ORGANIC LETTERS

2005
Vol. 7, No. 4
589−592

Novel Synthesis of α-Trifluoromethylated α-Amino Acid Derivatives from γ-Hydroxy-α-fluoro-α-trifluoromethyl Carboxamides

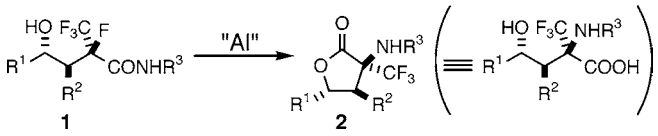
Kenichi Ogu, Shoji Matsumoto, Motohiro Akazome, and Katsuyuki Ogura*

Department of Applied Chemistry and Biotechnology, Faculty of Engineering, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263-8522, Japan

katsuyuki@faculty.chiba-u.jp

Received November 11, 2004

ABSTRACT



On treatment with an organoaluminum reagent such as trimethylaluminum or DIBAL-H, γ-hydroxy-α-fluoro-α-trifluoromethyl carboxamides (1) give a single diastereomer of α-amino-α-trifluoromethyl-γ-lactones (2), which are a ring-closed form of γ-hydroxy-α-trifluoromethyl-α-amino acids. This intriguing reaction results from intramolecular replacement of the fluorine atom on the α-carbon atom with the nitrogen atom of the amide group, which occurs in an S_N2 manner.

Organofluoro compounds have been attracting much attention in the fields of biochemistry and pharmacology because of their unique biological properties, which are ascribed to the so-called mimic effect. This is useful for developing new drugs.[1] Against this background, various methods have been investigated for synthesizing fluorine-containing α-amino acids.[2] Here, we would like to report a novel synthetic route leading from γ-hydroxy-α-fluoro-α-trifluoromethyl amides.

To date, we have developed some methods for the synthesis of organofluoro compounds bearing a perfluoroethylidene [$F(CF_3)C<$] moiety.[3] The reaction of various allylic alcohols with a perfluoropropene-diethylamine adduct (PPDA) affords α-fluoro-α-trifluoromethyl carboxylic acid derivatives. These products can be easily converted into γ-hydroxy-α-fluoro-α-trifluoromethyl carboxamides (**1**).

To obtain the α-amino-α-trifluoromethyl-γ-lactones, we examined the substitution of the α-fluorine atom with an amination reagent. As is known well, the leaving ability of the fluorine atom is enhanced by metal-fluorine affinity.[4] Especially, aluminum exhibits a strong affinity toward the fluorine atom.[5] Posner and co-workers utilized an organoalu-

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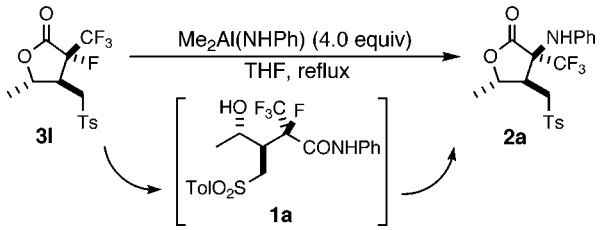
10.1021/ol047683y CCC: $30.25 © 2005 American Chemical Society
Published on Web 01/20/2005

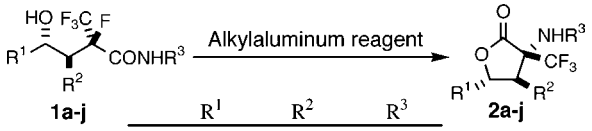
minum reagent for C-glycosylation of glycosyl fluorides.[6] Alkylaluminum reagents were employed by Maruoka et al. for the selective alkylation of fluorinated epoxides and carbonyl compounds.[7] Organoaluminum reagents also serve as catalysts in the nucleophilic substitution of tertiary alkyl fluorides.[8] On the basis of these facts, we examined the reaction of 2-fluoro-2-trifluoromethyl-3-tosylmethyl-4-pentanolide (**3l**) with dimethylaluminum anilide. To our great delight, the expected 2-phenylamino-2-trifluoromethyl-4-pentanolide (**2a**) was formed (Scheme 1). However, it was

Scheme 1. Formation of **2a** from **3l** Subjected to Reaction with Dimethylaluminum Anilide



found that *N*-phenyl-3-hydroxy-2-fluoro-3-tosylmethyl-2-(trifluoromethyl)pentanamide (**1a**) was mainly formed at the initial stage, and thence the amount of **2a** increased as the reaction proceeded.[9] With these findings, we started to investigate reacting various γ-hydroxy-α-fluoro-α-trifluoromethyl carboxamides (**1**) with organoaluminum amides.

