Synthesis of trifluoromethyl-substituted heteroaromatic aldehydes

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Trifluoromethylation of furfural and thiophene-2-carbaldehyde trifluoroacetates with XeF_2 and CF_3COOH afforded 5-trifluoromethylfuran-2-carbaldehyde and 5-trifluoromethylthiophene-2-carbaldehyde.

Key words: 5-trifluoromethylfuran-2-carbaldehyde, 5-trifluoromethylthiophene-2-carbaldehyde, trifluoromethylation, xenon difluoride.

Compounds containing trifluoromethyl group bound to the aromatic ring are substantial in the synthesis of biologically active compounds. Introduction of this (both electron-withdrawing and highly lipophilic) substituent into a structure is often accompanied by an increase in the physiological activity. The presence of perfluorinated groups enhances the penetrating ability of biologically active compounds owing to a better affinity for both the lipophilic and aqueous phases. Such an amphiphilic character[1] allows a reactive molecule to reach the target faster. Aromatic aldehydes are convenient starting reagents for the synthesis of various derivatives. However, only trifluoromethylbenzaldehydes are commercially accessible, though they are highly expensive; information on trifluoromethyl-substituted heteroaromatic aldehydes are desultory.

5-Trifluoromethylfuran-2-carbaldehyde (**1a**) was obtained for the first time in six steps from trifluoroacetoacetic ester in 11% overall yield.[2] A transformation of the carboxyl group of 5-methylpyromucic acid into a trifluoromethyl one under the action of sulfur tetrafluoride in anhydrous HF gave the same aldehyde in three steps in 33% overall yield.[3] A patented procedure[4] involves introduction of a trifluoromethyl group into furfural with trifluoroacetic acid and xenon difluoride. In this way, trifluoromethyl derivatives were obtained, mainly from substituted benzenes.[5] The resulting xenon fluoride trifluoroacetate generates, *via* its room-temperature decomposition, trifluoromethyl radicals which allow introduction of a trifluoromethyl group into the aromatic ring under mild conditions: *e.g.*, trifluoromethylbenzene was obtained[6] under these conditions in 42% average yield. Xenon difluoride also initiates fluorodecarboxylation of carboxylic acids, which makes it possible to synthesize monofluoro derivatives and, with the use of trifluoroacetic acid, yields carbon tetrafluoride as a by-product.[7]

Out of various ways of introducing trifluoromethyl groups,[8] we chosen the synthesis of 5-trifluoromethyl derivative **1a**, which is similar to that mentioned in the patent.[4] The reaction of furfural with trifluoroacetic acid and xenon difluoride at room temperature in methylene chloride gave a trifluoromethylation product; a mixture of 5-trifluoromethylfuran-2-carbaldehyde bis(trifluoroacetate) **2a** and the expected aldehyde **1a** was isolated by extraction. The IR spectrum of the mixture show characteristic absorption bands of the carbonyl group of trifluoroacetate at 1795 cm^{-1}. Prolonged acid hydrolysis of the mixture containing bis(trifluoroacetate) **2a** afforded 5-trifluoromethyl derivative **1a** in 20% yield. Preliminary protection of the formyl group by converting it into a diacylal one virtually did not affect the yield of aldehyde **1a** (19%) with furfural diacetate as an intermediate but substantially increased the yield in the trifluoromethylation of bis(trifluoroacetate) **3a** preliminarily prepared from furfural (the yield of aldehyde **1a** was increased to 30%). Despite a two-step synthesis through bis(trifluoroacetate) **3a**, this scheme provides the higher yield from trifluoromethylation, which makes it possible to reduce expenditure for comparatively expensive xenon difluoride. Novel 5-trifluoromethylthiophene-2-carbaldehyde (**1b**) was obtained analogously in a somewhat lower yield. Note that when distilled *in vacuo*, acetal **3b** partially decomposes to aldehyde **4b** and trifluoroacetic anhydride, although the reaction of the aldehyde with the anhydride occurs quantitatively: the IR spectrum of bis(trifluoroacetate) **3b** contains no absorption band characteristic of the carbonyl group in thiophene-2-carbaldehyde **4b** (1680 cm^{-1}). To complete the hydrolysis of the resulting aldehyde bis(trifluoroacetates) **2a** and **2b** in the isolation of the target compounds, a prolonged reaction with water in the presence of trifluoroacetic acid was required (Scheme 1).

