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Microwave Activated Diels-Alder Cycloaddition Reactions of 1, 2-Difluoro-1-chlorovinylphenylsulfone

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Abstract: Diels-Alder Cycloadditions of 1,2-difluoro-1-chlorovinylphenylsulfone with cyclopentadiene, furan and 1,3-diphenylisobenzofuran are studied under thermal and microwave activation conditions. Microwave heating is found to be more efficient method for condensation of fluorinated dienophile with dienes.

The Diels-Alder cycloaddition reaction is an important tool for construction of carbocycles and the application of this method for the preparation of fluorinated carbocycles using fluorinated dienophiles is the subject of current interest[1]. The main objective behind these studies is exploration of reactive fluorinated dienophiles and study of their application as building blocks in fluoroorganic synthesis[1,2].

Fluorinated vinyl compounds are sluggish dienophiles and the existing studies on these compounds are limited to reactions with reactive dienes such as cyclopentadiene. In most of these studies it is shown that cycloaddition of fluorinated dienophiles with furan is a failure since furan is a poor diene[3]. However, in cycloaddition of furan and fluorinated dienophiles is made feasible, it would give an easy entry to highly valuable functionalised carbocycles and exploration of easy and simple methods for this transformation are highly desired[2,4].

1,2-difluoro-1-chlorovinylphenylsulfone, **1** has been known in the literature for a long time[5,6]. However, studies on Diels-Alder cycloaddition reactions with this dienophile remained dormant. This has prompted us to study [4+2] cycloaddition reactions of this dienophile with typical dienes such as furan. cyclopentadiene and 1,3-diphenylisobenzofuran under conventional heating as well as under microwave irradiation. Under conventional heating (i.e. refluxing in a high boiling solvent, e.g. toluene), the dienophile. **1** has reacted excellently with cyclopentadiene and 1,3-diphenyl isobenzofuran in good yields (> 90%) taking reaction times 10 h and 36 h respectively but failed to react with furan even when refluxed in chlorobenzene (b. p. 132°C) for three days. However, under microwave irradiation **1** has shown remarkable

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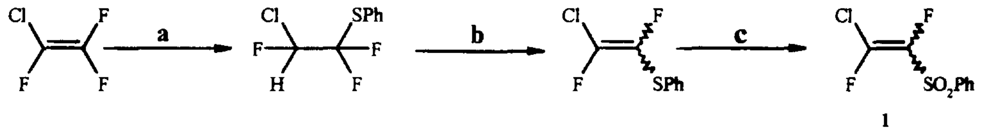
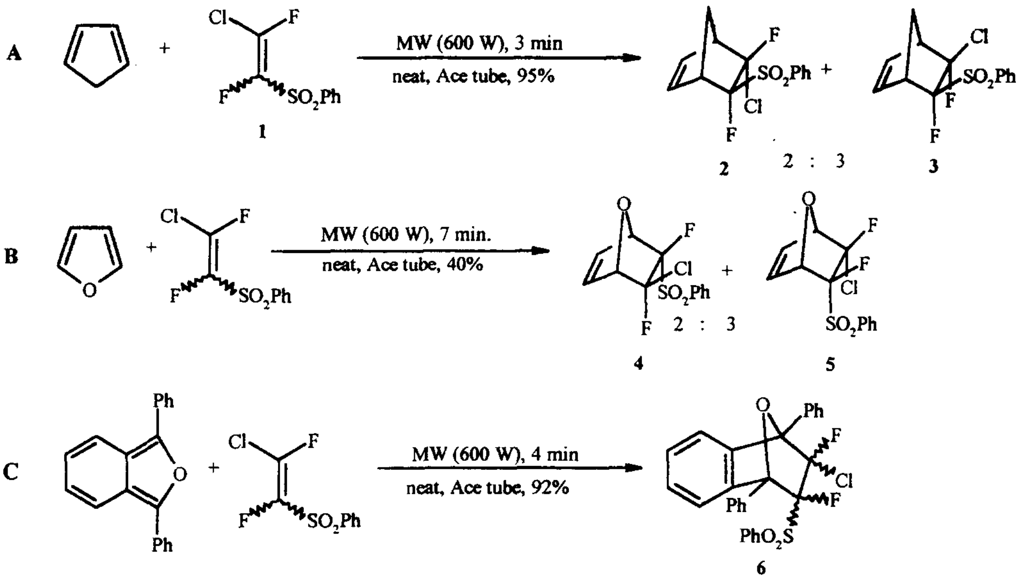
reactivity forming cycloadducts with the dienes including furan in appreciable yields in very short reaction times (< 7 min.). In this microwave irradiation method reactions are carried out in neat phase and hence is an envirobenign technique. These results are presented in **Scheme I**.



