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Sulfinimines of Trifluoropyruvate: Novel Intermediates for Chiral Non Racemic α-Trifluoromethyl α-Amino Acids

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Abstract: A new and preparatively useful method for the synthesis of non racemic α-trifluoromethyl (Tfm) α-amino acids (AAs) is presented. Key-building blocks are the sulfinimines (*S*)-**1a,b**, prepared *via* Staudinger reaction from trifluoropyruvic esters and the chiral *N*-sulfinyl iminophosphorane (*S*)-**5**, which were reacted with benzyl and alkylmagnesium halides. The resulting *N*-sulfinyl α-Tfm α-amino esters **6a,b** and **6c-g**, respectively, were produced with opposite stereoselectivity. The stereocontrol with alkyl Grignard reagents was progressively higher with increasing steric bulk. Some of the adducts **6** were transformed into α-Tfm-phenylalanine (*R*)-**8** (with regeneration and recycling the chiral auxiliary), α-Tfm-leucine (*S*)-**11e**, α-Tfm-butyrine (*S*)-**11f** and α-Tfm-alanine (*S*)-**11g** in two steps in one-pot.

α-Trifluoromethyl α-amino acids (α-Tfm-AAs) are synthetic analogues of naturally occurring amino acids (AAs), which are gaining a prominent position in the area of man-made fluorine containing AAs.[1] The great interest in α-Tfm-AAs arises from the fact that some of them exhibit attractive biological activity, and that some peptides containing α-Tfm-AAs have increased metabolic stability and biological activity.[2] Further interest arises from the synthetic challenge connected with the stereocontrolled formation of the trifluoromethylated quaternary amino acidic centre. Racemic α-Tfm-AAs can be efficiently obtained by reaction of *N*-protected imines of trifluoropyruvate with a huge variety of organometallic nucleophiles.[1] In contrast, the two generalized current methods for preparing non-racemic α-Tfm-AAs are affected by serious drawbacks. The stereoselective alkylation of 2,5-diketopiperazines of trifluoropyruvate with organomagnesium and organocadmium reagents is effective for the synthesis of homochiral dipeptide units, but single α-Tfm-AAs cannot easily be obtained by this route.[3] The reaction between chiral sulfoxide stabilized carbanions and *N*-alkoxycarbonyl imines of trifluoropyruvate[4] is not amenable to the straightforward synthesis of some complex or functionalized α-Tfm-AAs. Furthermore, in all cases the stereogenic quaternary amino acidic centres are formed in a random manner. For these reasons, the development of a new method for the synthesis of chiral non-racemic α-Tfm-AAs was desirable.

This paper describes the preparation of previously unknown chiral *p*-toluenesulfinimines[5] of trifluoropyruvate (*S*)-**1** (Scheme 1), the addition of benzyl and alkylmagnesium reagents across their C=N bond,[6] and the conversion of some of the resulting Grignard adducts **6** into non racemic α-Tfm-AAs.

The key sulfinimines (*S*)-**1** were prepared *via* Staudinger (aza-Wittig) reaction,[7] which is known to be an extremely useful tool for preparing strongly electrophilic imines.[8a] The chiral Staudinger reagent (*S*)-**5**[8b] (Scheme 1) was synthesized by reaction of DEAD/PPh_3[9] with the sulfinamide (*S*)-**4** (92%).[5b] The condensation between (*S*)-**5** and methyl or ethyl trifluoropyruvate (Scheme 1) occurred cleanly in benzene freshly distilled from Na (*ca.* 90 min. at 40 °C), providing (*S*)-**1a,b**. Sulfinimines (*S*)-**1a,b** can be readily handled because they are much less hygroscopic than the corresponding *N*-acyl and *N*-alkoxycarbonyl