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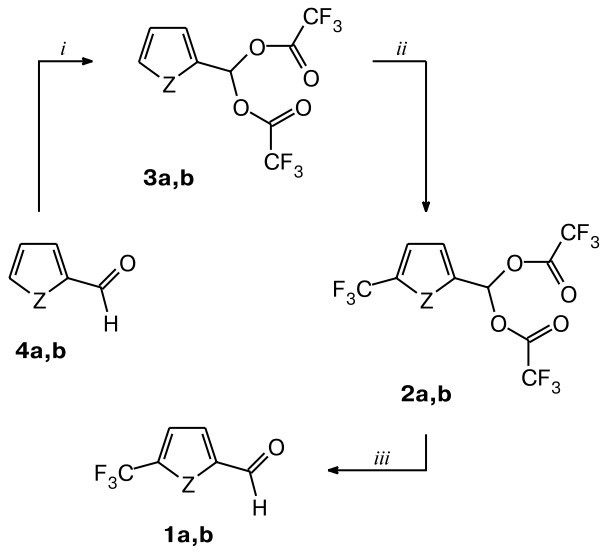
Scheme 1



Reagents and conditions: *i*. $(CF_3CO)_2O$, CF_3COOH, 10→20 °C; *ii*. CF_3COOH, XeF_2, CH_2Cl_2, 0→20 °C; *iii*. H_2O, CF_3COOH.

It is known that many thiosemicarbazones of aromatic aldehydes exhibit high biological activity. For instance, 4-acetylaminobenzaldehyde thiosemicarbazone (preparation thibone[9]) and 5-ethylsulfanylthiophene-2-carbaldehyde thiosemicarbazone[10] show antitubercular activity, while 4-isopropylbenzaldehyde and thiophene-2-carbaldehyde thiosemicarbazones have fungicidal properties and have been proposed as seed disinfectants.[11] The thiosemicarbazones of the synthesized trifluoromethyl derivatives of heterocyclic aldehydes (**5a,b**) were tested *in vitro* for fungicidal activity with potato agar against phytopathogenic fungi according to a generally accepted procedure[12] with the widely used fungicide triadimephon as a standard (Table 1). The activity of trifluoromethylfurancarbaldehyde thiosemicarbazone **5a** was lower than that of the standard, while trifluoromethylthiophene-2-carbaldehyde thiosemicarbazone **5b** proved to be highly active, being vastly superior to triadimephon with respect to three pathogenic fungi: *Venturia inaequalis*, *Rhizoctonia solani*, and *Helminthosporium sativum*.

Table 1. Growth suppression of the mycelium of pathogenic fungi *in vitro* by thiosemicarbazones **5a** and **5b** (c = 30 mg L^{-1})

Compound	Growth suppression of microorganisms (%)					
	V.i.	*R.s.*	*F.o.*	*F.m.*	*H.s.*	*S.s.*
5a	30	16	19	21	57	11
5b	97	84	51	77	82	45
Triadimephon	53	54	72	90	45	59

Note: V.i. stands for *Venturia inaequalis, R.s.* for *Rhizoctonia solani*, *F.o.* for *Fuzarium oxysporum*, *F.m.* for *Fuzarium maniliforme*, *H.s.* for *Helminthosporium sativum*, and *S.s.* for *Sclerotinia sclerotiorum*.

Experimental

IR spectra were recorded on a Specord M-80 instrument (Nujol for solids and thin film for liquids). NMR spectra were recorded on a Bruker AC 200 spectrometer (200 (^{1}H), 50.3 (^{13}C), and 188.3 MHz (^{19}F)) in $CDCl_3$ and $(CD_3)_2SO$ with Me_4Si and $CFCl_3$, respectively, as external standards. The course of the reaction was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates (spots were visualized under UV light and by treating with a solution of 2,4-dinitrophenylhydrazine).

Furan-2-carbaldehyde bis(trifluoroacetate) (3a) was obtained as described for furan-2-carbaldehyde diacetate.[13]

Furfural **4a** (9.6 g, 0.1 mol) was added dropwise at 10—15 °C to a stirred mixture of $(CF_3CO)_2O$ (TFAA) (21.9 g, 0.104 mol) and CF_3COOH (TFA) (0.015 g, 0.13 mmol). The reaction mixture was stirred for 1 h and AcONa (0.013 g, 0.156 mmol) was added. The mixture was twice fractionated *in vacuo* at 56—58 °C (8 Torr) to give bis(trifluoroacetate) **3a** (17.34 g, 57%), n_D^{19} = 1.3725. Found (%): C, 35.38; H, 1.36. $C_9H_4F_6O_5$. Calculated (%): C, 35.31; H, 1.32. IR, ν/cm^{-1}: 3140 (CH fur.),1795 ($CF_3\underline{C}=O$), 1230, 1170, 1110 (CF_3). ^{1}H NMR ($CDCl_3$), δ: 6.55 (dd, 1 H, CH fur., J = 3.4 Hz, J = 1.9 Hz); 6.78 (d, 1 H, CH fur., J = 3.4 Hz); 7.58 (d, 1 H, CH fur., J = 1.3 Hz); 7.86 (s, 1 H, $CH(OCOCF_3)_2$).

