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Substitution of Five-Membered Heteroarenes and Uracils with Trifluoroacetaldehyde Ethyl Hemiacetal

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A number of α-(trifluoromethyl)heteroarylmethanols **2a**—**c** are conveniently obtained in good yields by substitution of pyrole, furan, and thiophene with trifluoroacetaldehyde ethyl hemiacetal (TFAE); **2b** and **2c** are formed only in the presence of a catalyst such as $ZnCl_2$. Analogous methanols **8a** and **8b** are also prepared by catalytic substitution of uracils with TFAE in moderate yields.

Preparation of α-(trifluoromethyl)methanols has already been attracted much attention of chemists and biochemists because of some unique physical, chemical and biological properties.[1] They are mainly prepared (1) by reduction of α-trifluoromethyl ketones, which were obtained by a variety of methods; (2) by substitution of trifluoroacetaldehyde ethyl hemiacetal (TFAE) with electron-rich arenes, olefins or enolates;[2] (3) by addition of trifluoromethyltrimethylsilane (CF_3TMS) to carbonyl compounds;[3] and (4) by electrochemical trifluoromethylation of carbonyl compounds.[4]

As reported previously, thermal substitution of indoles and imidazoles with TFAE easily furnished the corresponding α-(trifluoromethyl)methanols,[5] respectively. Recently we found the substitution of pyrrole **1a** with TFAE also readily occurred. However, such a reaction did not take place in the case of furan **1b** or thiophene **1c**. Therefore the effect of such a catalyst as $ZnCl_2$ on the reaction of **1b** and **1c** was studied, and the details are given in Table 1.

The product formed in the reaction of pyrrole **1a** was greatly dependent upon the molar ratio of **1a**/TFAE. Monosubstituted compound **2a** (Chart 1), 2-(2,2,2-trifluoro-1-hydroxyethyl)pyrrole, was predominantly generated when equivalent amounts of **1a** and TFAE were caused to react at 0 °C (Entry 1), whereas disubstituted compound **2a′**, 2,5-bis(2,2,2-trifluoro-1-hydroxyethyl)pyrrole, was the main product when an excess amount of TFAE was used (Entry 2). On the other hand, no substitution product **2b** was detected by TLC when the mixture of furan **1b** and TFAE was heated at 110 °C in an autoclave (Entry 3). Similarly, only a trace amount of **2c** was observed when equivalent amounts of thiophene **1c** and TFAE were heated at reflux (Entry 6). However, the introduction of one electron-donating methyl group, e.g. 3-methylthiophene **3**, gave rise to the formation of a certain amount of 2-substituted product, 3-methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)thiophene **4** (Entry 8).

Table 1. Substitution of the Substrates with TFAE

Entry	Substrate	Molar ratio[a]	Catalyst	Conditions	Product (%)[b]
1	**1a**	1 : 1	None	0 °C, 30 min.	**2a** (85)
2	**1a**	1 : 2.4	None	R.T., 3 h	**2a′** (82)
3	**1b**[c]	1 : 1	None	110 °C, 12 h	**2b** (none)
4	**1b**[c]	1 : 1	$ZnCl_2$	110 °C, 10 h	**2b** (61)
5	**1b**[c]	1 : 2	$ZnCl_2$	120 °C, 24 h	**2b** (68)
6	**1c**	1 : 1	None	Reflux, 24 h	**2c** (trace)
7	**1c**[c]	1 : 1	$ZnCl_2$	120 °C, 24 h	**2c** (62)
8	**3**	1 : 2	None	Reflux, 24 h	**4** (14)
9	**3**	1 : 2	$ZnCl_2$	Reflux, 10 h	**4** (75)
10	**5**	1 : 2	$ZnCl_2$	Reflux, 10 h	(none)
11	**7a**[c]	1 : 3	None	200 °C, 24 h	**8a** (9)
12	**7a**	1 : 2	$ZnCl_2$	120 °C, 24 h	**8a** (7)
13	**7a**	1 : 2	K_2CO_3	120 °C, 12 h	**8a** (31)
14	**7b**	1 : 2	K_2CO_3	120 °C, 12 h	**8b** (28)

a) The substrate: TFAE. b) Isolated yields based on the substrate. c) The reaction was done in an autoclave.

