Synthesis of Oxetanes by Photoaddition of Carbonyl Compounds to Thiophene Derivatives

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2,3-Dimethyl, 3,4-dimethyl and 2,3,5-trimethylthiophene were synthesized and subjected to interaction with excited benzophenone. 2,3-Dimethylthiophene affords an oxetane in good yield. These experiments were carried out in order to generalize this reaction which thus far has only been successful with 2,5-dimethylthiophene.

Sir:

Thiophene and many of its derivatives undergo benzophenone photosensitized 2 + 2 cycloaddition reactions in the presence of substances such as methyl-substituted maleic anhydrides (1). However, it has been reported (2) and confirmed in this laboratory that thiophene is rather inert in the presence of photochemically excited benzophenone to undergo oxetane formation. Furthermore, 2-and 3-methylthiophene appear to be as inert as thiophene itself in oxetane forming reactions. Thus far the only thiophene derivative that has been reported to be a good substrate for excited carbonyl compounds is 2,5-dimethylthiophene (3). Several authors have speculated that the innertness of thiophene towards this kind of reaction is due to its highly aromatic character. Nevertheless, the lack of reactivity of thiophene may be viewed from another angle; it may well behave as a quencher of the triplet state of the ketones normally used to synthesize oxetanes or perhaps it may be explained as a combination of both factors. Since electron donating groups attached to an unsaturated system presumably raise its lower triplet energy level (4) one would expect that 2- and 3-methylthiophene would be more reactive than thiophene. However, one methyl group may not be as effective as two in raising the lowest $n\pi^*$ triplet energy level as may be inferred from the reactivity of 2,5-dimethylthiophene.

In order to test these speculations, based on the reactivity of one compound, 2,3- (I), 3,4-dimethylthiophene (II) and 2,3,5-trimethylthiophene (III) were prepared and used as substrates in the presence of excited benzophenone; 2,3-dimethylthiophene yields a product IV which results from the addition of one molecule of benzophenone to the heterocycle while 3,4-dimethylthiophene and 2,3,5-trimethylthiophene afford only polymeric materials.

The structural assignments for compound IV were made on the basis of spectral data, especially nmr and mass spectra, where the analogies to the many similar oxetanes previously studied in this laboratory were taken in to consideration.
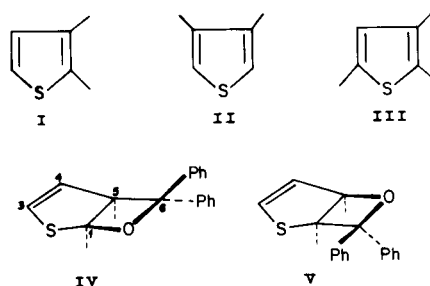

Figure 1

In compound IV, the preference of benzophenone for the double bond with a higher degree of substitution is consistent with its behavior towards methyl-substituted furans (5,6). The evidence for this structural assignment comes from the fact that the nmr spectrum of compound IV exhibits two mutually coupled olefinic proton signals. Therefore, the benzophenone must have added to the 2,3-dimethylthiophene C(1) = C(5) double bond bearing the methyl substituents.

The only ambiguity in the structural assignment for compound I would be in relation to the position of the oxygen. Several reasons would point to structure IV as a better choice than isomer V.

First of all, NOE studies carried out on several oxetanes derived both from methylfurans and from 2,5-dimethylthiophene left no doubt as to the position of the oxygen in oxetanes derived from addition of the molecule of benzophenone to five-membered heterocycles (5). On the other hand the biradical intermediate that gives rise to structure IV should be more stable than the one that could give rise to structure V. Furthermore, the chemical shift for the methyl group on C-1 is at a low enough field, δ 2.25 ppm, as could be expected for such a group being located between two heteroatoms such as S and O. Finally, the mass fragment M/e 251 corresponds to a loss of -CH$_3$CO (a on Table I) which has been observed in the mass fragmentation of the oxetane derived from benzophenone and 2,5-dimethylthiophene and it is rather strong evidence that the location of the oxygen atom in the four membered