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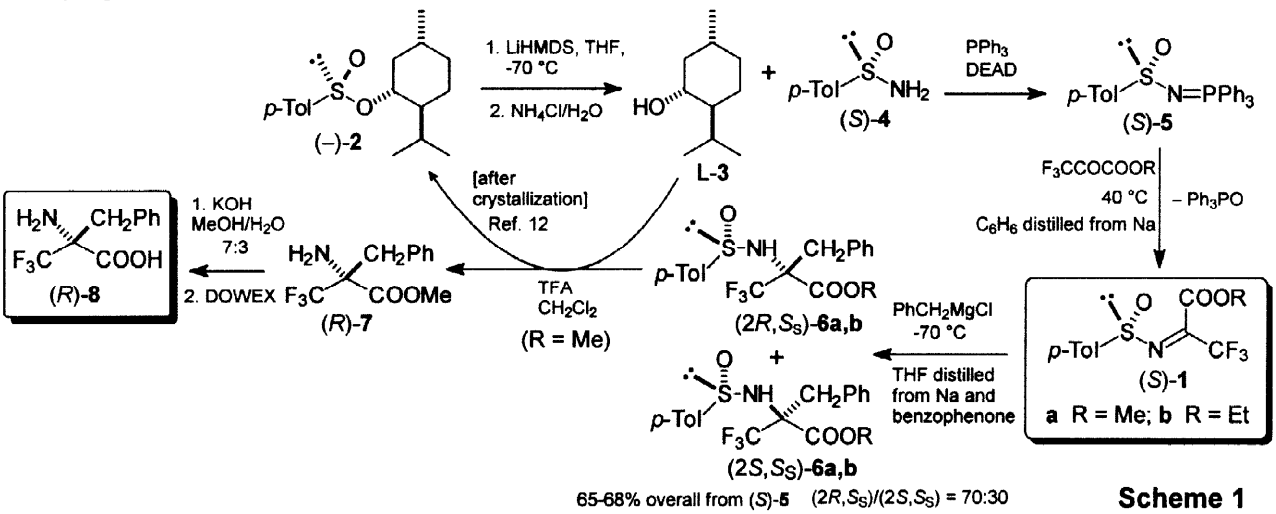
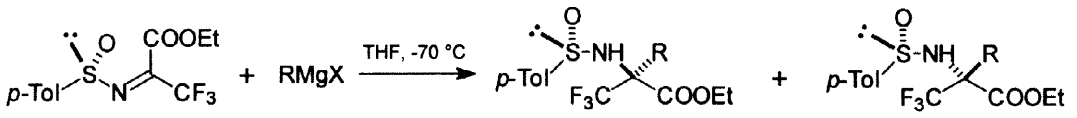
derivatives. The latter undergo immediate hydration of the C=N bond in the presence of a stoichiometric amount of water, whereas sulfinimine (*S*)-**1b** did not undergo detectable hydration after 15 min. at r.t. in the presence of a large excess of water. Although sulfinimines (*S*)-**1a,b** could not be isolated by flash chromatography due to hydrolysis occurring on silica gel, they could be characterized by ^{1}H, ^{19}F and ^{13}C NMR: a single set of signals was detected, as a likely consequence of rapid interconversion between the two *anti/syn* geometric isomers at r.t..[10]



Scheme 1

Both sulfinimines (*S*)-**1a,b** were reacted with benzylmagnesium chloride in THF. These reactions occurred smoothly at -70 °C (5 min), providing the corresponding diastereomeric *N*-sulfinyl amino esters **6a,b** in good yields and moderate diastereoselection in favour of the (2*R*,*S*S) diastereomers.[11] Diastereomerically pure sulfinamides **6a,b** were obtained by flash chromatography (FC) on silica gel. Transformation of the enantiopure sulfinamide (2*R*,*S*S)-**6a** into the α-Tfm-AA (*R*)-**8** was achieved as follows (Scheme 1). Treatment with trifluoroacetic acid (TFA) in the presence of recycled L-menthol **3**[5] provided known α-Tfm phenylalanine methyl ester (*R*)-**7** (90%),[4c] having $[\alpha]^{20}_{D}$ + 42.4 (c 1.9, $CHCl_3$), and menthyl sulfinate (80%).[12] The ester (*R*)-**7** was hydrolyzed with KOH in methanol/water 7:3, then treated with aqueous HCl, and finally purified with DOWEX-50W, providing α-Tfm-phenylalanine (*R*)-**8**, having $[\alpha]^{20}_{D}$ + 36.9 (c 1.04, H_2O).[4c]



