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A New and General Synthesis of *N*-Substituted Fluorinated β-Iminosulfoxides

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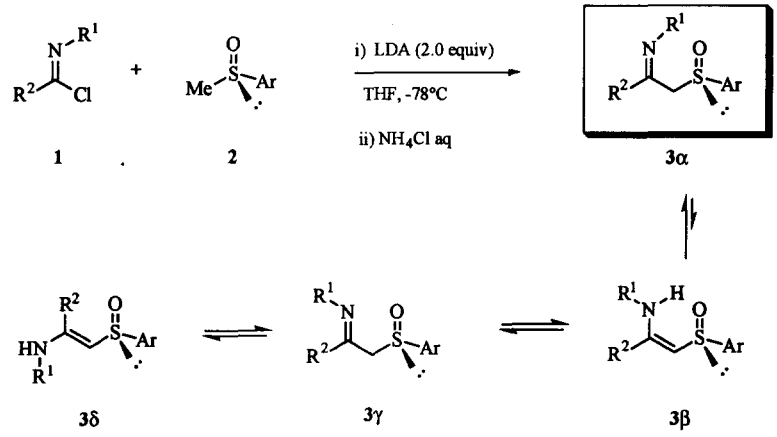
Abstract : Reaction of fluorinated imidoyl chlorides **1** with lithium enolates of chiral non-racemic methyl *p*-tolyl sulfoxide or racemic methyl phenyl sulfoxide **2** gave *N*-substituted γ-fluorinated β-iminosulfoxides **3** in excellent yields as the major tautomer with *Z* geometry.

Chiral sulfoxides, particularly β-ketosulfoxides, are widely used as chiral auxiliaries in asymmetric synthesis.[1] The much less-studied β-iminosulfoxide derivatives have also been used as intermediates in the synthesis of fluorinated and non-fluorinated biological active molecules such as optically active amines,[2a,b] aminoalcohols,[2a] aminoacids,[2a] and alkaloid precursors.[2c] Despite their increasing importance, few synthetic methods have been described for this class of compounds, and their utility in asymmetric synthesis has only recently been demonstrated.[2,3] These methods can be classified as follows: (a) condensation reaction between β-ketosulfoxides and aliphatic amines;[4] (b) addition of lithioenamines to sulfinic esters,[2c,4a,5a] following an Andersen-type synthesis;[5b] (c) Michael addition of primary and secondary amines to allenic[5a,6a] and alkynic chiral sulfoxides;[6b] and (d) reaction of metallated sulfoxides with aromatic nitriles to give *N*-unsubstituted β-enaminosulfoxides.[2b,7]

On the other hand, the introduction of fluorine or fluorinated substituents into organic molecules is currently receiving considerable attention due to the unique properties of organo-fluorine compounds in the fields of medicine, biology, agriculture and analytical chemistry.[8] Fluorine, partially fluorinated or perfluorinated substituents can be introduced into an organic compound directly through a fluorination reagent.[9] However, the poor regioselectivity and possible undesired transformation of functional groups, along with the high toxicity of the reagents, make this strategy problematic. While the building block strategy is an attractive alternative, it suffers from the lack of readily available fluorinated starting materials. Using this approach, Bravo *et al.*[2a] recently reported the first synthesis of fluorinated β-enaminosulfoxides from α-fluoroalkyl β-sulfinyl ketones and iminophosphoranes (Ph_3NR) through an aza-Wittig reaction. Their process works well, but it is limited to only a few examples (R = Cbz and H) and long reaction times are generally required. This led us to consider that perfluoroalkyl imidoyl halides could be excellent candidates as starting materials for the synthesis of such fluorinated sulfoxides. Imidoyl halides have been shown to be valuable synthetic intermediates, and have been used successfully in the synthesis of trifluoromethylated nitrogen heterocycles,[10a,b] trifluoromethyl ketimines,[10b] α,β-unsaturated trifluoromethyl ketones,[10c] and β-enamino acid derivatives.[10d] We report here our findings on the synthesis of γ-fluorinated β-iminosulfoxides **3** by the reaction of chiral non-racemic and racemic aryl methyl sulfoxides **2** with fluorinated imidoyl chlorides **1**.

