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Fluoro organics: synthesis of novel fluorinated 4-oxo-4*H*-pyrido[3′,2′:4,5]furo[3,2-*d*]-1,3-oxazines and their reactions ☆

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Abstract

Novel fluorinated 4-oxo-4*H*-pyrido[3′,2′:4,5]furo[3,2-*d*]-1,3-oxazines have been synthesised from 2-carbethoxy-3-amino-4-trifluoromethyl-6-aryl-substituted furo[2,3-*b*]pyridines via intermediates such as 2-carboxy-3-amino-4-trifluoromethyl-6-aryl-substituted furo[2,3-*b*]pyridines and 2-carboxy-3-trifluoroacetylamino-4-trifluoromethyl-6-aryl-substituted furo[2,3-*b*]pyridines. The CF_3 group induces changes in the reactivity in the molecule and the consequent regioselective attack of nucleophiles on the oxazine ring have been studied and utilized for mechanistic interpretation.

Keywords: Fluoro organics; Synthesis; Fluorinated oxopyridofuro-oxazines; NMR spectroscopy; IR spectroscopy; Mass spectrometry

1. Introduction

In continuation of our work on the synthesis of fluorinated heterocycles [1–4] of biological interest, our attention has been attracted towards the synthesis of pyrido-[3′,2′:4,5]furo[3,2-*d*]-1,3-oxazines by utilizing furo-[2,3-*b*]pyridines (**1**) [4] having two active functional groups *ortho* to each other.

2. Experimental details

2.1. General

Melting points were determined in open glass capillaries on a Mettler FP51 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometer with TMS as internal standard. IR spectra were recorded on a Pye–Unicam SP3-200 infrared spectrometer. Mass spectra were recorded on a VG Micromass 7070H instrument. Elemental analyses were carried out on a Perkin-Elmer 240B apparatus.

2.2. Starting materials

The 2-carbethoxy-3-amino-4-trifluoromethyl-6-aryl-substituted furo[2,3-*b*]pyridines were prepared according to the reported procedure [4]. All other reagents were obtained from commercial sources and employed as supplied.

2.3. Preparation of 2-carboxy-3-amino-4-trifluoromethyl-6-aryl-substituted furo[2,3-*b*]pyridines (**2a–d**): general procedure

The 2-carbethoxy-3-amino-4-trifluoromethyl-6-aryl-substituted furo[2,3-*b*]pyridines (0.001 mol) were suspended in potassium hydroxide solution (10%, 10 ml) and heated to reflux for 2 h at 100 °C with stirring. The reaction mixture was cooled to room temperature, diluted with water and neutralised with concentrated hydrochloric acid until acidic to litmus paper. The separated solid product was filtered, washed with cold water and dried. The dried product was purified by washing three times with n-hexane.

2-Carboxy-3-amino-4-trifluoromethyl-6-phenyl furo[2,3-*b*]pyridine (**2a**): yield, 0.272 g (84.5%); m.p. 156.8 °C. ^{1}H NMR (DMSO-d_6) δ: 5.8 (br., s, 2H, NH_2); 7.20 (s, 1H, H–C(5)); 7.25 (d, 2H, aromatic H); 7.55 (m, 3H, aromatic H); 10.9 (s, 1H, –COOH) ppm. IR (KBr) (cm^{-1}): 3300–3650; 1720. MS M^+, *m/z*: 322 (M^+, base peak); 304 ($M^+ - H_2O$); 278 ($M^+ - CO_2$); 248 ($278 - CH_2O$); 229

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(248 − F); 179 (248 − CF_3); 77 (C_6H_5). Analysis: Found for $C_{15}H_9F_3N_2O_3$: C, 55.98; H, 2.94; N, 8.73%. Calculated: C, 55.91; H, 2.81; N, 8.69%.

2-Carboxy-3-amino-4-trifluoromethyl-6-*p*-tolyl furo[2,3-*b*]pyridine (**2b**): yield, 0.305 g (90.8%); m.p. 178.2 °C. ^{1}H NMR (DMSO-d_6) δ: 2.45 (s, 3H, CH_3); 5.37 (br., s, 2H, NH_2); 7.32 (d, 2H, aromatic H); 7.95 (s, 1H, H–C(5)); 8.05 (d, 2H, aromatic H); 10.93 (s, 1H, –COOH) ppm. IR (KBr) (cm^{-1}): 3250–3600; 1728. MS M^+, *m/z*: 336 (M^+, base peak); 318 ($M^+ - H_2O$); 292 ($M^+ - CO_2$); 262 (292 − CH_2O); 243 (262 − F); 193 (262 − CF_3). Analysis: Found for $C_{16}H_{11}F_3N_2O_3$: C, 57.17; H, 3.32; N, 8.42%. Calculated: C, 57.15; H, 3.29; N, 8.33%.

2-Carboxy-3-amino-4-trifluoromethyl-6-*p*-anisyl furo-[2,3-*b*]pyridine (**2c**): yield, 0.301 g (85.6%); m.p. 163.1 °C. ^{1}H NMR (DMSO-d_6) δ: 3.84 (s, 3H, OCH_3); 5.35 (br., s, 2H, NH_2); 7.30 (d, 2H, aromatic H); 7.92 (s, 1H, H–C(5)); 8.0 (d, 2H, aromatic H); 10.91 (s, 1H, –COOH) ppm. IR (KBr) (cm^{-1}): 3250–3600; 1728. MS M^+, *m/z*: 352 (M^+, base peak); 334 ($M^+ - H_2O$); 308 ($M^+ - CO_2$); 278 (308 − CH_2O); 249 (278 − F); 209 (278 − CF_3). Analysis: Found for $C_{16}H_{11}F_3N_2O_4$: C, 54.61; H, 3.18; N, 7.98%. Calculated: C, 54.55; H, 3.14; N, 7.95%.

