ORGANIC LETTERS

2006
Vol. 8, No. 7
1379−1381

Solvent-Controlled Asymmetric Strecker Reaction: Stereoselective Synthesis of α-Trifluoromethylated α-Amino Acids

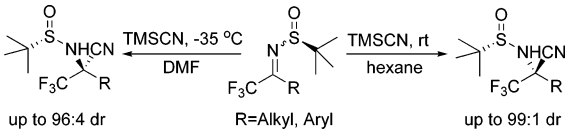
Hua Wang, Xiaoming Zhao, Youhua Li, and Long Lu*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PRC

lulong@mail.sioc.ac.cn

Received January 15, 2006

ABSTRACT



Stereoselective approaches to α-trifluoromethylated α-amino acids (α-Tfm AAs) have been developed. The stereoconfigurations of the resulting α-Tfm AA precursors were well controlled by using different solvents. The optically active (*S*)-2-amino-2-phenyl-1,1,1-trifluoropropanoic acid was synthesized by this method.

α-Trifluoromethylated (CF_3) α-amino acids (α-Tfm AAs) have been attracting much attention in the field of biochemistry and pharmacology because of their unique properties.[1] Several synthetic approaches of α-Tfm AAs have been developed; however they have suffered from some drawbacks such as, for instance, poor stereocontrol in the formation of the stereogenic quaternary center.[2] Consequently, stereoselective construction of the stereogenic quaternary center under mild conditions is a desirable method.

Chiral sulfinyl amide, which could coordinate with a Lewis acid as an electronic donor and direct the stereoselectivity of the products, is an efficient auxiliary group.[3] The use of *N-tert*-butylsulfinylimines as chiral templates is thoroughly described in the diastereoselective synthesis of trifluoromethylated derivatives.[4] However, there is no example concerning the nature of the sulfoxide group as a Lewis base that activates the Lewis acid.[5] Herein, we wish to report an example of the asymmetric Strecker reaction based on the principles of trimethylsilyl cyanide (TMSCN), a readily available reagent activated by the sulfoxide group in the absence of a catalyst.

Our research work began with the synthesis of the chiral CF_3-substituted (*R*)-*N-tert*-butylsulfinylketoimines (Tfm-NBSKIs, **1**) (derived from (*R*)-*tert*-butylsulfin amide).[6] The

(1) (a) Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (b) Sewald, N.; Burger, K. *Fluorine-containing Amino Acids: Synthesis and Properties*; Wiley: Chichester, 1995.

(2) (a) Asensio, A.; Bravo, P.; Crucianelli, M.; Farina, A.; Fustero, S.; Soler, G. J.; Meille, V. S.; Panzeri, W.; Viani, F.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem.* **2001**, 1449−1458. (b) Fustereo, S.; Navorro, A.; Pina, B.; Soler, G. J.; Bartolome, A.; Asensio, A.; Simon, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621−2624. (c) Crucianelli, M.; Bravo, P.; Arnone, A.; Corradi, E.; Meille, V. S.; Zanda, M. *J. Org. Chem.* **2000**, *65*, 2965−2971. (d) Amii, H.; Kishikawa, Y.; Kageyama, K.; Uneyama, K. *J. Org. Chem.* **2000**, *65*, 3404−3408. (e) Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313−315. (f) Qiu, X.; Meng, W.; Qing, F. *Tetrahedron* **2004**, *60*, 6711−6745. (g) Ogu, K.; Matsumoto, S.; Akazome, M.; ogura, K. *Org. Lett.* **2005**, *7*, 589−592. (h) Bravo, P.; Viani, F.; Zanda, M.; Soloshonok, V. *Gazz. Chim. Ital.* **1995**, *125*, 149−150. (i) Bravo, P.; Capelli, S.; Meille, S. V.; Viani, F.; Zanda, M.; Kukhar, V. P.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **1994**, *5*, 2009−2018.

(3) For review, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. (b) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13−18. (c) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651−3706.

(4) (a) Prakash, J. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589−590. (b) Prakash, J. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538−6539. (c) Xu, W.; Dolbier, W. R., Jr. *J. Org. Chem.* **2005**, *70*, 4741−4745.

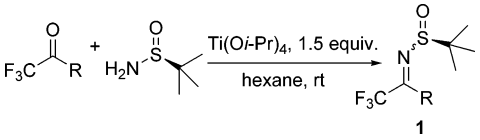
(5) (a) Gutmann, V. *The Donor−Acceptor Approach to Molecular Interactions*; Plenum: New York, 1978. (b) Jensen, W. B. *The Lewis Acid−Base Concepts*; Wiley: New York, 1980; pp 136−137. (c) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, *2*, 168−170. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793.

(6) (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913−9914. (b) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948−9957.

