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Reaction of α-halogen substituted β-ethoxyvinyl trifluoromethyl ketones with 2-aminopyridine: new route to trifluoroacetyl-containing heterocycles

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Dedicated to Professor Lev M. Yagupolskii on the occasion of his 80th birthday.

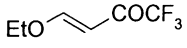
Abstract

The reaction of α-halosubstituted β-ethoxyvinyl trifluoromethyl ketones with 2-aminopyridine gives 3-trifluoroacetyl imidazo[1,2-*a*]pyridine and 3-halo-1,1,1-trifluoro-4-(2-pyridinylamino)-3-buten-2-ones. The product ratio depends on the nature of the α-halogen atom and the solvent.

Keywords: Fluorinated *a*-enamino ketones; Enones; Amination; Cyclization; Bicyclic heterocyclic compounds

1. Introduction

Over the last several decades, the use of fluorine substitution to tailor the physical and chemical properties of diverse organic compounds has been amply demonstrated [1,2]. Thus, methods for the synthesis of trifluoromethylated compounds have received considerable attention, especially following the synthon approach [3,4]. Easily accessible β-ethoxyvinyl trifluoromethyl ketone (**1**) [5,6], a chemical equivalent of trifluoroacetyl acetaldehyde, can be considered as a promising trifluoromethyl-containing C_4-synthon for the synthesis of various compounds, many of which have a certain biological interest. Enone **1** has already been used for the synthesis of dyes [7], heterocycles [8–15], drugs [5] and as a protective reagent for amino groups in peptide synthesis [16]. Recently, we have modified this useful synthon by adding one more reaction center to obtain a series of α-halogenated enones **2a–c** that generally have reactivity similar to that of the starting enone **1** [17,18]. The presence of halogen atom at the α-position, however, allows some new reactions of α-haloenones **2a–c**, such as cyclization with participation of halogen atoms that are obviously impossible for enone **1**.



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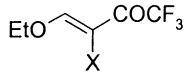

2a-c

X = Cl (**a**), Br (**b**), I (**c**)

The reaction of 1,2- or 1,3-binucleophiles with enone **1** is accompanied by heterocyclization with C=O group participation, and trifluoromethyl-containing heterocycles are formed [8–15]. In case of the reaction of α-haloenones **2a–c** with 1,3-binucleophiles, there is the possibility of forming trifluoroacetyl-containing five-member heterocycles via participation of the halogen atoms at the α-position. In this paper, we describe the results of our investigation on the reaction of α-haloenones **2a–c** with 2-aminopyridine as the 1,3-binucleophile.

2. Results and discussion

One of the most facile reactions of polyfluoroacylated vinyl ethers **1** and its α-halogenated derivatives **2a–c** is the replacement of the alkoxy group by amine moieties [5,15,17,18]. This reaction gives the corresponding enamino

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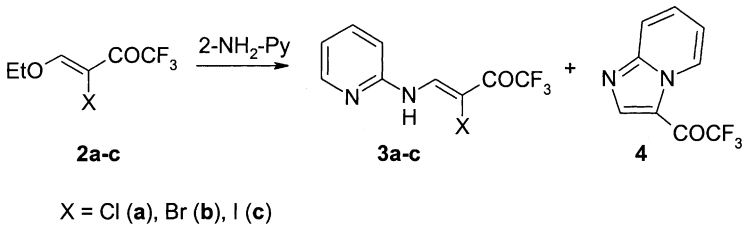


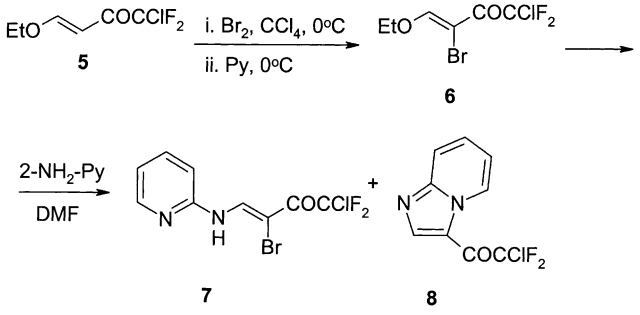
Scheme 1.

ketones in almost quantitative yields for enone **1** and with 40–80% yield for **2a–c**. The reaction of 2-aminopyridine with α-bromoenone **2b** in chloroform, however, produced not only enaminone **3b** but also 3-trifluoroacetyl imidazo[1,2-*a*]pyridine **4** as a main product (ratio 1/3) in high total yield (Scheme 1).

