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Stereoselective Synthesis of Optically Pure γ-Fluoro-β-Enaminosulfoxides and Reduction to γ-Fluoro-β-Aminosulfoxides

Pierfrancesco Bravo,* Marcello Crucianelli,† and Matteo Zanda

C.N.R. - Centro di Studio per le Sostanze Organiche Naturali.
Dipartimento di Chimica del Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy

† Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università de L'Aquila, Via Vetoio, I-67010 L'Aquila, Italy

Abstract: The aza-Wittig reaction of phospha-λ^5-azenes with optically pure γ-fluorosubstituted β-ketosulfoxides leads to the corresponding β-enaminosulfoxides, which were easily isolated in diastereomerically pure form. The stereoselective reduction of the enamine **3cb** afforded the optically pure β-sulphinyl-amine **5cb** in high overall yield.

In the last twenty years the interest in fluorine chemistry has dramatically increased.[1] New selectively fluorinated molecules can be synthesized by using fluorinating agents or, alternatively, employing the so called "building-block approach", which is milder than the former but suffers from the poorness of readily available functionalized fluorinated starting compounds, especially if optically pure.[2] We have already reported on the synthesis of chiral non racemic γ-fluorosubstituted β-ketosulfoxides **1** by means of a condensation between commercially available alkyl fluoroacetates and lithium derivatives of (*R*)- or (*S*)-alkyl *p*-tolyl sulfoxides.[3]

β-Iminosulfoxides, and their enamine tautomers, are well known and useful intermediates in organic chemistry. The first approach to these compounds dates back to 1966, when Stirling and co-workers added primary and secondary amines to acetylenic sulfoxides.[4a] Afterwards, they were obtained by addition of amines to allenic sulfoxides,[4b] by reaction of metallated sulfoxides with nitriles,[4c] by addition of lithioenamines to sulfinic esters,[4d] and more recently by acid-catalized condensation between aliphatic amines and β-ketosulfoxides.[4e] Among the above-mentioned methods, it seemed to us that the condensation of γ-fluorinated-β-ketosulfoxides **1** with amines would have been the most direct one, but in our hands the reaction occurred with increasing difficulty as fluorination grade increased, and was fully satisfying only with the monofluorinated compound **1a**.[5] This is not surprising considering that the condensation between fluorinated ketones and amines is well known to afford stable hemiaminals, which require very strong desiccants, incompatible with the presence of the stereogenic sulfinyl moiety, for their conversion to imines.[6]

Herein we wish to report on a general procedure for the synthesis of the enantiomerically pure γ-fluorinated-β-enaminosulfoxides **3** by aza-Wittig reaction, which can be carried out with equimolar amounts of reagents, in neutral conditions and in non nucleophilic solvents (scheme 1),[7] and on the stereoselective reduction of **3** to the corresponding β-sulfinylamines **5** (scheme 2).

The desired N-Cbz enamines **3(b-e)a** were obtained in good yields by aza-Wittig reaction of the stabilized iminophosphorane **2a** (R = Cbz)[8] with **1b-e**, mainly or exclusively existing as *gem*-diols, in benzene at reflux temperature for 16-20 hours, as shown in Table 1.

Scheme 1. Aza-Wittig Reaction between γ-Fluoro-β-ketosulfoxides **1** and Imino-phosphoranes **2**.

