Synthesis of trifluoroacetylketene *O*,*N*-acetals in water

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Dedicated to Professor Eusebio Juaristi on the occasion of his 55th birthday

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Abstract

The enamination of the trifluoroacetylketene *O*,*O*-acetal **1** with primary amines in water under mild conditions is described. Products **2** (trifluoroacetylketene *O*,*N*-acetals) were isolated after short reaction times (0.5-8 hours) in good yields (60-89%).

Keywords: Water, enaminones, trifluoroacetylketene *O*,*N*-acetals

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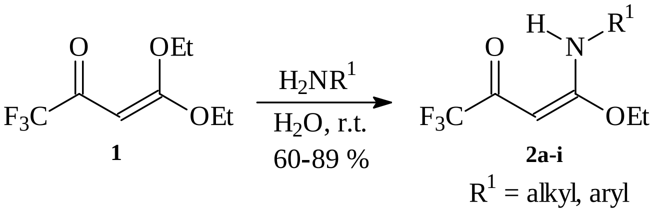
Introduction

The interest in the chemistry of enaminones has increased in the last several years and has been the subject of many reviews.[1] In particular, fluorine-containing enaminones represent interesting building blocks as starting reagents[2,3] for the synthesis of heterocyclic compounds, such as pyrazoles[4] and quinolines,[5] compounds with antimalarial activity.[6] The most commonly used method to synthesize haloalkyl-containing enaminones is the enamination of β-alkoxyvinyl polyhaloalkyl ketones.[7] The condensation of amines with of β-ketoesters using $Zn(ClO_4)_2.6H_2O$ as the catalyst to give *N*-substituted β-aminoesters has also been reported. In the same study, Bartoli et al. described the preparation of an enaminone containing the trifluoromethyl group in a reaction requiring 28 hours.[8] The synthesis of trifluoroacetylketene *O*,*N*-acetals starting from trifluoroacetylketene *O*,*O*-acetal was first reported by Hojo et al.[9] Trihaloacetylketene *O*,*O*-acetals are important heterocyclic synthons. For example, Venkataratnam et al. have described the preparation of oxazoles, thiazoles, imidazoles, quinazolines and trifluoroacetonyl substituted pyrimidines.[10,11] The synthesis of 4,5-dihydroisoxazoles, pyrazoles and polyhaloalkyl substituted 2-pyrrolidinones have also been reported.[12,13] Recently, Stefani et al.[14] described the synthesis of β-enaminones in an aqueous medium. More recently, Khosropour et al. described the use of $Bi(TFA)_3$ as catalyst and water as the solvent for the preparation of this class of compounds.[15] The use of water as a solvent in organic synthesis has been extensively studied,[16] with applications in the tetrahydropyranylation of alcohols, Diels-Alder reactions, Claisen rearrangements, Michael additions, Barbier-Grignard reactions, Reformatsky reactions and oxidation and reduction reactions, as well as reactions at high-temperature in an aqueous medium.[17] In connection with the research of reactions in water and our interest in the development of new methodologies for the synthesis of several fluorine-containing molecules, we herein report a green, mild and efficient procedure for the enamination of trifluoroacetylketene *O*,*O*-acetal **1** in water.

Results and Discussion

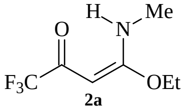
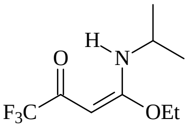
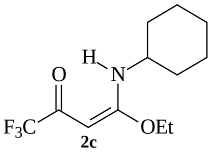
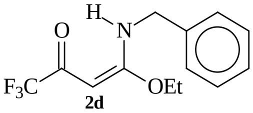
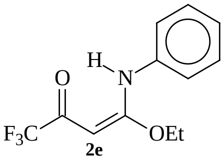
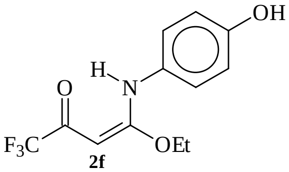
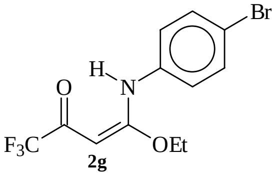
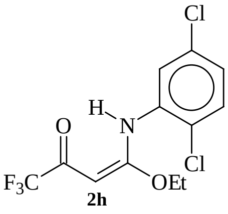
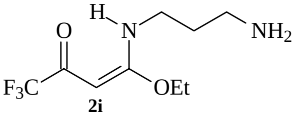
The synthon, trifluoroacetylketene *O*,*O*-acetal $F_3CC(O)CH=C(OEt)_2$ **1,** was easily prepared according to the literature.[18] Trifluoroacetylketene *O*,*O*-acetal **1** was reacted in water with primary amines to give the corresponding trifluoroacetylketene *O*,*N*-acetals **2** (enaminones) in good yields (Scheme 1, Table 1 and 2).



