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Halogenation of 1-trifluoromethyl enamines: A new and efficient synthesis of α-bromo- and α-iodo-trifluoromethyl ketones

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Abstract

Treatment of the 1-trifluoromethyl enamines **1a-d** with bromine or iodine results in the formation of the corresponding iminium salts. Treatment of any of these salts with methanol results in the formation of the corresponding α-halo-trifluoromethyl ketones.

Keywords: Halogenation; Trifluoromethyl enamine; α-Halo-trifluoromethyl ketone; Enamonium salt; Iminium salt; NMR spectroscopy; IR spectroscopy; Mass spectrometry

1. Introduction

Because of our general interest in the synthesis [1–3] and reactivity [4–8] of alkenes substituted by a trifluoromethyl group, we have studied the halogenation of the trifluoromethyl enamines **1a–d** [1]. It has been reported previously that the bromination of non-fluorinated enamines results in the formation of salts which can be converted to the corresponding bromo ketones by hydrolysis, or to vinyl bromides upon treatment with triethylamine [9]. We envisaged that halogenation of the 1-trifluoromethyl enamines **1a–d** would result in the formation of such salts which could be converted to α-halo-trifluoromethyl ketones or trifluoromethyl vinyl bromides by the appropriate reagent.

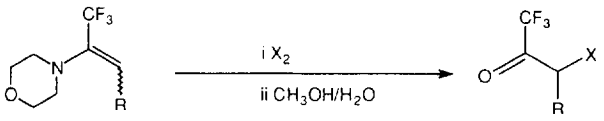
2. Results and discussion

Treatment of the enamines **1a–d** in dichloromethane with a 1.1 equiv. of bromine indeed resulted in the precipitation of a pale yellow solid, which upon hydrolysis (with methanol/water for **1a–c** and dilute hydrochloric acid for **1d**) provided the α-bromo-trifluoromethyl ketones **2a–d** in good yield (Table 1).

The success of this reaction prompted us to investigate the reaction of the trifluoromethyl enamines **1a–d** with iodine as a general route to the previously unreported α-iodo-trifluoromethyl ketones. Treatment of enamines **1a–d** with iodine under identical conditions to those employed for bromination resulted in only low conversion, with a mixture of the desired α-iodo-trifluoromethyl ketones and starting enamines recovered after non-acidic hydrolysis. However, changing the solvent to acetonitrile and employing 3 equiv. of iodine resulted, after hydrolysis, in complete conversion into the desired iodo ketones **3a–d** as the sole fluorinated products (Table 1).

Disappointingly, chlorination gave a complex mixture of compounds which could not be separated but were assumed to be, for example, α-chloro-trifluoromethyl ketones **4a** (^{19}F

Table 1
Halogenation of enamines **1**



1a-d — **2a-d**, X= Br; **3a-d**, X= I

	R	Yield %	
		2: X = Br	**3**: X = I
1a	$(CH_2)_5CH_3$	80	57
1b	$CH_2(C_6H_{11})$	70	54
1c	$(CH_2)_2Ph$	85	60
1d	Ph	50 [a]	40

[a] Acid hydrolysis was required for the formation of this ketone.

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[1] 1-Trifluoromethyl enamines were prepared by Wittig olefination of trifluoromethyl acetamides and were obtained as a mixture of *E*/*Z* isomers [1,2].

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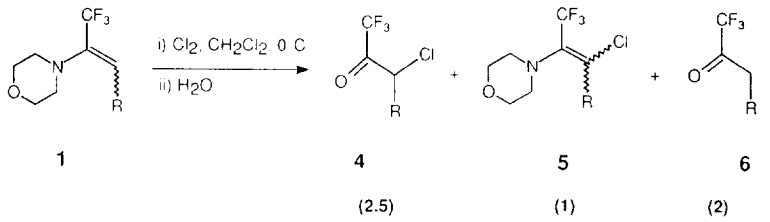
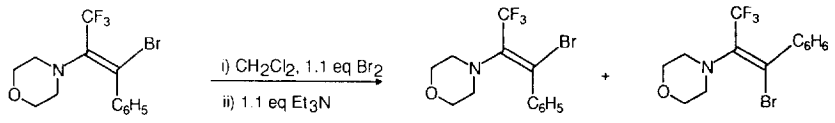


1 4 5 6

(2.5) (1) (2)

Scheme 1.