2-Carboxy-3-amino-4-trifluoromethyl-6-*p*-chlorophenyl furo[2,3-*b*]pyridine (**2d**): yield, 0.310 g (87.3%); m.p. 157.7 °C. ^{1}H NMR (DMSO-dC_6) δ: 5.40 (br., s, 2H, NH_2); 7.50 (d, 2H, aromatic H); 8.0 (s, 1H, H–C(5)); 8.15 (d, 2H, aromatic H); 11.02 (s, 1H, –COOH) ppm. IR (KBr) (cm^{-1}): 3200–3600; 1720. MS M^+, *m/z*: 356 (M^+, base peak); 338 ($M^+ - H_2O$); 312 ($M^+ - CO_2$); 282 (312 − CH_2O); 263 (282 − F); 247 (282 − Cl); 228 (247 − F). Analysis: Found for $C_{15}H_8ClF_3N_2O_3$: C, 50.56; H, 2.31; N, 7.88%. Calculated: 50.51; H, 2.26; N, 7.85%.

*2.4. Preparation of 2-carboxy-3-trifluoroacetylamino-4-trifluoromethyl-6-aryl-substituted furo[2,3-b]pyridines (**4a–c**): general procedure*

The 2-carboxy-3-amino-4-trifluoromethyl-6-aryl-substituted furo[2,3-*b*]pyridines (0.001 mol) were taken up in trifluoroacetic anhydride (4 ml) when the reaction mixture became homogeneous and solid then separated. The resultant reaction mixture after refluxing for 2 h at 40 °C, i.e. at the boiling point of trifluoroacetic anhydride, was cooled with ice water and poured into crushed ice. The product was filtered washed with water and dried.

2-Carboxy-3-trifluoroacetylamino-4-trifluoromethyl-6-phenyl furo[2,3-*b*]pyridine (**4a**): yield, 0.353 g (84.6%); m.p. 240.2 °C. ^{1}H NMR (DMSO-d_6) δ: 7.55 (m, 3H, aromatic H); 9.20 (s, 1H, NH); 8.15 (s, 1H, H–C(5)); 8.17 (d, 2H, aromatic H); 10.95 (s, 1H, –COOH) ppm. IR (KBr) (cm^{-1}): 3250–3570; 1745. MS M^+, *m/z*: 418 (M^+, base peak); 374 ($M^+ - CO_2$); 349 ($M^+ - CF_3$); 331 (349 − H_2O); 305 (349 − CO_2); 69 (CF_3). Analysis: Found for $C_{17}H_8F_6N_2O_4$: C, 48.86; H, 1.98; N, 6.73%. Calculated: C, 48.80; H, 1.92; N, 6.69%.

2-Carboxy-3-trifluoroacetylamino-4-trifluoromethyl-6-*p*-tolyl furo[2,3-*b*]pyridine (**4b**): yield, 0.397 g (92.1%); m.p. 244.7 °C. H NMR (DMSO-d_6) δ: 2.45 (s, 3H, CH_3); 7.36 (d, 2H, aromatic H); 9.17 (s, 1H, NH); 8.07 (d, 2H, aromatic H); 8.10 (s, 1H, H–C(5)); 10.95 (s, 1H, –COOH) ppm. IR (KBr) (cm^{-1}); 3200–3600; 1740. MS M^+, *m/z*: 432 (M^+); 414 ($M^+ - H_2O$); 388 ($M^+ - CO_2$, base peak); 345 ($M^+ - CF_3$); 319 ($M^+ - CF_3$ and CO_2); 69 (CF_3). Analysis: Found for $C_{18}H_{10}F_6N_2O_4$: C, 50.13; H, 2.36; N, 6.51%. Calculated: C, 50.00; H, 2.31; N, 6.48%.

2-Carboxy-3-trifluoroacetylamino-4-trifluoromethyl-6-*p*-chlorophenyl furo[2,3-*b*]pyridine (**4c**): yield, 0.373 g (82.6%); m.p. 227.1 °C. ^{1}H NMR (DMSO-d_6) δ: 7.61 (d, 2H, aromatic H); 9.22 (s, 1H, NH); 8.21 (s, 1H, H–C(5)); 8.28 (d. 2H, aromatic H); 10.95 (s, 1H, –COOH) ppm. IR (KBr) (cm^{-1}): 3250–3510; 1745. MS M^+, *m/z*: 452 (M^+, base peak); 434 ($M^+ - H_2O$); 408 ($M^+ - CO_2$); 339 ($M^+ - CF_3$ and CO_2); 311 (339 − CO); 304 (339 − Cl); 111 (C_6H_4Cl); 69 (CF_3). Analysis: Found for $C_{17}H_7ClF_6N_2O_4$: C, 45.16 H, 1.18; N, 6.22%. Calculated: C, 45.10; H, 1.55; N, 6.18%.