Scheme 1

While the classical work of Hojo et al. describes the synthesis of enaminones in CH_3CN and a reaction time of 18 h,[9] our procedure is very simple since it does not require organic solvents or long reaction times and minimizes solvent usage. The main limitation of this procedure was the low water solubility of the substituted aromatic amines, resulting in longer reaction times (8 hours) with moderate yields, when compared with aliphatic amine reactions, that proceeded smoothly at room temperature and led to products in good yields (71-89 %) and satisfactory times (30 minutes-4 hours). An alternative method to synthesize trifluoroacetylketene *O*,*N*-acetals **2b-e** is also presented (Method B). In this case, compound **1** was reacted with respective amines in a cold aqueous medium (5°C). Product formation could be verified by the precipitation of a yellow solid (**2d-e**) for solid compounds. Although final yields were somewhat lower when compared to method A, method B showed the advantage of easy purification of products, by a simple filtration in a Büchner funnel and subsequent washings with cold water.

Table 1. Preparation of trifluoroacetylketene *O,N*-acetals **2** in water

Trifluoroacetylketene *O,N*-acetals **2**	Molecular formula (molecular weight)	CG-MS *m/z* (%)	Time (h)	Melting point (°C) [literature][9]	Yield (%)
 **2a**	$C_7H_{10}F_3NO_2$ (197.1)	197 (M^+, 3), 69 (CF_3, 25), 82 (100)	0.5 [a]	95-96 [95-96]	71 [a]
 **2b**	$C_9H_{14}F_3NO_2$ (225.1)	225 (M^+, 15), 69 (CF_3, 50), 58 (90), 44 (100)	4 [a] 1 [b]	Oil	70 [a] 62 [b]
 **2c**	$C_{12}H_{18}F_3NO_2$ (265.1)	265 (M^+, 25), 69 (CF_3, 50), 55 (100)	4 [a] 0.7 [b]	Oil	78 [a] 73 [a]
 **2d**	$C_{13}H_{14}F_3NO_2$ (273.1)	273 (M^+, 5), 69 (CF_3, 6), 91 (100)	4 [a] 0.7 [b]	80-82	85 [a] 71[b]
 **2e**	$C_{12}H_{12}F_3NO_2$ (259.1)	259 (M^+, 8), 69 (CF_3, 50) 91 (100)	4 [a] 0.7 [b]	38-40 [37-38]	89 [a] 74 [b]
 **2f**	$C_9H_{12}F_3NO_3$ (275.1)	275 (M^+, 5), 69 (CF_3, 100)	8 [a]	174-175	62 [a]
 **2g**	$C_{12}H_{11}F_3NO_2Br$ (337.0)	337 (M^+, 5), 69 (CF_3, 80), 55 (100)	8 [a]	88-89	60 [a]
 **2h**	$C_{12}H_{10}F_3NO_2Cl_2$ (327.0)	327 (M^+, 4), 69 (CF_3, 100)	8 [a]	102-104	60 [a]
 **2i**	$C_9H_{15}F_3N_3O_2$ (240.0)	69 (CF_3, 100)	1 [a]	90-92	67 [a]

[a] Synthesis of trifluoroacetylketene *O,N*-acetals **2** (method A)

[b] Synthesis of trifluoroacetylketene *O,N*-acetals **2** (method B)

