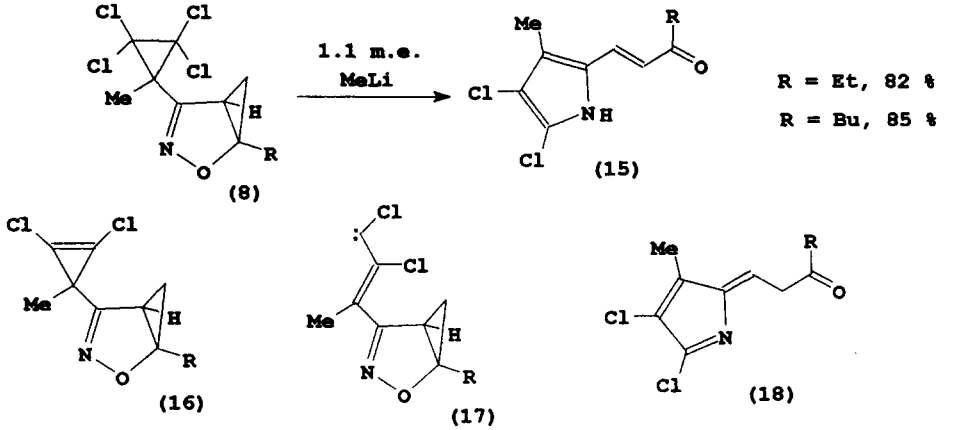
Fig. 1 X-Ray crystal structure of (11)



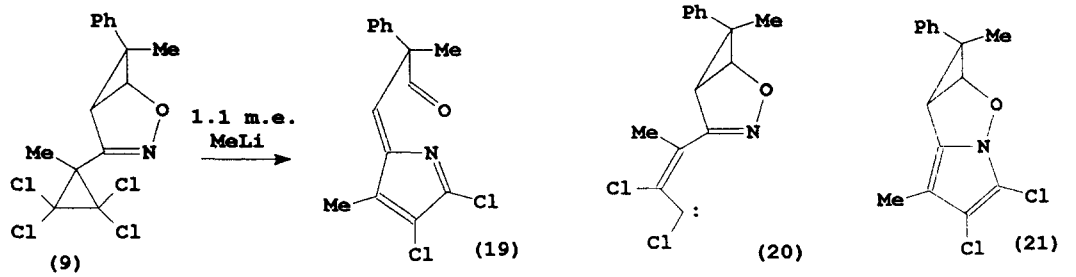
The 1-azafulvene sub-unit is present in roseophilin, which shows submicromolar cytotoxicity against a number of human cancer cell lines.[15] A 2,3-dibromo-2-azafulvene has been reported as an intermediate in the synthesis of hymenin, a sponge metabolite which shows potent α-andrenoreceptor blocking properties, and which itself contains the 2,3-dibromopyrrole-5-carboxamide functionality.[16] Hydrolysis of 6-dialkylamino-1-azafulvenes has been used in routes to synthetically valuable 5-substituted pyrrolecarboxaldehydes.[17] 1-Azafulvene itself has been used as an intermediate in routes to 2-aminomethylpyrroles.[18]

In a related reaction, the cyclopropanes (8), derived by trapping of the nitrile oxide (6) with 1-alkyl-cyclopropenes,[19] react with methyllithium to give pyrroles (15).[20] The reaction may again be explained in terms

of the formation of the cyclopropene (16) and ring-opening to (17) followed by cyclisation as above; however, in this case fragmentation apparently generates a methylenepyrrole (18) which may rearrange to the corresponding pyrrole through a prototropic shift:



Support for this is seen in the reaction of the corresponding 3,3-disubstituted compound (9), derived by trapping of (6) with 3-methyl-3-phenylcyclopropene,[21] when the prototropic shift is not available and the 1-azafulvene (19)[22] is isolated in moderate yield (40 %):



This may again be explained in terms of the 1,2-dechlorination of (9) to the corresponding cyclopropene (which could be trapped in reasonable yield when the reaction was carried out in the presence of diphenylisobenzofuran), ring-opening to (20) and cyclisation of this as before to (21), which could rearrange to the 1-azafulvene. Unlike (10), compound (19) was not trapped by reaction with diphenylisobenzofuran.