The starting γ-hydroxy-α-fluoro-α-trifluoromethyl amides (**1**) were prepared from α-fluoro-α-trifluoromethyl-γ-lactones (**3**) with aniline, benzylamine, or *p*-anisidine. Detailed procedures for the preparation of **1** are given in Supporting Information.



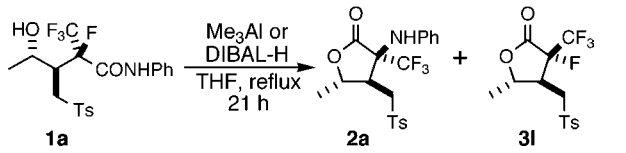
	R^1	R^2	R^3
a	Me	CH_2Ts[a]	Ph
b	Me	CH_2Ts	Bn
c	Me	CH_2Ts	PMP[b]
d	H	CH_2Ts	Bn
e	H	CH_2Ts	PMP
f	Me	Me	Bn
g	Me	Me	PMP
h	Me	H	Bn
i	*i*-Bu	H	Bn
j	*n*-Bu	H	Bn

[a] Ts=*p*-$TolSO_2$, [b] PMP=*p*-$MeOC_6H_4$

At first, we examined the types of organometallic reagent that would be effective for the conversion of **1** to **2**. *N*-Benzyl-4-hydroxy-2-fluoro-3-tosylmethyl-2-(trifluoromethyl)pentanamide (**1b**) was treated with various organometallic compounds (2.0−2.2 molar equiv), and it was found that *n*-butyllithium, triethylborane, *n*-butyltitanium triisopropoxide, diethylzinc and ethylmagnesium bromide did not give **2b** at all. In contrast, some organoaluminum reagents effectively formed **2b** from **1b**. On treatment with aluminum trialkoxide such as $Al(OPh)_3$ and $Al(O\textit{i}\text{-}Pr)_3$ in refluxing THF, **3l** was formed together with the unchanged **1b**. Among the alkylaluminum reagents examined herein, trimethylaluminum and diisobutylaluminum hydride (DIBAL-H) were the most effective at giving **2b**, affording the latter in 68% and 77% yields, respectively. It is worth noting that the product (**2b**) was formed as a single diastereomer.

From these preliminary experiments, we selected two aluminum reagents, trimethylaluminum and DIBAL-H, and they were subjected to the reaction with *N*-phenyl-4-hydroxy-2-fluoro-3-tosylmethyl-2-(trifluoromethyl)pentanamide (**1a**). The reaction took place in THF at reflux. After 21 h, the expected 2-phenylamino-3-tosylmethyl-2-trifluoromethyl-4-pentanolide (**2a**) was formed along with a small amount of the γ-lactone **3l**. As shown in Table 1, a high yield in the

Table 1. Reaction of **1a** with Trimethylaluminum or DIBAL-H



			yield (%)[a]		
entry	aluminum reagent	equiv	**2a**	**3l**	**1a**
1	Me_3Al	none	0	19[b]	76[b]
2		1.2	66	23	3
3		2.2	69	14	0
4		3.2	63	15	0
5	DIBAL-H	1.2	56	34	0
6		2.2	78	7	0
7		3.2	66	0	0

[a] Yields were determined by ^1H NMR using Ph_3CH as an internal standard. [b] Isolated yield.

formation of **2a** was attained using more than 1 molar equiv of the aluminum reagent, though the yield of **2a** became maximal at 2.2 molar equiv of the aluminum reagent.