*2.5. Preparation of 2,7-disubstituted-9-trifluoromethyl-4-oxo-4H-pyrido[3′,2′:4,5]furo[3,2-d]-1,3-oxazines (**3a–c** and **5a–c**): general procedure*

The 2-carboxy-3-amino-4-trifluoromethyl-6-aryl-substituted furo[2,3-*b*]pyridines (0.001 mol) (for compounds **3a–c**) and 2-carboxy-3-trifluoroacetylamino-4-trifluoromethyl-6-aryl-substituted furo[2,3-*b*]pyridines (0.001 mol) (in the case of compounds **5a–c**) were taken up in acetic anhydride (4 ml), heated to 110 °C and stored for 2 h with stirring. The reaction mixture was cooled to room temperature and poured into crushed ice. The separated solid product was filtered, washed with cold water and dried.

2-Methyl-7-phenyl-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]furo[3,2-*d*]-1,3-oxazine (**3a**): yield, 0.274 g (79.4%); m.p. 198.0 °C. ^{1}H NMR ($CDCl_3$) δ: 2.60 (s, 3H, CH_3–C(2)); 7.55 (m, 3H, aromatic H); 8.10 (d, 2H, aromatic H); 8.20 (s, 1H, H–C(8)) ppm. IR ($CHCl_3$) (cm^{-1}): 1770; 1590; 1370; 1120. MS M^+, *m/z*: 346 (M^+, base peak); 331 ($M^+ - CH_3$); 302 ($M^+ - CO_2$); 277 ($M^+ - CF_3$); 69 (CF_3). Analysis: Found for $C_{17}H_9F_3N_2O_3$:C, 58.93; H, 2.63; N, 8.13%. Calculated: C, 58.90; H, 2.61; N, 8.09%.

2-Methyl-7-*p*-tolyl-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]furo[3,2-*d*]-1,3-oxazine (**3b**): yield, 0.335 g (93.3%); m.p. 238.0 °C. ^{1}H NMR ($CDCl_3$) δ: 2.45 (s, 3H, CH_3); 2.62 (s, 3H, CH_3–C(2)); 7.38 (d, 2H, aromatic H); 8.09 (s, 1H, H–C(8)); 8.15 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 1765; 1590; 1370; 1125. MS M^+, *m/z*: 360 (M^+, base peak), 345 ($M^+ - CH_3$); 316 ($M^+ - CO_2$); 291 ($M^+ - CF_3$); 69 (CF_3). Analysis: Found for $C_{18}H_{11}F_3N_2O_3$: C, 60.11; H, 3.09; N, 7.81%. Calculated: C, 60.00; H, 3.06; N, 7.77%.

2-Methyl-7-*p*-clorophenyl-9-trifluoromethyl-4-oxo-4*H*-pyrido[3′,2′:4,5]furo[3,2-*d*]-1,3-oxazine (**3c**): yield, 0.329

g (86.8%); m.p. 231.0 °C. ^{1}H NMR ($CDCl_3$) δ: 2.62 (s, 3H, CH_3–C(2)); 7.53 (d, 2H, aromatic H); 8.15 (m, 1H, H–C(8); (2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 1770; 1580; 1370; 1120. MS M^+ *m/z*: 380 (M^+, base peak); 365 ($M^+ - CH_3$); 336 ($M^+ - CO_2$); 311 ($M^+ - CF_3$); 69 (CF_3). Analysis: Found for $C_{17}H_8ClF_3N_2O_3$: C, 53.68; H, 2.17; N, 7.39%. Calculated: C, 53.60; H, 2.11; N, 7.35%.

2,9-Bis(trifluoromethyl)-7-phenyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]furo[3,2-*d*]-1,3-oxazine (**5a**): yield, 0.292 g (73.2%); m.p. 215.0 °C. ^{1}H NMR ($CDCl_3$) δ: 7.6 (m, 3H, aromatic H); 8.2 (m, 2H, aromatic H); 8.29 (s, 1H, H–C(8)) ppm. IR ($CHCl_3$) (cm^{-1}): 1800; 1610; 1360; 1170. MS M^+, *m/z*: 400 (M^+, base peak); 381 ($M^+ - F$); 331 ($M^+ - CF_3$); 323 ($M^+ - C_6H_5$); 77 (C_6H_5); 69 (CF_3). Analysis: Found for $C_{17}H_6F_6N_2O_3$: C, 51.13; H, 1.56; N, 6.71%. Calculated: C, 51.00; H, 1.51; N, 6.99%.

2,9-Bis(trifluoromethyl)-7-*p*-tolyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]furo[3,2-*d*]-1,3-oxazine (**5b**): yield, 0.364 g (88.0%); m.p. 222.0 °C. ^{1}H NMR ($CDCl_3$) δ: 2.51 (s, 3H, CH_3); 7.40 (d, 2H, aromatic H); 8.12 (d, 2H, aromatic H); 8.25 (s, 1H, H–C(8)) ppm. IR ($CHCl_3$) (cm^{-1}): 1810; 1605; 1360; 1170. MS M^+, *m/z*: 414 (M^+, base peak); 399 ($M^+ - CH_3$); 395 ($M^+ - F$); 345 ($M^+ - CF_3$); 323 ($M^+ - C_6H_4CH_3$); 69 (CF_3). Analysis: Found for $C_{18}H_8F_6N_2O_3$: C, 52.14; H, 1.98; N, 6.79%. Calculated: C, 52.10; H, 1.94; N, 6.76%.

