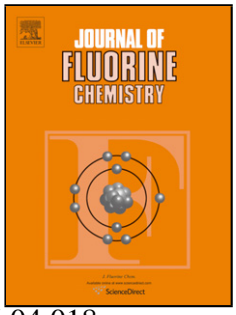

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Short Communication

Trifluoroacetylation of electron-rich thiophenes

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ABSTRACT

Electron-rich thiophenes were trifluoroacetylated by trifluoroacetic anhydride with different nitrogen bases in dichloromethane at room temperature in good yields. Trifluoroacetylation without a base gave significantly lower yields.

Highlights

- Trifluoroacetylation of electron-rich thiophenes under mild conditions
- TFAA (1.2 equivalents) and pyridine (1.1 equivalent) are the reagents of choice
- Thiophenes with strong electron-donating groups give very good yields.
- Thiophenes with weak electron-donating groups give low yields.

Keywords:

Thiophenes

Trifluoroacetic anhydride

Trifluoroacetylation

Nitrogen bases

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1. Introduction

Trifluoroacetylation is an important reaction in organic synthesis [1] and trifluoroacetylation of aromatic compounds has been effected in a number of ways [2-7]. The simplest way is to use trifluoroacetic anhydride as the only reagent. Trifluoroacetic anhydride will react with electron-rich aromatic compounds without any activation [8].

Trifluoroacetylated thiophenes are useful intermediates in organic chemistry and have, for example, been utilized in the preparation of biological active compounds [9,10] in polymer chemistry [11,12], in asymmetric syntheses [13-16] and in palladium catalyzed coupling reactions[17,18]. We needed trifluoroacetylated thiophenes as a part our investigations on biofilm inhibitors [19] and were interested in the trifluoroacetylation of thiophenes having strong electron-donating substituents. One problem with these thiophenes is that they are sensitive to both Lewis and Brønsted acids. This would make it difficult to use trifluoroacetic anhydride alone as a trifluoroacetylating agent since trifluoroacetic acid is produced in the reaction.

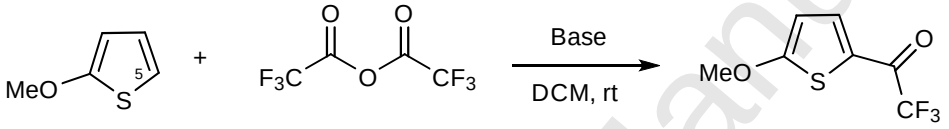
We wanted to investigate if it was possible to trifluoroacetylate electron-rich thiophenes with trifluoroacetic anhydride in the presence of a proton acceptor. Trifluoroacetylation of some five-membered nitrogen heterocycles with trifluoroacetic anhydride and a nitrogen base has been reported.[6,20]

2. Results and discussion

Trifluoroacetylation of commercially available 2-methoxythiophene in dichloromethane was set up as a standard reaction. It is possible to trifluoroacetylate 2-methoxythiophene with trifluoroacetic anhydride alone [8], even though 2-methoxythiophene

will dimerize in the presence of a strong acid [21], but the yield is low (entry 1, Table 1). We imagined that the yield in this reaction could be improved if the generated trifluoroacetic acid was neutralized. Performing the reaction in the presence of a nitrogen base gave indeed a significant increase in the yield. Initial experiments showed that a slight excess of trifluoroacetic anhydride compared to the base gave the best results. Table 1 shows the results from trifluoroacetylation of 2-methoxythiophene with trifluoroacetic anhydride in the presence of some nitrogen bases. Only trifluoroacetylation in the 5-position was observed.

Table 1. Trifluoroacetylation of 2-methoxythiophene



1c **2c**

Entry	Base[a]	Reaction time[b]	Yield (%) **2c** [8] [c]
1	-	40 min	36
2	$(Et)_3N$	24 h	76
3	$(iPr)_2EtN$	24 h	53
4	Proton sponge[d]	1 h	0
5	Pyridine	20 min	96
6	2,6-Lutidine	30 min	90
7	DMAP[e]	18 h	90
8	$(Et)_3N$/pyridine[f]	18 h	96
9	$(Et)_3N$/DMAP[g]	18 h	95

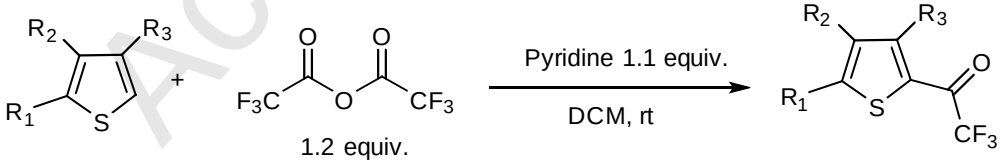
[a] Ratio of trifluoroacetic anhydride to the base: 1.1 -1.0; [b] Until TLC showed that all starting material was consumed; [c] Isolated; [d] 1,8-Bis(dimethylamino)naphthalene; [e] 4-

Dimethylaminopyridine; [f] 10% of the base was pyridine; [g] 10% of the base was 4-dimethylaminopyridine.