This is the first example of a cyclization reaction of α-halogenated enones **2a–c** with substitution of halogen atoms. Since imidazopyridine **4** was previously unknown, the position of the trifluoroacetyl group was determined on the basis of the literature ^{1}H and ^{19}F NMR spectral data for the known 3-chlorodifluoroacetyl imidazo[1,2-*a*]pyridine **8** [19]. We synthesized a sample of the compound **8** from α-bromo-(β-ethoxyvinyl) chlorodifluoromethyl ketone **6** and 2-aminopyridine in DMF (conditions where enaminone **7** is a minor product, see below). The starting α-bromoenone **6** was synthesized by the bromination of enone **5** as described earlier [17] (Scheme 2).

These results attracted our attention because of the high interest to biological properties of 3-acyl imidazo[1,2-*a*]pyridines [20–23]. Despite numerous applications of the most common route to this heterocyclic system — condensation of 2-aminopyridines with α-halodicarbonyl compounds [24]—alternative methods are still required [25–28] due to possible low selectivity of the general approach.

Only few examples of the synthesis of related non-fluorinated compounds, such as imidazoles, based on α-halo-β-alkoxyvinyl carbonyl compounds are described in literature. The reaction of α-halo-β-methoxyvinyl methyl ketone with acetamidine [29] leads to 2-methyl-5-acetylimidazole (together with 2,4-dimethyl-5-halosubstituted pyrimidines) and the reaction of 2-bromo-3-(*iso*-propoxy)-2-propenal



Scheme 2.

with different non-cyclic amidines [30] yields mixtures of isomeric 1,4- and 1,5-disubstituted imidazoles containing aldehyde group at position 4 or 5. No enaminones and no pyrimidines were found among the reaction products [29,30].

On varying of the reaction conditions and structure of starting enones **2a–c** (Table 1) we have found that the change of the halogen atom from Cl to I and increase of solvent polarity generally result in preferred formation of imidazopyridine **4**. But surprisingly, the reaction in water produces enaminones **3a** and **b** as the only products, which will be discussed below. Temperature has a negligible effect on product ratio (for **2b** in $CHCl_3$ at −20 to 60 °C). Thus, by varying the reaction conditions we can obtain enaminones **3a–c** or 3-trifluoroacetyl imidazo[1,2-*a*]pyridine **4** as the main product.