2,9-Bis(trifluoromethyl)-7-*p*-chlorophenyl-4-oxo-4*H*-pyrido[3′,2′:4,5]furo[3,2-*d*]-1,3-oxazine (**5c**): yield, 0.401 g (92.6%); m.p. 181.0 °C. ^{1}H NMR ($CDCl_3$) δ: 7.49 (d, 2H, aromatic H); 8.15 (d, 2H, aromatic H); 8.23 (s, 1H, H–C(8)) ppm. IR ($CHCl_3$) (cm^{-1}): 1810; 1615; 1365; 1165. MS M^+, *m/z*: 434 (M^+, base peak); 415 ($M^+ - F$); 365 ($M^+ - CF_3$); 323 ($M^+ - C_6H_4Cl$); 69 (CF_3). Analysis: Found for $C_{17}H_5ClF_6N_2O_3$: C, 46.94; H, 1.18; N, 6.49%. Calculated: C, 46.90; H, 1.15; N, 6.44%.

*2.6. Preparation of 2-piperidinoyl-3-acetylamino-4-trifluoromethyl-6-aryl-substituted furo[2,3-b]pyridines (**6a–c**): general procedure*

Compounds **3a–c** (0.003 mol) were dissolved in toluene (8 ml) and piperidine (0.3 ml) was added. The reaction mixture was refluxed for 4 h with stirring at 110 °C. The toluene was removed under vacuum and the residue washed repeatedly with n-hexane to remove excess piperidine. The separated solid products (**6a–c**) were dried.

2-Piperidinoyl-3-acetylamino-4-trifluoromethyl-6-phenyl furo[2,3-*b*]pyridine (**6a**): yield, 0.953 g (73.9%); m.p. 204.5 °C. ^{1}H NMR ($CDCl_3$) δ: 1.68 (s, 6H, $-CH_2-CH_2-CH_2$); 2.2 (s, 3H, $COCH_3$); 3.4–3.7 (br, d, 4H, $N<^{CH_2-}_{CH_2-}$); 7.2 (d, 2H, aromatic H); 7.75 (m, 2H, aromatic H, 1H, H–C(5)); 8.65 (s, 1H, NH) ppm. IR (KBr) (cm^{-1}): 3200; 1690; 1600; 1260. MS M^+, *m/z*: 431 (M^+); 278 ($M^+ - N$⟨⟩, CO); 84 ($C_5H_{10}N$, base peak); 77 (C_6H_5); 69 (CF_3). Analysis: Found for $C_{22}H_{20}F_3N_3O_3$: C, 60.90; H, 4.08; N, 9.10%. Calculated: C, 61.25; H, 4.67; N, 9.74%.

2-Piperidinoyl-3-acetylamino-4-trifluoromethyl-6-*p*-tolyl furo[2,3-*b*]pyridine (**6b**): yield, 1.2 g (91.0%); m.p. 211.5 °C. ^{1}H NMR ($CDCl_3$) δ: 1.74 (s, 6H, $-CH_2-CH_2-CH_2$); 2.25 (s, 3H, CH_3); 2.45 (s, 3H, $COCH_3$); 3.6–3.7 (br., d, 4H, $N<^{CH_2-}_{CH_2-}$); 7.2 (d, 2H, aromatic H); 7.87 (m, 2H, aromatic H and 1H, H–C(5)); 8.25 (s, 1H, NH) ppm. IR (KBr) (cm^{-1}); 3250; 1700; 1610; 1260. MS M^+, *m/z*: 445 (M^+); 403 ($M^+ - CH_2CO$); 320 (403 − N⟨⟩); 292 (320 − CO); 84 ($C_5H_{10}N$, base peak). Analysis: Found for $C_{23}H_{22}F_3N_3O_3$: C, 61.92; H, 4.45; N, 9.09%. Calculated: C, 62.01; H, 4.97; N, 9.43%.

2-Piperidinoyl-3-acetylamino-4-trifluoromethyl-6-*p*-chlorophenyl furo[2,3-*b*]pyridine (**6c**): yield, 1.20 g (86.8%); m.p. 197.2 °C. ^{1}H NMR ($CDCl_3$) δ: 1.63 (s, 6H, $-CH_2-CH_2-CH_2$); 2.16 (s, 3H, $COCH_3$); 3.48–3.70 (br., d, 4H, $N<^{CH_2-}_{CH_2-}$); 7.37 (d, 2H, aromatic H); 7.88 (d, 2H, aromatic H); 7.90 (s, 1H, H–C(5)); 8.28 (s, 1H, NH) ppm. IR (KBr) (cm^{-1}): 3230; 1700; 1600; 1250. MS M^+, *m/z*: 465 (M^+); 422 ($M^+ - COCH_3$); 311 (422 − C_6H_4Cl); 84 ($C_5H_{10}N$, base peak). Analysis: Found for $C_{22}H_{19}ClF_3N_3O_3$: C, 56.54; H, 4.04; N, 9.09%. Calculated: C, 56.72; H, 4.11; N, 9.11%.