Interestingly, **2a** was also formed as a single diastereomer in any case. Because its ^1H NMR spectrum was very similar to that of **2b**, the structure of **2a** was likely to have the same pentanolide skeleton. Fortunately, this product gave good quality single crystals. From the ORTEP structure of **2a** (see Supporting Information) obtained by single-crystal X-ray

(4) Bond strength of metal−fluorine: Al−F, 663.6 ± 6.3 kJ/mol; Li−F, 577 ± 21 kJ/mol; Ti−F, 569 ± 34 kJ/mol; Si−F, 552.7 ± 2.1 kJ/mol; Sn−F, 466.5±13 kJ/mol; Mg−F, 461.9 ± 5.0 kJ/mol. See: Weast, R. C. *Handbook of Chemistry and Physics*, 65th ed.; CRC Press: New York, 1984−1985.

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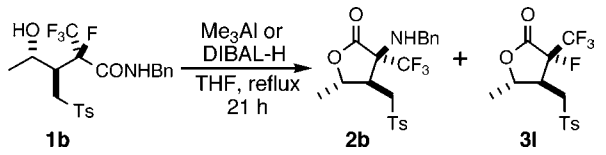
(9) See Supporting Information

crystallographic analysis, the α-fluorine atom was replaced by the phenylamino group with inversion of the configuration.

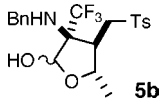
Further, the reaction of **1b** with trimethylaluminum and DIBAL-H was studied in detail. The results using various amounts of the aluminum reagent are given in Table 2. With

Table 2. Reaction of **1b** with Trimethylaluminum or DIBAL-H



			yield (%)[a]		
entry	aluminum reagent	equiv	**2b**	**3l**	**1b**
1	Me_3Al	none	0	7[b]	90[b]
2		1.2	10	16	72
3		2.2	68	12	17
4		3.2	35	0	0
5	DIBAL-H	1.2	15	31	45
6		2.2	78	7	0
7[c]		3.2	27	3	0

[a] Yields were determined by ^{1}H NMR using Ph_3CH as an internal standard. [b] Isolated yield. [c] A lactol (**5b**) was formed as a byproduct in 30% yield.

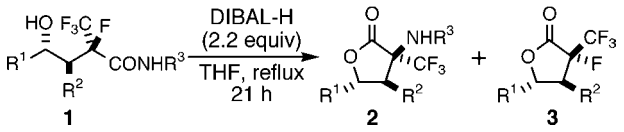


1.2 molar equiv of trimethylaluminum and DIBAL-H, the yield of **2b** was low (10% and 15%, respectively; entries 2 and 5 in Table 2). The use of an excess amount (3.2 molar equiv) of the aluminum reagent brought about further reduction of **2b** to give a lactol (**5b**) (entry 7 in Table 2). The optimal amount of aluminum reagent used was shown to be 2.2 molar equiv (entries 3 and 6 in Table 2).

Under these optimal conditions, various 4-hydroxy-2-fluoro-2-(trifluoromethyl)carboxamides (**1**) were converted to α-amino-α-trifluoromethyl-γ-lactones (**2**). The results are summarized in Table 3. Although aromatic and aliphatic amines could be utilized as the amino group (R^3NH), the *p*-methoxyphenylamino group afforded the best results. This seems to imply that the electron-donating group accelerates the migration of the amino group. Furthermore, it was found that the substituent at the β-position of **1** plays an important role in the formation of **2**. In the absence of the β-substituent (entries 8−10 in Table 3), the reaction became slower, giving **2** in moderate yield.

