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FACILE SYNTHESIS OF E-γ-HYDROXY-α,β-UNSATURATED SULFONES FROM ALDEHYDES

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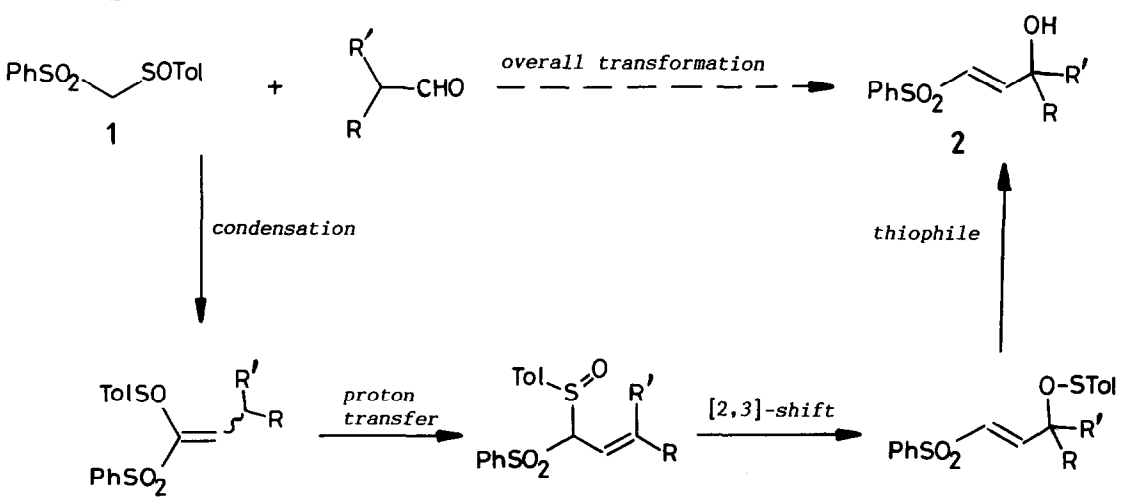
SUMMARY: *Reaction of enolizable aldehydes with p-tolylsulfinylmethyl phenyl sulfone (1), in the presence of piperidine in acetonitrile at 0°C, gave selectively E-γ-hydroxy-α,β-unsaturated phenyl sulfones in good yields.*

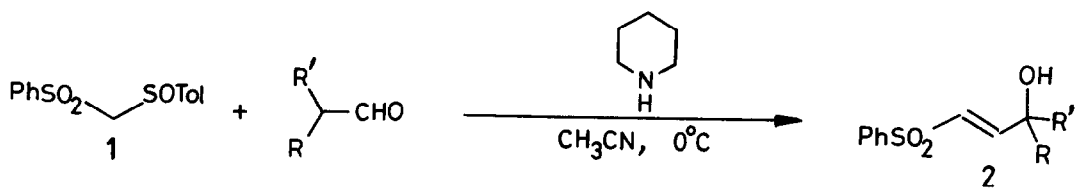
Considerable attention has recently been paid to the synthesis and reactivity of γ-hydroxy-α,β-unsaturated sulfones and derivatives. These compounds are currently used in highly stereocontrolled processes such as conjugate additions[1] and cycloaddition reactions[2]. We hereby report a practical and general synthetic method for the preparation of this kind of functionality from aldehydes and p-tolylsulfinylmethyl phenyl sulfone[3] (1). This one-step procedure is based on a sequential Knoevenagel condensation, prototropic shift, and allylic sulfoxide-sulfenate rearrangement[4] (scheme 1).

Scheme 1



Reagent 1 was readily prepared on multigram scale by treatment of methyl p-tolylsulfinate with the anion, derived from phenyl methyl sulfone and ^{n}BuLi, at 0°C in THF (80% Yield). Aldehyde (2.0 equiv.) was treated with 1 (1.0 equiv.) and piperidine (2.0 equiv.) in acetonitrile[5] at 0°C for 1-8 h. Work-up with diluted hydrochloric acid and dichloromethane and further purification by flash chromatography afforded stereoselectively E-γ-hydroxy-α,β-unsaturated phenyl sulfones (2) in good yields[6] (table 1).

Table 1: Synthesis of E-γ-hydroxy-α,β-unsaturated sulfones 2



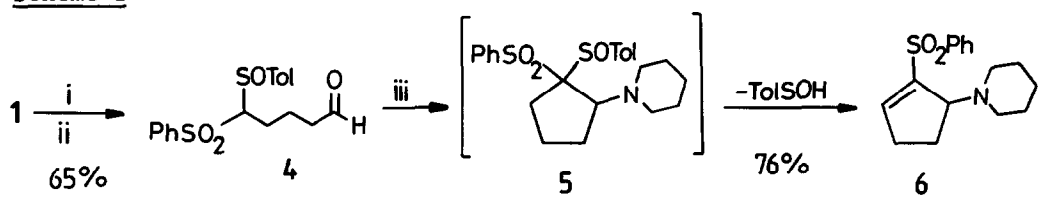
Entry	R	R'	t(h)	Product	Yield(%)[a]
a	CH_3	H	5	2a	77
b	$CH_3(CH_2)_4CH_2$	H	5	2b	89
c	$(CH_3)_2CH$	H	5	2c	86
d	$(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)$	H	5	2d	77
e	$PhCH_2OCH_2CH_2$	H	1	2e	87
f	$PhSCH_2$	H	3	2f	45[b]
g	CH_3	CH_3	8	2g	75[c]
h	$-(CH_2)_5-$		8	2h	81[c]

[a] *Yield of pure products after silica gel chromatography (0.5-2.0 mmole scale). All new compounds gave satisfactory analytical and spectral data.* [b] *Carried out with 1.3 equiv. of aldehyde.* [c] *Carried out at room temperature.*

As it is shown in table 1 the method is quite general[7]. Unbranched (entries a and b), β-branched (entries c and d) as well as α-branched enolizable aldehydes (entries g and h) can be used. Good results were also obtained with functionalized aldehydes (entries e and f).

