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Trifluoroacetic acid Catalysed [1,3]-Rearrangement of Aryl 2-Halocyclohexenylmethyl Ethers

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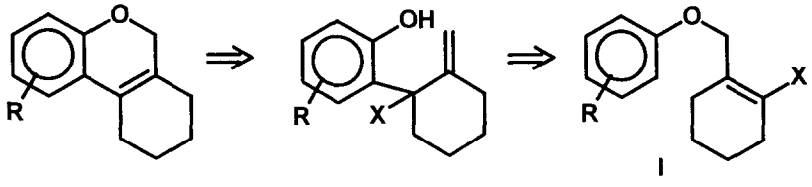
Absract : Unusual [1,3]- rearrangement of aryl 2-halocyclohexenylmethyl ethers promoted by trifluoroacetic acid was observed. Products due to Claisen rearrangement were not formed.

Cannabinoids are naturally occuring benzopyrans[1a] possesing potent medicinal properties. Though many synthetic routes have been reported[1b] for cannabinoids, we envisaged a new approach for the construction of the basic framework based on the Claisen rearrangement[2] of aryl 2-halocyclohexenylmethyl ether **I** followed by cyclisation[3,4] (Scheme-1). In particular, the successful thermal Claisen rearrangement and cyclisation of γ-halocrotyl aryl ethers to chromenes reported by Anderson[3], tempted us to explore the approach, as envisaged in scheme-1.



SCHEME-1

In view of this, we synthesised a few aryl 2-chlorocyclohexenylmethyl ethers and investigated their thermal Claisen rearrangement. To our disappointment, ether **1a** was found to be stable under the usual conditions of thermal Claisen rearrangement, viz. in *N,N*-diethylaniline or in polyethylene glycol (PEG-200) at 220-240^{0}C.

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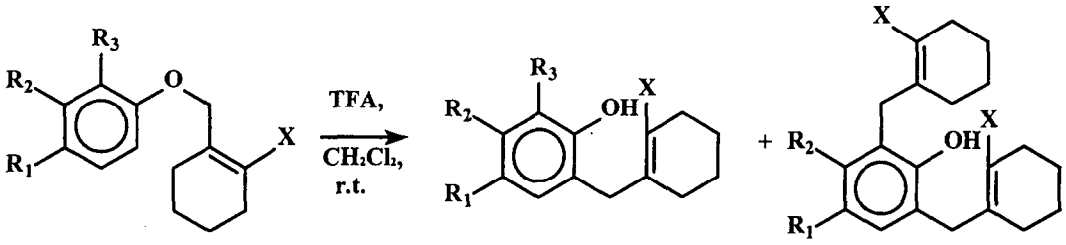
Even after prolonged heating under pressure, no reaction was observed in the case of ether **1a**. Our efforts to bring about the Claisen rearrangement of these ethers under flash vacuum pyrolysis were also unsuccessful. The use of trifluoroacetic acid (TFA) as a solvent in *ortho*-Claisen rearrangement has been reported to cause tremendous rate enhancement[5,6] as much as 10^5 as compared to that in other solvents. TFA has been used as a catalyst for the synthesis of mellein[7] via an *ortho*-Claisen rearrangement as well as for the rearrangement of sevaral α-aryloxymethyl cinnamic acids[8]. These reports prompted us to apply this method to the ether **1a**. Interestingly, when ether **1a** was exposed to TFA at room temperature, an extremely facile reaction was observed leading to the respective [1,3]-rearrangement[9,10,11] product **2a** in good yield. A small amount of the diallylated product **3** was also observed (< 5%). The reaction was found to be general in both the cases of 2-chloro and 2-bromocyclohexenylmethyl aryl ethers **1a-1i** (Scheme-2, Table-1). In all the aryl ethers studied, **1a-1g**, the monoallylated phenol was found to be the major product. In the case of the naphthyl ethers **1h** and **1i**, the respective monoallylated phenol was found to be the sole product .



1a-1i **2a-2i, (Major Product)** **3 (<5%)**

	X	R_1	R_2	R_3
1a,2a	**Cl**	CH_3	**H**	**H**
1b,2b	**Cl**	**H**	**H**	**H**
1c,2c	**Cl**	**Cl**	**H**	**H**
1d,2d	**Cl**	OCH_3	**H**	**H**
1e,2e	**Br**	CH_3	**H**	**H**
1f,2f	**Br**	OCH_3	**H**	**H**
1g,2g	**Br**	**Cl**	**H**	**H**
1h,2h	**Cl**	**H**	**-CH=CH-**	**-CH=CH-**
1i,2i	**Cl**	**-CH=CH-**	**-CH=CH-**	**H**

SCHEME-2

Table-1

TFA Catalysed Rearrangement Reactions of Aryl 2-halocyclohexenylmethyl Ethers

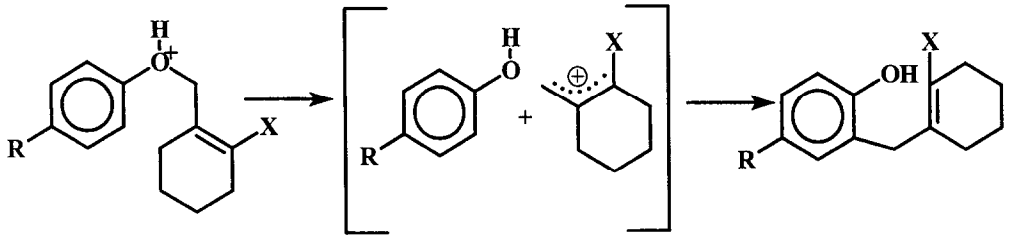
Ether	Reaction Time	Major Product	Yield* (%)
1a	15 min.	2a	80
1b*	15 min	2b	75
1c	15 min	2c	75
1d	10 min	2d	70
1e	15 min	2e	80
1f	10 min	2f	70
1g	15 min	2g	70
1h	40 min	2h	60
1i	30 min	2i	65
4	---	---	---
5	14.5 h	7	69
6	3h	8	---

All the reactions were conducted with 1mmol of the ether in TFA at ambient temperature.

