Photochemical trifluoromethylation of tyramine and L-tyrosine derivatives

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Abstract

Ultraviolet irradiation (254 nm) of methanolic solutions of trifluoromethyl iodide (CF_3I) in the presence of side-chain-protected tyramine and L-tyrosine results in trifluoromethylation of the aromatic ring. The presence of an amine base to neutralize HI formed during the reaction is essential. The electrophilic trifluoromethyl radical preferentially attacks the ring *ortho* to the phenolic group, and 3-trifluoromethyltyramine and 3-trifluoromethyl-L-tyrosine derivatives were obtained in yields of 27% and 33%, respectively.

Introduction

Several years ago we reported that irradiation of a mixture of imidazole and CF_3I in methanol leads to the direct introduction of the trifluoromethyl group into the imidazole ring [1]. This procedure, noteworthy for its simplicity and ease of scale-up, led to the synthesis of trifluoromethylated analogs of a series of biologically important imidazoles, including histidine and histamine [2]. Furthermore, the trifluoromethyl group of 1-unsubstituted imidazoles readily suffers base-promoted loss of HF leading to a variety of functional group transformations [3].

We report herein a variation of our original photochemical procedure that allows facile direct introduction of the trifluoromethyl group into phenols and phenolic ethers. Several factors prompted our interest in exploring the applicability of this procedure to phenols and derivatives. For example, this process would represent potentially a simple route to trifluoromethyl-substituted analogs of important phenolic amines such as tyramine and amino acids such as tyrosine. This would permit an investigation of the presence of the highly electronegative CF_3 group on biological properties of these amines, a study that would complement our on-going research with ring-fluorinated biogenic amines [4]. In addition, the expected loss of HF from *ortho*- or *para*-trifluoromethylphenols [5] under basic conditions could result

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in mechanistic probes for the action of enzymes acting on the phenolic group, especially when such activity is initiated by base or general base catalysis. Relevant to this idea, McDonald *et al.* have recently described exploitation of the reactivity of 2-fluoromethyl- and 2-difluoromethyl-tyrosine as a strategy to develop inhibitors of tyrosine hydroxylase [6]. Sawada *et el.* [7] have recently reported direct trifluoromethylation of electron-rich aromatic compounds, including anisole, using bis(trifluoroacetyl) peroxide. Umemoto and coworkers have developed *N*-trifluoromethyl-*N*-nitrobenzenesulfonate as a trifluoromethylating agent and have applied this to the trifluoromethylation of phenols and anisoles [8].

Results and discussion

Initial photochemical trifluoromethylation experiments using phenols and anisoles as substrates met with failure. In every case, the reaction mixture rapidly turned dark while CF_3I was slowly consumed, but no trifluoromethylated products could be obtained. We reasoned that generation of HI and subsequent reduction of CF_3I with formation of molecular iodine might be a source of problems. From this, it became apparent that the presence of the basic imidazole ring in our previous work contributed to the facile production of trifluoromethylimidazoles by neutralizing HI formed during the reaction. A simple expedient which we adopted for the trifluoromethylation of expensive imidazoles [1, 2] is the addition of 1 equiv. triethylamine to the reaction mixture. However, since *ortho*-trifluoromethylphenols are known to release HF under basic conditions, we anticipated difficulties in the photochemical trifluoromethylation of free phenols in methanolic triethylamine solutions. Accordingly, we initially explored this procedure with the anisole derivative, *N*-trifluoroacetyl-4-methoxyphenethylamine (**1a**).

The photochemical trifluoromethylation of **1a** illustrates the general procedure. A solution of **1a** (0.050 mol), triethylamine (0.025 mol) and CF_3I (0.025 mol) in 25 ml methanol was irradiated in a quartz ampoule by a low-pressure mercury lamp (60 W) for 3 d. The course of the reaction was monitored directly by ^{19}F NMR and by GC–MS methods. Two products identified as *N*-trifluoroacetyl-4-methoxy-2-trifluoromethylphenethylamine (**2a**) and *N*-trifluoroacetyl-4-methoxy-3-trifluoromethylphenethylamine (**3a**) were obtained in the ratio of 15:85, as estimated by integration of the ^{19}F NMR peak areas. Isolation of the products was easily achieved by silica gel column chromatography, and **2a** and **3a** were obtained in 5% and 29% yield, respectively. The structures of the isomers were assigned on the basis of their ^1H NMR spectra. The proton signals of the 3 (or 5) position of the *para*-methoxyphenethylamines are usually found at higher field than those of the 2 (or 6) position* [9]. The isolated proton signal appeared as a singlet