Thanks are due to the EPSRC for the provision of equipment to WC.

* In the reactions reported here, it has not yet been possible to trap an intermediate carbene intermolecularly, and mechanisms not involving carbenes cannot be completely excluded.

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10. Compound (7) (81 %) showed 6.1 (1 H, s), 2.8 (2 H, q, J 7.5 Hz), 1.7 (3 H, s), 1.3 (3 H, q, J 7.5 Hz). Attempted trapping of (6) by non-terminal alkynes such as but-2-yne did not proceed in high yield and dimers of the nitrile oxide were obtained.
11. Compound (8, R = Et) (76 %) showed δ_H 2.4 (1 H, dd, J 3.7, 9.4 Hz), 2.0 (1 H, sex, J 7.5 Hz), 1.8 (1 H, sex, J 7.5 Hz), 1.7 (3 H, s), 1.1 (1 H, dd, J 5.5, 9.4 Hz), 1.0 (3 H, t, J 7.5 Hz), 0.4 (1 H, dd, J 3.7, 5.5 Hz); δ_c 159.3, 65.8, 40.7, 29.9, 24.4, 20.4, 20.3, 15.3, 11.9, 10.3.
12. Compound (10) showed δ_H 5.7 (1 H, s), 2.8 (2 H, q, J 7.5 Hz), 1.7 (3 H, s), 1.3 (3 H, t, J 7.5 Hz). Although it was stable for some minutes in deuterochloroform, (10) decomposed relatively quickly to a mixture; in the absence of solvent, this decomposition could be very **VIGOROUS**.
13. Compound (11), m.p. 160 - 162 °C, showed δ_H 7.6 - 7.0 (14 H, m), 4.4 (1 H, s), 2.7 (1 H, dq, J 18.6, 7.2 Hz), 2.4 (1 H, dq, J 18.6, 7.5 Hz), 1.7 (3 H, s), 0.7 (3 H, t, J 7.2 Hz); δ_c 206.7, 144.9, 142.1, 137.7, 130.1, 129.0, 128.7, 128.4, 128.3, 122.1, 121.1, 120.8, 118.7, 113.5, 111.4, 98.7, 86.7, 58.1, 53.4, 32.6, 8.6, 7.6.
14. Compound (11) crystallises in the monoclinic space group P2/n with a = 9.3161(5), b = 16.4939 (8), c = 15.4460(8)Å, β = 96.992(2)°, Z = 4. The structure was solved from 5418 independent diffractometer reflections ($2\theta<57°$, Mo-Kα radiation) collected at 160 K and refined on F° values to R_w = 0.0867 (conventional R = 0.0338 for 4965 observed F values).
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19. The regiochemistry of such additions is often controlled by steric factors (see eg., Al Dulayymi, J.R.; Baird, M.S.; Pavlov, V.A.; Kurdjukov, A.I. *Tetrahedron*, **1996**, *52*, 8877.
20. Compound (15, R = Et) showed showed δ_H 9.4 (1 H, br.s), 7.4 (1 H, d, J 16.0 Hz), 6.3 (1 H, d, J 16.0 Hz), 2.66 (2 H, q, J 7.3 Hz), 2.1 (3 H, s), 1.1 (3 H, t, J 7.3 Hz).
21. The stereochemistry of this was assigned by analogy with related compounds (Bolesov, I.G.; Ignatchenko, A.V.; Bovin, N.V.; Prudchekno, I.A.; Surmina, L.S.; Plemenkov, V.V.; Petrovskii, I.A.; Romanov, I.V.; Mel'nik, I.I. *J.Org.Chem.(USSR)*, **1990**, *26*, 87.
22. Compound (19) showed δ_H 9.1 (1 H, s), 7.5 - 7.1 (5 H, m), 6.7 (1 H, br.s), 2.0 (3 H, br.s), 1.9 (3 H, br.s); δ_C 157.6, 141.3, 127.8, 127.5, 127.4, 126.1, 122.8, 117.9, 18.0, 10.3.

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