

Synthesis of Optically Active Trifluoromethylated Indolizidine Derivatives via Stereoselective Radical Cyclization

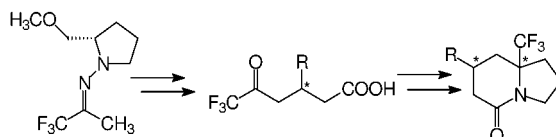
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ABSTRACT



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 heterocycles¹ 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 SAMP⁷ ((*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 Katzenellenbogen⁸ 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.

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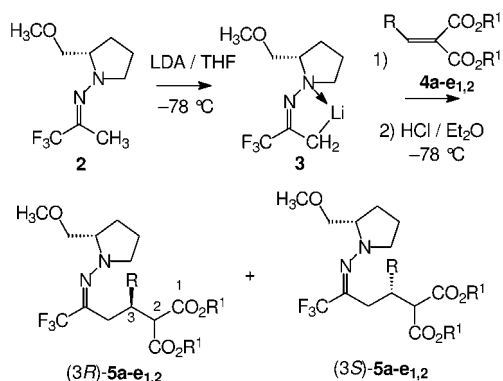
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(7) Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967–4970. Enders, D.; Rendenbach, B. E. M. *Tetrahedron* **1986**, *42*, 2235–2242.

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 <i>R</i>):(3 <i>S</i>) ^a
4a₁	5a₁	C ₆ H ₅	C ₂ H ₅	75	79:21
4a₂	5a₂	C ₆ H ₅	CH ₃	77	92:8
4b₁	5b₁	4-CH ₃ OC ₆ H ₄	C ₂ H ₅	64	38:62
4b₂	5b₂	4-CH ₃ OC ₆ H ₄	CH ₃	70	83:17
4c₁	5c₁	(CH ₃) ₂ CH	C ₂ H ₅	77	74:26 ^b
4c₂	5c₂	(CH ₃) ₂ CH	CH ₃	75	68:32 ^b
4d₁	5d₁	C ₄ H ₉	C ₂ H ₅	84	68:32
4d₂	5d₂	C ₄ H ₉	CH ₃	58	61:39
4e₁	5e₁	CH ₃	C ₂ H ₅	80	72:28
4e₂	5e₂	CH ₃	CH ₃	83	56:44

^a The ratios of diastereomers were estimated by integrating the ¹⁹F 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 **5a₂** 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

(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.

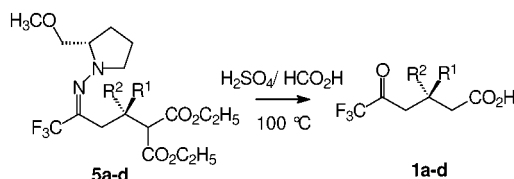
(9) All new compounds were characterized by spectroscopic and elemental analyses.

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comparison of the HPLC retention times on a chiral column and the ¹H and ¹⁹F NMR spectra of (3*R*)-**5a₁** and (3*S*)-**5a₁** 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 **4a₂** and **4b₂** were better than those of ethyl esters **4a₁** and **4b₁**, whereas ethyl esters **4c₁–e₁** gave Michael products more stereoselectively than methyl esters **4c₂–e₂** for alkylidenemalonates. Particularly, the stereoselectivity of 3-anisyl ethyl ester **4b₁** was reversed to give preferentially (3*S*)-**5b₁**. Except for the methyl derivatives **5e_{1,2}**, the Michael products **5a₁–d₁** were separated by simple SiO₂ column chromatography.

The acidic hydrolysis of the isolated major ethyl esters **5a₁–d₁** 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 Enantiomerically Pure 3-Substituted 6,6,6-Trifluoro-5-oxohexanoic Acids **1a–d**



product	R ¹	R ²	yield (%)	[α] _D ¹⁶ (c 0.4, CHCl ₃)
(3 <i>R</i>)- 1a	C ₆ H ₅	H	92	+24.5
(3 <i>S</i>)- 1b	H	4-CH ₃ OC ₆ H ₄	90	–18.4
(3 <i>R</i>)- 1c	(CH ₃) ₂ CH	H	97	+40.5
(3 <i>R</i>)- 1d	C ₄ H ₉	H	97	+35.4

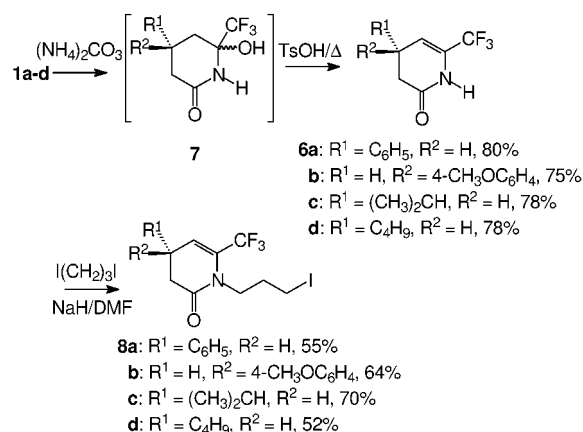
The dehydration reaction of chiral acids **1a–d** with ammonium carbonate under refluxing in toluene followed by addition of a catalytic amount of *p*-toluenesulfonic acid gave dihydropyridinones **6a–d** in 74–80% yields, presumably through the hemiaminal intermediates **7**. An iodopropyl group as 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)silane¹² was employed as the radical chain transfer reagent despite the lower reactivity compared to that

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Scheme 1



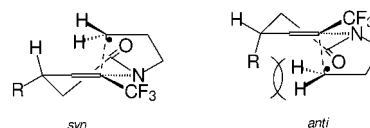
of tin hydrides. Thus, the radical cyclization of the iodopropylpyridinones **8a–d** (0.1 mmol) was achieved by the reaction with triethylborane (0.2 mmol) and slow addition of oxygen (3 mL) using a syringe pump in the presence of tris(trimethylsilyl)silane (0.2 mmol) at room temperature. The desired optically active indolizidines **9a–d** and **10a–d**, which have a trifluoromethyl group at the bridgehead position, were obtained as *syn/anti* (R/CF₃) 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 ¹⁹F 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, %)		R ¹	R ²	products ratio (<i>syn:anti</i>)
9	10			
9a (46)	10a (14)	C ₆ H ₅	H	71:29
9b (10)	10b (32)	H	4-CH ₃ OC ₆ H ₄	74:26
9c (44)	10c (16)	(CH ₃) ₂ CH	H	70:30
9d (46)	10d (23)	C ₄ H 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>.

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