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# Synthesis of β-Amino-α,α-difluoroketones by Reactions of 1,1-Difluorovinyl Methyl Ethers with *N*-Acyliminium Intermediates

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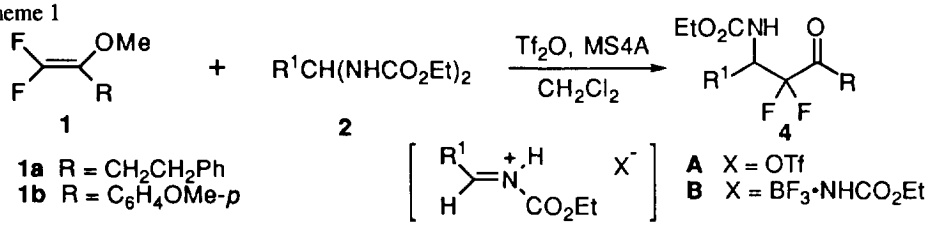
***Abstract:*** An efficient preparation of β-amino-α,α-difluoroketones **4** was developed. Reactions of 1,1-difluorovinyl methyl ethers **1** with *N*-acyliminium intermediates, generated by treating biscarbamates **2** with trifluoromethanesulfonic anhydride ($Tf_2O$) in the presence of molecular sieves 4A (MS 4A), provided **4** in good yields.

α,α-Difluorinated ketones are recognized as an important class of compounds particularly in the field of medicinal chemistry.[1,2] Aldol reactions of difluoro enolates and their equivalents are the fundamental reactions for the preparation of β-hydroxy-α,α-difluoroketones.[3,4] In these reactions, *in situ* generated reactive intermediates, such as metalo-enolates or silyl enol ethers are commonly used,[3] but only few examples for the preparation of β-amino-α,α-difluoroketones have been reported,[5] probably due to the low reactivity of such difluorinated reactive species with imine compounds[5,6] or lack of an efficient method for the generation of suitable reactive iminium intermediates. Contrary to the instability of these reactive species, 1,1-difluoroviny methyl ethers **1** are stable enough to store without special cautions, and recently we have reported a high yield aldol-type reaction of **1** with aldehyde mediated by ROTMS and TMSOTf giving rise to *O*-alkylated aldol product.[7] To extend the utilization of **1** to imine-condensation, we have searched for an efficient method for generation of an iminium intermediate which can react with **1** to give β-amino-α,α-difluoroketones **4**. To this end, we found that *N*-protonated *N*-acyliminium salt **A** generated by treatment of biscarbamate **2**, readily obtainable in a stable crystalline form,[8] with trifluoromethanesulfonic anhydride ($Tf_2O$) in the presence of MS 4A reacts with **1** to give **4** in good yield (Scheme 1).

Scheme 1




As typical difluorovinyl methyl ethers **1**, we chose **1a** (R=$CH_2CH_2Ph$) having an allylic hydrogen and **1b** (R=$C_6H_4OMe$-*p*) of aromatic substituent.[7] As compared with imines derived from aldehydes and primary amines,[9] *N*-acylimine and *N*-acyliminium salts show high reactivity in nucleophilic addition reaction, and a variety of methods for their generation are reported.[10]

First, reactions of **1** with biscarbamate **2a** or bissulfonamide **2h** and their corresponding imine compounds **3a**, **3h** were conducted to find out the reaction conditions for the preparation of the aldol-type product **4**. Results are summarized in Table 1. In the presence of $BF_3$•$Et_2O$,[11] **1a** having an allylic

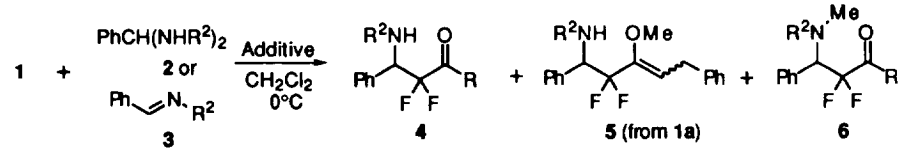
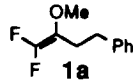
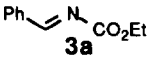
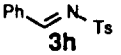
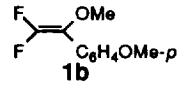