5-Trifluoromethylfuran-2-carbaldehyde (1a). Xenon difluoride (4.23 g, 25 mmol) was added in portions under argon at 0 °C for 30 min to a stirred solution of bis(trifluoroacetate) **3a** (7.65 g, 25 mmol) and TFA (2.85 g, 25 mmol) in CH_2Cl_2 (50 mL) in a teflon reaction vessel. The reaction mixture was allowed to stand for 16 h, poured into ice water (50 mL), and stirred for 1 h. The organic phase was separated and the product from the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic phases were washed with a solution of $NaHCO_3$ and dried with $MgSO_4$. The solvent was removed and the residue was distilled *in vacuo*. A fraction with b.p. 49—50 °C (25 Torr) was collected, n_D^{25} = 1.4239 (*cf.* Ref. 2: b.p. 66 °C (40 Torr), n_D^{25} = 1.4256). The yield of aldehyde **1a** was 1.27 g (30%). IR, ν/cm^{-1}: 3140 (CH fur.), 2850 ($\underline{CH}O$), 1685 (C=O), 1300, 1182, 1140, 1110 (CF_3). ^{1}H NMR ($CDCl_3$), δ: 6.99 (d, 1 H, CH fur., J = 3.2 Hz); 7.31 (d, 1 H, CH fur., J = 3.3 Hz); 9.77 (s, 1 H, CHO). ^{19}F NMR, δ: –64.38.

5-Trifluoromethylfuran-2-carbaldehyde thiosemicarbazone 5a, m.p. 163—164 °C (from C_6H_6) (*cf.* Ref. 2: m.p. 162—164 °C (from C_6H_6)). ^{1}H NMR ($(CD_3)_2SO$), δ: 7.09 (d, 1 H, CH fur., J = 3.1 Hz); 7.18 (d, 1 H, CH fur., J = 3.1 Hz); 7.74 (br.s, 1 H, NH_2); 7.98 (s, 1 H, CH=N); 8.33 (br.s, 1 H, NH_2); 11.61 (br.s, 1 H, NH—N=).

Thiophene-2-carbaldehyde bis(trifluoroacetate) (3b) was obtained as described for bis(trifluoroacetate) **3a**. The yield of compound **3b** was 98%, n_D^{19} = 1.4061. Found (%): C, 33.71; H, 1.36; S, 9.73. $C_9H_4F_6O_4S$. Calculated (%): C, 33.55; H, 1.25; S, 9.95. When distilled *in vacuo* (b.p. 70—72 °C (2 Torr), 35—38 °C (0.2 Torr)), bis(trifluoroacetate) **3b** partially decomposes to compound **4b**. IR, ν/cm^{-1}: 3120 (CH thioph.), 1798

($CF_3\underline{C}{=}O$), 1230, 1175, 1110 (CF_3). ^{1}H NMR ($CDCl_3$), δ: 7.11 (dd, 1 H, CH thioph., J = 5.1 Hz, J = 3.7 Hz); 7.44 (dd, 1 H, CH thioph., J = 3.7 Hz, J = 1.2 Hz); 7.55 (dd, 1 H, CH thioph., J = 5.1 Hz, J = 1.2 Hz); 8.06 (s, 1 H, $CH(OCOCF_3)_2$). ^{19}F NMR, δ: −75.37.

5-Trifluoromethylthiophene-2-carbaldehyde (1b) was obtained as described for aldehyde **1a**. Compound **1b** contains an impurity of the starting aldehyde **4b**. Aldehyde **1b** was isolated by column chromatography on Acros Organics silica gel (0.030—0.070 mm) with CH_2Cl_2 as an eluent. The yield of compound **1b** was 24%, b.p. 75—78 °C (20 Torr), n_D^{20} = 1.4694. Found (%): C, 39.81; H, 1.73; S, 17.69. $C_6H_3F_3OS$. Calculated (%): C, 40.00; H, 1.68; S, 17.80. IR, ν/cm^{-1}: 3115 (CH thioph.), 2840 ($\underline{CH}O$), 1670 (C=O), 1285, 1210, 1165, 1130 (CF_3). ^{1}H NMR ($CDCl_3$), δ: 7.55 (d, 1 H, CH thioph., J = 4.0 Hz); 7.76 (d, 1 H, CH thioph., J = 4.0 Hz); 10.01 (s, 1 H, CHO). ^{13}C NMR, δ: 121.8 (q, CF_3, $^1J_{C,F}$ = 266 Hz); 128.8 (C(4)); 133.7 (C(3)); 134.8 (q, C(5), $^2J_{C,F}$ = 144 Hz); 146.1 (C(2)); 182.9 (COH). ^{19}F NMR, δ: −56.28.

5-Trifluoromethylthiophene-2-carbaldehyde thiosemicarbazone 5b, m.p. 161—162 °C (from C_6H_6). Found (%): C, 33.41; H, 2.62; N, 16.37. $C_7H_6F_3N_3S$. Calculated (%): C, 33.20; H, 2.39; N, 16.59. ^{1}H NMR ($(CD_3)_2SO$), δ: 7.53 (d, 1 H, CH thioph., J = 3.8 Hz); 7.81 (d, 1 H, CH thioph., J = 3.8 Hz); 7.84 (br.s, 1 H, NH_2); 8.23 (s, 1 H, CH=N); 8.34 (br.s, 1 H, NH_2); 11.67 (br.s, 1 H, NH—N=). ^{19}F NMR, δ: −54.25.

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