7a minor **7b** major

Scheme 2.

NMR δ: −77.0 ppm), vinyl chlorides **5a** (^{19}F NMR δ: −58.1 ppm) and trifluoromethyl ketone **6a** (^{19}F NMR δ: −80 ppm) (Scheme 1). Although the composition of the reaction mixture could be simplified to a mixture of the desired compounds **4** and trifluoromethyl ketones **6** upon acid hydrolysis, the problem of separation of the two compounds is a great limitation to this method.

Surprisingly, chemical treatment with triethylamine of the salts formed by the bromination of enamines **1a–c** did not result in neutralisation leading to the corresponding vinyl bromides, but only resulted in the formation of the α-bromo-trifluoromethylketones **2a–c** after aqueous work-up. Even with the use of a stronger base, for example with 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU), no vinyl bromides were obtained. However such neutralisation could be performed with triethylamine for the salt obtained from **1d** with the corresponding vinyl bromide **7** being formed as two stereoisomers (ratio 1:9) in good yield. The stereochemistry of the double bond in the minor isomer was determined by NOE NMR spectroscopy; irradiation of the CH_2 attached to the nitrogen of the morpholine ring resulted in an enhancement of the *ortho* aromatic protons (8%), indicating a spatial proximity of these two substituents. The minor product is thus the *E* isomer (Scheme 2).

These results were quite unexpected since it has been demonstrated that the formation of enamonium salts is favoured when an α-trifluoromethyl group is present [10], and that these enamonium salts are easily neutralised by amines. In the non-fluorinated series, the postulated iminium salts easily undergo elimination of hydrogen bromide whatever the substituent, indicating that the α-amino carbenium ion makes the β-hydrogen acidic [11–13]. The observed resistance to neutralisation prompted us to investigate the structure of the intermediates formed in the halogenation of enamines **1a–d** by high-field NMR spectroscopy. Brominations were investigated in $CDCl_3$ and in all cases the major intermediate salts were identified by ^{13}C NMR and ^{19}F NMR spectroscopy as the iminium salts **8** and not the enamonium salts **9** (see Fig. 1) [2]. The specific role of the trifluoromethyl group in the stabilisation of the iminium salt **8** is still unclear. The success of the neutralisation of the salt arising from bromination of **1d** in giving the corresponding vinyl bromide **7** can be attributed to the increased acidic character of the proton α to the phenyl substituent.

8 9

Fig. 1. Iminiums salts **8** and enamoniums salts **9**.

The iodination of **1a** was also investigated by ^{19}F NMR spectroscopy in $CDCl_3$. Little formation of salts was observed probably because of the poor solubility of the iodine. When the reaction was performed in deuterated acetonitrile, the iminium salt was always the major product [3].

In summary we have developed a new preparation of α-bromo-trifluoromethyl ketones, which is cleaner and more concise than those previously described [14,15] and access to the previously unreported α-iodo-trifluoromethyl ketones in only two steps from the trifluoromethyl acetamides.

3. Experimental details

NMR spectra were obtained with $CDCl_3$ solutions on a Varian EM390, FH dual probehead, and/or Bruker AC 200 and ARX 400 (^{1}H: 90, 200 or 400 MHz; ^{19}F: 84, 188 or 376 MHz; ^{13}C: 75 or 100 MHz) spectrometers. Chemical shifts δ are reported in ppm relative to Me_3Si and $CFCl_3$ (for ^{19}F

[2] We have detected enamonium salts at the start of the reaction in certain cases and on one occasion we were able to record the NMR data for enamonium salts **9**. ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −58.5, −53.8 (*Z*/*E*:1) ppm. ^{13}C NMR (*Z*) δ: 14.8, 22.7, 28.7, 29.0, 31.4, 61.2, 67.9, 117.7 (q, $^7J_{CF}$ = 287 Hz); 125.2 (q, $^1J_{CF}$ = 35 Hz); 148.4 (q, $^3J_{CF}$ = 3 Hz) ppm.

[3] ^{19}F NMR (CD_3CN, $CFCl_3$) δ: −77.0 ppm for the iminium salt formed from **1a** and iodine.

