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Cycloaddition profile of pentafulvenes with 3-oxidopyrylium betaine: experimental and theoretical investigations

Jinesh M. Kuthanapillil[a,b], A. Nijamudheen[c], Nayana Joseph[a], Praveen Prakash[a], E. Suresh[d], Ayan Datta[c,*], K.V. Radhakrishnan[a,*]

[a] National Institute for Interdisciplinary Science and Technology, CSIR (Formerly Regional Research Laboratory), Trivandrum 695019, Kerala, India
[b] Department of Chemistry, St. Berchmans College, Changanacherry, Kottayam 686101, Kerala, India
[c] Indian Association for the Cultivation of Science, 2A&2B Raja S.C. Mullick Road, Jadavpur, Kolkata 700032, India
[d] Central Salt and Marine Chemicals Research Institute, Bhavnagar 364 002, India

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ABSTRACT

A detailed investigation on the effect of solvent polarity, temperature, and microwave irradiation on periselectivity in cycloaddition reactions of pentafulvenes with 3-oxidopyrylium betaine is described. The base catalyzed generation of 3-oxidopyrylium betaine in $CHCl_3$ resulted in the exclusive formation of [6+3] adducts. With increase in solvent polarity and temperature, mixtures of [6+3] and [3+2] adducts were formed, where as under microwave irradiation, [3+2] adducts were formed exclusively. The experimental results have been rationalized on the basis of theoretical calculations.

1. Introduction

Pentafulvenes have invoked considerable interest in organic synthesis due to their excellent reactivity in cycloaddition reactions and the versatility of the reaction products.[1] They perform flexibly as 2π,[2] 4π[3] or 6π[4] candidates in cycloaddition reactions and have been identified as the well known construction unit for many fused ring systems through intra- and intermolecular cycloaddition reactions.[5] In addition, they have been exploited as key intermediates in the synthesis of many biologically active natural products such as hirsutene,[6] capnellene,[7] β-vetivone,[8] titanocene anticancer drugs[9] and various aminocyclopentitols with glycosidase inhibitory activity.[10]

3-Oxidopyrylium betaines, derived from pyranulose acetate, are versatile cycloaddition components capable of demonstrating various cycloaddition profiles.[11] 3-Oxidopyrylium betaines have been well utilized in the synthesis of cycloheptanoids. Hendrickson has reported the generation and cycloaddition of 3-oxidopyrylium betaines with a few electrophilic alkenes leading to oxabicyclo [3.2.1] systems.[12] Later, Sammes has demonstrated the utility of 3-oxidopyrylium betaines for the synthesis of oxabicyclic systems by cycloaddition with electron rich and electron deficient alkenes.[13] Wender has exploited the intermolecular cycloaddition of 4-methoxy and 4-silyloxy-3-oxidopyrylium betaines in the construction of phorbol framework.[14] In recent work, we have reported a novel and efficient dipolar cycloaddition of pentafulvenes with 3-oxidopyrylium betaines, leading to oxabridged bicyclo[6.3.0] undecanes and polycyclic systems.[15] In this contribution, we disclose an easy preparation of a wide range of oxabridged bicyclo [5.3.0]decane systems with potential applications in the synthesis of a variety of bioactive natural products. The 3-oxidopyrylium betaine used in the study was generated from pyranulose acetate either by adding a base at room temperature or by heating pyranulose acetate at 140 °C or under microwave irradiation. The experimental findings were rationalized by theoretical calculations. The details of our investigations are presented in the following sections.

2. Results and discussion

2.1. Base catalyzed generation of 3-oxidopyrylium betaine

Pentafulvenes selected for our studies were synthesized from the corresponding ketone following Little's procedure.[16] The pyranulose acetate,[17] precursor for 3-oxidopyrylium betaine, was

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* Corresponding authors. Fax: +91 471 2491712 (K.V.R.); e-mail addresses: spad@iacs.res.in (A. Datta), radhu2005@gmail.com, radhu@niist.res.in (K.V. Radhakrishnan).

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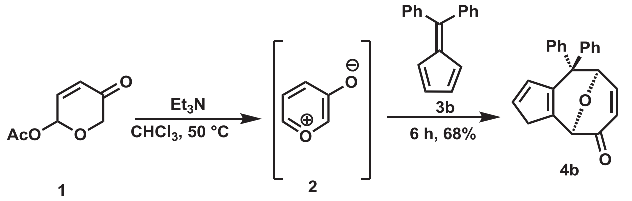
synthesized from corresponding furfuryl alcohol by oxidation with *N*-bromosuccinimide followed by protection with acetic anhydride in the presence of pyridine and DMAP.

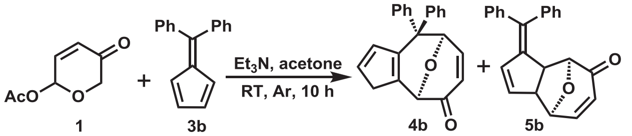
In our previously reported [6+3] cycloaddition approach,[15a] pentafulvenes were allowed to react with 3-oxidopyrylium betaine in chloroform under basic conditions whereby obtaining moderate to good yields of the 5–8 fused adduct (Scheme 1). We also carried out theoretical calculations to rationalize these results, which envisioned several modes of cycloadditions between pentafulvenes and 3-oxidopyrylium betaine.[15b] Theoretical studies supported the formation of the experimentally observed [6+3] adduct, as it had most stable optimized geometry with the least activation barrier.