The less hindered base triethylamine gave a better yield compared to diisopropylethylamine (entries 2 and 3). The proton sponge 1,8-bis(dimethylamino)naphthalene did not give anything of the wanted product after all the starting material had been consumed (entry 4). All the pyridine bases gave good yields but the reaction with 4-dimethylaminopyridine was much slower than the reaction of pyridine and 2,6-lutidine (entries 5-7). This we think is attributed to the higher stability of the 4-dimethylaminopyridine /trifluoroacetic anhydride complex compared to the other two pyridine/trifluoroacetic anhydride complexes [6,22]. The trifluoroacetylation could also be performed in good yields with a catalytic amount of pyridine or 4-dimethylaminopyridine together with triethylamine but the reaction time was relatively long (entries 8-9).

According to Table 1, the best base for the trifluroacetylation of 2-methoxythiophene is pyridine. In Table 2 are the results from trifluoroacetylation of some electron-rich thiophenes with pyridine as base presented. These results are in many cases compared with trifluoacetylation without pyridine.

Table 2: Trifluoroacetylation of some electron-rich thiophenes.



1a-i **2a-i**

Entry	Compound	R_1	R_2	R_3	Reaction time	Product	Yield (%)[a,b]
1	**1a**[c]	H	H	Me	10 d	**2a**	0 (9)

2	**1b**[c]	H	Me	Me	4 d	**2b**	27(81)
3	**1c**[23]	SMe	H	H	24 h	**2c**[8]	32(52)
4	**1d**[c]	OMe	H	H	20 min	**2d**[8]	96(36)
5	**1e[24]**	OEt	H	H	30 min	**2e**	90(37)
6	**1f**[c]	H	H	OMe	24 h	**2f**[25]	95(43)
7	**1g[26]**	OMe	Me	H	1 h	**2g**	95(38)
8	**1h[27]**	OEt	Me	H	20 min	**2h**	99(46)
9	**1i**	OEt	Me	Me	20 min	**2i**	91(20)

[a] Isolated; [b] Yields in parenthesis are without pyridine; [c] Commercially available.

3-Methylthiophene did not give any trifluoroacetylation with trifluoroacetic anhydride and pyridine even after a long reaction time (Table 2, entry 1). Without pyridine the yield was 9%. Adding one more methyl group to the thiophene ring, gave increased yield both with and without base, 27 and 81% respectively (entry 2). The reaction time was 4 days. Performing the reaction at reflux temperature for 24 hours did not increase the yield. A methylthio group in the 2-position gave a moderate yield (32%) after 24 hours at ambient temperature with pyridine as base (entry 3). Without the base the yield was 52%. Obviously, methyl groups both in 3- and 4-position or a 2-methylthio group make the thiophene reactive enough to be trifluoroacetylated by trifluoroacetic anhydride alone but not so reactive that it will dimerize very rapidly by the formed trifluoroacetic acid.

All the other thiophenes, having at least one strong electron-donating group, gave all very good yields, but the reaction time varied from 20 minutes to 24 hours (entries 4-9). Trifluoroacetylation without pyridine gave in these cases much lower yields (entries 4- 9). A

methoxy or an ethoxy group in the 2-position gave similar yields (entries 4,5,7,8) but 2-ethoxythiophenes are in many cases easier to prepare than 2-methoxythiophenes.[28]

3. Conclusion

3-Methylthiophene can not be trifluoroacetylated with trifluoroacetic anhydride in the presence of pyridine. Without pyridine the trifluoroacetylated product was obtained in low yield (9%). On the other hand 3,4-dimethylthiophene and 2-methylthiothiophene can be trifluoroacetylated with trifluoroacetic anhydride alone in moderate to good yields, 52 and 81% respectively. Thiophenes having at least one strong electron-donating group can be trifluoroacetylated with 1.2 equivalents of trifluoroacetic anhydride and 1.1 equivalents of pyridine in dichloromethane at room temperature in very good yields (90-99%). Without pyridine the yields were much lower (20-46%).