Scheme I
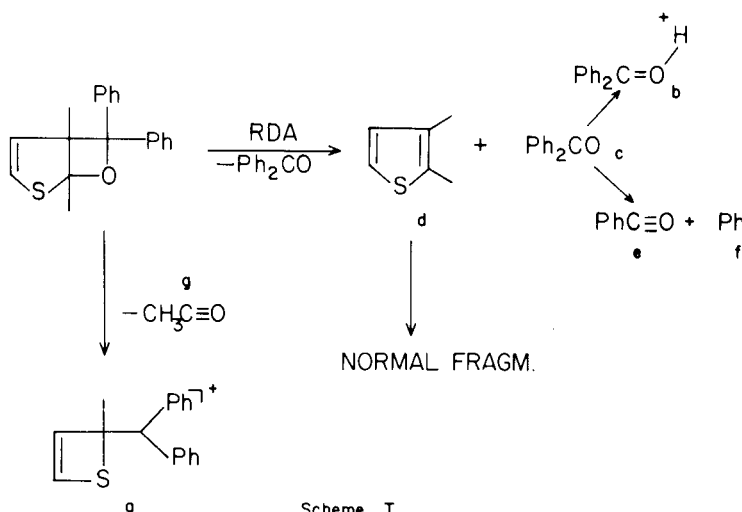
ring is next to the carbon atom adjacent to the heteroatom in the five-membered ring (6).

It is interesting to note that single oxetanes, namely those derived from addition of one molecule of benzophenone to one molecule of a five-membered heterocycle have always been found to have the oxygen atom of the oxetane ring located in position 7. There are very few examples reported in the literature of oxetanes of this type with oxygen in position 6 (8).

The stereochemistry of compound IV may presumably be depicted as illustrated in Figure 1 by analogy to that of many oxetanes studied using NOE techniques (5). That these cycloadditions generally occur in a cis manner has been demonstrated for many analogous oxetanes by observing the NOE interactions between protons located at C-1 and C-5.

Table I

Nmr, Mass Spectral and Physical Data for Compound IV

Kind of Data	Protons	Chemical Shift (ppm)	Integral and Multiplicity	Coupling Constants (Hz)
Nmr (a)	C-3	6.80	1d	
	C-4	6.60	1d	$J_{3,4}$ 3.8
	CH_3-1	2.25	3s	$J_{4,3}$ 3.8
	CH_{3-5}	2.08	3s	

Mass (b)								
m/e	M^+	a	b	c	d	e	f	g
	249	251	183	182	112	105	77	43
%	5	6	82	62	100	98	92	24

Physical	Mp. °C	Yield %	Empirical Formula	Analysis			
				C	H	S	O
	148	60	$C_{19}H_{18}SO$ (c)	77.50	6.12	10.88	5.44
			(d)	77.30	6.90	10.78	5.53

(a) Aromatic protons appear as a multiplet at 7.2 ppm. (b) All the mass fragments on this Table refer to Scheme I. (c) Calculated. (d) Found.

Further studies on cycloadditions of other carbonyl compounds, different from benzophenone, to 2,3-dimethylthiophene as well as the use of other di- tri- and tetramethyl substituted substituted thiophenes in these type of reactions are in hand. In addition to arguments based on synthetic studies, quantitative data on the thiophene quenching of photoreduction and photocycloaddition reactions of carbonyl compounds are gathered and analysed and will be reported at a later date.

EXPERIMENTAL

All nmr spectra were measured at approximately 30° with a Varian 390 spectrometer, TMS as an internal standard. The mass spectra were determined in a Dupot 21492B spectrometer. The elemental analyses were performed by Franz Pascher Mikroanalytisches Laboratorium, Bonn, Germany.

2,3-Dimethyl and 2,3,5-trimethylthiophene were prepared by Wolf-Kishner reduction of 3-methyl-2-thiophenecarboxaldehyde and 2,5-dimethyl-3-thiophenecarboxaldehyde, respectively, according to the method of King and Nord (10). 3,4-Dimethylthiophene was prepared by decarboxylation of 3,4-dimethylthiophene-2,5-dicarboxylic acid according to the method of Trost, Atkins and Hoffman (11).

The general procedure for the photolysis reactions was to dissolve stechiometric amounts (0.003 mole) of benzophenone and of the corresponding thiophene derivative in 100 ml. of dry benzene. The reaction mixture was irradiated with a Hanovia 450 watt medium pressure mercury arc in a quartz apparatus with a pyrex filter sleeve at approximately 0°. Nitrogen was bubbled through the solution before and during irradiation.

1,5-Dimethyl-6,6-diphenyl-2-aza-7-oxabiciclo[3,2,0]-Δ³-heptene (IV).

Benzophenone 550 mg (0.003 mole) and 2,3-dimethylthiophene (I) 350 mg (0.003 mole) were dissolved in dry benzene (100 ml) and irradiated as described in the general procedure. Crystals begin to appear on the walls of the irradiation vessel shortly after turning on the uv light. After 10 hours exposure the irradiation was stopped and the solvent distilled under vacuum; the crystalline residue was recrystallized from chloroform-petroleum ether (1:1) and dried under vacuum. The chemical yield was calculated on the basis of benzophenone consumed. All the spectral and physical data are presented in Table I.

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