**Table 1.** Reaction of Difluorovinyl Methyl Ether **1** with **2** or **3** [a]

| Entry | 1 | 2 or 3 | Additive(s) | 4 (%) [b] | 5 (%) [b] | 6 (%) [b] |
|---|---|---|---|---|---|---|
| 1 |  **1a** | $PhCH(NHCO_2Et)_2$ **2a** | $BF_3 \cdot Et_2O$ | **4a** 58 | **5a** 17 | – |
| 2 | **1a** | **2a** | $Tf_2O$, MS4A | **4a** 84 | – | – |
| 3 | **1a** |  **3a** | TfOH | **4a** 85 | – | trace |
| 4 | **1a** | **3a** | $BF_3 \cdot Et_2O$ | **4a** 30 | – | **6a** 53 |
| 5 | **1a** | $PhCH(NHTs)_2$ **2h** | $BF_3 \cdot Et_2O$ | **4h** 80 | – | – |
| 6 | **1a** |  **3h** | $BF_3 \cdot Et_2O$ | – | **5h** 87 | – |
| 7 |  **1b** | **2a** | $Tf_2O$, MS4A | **4b-a** 73 | – | – |
| 8 | **1b** | **2a** | $BF_3 \cdot Et_2O$ | **4b-a** 80 | – | – |

a) Reaction conditions : 1 equiv. of **1**, 1.2 equiv. of **2** or **3**, 1.2 equiv. of $Tf_2O$ (1 -2 h), 1.2 equiv. of TfOH (1 h), or 3 equiv. of $BF_3 \cdot Et_2O$ (48 h), $CH_2Cl_2$, 0°C. b) Isolated yield.

hydrogen reacted with **2a** to give a mixture of the aldol-type product **4a** and the ene product **5a** (Entry 1). On the other hand, when $Tf_2O$ was used as an activator for generation of an iminium intermediate, **4a** was formed exclusively (Entry 2). Moreover, in the presence of triflic acid (TfOH), *N*-acylimine **3a** reacted smoothly with **1a** to give a good yield of **4a** along with a trace amount of **6a** (Entry 3). Since the ene product **5a** is so stable, due to the presence of fluorines,[12] that **5a** is not converted to **4a** during the $BF_3 \cdot Et_2O$-catalyzed reaction or by treating with TfOH in aqueous $CH_2Cl_2$, **5a** is not an intermediate for **4a** in those reactions (Entries 1-3). *N*-Acylimine **3a** showed a different behavior in $BF_3 \cdot Et_2O$-catalyzed reaction with **1a** to give *N*-methylated product **6a** as a major product along with **4a** (Entry 4). This result is similar to that in the Lewis acid-catalyzed reaction of **1a** with benzaldehyde giving rise to *O*-methylated aldol product.[7] From NMR study, while no appreciable change in NMR spectra between *N*-acylimine **3a** and a mixture of **3a** and $BF_3 \cdot Et_2O$ (3 equiv.) in $CDCl_3$ was observed, *N*-protonated *N*-acyliminium salt **A** ($R^1$=Ph) or **B** ($R^1$=Ph) was possibly formed by treating the biscarbamate **2a** with $Tf_2O$ (1 equiv.) or with $BF_3 \cdot Et_2O$ (>3 equiv.) in $CDCl_3$ at 25 °C.[13] The iminium salt **A** was also formed from **3a** and TfOH (1 equiv.).[13] These may be reactive intermediates in the condensation reaction with **1a** to afford **4a**. A remarkable difference in product (aldol-type or ene-type) was found with sulfonamide derivatives; bissulfonamide **2h** gave the aldol-type product **4h** possibly through the reaction of **1a** with *N*-protonated *N*-sulfonyliminium intermediate, while *N*-tosylimine **3h** gave the ene product **5h** (Entries 5, 6). The vinyl ether **1b** of aromatic subsituent reacted with **2a** in the presence of both $Tf_2O$ and $BF_3 \cdot Et_2O$ to give a good

