ORGANIC LETTERS

2002
Vol. 4, No. 9
1571−1573

Synthesis of Optically Active Trifluoromethylated Indolizidine Derivatives via Stereoselective Radical Cyclization

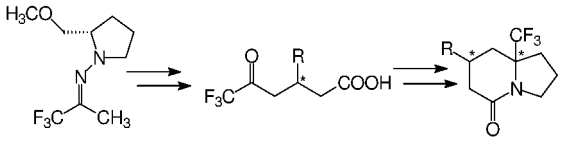
Takashi Okano,* Masataka Fumoto, Takahiro Kusukawa, and Makoto Fujita

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan

okano@apchem.nagoya-u.ac.jp

Received February 28, 2002

ABSTRACT



Asymmetric Michael reaction of lithiated trifluoroacetone SAMP-hydrazone with alkylidenemalonates gave addition products stereoselectively. Hydrolyzed enantiomerically pure ketoacids were cyclized to dihydropyridinones. N-Iodopropylation followed by radical cyclization gave optically active trifluoromethylated indolizidinones stereoselectively.

Fluorinated heterocycles[1] are of current interest as a class of potentially biologically active compounds.[2] Compared to the common approaches for trifluoromethylated aromatic heterocycles,[3] fewer syntheses of trifluoromethylated aliphatic nitrogen heterocycles have been reported, even though the introduction of a trifluoromethyl group into the alkaloid-related heterocycle is a hopeful modification procedure to develop new biologically active compounds.[4] Particularly, synthesis of optically active trifluoromethylated aliphatic nitrogen heterocycles has been rarely reported. Jiang et al. reported the synthesis of optically active trifluoromethylated piperidine and quinolidine from 6,6,6-trifluoro-5-oxohexanoic acid.[5] Previously, we prepared the ketoacid in an awkward way that involved the low-yield cross Claisen condensation of trifluoroacetate and glutarate.[6] Usually, such 1,5-dicarbonyl compounds are prepared by the Michael reaction of ketone and α,β-unsaturated carboxylic acid derivatives, and if an asymmetric conjugate addition is possible, a versatile optically active building block for the potential biologically active aliphatic nitrogen heterocycles is available. We report here the asymmetric Michael reaction of Enders's SAMP[7] ((*S*)-*N*-amino-2-methoxymethylpyrrolidine) hydrazone of trifluoroacetone and alkylidenemalonate esters to give chiral 3-alkyl-6,6,6-trifluoro-5-oxohexanoic acids **1** and the following radical cyclization to optically active indolizidine derivatives bearing a trifluoromethyl group at the bridgehead carbon.

Reed and Katzenellenbogen[8] reported the preparation of SAMP-hydrazone **2** and the following Michael addition of

(1) For recent reviews of the synthesis of trifluoromethylated compounds, see: (a) Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635−3671. (b) Elguero, J.; Fruchier, A.; Jagerovic, N.; Werner, A. *Org. Prep. Proced. Int.* **1995**, *27*, 33−74.

(2) (a) *Fluoroorganic Chemistry: Synthetic Challenge and Biomedical Rewards*; Resnati, G., Soloshonok, V. A., Eds.; Tetrahedron Symposium-in-Print N 58; *Tetrahedron* **1996**, *52*, 1−330. (b) Welch, J. T.; Eswarakrishnan, A. In *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (c) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. In *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1993.

(3) Andrew, R. J.; Mellor, J. M. *Tetrahedron* **2000**, *56*, 7267−7272 and references therein.

(4) Bravo, P.; Crucianelli, M.; Farina, A.; Meille, S. V.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem.* **1998**, 435−440.

(5) Jiang, J.; DeVita, R. J.; Doss, G. A.; Goulet, M. T.; Wyvratt, M. J. *J. Am. Chem. Soc*. **1999**, *121*, 593−594.

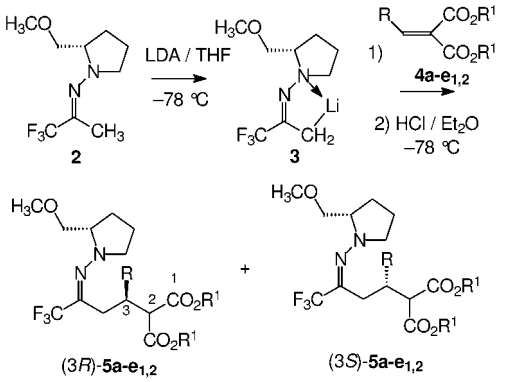
(6) Okano, T.; Sakaida, T.; Eguchi, S. *J. Org. Chem*. **1996**, *61*, 8826−8830.

(7) Enders, D.; Papadopoulas, K. *Tetrahedron Lett*. **1983**, *24*, 4967−4970. Enders, D.; Rendenbach, B. E. M. *Tetrahedron* **1986**, *42*, 2235−2242.

