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Stereoselective Generation and Aldol Reaction of Tetrafluoropropanamide Boron Enolates Leading to threo-2-Fluoro-2-trifluoromethyl-3-hydroxy Alkanamides

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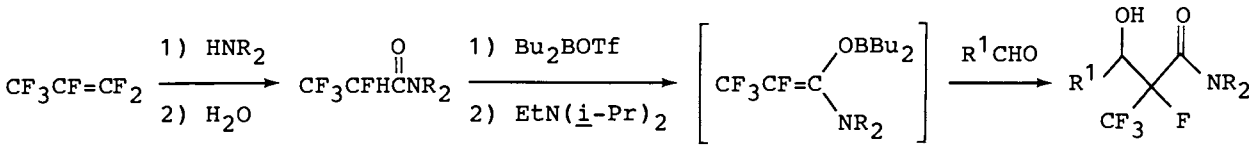
Treatment of N,N-dialkyl-2-hydryltetrafluoropropanamide, readily available from hexafluoropropene and a secondary amine, with dibutylboryl triflate and ethyldiisopropylamine gave isomerically pure tetrafluoropropanamide boron enolate, which was allowed to react with various aldehydes at -10 °C to afford the corresponding threo-2-fluoro-2-trifluoromethyl-3-hydroxy alkanamides in good yields.

There is increasing attention to the chemistry of fluorinated ketone or ester enolates[1-3] as well as to their synthetic applications to biologically interesting compounds.[4] In the course of our recent studies[3] on the chemistry of enolates of the type $CF_3CF{=}CR(OM)$, we have intended to develop the method for generating the metal enolate of 2-hydryltetrafluoropropanamide along our concept that this species would be accessible if strong coordination of a Lewis acidic metal to the carbonyl oxygen precedes α-deprotonation with a base, so as to prevent any anionic charge from emerging.

This communication describes, for the first time, the successful generation of N,N-dialkyltetrafluoropropanamide boron enolates (**2**) employing a dialkylboryl triflate and hindered amine reagent[5] and their aldol reaction with various aldehydes giving predominantly threo-2-fluoro-2-trifluoromethyl-3-hydroxy alkanamides (**3**) in high yields.

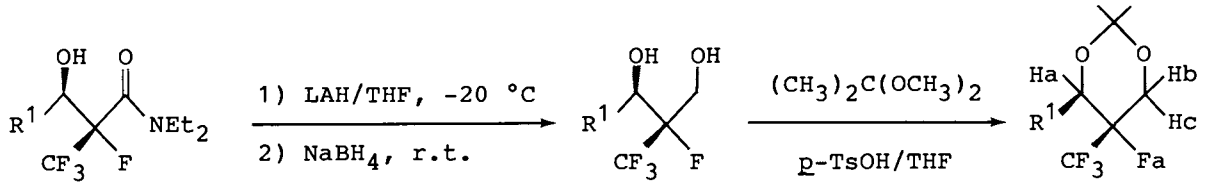
The starting 2-hydryltetrafluoropropanamides (**1**) were prepared in 87-92% yields by the addition of diethylamine or piperidine to hexafluoropropene in diethyl ether at room temperature[6] and hydrolysis with an aqueous $NaHCO_3$ solu-



δ_{CF_3} -75.7 (12.2 and 6.1 Hz) δ_{CF_3} -70.5 (12.2 Hz)
δ_{CF} -199.4 (12.2 and 45.2 Hz) δ_{CF} -201.2 (12.2 Hz)

1a: R = CH_3CH_2 **2** **3**

tion. Successive treatment of the amide **1a** in dichloromethane with dibutylboryl triflate (Bu_2BOTf) (1.1 equiv.) for 5 min at 0 °C and with ethyldiisopropylamine (1.2 equiv.) for 10 min at -10 °C resulted in clean generation of isomerically pure (E)-enolate **2**,[7] which could be confirmed with ^{19}F NMR showing that both vicinal (6.1 Hz) and geminal (45.2 Hz) fluorine-hydrogen couplings observed in **1** disappeared during the course of the reaction. On addition of butanal (1.1 equiv.) to this reaction mixture, followed by stirring for 30 min at -10 °C and quenching with 30% hydrogen peroxide, 2-fluoro-2-trifluoromethyl-3-hydroxyhexanamide (**3a**)[8] was obtained in 88% yield as a 94:6 mixture of threo and erythro isomers. Other aliphatic and aromatic aldehydes also reacted smoothly with thus generated enolate species **2** to afford, in good diastereoselectivities and chemical yields, the corresponding aldol products **3**, whose stereochemical assignment was made based on ^1H and ^{19}F NMR of acetonides **4** derived from **3**, as shown below.