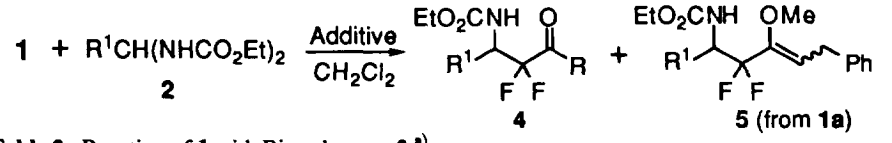
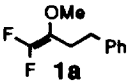
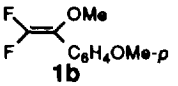



**Table 2.** Reaction of **1** with Biscarbamate **2** [a)]

| Entry | 1 | 2 | Additive(s) | 4 (%) [b)] | 5 (%) [b)] |
|---|---|---|---|---|---|
| 1 |  **1a** | **2b** $R^1$ = H | $Tf_2O$, MS4A | **4b** 83 | – |
| 2 | **1a** | **2c** $R^1$ = Me | $Tf_2O$, MS4A | **4c** 88 | – |
| 3 | **1a** | **2d** $R^1$ = $CH_2CH_2Ph$ | $Tf_2O$, MS4A | **4d** 55 | – |
| 4 | **1a** | **2e** $R^1$ = *i*-Pr | $Tf_2O$, MS4A | **4e** 62 | – |
| 5 | **1a** | **2f** $R^1$ = *c*-$C_6H_{11}$ | $Tf_2O$, MS4A | **4f** 78 | – |
| 6 |  **1b** | **2f** | $Tf_2O$, MS4A | **4b-f** 65 | – |
| 7 | **1a** | **2d** | $BF_3$•$Et_2O$ | – | **5d** 44 |
| 8 | **1a** | **2f** | $BF_3$•$Et_2O$ | **4f** 15 | **5f** 40 |
| 9 | **1a** | **2g** $R^1$ = $CO_2n$-Bu | $BF_3$•$Et_2O$ | **4g** 15 | **5g** 51 |

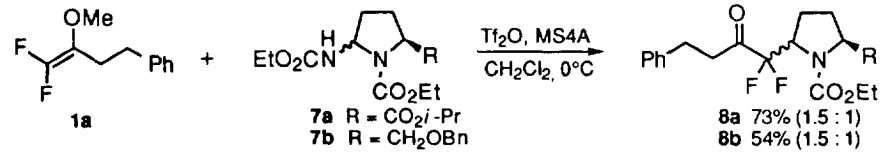
a) Reaction conditions: See Table 1. b) Isolated yield.

yield of the condensation product **4b-a** (Entries 7, 8). From these results, the aldol-type reaction of **1** with biscarbamate **2a** can efficiently be carried out by using $Tf_2O$ as an activator for generation of *N*-protonated *N*-acyliminium intermediate **A** ($R^1$=Ph).

This method for activation is quite general as can be seen from the results of reactions of both **1a** and **1b** with biscarbamates **2** derived from aliphatic aldehydes (Table 2) and pyrrolidine derivatives (Scheme 2). Using $Tf_2O$ as an activator, the aldol-type products **4** were obtained in good yields, even in the cases of biscarbamtes **2** having β-hydrogen, which are reported to easily isomerize to enamide forms[10c] (Entries 2-6). When $BF_3$•$Et_2O$ was used, reaction of **1a** with these biscarbamates **2** gave the ene products **5** as major products in moderate yields (Entries 7-9). From NMR study, *N*-protonated *N*-acyliminium salt **A** generated from biscarbamate and $Tf_2O$ in $CDCl_3$ showed a longer life-time than that **B** from biscarbamate and $BF_3$•$Et_2O$. The shorter life time of **B** may cause the relatively low yields of the products in $BF_3$•$Et_2O$-catalyzed reaction.

In a similar manner as above, reaction of **1a** with pyrrolidine derivatives **7**, prepared from (*S*)-pyroglutamic acid, in the presence of $Tf_2O$ and MS 4A gave the aldol-type products **8** in good yields (Scheme 2).

Scheme 2



We have shown that β-amino-α,α-difluoroketones **4**, **8** can efficiently be prepared by reactions of 1,1-difluorovinyl methyl ethers **1** with biscarbamates **2**, **7** in the presence of $Tf_2O$-MS 4A. It is noted that easy preparative procedures and storable stability of both starting materials are also some advantages of the present method.