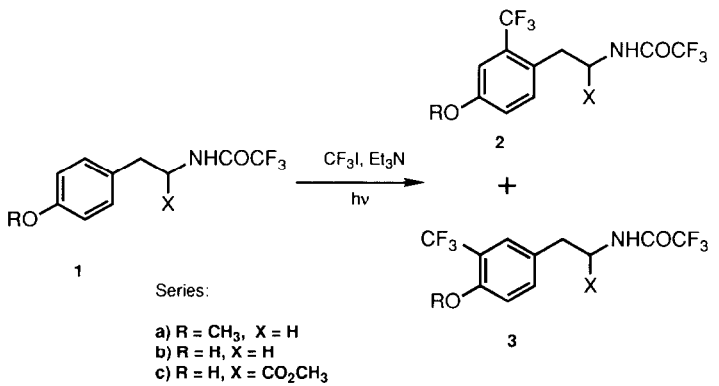
*This is consistent with the relatively large upfield shift of an aromatic proton *ortho* to a methoxyl group.

at 7.14 ppm in **2a** and at 7.43 ppm in **3a**, respectively, demonstrating the presence of a 3-ArH in **2a** and a 2-ArH in **3a**.

Initial attempts to prepare the trifluoromethylated tyramine analog **3b** by demethylation of **3a** have been thwarted by the extreme acid sensitivity of the trifluoromethyl group in this series [5f]. We were thus gratified to find that direct trifluoromethylation of free phenols could be carried out under these conditions with no apparent degradation of the trifluoromethyl group. Using conditions similar to that described above, *N*-trifluoroacetyltyramine (**1b**) gave *N*-trifluoroacetyl-3-trifluoromethyltyramine (**3b**) in 47% yield. A small amount of the isomeric *N*-trifluoroacetyl-2-trifluoromethyltyramine (**2b**) was detected by ^{19}F NMR and GC–MS methods. The ^{19}F NMR spectrum showed a **2b**/**3b** ratio of 6:94. A combination of steric and electronic factors presumably combine to produce the greater selectivity seen in the trifluoromethylation of **1b** over **1a**. The greater polarity of **2b** and **3b** (vis à vis **2a** and **3a**) made chromatographic separation difficult, and we were unable to isolate the minor isomer.

While the previously demonstrated lability of trifluoromethylphenols to basic hydrolysis would suggest that the stability of **3b** under these basic reaction conditions is surprising, we can note that the rate of alcoholysis of trifluoromethylimidazoles is almost 200-fold less than the rate of hydrolysis [3]. Furthermore, during the reaction, the triethylamine is rapidly consumed by the HI generated, and product exposure to basic solutions becomes minimal. A kinetic study of the alkaline hydrolysis and alcoholysis of **3b** is in progress.

N-Trifluoroacetyl-L-tyrosine methyl ester (**1c**) was converted to the 2- and 3-trifluoromethyl analog **2c** and **3c** in a 5:95 ratio at an overall yield of 33%. Commercially available (Aldrich) *N*-acetyltyrosine ethyl ester gave comparable results, but the chromatographic separation of these more polar products proved to be more difficult.



Deprotection of the side-chain of phenethylamines and amino acids has proven to be difficult, with both acidic and basic conditions leading to hydrolysis of the trifluoromethyl group to give carboxylic acid derivatives.

Work is underway to design neutral conditions, such as enzymatic hydrolysis, whereby this can be achieved.

Experimental

General

Solution of CF_3I in methanol were prepared by passing CF_3I into methanol until the required weight of gas had been absorbed. Solutions in methanol were irradiated in a quartz ampoule using a low-pressure mercury lamp (60 W) with a Vycor filter. Reactions were followed by direct analysis using GC–MS (Simadzu 7000, 3 mm×3 m glass column packed with 1.5% silicone OV-17 Chromosorb WAW DMCS 80–100 mesh: He 30 ml min^{-1}; total ion monitor) and/or ^{19}F NMR spectroscopy (Hitachi R20b, 56.5 MHz, trifluoroacetic acid as external standard). ^1H NMR spectra were measured on a Hitachi R-22 90 MHz spectrometer in acetone-d_6 with TMS as an internal standard. Positive chemical shifts are downfield from the reference peaks.