Table 2. NMR and infrared data of trifluoroacetylketene *O*,*N*-acetals **2**

Product[a]	**^{1}H NMR**[a] **δ (*J*, Hz)**	**^{13}C NMR**[a] **δ (J_{CF} , Hz)**	**^{19}F NMR**[a] **δ (*J*, Hz)**	**IR (KBr), cm^{-1}**
2a	1.43 (t, 3H, CH_3, *J* = 7.0), 2.95 (d, 3H, NMe, *J* = 5.1), 4.18 (q, 2H, OCH_2, *J* = 7.0), 5.12 (s, 1H, H-3), 10.5 (b, 1H, NH)	14.0 (CH_3), 26.7 (NMe), 65.6 (OCH_2), 72.6 (C-3), 118.0 (q, *J* = 287, CF_3), 170.0 (C-4), 174.2 (q, *J* = 33, C=O)	- 76.37	1732 C=O 1620 C=C
2b	1.25 (d, $2CH_3$, 6H, *J* = 6.5), 1.42 (t, 3H, CH_3, *J* = 7.0), 4.07 (m, 1H, CH), 4.31(q, 2H, OCH_2, *J* = 7.0), 5.18 (s, 1H, H-3), 10.40 (b, 1H, NH)	14.6 (CH_3), 23.2 (2Me), 44.0 (CH), 67.1 (OCH_2), 73.0 (C-3), 120.5 (q, *J* = 288 CF_3), 170.4 (C-4), 174.2 (q, *J* = 32, C=O)	- 76.89	1735 C=O 1631 C=C
2c	1.38 (t, CH_3, 3H, *J* = 7.0), 1.43, 1.73, 1.91 (m, 10H, $5CH_2$), 3.80 (m, 1H, CH), 4.29 (q, OCH_2, 2H, *J* = 7.6) 5.19 (s, 1H, H-3), 10.60 (b, 1H, NH)	14.6 (CH_3), 25.0 – 50.2 (6C, c-hexyl,) 67.0 (OCH_2), 73.0 (C-3), 119.0 (q, *J* = 286 CF_3), 170.3 (C-4), 174.5 (q, *J* = 31, C=O)	- 76.82	1710 C=O 1626 C=C
2d	1.37 (t, CH_3, 3H, *J* = 7.0), 4.27 (q, 2H, OCH_2, *J* = 7.0), 4.61 (s, 2H, NCH_2), 5.23 (s, 1H, H-3) 7.36 (m, 5H, Ph), 10.40 (b, 1H, NH)	13.6 (CH_3), 43.8 (NCH_2), 6.1 (OCH_2), 72.0 (C-3), 118.3 (q, *J* = 287, CF_3), 127.5, 127.6, 128.7, 137.7 (6C, Ph), 169.9 (C-4), 173.8 (q, *J* = 32, C=O)	- 76.80	1728 C=O 1631 C=C
2e	1.47 (t, CH_3, 3H, *J* = 7.0), 4.45 (q, 2H, OCH_2, *J* = 7.0), 5.44 (s, 1H, H-3), 7.41 (m, 5H, Ph) 12.50 (b, 1H, NH)	14.5 (CH_3), 67.5 (OCH_2), 74.0 (C-3), 119.5 (q, *J* = 320, CF_3), 116.2, 125.0, 128.6, 156.5 (6C, Ph), 175.7 (C-4), 175.6 (q, *J* = 30, C=O)	- 76.84	1739 C=O 1630 C=C
2f	1.43 (t, CH_3, 3H, *J* = 7.0), 4.40 (q, 2H, OCH_2, *J* = 7.0), 5.39 (s, 1H, H-3), 6.88 (d, 2H, Ar, *J* = 8.8), 7,28 (d, 2H, Ar, *J* = 8.8), 8.90 (s, 1H, OH) 12.40 (b, 1H, NH)	14.4 (CH_3), 67.5 (OCH_2), 73.9 (C-3), 118.4 (q, *J* = 300, CF_3), 116.5, 124.9, 128.6, 156.4 (6C, Ar), 168.9 (C-4), 175.0 (q, *J* = 32, C=O)	- 76.71	1722 C=O 1625 C=C
2g	1.43 (t, CH_3, 3H, *J* = 7.0), 4.40 (q, 2H, OCH_2, *J* = 7.0), 5.39 (s, 1H, H-3), 6.88 (d, 2H, Ar, *J* = 8.8),	14.4 (CH_3), 67.6 (OCH_2), 74.0 (C-3), 119.2 (q, *J* = 287, CF_3), 116.5, 125.0, 128.7, 156.5 (6C, Ar), 168.9 (C-4), 174.7 (q, *J* = 30, C=O)	- 76.95	1733 C=O 1622 C=C