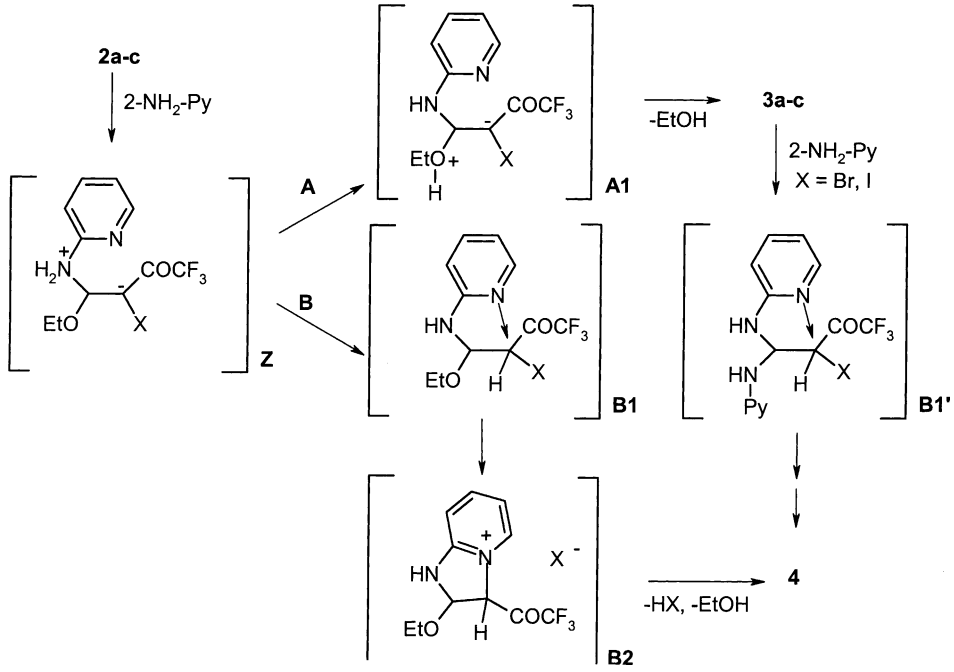
We propose possible reaction pathways to **4** in Scheme 3. 2-Aminopyridine contains two nucleophilic nitrogen sites for attack on **2a–c**. We found, however, that α-bromoenone **2b** does not react with highly nucleophilic 4-dimethylaminopiridine (DMAP), which therefore excludes primary attack of the pyridine ring nitrogen atom of 2-aminopyridine on the α-carbon atom of enones **2a–c** bearing not only the halogen atom but also partial negative charge as a result of strong polarization of carbon–carbon double bond. Thus, the initial step of this reaction is attack of the NH_2-group on the β-carbon atom of α-haloenones **2a–c** that usually gives enaminones **3** after ethanol elimination. We have examined the possibility of the formation of imidazopyridine **4** from enaminones **3** via intramolecular nucleophilic attack of the pyridine ring nitrogen atom on the α-carbon atom of enaminones **3**. But treating enaminone **3b** with bases, such as

Table 1
Ratios[a] of products **3a–c/4** in the reaction[b] of enones **2a–c** with 2-aminopyridine in various solvents

Enone	Solvents				
	$CHCl_3$	McCN	DMF	DMSO	H_2O
2a	>99/<1	80/20	61/39	50/50	>99/<1
2b	25/75	12/88	8/92	7/93	>99/<1
2c	14/86	5/95	4/96	2/98	75/25

[a] Ratios of products were determined by ^{19}F NMR analyses of crude reaction mixtures.

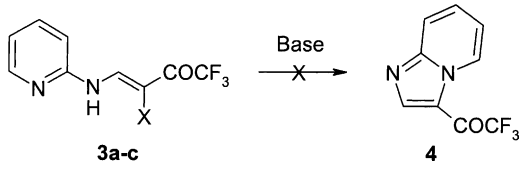
[b] All reactions were run at 18–23 °C in the solvent indicated in the table, reaction time was 24 h, ratio **2a–c**/2-NH_2Py = 1/2, 0.5–5 mmol scale.



Scheme 3.

NEt_3, DMAP, DBU, *t*-BuOK produced no traces of imidazopyridine **4**. This demonstrates that compound **4** is not formed via intramolecular cyclization of enaminones **3a–c** under the basic conditions (Scheme 4).