3 **4**

4a: R^1 = $CH_3(CH_2)_2$
J_{Fa-Ha} = 14.4 Hz
J_{Fa-Hb} = 26.5 Hz
J_{Fa-Hc} = 23.5 Hz

4g: R^1 = C_6H_5
J_{Fa-Ha} = 15.2 Hz
J_{Fa-Hb} = 25.0 Hz
J_{Fa-Hc} = 22.2 Hz

The reaction with ketones, however, was very sluggish to give **3** in only less than 40% yields. Table 1 summarizes the results of the aldol reaction. 9-Borabicyclo[3.3.1]nonyl triflate was much less effective than Bu_2BOTf.[9] Out of the amines examined, such as ethyldiisopropylamine, triethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-ene, ethyldiisopropylamine gave the best results.

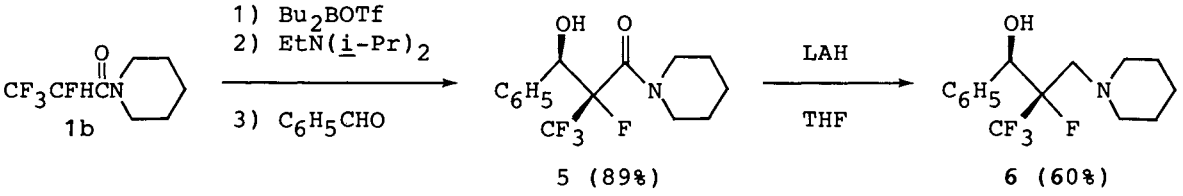
The present reactions are applicable to the synthsis of a fluorinated analog of threo-N-(3-hydroxy-2-methyl-3-phenylpropyl)piperidine,[10,11] one of the

Table 1. Aldol Reaction of the Amide Boron Enolate 2 with Aldehydes

Entry	Aldehyde	Product 3 R^1		Yield[a] %	Isomer ratio[b] threo : erythro
1	$CH_3CH_2CH_2CHO$	$CH_3CH_2CH_2$	(3a)	88	94 : 6
2	$(CH_3)_2CHCHO$	$(CH_3)_2CH$	(3b)	86	92 : 8
3	$(CH_3)_3CCHO$	$(CH_3)_3C$	(3c)	74	86 : 14
4	(E)-$CH_3CH=CHCHO$	(E)-$CH_3CH=CH$	(3d)	85	94 : 6
5	(E)-$CH_3CH=C(CH_3)CHO$	(E)-$CH_3CH=CCH_3$	(3e)	82	92 : 8
6	(E)-$C_6H_5CH=CHCHO$	(E)-$C_6H_5CH=CH$	(3f)	86	100 : 0
7	C_6H_5CHO	C_6H_5	(3g)	84	93 : 7
8	p-$CH_3C_6H_4CHO$	p-$CH_3C_6H_4$	(3h)	78	100 : 0
9	p-$CH_3OC_6H_4CHO$	p-$CH_3OC_6H_4$	(3i)	82	94 : 6
10	p-ClC_6H_4CHO	p-ClC_6H_4	(3j)	76	100 : 0

a) Yields are of pure isolated products. b) Determined by ^{19}F NMR.

pharmacologically interesting γ-amino alcohols. Thus, treatment of the amide 1b with Bu_2BOTf and ethyldiisopropylamine and with benzaldehyde under the conditions described above afforded an 89% yield of the aldol product 5[8] (threo : erythro = 95 : 5), which was reduced with lithium aluminium hydride (LAH) (5 equiv.) in refluxing tetrahydrofuran (THF) for 5 h to give almost diastereomerically pure threo-N-[2-fluoro-2-(trifluoromethyl)-3-hydroxy-3-phenylpropyl]piperidine (6)[12] in a 60% yield, as illustrated below.



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7) Dertermined tentatively on the basis of the stereochemical outcome of the aldol reaction.

8) Spectral data of the products were fully consistent with the assigned structures including stereochemistry.

9) Trimethylsilyl triflate has been used for generating the enolate of methyl 3,3,3-trifluoropropionate,[2] but was ineffective in the present reaction.

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12) Typical spectral data of **6** are as follows: IR (film) 3170, 2938, 2852, 1455, 1442, 1308, 1208, 1187, 1124, 1086, 1052, 966, 786, 760, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 7.5-7.3 (m, 5H), 5.27 (d, J = 10.8 Hz, 1H), 3.3-2.3 (m, 6H), 1.9-1.7 (m, 4H), and 1.7-1.4 (m, 3H); ^{19}F NMR ($CDCl_3$) δ = -76.55 (d, J = 6.1 Hz, 3F) and -168.29 to -169.09 (m, 1F).

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