* Isolated yield of purified, fully characterised product.

♣ In entry 1b, a small amount of the para-allylated product was also isolated.

The formation of the diallylated product suggests that the TFA catalysed rearrangement proceeds by a non-concerted mechanism as depicted in scheme-4.



SCHEME-4

While γ-chloroallyl p-tolyl ether **4** is stable in TFA, γ-methylallyl p-tolyl ether **5** (viz. crotyl aryl ether) undergoes a charge accelerated 3,3-rearrangement[12,13]. In remarkable contrast to these two ethers, exposure of γ-phenylallyl p-tolyl ether **6** to TFA leads mainly to p-cresol **8**, arising out of ether cleavage. These findings highlight the importance of electronic effects of γ-substituents of the allyl moiety in the acid catalysed rearrangement of aryl allyl ethers. When the allylic terminus bears a halogen atom and an alkyl group, the opposing influence of the two substituents and added steric factors dramatically alter the behaviour of such ethers resulting in a high preference for 1,3-rearrangement. This is in contrast to the case of prenyl aryl ethers, where the course of the reaction has been found to be highly dependant upon the nature of the substituent on the aromatic ring as well as on the nature of the catalyst and conditions[10]. It is also worth mentioning here that

neither montmorillonite nor florisil has been found to be effective in bringing out the 1,3-rearrangement of the aryl 2-halocyclohexenylmethyl ethers whereas γ,γ-dimethylallyl aryl ethers smoothly undergo 1,3-rearrangement when exposed to clay or florisil[10,12], thereby revealing the greater efficiency of TFA as a catalyst for the rearrangement of these γ-haloethers.

In a typical experiment, 1 mmole of the aryl ether in 1ml of TFA was stirred at ambient temperature. After completion of reaction (tlc), the reaction mixture was treated with aqueous sodium bicarbonate and extracted with dichloromethane. The solvent was separated, evaporated and the residue chromatographed on silica gel. H^1 NMR data[14] for **2a** and **2e** are consistent with the structures assigned.

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References and Notes :

1. a) Mechoulam, R.; Mecallum, N.K.; and Burstein, S. *Chem.Rev.*,**1976**, *76*, 75. b) Razdan, R.K., The Total Synthesis of Cannabinoids. In *The Ttotal Synthesis Of Natural Products*; ApSimon, J., Eds.; John Wiley: New York, **1981**; pp. 185-262.
2. Rhoads, S.J.; Raulins, N.R. *Org.Reactions*, **1975**, *22*, 1.
3. Anderson, W.K.; Lavoie, E.J.; and Bottaro, J.C. *J.Chem.Soc .Perkin Trans.I*, **1976**,1.
4. Gopal,D and Rajagopalan, K. *Tetrahedron Lett.* **1986**, *27*, 5883.
5. Svanholm, U.; and Parker, V.D. *J.Chem.Soc., Chem.Comm.*, **1972**, 645.
6. Svanholm, U.; and Parker, V.D. *J.Chem.Soc., Perkin Trans.II*, **1974**, 169.
7. Harwood, L.M. *J.Chem.Soc., Chem.Comm.*, **1982**, 1120.
8. Andreev, N.A.; Bunina-Krivirukova, L.I.; Levashova, V.I. *Zh.Org.Kh.*, **1986**, *22*, 392.
9. Dauben, W.G.; Cogen, J.M.; and Behar, V. *Tetrahedron Lett.*, **1990**, *31*, 3241.
10. Corey, E.J.; and Wu, L.I. *J.Am.Chem.Soc.*, **1993**, *115*, 9327.
11. Talamas, F.X.; Smith, D.B.; Cervantes, A.; Franco, F.; Cutler, S.T.; Loughhead, D.G.; Morgans, D.J.; Jr, and Weikert, R.J. *Tetrahedron Lett.*, **1997**, *38*, 4725.
12. Widmer, V.U.; Hansen, H.J.; and Schmid, H. *Helvetica Chimica Acta*, **1973**, *56*, 2644.
13. Lutz, R.P. *Chem.Rev.*, **1984**, *84*, 205.
14. ^{1}H NMR (400 MHZ, $CDCl_3$) : **2a**: δ 6.68-6.92 (m, 3H), 5.5 (s, 1H), 3.5 (s, 2H), 2.38-2.44 (m, 2H), 2.24 (s, 3H), 1.94-2.0 (m, 2H), 1.52-1.72 (m, 4H). **2e**: δ 6.65-6.75 (m, 3H), 5.5 (s, 1H), 3.5 (s, 3H), 2.4-2.6 (m, 2H), 2.24 (s, 3H), 1.92-2.1 (s, 2H), 1.55-1.75 (m, 4H).