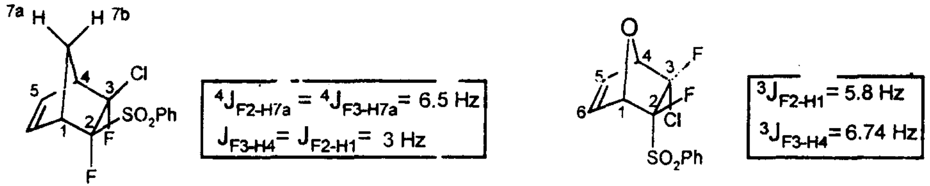
Reagents and conditions: a. PhSH, NaOH, autoclave (120°C), 6 h (85%); b. KOH,autoclave(120°C), 4 h (60%); c. m-CPBA, DCM, RT, 24 h (90%)



Scheme I

The general procedure used for the cycloaddition of a diene with **1** under microwave irradiation is as follows: furan (1ml, 13.7mmols) and 1,2-difluoro-1-chlorovinylphenylsulfone **1** (358 mg, 1.5 mmol) were taken in ACE tube, flushed with Argon and tightly capped. The mixture is subjected to microwave heating for 7 min. in a domestic microwave oven (600 watt, BPL BMO 700T) and then it is allowed to come to room temperature. Then the reaction mixture is charged over 100-200 mesh silicagel column and eluted with 4% EtOAc in hexane. It afforded first 100 mg of unreacted sulfone **1** and 53 mg of **4** (mp 118-119°C) and 79 mg of **5** (mp 157-158°C). Yields are calculated based on consumed **1** in the reaction.

The dienophile **1** is easily prepared from trifluorochloroethylene using the reported procedures[5,6]. **1** is an inseparable mixture of its geometrical isomers which are in the ratio 2:3 (glc analysis, 10% OV-17, 10 ft) and is used as it is in cycloaddition reaction studies. **1** is expected to form cycloadduct as a mixture of four stereoisomers, but we observed that each of the adducts formed with the dienophile is a mixture of only two stereoisomers in the ratio 2:3 which are easily separated by normal column chromatography and confirmed from their ^{1}H NMR and Mass spectrometry data[7]. From comparison of vicinal and long range ($J_{H\text{-}F}$) coupling constants of these compounds with corresponding data of the structurally related molecules in literature,[2,8,9,10,11] we have assigned relative ***exo/endo*** spatial orientations of the fluorines on each of these molecules. For example, this has been depicted for compounds **3** and **5** in **Figure1.** Accordingly, the two fluorines in **3** were assigned to be endo as they gave coupling constant of 3 Hz with the adjacent bridge head hydrogens. In case of **5**, however the coupling constants $^3J_{F2\text{-}H1} = 5.8$ Hz and $^3J_{F3\text{-}H4} = 6.74$ Hz indicate that the two fluorines are in exo position.



3

$^4J_{F2\text{-}H7a} = {}^4J_{F3\text{-}H7a} = 6.5$ Hz
$J_{F3\text{-}H4} = J_{F2\text{-}H1} = 3$ Hz

5

$^3J_{F2\text{-}H1} = 5.8$ Hz
$^3J_{F3\text{-}H4} = 6.74$ Hz

Figure 1

In earlier reports with dienophiles such as vinylphenylsulfone[12], monofluorovinylphenylsulfone[13] and 1,2-difluorovinylphenylsulfone[11], there is an increasing order in the exoselectivity of phenylsulfone group (viz., 2.4:1, 1:1 and 1:19 respectively) in Diels-Alder cycloadditions with cyclopentadiene. In the present case also the formation of cyclopentadiene adduct **2** and **3** is normal and consistent with the expectation. However, in the case of the furan adduct **5** the stereochemistry appears to be completely reversed as the two fluorines in it have occupied the exo position. The reason behind this discrepancy is not clearly known but we believe that secondary orbital interactions of fluorines with bridged oxygen[14] are possibly responsible which are often considered to play important role in the control of stereochemistry of fluorinated compounds.