NMR) as internal standards. For the determination of fine coupling constants, the acquisition of 16k data points, a Lorenz–Gauss transformation of the FID and a zero filling to 64k were performed in order to obtain a minimum resolution of 0.2 Hz pt^{-1} (^1H and ^{19}F) or 0.5 Hz pt^{-1} (^{13}C). COSY, HMQC and HMBC experiments were performed on a multinuclear probehead equipped with a Z-gradient coil. The $\{^1H\}$, ^{19}F, $\{^{19}F\}$, ^1H and heteroNOE experiments were performed on an inverse dual probehead. GC analysis was performed on a capillary column SE30, 10 or 25 m).

3.1. Bromation of enamines 1a–d: typical procedure

To a solution of enamine **1a–c** (4.5 mmol) in dichloromethane (20 ml) at 0°C was added bromine (0.8 g, 5 mmol). After 5 min the resultant solid was hydrolysed with methanol/water 3:1 (10 ml) and then poured into a saturated ammonium chloride solution, the layers separated and the aqueous phase extracted with dichloromethane (3×50 ml). The combined organics were dried and evaporated to afford an orange oil which was purified by column chromatography (eluent pentane) to give the corresponding α-bromo-trifluoromethyl ketones **2a–c** as clear oils.

3-Bromo-1,1,1-trifluoro-non-2-one (**2a**): Prepared from **1a** (1.2 g, 4.5 mmol) and bromine (0.8 g, 5 mmol) to give **2a** (1.0 g, 80%). IR (neat) (cm^{-1}): 1763 (νC=O). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −75.6 ppm. ^1H NMR δ: 0.85 (m, 3H); 1.8 (m, 8H); 2.0 (m, 2H); 4.5 (t, ^3J=7.5 Hz, 1H) ppm. ^{13}C NMR δ: 22.6, 27.1, 29.7, 31.6, 32.6, 43.6 (*C*HBr); 115.4 (q, $^1J_{CF}$=291.7 Hz, *C*F_3); 185.0 (q, $^2J_{CF}$=35.5 Hz, *C*O*C*F_3) ppm. Analysis: Calc. for $C_9H_{14}F_3O$: C, 39.3; H, 5.13%. Found: C, 39.04; H, 5.45%.

3-Bromo-4-cyclohexyl-1,1,1-trifluoro-but-2-one (**2b**): Prepared from **1b** (1.25 g, 4.5 mmol) and bromine (0.8 g, 5 mmol) to give **2b** (0.9 g, 70%) [14].

3-Bromo-5-phenyl-1,1,1-trifluoro-pent-2-one (**2c**): Prepared from **1c** (1.3 g, 4.5 mmol) and bromine (0.8 g, 5 mmol) to give **2c** (1.1 g, 85%) [14].

Bromo-5-phenyl-1,1,1-trifluoro-propan-2-one (**2d**): Prepared from **1d** (1.15 g, 4.5 mmol) and bromine (0.8 g, 5 mmol) to give **2d** (0.6 g, 50%) [16].

3.2. Iodination of enamines 1: typical procedures

To a solution of **1a–d** (4.5 mmol) in acetonitrile (20 ml) at 0°C was added iodine (3.8 g, 15 mmol). After 5 min the black suspension was hydrolysed with methanol/water 3:1 (10 ml) and then poured into a saturated ammonium chloride solution, the layers separated and the aqueous phase extracted with dichloromethane (3×50 ml). The combined organics were dried and evaporated to afford a dark brown oil which was redissolved in dichloromethane (50 ml), washed with saturated sodium thiosulphate solution (20 ml), dried and evaporated to give a colourless oil. Purification by column chromatography (eluent pentane) gave the corresponding α-iodo-trifluoromethyl ketones **3a–d** as clear oils.

3-Iodo-1,1,1-trifluoro-non-2-one (**3a**): Prepared from **1a** (1.2 g, 4.5 mmol) and iodine (3.8 g, 15 mmol) to give **3a** (0.78 g, 57%). IR (neat) (cm^{-1}): 1750 (νC=O). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −74.9 ppm. ^1H NMR δ: 0.8 (m, 3H); 1.3 (m, 8H); 1.95 (m, 2H); 4.8 (t, J=6.7 Hz, 1H) ppm. ^{13}C NMR δ: 14.0 (*C*HI); 20.0, 22.6, 28.5, 29.2, 31.5, 34.0, 115.5 (q, $^1J_{CF}$=288.5 Hz, *C*F_3); 187.1 (q, $^2J_{CF}$=34.2 Hz, *C*O*C*F_3) ppm.