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance AV 600 and a AVII400 spectrometer. Chemical shifts (δ) are given as ppm relative to the residual solvent peak. Melting points are uncorrected. Mass spectra were recorded on a Fision ProSpec instrument using 70 eV as ionization energy. Column chromatography for purification was performed on silica gel 60 (70-230 mesh).

Ethoxylation of bromothiophenes

General method

Sodium was dissolved in EtOH at 0 ^{o}C. Excess of alcohol was removed using a Stark trap until the solution reached 105 ^{o}C. Bromothiophene was added followed by CuBr. The mixture was refluxed at temperatures ranging from 100-105 ^{o}C until no more staring material could be seen on TLC. The reaction mixture was cooled to room temperature before an aqueous solution of KCN (0.4 M, 4 mol eq. to CuBr) was added under stirring. The product was extracted with Et_2O (3x), and the combined organic layers were dried over $MgSO_4$, and solvent was removed *in vacuo.*

*2-Ethoxy-3-methylthiopene (**1h**)*

EtOH (200 mL), Na (5.75 g, 0.25 mol), 2-bromo-3-metylthiophen (1.50 g, 8.47 mmol), CuBr (0.19 g, 1.33 mmol). Reaction time 3 h. The product was purified using silica-gel chromatography (hexane) to give 0.65 g (54% yield) of 2-ethoxy-3-methylthiopene as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3), 2.07 (s, 3H, $ArCH_3$), 4.06 (q, 2H, *J* = 7.0 Hz, OCH_2CH_3), 6.54 (d, 1H, *J* = 5.8 Hz, Ar*H*), 6.61 (d, 1H, *J* = 5.8 Hz, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.4 ($ArCH_3$), 15.0 (OCH_2CH_3), 71.1 (OCH_2CH_3), 111.4 (C-5), 118.2 (C-4), 127.7 (C-3), 158.1 (C-2). MS (EI) m/z (rel. int.) 142 (100, M^+), 114 (100), 113 (87), 86 (16), 85 (73), 84 (13), 81 (11), 53 (13), 49 (11), 45 (51), 29 (11), 17 (15); HRMS (EI) m/z: calcd. for $C_7H_{10}OS$ [M^+] 142.0452, found 142.0449.

*2-Ethoxy-3,4-dimethylthiophene (**1i**)*

EtOH (150 mL), Na (2.20 g, 95.70 mmol), 2-Bromo-3,4-dimetylthiophen (0.90 g, 4.76 mmol), CuBr (0.15 g, 1.05 mmol). Reaction time 4 h. The product was purified using silica-gel chromatography (hexane) to give 0.48 g (65% yield) of 2-ethoxy-3,4-dimethylthiophene

as a clear pale yellow oil. ^{1}H NMR (400 MHz): δ 1.38 (t, 3H, *J*= 7.0 Hz, OCH2C*H*$_3$), 1.97 (s, 3H, Ar*CH*$_3$), 2.08 (s, 3H, Ar*CH*$_3$), 4.05 (q, 2H, *J*= 7.0 Hz, OC*H*$_2$CH$_3$), 6.23 (s, 1H, Ar*H*). ^{13}C NMR (101 MHz): δ 10.1 (Ar*CH*$_3$), 15.1 (OCH$_2$*C*H$_3$), 15.7 (Ar*C*H$_3$), δ70.7 (O*CH*$_2$CH$_3$), 106.6 (C-5), 118.3 (C-4), 135.7 (C-3), 157.9 (C-2). MS (EI) m/z (rel. int.) 156 (95, M^+), 128 (100), 126 (79), 99 (55), 65 (27), 45 (24); HRMS (EI) m/z: calcd. for $C_8H_{12}OS$ [M^+] 156.0607, found 156.0609.

Trifluoroactylation of thiophenes with TFAA in DCM

General method

Starting material was dissolved in DCM (molarity from 0.40 M – 0.45 M) before TFAA (1.1 eq) was added dropwise under stirring. Reaction mixture was left stirring from 20 min to10 days at ambient temperature (Table 2). The reaction mixture was quenched with a sat. aq. $NaHCO_3$ and extracted with Et_2O (3x). The organic phase was washed with sat. aq. NaCl before drying ($MgSO_4$). The product was purified using flash column chromatography on silica (5% EtOAc in hexane).