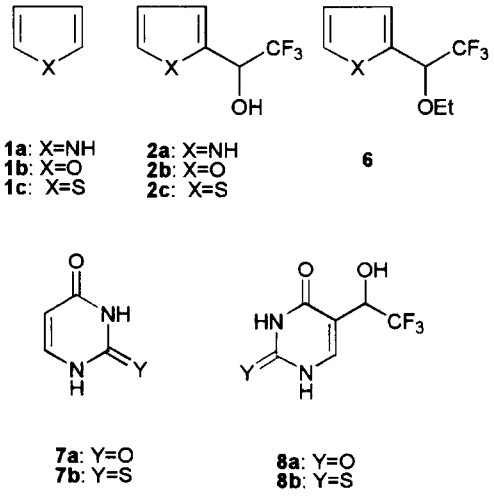

Chart 1.

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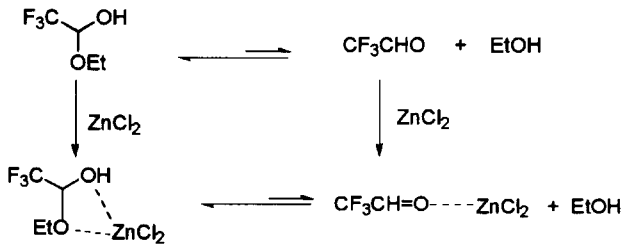
The catalytic reaction was carried out by heating the mixture of equivalent amounts of furan **1b** and TFAE in the presence of 10 mol% of anhydrous $ZnCl_2$ in an autoclave. Product analysis by TLC showed that the monosubstituted compound **2b** was predominantly formed (Entry 4), and no detectable amount of disubstituted compound was observed by GC, even though an excess amount of TFAE was used (Entry 5). The methanols **2c** and **4** were also afforded in a good yield when **1c** and **3** were reacted under the same conditions, respectively (Entries 7 and 9). However, such a substitution product was not produced when one electro-withdrawing group was introduced into the thiophene, e.g. 3-thiophenecarboxylic acid **5** (Entry 10).

Actually, all the three heteroarenes with TFAE only produced the α-(trifluoromethyl)methanols **2** rather than the corresponding ether **6**, regardless the presence or absence of



Scheme 1.

catalyst. Thus, we suggested that the methanol **2a** (or **2a′**) may be formed by the electrophilic substitution of pyrrole with trifluoroaldehyde, which was in equilibrium with TFAE (Scheme 1). In the presence of $ZnCl_2$, the formation of a Zn-(II) complex promoted charge separation of the C–O bonds of trifluoroaldehyde and TFAE (Scheme 1), and hence led to the electrophilic substitution of **1b** or **1c**.

The satisfactory results encouraged us to investigate the substitution reaction of uracils **7a,b** (Chart 1) with TFAE, because of the impressive antimetabolic activities. Actually, 5-substituted uracil **8a** was formed by heating the mixture of uracil **7a** and an excess amount of TFAE at 200 °C in water, albeit in a low yield (Entry 11). Unfortunately, the yield was not improved in water or in DMF in the presence of 10 mol% of anhydrous $ZnCl_2$ (Entry 12). In order to promote the reaction of uracil, an alternative catalyst, K_2CO_3, was used considering the weak acidity. In fact, the yield of **8a** was markedly raised comparatively in the presence of 10 mol% of K_2CO_3 (Entry 13). An analogous compound **8b** was also formed in 28% yield when 2-thiouracil **7b** was used to react with TFAE under the same conditions (Entry 14).

Experimental

2-(2,2,2-Trifluoro-1-hydroxyethyl)pyrrole (2a). A mixture of 7.20 g (50.0 mmol) of TFAE and 3.35 g (50.0 mmol) of pyrrole was stirred at 0 °C for 0.5 h. The mixture, solidified during the reaction, was directly recrystallized from hexane–dichloromethane to afford 7.02 g (85%) of the product **2a**. Mp 55—56.5 °C, white plates. ^{1}H NMR ($CDCl_3$, TMS) δ = 2.56 (1H, br, s), 5.07 (1H, q, J = 6.55 Hz), 6.20 (2H, m), 6.84 (1H, d, J = 1.30 Hz), 8.55 (1H, br, s). ^{19}F NMR ($CDCl_3$, C_6F_6) δ = 83.42 (3F, d, J = 6.55 Hz); MS m/z 165 (M^+; 66.6), 96 (100.0). HRMS Calcd: M, 165.0402. Found: m/z 165.0425.