Furthermore, we performed some experiments to gain insight into the mechanism for the conversion of **1** to **2**. First, we checked whether the γ-hydroxy group is crucial in the conversion of **1** to **2**. When *N*-benzyl-2-fluoro-4-methoxy-3-tosylmethyl-2-(trifluoromethyl)pentanamide (**6**) was subjected to the reaction with 2.2 molar equiv of DIBAL-H in

Table 3. Reaction of **1** with DIBAL-H

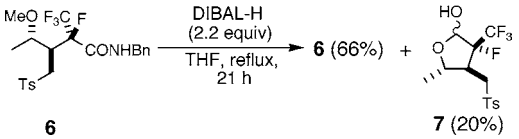


					yield (%)[a]		
entry	**1**	R^1	R^2	R^3	**2**	**3**	**1**
1	**1a**	Me	CH_2Ts	Ph	85	31	0
2	**1b**			Bn	78	7	0
3	**1c**			PMP	80	0	0
4	**1d**	H	CH_2Ts	Bn	64	0	10
5	**1e**			PMP	70	0	0
6	**1f**	Me		Bn	79	0	0
7[c]	**1g**		Me	PMP	84	0	0
8[b]	**1h**	Me		Bn	60	0	4
9[c]	**1i**	*i*-Bu	H		46	0	16
10[d]	**1j**	*n*-Bu			56	0	5

[a] Isolated yield. [b] Reaction time: 25 h. [c] Reaction time: 48 h. [d] Reaction time: 50 h.

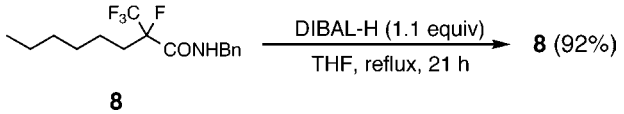
refluxing THF, we obtained a lactol (**7**) in 20% yield instead of the corresponding α-benzylamino-γ-lactone (**2b**) (Scheme 2).

Scheme 2. Reaction of **6** with DIBAL-H



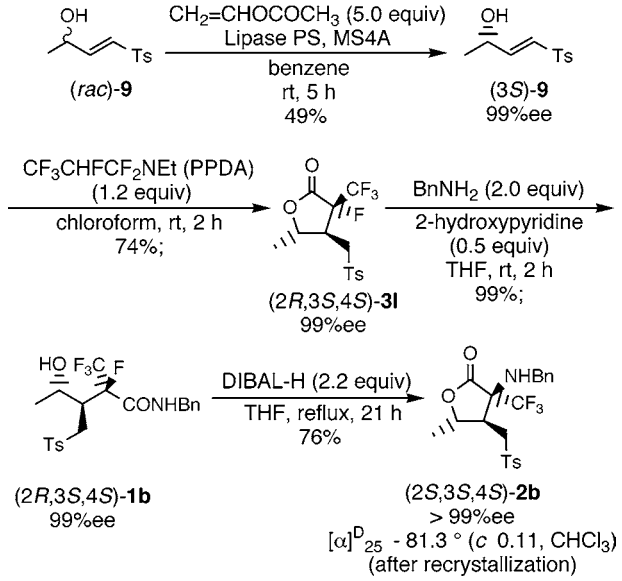
In addition, *N*-benzyl-2-fluoro-2-(trifluoromethyl)octanamide (**8**) remained unchanged under the same reaction conditions (Scheme 3). Therefore, it is evident that the present reaction of **1** needs the γ-hydroxy group.