*2,2,2-Trifluoro-1-(3-methylthiophen-2-yl)ethan-1-one (**2a**)*

3-Methylthiophene (110 mg, 1.12 mmol), DCM (2.5 mL) and TFAA (0.17 mL, 1.21 mmol). Yield 19 mg (9%) as a yellow oil. ^{1}H NMR (600 MHz): δ 2.62 (s, 3H, Ar*CH*$_3$), 7.04 (d, 1H, *J* = 4.9 Hz), 7.69 (d, 1H, *J* = 4.9 Hz).13C NMR (151 MHz, CDCl3), δ 17.5 (Ar*CH*$_3$), 116.4 (q, *J* = 290.9 Hz, ArCO*CF*$_3$), 126.6 (C-5), 132.5 (C-4), 135.0 (C-3), 152.9 (C-2),

174.04 (q, 2*J* = 36.3 Hz, Ar*C*OCF$_3$). MS (EI) m/z (rel. int.) 194 (50, M$^+$), 125 (100), 97 (5), 53 (13); HRMS (EI) m/z: calcd. for $C_7H_5F_3OS$ [M$^+$] 194.0013, found 194.0015.

*1-(3,4-Dimethylthiophen-2-yl)-2,2,2-trifluoroethan-1-one (**2b**)*

3,4-Dimethylthiophene (113 mg, 1.01 mmol), DCM (2.5 mL) and TFAA (0.16 mL, 1.13 mmol). Yield 171 mg (81%) as a yellow oil. ^{1}H NMR (600 MHz): δ 2.22 (s, 3H, Ar*CH$_3$*), 2.52 (s, 3H, Ar*CH$_3$*), 7.40 (s, 1H).^{13}C NMR (151 MHz): δ 14.5(Ar*CH$_3$*), 15.3 (Ar*CH$_3$*), 116.5 (q, *J* = 291.2 Hz, ArCO*CF$_3$*), 126.9 (C-2) 131.8 (C-5), 140.3 (C-4), 151.8 (C-3), 174.2 (q, 2*J* = 35.9 Hz, Ar*C*OCF$_3$). MS (EI) m/z (rel. int.) 208 (55, M$^+$), 139 (100), 69 (10), 45 (7); HRMS (EI) m/z: calcd. for $C_8H_7F_3O$Scalculated 208.0170, found 208.0166.

Trifluoroactylation of thiophenes with TFAA and pyridine in DCM

General method

Starting material was dissolved in DCM (molarity from 0.33 M - 0.46 M) before pyridine (1.1 equiv.) was added followed by dropwise addition of TFAA (1.2 equiv.) under stirring. After the starting material was consumed (Table 2) according to TLC the reaction was mixture quenched with a sat. aq. $NaHCO_3$ and extracted with Et_2O (3x). The organic phase was washed with 1.0 M HCl (2x) and sat.aq. NaCl (1x) before drying ($MgSO_4$). The solvent was removed *in vacuo* to give the compounds **2a -2i**. Only compounds **2a-2c** needed chromatography (silica gel, 5-12% EtOAc in hexane) in order to get a > 95% pure ^{1}H NMR spectrum.

*1-(5-Ethoxythiophen-2-yl)-2,2,2-trifluoroethan-1-one (**2e**)*

2-Ethoxythiophene (312 mg, 2.76 mmol), DCM (6.0 mL), pyridine (0.25 mL, 3.10 mmol) and TFAA (0.47 mL, 3.33 mmol). Yield 548 mg (90%) as a clear pale yellow oil. ^{1}H NMR (400 MHz): δ 1.48 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3). 4.23 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 6.33 (d, 1H, *J* = 4.6 Hz, Ar*H*), 7.72 (dd, 1H, 2*J*HH = 4.6, 4*J*HF = 1.5 Hz, Ar*H*). ^{13}C NMR (101 MHz): δ 14.4 (OCH_2CH_3), 70.7(OCH_2CH_3), 108.5 (C-4) 116.7 (q, *J* = 290.9, $ArCOCF_3$), 122.5 (C-2), 138.1 (C-3), 172.3 (q, 2*J* = 35.4, $COCF_3$), 177.7 (C-5). MS (EI) m/z (rel. int.) 224 (47, M^+) 196 (21), 155 (5), 127 (100), 98 (6), 29 (16); HRMS (EI) m/z: calcd. for $C_8H_7F_3O_2S$ [M^+] 224.0119, found 224.0121.

