

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

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Received 23 March 1998; revised 6 August 1998; accepted 11 August 1998

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-butyrate (S)-11f and α -Tfm-alanine (S)-11g in two steps in one-pot.

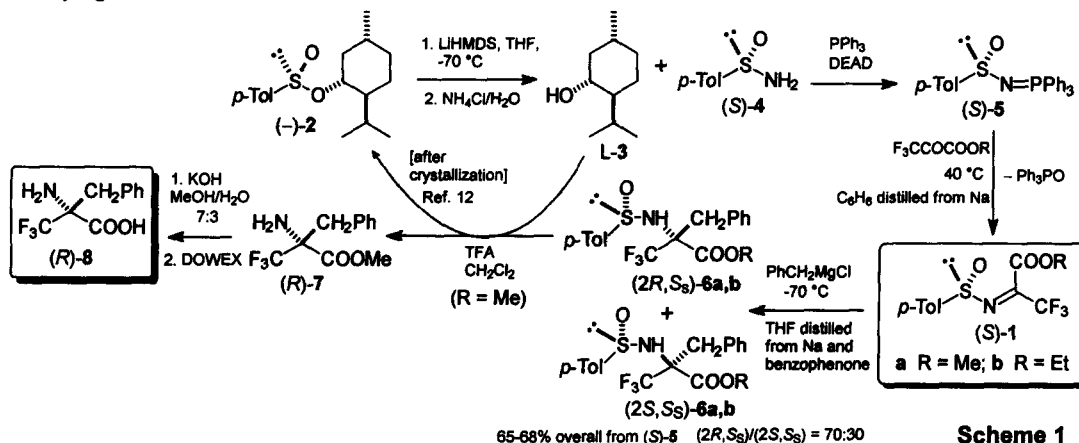
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α -Trifluoromethyl α -amino acids (α -Tfm-AAs) are synthetic analogues of naturally occurring amino acids (AAs), which are gaining a prominent position in the area of man-made fluorine containing AAs.¹ The great interest in α -Tfm-AAs arises from the 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 trifluoropyruvate⁴ 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.

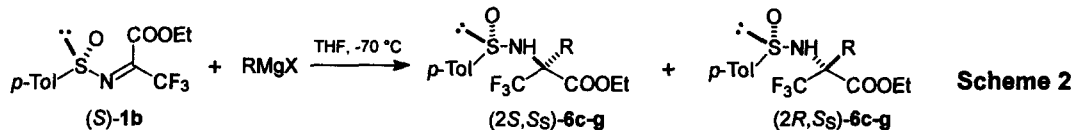
This paper describes the preparation of previously unknown chiral *p*-toluenesulfinimines⁵ of trifluoropyruvate (S)-1 (Scheme 1), the addition of benzyl and alkylmagnesium reagents across their C=N bond,⁶ and the conversion of some of the resulting Grignard adducts 6 into non racemic α -Tfm-AAs.

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/PPh₃⁹ with the sulfonamide (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

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 ^1H , ^{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



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 (2R,S₅) diastereomers.¹¹ Diastereomerically pure sulfinamides 6a,b were obtained by flash chromatography (FC) on silica gel. Transformation of the enantiopure sulfinamide (2R,S₅)-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 3⁵ provided known α -Tfm phenylalanine methyl ester (R)-7 (90%),^{4c} having $[\alpha]_{\text{D}}^{20} + 42.4$ (c 1.9, CHCl₃), 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 $[\alpha]_{\text{D}}^{20} + 36.9$ (c 1.04, H₂O).^{4c}

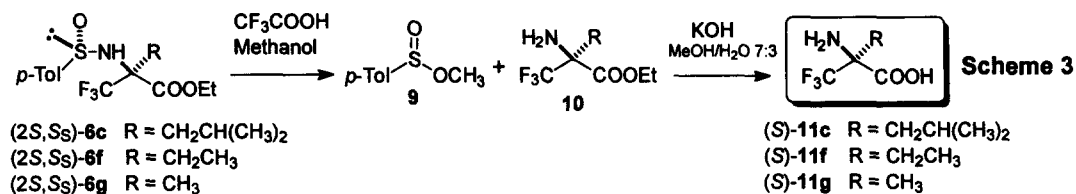


Scheme 2 and Table 1. Addition of alkyl Grignard reagents to the *p*-toluenesulfinimine (S)-1b.^{a,b}

Product	R	X	Yield (%) from trifluoropyruvate	e.e. (%) ^c	diast. ratio (2S,S ₅)/(2R,S ₅)-6	^{19}F NMR ^d (2S,S ₅)-6	^{19}F NMR ^d (2R,S ₅)-6
6c	CH ₂ CH(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) ₃ CH ₃	Cl	55	> 96	74/26	-76.30	-76.40
6f	CH ₂ CH ₃	Br	70	> 96	73/27	-76.15	-76.35
6f	CH ₂ CH 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 C₆H₆ 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*₅)-6c¹³ 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*₅)-6e,f products, while methylmagnesium chloride produced an almost equimolar mixture of diastereomers 6g.



The *N*-sulfinyl amino esters (2*S*,*S*₅)-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 [α]_D²⁰ + 7.9 (c 0.63, H₂O), α-Tfm butyrine (*S*)-11f (58% from 6f),^{4c} having [α]_D²⁰ - 11.0 (c 1.1, EtOH), and α-Tfm alanine (*S*)-11g, (55% from 6g),^{4a} having [α]_D²⁰ - 12.6 (c 0.17, H₂O).

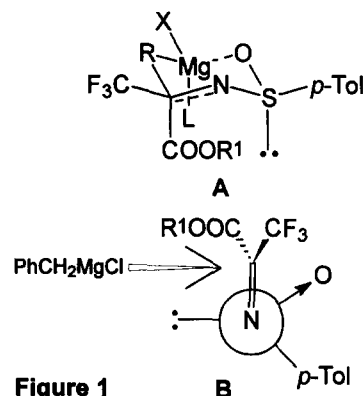
The results obtained with alkylmagnesium reagents might be rationalized with the chelated model reported in Fig. 1A, as already proposed by Wills for analogous reactions.¹⁷ The carbanion is directed to the *Re* face of the imine via coordination of magnesium to the sulfinimine oxygen. In contrast, the Fujisawa's non-chelation model¹⁸ (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 COOR¹ group, would react faster.

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.

Acknowledgment. B.V. thanks Politecnico di Milano for a scholarship.

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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 Ph₃PNH, *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*₈)-**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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