4-Cyclohexyl-3-iodo-1,1,1-trifluoro-but-2-one (**3b**): Prepared from **1b** (1.25 g, 4.5 mmol) and iodine (3.8 g, 15 mmol) to give **3b** (0.8 g, 54%). IR (neat) (cm^{-1}): 1750 (νC=O). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −74.6 ppm. ^1H NMR δ: 0.7, 1.2, 1.6, 1.9, 2.1 (m, 13H); 4.8 (t, ^3J=6.7 Hz) ppm. ^{13}C NMR δ: 14.2 (*C*HI); 18.2, 25.9, 26.1, 32.5, 32.9, 37.6, 41.5, 115.5 (q, $^1J_{CF}$=288.5 Hz, *C*F_3); 186.4 (q, $^2J_{CF}$=32.75 Hz, *C*O*C*F_3) ppm.

3-Iodo-5-phenyl-1,1,1-trifluoro-pent-2-one (**3c**): Prepared from **1c** (1.3 g, 4.5 mmol) and iodine (3.8 g, 15 mmol) to give **3c** (0.92, g, 60%) IR (neat) (cm^{-1}): 1748 (νC=O). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −76 ppm. ^1H NMR δ: 2.4 (m, 2H); 2.8 (m, 2H); 4.8 (t, J=6.7 Hz, 1H); 7.4 (m, 5H) ppm. ^{13}C NMR δ: 14.2 (*C*HI); 34.7, 35.2, 115.2 (q, $^1J_{CF}$=292 Hz); 126.7, 128.3 128.5, 138.9, 186.5 (q, $^2J_{CF}$=35.2 Hz) ppm.

3-Iodo-5-phenyl-1,1,1-trifluoro-propan-2-one (**3d**): Prepared from **1d** (1.15 g, 4.5 mmol) and iodine (3.8 g, 15 mmol) to give **3d** (0.53 g, 40%). IR (neat) (cm^{-1}): 1750 (νC=O). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −74.5 ppm. ^1H NMR δ: 6.0 (s, 1H); 7.3−7.6 (m, 5H) ppm. ^{13}C NMR δ: 19.6 (*C*HI); 115.0 (q, $^1J_{CF}$=288.5 Hz, *C*F_3); 130.0, 184.5 (q, $^2J_{CF}$=35.5 Hz, *C*O*C*F_3) ppm.

3.3. Preparation of 3-bromo-2-morpholino-1,1,1-trifluoro-3-phenylprop-2-ene (7)

To a solution of *Z*-enamine **1d** (0.85 g, 3 mmol) in dichloromethane (20 ml) at 0°C was added bromine (0.8 g, 5 mmol). After 5 min, triethylamine (0.4 g, 0.004 mol) was added, stirred for a further 10 min and then poured into a saturated ammonium chloride solution. The layers were separated and the aqueous phase extracted with dichloromethane (3×50 ml). The combined organics were dried and evaporated to afford the desired 3-bromo-2-morpholino-1,1,1-trifluoro-3-phenylprop-2-ene (**7**) as a clear oil (0.8 g, 80%). IR (neat): (cm^{-1}) 1750 (νC=C). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −57.9 (major); −63.1 (minor) (90:10) ppm. ^1H NMR δ: 2.57 (t, J=4.5 Hz); 3.5 (t, J=4.5 Hz) (minor); 3.12 (t, J=4.5 Hz); 3.8 (t, J=4.5 Hz) (major); 7.1–7.24 (m, 5H) ppm. ^{13}C NMR δ: 49.7, 67.2, 122.0 (q, $^1J_{CF}$=283 Hz, CF_3); 128.0, 129.0, 137.8, 139.5, 130.7 (q, $^3J_{CF}$=3.4 Hz, *C*Br); 135.8 (q, $^2J_{CF}$=29.2 Hz) ppm. Mass spectrum: 362 (2.7%) and 362 (2.1%) (M^+): 274 (100%); 272 (80%) ($M-C_7H_7$); 91 (68%).

Iminium salt **8** formed from enamine **1a**: ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −75.6 ppm. ^{13}C NMR δ: 14.5, 23.3,

27.4, 29.4, 32.4, 33.0, 45.5, 46.1, 64.6, 116.4 (q, $^{1}J_{CF}=292$ Hz); 186.9 (q, $^{2}J_{CF}=34.7$ Hz) ppm.

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