Tetrahedron Letters 50 (2009) 2994–2997

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Trifluoromethylation of enamines under acidic conditions

Roman T. Gritsenko, Vitalij V. Levin, Alexander D. Dilman *, Pavel A. Belyakov, Marina I. Struchkova, Vladimir A. Tartakovsky

N.D. Zelinsky Institute of Organic Chemistry, 119991 Moscow, Leninsky prosp. 47, Russia

ARTICLE INFO

Article history:
Received 27 January 2009
Revised 17 March 2009
Accepted 27 March 2009
Available online 2 April 2009

Keywords:
Enamines
Iminium ions
Trifluoromethylation

ABSTRACT

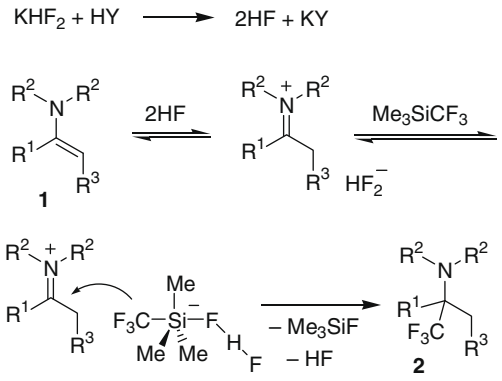
A method for the trifluoromethylation of enamines using Me_3SiCF_3 leading to α-CF_3-substituted amines is described. The reaction is promoted by hydrofluoric acid generated from KHF_2 and either trifluoroacetic or triflic acid, and involves protonation of the enamine followed by transfer of the CF_3-carbanion from the silicon reagent to the cationic electrophile.

Amines bearing a trifluoromethyl group at the α-position constitute an important class of biologically active compounds.[1] Among methods for the synthesis of these compounds,[2] the approach based on the direct introduction of the CF_3 group via nucleophilic trifluoromethylation is arguably the most effective, owing to the ready availability of electrophilic precursors with a C=N bond.[3–5] In the latter processes, the combination of trifluoromethyltrimethylsilane (Me_3SiCF_3, the Ruppert–Prakash reagent) and a Lewis base serves as an equivalent of a trifluoromethyl carbanion.[4–6]

Recently, we introduced a method for the nucleophilic trifluoromethylation of imines with Me_3SiCF_3 under acidic conditions, where hydrofluoric acid, generated in situ, played the key role as an activator.[7] Herein we report the application of this methodology for the trifluoromethylation of enamines leading to various α-CF_3-substituted amines.[8]

The general mechanism of the reaction is shown in Scheme 1. Hydrofluoric acid, which is generated in situ from potassium hydrogen difluoride and a strong acid (TfOH or TFA), reversibly protonates the enamine substrate **1** to give the iminium ion and hydrodifluoride anion. Subsequent activation of the silane followed by transfer of the CF_3-group provides product **2**. According to this mechanism, the reaction should proceed faster for enamines giving, upon protonation, more stable iminium ions.

The use of HF is crucial, since it provides the optimal balance required for the activation of both the enamine and the silane, and at the same time minimizing decomposition of the silicon reagent with the formation of trifluoromethane. Indeed, earlier we tried to employ carboxylic acids of different strengths, and even with the optimal conditions, the scope of substrates was quite narrow and product yields were moderate.[9]



Scheme 1.

Following our previous observations on reactions of imines,[7] in this work, we used two protocols for the trifluoromethylation of enamines (Table 1). Method A, in which trifluoroacetic acid is used to generate HF, is suitable for more reactive substrates, whereas method B requiring expensive triflic acid and a larger excess of the silane is more general and applicable for less reactive enamines.

* Corresponding author. Fax: +7 499 135 53 28.
E-mail address: adil25@mail.ru (A.D. Dilman).