In summary, this work demonstrates rapid, efficient and envirofriendly method of Diels-Alder cycloaddition of fluorinated dienophiles under microwave thermolysis. This method has efficiently prompted [4+2] cycloaddition of 1,2-difluoro-1-chlorovinylphenylsulfone with furan which otherwise is difficult to accomplish.

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7. ^{1}H NMR data: δ (CDCl$_3$, 400 MHz) and Mass spectral data: (VG Macro Mass 7070H, 70eV):

   For Compd. **2** (mp 148-149°C): 2.30 (ddq, J_1= 11 Hz, J_2= 6.5 Hz, J_3= 2 Hz and J_4= 2 Hz, 1H), 2.7 (ddd, J_1= 10.6 Hz, J_2= 4 Hz and J_3= 2 Hz, 1H), 3.4 (dm, J = 6.6 Hz, 1H), 3.6 (m, 1H), 6.3 (m, 2H), 7.6 (m, 2H), 7.7 (m, 1H), 8.0 (m, 2H). MS: m/z $(M+1)^{+\cdot}$ = 304 (75%), 269 (15%), 163 (15%), 125 (100%), 77 (30%), 66 (30%). HRMS: Calculated for $C_{13}H_{11}O_2F_2SCl$. 304.0136, Found; 304.0129.

   For Compd. **3** (mp 174-175°C): 2.0 (dtt, J_1= 11 Hz, J_2= 6.5 Hz, J_3= 2 Hz, 1H), 2.5 (dm, J = 11 Hz 1H), 3.39 (m, 1H), 3.47 (m, 1H), 6.2 (dd, J_1= 5.6 Hz, J_2 = 3.2 Hz, 1H), 6.37 (dd, J_1= 5.4 Hz, J_2= 3.2 Hz, 1H), 7.6 (m, 2H), 7.65 (m, 1H), 8.0 (m, 2H). MS: m/z $(M+1)^{+\cdot}$ = 304 (25%), 269 (20%), 163 (30%), 125 (100%), 77 (60%), 66 (40%). HRMS: Calculated for $C_{13}H_{11}O_2F_2SCl$. 304.0136, Found: 304.0128.

   For Compd. **4**: 5.0 (m, 1H), 5.14 (dq, J_1= 6 Hz, J_2= 1.6 Hz, J_3= 1.6 Hz, 1H), 6.7 (ddd, J_1= 6 Hz, J_2= 1.6 Hz, J_3= 1.8 Hz, 1H), 6.87 (ddd, J_1= 6 Hz, J_2= 0.9 Hz, J_3= 1 Hz, 1H), 7.6 (m, 2H), 7.75 (m, 1H), 7.95 (m, 2H). MS: m/z $(M+1)^{+\cdot}$ = 307 (10%), 271 (15%), 166 (20%), 141 (15%), 125 (40%), 77 (10%), 68 (100%). HRMS (LSIMS): Calculated for (M+H) $C_{12}H_{10}O_3F_2SCl$. 307.0007, Found: 307.0015.

   For Compd. **5**: 4.94 (ddd, J_1= 6.74 Hz, J_2= 3.1 Hz, J_3= 1.8 Hz, 1H), 5.09 (ddd, J_1= 5.8 Hz, J_2= 3.1 Hz. J_3= 1.44 Hz, 1H), 6.66 (m, 1H), 6.80 (ddd, J_1= 5.8 Hz, J_2= 1.7 Hz, J_3=0.9 Hz, 1H), 7.6 (m, 2H), 7.8 (9m, 1H), 8.0 (m, 2H). MS: m/z $(M+1)^{+\cdot}$ = 307 (10%),271 (5%), 166 (20%), 141 (5%), 125 (30%), 77 (25%), 68(100%). HRMS (LSIMS): Calculated for (M+H) $C_{12}H_{10}O_3F_2SCl$. 307.0007, found; 307.0015.

   For Compd. **6**: Obtained as a mixture of two isomers MS: m/z $(M+1)^{+\cdot}$ = 509 (10%), 367 (10%), 270 (100%), 105 (25%), 77 (60%). HRMS (LSIMS): Calculated for (M+H) $C_{28}H_{20}O_3F_2SCl$. 509.0789. Found; 509.0805.
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