*2.7. Preparation of 2-carbohydrazide-3-acetylamino-4-trifluoromethyl-6-phenyl furo[2,3-b]*pyridine (*7*)

Compound **3a** (0.13 g, 0.00034 mol) was dissolved in ethanol (12 ml) and hydrazine hydrate (5 ml) added. The reaction mixture was refluxed for 6 h while stirring, cooled and poured into crushed ice. The separated solid product was filtered, washed with water and dried. Yield, 0.105 g (82.3%); m.p. 153.8 °C. ^{1}H NMR ($CDCl_3$) δ: 2.81 (s, 3H, CH_3); 4.3 (br., s, 2H, N–NH_2); 5.09 (s, 1H, $NHCOCH_3$); 7.52 (m, 3H, aromatic H); 7.95 (s, 1H, H–C(5)); 8.1 (m, 2H, aromatic H) ppm. IR (KBr) (cm^{-1}): 3320; 1710; 1600; 1270. MS M^+, *m/z*: 378 (M^+); 336 ($M^+ - CH_2CO$); 305 (336 − $NHNH_2$); 277 (305 − CO, base peak); 77 (C_6H_5); 69 (CF_3). Analysis: Found for $C_{17}H_{13}F_3N_4O_3$: C, 53.65; H, 3.28; N, 14.62%. Calculated: C, 53.97; H, 3.46; N, 14.80%.

2.8. Preparation of 2-methyl-3-amino-7-phenyl-9-trifluoromethyl-4-oxo-4H-pyrido[3′,2′:4,5]furo[3,2-d]-1,3-pyrimidine (8) [4]

Compound **13** (0.3 g, 0.0007 mol) was dissolved in ethanol (20 ml) and hydrazine hydrate (4 ml) added. The reaction mixture was refluxed for 8 h with stirring, cooled and poured into crushed ice. The separated solid product was filtered, washed with water and dried. The product was char-

acterised as compound **8**. Yield, 0.126 g (50.1%); m.p. 243.0 °C.

2.9. Preparation of 2-carboxy-3(2-trifluoromethyl piperidinyl methyleneamino)-4-trifluoromethyl-6-aryl-substituted furo[2,3-b]pyridines (9a–c): general procedure

Compounds **5a–c** (0.0017 mol) were dissolved in toluene (10 ml) and piperidine (0.3 ml) added. The reaction mixture was refluxed for 4 h with stirring at 110 °C. The toluene was removed under vacuum and the residue repeatedly washed with n-hexane to remove excess piperidine. The separated solid products **9a–c** were dried and purified by passing through a column of Al_2O_3 in $CHCl_3$.

2-Carboxy-3(2-trifluoromethyl piperidinyl methyleneamino)-4-trifluoromethyl-6-phenyl furo[2,3-*b*]pyridine (**9a**): yield, 0.624 g (75.8%); m.p. 202.2 °C. ^{1}H NMR ($CDCl_3$) δ: 1.73 (s, 6H, $-CH_2-CH_2-CH_2$); 3.55–3.75 (br., d, 4H, N<(CH2– / CH2–)); 7.36 (d, 2H, aromatic H); 7.95 (m, 3H, aromatic H, 1H, H–C(5)); 10.9 (s, 1H, –COOH) ppm. IR (KBr) (cm^{-1}): 3530–3220; 1730; 1640; 1220. MS M^+, *m/z*: 485 (M^+); 416 ($M^+ - CF_3$); 84 ($C_5H_{10}N$, base peak); 77 (C_6H_5); 69 (CF_3). Analysis: Found for $C_{22}H_{17}F_6N_3O_3$: C, 54.70; H, 3.80; N, 8.80%. Calculated: C, 54.43; H, 3.53; N, 8.65%.

2-Carboxy-3(2-trifluoromethyl piperidinyl methyleneamino)-4-trifluoromethyl-6-*p*-tolyl furo[2,3-*b*]pyridine (**9b**): yield, 0.620 g (73.2%); m.p. 195.4 °C. ^{1}H NMR ($CDCl_3$) δ: 1.74 (s, 6H, $-CH_2-CH_2-CH_2$); 2.43, (s, 3H, CH_3); 3.54–3.80 (br., d, 4H, N<(CH2– / CH2–)); 7.17 (d, 2H, aromatic H); 7.83 (d, 2H, aromatic H); 7.98 (s, 1H, H–C(5)); 10.92 (s, 1H, –COOH) ppm. IR (KBr) (cm^{-1}): 3200; 1750; 1640; 1240. MS M^+, *m/z*: 499 (M^+); 430 ($M^+ - CF_3$); 415 ($430 - CH_3$); 84 ($C_5H_{10}N$, base peak); 69 (CF_3). Analysis: Found for $C_{23}H_{19}F_6N_3O_3$: C, 55.80; H, 3.90; N, 8.62%. Calculated: C, 55.30; H, 3.83; N, 8.41%.

2-Carboxy-3(2-trifluoromethyl piperidinyl methyleneamino)-4-trifluoromethyl-6-*p*-chlorophenyl furo[2,3-*b*]-pyridine (**9c**): yield, 0.677 g (76.8%); m.p. 192.7 °C. ^{1}H NMR ($CDCl_3$) δ: 1.71 (s, 6H, $-CH_2-CH_2-CH_2$); 3.55–3.79 (br., d, 4H, N<(CH2– / CH2–)); 7.42 (d, 2H, aromatic H); 7.95 (m, 2H, aromatic H, 1H, H–C(5)); 10.88 (s, 1H, –COOH) ppm. IR (KBr) (cm^{-1}): 3300; 1740; 1630; 1250. MS M^+, *m/z*: 519 (M^+); 408 ($M^+ - C_6H_4Cl$); 339 ($408 - CF_3$); 311 ($408 - COCF_3$); 84 ($C_5H_{10}N$, base peak); 69 (CF_3). Analysis: Found for $C_{22}H_{16}ClF_6N_3O_3$: C, 50.96; H, 3.30; N, 8.12%. Calculated: C, 50.83; H, 3.10; N, 8.08%.