10.1021/ol025792b CCC: $22.00
Published on Web 04/02/2002

lithiated hydrazone **3** with methyl cinnamate followed by alkaline hydrolysis to an "unstable" ketoacid **1a**, which was not purified. However, in our hands this reaction failed completely. Probably because of the unusually stable nature of the lithiated hydrazone **3**, the reverse Michael reaction prevents obtaining the addition product. Successful Michael addition of **3** was achieved by employing activated alkylidenemalonate esters **4a**$_{1,2}$−**e**$_{1,2}$ as Michael acceptors at −78 °C to give diastereomer mixtures of (*E*)-hydrazones **5a**$_{1,2}$−**e**$_{1,2}$ in 58−84% yields (Table 1).[9] To avoid the reverse

Table 1. Asymmetric Michael Reaction of Lithiated Hydrazone **3** with Alkylidenemalonates **4**



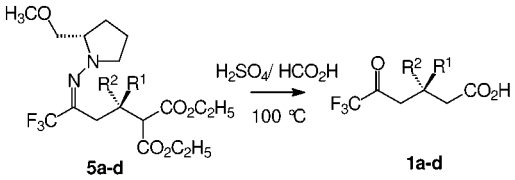
substrate	product	R	R^1	yield (%)	products ratio (3*R*):(3*S*)[a]
4a$_1$	**5a**$_1$	C_6H_5	C_2H_5	75	79:21
4a$_2$	**5a**$_2$	C_6H_5	CH_3	77	92:8
4b$_1$	**5b**$_1$	4-$CH_3OC_6H_4$	C_2H_5	64	38:62
4b$_2$	**5b**$_2$	4-$CH_3OC_6H_4$	CH_3	70	83:17
4c$_1$	**5c**$_1$	$(CH_3)_2CH$	C_2H_5	77	74:26[b]
4c$_2$	**5c**$_2$	$(CH_3)_2CH$	CH_3	75	68:32[b]
4d$_1$	**5d**$_1$	C_4H_9	C_2H_5	84	68:32
4d$_2$	**5d**$_2$	C_4H_9	CH_3	58	61:39
4e$_1$	**5e**$_1$	CH_3	C_2H_5	80	72:28
4e$_2$	**5e**$_2$	CH_3	CH_3	83	56:44

[a] The ratios of diastereomers were estimated by integrating the ^{19}F NMR signals of the crude reaction mixtures. [b] The formal configurations of these products are (3*S*) and (3*R*), respectively.

Michael reaction during warming up, the reaction mixture was quenched by addition of an ethereal solution of hydrogen chloride at −78 °C. X-ray crystallography of the major isomer of 3-phenyl product **5a**$_2$ revealed that the configuration of the 3-position was *R*, similar to the results of the acetone SAMP-hydrazone and benzylidenemalonates reported by Enders.[10] The diastereomeric ratios and the configurations of the other products were established by comparison of the HPLC retention times on a chiral column and the ^{1}H and ^{19}F NMR spectra of (3*R*)-**5a**$_1$ and (3*S*)-**5a**$_1$ with those of the products **5b**$_{1,2}$−**e**$_{1,2}$. Interestingly, for the products from arylmethylenemalonates **4a**$_{1,2}$ and **4b**$_{1,2}$, the stereoselectivities of the methyl esters **4a**$_2$ and **4b**$_2$ were better than those of ethyl esters **4a**$_1$ and **4b**$_1$, whereas ethyl esters **4c**$_1$−**e**$_1$ gave Michael products more stereoselectively than methyl esters **4c**$_2$−**e**$_2$ for alkylidenemalonates. Particularly, the stereoselectivity of 3-anisyl ethyl ester **4b**$_1$ was reversed to give preferentially (3*S*)-**5b**$_1$. Except for the methyl derivatives **5e**$_{1,2}$, the Michael products **5a**$_1$−**d**$_1$ were separated by simple SiO_2 column chromatography.

The acidic hydrolysis of the isolated major ethyl esters **5a**$_1$−**d**$_1$ was conducted by heating in formic acid in the presence of sulfuric acid to give the desired enantiomerically pure 3-substituted (+)-6,6,6-trifluoro-5-oxohexanoic acids **1a**,**c**,**d** and (−)-acid **1b** (Table 2) as stable forms.

Table 2. Preparation of Enatiomerically Pure 3-Substituted 6,6,6-Trifluoro-5-oxohexanoic Acids **1a**−**d**



product	R^1	R^2	yield (%)	$[\alpha]^{16}_D$ (*c* 0.4, $CHCl_3$)
(3*R*)-**1a**	C_6H_5	H	92	+24.5
(3*S*)-**1b**	H	4-$CH_3OC_6H_4$	90	−18.4
(3*R*)-**1c**	$(CH_3)_2CH$	H	97	+40.5
(3*R*)-**1d**	C_4H_9	H	97	+35.4

The dehydration reaction of chiral acids **1a**−**d** with ammonium carbonate under refluxing in toluene followed by addition of a catalytic amount of *p*-toluenesulfonic acid gave dihydropyridinones **6a**−**d** in 74−80% yields, presumably through the hemiaminal intermediates **7**. An iodopropyl group as a tether for the radical cyclization was attached by deprotonation of enamide **6a**−**d** with NaH in anhydrous DMF followed by addition of an excess amount of 1,3-diiodopropane at room temperature in 52−70% yields (Scheme 1).