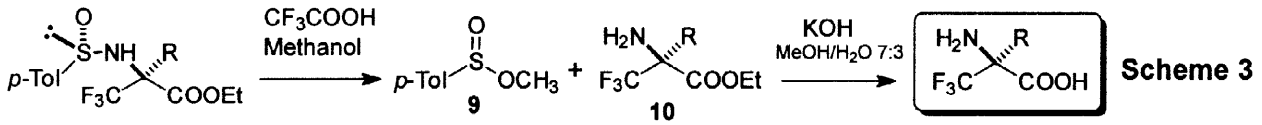
Scheme 2

Scheme 2 and Table 1. Addition of alkyl Grignard reagents to the *p*-toluenesulfinimine (*S*)-**1b**.[a,b]

Product	R	X	Yield (%) from trifluoropyruvate	e.e. (%)[c]	diast. ratio (2*S*,*S*S)/(2*R*,*S*S)-**6**	^{19}F NMR[d] (2*S*,*S*S)-**6**	^{19}F NMR[d] (2*R*,*S*S)-**6**
6c	$CH_2CH(CH_3)_2$	Br	65	88	87/13	-76.15	-76.25
6d	$CH(CH_3)_2$	Cl	72	90.5	84/16	-70.10	-70.35
6e	$(CH_2)_3CH_3$	Cl	55	> 96	74/26	-76.30	-76.40
6f	CH_2CH_3	Br	70	> 96	73/27	-76.15	-76.35
6f	CH_2CH_3	Cl	55	92	72/28	-76.15	-76.35
6g	CH_3	Cl	52	> 96	55/45	-78.10	-79.45

[a] Sulfinimine (*S*)-**1** prepared in C_6H_6 freshly distilled from Na. [b] Addition of the Grignard reagent to (*S*)-**1** performed in THF freshly distilled from Na and benzophenone. [c] E.e.'s determined by chiral HPLC analyses (Chiralcel OD, *n*-hexane/*iso*-propanol 85:15, 0.8 ml/min) of the sulfinamides **6**. [d] Hexafluorobenzene as external standard.

To investigate the generality of the new methodology several alkylmagnesium reagents were added to the sulfinimine (*S*)-**1b** (Scheme 2) in THF distilled from Na/benzophenone (-70 °C, 5 min). The corresponding products **6c-g** were produced with reverse stereoselectivity with respect to the benzyl derivatives **6a,b**. As it can be seen from Table 1, the stereocontrol was progressively higher with increasing steric bulk of the Grignard reagent. Good stereoselectivity in favour of (2*S*,*S*$_S$)-**6c**[13] and **6d** was obtained with *iso*-butylmagnesium bromide and *iso*-propylmagnesium chloride,[14] respectively. However, in both cases a slight racemization of the sulfinyl centre was observed (Table 1).[15] The reactions of (*S*)-**1b** with *n*-butylmagnesium chloride and ethylmagnesium chloride/bromide showed modest preference for the (2*S*,*S*$_S$)-**6e,f** products, while methylmagnesium chloride produced an almost equimolar mixture of diastereomers **6g**.



Scheme 3

(2*S*,*S*$_S$)-**6c** R = $CH_2CH(CH_3)_2$
(2*S*,*S*$_S$)-**6f** R = CH_2CH_3
(2*S*,*S*$_S$)-**6g** R = CH_3

(*S*)-**11c** R = $CH_2CH(CH_3)_2$
(*S*)-**11f** R = CH_2CH_3
(*S*)-**11g** R = CH_3

The *N*-sulfinyl amino esters (2*S*,*S*$_S$)-**6c,f,g**, obtained in diastereomerically pure form by FC, treated with TFA in methanol at r.t., afforded the ethyl esters of (*S*)-α-Tfm-leucine (**10c**), (*S*)-butyrine (**10f**) and (*S*)-alanine (**10g**) respectively, with methyl sulfinate **9** (Scheme 3).[16] Alkaline hydrolysis of (*S*)-**10c,f,g** and subsequent purification with DOWEX-50W produced the desired α-Tfm leucine (*S*)-**11c** (50% from **6c**), having $[\alpha]^{20}_D$ + 7.9 (c 0.63, H_2O), α-Tfm butyrine (*S*)-**11f** (58% from **6f**),[4c] having $[\alpha]^{20}_D$ – 11.0 (c 1.1, EtOH), and α-Tfm alanine (*S*)-**11g**, (55% from **6g**),[4a] having $[\alpha]^{20}_D$ – 12.6 (c 0.17, H_2O).