Metallation of commercially available (*R*)-(+) or (*S*)-(-) methyl *p*-tolyl sulfoxide [or (±)-methyl phenyl sulfoxide] **2** with LDA (2.0 equiv.) and subsequent addition of a variety of fluorinated imidoyl chlorides **1**[11] at -78 °C gave, in a few minutes, γ-fluorinated β-iminosulfoxides **3** as the only products in good to excellent yield (65-92%, Table) (Scheme I). Pure compounds **3** were obtained after flash chromatography or by recrystallization of the crude mixture.



Scheme I

This process works well regardless of the nature of the substituents in the imidoyl chlorides **1** (R^1= alkyl or aryl, and R^2= R_f) and in the sulfoxide **2**, and does not require the use of an excess of reagents except for LDA. The scope of this methodology was also extended to non-fluorinated imidoyl halides derived from aliphatic and aromatic carboxylic acids (R^2= alkyl or aryl, entries 3 and 7, Table) showing thereby their general applicability. The reaction does not affect the configurational stability of the sulfur atom, and gives β-iminosulfoxides with optical purities comparable to that of the starting sulfoxide **2**.

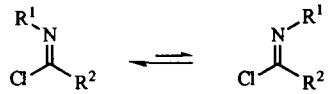
All of the title compounds were essentially obtained in the imino tautomeric form **3α**, based on spectroscopy data.[12] However, the tautomeric composition of the crude mixture seems to be affected by the nature of R^1 in **1**. Therefore, while fluorinated *N*-aryl derivatives **3** were obtained only as the imino tautomer **3α**, fluorinated *N*-alkyl derivatives showed small amounts of the three isomers **3β**, **3γ** and **3δ** (~10% in all, for **3f**, **3i** in the Table), as clearly detected by ^{19}F NMR. Furthermore, a slow tautomerization to the enaminic form **3β** was observed in the case of **3i** (R^1 = CH_2CH_2Ph), although the imino form **3α** was always predominant.

The configuration of the C=N double bond in **3** (α or γ) was assigned as *Z* or *E* based on NOE difference tests with compound **3f** (entry 6, Table). This study showed unequivocally that this compound exists predominantly in the *Z* configuration of the iminic double bond in $CDCl_3$ solution. Thus, by irradiation of the multiplet at 3.21 ppm, which corresponds to the C*H* protons of the cyclohexyl moiety, a positive NOE (5.46 and 4.01%) was observed for the diastereotopic hydrogens (CH_2) at 3.69 and 3.92 ppm respectively. An additional NOE (1.61%) was observed with the *ortho*-hydrogens of the *p*-tolyl ring at 7.51 ppm.

This result also allowed us to determine the structure of the starting imidoyl chlorides **1**. Although these compounds were always obtained as a single isomer, the geometry (*Z vs E*) of the C=N double bond was not clear.[10a] (Scheme II). Since the results of our spectroscopic studies were not meaningful, ***ab initio*** molecular

orbital calculations were performed. The geometry of imidoyl chlorides **1*Z*** and **1*E*** were fully optimized at the HF/6-31-G* level of theory.

