APPLICATIONS OF SULFUR YLIDES IN THE SYNTHESIS OF DIHYDROBENZOFURANS AND AZETIDINES

by

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Submitted

in fulfillment of the requirements of the degree of

Doctor of Philosophy

to the

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Dedicated

To

My Parents

CERTIFICATE

This is to certify that the thesis entitled, **"Applications of sulfur ylides in the synthesis of dihydrobenzofurans and azetidines"**, being submitted by Ms. Sarika Malik, to the Indian Institute of Technology, Delhi, for the award of the degree of 'Doctor of Philosophy in Chemistry', is a record of bonafide research work carried out by her. Ms. Sarika Malik has worked under my guidance and supervision and has fulfilled all the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard. The results embodied in this thesis have not been submitted, in part or in full to any other University or Institute for the award of any degree or diploma.

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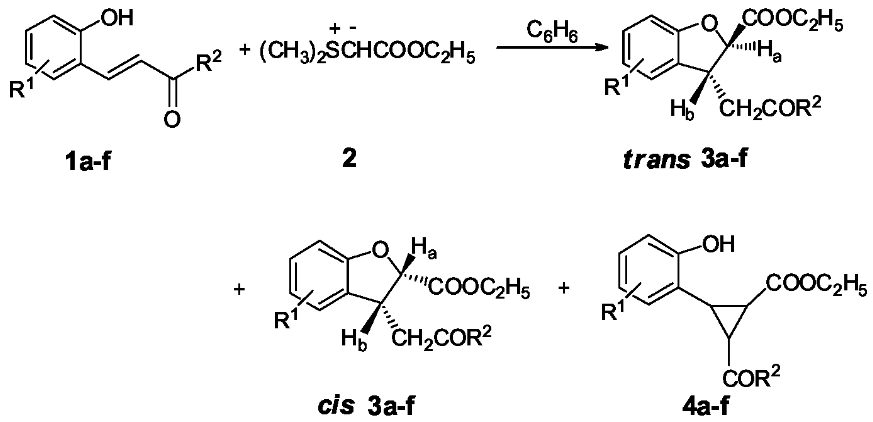
SARIKA MALIK

ABSTRACT

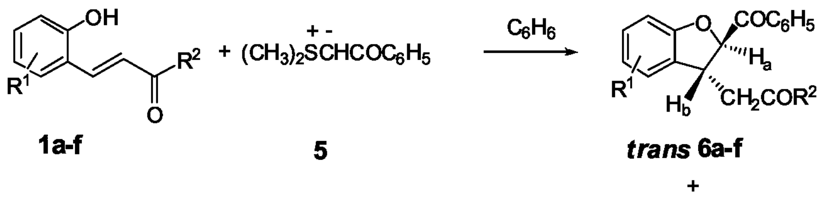
Sulfur ylide mediated reactions have attracted much attention in synthetic organic chemistry. Methylene group transfer from sulfur ylides has been extensively used for the synthesis of cyclopropanes, oxiranes and aziridines.

2,3-Dihydrobenzofurans and azetidines are important class of compounds because of their presence in a variety of biologically active natural products. The thesis deals with the applications of sulfur ylides for the synthesis of 2,3-dihydrobenzofurans and azetidines. Stereochemical investigations of azetidines through single crystal X-ray have also been done. The thesis has been divided into four chapters. **Chapter I** describes a brief literature survey on the recent developments in the synthesis of various kinds of compounds through sulfur ylide mediated reactions. **Chapter II** deals with the diastereoselective synthesis of 2,3-disubstituted dihydrobenzofurans through the reactions of 2-hydroxyaryl-α,β-unsaturated ketones with dimethylsulfonium carbonyl methylides. The methylene group transfer reactions of 2-hydroxyaryl-α,β-unsaturated ketones **1a-f** with dimethylsulfonium carboethoxymethylide **2** gave diastereoisomeric mixtures (*trans*>>*cis*) of 2-ethoxycarbonyl-3-substitutedmethyl-2,3-dihydrobenzofurans **3a-f** along with minor inseparable stereoisomeric mixtures of cyclopropanes **4a-f** (Scheme 1). The methylene group transfer reactions of dimethylsulfonium phenacylide **5** with 2-hydroxyaryl-α,β-unsaturated ketones **1a-f** yielded exclusively *trans* isomers of 2-benzoyl-3-substitutedmethyl-2,3-dihydrobenzofurans **6a-f** along with cyclopropane derivatives **7a-f** (Scheme 2).



(a) R^1 = H, R^2 = CH_3 (b) R^1 = H, R^2 = C_6H_5
(c) R^1= H, R^2 = 4-Cl-C_6H_4 (d) R^1 = H, R^2 = 4-OC_2H_5-C_6H_4
(e) R^1= 3-CH_3, R^2 = C_6H_5 (f) R^1= 5-Cl, R^2 = C_6H_5

Scheme 1



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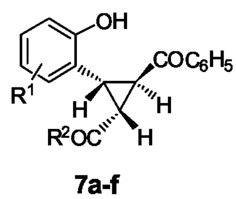
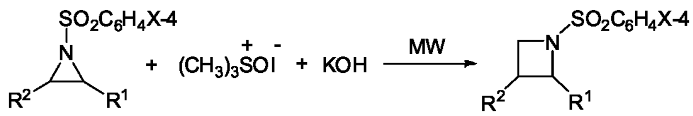