10.1021/ol0601186 CCC: $33.50
Published on Web 03/04/2006

optimized reactions were performed in hexane distilled from Na/benzophenone in the presence of 1.5 equiv of $Ti(O^iPr)_4$, where Tfm-NBSKIs were obtained in 47−80% yields (Table 1). It must be pointed out that Tfm-NBSKIs have to be

Table 1. Preparation of the Tfm-NBSKIs



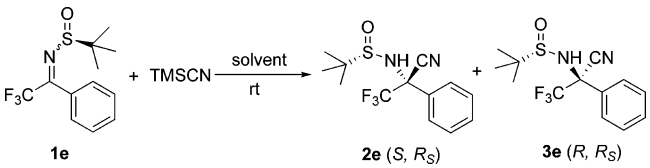
entry	R	product	t (h)	yield[a] (%)
1	Me−	**1a**	3	47
2	Et−	**1b**	3	61
3	n-C_6H_{13}−	**1c**	12	81
4	$BnCH_2$−	**1d**	4	56
5	Ph−	**1e**	4	58
6	p-MePh−	**1f**	12	50
7	p-MeOPh−	**1g**	8	65
8	p-ClPh−	**1h**	8	80

[a] Yields were determined by ^{19}F NMR.

generated and isolated quickly prior to use because they are readily hydrolyzed upon prolonged standing on silica gel. **1** was not fully characterized because of the same reason.

With these compounds in hand, we investigated the Strecker reaction of **1e** with TMSCN in hexane at room temperature. A mixture of **2e** and **3e** was obtained in 91% yield and 99:1 dr (**2e**/**3e**) (Table 2, entry 1). Solvent effects

Table 2. Effect of Solvents on the Asymmetric Strecker Reaction



entry	solvent	dr[a] (**2e**/**3e**)	total yield[b] (%)
1	hexane	99:1	91
2	Et_2O	3:1	73
3	EtOAc	1:1	70
4	1,4-dioxane		
5	DMSO	1:3	33
6	DMF	1:6	86

[a] Diastereomeric ratios were determined by ^{19}F NMR spectroscopy on the crude reaction mixture. [b] Total yields of two analytically pure isomers.

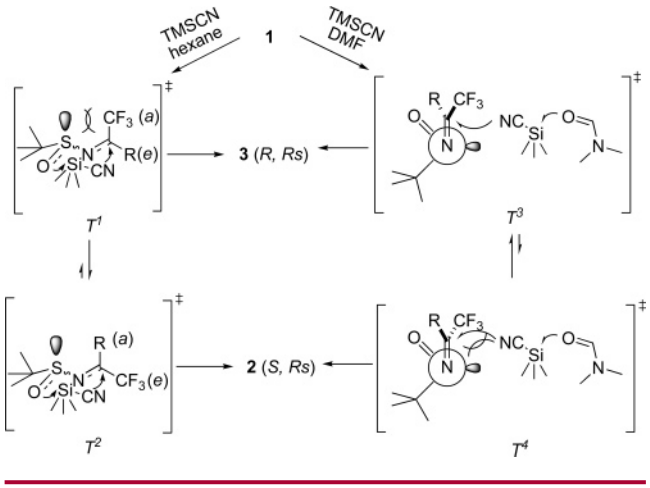
were investigated and summarized in Table 2. Polar solvents usually led to a decrease in the **2e**/**3e** ratio except for 1,4-dioxane, in which a decomposition of imine was observed. It is noteworthy that the reaction in DMF afforded **2e** and **3e** in a 1:6 ratio, which is a diastereoselectivity opposite to the reaction in hexane (Table 2, entry 6).

The Strecker reaction in hexane was successful with a variety of substrates, and the scope of the reaction was outlined in Table 3. **2a**−**h** were obtained in 69−92% yields with good dr value. The addition of 0.2 equiv of $Ti(O^iPr)_4$ accelerated the reaction; however, this resulted in a decrease of stereoselectivity, presumably because of the strong Ti−O interaction that inhibits the activation of TMSCN by sulfoxide (Table 3). An X-ray diffraction study of both **2e** and **2a**[7] indicated that the absolute configuration of **2** was (*S*, *Rs*). Therefore, we deduced the absolute configuration of **3** was (*R*, *Rs*).

To study this Strecker reaction in DMF, **1a**−**h** were subjected to the optimized reaction conditions. All of them underwent the Strecker reaction in several hours at −35 °C and gave **2** and **3** in 69−89% yields with up to a 1:19 dr value (Table 3).

On the basis of the diastereoselectivity observed (Table 1), a possible mechanism was proposed. The Strecker reaction in hexane proceeds via the six-membered chairlike models[8] (T^1 and T^2, Scheme 1), and the chiral *tert*-

Scheme 1. Proposed Mechanism for Asymmetric Strecker Reaction



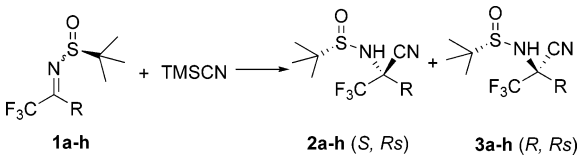
butylsulfinyl group directs the configuration of T^1 and T^2. As mentioned before, the sulfinyl group in Tfm-NBSKI activates TMSCN to undergo the Strecker reaction. T^1 is unfavored because of the predominant electrostatic repulsion between the lone pairs on the sulfur and the electron-rich CF_3 group. The six-membered transition state in hexane gives **2** (*S*, *Rs*) as the major product. However, the Strecker reaction in DMF undertakes Fujisawa's model[9] (T^3 and T^4 transition state) because DMF is not only a polar solvent but also a Lewis base, which activates TMSCN instead of the sulfinyl