The reaction of triethylborane and a small amount of oxygen is a promising route to generate an ethyl radical that abstracts iodine from alkyl iodides to give another alkyl radical at low temperature.[11] After radical addition to a C−C double bond, the generated alkyl radical is reduced by usually trialkyltin hydrides. However, for environmental reasons, tris(trimethylsilyl)silane[12] was employed as the radical chain transfer reagent despite the lower reactivity compared to that

(8) Instead of the reported procedure, SAMP-hydrazone **2** was prepared by dehydrative heating in toluene with a Dean−Stark apparatus in the presence of a catalytic amount of *p*-toluenesulfonic acid in 90% yield after mixing trifluoroacetone and SAMP at room temperature for 2 days. Reed, P. E.; Katzenellenbogen, J. A. *J. Med. Chem.* **1991**, *34*, 1162−1176.

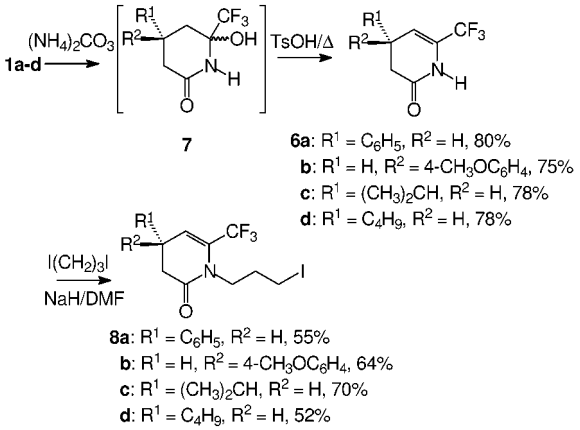
(9) All new compounds were characterized by spectroscopic and elemental analyses.

(10) Enders, D.; Demir, A. S.; Rendenbach, B. E. M. *Chem. Ber.* **1987**, *120*, 1731−1735.

(11) Fujita, K.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 3137−3138.

(12) Ikeda, M.; Hamada, M.; Yamashita, T.; Matsui, K.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1949−1956.

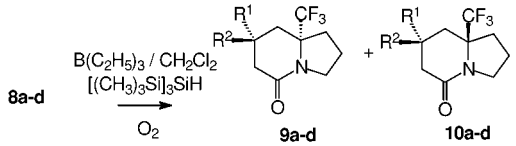
Scheme 1



of tin hydrides. Thus, the radical cyclization of the iodopropylpyridinones **8a**−**d** (0.1 mmol) was achieved by the reaction with triethylborane (0.2 mmol) and slow addition of oxygen (3 mL) using a syringe pump in the presence of tris(trimethylsilyl)silane (0.2 mmol) at room temperature. The desired optically active indolizidines **9a**−**d** and **10a**−**d**, which have a trifluoromethyl group at the bridgehead position, were obtained as *syn*/*anti* (R/CF_3) mixtures (Table 3). The minor isomer of isopropyl derivative **10c** was crystallized, and the molecular structure was analyzed by X-ray crystallography to reveal that the relative configuration was *anti*.[13] Since the structural similarities among each series of the major and minor products were evident from both the ^1H and ^{19}F NMR spectra, all major products can be speculated to have the *syn* relative configurations. Although the origin of this moderate stereoselectivity in the radical cyclization of **8a**−**d** is not clearly understood, as illustrated in Figure 1, in the transition states for the *anti* products, unfavorable 1,3-di-pseudoaxial interaction between the alkyl group attached on the carbon at the 4-position of the dihydropyridine ring and the developing C−C bond is possible. This type of 1,3-stereoselection of the radical

(13) The absolute configuration of **10c** was deduced from the (3*R*)-configuration of the starting **1c**.

Table 3. Radical Cyclization of Iodoenamides **8** to Optically Active Indolizidinones **9** and **10**



products (yield, %)				products ratio
9	**10**	R^1	R^2	(*syn*:*anti*)
9a (46)	**10a** (14)	C_6H_5	H	71:29
9b (10)	**10b** (32)	H	$4\text{-}CH_3OC_6H_4$	74:26
9c (44)	**10c** (16)	$(CH_3)_2CH$	H	70:30
9d (46)	**10d** (23)	C_4H_9	H	61:39

cyclization of a six-membered ring was also observed in the radical cyclization of a more rigid cyclohexenyl ester.[14]

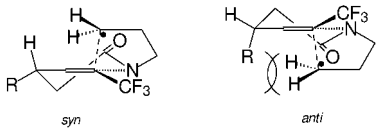


Figure 1. Transition states for the *syn* and *anti* radical products.

In summary, optically active indolizidinones having a trifluoromethyl group on the bridgehead carbon were prepared via stereoselective radical cyclization, starting from asymmetric Michael addition of trifluoroacetone SAMP-hydrazone with alkylidenemalonate esters.

Supporting Information Available: Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025792B

(14) Srikrishna, A.; Kumar, P. P.; Reddy, T. J. *Tetrahedron Lett*. **1998**, *39*, 5815−5818.