*2,2,2-Trifluoro-1-(5-methoxy-4-methylthiophen-2-yl)ethan-1-one (**2g**)*

2-Methoxy-3-methylthiophene (112 mg, 0.87 mmol), DCM (2.5 mL), pyridine (0.08 mL, 0.96 mmol) and TFAA (0.15 mL, 1.05 mmol). Yield 187 mg (95%) as a pale yellow solid, m.p. 44-45 °C. ^{1}H NMR (400 MHz): δ 2.08 (s, 3H, ArCH_3), 4.05 (s, 3H, OCH_3), δ 7.63 (s, 1H, Ar*H*). ^{13}C NMR (101 MHz): δ 11.1 ($ArCH_3$), 61.7 (OCH_3), 116.9 (q, *J* = 289.0, Ar$COCF_3$), 120.2 (C-2) 120.5 (C-4), 139.9 (C-3), 171.9 (q, 2*J* = 35.4, Ar$COCF_3$), 173.8 (C-5). MS (EI) m/z (rel. int.) 224 (68, M^+), 155 (100), 112 (23), 84 (15), 69 (12); HRMS (EI) m/z: calcd. for $C_8H_7F_3O_2S$ [M^+] 224.0119, found 224.0121.

*1-(5-Ethoxy-4-methylthiophen-2-yl)-2,2,2-trifluoroethan-1-one (**2h**)*

2-Ethoxy-3-methylthiophene(126 mg, 0.89 mmol), DCM (2.5 mL), pyridine (0.08 mL, 0.99 mmol) and TFAA (0.15 mL, 1.06 mmol). Yield 209 mg (99%) as a pale pink solid, m.p. 55-56 °C. ^{1}H NMR (400 MHz): δ 1.49 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3), 2.07 (s, 3H, ArCH_3), 4.23 (q, 2H, *J* = 7.0 Hz, OCH_2CH_3), 7.61 (s, 1H, Ar*H*). ^{13}C NMR (151MHz): δ 11.1 ($ArCH_3$),

14.6 ($OCH_2\mathit{CH_3}$), 71.3 ($O\mathit{CH_2}CH_3$), 116.9 (q, J = 298.9, $ArCO\mathit{CF_3}$), 120.1 (C-2), 120.7 (C-4), 139.9 (C-3), 171.7 (q, $2J$ = 36.3, $Ar\mathit{C}OCF_3$), 172.8 (C-5). MS (EI) m/z (rel. int.) 238 (57, M^+), 210 (24), 141 (100), 85 (10), 29 (13); HRMS (EI) m/z: calcd. for $C_9H_9F_3O_2S$ [M^+] 238.0275, found 238.0279.

*1-(5-Ethoxy-3,4-dimethylthiophen-2-yl)-2,2,2-trifluoroethan-1-one (**2i**)*

2-Ethoxy-3,4-dimethylthiophene (128 mg, 0.82 mmol), DCM (2.5 mL), pyridine (0.07 mL, 0.87 mmol) and TFAA (0.14 mL, 0.99 mmol). Yield 189 mg (91%) as a clear white solid, m.p. 83-84 °C. ^{1}H NMR (600 MHz): δ 1.49 (t, 3H J = 7.0 Hz, $OCH_2\mathit{CH_3}$), 2.00 (s, 3H, $Ar\mathit{CH_3}$), 2.51 (s, 3H, $Ar\mathit{CH_3}$), 4.23 (q, 2H J = 7.0 Hz, $O\mathit{CH_2}CH_3$), ^{13}C NMR (151 MHz): δ 9.7 ($Ar\mathit{CH_3}$), 14.7 ($OCH_2\mathit{CH_3}$), 16.1 ($Ar\mathit{CH_3}$), 70.5 ($O\mathit{CH_2}CH_3$), 112.3 (C-2), 117.0 (q, J = 291.1 Hz, $ArCO\mathit{CF_3}$), 121.5 (C-4), 154.2 (C-3), 170.4 (C-5) , 172.0 (q, $2J$ = 34.8 Hz, $Ar\mathit{C}OCF_3$). MS (EI) m/z (rel. int.) 252 (52, M^+), 224 (9), 183 (12), 156 (3), 155 (100), 99 (8); HRMS (EI) m/z: calcd. for $C_{10}H_{11}F_3O_2S$ [M^+] 252.0432, found 252.0426.

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