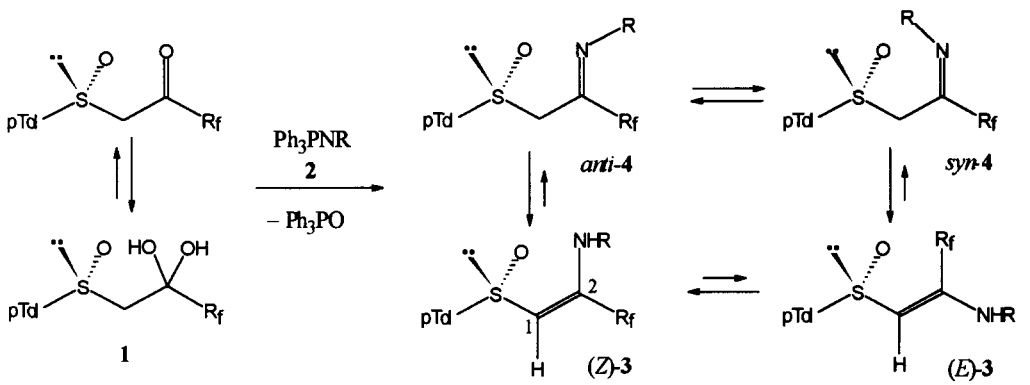


Table 1. Selected data for the β-enaminosulfoxides **3**.

Ketone	Product[a]	R_f	R	Yield (conv.)	(*Z*)-3:(*E*)-3	^{19}F of (*Z*)-3	^{19}F of (*E*)-3
1a	3aa	CFH_2	Cbz	10% (95%)	> 98:2	– 221.6 (t)	not detected
1b	3ba	CF_2H	Cbz	80% (87%)	3:2	– 122.4 (d)	– 120.2 (ABq)
1c	3ca	CF_3	Cbz	78% (85%)	> 98:2	– 70.5 (s)	not detected
1d	3da	CF_2Cl	Cbz	72% (78%)	12:1	– 60.0 (ABq)	– 58.4 (ABq)
1e	3ea	CF_2CF_3	Cbz	58% (70%)	3:1	– 84.6, – 121.1	– 83.8, – 119.2
1b	3cb	CF_3	H	91%	> 98:2	– 73.0 (s)	not detected
1d	3db	CF_2Cl	H	85%	> 98:2	– 60.3 (ABq)	not detected

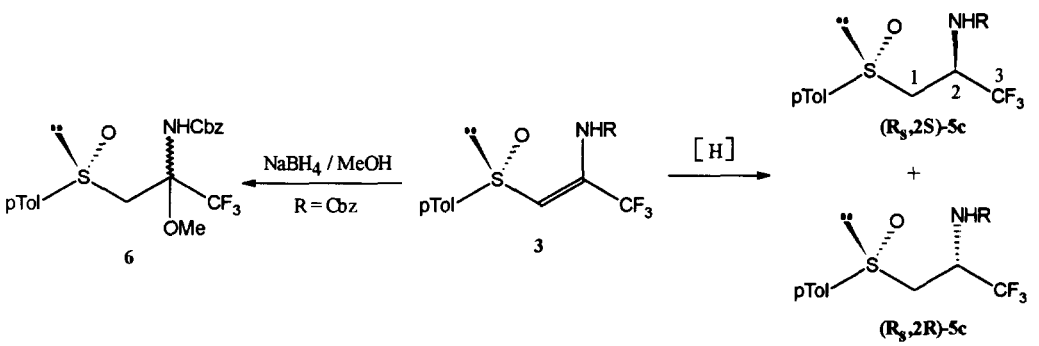
[a] The first letter index concerns the fluorinated residue, the second the N-substituent.

It is noteworthy that the unfluorinated [(4-methylphenyl)-sulfinyl]acetone **1f** after one day at reflux in benzene was recovered unchanged and the monofluorinated **3a** was obtained in low yield after 60 hours.

The primary enamines **3cb** and **3db** were obtained in high yields after 16 hours at room temperature (r.t.) employing the more reactive imino-phosphorane **2b** (R = H), generated *in situ* from $Ph_3PNSiMe_3$.[9]

The (*Z*)-enamines **3aa**, **3c(a-b)** and **3db** were recovered stereoisomerically pure, while **3ba** and **3(d-e)a** were obtained as a mixture of *(E)*- and *(Z)*-geometrical isomers, which required chromatographic purification to be separated.[10] The imine tautomers **4** (Scheme 1) were never isolated or detected by ^1H or ^{19}F NMR in the reaction mixture. The *(E)* or *(Z)* double bond configuration of **3** was assigned by heteronuclear NOE difference tests between the H-1 and the fluorine atoms.

