Enamine-assisted facile generation of trifluoroacetaldehyde from trifluoroacetaldehyde ethyl hemiacetal and its carbon–carbon bond forming reaction leading to β-hydroxy-β-trifluoromethyl ketones

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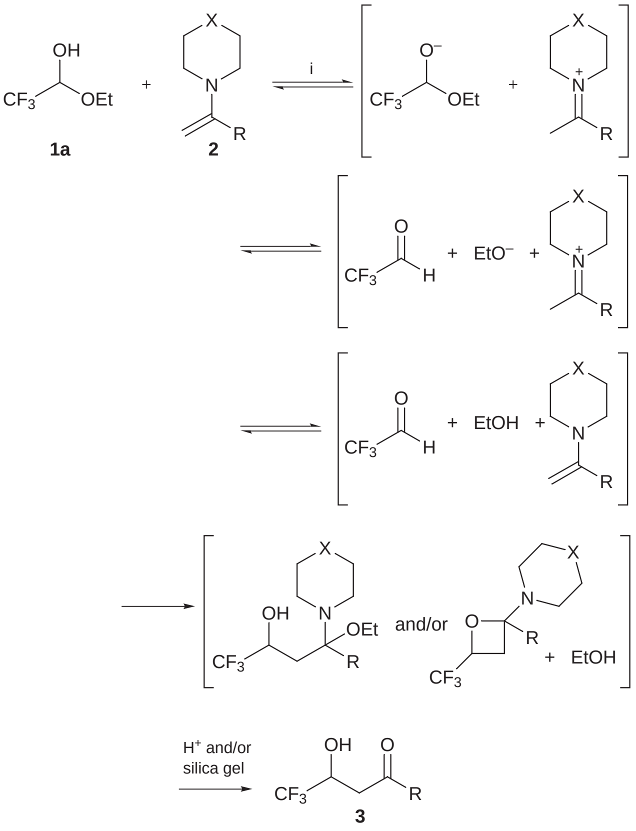
Trifluoroacetaldehyde ethyl hemiacetal 1 readily reacts with various enamines 2 in hexane at room temperature for 1 h to give the corresponding β-hydroxy-β-trifluoromethyl ketones in good yields.

Much attention has been recently addressed to trifluoromethylated compounds, since they are widely used for the construction of new types of biologically active compounds and liquid crystals. In connection with these circumstances, the development of new strategies and methodologies for the efficient synthesis of trifluoromethylated molecules has become the subject of growing interest.[1] Among the many approaches to such compounds, trifluoroacetaldehyde is one of the most useful compounds, and is employed for the construction of functionalized trifluoromethylated components *via* reaction with a number of reagents, such as metal enolates,[2] ketene silyl acetals[3] (phenylthio)bis(trimethylsilyl)methyllithium,[4] aromatic compounds,[5] olefins[3,6] and dienes.[7] In previous methods for the generation of trifluoroacetaldehyde, however, there exist serious disadvantages, including high reaction temperatures and the use of an excess amount of concentrated H_2SO_4.[8] In addition, trifluoroacetaldehyde is gaseous (bp −18 °C) and very miscible with water, and therefore it must be carefully handled.



Scheme 1 *Reagents and conditions:* i, room temp., 1 h

Here we describe for the first time the enamine-assisted facile generation of trifluoroacetaldehyde under extremely mild conditions from trifluoroacetaldehyde ethyl hemiacetal,‡ and its carbon–carbon bond forming reaction with enamines in the absence of additives, which permits highly efficient and convenient access to β-hydroxy-β-trifluoromethyl ketones.

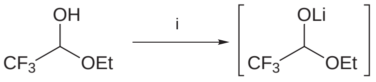
When hemiacetal **1a** was allowed to react with an equimolar amount of enamine **2a**, prepared from acetophenone with morpholine, in hexane at room temperature for 1 h, the corresponding β-hydroxy-β-trifluoromethyl ketone **3a** was obtained in 88% yield (Scheme 1 and Table 1, entry 1).

The use of other solvents, such as dichloroethane, THF, PhMe and MeCN, gave comparable yields of **3a**, irrespective of their polarities (entries 2–5). It is noteworthy that the reaction of **1a** proceeded smoothly to furnish the product **3a** in satisfactory yield in the presence of water (entry 6). The substituents on the nitrogen atom of the enamines did not influence the yields of **3a** (entries 1 and 7). Various enamines bearing aromatic and heteroaromatic substituents could successfully participate in the reaction to afford the corresponding β-hydroxy-β-trifluoromethyl ketones **3** in good to excellent yields (entries 8–11, 14–15). The reaction with enamine **2f** carrying a nitro group on the aromatic ring was very sluggish, producing **3e** in only 13% yield because of the lower solubility of **2f**, which could be improved by replacing hexane with toluene as solvent (entries 12 and 13). The electronic character of the aromatic ring has little influence on the rate of the reaction, according to the yields of **2** for the same reaction time (p-NO_2 < 2-thienyl =

