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SULFONE MEDIATED RUPE AND RAPHAEL REARRANGEMENTS

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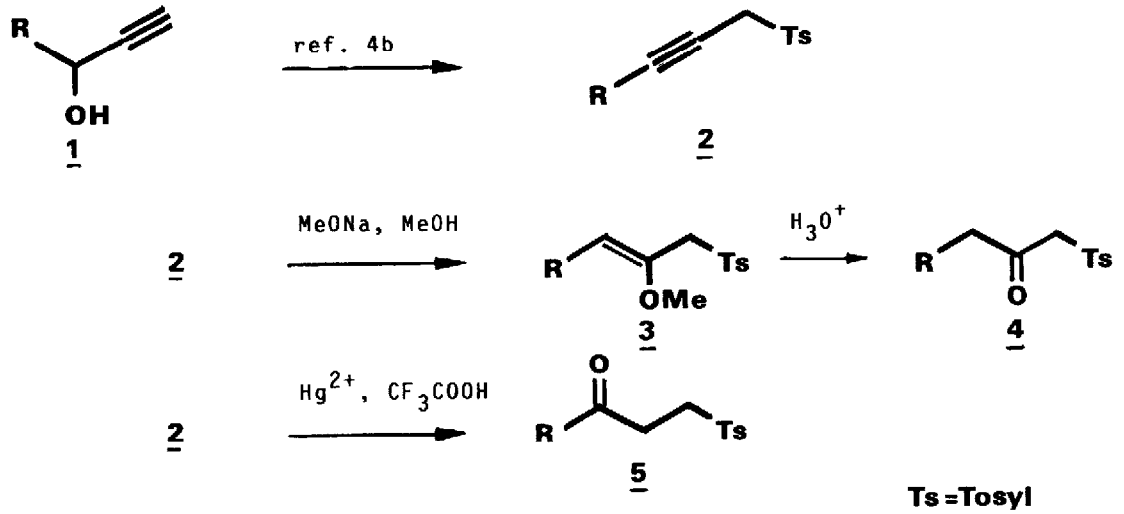
Summary: Base-catalysed addition of methanol to propargylic sulfones selectively gave β -ketosulfones whereas mercuric salts catalysed additions gave γ-ketosulfones. The latter process has been used to prepare one half of pyrenophorine.

Propargylic alcohols are prone to the two well known Meyer-Schuster and Rupe rearrangements (1). A less common isomerization, discovered by Raphael (2), gives an α,β-unsaturated ketone through two successive proton shifts. Though the three processes are of synthetic interest, the Rupe and the Raphael reactions are not always easy to perform since they require either a peculiar substitution pattern or the use of hard conditions (1-3).
A simple procedure, summarized in scheme 1 and involving first the transformation of acetylenic alcohols 1 (4a) into sulfones 2 (4b), allowed us to perform the title reactions under very mild conditions.



scheme 1

RUPE-LIKE PRODUCTS: 2 ⟶ 3 ⟶ 4

A 0.1N methanolic solution of sulfones 2 was treated, at room temperature, with commercial sodium methoxide (1 molar-eq.)(4c). After a few minutes, water was added, and the methoxy sulfones 3 were eventually isolated in good yield. Hydrolysis into the β-keto sulfones 4 was then performed by stirring these enol-ethers in a 1/1 mixture of 1N aqueous hydrochloric acid and THF (table 1). Hydrogenolysis of the sulfonyl group gave the methyl ketone, hence ending this pseudo-Rupe process (5).

Table 1: $R-C\equiv C-CH_2-Ts$ (2) ⟶ $R-CH=C(OMe)-CH_2-Ts$ (3) ⟶ $R-CH_2-CO-CH_2-Ts$ (4)

R	3		4		$R-CH_2-CO-CH_3$
	Yield* %	mp	Yield %	mp	Yield %
CH_3	100	77	93	48	73
$n\text{-}C_{10}H_{21}$	100	oil	92	65	
C_6H_5	98	133	89	90	67
$C_6H_5\text{-}CH(CH_3)$	98	oil	91	oil	

* All yields refer to isolated products

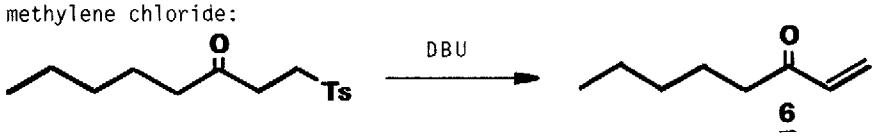
RAPHAEL PRODUCTS: 2 ⟶ 5

Hennion's catalyst (6) (0.01 molar-equ.) was prepared by treating a slurry of HgO in boron trifluoride etherate with an excess of trifluoroacetic acid (instead of trichloroacetic acid as originally described) and the sulfone was added all at once in methylene chloride. After a few minutes, treatment with sodium methoxide (6b), then water, gave the γ-ketosulfone (table 2).