Scheme 3. Reaction of **8** with DIBAL-H

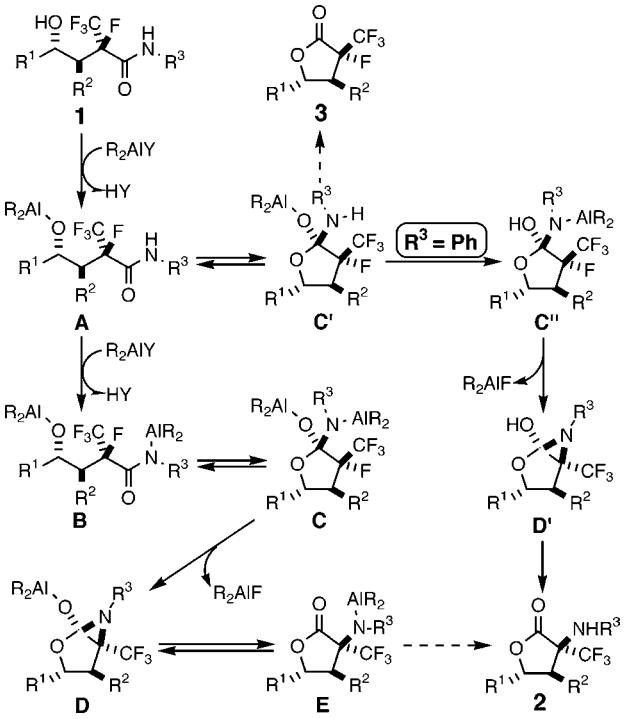


As mentioned above, the present reaction gave one diastereomer of **2**. Here, we synthesized an optically active (2*R*,3*S*,4*S*)-**1b** according to the synthetic route in Scheme 4. In the reaction of the optically active **1b** with 2.2 equiv of DIBAL-H in refluxing THF, (2*S*,3*S*,4*S*)-**2b** was obtained in 76% yield (> 99%ee). The enantiomeric excess of the product was analyzed by HPLC equipped with a chiral column to be more than 99%. Thus, it was shown that the chiral centers of **1** do not undergo any epimerization during the reaction.

Scheme 4. Synthesis of Optically Active **2**



Scheme 5. Plausible Mechanism for Formation of **2** from **1** Subjected to Reaction with Alkylaluminum Reagent



From the above results, we propose a plausible mechanism for forming **2** from **1** (Scheme 5). The starting material (**1**) has two reactive sites, a γ-hydroxy group and an amido group, for the reaction with trimethylaluminum or DIBAL-H. With 2 molar equiv of the aluminum reagent, it is reasonably assumed that a dialumino intermediate (**B**) is formed. If **B** cyclizes intramolecularly by the attack of the resulting aluminum alkoxide on the amide carbonyl group, a cyclic *N*-ortho ester (**C**) would be formed. The subsequent intramolecular substitution of the α-fluorine atom for the amide nitrogen leads to an aziridine derivative (**D**), which can be transformed to the final product (**2**) via a ring-opened intermediate **E** followed by hydrolysis (workup process). An analogous reaction to the ring opening of **D** to form **E** was reported by Fioravanti et al.;[10] the reaction of an enol ether of cyclohexanone with an (ethoxycarbonyl)nitrene affords the corresponding aziridine derivative, which is led to 2-amino-cyclohexan-1-one by the subsequent hydrolysis. It is likely that, with 1 molar equiv of the aluminum reagent, **1** forms a monoalumino intermediate (**A**) predominantly. The intermediate **A** cyclizes intramolecularly to form an *N*-ortho ester (**C′**) that gives α-fluoro-α-trifluoromethyl-γ-lactone (**3**) by hydrolysis (workup). This is the case when R^3 is a phenyl group. Since the amino proton of **C′** (R^3 = phenyl) is more acidic than that of **C′** (R^3 = benzyl), it is reasonably supposed that the intermediate (**D′**; R^3 = phenyl) can be transformed to an *N*-alumino intermediate (**C″**; R^3 = phenyl) that undergoes intramolecular cyclization to give another aziridine derivative (**D′**). This path can explain why 1 molar equiv of the aluminum reagent can transform **1a** into **2a** in a reasonable yield.

Thus, we have found a novel synthetic route to α-trifluoromethyl-α-aminolactones (**2**), synthetic equivalents of γ-hydroxy-α-trifluoromethyl-α-amino acids, by the reaction of γ-hydroxy-α-fluoro-α-trifluoromethyl carboxamides (**1**) with organoaluminum reagents, especially DIBAL-H. This method is most intriguing in the following aspects. First is the intramolecular migration of the amine part of **1** from the amide group to the α-position to substitute the α-fluorine atom in an S_N2 manner. Second, the reaction path is so stereospecific that only one diastereomer of **2** is formed. We are now investigating the application of present reaction for developing a new type of biologically active compounds.

Supporting Information Available: Experimental procedures, spectroscopic data (NMR, IR, MS), analytical data of all new synthetic compounds, X-ray crystallographic data of **2a**, and specific rotations of optically active compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047683Y

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