2.10. Preparation of 2-carbohydrazide-3-amino-4-trifluoromethyl-6-phenylfuro[2,3-b]pyridine (10) [4]

Compound **11** (0.2 g, 0.004 mol) was dissolved in ethanol (20 ml) and hydrazine hydrate (5 ml) added. The reaction mixture was refluxed for 6 h with stirring, cooled and poured into crushed ice. The separated solid product was filtered, washed with water and dried. The product was characterised as compound **10**. Yield, 1.03 g (77.3%); m.p. 202.0 °C. The same compound **10** was also obtained when compound **5** was refluxed with hydrazine hydrate in ethanol.

2.11. Preparation of 2-carbethoxy-3-trifluoroacetylamino-4-trifluoromethyl-6-phenyl furo[2,3-b]pyridine (11)

Compound **1** (0.9 g, 0.0025 mol) was suspended in trifluoroacetic anhydride (4 ml), refluxed for 2 h, the mixture cooled and poured into crushed ice. The separated solid product was filtered, washed with water and dried. Yield, 0.939 g (84.3%); m.p. 160.7 °C. ^{1}H NMR ($CDCl_3$) δ: 1.42 (t, 3H, CH_3); 4.48 (q, 2H, CH_2); 7.52 (m, 3H, aromatic H); 8.3 (br., s, 1H, NH); 8.13 (m, 2H, aromatic H, 1H, H–C(5)) ppm. IR (KBr) (cm^{-1}): 3375; 2950; 1750; 1700. MS M^+, *m/z*: 446 (M^+, base peak); 418 ($M^+ - C_2H_4$); 401 ($M^+ - OC_2H_5$); 374 ($M^+ - C_6H_4$ and CO_2); 305 ($374 - CF_3$); 69 (CF_3). Analysis: Found for $C_{19}H_{12}F_6N_2O_4$: C, 51.40; H, 2.83; N, 6.37%. Calculated: C, 51.13; H, 2.70; N, 6.27%.

2.12. Preparation of 2-piperidinoyl-3-trifluoroacetylamino-4-trifluoromethyl-6-phenyl furo[2,3-b]pyridine (12)

Piperidine (5 ml) was added to compound **11** (0.28 g, 0.00057 mol), the reaction mixture heated to 100 °C and stored for 4 h with stirring. The ethanol formed and the excess piperidine were removed under vacuum and the residue washed with n-hexane. The separated solid product was dried under vacuum. Yield, 0.166 g (60.2%); m.p. 123.4 °C. ^{1}H NMR ($CDCl_3$) δ: 1.87 (s, 6H, $-CH_2-CH_2-CH_2$); 3.82–3.96 (br., d, 4H, N<(CH2– / CH2–)); 7.50 (d, 2H, aromatic H); 8.1 (m, 3H, aromatic H); 7.93 (s, 1H, H–C(5)); 9.25 (br., s, 1H, NH) ppm. IR ($CHCl_3$) (cm^{-1}): 3100; 1745; 1723; 1235. MS M^+, *m/z*: 485 (M^+); 401 ($M^+ - C_5H_{10}N$); 373 ($401 - CO$); 304 ($373 - CF_3$); 84 ($C_5H_{10}N$, base peak); 77 (C_6H_5); 69 (CF_3). Analysis: Found for $C_{22}H_{17}F_6N_3O_3$: C, 54.66; H, 3.84; N, 8.87%. Calculated: C, 54.43; H, 3.53; N, 8.65%.

2.13. Preparation of 2-carbethoxy-3-acetylamino-4-trifluoromethyl-6-phenyl furo[2,3-b]pyridine (13)

Compound **1** (0.5 g, 0.0014 mol) was taken up in acetic anhydride (4 ml) and refluxed for 2 h at 110 °C with stirring, then cooled and poured into crushed ice. The separated solid product was filtered, washed with water and dried. Yield, 0.473 g (86.3%); m.p. 153.6 °C. ^{1}H NMR ($CDCl_3$) δ: 1.4 (t, 3H, CH_3); 2.38 (s, 3H, $COCH_3$); 4.45 (q, 2H, CH_2); 7.52 (m, 3H, aromatic H); 8.13 (m, 2H, aromatic H, 1H,

H–C(5)) ppm. IR (KBr) (cm^{-1}): 3375; 2950; 1750; 1700. MS M^+, m/z: 392 (M^+); 350 ($M^+ - CH_2CO$, base peak), 277 ($350 - COOC_2H_5$). Analysis: Found for $C_{19}H_{15}F_3N_2O_4$: C, 58.23; H, 3.96; N, 7.21%. Calculated: C, 58.16; H, 3.85; N, 7.14%.

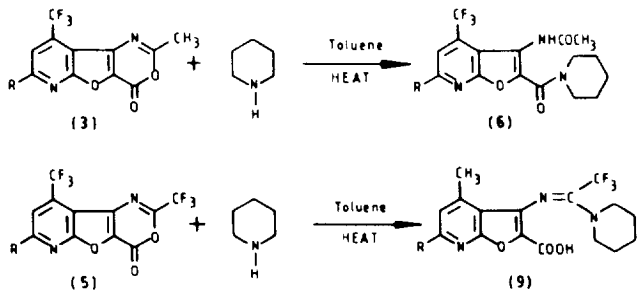
3. Results and discussion

The 2-carbethoxy-3-amino-4-trifluoromethyl-6-aryl-substituted furo[2,3-*b*]pyridines (**1**) were chosen as starting materials since they possess two functional groups *ortho* to each other. Hydrolysis of **1** in 10% potassium hydroxide gave compounds **2** which in turn gave a variety of products (**3**, **3′**, **4**, **5** and **5′**) under different conditions (Scheme 1).