Scheme 1. Base catalyzed cycloaddition of diphenyl fulvene with 3-oxidopyrylium betaine in chloroform as the solvent.

Later we found that the cycloaddition of adamantylidenefulvene and 6,6-dithiodimethylene fulvene with 3-oxidopyrylium betaine in chloroform gave [6+3] adduct as the major product and [3+2] adduct as the minor product.[15c] In the context of our general interest in the chemistry of pentafulvenes, aimed at the construction of complex and structurally interesting polycyclic systems,[15,18] we undertook a detailed study on the effect of solvent, temperature and microwave irradiation on periselectivity in cycloaddition reaction of a variety of pentafulvenes towards 3-oxidopyrylium betaine.

In an initial experiment, when chloroform was replaced with acetone a mixture of [6+3] and [3+2] adducts were obtained (Scheme 2).



Scheme 2. Base catalyzed cycloaddition of diphenyl fulvene with 3-oxidopyrylium betaine in acetone as the solvent.

The product **5b** was characterized on the basis of spectroscopic data and stereochemistry was unambiguously confirmed by single crystal X-ray analysis (Fig. 1).[19]

Similar reactivity was observed with other pentafulvenes and 3-oxidopyrylium betaine in acetone (entries 4–6, Table 1). The reaction was repeated with a number of solvents with different polarity and the results are summarized in Table 1. On employing chloroform as the solvent, the reactions furnished exclusively the [6+3] adduct (entries 1–3, Table 1). With increase in polarity of the solvent, percentage of [3+2] adduct increases and finally we obtained better yield of [3+2] adduct in DMSO (entries 16–18, Table 1). It is to be noted that diphenyl fulvene gave only a single [3+2] adduct where as dimethyl fulvene and cycloalkyl fulvenes afforded an inseparable (1:1) regioisomeric mixture of [3+2] adducts. This can be attributed to the difference in the electronic nature between phenyl substituents and alkyl substituents at the exocyclic position

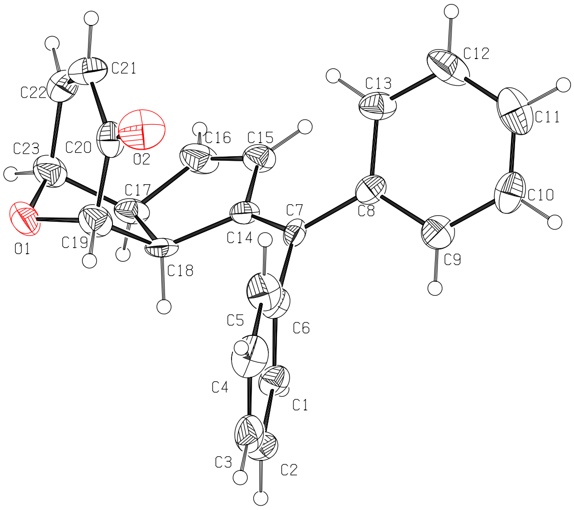
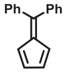
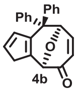
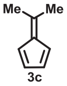
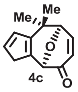
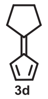
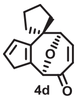
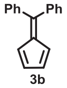
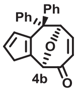
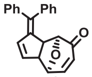
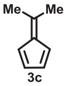
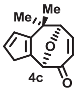
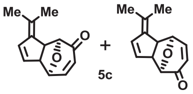
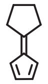
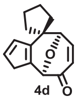
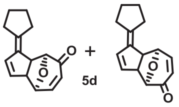
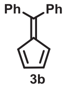
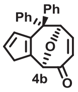
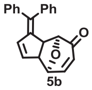
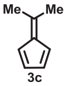
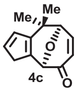
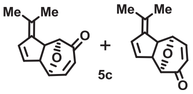
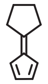
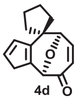
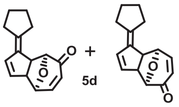
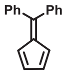
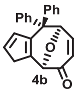
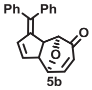


Fig. 1. ORTEP plot for X-ray crystal structure of **5b**.

Table 1
Solvent optimization studies for the better yield of [3+2] adduct in the cycloaddition of pentafulvenes with 3-oxidopyrylium betaine **2**

Entry	Fulvene	Solvent	Products		Yield	
			6+3	3+2	6+3	3+2
1	 3b	$CHCl_3$	 4b		72	0
2	 3c	$CHCl_3$	 4c		83	0
3	 3d	$CHCl_3$	 4d		72	0
4	 3b	$(CH_3)_2CO$	 4b	 5b	54	14
5	 3c	$(CH_3)_2CO$	 4c	 5c	58	18
6	 3d	$(CH_3)_2CO$	 4d	 5d	55	15
7	 3b	CH_3CN	 4b	 5b	44	26
8	 3c	CH_3CN	 4c	 5c	50	30
9	 3d	CH_3CN	 4d	 5d	42	28
10	 3b	DMF	 4b	 5b	38	36