With the above explanation for the formation of imidazopyridine **4**, we now consider the interaction of α-haloenones **2a–c** with 2-aminopyridine in detail. It is known that enone **1** rapidly reacts with amines through the zwitterions, followed by elimination of ethanol [15,31–33]. Because α-haloenones **2a–c** react with primary and secondary amines in the same way forming corresponding α-haloenaminones [17,18], we assume that the instant reaction proceeds through a similar zwitterion **Z** (Scheme 3). Its further transformations may lead to enaminones **3a–c** or imidazopyridine **4** depending upon the reaction conditions. In low polar solvents or in water (Scheme 3, route **A**) enaminones **3a–c** are formed predominantly as a result of either ethoxy anion and proton eliminations (not shown in Scheme 3) or by proton migration to the oxygen atom of the ethoxy group with the formation of intermediate **A1**. The latter prevents the nucleophilic substitution of α-halogen atom and facilitates ethanol elimination to produce enaminones **3a–c**. In polar solvents (route **B**), solvation of the zwitterion **Z** favors the proton migration from the nitrogen atom to the α-position to the carbonyl group with the formation of intermediate **B1**. Subsequent intramolecular alkylation of the pyridine ring on nitrogen atom leads to ring closure (intermediate **B2**). The α-halogen atom mobility (Cl < Br < I) on saturated carbon atom (intermediate **B1**) is consistent with the percentage of imidazopyridine **4** in the reaction mixture (see Table 1). The HX and EtOH eliminations then lead to the final imidazo[1,2-*a*]pyridine structure. Thus, the formation of imidazopyridine **4** is possible only when the α-carbon atom is protonated, which leads to the formation of an intermediate type **B1**.



Scheme 4.

The suggested mechanism is also supported by the highly selective and effective transformation of enaminone **3b** and **c** into imidazopyridine **4** upon heating (80 °C, 5 h) with 2 eq. of 2-aminopyridine in DMF (monitored by ^{19}F NMR). This transformation proceeds through the intermediate **B1′** (Scheme 3) whose structure resembles that of intermediate **B1**. Known re-amination reactions [31] of non-α-halogenated analogs of enaminones **3a–c** also suggests the addition–elimination mechanism. However, the rate of the re-amination at room temperature is slow and this process does not affect the product ratio in the reactions of α-haloenones **2a–c** with 2-aminopyridine.

In summary, we have found that α-halogenated enones **2a–c** react with 2-aminopyridine to form enaminones **3a–c** or 3-trifluoroacetyl imidazo[1,2-*a*]pyridine **4**. These fluorinated substances can be used as practical building blocks for the synthesis of bioactive fluorinated compounds.

A broader investigation of the route to the synthesis of various polyfluoroacyl-containing heterocycles is now underway.

3. Experimental

3.1. General

^{1}H and ^{19}F NMR spectra were recorded on Varian VXR instrument (300 and 282.2 MHz) in $CDCl_3$ solutions using TMS and CCl_3F as internal standards, respectively. Solvents were distilled and 2-aminopyridine was crystallized from hexane before using. Starting enones were prepared according to literature procedures **2a** and **b** [17], **2c** [18] and **5** [34,35].

3.2. (E)-3-Bromo-1,1,1-trifluoro-4-(2-pyridinylamino)-3-buten-2-ones (3b): typical procedure for enaminones 3a–c

To a stirred emulsion of haloenone **2b** (0.4 g, 1.6 mmol) in 20 ml H_2O was added solution of 2-aminopyridine (0.15 g, 1.6 mmol) in 5 ml H_2O. After 2 h, the precipitated product was filtered off, washed with water, dried and crystallized from hexane. The yield of enaminone **3b** is 0.33 g (70%) as white needles (mp 128–129 °C). ^{1}H NMR: δ_H 9.13 (d, 1H, $J = 12.7$ Hz), 8.38 (dm, 1H, $J = 4.7$ Hz), 7.83 (br d, 1H, $J = 8.2$ Hz), 7.72 (m, 1H), 7.11 (m, 1H), 6.95 (d, 1H, $J = 8.2$ Hz). ^{19}F NMR: δ_F −68.60 (s). Anal. Calcd. for $C_9H_6BrF_3N_2O$: C, 36.64; H, 2.05; N, 9.49. Found: C, 36.72; H, 2.01; N, 9.56.