The main limitation of this procedure comes from the fact that it cannot be applied to C-substituted reagents of type 1, due to the necessary presence of two acidic hydrogens between both sulfur functions. This limitation has been shown in an intramolecular process (scheme 2). Deprotonation of 1 with NaH in DMF and treatment with the bromoketal 3 gave the corresponding alkylated product as a 5:1 mixture of diastereomers (65 % yield). Subsequent hydrolysis with diluted hydrochloric acid afforded aldehyde 4 quantitatively. When 4 was submitted to the standard conditions (2.0 equiv. of piperidine in CH_3CN), the cyclopentannulated product 6 was obtained as the major product in 76% yield[8]. The absence of one hydrogen in α position with respect to the sulfonyl group determines that intermediate 5 cannot accomplish the Knoevenagel condensation (first step of scheme 1), giving 6 *via* sulfenic acid elimination

Scheme 2



i: NaH (1.4 equiv.), $Br(CH_2)_3$-$CH(OMe)_2$ (3), DMF, 25°, 12h; ii: HCl 3N-THF (1:3), 25°C, 1h; iii: piperidine (2.0 equiv.), CH_3CN, 25°C, 2h.

In summary, the present one-step method of synthesis of acyclic γ-hydroxy-α,β-unsaturated sulfones has the following advantages: the reagent is readily available, the procedure is very simple, the experimental conditions are mild and the reaction can be performed with a wide range of aldehydes[9]. The application of this methodology in asymmetric synthesis from enantiomerically pure sulfoxide 1 is in progress in our laboratory and will be published elsewhere.

REFERENCES AND NOTES

(1)- a) D.L. Barton, P.C. Conrad and P.L. Fuchs, *Tetrahedron Lett.*, **1980**, *21*, 1811. b) P.R. Hamann and P.L. Fuchs, *J. Org. Chem.*, **1983**, *48*, 914; c) P.R. Hamann, J.E. Toht and P.L. Fuchs, *J. Org. Chem.*, **1984**, *49*, 3867; d) M. Isobe, Y. Funabashi, Y. Ichikawa, S. Mio and T. Goto, *Tetrahedron Lett.*, **1984**, *25*, 2021; e) M. Isobe, Y. Ichikawa, D. Bai and T. Goto, *Tetrahedron Lett.*, **1985**, *26*, 5203.

(2)- B.M. Trost, P. Seoane, S. Mignani and M. Acemoglu, *J. Am. Chem. Soc.*, **1989**, *111*, 7487.

(3)- Compound **1** has been reported by R. Annunziata, M. Cinquini and F. Cozzi, *Synthesis*, **1979**, 535.

(4)- This reaction sequence has been previously applied to the synthesis of other functionalities such as γ-hydroxy-α,β-unsaturated ketones: J. Nokami, A. Nishimura, M. Sunami and S. Wakabayashi, *Tetrahedron lett.*, **1987**, *28*, 649; γ-hydroxy-α,β-unsaturated esters: R. Tanikaga, Y. Nozaki, T. Tamura and A. Kaji, *Synthesis*, **1983**, 134; and γ-hydroxy-α,β-unsaturated nitriles: T. Ono, T. Tamaoka, Y. Yuasa, T. Matsuda, J. Nokami and S. Wakabashi, *J. Am. Chem. Soc.*, **1984**, *106*, 7890.

(5)- The reaction can be performed in other solvents like CH_2Cl_2, CCl_4, THF, C_6H_6 and DMSO.

(6)- The reaction is quite stereoselective. The Z-isomer has never been detected.

(7)- General procedure for the preparation of **2**:

130 µl (1.36 mmol, 2.0 equiv.) of piperidine and 1.36 mmol (2.0 equiv.) of aldehyde were added at 0°C to a solution of 200 mg (0.68 mmol) of **1** in 3 ml of dry acetonitrile. Afterwards the stirring was continued for 1-8 h at 0°C (see table 1), and 10 ml of 5% hydrochloric acid were added. The reaction mixture was extracted with dichloromethane (2x15 ml), the combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by flash chromatograpy (hexane:ethyl acetate 2-5:1 as eluent) to give pure unsaturated sulfones **2**.

(8)- β-Amino cyclopentenyl sulfones related to **6** have been widely used in a variety of stereoselective conjugate-addition reactions: a) R.E. Donaldson and P.L. Fuchs, *J. Am. Chem. Soc.*, **1981**, *103*, 2108; b) D.K. Hutchinson and P.L. Fuchs, *J. Am. Chem. Soc.*, **1985**, *107*, 6137.

(9)- Ketones fail to react with compound **1** even in refluxing benzene.

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