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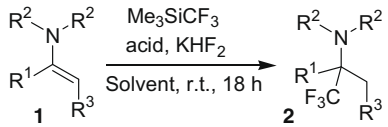
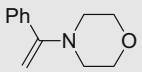
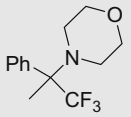
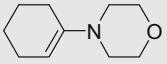
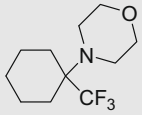
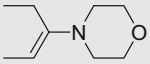
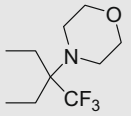
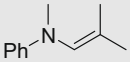
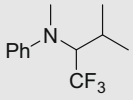
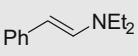
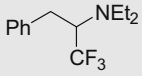
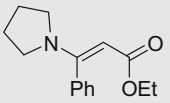
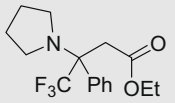
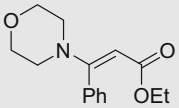
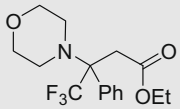
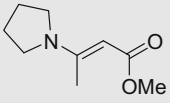
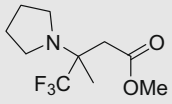
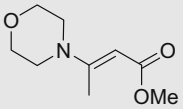
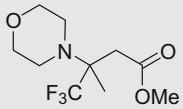
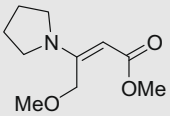
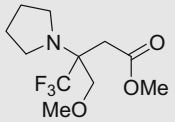
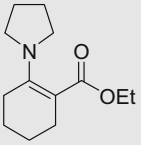
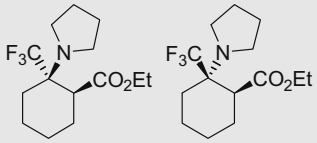
doi:10.1016/j.tetlet.2009.03.187

Table 1
Trifluoromethylation of enamines **1**

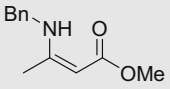
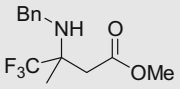


Method	Me_3SiCF_3 (eq.)	Acid (eq.)	KHF_2 (eq.)	Solvent
A	2.0	TFA (1.5)	1.0	MeCN
B	3.0	TfOH (1.6)	1.5	MeCN/3 eq. DMF

Entry	Substrate		Method	Product		Yield of **2**,%[a]
1		**1a**	A		**2a**	86
2[b]		**1b**	A		**2b**	88
3[b]		**1c**	A		**2c**	71 (86)[c]
4		**1d**	A		**2d**	81
5		**1e**	A		**2e**	59
6			B			82
7		**1f**	A		**2f**	71
8			B			87
9		**1g**	B		**2g**	75
10		**1h**	B		**2h**	80
11		**1i**	B		**2i**	84
12		**1j**	A		**2j**	74
13			B			72
14		**1k**	A		**2k**[d]	78
15			B	88 : 12		90

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate		Method	Product		Yield of **2**,%[a]
16		**1l**	A		**2l**	36
17			B			55

[a] Isolated yield.
[b] Reaction time 6 h.
[c] Yield is denoted in parentheses determined by NMR, the losses upon isolation are due to the volatility of the product.
[d] The relative configurations were determined by 2D-NOESY experiments.

Enamines **1a–e** derived from ketones and aldehydes gave trifluoromethylated products **2a–e** in good yields according to method A (entries 1–5). The substrates **1f–k** bearing an ester group at the β-position also took part in the trifluoromethylation reaction affording products **2f–k**, though in order to obtain good yields, method B should be used. The decreased reactivity of enamines **1f–k** compared to that of enamines **1a–e** is likely to be associated with the presence of the ester group, which makes the formation of an iminium ion less favorable. Thus, the protonation of ester-substituted enamines can form cations **3**–**5** which exist in equilibrium, and subsequent reaction of either of these species can give the desired product (Scheme 2).

Trifluoromethylation of substrate **1l** containing an N–H fragment gave the desired product **2l** in moderate yields of 36–55% (entries 16–17). Probably, the diminished reactivity of **1l** is due to the presence of an intramolecular hydrogen bond, which imparts additional stability to the enamine and decreases its basicity (Fig. 1). In this regard, we were surprised to find, that the cyclic enamine **1m** having a fixed anti arrangement of the N–H and ester moieties, proved to be completely unreactive. Compound **1n** also did not undergo trifluoromethylation, even under the conditions of method B. The latter observations suggest that a cis-arrangement of amino and ester fragments may be necessary for the reaction to proceed, presumably owing to formation of a cyclic cationic intermediate species **5** stabilized by a hydrogen bond.