The reduction of the trifluoro-enamines **3c(a-b)** to the β-aminosulfoxides **5c(a-b)**[11] was systematically studied. The presence of three electron-withdrawing groups (NHCbz, CF_3 and the sulfinyl residue) on the double bond of **3ca** makes it quite electrophilic, and its reactivity toward the reducing agents was rather different from that of the known unfluorinated analogues.[4] When THF, ethanol or a THF/H_2O mixture were used as solvent the reduction with an excess of $NaBH_4$ took place smoothly at r.t. and the expected amines **5ca** were obtained as a $(2R,R_S)/(2S,R_S)$ = 60:40 diastereomeric mixture (70% yield), but when the reaction was carried out at −25°C the diastereoselectivity reversed and improved to 26:74. Interestingly, when methanol was used as solvent the N,O-disubstituted hemiaminal **6** quantitatively formed.



Scheme 2. Treatment of β-Enaminosulfoxides **3** with Reducing Agents.

The reduction of the unprotected β-enaminosulfoxide **3cb** with K- or L-Selectride® proved to be highly stereoselective affording **5cb** with a $(2S,R_S)/(2R,R_S)$ = 90:10 diastereomeric ratio in CH_2Cl_2 and 93:7 in THF, with an yield of 75% and 50% respectively (unreacted **3cb** was almost quantitatively recovered),[12] while upon treatment with $NaBH_4$ in dry THF an 80:20 mixture of **5cb** (85%) was obtained. In our hands no reaction occurred with the electrophilic reducing agents DIBAH (even in the presence of $ZnBr_2$) and BH_3·THF.

The absolute stereochemistry of **5cb** was assigned by derivatization of the corresponding optically pure β-aminosulfide with the (+)-(*S*) and (−)-(*R*) α-phenylpropionic acids and analysis of the chemical shift differences in the ^{1}H-NMR spectra of the diastereomeric amides.[14] The treatment of **5cb** with benzyl chloroformate afforded **5ca**, thus allowing a chemical correlation.

The stability, ready availability and handling easiness of the β-enamino and β-aminosulfoxides **3** and **5** warrant a future employment of these chiral non racemic building blocks in the synthesis of fluoroorganic compounds. We are actually studying and exploiting them in the stereoselective synthesis of fuorinated analogues of naturally occurring amines and aminoacids.

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9. Kloek, J. A.; Leschinsky, K. L. *J. Org. Chem.* **1978**, *43*, 1460-1462 and references cited therein.
10. N-Cbz-β-enaminosulfoxides **3(b-e) a** are stable and crystalline compounds which can be stored for undefined time at room temperature. The primary enamines **3(c-d)b** are oily compounds which can be purified by flash chromatography and stored at 0°C for long time.
11. For an overview on the chemistry of β-aminosulfoxides see: Pyne, S. G.; Hajipour, A. R. *Tetrahedron*, **1994**, *50*, 13501-13510 and references cited therein.
12. To a solution of **3cb** in dry CH_2Cl_2 cooled at –20°C a THF solution of L- or K-Selectride® (1 eq.) was added. After 5 min. at –20 °C the reaction was quenched with a small excess of ethanol. The solvent was carefully removed and the procedure was repeated twice. The reaction was finally quenched with saturated aqueous NH_4Cl and routinely worked up. This *one-pot* stepwise procedure is necessary to enhance the yield, because only about 40% of **5cb** formed after the first addition of 1 eq. of reducing agent, as already reported.[13,4e]
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14. The (2S,2S') configuration was confidentially assigned to the amide showing a higher fields shift (about 0.04 p.p.m.) of the thiomethylene protons in comparison with the corresponding signals of the (2S,2R')-amide, because of the shielding effect exerted by the phenyl residue of the acid part. For further data see: Helmchen, G.; Nill, G.; Flockerzi, D.; Schuhle, W.; Youssef, M. S. K. *Angew. Chem. Int. Ed. Engl.*, **1979**, *18*, 62-63 and references cited therein.

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