Table 2: $R-C\equiv C-CH_2-Ts$ (2) ⟶ $R-CO-CH_2-CH_2-Ts$ (5)

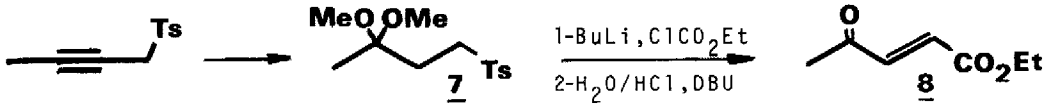
R	5	
	Yield %	mp
CH_3	94	72-73
$n\text{-}C_5H_{11}$	100	56-57
C_6H_5	"	127
$C_6H_5\text{-}CH(CH_3)$	98	oil

The unsaturated ketone **6** could be easily obtained from the sulfone **5**;R=C_5H_{11}, by stirring with DBU (7) in methylene chloride:



6

Using a reduced amount of trifluoroacetic acid (BF_3Et_2O-HgO-CF_3COOH: 1 mole each), and methanol as solvent, the methyl ketal **7** was directly obtained, starting with the sulfone **2**;R=CH_3. Anionization of sulfone **7** with butyllithium, treatment with ethyl chloroformate, and removal of the sulfonyl moiety with DBU, then furnished the unsaturated ketoester **8** (8):



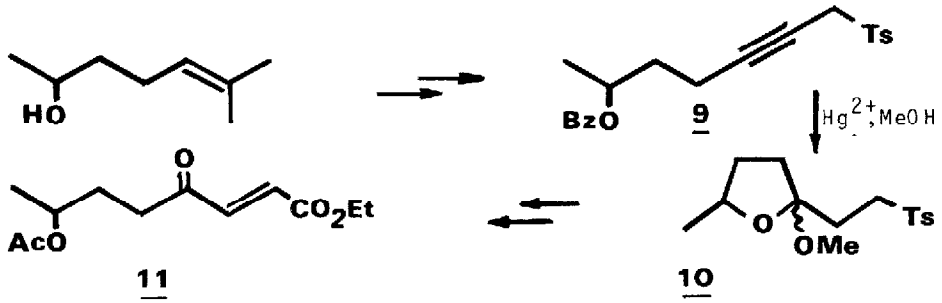
7 **8**

The exclusive formation of the γ-isomer in these mercuration processes could be explained assuming that the strongly electron withdrawing sulfonyl group directs the nucleophilic attack, in the transcient mercurinium ion, to the remote, less destabilised, γ-position:

PREPARATION OF ONE HALF OF PYRENOPHORINE FROM SULCATOL

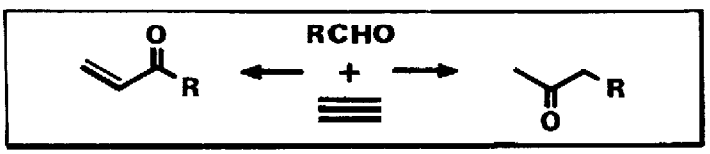
An application of this Raphael-like pathway started with the benzyl ether of sulcatol (9), which was ozonolysed. Sequential treatment of the resulting aldehyde with lithium acetylide, toluenesulfinyl chloride, then thermal rearrangement, afforded the sulfone **9**. Treatment with Hennion's catalyst directly gave a mixed ketal, **10**, in which the benzyl protecting group was removed.

scheme 2



Homologation with ethyl chloroformate, hydrolysis, acetylation, then basic elimination of the arylsulfonyl residue, led to a synthon, **11**, we already obtained (8).

In conclusion, the fundamental property of the sulfonyl group (10) to strongly withdraw electrons has been utilized to selectively direct the overall hydration of propargylic sulfones. The resulting soft version of the two title rearrangements could prove very useful since the general transformations shown could be performed very conveniently:



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5- All the compounds described in this letter have been identified by ^{1}H NMR, mass, IR and elemental analysis. Conversion of the methoxy sulfones into α-hydroxy ketones could be performed at this stage: J.E. Baldwin, O.W. Lever and N.R. Tzodikov, J.Org.Chem., 1976, 41, 2312. The removal of the sulfonyl group was performed using aluminium amalgam in refluxing THF/water and the ketones, so formed, identified in glc with commercially available samples.

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b) D.J.Faulkner and M.R. Petersen, J.Amer.Chem.Soc., 1973, 95, 553.

7- A mixture of DBU and triethylamine could be used. **6** had bp 63-65° at 13τ; S. Archer, W.B. Dickinson and M.J. Unser, J.Org.Chem.,1957, 22, 92, gave 58-61° at 11τ.

8- a) P. Breuilles and D. Uguen, Tetrahedron Lett., 1984, 25, 5759.
b) P. Breuilles and D. Uguen, Bull.Soc.Chim.Fr., 1988, 705.

9- Prepared by sodium borohydride reduction of 6-methyl-5-heptene-2-one, followed by treatment with KH and benzyl bromide, at room temp., in THF. The synthesis of chiral pyrenophorine, starting with optically active sulcatol, will be described in the full paper.

10-For an outstanding review on sulfones and sulfone chemistry, see: K. Schank, Methoden der organischen Chemie (Houben-Weyl), 1985, E11, 1132.

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