Scheme 2

The geometry of these isomers was assigned by coupling constant derived from ^{1}H NMR analysis. The geometry of compound **6c** has also been confirmed by single crystal X-ray. On the basis of results a plausible mechanism has been proposed which involves the initial formation of an intermediate by the attack of the ylide on the double bond, which undergoes elimination-cyclization to give the dihyrobenzofuran derivatives. The possibility of the formation of the dihydrobenzofurans through the opening of the initially formed cyclopropanes was ruled out as there was no change in their ratio even after prolonging the reaction time for additional 2 h. It has been observed that the reactions under microwave irradiation gave better yield of dihyrobenzofurans. **Chapter III** highlights the investigations of the synthesis of 1-arenesulfonylazetidines **9a-l** through the reactions of 1-arenesulfonylaziridines **8a-l** and dimethylsulfoxonium methylide (generated from trimethylsulfoxonium iodide and KOH) under microwave irradiation (Scheme 3). The results indicate that the reaction is highly stereospecific, *cis*-aziridines yield *trans*-azetidines and *trans*-aziridines leads to the formation of *cis*-azetidines. The regioselectivity of the reaction is substituent dependent and governed by both steric and electronic factors.

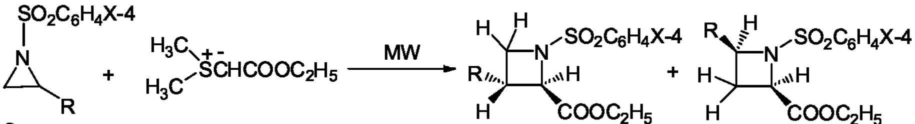


8a-l **9a-l**

(a) $R^1 = C_6H_5$, $R^2 = H$, $X = CH_3$ (b) $R^1 = C_6H_5$, $R^2 = H$, $X = H$
(c) $R^1 = C_6H_5$, $R^2 = H$, $X = Cl$ (d) $R^1 = 4\text{-}Cl\text{-}C_6H_4$, $R^2 = H$, $X = CH_3$
(e) $R^1 = 4\text{-}Br\text{-}C_6H_4$, $R^2 = H$, $X = CH_3$ (f) $R^1 = 4\text{-}CH_3\text{-}C_6H_4$, $R^2 = H$, $X = CH_3$
(g) $R^1 = C_6H_{13}$, $R^2 = H$, $X = CH_3$ (h) $R^1 = CH_3$, $R^2 = H$, $X = CH_3$
(i) $R^1 = CH_3$, $R^2 = C_6H_5$, $X = CH_3$ (j) $R^1 = C_6H_5$, $R^2 = C_6H_5$, $X = CH_3$
(k) $R^1 = C_6H_5$, $R^2 = C_6H_5$, $X = H$ (l) $R^1 = C_6H_5$, $R^2 = C_6H_5$, $X = Cl$

Scheme 3

The reactions of 1-arenesulfonylaziridines **8a-c** with dimethylsulfonium carboethyoxymethylide **2** under microwave irradiation yielded regioisomeric mixtures of 1-arenesulfonyl-*trans*-3-aryl-2-ethoxycarbonylazetidines **10a-c** and 1-arenesulfonyl-*cis*-4-aryl-2-ethoxycarbonylazetidines **11a-c** (**10a-c>>11a-c**) (Scheme 4). The stereochemical course of the reaction has been investigated on the basis of ^{1}H NMR and single crystal X-ray studies.

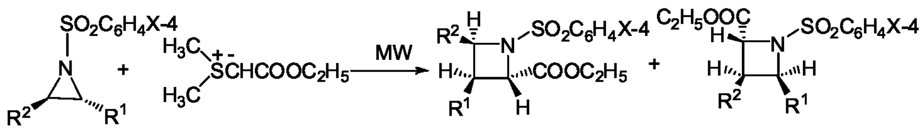


8a-c **2** **10a-c** **11a-c**

(a) R = C_6H_5, X = CH_3
(b) R = C_6H_5, X = H
(c) R = C_6H_5, X = Cl

Scheme 4

The reactions of *trans*-2,3-disubstituted aziridines **8i-k** and dimethylsulfonium carboethoxymethylide **2** gave 2,3,4-trisubstituted azetidines **12i-k** and **13i-k** (Scheme 5).



8i-k **2** **12i-k** **13i-k**

(i) R^1 = C_6H_5, R^2 = CH_3, X = CH_3
(j) R^1 = C_6H_5, R^2 = C_6H_5, X = CH_3
(k) R^1 = C_6H_5, R^2 = C_6H_5, X= H

Scheme 5

The results indicate that the reactions proceed with the inversion at the carbon suffering the nucleophilic attack of the ylide. **Chapter IV** focuses on the conformational studies of various 1-arenesulfonylazetidines through ^{1}H NMR and single crystal X-ray analysis. It has been found that in 1-arenesulfonylazetidines, the azetidine ring is not planar but puckered and puckering is relatively small. As substitution increases on the azetidine ring it tends to be more planar. A comparison of X-ray diffraction analysis of *cis*- and *trans*-2,3-diphenyl-1-(4-toluenesulfonyl)azetidines suggests that the *cis* isomers are somewhat more puckered than the corresponding *trans* isomers. Intermolecular hydrogen bonding (2.679 Å - 2.896 Å) and CH$\cdots\pi$ interactions (2.733 Å - 3.738 Å), in general, cause aggregation of these molecules in solid state.

CONTENTS