3.2.1. (E)-3-Chloro-1,1,1-trifluoro-4-(2-pyridinylamino)-3-buten-2-one (3a)

This was synthesized in 87% yield as described above for enaminone **3b**. Compound **3a**: white crystals (mp 135–136 °C). ^{1}H NMR: δ_H 9.09 (d, 1H, $J = 12.0$ Hz), 8.38 (dm, 1H, $J = 4.4$ Hz), 7.96 (br d, 1H, $J = 8.1$ Hz), 7.73 (m, 1H), 7.11 (m, 1H), 6.99 (d, 1H, $J = 8.1$ Hz). ^{19}F NMR: δ_F −68.40 (s). Anal. Calcd. for $C_9H_6ClF_3N_2O$: C, 43.14; H, 2.41; N, 11.18. Found: C, 43.22; H, 2.40; N, 11.29.

3.2.2. (E)-3-Iodo-1,1,1-trifluoro-4-(2-pyridinylamino)-3-buten-2-one (3c)

This was synthesized in 52% yield as described above for enaminone **3b**. Compound **3c**: white needles (mp 144–145 °C). ^{1}H NMR: δ_H 8.82 (d, 1H, $J = 12.7$ Hz), 8.37 (br d, 1H, $J = 4.6$ Hz), 7.82 (br d, 1H, $J = 8.2$ Hz), 7.72 (m, 1H), 7.12 (m, 1H), 6.95 (d m, 1H, $J = 8.2$ Hz). ^{19}F NMR: δ_F −68.20 (s). Anal. Calcd. for $C_9H_6F_3IN_2O$: C, 31.60; H, 1.77; N, 8.19. Found: C, 31.52; H, 1.70; N, 8.23.

3.3. 3-Trifluoroacetylimidazo[1,2-a]pyridine (4)

A solution of 2-aminopyridine (0.76 g, 8 mmol) and enone **2b** (1 g, 4 mmol) in 4 ml DMF was heated at 70–80 °C for 2 h. Then reaction mixture was poured in 50 ml of water, precipitated product was filtered off, washed with water, dried and crystallized from hexane. The yield of ketone **4** is 0.73 g (85%) as white crystals (mp 133–134 °C). ^{1}H NMR: δ_H 9.63 (br d, 1H, $J = 6.8$ Hz), 8.60 (br s, 1H), 7.92 (br d, 1H, $J = 8.9$ Hz), 7.71 (m, 1H), 7.29 (m, 1H). ^{19}F NMR: δ_F −72.80 (s). Anal. Calcd. for $C_9H_5F_3N_2O$: C, 50.48; H, 2.35; N, 13.08. Found: C, 50.57; H, 2.50; N, 13.05.

3.4. (Z)-3-Bromo-4-ethoxy-1-chloro-1,1-difluorobut-3-en-2-one (6)

Bromine (2.86 g, 17.9 mmol) was added dropwise to a stirred solution of 3 g (16.3 mmol) of enone **1** in $CHCl_3$ (15 ml) at 0–5 °C. After 20 min, pyridine (1.41 g, 17.9 mmol) was added dropwise at the same temperature. After 30 min to the reaction mixture was added water (20 ml), the water phase was extracted with hexane (3 × 10 ml). The combined organic layers were dried by $MgSO_4$ and the solvent was evaporated. The residue was distilled in vacuum. Yield 3.62 g (85%), bp 120–122 °C/16 mmHg. ^{1}H NMR: δ_H 8.08 (s, 1H), 4.40 (q, 2H, $J = 7.0$ Hz), 1.49 (t, 3H, $J = 7.0$ Hz). ^{19}F NMR: δ_F −58.34 (s).

3.5. 3-Chlorodiuoroacetylimidazo[1,2-a]pyridine (8)

The compound was synthesized in 72% yield as described above for ketone **4** using 2-aminopyridine (1 g, 10.6 mmol) and enone **6** (1.22 g, 4.6 mmol) in DMF (5 ml). Compound **8**: white needles, mp 144–145 °C, [19] 145 °C. ^{1}H NMR: δ_H 9.63 (br d, 1H, $J = 7.0$ Hz), 8.62 (br s, 114), 7.91 (br d, 1H, $J = 9.0$ Hz), 7.69 (m, 1H), 7.28 (m, 1H). ^{19}F NMR: δ_F −61.63 (s).

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