	7,28 (d, 2H, Ar J = 8.8), 12.37 (b, 1H, NH)			
2h	1.31(t, CH_3, 3H, J = 7.0), 4.24 (q, 2H, OCH_2, J = 7.0), 5.31 (s, 1H, H-3), 6.38 – 7.60 (m, 3H, Ar), 12.4 (b, 10.5, NH)	14.3 (CH_3), 64.3 (OCH_2), 75.2 (C-3), 117.2 (q, J = 290, CF_3), 115.4, 117.7, 130.7, 131.3, 146.2 (6C, Ar), 168.6 (C-4), 75.7 (q, J = 33, C=O)	- 76.85	1724 C=O 1625 C=C
2i	1.41 (t, CH_3, 3H, J = 7.0), 2.05 (m, 2H, CH_2), 3.52, 3.51 (2t, 4H, $2CH_2$), 4.32 (q, 2H, OCH_2, J = 7.1), 5.20 (s, 1H, H-3), 12.4 (b, 10.5, NH)	14.6 (CH_3), 38.8 - 63.1 ($3CH_2$), 67.4 (OCH_2), 73.4 (C-3), 117.2 (q, J = 299, CF_3), 168.6 (C-4), 174.8 (q, J = 33, C=O)	- 76.85	1735 C=O 1628 C=C

[a] Acquired on a Bruker DPX-300 NMR spectrometer (^{1}H at 300.13 MHz and ^{13}C at 75.47 MHz) 300K, in acetone-d_6 containing TMS as internal standard, ^{19}F at 282 MHz (external reference CCl_3F, δ= 0.0 ppm).

The generality of this process was illustrated by, the wide range of aromatic and aliphatic primary amines examined. The products **2b-d and 2f-i** have not been previously prepared. In summary, we demonstrated a new method for the enamination reaction of trifluoroacetylketene *O,O*-acetals with aromatic and aliphatic amines under mild conditions in an aqueous medium. The choice of water as reaction solvent makes the present method a practical protocol for the preparation of fluorine compounds using a green chemistry concept. Extension of this reaction to other substrates and organic species is currently in progress and will be reported in due course.

Experimental Section

General Procedures. 1H , 13C and 19F NMR spectra were acquired on a Bruker DPX 300 instrument (300.13 MHz for 1H, 75.48 MHz for 13C and 282.38 MHz for 19F), at 300 K in acetone-d6 as solvent 19F NMR chemical shifts were referenced to external with CCl3F (δ = 0.0 ppm). Low resolution mass spectra were obtained on a Shimadzu QP5050 spectrometer operating at 70 eV. IR spectra were recorded on a Bohmen FT-IR spectrometer. All products gave satisfactory elemental analysis: C, ± 0.30; H, ± 0.20. The melting points are uncorrected. Standard flash chromatography procedures were followed using 230-400 mesh silica gel 60A. All water used was degassed with argon.

Synthesis of trifluoroacetylketene *O,N*-acetals 2 (method A)

Trifluoroacetylketene *O,O*-acetal **1** (2 mmol) and amino compound (4 mmol) were added in water (10 mL), at room temperature, and stirring for the time indicated (Table 1). The progress of the reaction was followed by GC. After the time indicated in the Table 1, the organic phase extracted with ethyl acetate (10 mL). The organic extract was dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was purified by flash column chromatography when necessary (silica gel, hexane/ethyl acetate 8:2).

Synthesis of trifluoroacetylketene *O,N*-acetals 2b-e (method B)

To a mixture of amino compound (5.5 mmol) in water (10 mL) was added trifluoroacetylketene *O,O*-acetal **1** (5 mmol) at room temperature, and the mixture was then cooled to 5 °C and stirred for 40 minutes. The organic phase was extracted with ethyl acetate (15 mL), washed with water (two times), dried (Na_2SO_4) and the solvent removed under reduced pressure. The products were obtained with excellent purity. For the compounds **2d-e** a yellow precipitate was observed. The products were isolated by filtering through a Büchner funnel, washing with ice-water and dried on a high-vacuum to give the pure products.

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