N-*trifluoroacetyl-4-methoxyphenethylamine (**1a**)*

4-Methoxyphenethylamine (15.12 g, 0.100 mol) was added in small portions to 100 ml trifluoroacetic anhydride with stirring. After the solution was stirred at ambient temperature for 2 h, the excess trifluoroacetic anhydride was removed under reduced pressure and the residual material dissolved in 100 ml methanol. The methanolic solution was heated at reflux for 1 h, cooled and evaporated under reduced pressure to give a yellowish oil which crystallized on standing. Recrystallization from benzene/cyclohexane gave 22.6 g (91.4%) of **1a** as colorless needles, m.p. 84.5–85 °C (lit. value [10]: m.p., 82.5–84 °C).

Using a similar procedure, tyramine produced *N*-trifluoroacetyltyramine (**1b**) as needles from aqueous ethanol, m.p. 148.5–149 °C (lit. value [11]: 151 °C) and tyrosine methyl ester gave *N*-trifluoroacetyltyrosine methyl ester (**1c**) as colorless grains from chloroform, m.p. 139.5–140 °C (lit. value [12]: 137–138.5 °C).

Photochemical trifluoromethylation of N-*trifluoroacetyl-4-methoxyphenethylamine (**1a**)*

A solution of **1a** (12.36 g, 0.050 mol), triethylamine (2.53 g, 0.025 mol) and CF_3I (4.90 g, 0.025 mol) in methanol (25 ml) was irradiated for 3d. ^{19}F NMR analysis showed product peaks at 18.0 ppm (**2a**) and 15.2 ppm (**3a**) in a 15:85 ratio. GC–MS analysis (160 °C) showed the presence of peaks at RT 4.8 min (*m/e* 315 M^+, **2a**), at 6.9 min (*m/e* 247 M^+, **1a**) and at 8.2 min (*m/e* 315 M^+, **3a**). The solvent was evaporated and the residue eluted through a silica gel column (180 ml; 1.0–3.0×50 cm column) with hexane/benzene/methanol (75:24:1). The fractions containing products

were pooled and rechromatographed on smaller silica gel columns to give 0.57 g (5.3%) of *N*-trifluoroacetyl-4-methoxy-2-trifluoromethylphenethylamine (**2a**): colorless needles from benzene/cyclohexane, m.p., 70–71 °C. MS *m/e* (relative intensity): 315 (11.4) M^+; 272 (4.5); 256 (6.4); 202 (92.3); 189 (100) $M^+ - CH_2NHCOCF_3$. ^1H NMR δ: 3.81 (s, 3H, $ArOCH_3$); 3.01 (t, 2H, J = 7Hz, α-CH_2); 3.54 (t, 2H, $J = 7$ Hz, β-CH_2); 7,14 (s, 1H, 3-ArH); 7.10 (AB q, 1H, $J = 8$ Hz, 5-ArH); 7.34 (AB q, 1H, $J = 8$ Hz, 6-ArH); 8.5 (broad s, 1H, NH) ppm. ^{19}F NMR δ: 1.5 (s 3F, CF_3CO); 18.2 (s, 3F, 2-ArCF_3) ppm. Anal.: Calcd. for $C_{12}H_{11}F_6NO_2$: C, 45.72; H, 3.52; N, 4.44%. Found: C, 45.81; H, 3.49, N, 4.47%.

There was also obtained 2.29 g (29.1%) of **3a** as colorless needles from benzene/cyclohexane, m.p., 105–106 °C. MS *m/e* (relative intensity): 315 (6.7) M^+; 296 (5.6); 202 (100) $M^+ - NH_2COCF_3$; 189 (85.1); 155 (13.3); 128 (10.3). ^1H NMR δ: 3.89 (s, 1H, $ArOCH_3$); 2.90 (t, 2H, $J = 7$Hz, α-CH_2); 3.55 (t, 2H, $J = 7$ Hz, β-CH_2); 7.43 (s, 1H, 2-ArH); 6.84 (AB q, 1H, $J =$ 8 Hz, 5-ArH); 7.12 (AB q, 1H, 6-ArH); 8.5 (broad s, 1H, NH) ppm. ^{19}F NMR δ; 1.3 (s, 3F, $COCF_3$); 15.5 (s, 3F, 3-ArCF_3) ppm. Anal.: Calcd. for $C_{12}H_{11}F_6NO_2$: C, 45.72; H, 3.52; N, 4.44%. Found: C, 45.82; H, 3.54; N, 4.40%.