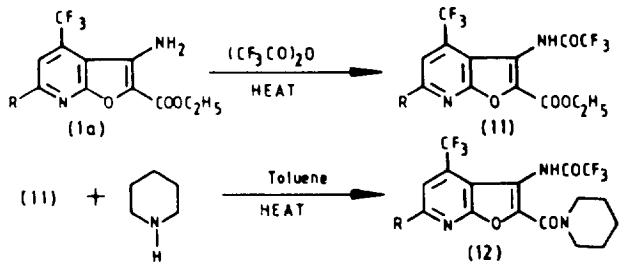
The mode of formation of the oxazines is through the initial acylation of the 3-amino function at low temperature followed by cyclisation to 1,3-oxazines at high temperature [5,6], as exemplified by the exclusive formation of intermediates **4** at 40 °C and cyclisation to **5** at 110 °C. Side-products (**3′** and **5′**) are formed in minor quantities by decarboxylation.

The CF_3 group induced changes in reactivity which have been realised in two respects: (1) regioselective attack of nucleophiles at the 2-position of the oxazine ring carrying the CF_3 group and (2) addition of hydrazine to $COCF_3$ in systems such as $RNHCOCF_3$ and subsequent fragmentation to RNH_2 and $CF_3CONHNH_2$. These two aspects have been well brought out in this work.

Compounds **3** and **5** were chosen to study the site of nucleophilic attack on the oxazine ring because they possess $-CH_3$ and $-CF_3$ groups at the C-2 position. When compounds **3** and **5** were reacted with piperidine in toluene, the products formed were **6** and **9**.

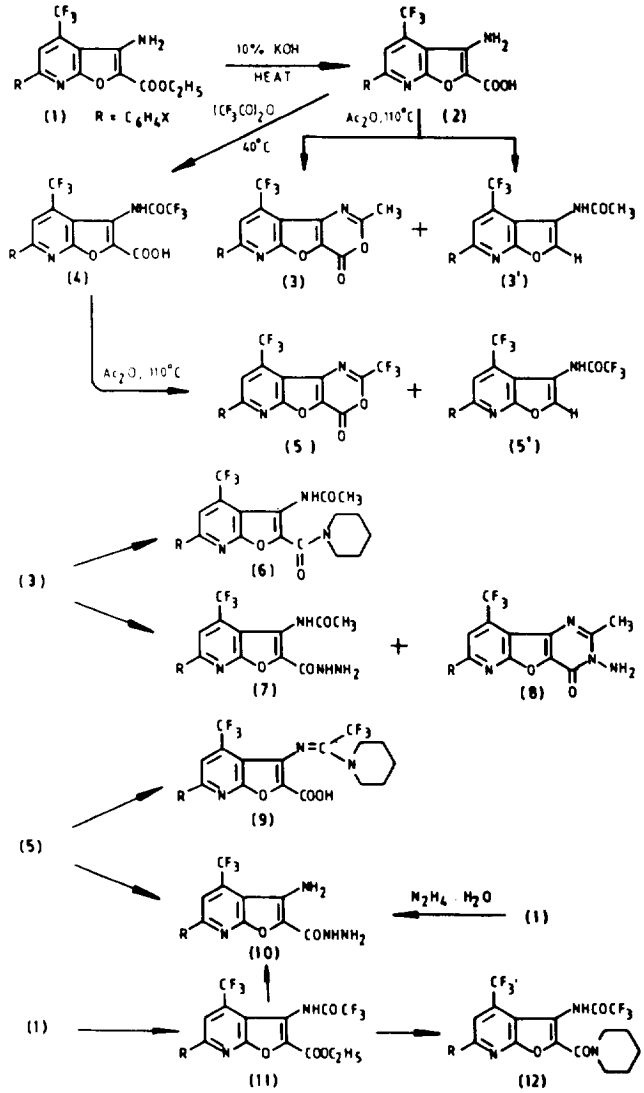


Compound **6** was formed as a result of attack on the carbonyl of the oxazine ring and **9** was formed due to attack at the 2-position. A compound with the alternate structure **12** for product **9** was prepared independently and shown to be different from **9**.



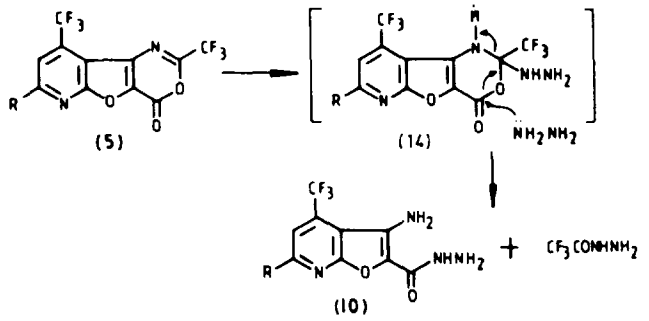
The differences in melting point, ^1H NMR spectra and mass spectra are discussed in the Experimental section as well as under the spectral discussion.