In the reaction of substrate **1o** containing an α-hydrogen atom at the enamine double bond, the trimethyl ester of benzene-1,3,5-tricarboxylic acid **6** was obtained exclusively, while the product of trifluoromethylation was detected only in a trace amount (Scheme 3). The formation of **6** can be readily explained by the increased reactivity of the sterically unhindered iminium cation that interacts with enamine **1o**, leading to trimerization and aromatization.[10]

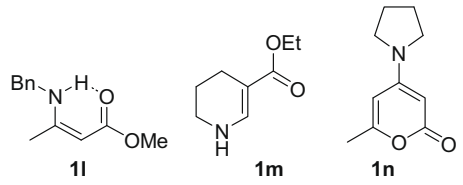
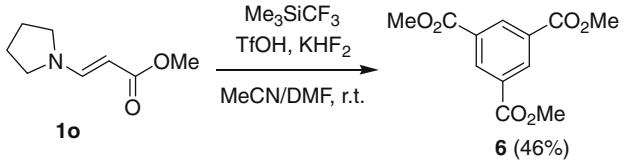


Figure 1.

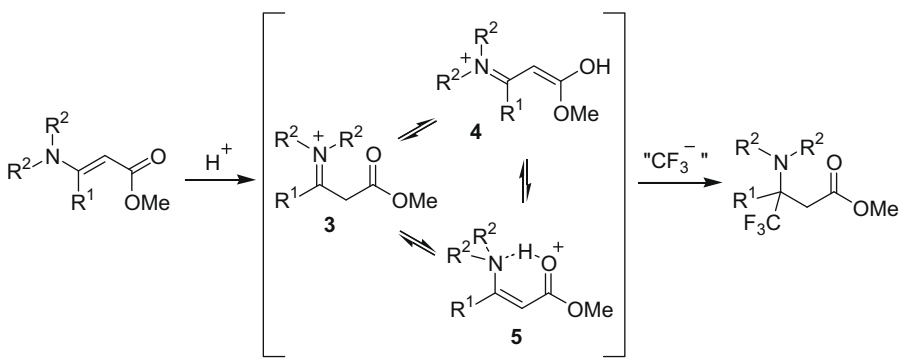


Scheme 3.

In summary, a new method for the trifluoromethylation of enamines using the Ruppert–Prakash reagent has been described.[11,12] The method gives high yields of products for reactions of conventional enamines, as well as for enamines substituted with an ester group. The key feature of the reaction is the transfer of a trifluoromethyl carbanion to the electrophilic species generated from enamines under acidic conditions.

Acknowledgments

This work was supported by the Russian Academy of Sciences (Program # 18), Ministry of Science, Russian Foundation for Basic Research (Project 08-03-00428), and the Russian Science Support Foundation.



Scheme 2.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.187.

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9. Dilman, A. D.; Gorokhov, V. V.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, A. D. *Russ. Chem. Bull.* **2007**, *56*, 1522.
10. In a reference experiment, when enamine **1o** was treated with KHF_2/TfOH in MeCN/DMF, compound **6** was obtained in 48% yield. Similar acid-catalyzed trimerization of 3-dialkylaminoacrylic esters to benzenetricarboxylic esters has been described, see: Al-Saleh, B.; Makhseed, S.; Hassaneen, H. M. E.; Elnagdi, M. H. *Synthesis* **2006**, 59.
11. All reactions were performed in conventional glass vessels. No deterioration of reaction flasks, even after prolonged use, was noted. Presumably, HF formed in situ reacts faster with the silicon reagent than with the glass surface.
12. *General procedures.* Method A. Trifluoroacetic acid (116 μL, 1.5 mmol) was added to a mixture of enamine (1 mmol) and KHF_2 (78 mg, 1.0 mmol) in acetonitrile (2 mL) at 0 °C, and the suspension was stirred for 5 min. Me_3SiCF_3 (295 μL, 2.0 mmol) was added, the cooling bath was removed, and the mixture was stirred for 18 h (or 6 h for enamines **1b,c**) at room temperature. For the work-up, saturated aqueous Na_2CO_3 (0.5 mL) was added dropwise, the mixture was stirred for an additional two minutes, diluted with water (7 mL) and extracted with ether/hexane (1:1, 3 × 5 mL). The combined organic phase was filtered through Na_2SO_4, concentrated under vacuum, and the crude product was chromatographed on silica gel. Method B. Triflic acid (142 μL, 1.6 mmol) was added to a mixture of enamine (1 mmol) and KHF_2 (117 mg, 1.5 mmol) in acetonitrile (2 mL) and DMF (232 μL, 3 mmol) at 0 °C, and the suspension was stirred for 5 min. Me_3SiCF_3 (443 μL, 3.0 mmol) was added, the cooling bath was removed, and the mixture was stirred for 18 h at room temperature. The work-up was the same as in method A.