Photochemical trifluoromethylation of N-*trifluoroacetyltyramine (**1b**)*

A solution of **1b** (11.66 g, 0.050 mol), triethylamine (2.53 g, 0.025 mol) and CF_3I (4.90 g, 0.025 mol) in methanol (40 ml) was irradiated for 5 d. At this time the ^{19}F NMR spectrum showed a large peak at 15.2 ppm and four small peaks in the range of 14–18 ppm. GC–MS showed the presence of peaks at RT 2.5 min (*m/e* 301 M^+) and at 3.5 min (*m/e* 233 M^+) in a 18:82 ratio. The solvent was evaporated and the residue eluted through a silica gel column (200 ml; 3.0×30 cm column) with ether. Evaporation of the eluant and recrystallization of the residue from benzene gave 6.50 g of the starting material. Analysis of the mother liquor by GC–MS showed products at RT 2.6 min (56.9% of total) identified as **3b**, RT 3.6 min (4.5%, **2b**), RT 2.1 min (1.5%, bis-CF_3, *m/e* 369 M^+), along with **1b** at RT 4.0 min (36%) and a small unidentified peak at RT 7.1 min (1.1%). The **2b**:**3b** ratio estimated by ^{19}F NMR spectroscopy was 6:94. The solvent was removed and the residue chromatographed on a silica gel column (180 ml, 1.0–3.0×50 cm column, eluted with dichloromethane/ether, 98:2) to give 3.53 g (46.9%) of **3b** as colorless plates recrystallized from dichloromethane, m.p., 108.5–109 °C. MS *m/e* (relative intensity): 301 (1.4) M^+; 282 (7.1) $M^+ - F$; 188 (100) M^+-CF_3CONH_2; 175 (28.5); 168 (46.1); 155 (92.2). ^1H NMR δ: 2.88 (t, 2H, $J = 7$ Hz, α-CH_2); 3.58 (t–d, 2H, $J = 7$ Hz, β-CH_2); 7.00 (AB q, 1H, $J = 8$ Hz, 5-ArH); 7.31 (AB q, 1H, $J = 8$ Hz, 6-ArH); 7.39 (s, 1H, 2-ArH); 8.46 (broad, s, 1H, NH) ppm. ^{19}F NMR δ: 1.3 (s, 3F, $COCF_3$); 15.5 (s, 3F, 3-ArCF_3) ppm. The bis-CF_3 product and **2b** could not be isolated because of their low yields and similar chromatographic behaviour to **2b** and **1b**. Anal.: Calcd. for $C_{11}H_9F_6NO_2$; C, 43.87; H, 3.01; N, 4.65%. Found: C, 43.92; H, 3.02; N, 4.65%.

Photochemical trifluoromethylation of N-*trifluoroacetyl-*L-*tyrosine methyl ester* (**1c**)

A solution of **1c** (29.12 g, 0.100 mol), triethylamine (5.06 g, 0.05 mol) and CF_3I (9.80 g, 0.05 mol) in methanol (40 ml) was irradiated as above for 3 d. ^{19}F NMR spectroscopy showed a large peak at 15.0 ppm (**3c**) and a very small peak (5%) at 18.1 ppm (**2c**). GC–MS (180 °C) showed two product peaks (*m/e* 359 M^+) at RT 4.2 min (**3c**) and 8.0 min (**2c**) and **1c** at RT 8.5 min. The solvent was evaporated and the residue was separated on a silica gel column (200 ml, 1.0–3.0×50 cm column, eluted with ethyl acetate). The products and **1c** were eluted in four early fractions without separation. These fractions were combined and rechromatographed on the same column eluted with dichloromethane. There was obtained 3.23 g (18.0%) of **3c** as colorless needles from chloroform, m.p., 173–173.5 °C. MS *m/e* (relative intensity): 359 (0.5) M^+; 340 (4.3); 300 (5.1); 280 (12.8); 246 (61.4); 215 (18.7); 175 (79.2); 155 (100); 127 (22.7). ^1H NMR δ: 3.72 (ss 3H, OCH_3); 3.07 (AB q–d, 1H, J=15 Hz, 9 Hz, β-C*H*H); 3.27 (AB q–d, 1H, J=15 Hz, 6 Hz, β-CH*H*); 4.78 (t–d, 1H, J=9 Hz, 6Hz, α-C*H*); 6.99 (Ab q, 1H, J=8 Hz, 5-Ar*H*); 7.34 (Ab q–d, 1H, J=8 Hz, 2 Hz, 6-Ar*H*); 7.43 (d, 1H, J=2 Hz, 2-Ar*H*); 8.65 (broad d, 1H, J=9 Hz, N*H*) ppm. ^{19}F NMR δ: 1.6 (s, 3F, $COCF_3$); 15.4 (s, 3F, 3-ArCF_3) ppm. Anal.: Calcd. for $C_{13}H_{11}F_6NO_4$: C, 43.47; H, 3.09; N, 3.90%. Found; C, 43.54; H, 3.09; N, 3.88%.

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