2,5-Bis(2,2,2-trifluoro-1-hydroxyethyl)pyrrole (2a′). 4.49 g (82%). Mp 83—84.5 °C, white needles. ^{1}H NMR ($CDCl_3$) δ = 2.73 (2H, br, s), 5.09 (2H, q, J = 6.94 Hz), 6.27 (2H, d, J = 2.20 Hz), 8.85 (1H, br, s). ^{19}F NMR ($CDCl_3$) δ = 83.26 (6F, d, J = 6.94 Hz); MS m/z 263 (M^+; 73.5), 194 (100.0), 176 (32.1). HRMS Calcd: M, 263.0381. Found: m/z 263.0397.

2-(2,2,2-Trifluoro-1-hydroxyethyl)thiophene (2c). A mixture of 7.20 g (50.0 mmol) of TFAE, 4.20 g (50.0 mmol) of thiophene and 0.68 g (5.00 mmol) of anhydrous zinc chloride was heated in an autoclave at 120 °C for 24 h, and then evaporated under reduced pressure. The residue was passed through a silica gel column (hexane/ethyl acetate, 5 : 1) to give 5.64 g (62 %) of the product **2c**, a colorless liquid. ^{1}H NMR ($CDCl_3$) δ = 7.38 (1H, dd, J = 4.85, 1.21 Hz), 7.18 (1H, dd, J = 3.64, 1.21 Hz), 7.02 (1H, dd, J = 4.85, 3.64 Hz), 5.26 (1H, q, J = 6.37 Hz), 3.68 (1H, br. s). ^{19}F NMR ($CDCl_3$) δ = 83.34 (3F, d, J = 6.37 Hz); MS m/z 182 (M^+; 58.6), 113 (100.0), 85 (45.8). HRMS Calcd: M, 182.0014. Found: m/z 182.0011. The corresponding reaction of furan was done in the same procedures. The product **2-(2,2,2-trifluoro-1-hydroxyethyl)-furan (2b)** has been already reported.[4]

3-Methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)thiophene (4). A mixture of 7.20 g (50.0 mmol) of TFAE, 2.45 g (25.0 mmol) of 3-methylthiophene was refluxed for 24 h, and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 5 : 1) to give 0.69 g (14%) of the product **4**, a colorless liquid. ^{1}H NMR ($CDCl_3$) δ = 7.27 (1H, d, J = 5.06 Hz), 6.82 (1H, d, J = 5.06 Hz), 5.30 (1H, dq, J = 6.22, 4.84 Hz), 3.47 (1H, d, J = 4.84 Hz), 2.24 (3H, s). ^{19}F NMR ($CDCl_3$) δ = 83.55 (3F, d, J = 6.22 Hz); MS m/z 196 (M^+; 64.8), 127 (100.0), 99 (58.3). HRMS Calcd: M, 196.0170. Found: m/z 196.0166.

5-(2,2,2-Trifluoro-1-hydroxyethyl)uracil (8a). A mixture of 1.12 g (10.0 mmol) of uracil and 2.88 g (20.0 mmol) of TFAE in 6.0 ml of *N*,*N*-Dimethylformamide (DMF) was heated with stirring in the presence of anhydrous K_2CO_3 (1.0 mmol) at 120 °C for 12 h under argon. Then the mixture was poured into 40 ml of water, neutralized with aqueous NH_4Cl and extracted with 3×50 ml of ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 1 : 5) to give 0.65 g (31%) of the product **8a**. Mp 261—264 °C (decomp), white prisms.[4] ^{1}H NMR (DMSO-d_6) δ = 5.00 (1H, q, J = 6.94 Hz), 6.65 (1H, br, s), 7.46 (1H, s), 11.24 (2H, br, s). ^{19}F NMR (DMSO-d_6) δ = 85.45 (3F, d, J = 6.94 Hz). MS m/z 210 (M^+; 3.7), 174 (79.5), 141 (100.0). HRMS Calcd: M, 210.0252. Found: m/z 210.0250.

5-(2,2,2-Trifluoro-1-hydroxyethyl)-2-thiouracil (8b). The corresponding reaction of 2-thiouracil was carried out in the same way as above. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate, 5 : 3) to give 0.63 g (28%) of the product **8b**. Mp 197—198 °C (decomp), yellowish prisms. ^{1}H NMR (acetone-d_6) δ = 5.20 (1H, q, J = 7.06 Hz), 6.05 (1H, br, s), 7.65 (1H, s), 11.44 (2H, br, s). ^{19}F NMR (acetone-d_6) δ = 85.23 (3F, d, J = 7.06 Hz); MS m/z 226 (M^+; 48.6), 157 (70.2), 98 (100.0). HRMS Calcd: M, 226.0024. Found: m/z 226.0018.

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