**References and Notes**


1. a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. b) *"Selective Fluorination in Organic and Bioorganic Chemistry"*, Welch, J. T. Ed.; ACS Symposium Series 456, ACS; Washington DC, 1991.
2. Fluoroalkyl ketones serve as ideal mimics of the tetrahedral transition state for peptide or ester bond hydrolysis. For examples: a) Gelb, M. H.; Svaren, J. P.; Ables, R. H. *Biochemistry* **1985**, *24*, 1813. b) Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thamasco, L. M.; Watt, W. *J. Med. Chem.* **1986**, *29*, 2080. c) Gelb, M. H. *J. Am. Chem. Soc.* **1986**, *108*, 3146.
3. a) Welch, J. T.; Eswarakrishnan, S. In *Fluorine-Containing Molecules; Structure, Reactivity, Synthesis,* Liebman, J. F.; Greenberg, A.; Dolbier, Jr., W.R. Eds.; VCH publisher; New York, 1988, p123. b) Ishihara, T. *J. Synth. Org. Chem. Jpn.* **1992**, *50*, 347 and references cited therein. c) Howarth, J.; Martin Owton, W.; Percy, J. M. *J. Chem. Soc. Chem. Commun.* **1995**, 757.
4. Methods involving conversion of a carbonyl group to difluoride by DAST are also reported. For example: Dreyer, G. B.; Metcalf, B. W. *Tetrahedron Lett.* **1988**, *29*, 6885.
5. a) Shah, N. V.; Cama, L. D. *Heterocycles* **1987**, *25*, 221. b) Whitten, J. P.; Barney, C. L.; Huber, E. W.; Bey, P.; McCarthy, J. R. *Tetrahedron Lett.* **1989**, *30*, 3649.
6. Imine-condensation of difluoroacetate: Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, S.; Hashimoto, A.; Iitaka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 5291.
7. Kodama, Y.; Yamane, H.; Okumura, M.; Shiro, M.; Taguchi, T. *Tetrahedron* **1995**, *51*, 12217.
8. Although biscarbamate **2** can be prepared by mixing aldehyde and ethyl carbamate (2 equiv), *N*-acylimine **3a** is prepared *via N*-trimethylsilyl imine obtained by reaction of aldehyde with lithium hexamethyldisilazide [$LiN(TMS)_2$].
9. We could not obtain the condensation product by reaction of **1** with imines derived from aldehydes and primary amines in the presence of a variety of Lewis acids.
10. a) *"Iminium Salts in Organic Chemistry"*, Bohme, H.; Viehe, H. G. Eds.; Wiley, New York, 1979. b) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. d) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121.
11. $BF_3$•$Et_2O$ showed a relatively clean reaction, while other Lewis acids, such as $SbCl_5$, $AlCl_3$, $TiCl_4$ or TMSOTf, were not effective and gave only low yield of product(s) along with decomposition of the vinyl ether **1**.
12. Fluorine-substituent strongly destabilizes β-carbonium ion. For example: Fried, J.; Hallinan, E. A.; Szwedo, Jr., M. J. *J. Am. Chem. Soc.* **1984**, *106*, 3871.
13. In NMR spectrum of **A**, the methine hydrogen on C=N bond appears at 9.43 ppm as a doublet ($J$ = 16.2 Hz).[14] On the other hand, the corresponding hydrogen of **B** has a similar chemical shift (9.38 ppm) but a singlet peak; probably there exists a rapid equilibrium between *N*-protonated form **B** and deprotonated form **3a**.[10d]
14. The structures of protonated aldimines formed by treating imines with $HSO_3F$-$SbF_5$ in $SO_2$ (liq.) are discussed on the basis of NMR spectra. a) Olah, G. A.; Kreinbuhl, P. *J. Am. Chem. Soc.* **1967**, *89*, 4756. b) Krow, G. R.; Pyun, C.; Leitz, C.; Marakowski, J.; Ramey, K. *J. Org. Chem.* **1974**, *39*, 2449. See also ref. 10d.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