Table 1 Reactions of trifluoroacetaldehyde ethyl hemiacetal with enamines[a]

Entry	Enamine	X	R	Solvent	Product	Yield (%)[b]
1	**2a**	O	Ph	hexane	**3a**	88
2	**2a**	O	Ph	$ClCH_2CH_2Cl$	**3a**	78
3	**2a**	O	Ph	THF	**3a**	73
4	**2a**	O	Ph	PhMe	**3a**	88
5	**2a**	O	Ph	MeCN	**3a**	75
6	**2a**	O	Ph	hexane–H_2O (40:1)	**3a**	68
7	**2b**	CH_2	Ph	hexane	**3a**	86
8	**2c**	O	p-MeC_6H_4	hexane	**3b**	87
9	**2c**	O	p-MeC_6H_4	PhMe	**3b**	87
10	**2d**	O	p-$MeOC_6H_4$	hexane	**3c**	72
11	**2e**	O	p-ClC_6H_4	hexane	**3d**	86
12	**2f**	O	p-$O_2NC_6H_4$	hexane	**3e**	13
13	**2f**	O	p-$O_2NC_6H_4$	PhMe	**3e**	52
14	**2g**	O	o-MeC_6H_4	hexane	**3f**	87
15	**2h**	O	2-thienyl	hexane	**3g**	75
16[c]	**2i**	O	$\mathrm{Pr^i}$	hexane	**3h**	25

[a] All the reactions were carried out with trifluoroacetaldehyde ethyl hemiacetal (1 mmol) and enamine (1 mmol) in solvent (4 ml) at room temperature for 1 h. [b] Isolated yields of analytical pure products. [c] A mixture of enamines **2i** and **4** (29:71) was employed.



1a **1b**

Scheme 2 *Reagents and conditions:* i, Bu^nLi (1.5 equiv.), hexane, 0 °C, 15 min

p-Cl = *p*-H = *p*-Me = *p*-MeO). The reaction of **1a** with the mixture of aliphatic enamines **2i** and 4-(3-methylbut-2-en-2-yl)morphorine **4** (29:71) (1 equiv.) resulted in the exclusive formation of **3h** in 25% yield, and none of the product derived from enamine **4** was detected in the reaction mixture (entry 16). According to these results, the steric effect of the substituents at the β-carbon of the enamines is more important for the the reaction than the electronic effect of the substituents at the α-carbon.

The formation of **3** can be explained by assuming the mechanism shown in Scheme 1. It is significant that the reaction requires only an equimolar amount of enamine, which may act as a base, counter ammonium cation and carbon nucleophile.

More significantly, the reaction of lithium alcoholate **1b**§ with the enamine **2a** did not proceed at all; the acetophenone was recovered in quantitative yield (Scheme 2). According to this result, the ammonium cation, which is generated *via* protonation of the enamine, plays a very important role in the effective generation of trifluoroacetaldehyde in the reaction.

In conclusion, we have demonstrated the enamine-assisted *in situ* generation of trifluoroacetaldehyde and its reaction with enamines, producing the corresponding β-hydroxy-β-trifluoromethyl ketones **3** in high yields. The present method can serve as a synthetically useful entry to β-hydroxy-β-trifluoromethyl ketones, with simple manipulations and high yields of the products. Application of the present methodology to stereoselective synthesis using asymmetric secondary amines or β-monosubstituted enamines is currently in progress in our laboratory.

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Notes and References

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‡ Recent reports have presented the coupling reaction of trifluoroacetaldehyde ethyl hemiacetal, which is considered as an equivalent of trifluoroacetaldehyde. These methods, however, require the use of an excess amount of reagents and/or of limited solvents, the formation of by-products, and relatively low yields of the products, see ref. 9.

§ Kitazume and Yamazaki reported that the tetrahedral form of **1b** is too stable to be converted to trifluoroacetaldehyde due to the strong electron-withdrawing effect of a trifluoromethyl group, see ref 10.

1 For recent examples, see: K. Uneyama, J. Hao and H. Amii, *Tetrahedron Lett.*, 1998, **39**, 4079; A. Ishii, F. Miyamoto, K. Higashiyama and K. Mikami, *Tetrahedron Lett.*, 1998, **39**, 1199; T.-P. Loh and X.-R. Li, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 980; G. Foulard, T. Brigaud and C. Portella, *J. Org. Chem.*, 1997, **62**, 9107; A. Abouabdellah, J.-P. Bégué, D. Bonnet-Delpon and T. T. T. Nga, *J. Org. Chem.*, 1997, **62**, 8826; P. Bravo, A. Farina, V. P. Kukhar, A. L. Markovsky, S. V. Meille, V. A. Soloshonok, A. E. Sorochinsky, F. Viani, M. Zanda and C. Zappalá, *J. Org. Chem.*, 1997, **62**, 3424; V. A. Soloshonok and T. Ono, *J. Org. Chem.*, 1997, **62**, 3030; S. Hiraoka, T. Yamazaki and T. Kitazume, *Chem. Commun.*, 1997, 1497; V. A. Soloshonok, D. V. Avilov, V. P. Kukhar, L. V. Meervelt and N. Mischenko, *Tetrahedron Lett.*, 1997, **38**, 4671; Y. Yokoyama and K. Mochida, *Tetrahedron Lett.*, 1997, **38**, 3443; T. Katagiri, H. Ihara, M. Takahashi, S. Kashino, K. Furuhashi and K. Uneyama, *Tetrahedron: Asymmetry*, 1997, **8**, 2933.