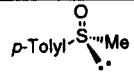
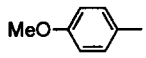
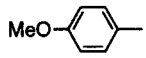
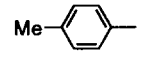
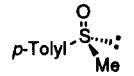
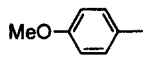
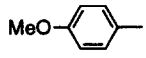
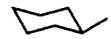
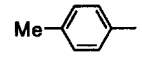
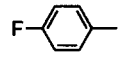
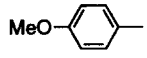
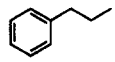
According to our results these systems appear only as the *Z* isomer. Thus, in the case of **1** (R^1= *p*-$MeOC_6H_4$ and R^2= CF_3) the *Z* isomer is 5.6 kcal mol^{-1} more stable than the *E* form. This result is in good agreement with the experimental evidence.[10a,13]



1*Z* **1*E***

Scheme II

Table. *N*-Substituted β-iminosulfoxides **3** obtained from aryl methyl sulfoxides **2** and imidoyl chlorides **1**

Entry	**2**	R^1	R^2	Product	Yield(%)[a]	mp (°C)[b]
1			CF_3	**3a**	85	97-9
2			CF_3CF_2	**3b**	82	58-60
3			$(CH_3)_3C$	**3c**	65	oil
4			$CF_3(CF_2)_6$	**3d**	92	62-64
5			CF_2Cl	**3e**	72	59-61
6			CF_3	**3f**	78	oil
7				**3g**	87	241-3
8			$CF_3(CF_2)_7$	**3h**	75	84-6
9			CF_3	**3i**	87	oil

[a] Yield after purification. [b] Melting points are uncorrected

In summary, we have developed for the first time a new, simple and efficient method for the synthesis of fluorinated *N*-substituted-β-iminosulfoxides **3** and have determined that the predominant tautomer exhibits *Z* geometry. We regard this procedure as the method of choice for synthesizing the title compounds.

Acknowledgments

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12. All compounds **3** exhibited ^{1}H, ^{13}C, ^{19}F NMR and mass spectra consistent with the assigned structure. For example, **3a**: $[\alpha]^{25}_{D}$ -327.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 2.41 (s, 3H), 3.75 (d, 1H, J = 12.6 Hz), 3.82 (s, 3H), 4.09 (d, 1H, J = 12.6 Hz), 6.87 (s, 4H), 7.28 (d, 2H, J = 8.0 Hz), 7.45 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, TMS, 62.5 MHz) δ 21.43 (CH_3), 55.44 (CH_3), 55.89 (CH_2), 114.23 (CH), 119.11 (CF_3, J_{CF} = 261.9 Hz), 121.40 (CH), 123.82 (CH), 130.22 (CH), 138.89 (C), 140.08 (C), 142.70 (C), 148.97 (C, J_{CCF} = 34.7 Hz), 158.25 (C); ^{19}F NMR ($CDCl_3$, $CFCl_3$, 235 MHz) δ -71.16; HRMS (FAB): calcd. for (M^++1) $C_{16}H_{17}NO_2SF_3$ 356.0932, found 356.0930. **3f**: $[\alpha]^{25}_{D}$ -158.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) (major tautomer) δ 1.09-1.79 (m, 10H), 2.35 (s, 3H), 3.21 (m, 1H), 3.69 (d, 1H, J = 12.6 Hz), 3.92 (d, 1H, J = 12.6 Hz), 7.30 (d, 2H, J = 8.0 Hz), 7.51 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, TMS, 62.5 MHz) (major tautomer) δ 21.23 (CH_3), 23.70 (CH_2), 23.83 (CH_2), 25.02 (CH_2), 32.46 (CH_2), 32.73 (CH_2), 54.19 (CH_2), 60.98 (CH), 119.04 (CF_3, J_{CF} = 277.5 Hz), 123.79 (CH), 130.07 (CH), 139.63 (C), 142.69 (C), 146.03 (C, J_{CCF} = 33.6 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$, 235 MHz) δ -71.95 (87.0 %), -68.13 (5.5 %), -64.17 (1.0 %), -61.82 (6.5%); HRMS (FAB): calcd. for (M^++1) $C_{16}H_{21}NOSF_3$ 332.1296, found 332.1293.
13. Full details of this theoretical study will be reported elsewhere.

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