This established conclusively that the nucleophilic reagent regioselectively attacks the 2-position if it carries the CF_3 substituent, otherwise the seat of attack is the carbonyl of the oxazine ring. If a stronger base such as hydrazine hydrate was used, reaction with **5** led to the remarkable product **10** in



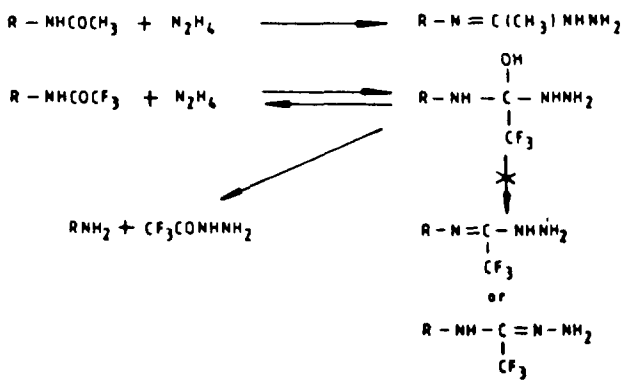
Scheme 1.

which the CF_3 at the 2-position was removed, while reaction with **3** followed a normal course producing **7** and **8**. Since product **10** could also be prepared from **1** [4], the structure of product **10** is thoroughly established. The mode of formation of **10** resolves the difference in reactivity of **5** and **3** towards hydrazine as depicted below:

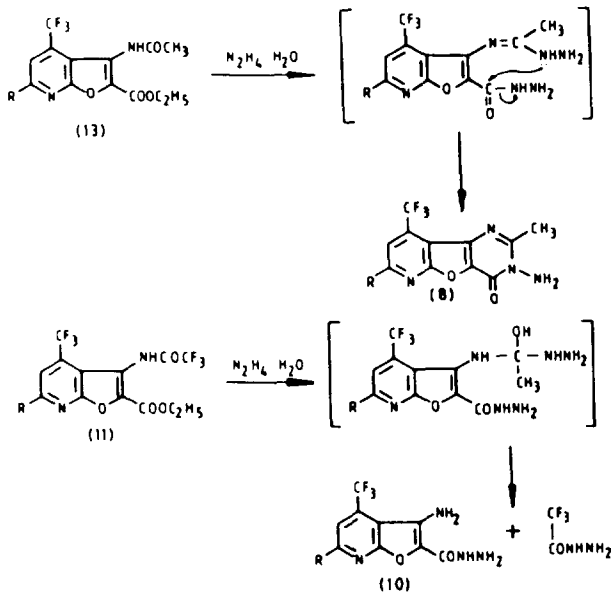


Since **5** carries a CF_3 group at the 2-position, the hydrazine molecule attacks regioselectively at that position and the intermediate formed is **14**. Because the base is more reactive than piperidine, a second molecule of hydrazine attacks the carbonyl and liberates the CF_3 group at the 2-position as $CF_3CONHNH_2$, producing **10** as the product. This is evidently the consequence of CF_3-induced regioselective attack on the oxazine ring. This is the only plausible explanation for the formation of **10** with the loss of CF_3 group from **5** during the reaction, and for the absence of products similar to **7** and **8**. Other secondary amines when used as nucleophiles behaved similarly to piperidine.

The second aspect of the CF_3-induced change of reactivity concerns the addition of hydrazine to $RNHCOCH_3$ and $RNHCOCF_3$. Normally $RNHCOCH_3$ reacts with N_2H_4 and produces the intermediate $RN{=}C(CH_3)NHNH_2$, which is responsible for further cyclisation reactions. In the case of $RNHCOCF_3$, the hydrazine adduct is incapable of dehydration because of the strong electron-withdrawing effect of the CF_3 group, as seen below:



This differentiating mechanistic aspect has been exemplified by the following reactions:



The same mechanistic approach holds good for the formation of **10** from **5**, but, because of the well-established regioselectivity in the reaction of piperidine, formation of **9** and not **12** occurs from **5**. It is reasonable to visualize the primary attack occurring at the 2-position followed by attack of the second molecule of hydrazine at the carbonyl as discussed above. The postulated mechanism appears to be the most appropriate.

3.1. Spectra

The IR spectra of compounds **2** showed a broad band in the 3300–3650 cm^{-1} region corresponding to =OH and $-NH_2$ stretching and one band at 1235 cm^{-1} corresponding to C–F stretching arising from CF_3. The disappearance of the broad band in the 3300–3650 cm^{-1} region and the appearance of a lactone carbonyl band at 1775 cm^{-1} in compounds **3** and **5**, indicates the participation of $-NH_2$ and –COOH groups in cyclisation. This is further confirmed by the ^1H NMR spectra and mass spectra.

The ^1H NMR spectra of compounds **2** showed a broad signal at δ 10.9–10.95 ppm corresponding to the –COOH proton and another broad signal at δ 5.8 ppm for the $-NH_2$ protons, both being exchangeable with D_2O. In compounds **3**, the signal at δ 2.65 ppm is specific for $-CH_3$ protons in the oxazine ring. The disappearance of signals at δ 5.8 and 10.9 ppm for the $-NH_2$ and –COOH protons respectively in compounds **3** and **5** confirms the cyclized structure. The ^1H NMR and mass spectra of compounds **9a** and **12** showed different patterns as described in the Experimental section.

The mass spectra of all the compounds exhibited a stable molecular ion as the base peak.

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