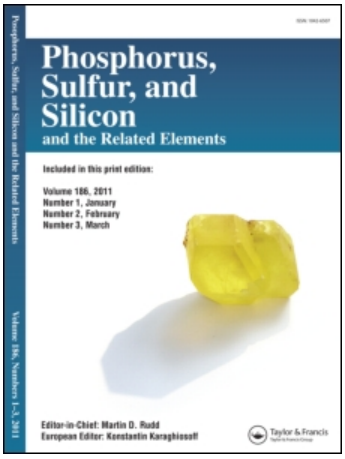

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Highly Stereoselective Tandem Pummerer Reaction/ α-Hydroxy Imine Rearrangement of E.P. β-Sulfinylenamines

PIERFRANCESCO BRAVO, MARCELLO CRUCIANELLI,† ALESSANDRO VOLONTERIO AND MATTEO ZANDA

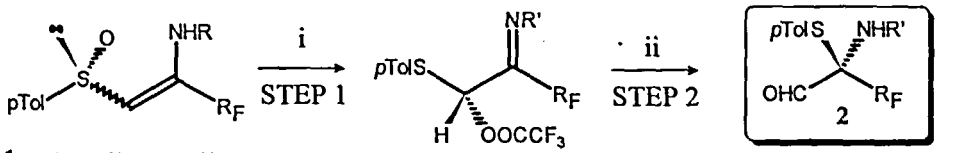
C.N.R. - C.S.S.O.N. Dipartimento di Chimica del Politecnico, via Mancinelli 7, I-20131 Milano, Italy. † Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università di L'Aquila, Via Vetoio, I-67010, Italy

Abstract. The highly stereoselective tandem Pummerer reaction/α-hydroxy imine rearrangement of E.P. α-fluoroalkyl-β-sulfinylenamines affording chiral non-racemic fluoropyruvaldehydes *N*,*S*-ketals is described.

The synthesis of fluorosubstituted organic fine chemicals is an important goal, owing to the outstanding chemical and biomedicinal properties induced by the insertion of fluorine. However, the stereoselective synthesis of fluoroorganic molecules represents a significant challenge for the chemist.

We have recently reported the synthesis of enantiomerically pure α-fluoroalkyl-β-sulfinylenamines **1**, new useful fluorinated chiral templates.[1]

Treatment of **1** with trifluoroacetic anhydride, followed by addition of silica gel or of an aqueous $NaHCO_3$ solution, gives rise to a stereoselective tandem Pummerer reaction/arylthio group migration, producing the corresponding fluoro pyruvaldehydes *N*,*S*-ketals **2** in high enantiomeric excess (figure 1 and table 1).[2]



1 a : $R_F = CF_3$; R = Cbz
1 b : $R_F = CF_3$; R = H
1 c : $R_F = CF_2H$; R = Cbz
1 d : $R_F = CF_2Cl$; R = Cbz

3

2 a : $R_F = CF_3$; R' = Cbz
2 b : $R_F = CF_3$; R' = $COCF_3$
2 c : $R_F = CF_2H$; R' = Cbz
2 d : $R_F = CF_2Cl$; R' = Cbz

FIG. 1. Key: (i) TFAA, THF, 0°C, 1 min; (ii) $NaHCO_3$ 5% or SiO_2/H_2O (see table 1), 0°C, 10 min.

TABLE 1. Stereoselective formation of fluoropyruvaldehydes *N,S*-ketals **2** from sulfoxides **1**.

Enamine	R_F	Product	$NaHCO_3$ 5%; e.e. (yield)	SiO_2 then H_2O; e.e. (yield)
(*R*)-(*Z*)-**1a**	CF_3	(+)-(*R*)-**2a**	68 % (85 %)	74 % (49 %)
(*S*)-(*Z*)-**1a**	CF_3	(–)-(*S*)-**2a**	68 % (85 %)	not performed
(*R*)-(*Z*)-**1b**	CF_3	(+)-(*R*)-**2b**	67 % (88 %)	73 % (71 %)
(*R*)-(*Z*)-**1c**	CF_2H	(+)-(*R*)-**2c**	42 % (86 %)	62 % (58 %)
(*R*)-(*E*)-**1c**	CF_2H	(+)-(*R*)-**2c**	6 % (86 %)	8 % (56 %)
(*R*)-(*Z*)-**1d**	CF_2Cl	(+)-(*R*)-**2d**	not performed	79 % (70 %)

The formation of the intermediate imine **3** was confirmed by performing the reaction in a NMR tube. Indeed, addition of trifluoroacetic anhydride (1 equiv) to a THF-d_8 solution of enamine **1**, resulted in the clean formation of **3**, stable for several days at room temperature.

In the light of these results, a reasonable mechanism for the stereoselective formation of the aldehydes **2** from **1** involves a Pummerer reaction (step 1), followed by an α-hydroxy imine rearrangement (step 2), both occurring with high stereoselection.

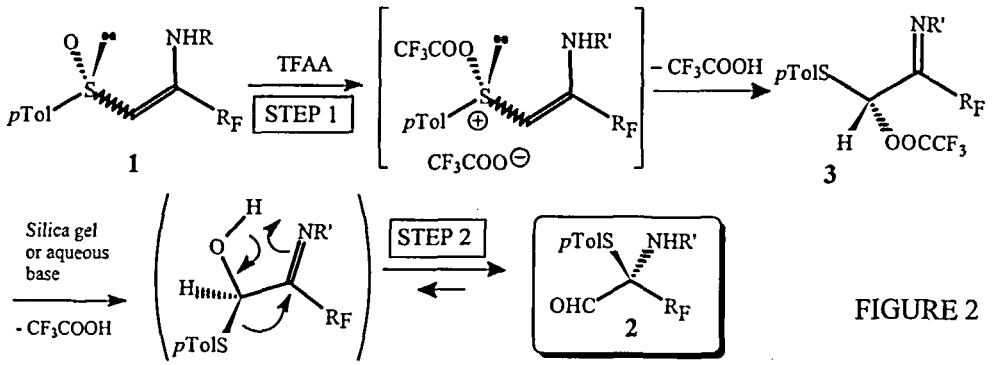
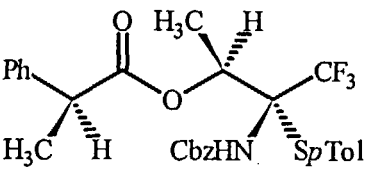


FIGURE 2

The absolute stereochemistry of the aldehydes **2** has been determined by X-ray crystallographic analysis of the enantiomerically pure molecule **4**, obtained by addition of CH_3MgCl to (*R*)-**2a** and subsequent esterification with (+)-(*S*)-α-phenylpropionic acid (figure 3).



4 FIGURE 3

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