2 For boron enolates, see: K. Iseki, S. Oishi and Y. Kobayashi, *Chem. Pharm. Bull.*, 1996, **44**, 2003; K. Iseki, S. Oishi and Y. Kobayashi, *Tetrahedron*, 1996, **52**, 71; Y. Makino, K. Iseki, K. Fujii, S. Oishi, T. Hirano and Y. Kobayashi, *Tetrahedron Lett.*, 1995, **36**, 6527; K. Iseki, S. Oishi and Y. Kobayashi, *Chem. Lett.*, 1994, 1135. For a lithium enolate, see: D. V. Patel, K. Rielly-Gauvin and D. E. Ryono, *Tetrahedron Lett.*, 1988, **29**, 4665.

3 (*a*) K. Mikami, T. Yajima, T. Takasaki, S. Matsukawa, M. Terada, T. Uchimaru and M. Maruta, *Tetrahedron*, 1996, **52**, 85; (*b*) K. Mikami, T. Takasaki, S. Matsukawa and M. Maruta, *Synlett*, 1995, 1057.

4 T. Yamazaki, K. Takita and N. Ishikawa, *J. Fluorine Chem.*, 1985, **30**, 357.

5 For an asymmetric Friedel–Crafts reaction, see: A. Ishii, V. A. Soloshonok and K. Mikami, *74th National Meeting of the Chemical Society of Japan*, Kyoto, March, 1998, Abstr. No. 1D641.

6 R. Pautrat, J. Marteau and R. Cheritat, *Bull. Soc. Chim. Fr.*, 1968, 1182; K. Ogawa, T. Nagai, M. Nonomura, T. Takagi, M. Koyama, A. Ando, T. Miki and I. Kumadaki, *Chem. Pharm. Bull.*, 1991, 39, 1707. For an asymmetric reaction, see: K. Mikami, T. Yazima, N. Siree, M. Terada, Y. Suzuki and I. Kobayashi, *Synlett*, 1996, 837; K. Mikami, T. Yajima, M. Terada, E. Kato and M. Maruta, *Tetrahedron: Asymmetry*, 1994, **5**, 1087; K. Mikami, T. Yajima, M. Terada and T. Uchimaru, *Tetrahedron Lett.*, 1993, **34**, 7591 and ref. 3(*a*).

7 L. Lévêque, M. L. Blanc and R. Pastor, *Tetrahedron Lett.*, 1997, **38**, 6001. For an asymmetric reaction, see: K. Mikami, T. Takasaki, T. Yazima, S. Matsukawa and M. Terada, *72nd National Meeting of the Chemical Society of Japan*, Tokyo, March, 1997, Abstr. No. 4H332.

8 M. Braid, H. Isersone and F. Lawlore, *J. Am. Chem. Soc.*, 1954, **76**, 4027; A. Henne, R. Pelley and R. Alm, *J. Am. Chem. Soc.*, 1950, **72**, 3370; H. Shechter and F. Conrad, *J. Am. Chem. Soc.*, 1950, **72**, 3371.

9 For carbon nucleophiles, see: A. Ishii, K. Higashiyama and K. Mikami, *Synlett*, 1997, 1381; T.-P. Loh and X.-R. Li, *Chem. Commun.*, 1996, 1929; T. Ishihara, H. Hayashi and H. Yamanaka, *Tetrahedron Lett.*, 1993, **34**, 5777; T. Kubota, M. Iijima and T. Tanaka, *Tetrahedron Lett.*, 1992, **33**, 1351; B. Imperiali and R. H. Abeles, *Tetrahedron Lett.*, 1986, **27**, 135; A. Guy, A. Lobgeois and M. Lemaire, *J. Fluorine Chem.*, 1986, **32** 361; D. J. Cook, O. R. Pierce and E. T. McBee, *J. Am. Chem. Soc.*, 1954, **76**, 83. For phosphorus nucleophiles, see: Y. Shen and M. Qi, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1179. For amino acids and nucleotides, see: H. Yin, R. J. Crowder, J. P. Jones and M. W. Anders, *Chem. Res. Toxicol.*, 1996, **9**, 140.

10 S. Kaneko, T. Yamazaki and T. Kitazume, *J. Org. Chem.*, 1993, **58**, 2302.

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