The results obtained with alkylmagnesium reagents might be rationalized with the chelated model reported in Fig. 1A, as already proposed by Wills for analogous reactions.[17] The carbanion is directed to the *Re* face of the imine *via* coordination of magnesium to the sulfinimine oxygen. In contrast, the Fujisawa's non-chelation model[18] (Fig. 1B) may account for the opposite stereoselectivity featured by benzylmagnesium chloride, which might react through a radical process. In both cases, the more stable geometrical isomer of (*S*)-**1** having the *N*-sulfinyl moiety *anti* with respect to the stereoelectronically demanding trifluoromethyl group and *syn* to the flat COOR[1] group, would react faster.

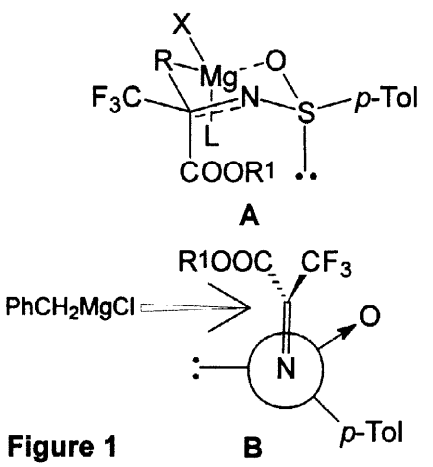


Figure 1

In conclusion, the novel methodology presented in this paper has several unique advantages: (a) a single chiral building block, namely the sulfinimine (*S*)-**1**, can be used as starting material for preparing a library of non-racemic α-Tfm-AAs, by simply changing the nucleophiles to be reacted with; (b) the diastereomeric sulfinamides (**6**) can be easily transformed into the corresponding α-Tfm AAs, and (c) the source of chirality, menthyl sulfinate (–)-**2**, can be recovered and recycled, that is very attractive for preparing non-racemic α-Tfm-AAs in multi-gram quantities. Current studies are evaluating full scope and limits of this method.

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8. (a) Preliminary attempts to obtain the sulfinimines (*S*)-**1** by the method of Davis (see Ref. 5) met with failure. In fact, reaction of lithium hexamethyldisilazane (LiHMDS) with menthyl sulfinate (–)-**2** (see Scheme 1), followed by addition of ethyl trifluoropyruvate (with or without CsF) invariably produced complex mixtures of products. (b) Racemic **5** has been obtained in low yields from Ph_3PNH, *p*-TolSOCl and triethylamine: Senning, A.; Kelly, P. *Naturwissenschaften* **1968**, *55*, 543. *Chem. Abstr.* 70:47555v.
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11. Adducts **6a,b** were obtained with e.e. 92.5%, owing to a slight racemization of the sulfinyl centre probably brought about by benzylmagnesium chloride. Crystallization of (2*R*,S_S)-**6a** from diisopropyl ether increased its e.e. to 99.9%.
12. Menthyl sulfinate was recovered as a 3/2 mixture of diastereomers, which can be regenerated in diastereomerically pure form (–)-**2** by the method of Posner/Solladié, and therefore recycled: (a) Mioskowski, C.; Solladié, G. *Tetrahedron* **1980**, *36*, 227-236. (b) Hulce, M.; Mallamo, J. P.; Frye, L. L.; Kogan, T. P.; Posner, G. H. *Org. Synth.* **1984**, *64*, 196-206.
13. Stereochemistry of **6c** was determined by X-ray diffraction. Full data will be reported in a full paper.
14. In the latter case, it is worth noting that no reduction of the C=N bond of (*S*)-**1b** was detected by careful examination of the crude reaction mixture, in sharp contrast with the reactions between *iso*-propylmagnesium halides and *N*-alkoxycarbonyl imines of trifluoropyruvate, in which 40% of reduction occurs (Ref. 1).
15. When commercially available THF or benzene stored on molecular sieves were used without preliminary distillation from sodium, the *N*-sulfinyl α-amino esters **6c-g** obtained from alkylmagnesium halides were isolated with only 20-50% e.e. The reasons for this dramatic racemization are currently under investigation.
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