(7) See Supporting Information. Crystallographic data for X-ray structures have been deposited with the Cambridge Crystallographic Center [**2a** (CCDC 280989), **2e** (CCDC 280988)]. Copies of the data can be obtained free of charge from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K.. E-mail: deposit@ccdc.cam.ac.uk.

(8) Hose, D. R. J.; Mahon, M. F.; Molly, K.; Raynham, C.; Wills, T. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 691−703.

(9) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881−3884.

Table 3. Asymmetric Strecker Reaction between Tfm-NBSKIs and TMSCN in Hexane and DMF



entry	substrate (R)		product[c]	t (h) hexane[f]	t (h) DMF[g]	total yield[e] (%) hexane	total yield[e] (%) DMF	dr[a,b] (2/3) hexane	dr[a,b] (2/3) DMF
1	**1a**	(Me−)	**2a**,[d] **3a**	24	8	69	71	27:1 (4:1)	1:19
2	**1b**	(Et−)	**2b**, **3b**	24	8	77	76	7:1 (3:1)	1:10
3	**1c**	(n-C_6H_1−)	**2c**, **3c**	48	8	88	84	14:1 (2:1)	1:11
4	**1d**	($BnCH_2$−)	**2d**, **3d**	48	12	92	89	7:1 (7:1)	1:15
5	**1e**	(Ph−)	**2e**,[d] **3e**	24	12	85	72	99:1 (7:1)	1:6
6	**1f**	(p-MePh−)	**2f**, **3f**	24	12	87	69	11:1 (1:1)	1:7
7	**1g**	(p-MeOPh−)	**2g**, **3g**	12	12	89	78	14:1 (4:1)	1:9
8	**1h**	(p-ClPh−)	**2h**, **3h**	12	12	83	71	8:1 (1:1)	1:6

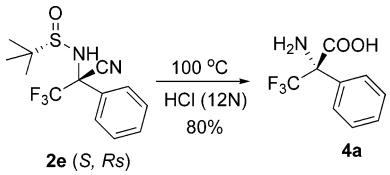
[a] Diastereomeric ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture. [b] In parentheses are the dr values with 20 mol % of $Ti(O^iPr)_4$ as catalyst. [c] Configurations were assigned from the transition-state model. [d] Configurations were determined by X-ray crystallographic data. [e] Total yields of two analytically pure isomers. [f] Hexane as the solvent at room temperature. [g] DMF as solvent at −35 °C.

group of Tfm-NBSKIs. T^3 is more favored than T^4 because of the electrostatic repulsion between CF_3 and the lone pairs of sulfur in T^4. Hence, **3** (*R*, *Rs*) is obtained as the major product (Scheme 1).

It must be indicated that the sulfinimines without CF_3 cannot proceed in such reactions under similar conditions. The CF_3 group might play an important role: (1) electrostatic repulsion causes CF_3 to be far away from the lone pairs of the sulfur atoms; (2) the steric effect of CF_3 is approximately equivalent to isopropyl,[10] and therefore an *e* bond is more stable than an *a* bond in six-membered chairlike models; (3) the electron-withdrawing nature of the CF_3 group increases the reactivity of sulfinimines, therefore facilitating the Strecker reaction.

To demonstrate further the synthetic utility of these findings, (*S*)-2-amino-2-phenyl-1,1,1-trifluoropropanoic acid (**4a**) was readily synthesized from **2e** (Scheme 2). The deprotection and hydrolysis of **2e** in HCl (12 N) at refluxing temperature gave the desired optically active α-CF_3 α-amino acid in one pot. (*S*)-2-amino-2-methyl-1,1,1-trifluoropropanoic acid (**4b**)[2i] was synthesized from **2a** in the same way.

Scheme 2. Hydrolysis and Deprotection of **2e**



In summary, an effective method for the formation of stereogenic quaternary centers via solvent-controlled asymmetric Strecker reactions was developed. The reaction in hexane afforded predominantly (*S*, *Rs*)-product, whereas in DMF, the (*R*, *Rs*)-isomer was the major product. Further deprotection and hydrolysis resulted in α-trifluoromethyl α-amino acid. This method provided a stereoselective approach to the optically active α-trifluoromethyl α-amino acids

Acknowledgment. We thank the National Natural Science Foundation of China (Grant Numbers 29825104 and 29632003) and the Chinese Academy of Science for financial support.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

OL0601186

(10) Riggi, I.; Virgili, A.; Moragas, de M.; Jaime, C. *J. Org. Chem.* **1995**, *60*, 27−31.