A novel synthetic route to 2-amino-3-cyano-4-trifluoromethyl-6-substituted pyridines*

B. Narsaiah, A. Sivaprasad** and R.V. Venkataratnam
Indian Institute of Chemical Technology, Hyderabad 500007 (India)

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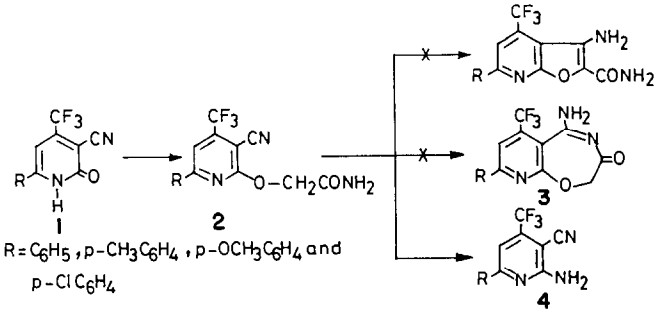
Abstract

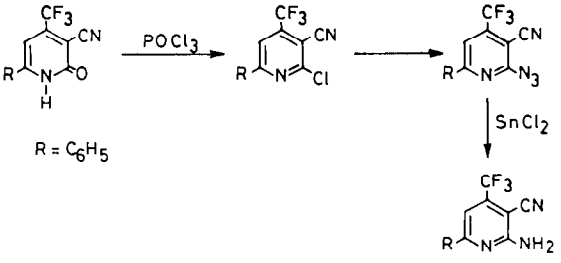
2-Amino-3-cyano-4-trifluoromethyl-6-substituted pyridines have been obtained from 3-cyano-4-trifluoromethyl-6-substituted-2(1*H*)pyridones via an interesting rearrangement of 2-*O*-acetamido-3-cyano-4-trifluoromethyl-6-substituted pyridine intermediates.

Introduction

The growing importance of fluorinated heterocycles has encouraged the search for new fluorinated 2(1*H*)pyridones (**1**) [1] and their utilization to build fluorinated furo[2,3-*b*]pyridine derivatives. Derivatives of the furo[2,3-*b*]pyridine ring system have been claimed as potent herbicides and as integral components of cephalosporine derivatives [2].



With this in view, the 3-cyano-4-trifluoromethyl-6-substituted-2(1*H*) pyridones (**1**) have been reacted with 2-chloroacetamide which resulted in the selective formation of 2-*O*-acetamido-3-cyano-4-trifluoromethyl-6-substituted pyridines (**2**) [3]. These compounds were treated with potassium carbonate in *N*,*N*-dimethylformamide at 110–120 °C to obtain 2-carboxamido-3-amino-4-trifluoromethyl-6-substituted furo[2,3-*b*]pyridines. However, isolated products were found to be 2-amino-3-cyano-4-trifluoromethyl-6-substituted pyridines (**4**), formed by an interesting rearrangement. The reported method [4] for the synthesis of the 6-phenyl-substituted derivative is as follows:



The present reported method involves the rearrangement of compounds **2** to the products **4**.

Experimental

General

Melting points were determined in open glass capillaries on a Mettler FP 51 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometer with TMS as the internal standard. IR spectra were recorded on a PYE Unicam SP3-200 infrared spectrophotometer. Mass spectra were recorded on a VG Micromass 7070H instrument. Elemental analyses were carried out on a Perkin-Elmer 240B apparatus.

Starting materials

The 3-cyano-4-trifluoromethyl-6-substituted-2(1*H*)-pyridones were prepared according to the reported procedure. All other reagents were obtained from commercial sources and used as supplied.

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**Author to whom correspondence should be addressed.

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2-O-Acetamido-3-cyano-4-trifluoromethyl-6-substituted pyridines (2a–d): general procedure

The 3-cyano-4-trifluoromethyl-6-substituted-2(1*H*)-pyridones (0.700 g, 0.0026 mol) were dissolved in dry acetone (50 ml). To the homogeneous solution, 2-chloroacetamide (0.243 g, 0.0026 mol), potassium carbonate (0.730 g, 0.0053 mol) and a pinch of sodium iodide (0.010 g) were added. The reaction mixture was refluxed for 6 h at 60 °C and cooled to room temperature. The separated salt was filtered off and washed with acetone (30 ml). The total filtrate was concentrated under vacuum and the residue treated with water. The separated white solid was filtered, dried and recrystallized from ethyl alcohol.

2-*O*-Acetamido-3-cyano-4-trifluoromethyl-6-phenylpyridine (**2a**): ^{1}H NMR (DMSO-d_6) δ: 5.05 (s, 2H, OCH_2); 7.20 and 7.49 (br., s, 2H, NH_2); 7.57 (m, 3H, aromatic H); 7.90 (s, 1H, C–H(5)); 8.15 (m, 2H, aromatic H) ppm. IR (Nujol) (cm^{-1}): 3400; 3200; 2225; 1680–1665. MS M^+, *m/z*: 321; 302; 277; 69; 44 (base peak). Analysis: Calc. for $C_{15}H_{10}F_3N_3O_2$: C, 56.08; H, 3.13; N, 13.08%. Found: C, 56.15; H, 3.19; N, 13.12%.

2-*O*-Acetamido-3-cyano-4-trifluoromethyl-6-*p*-tolylpyridine (**2b**): ^{1}H NMR (DMSO-d_6) δ: 2.40 (s, 3H, CH_3); 5.0 (s, 2H, OCH_2); 7.09 and 7.32 (br., s, 2H, NH_2); 7.38 (d, 2H, aromatic H); 8.12 (s, 1H, C–H(5)); 8.18 (d, 2H, aromatic H) ppm. IR (Nujol) (cm^{-1}): 3380; 3200; 2220 and 1650. MS M^+, *m/z*: 335; 316; 291 (base peak). Analysis: Calc. for $C_{16}H_{12}F_3N_3O_2$: C, 57.32; H, 3.60; N, 12.53%. Found: C, 57.28; H, 3.58; N, 12.46%.

2-*O*-Acetamido-3-cyano-4-trifluoromethyl-6-*p*-anisylpyridine (**2c**): ^{1}H NMR (DMSO-d_6) δ: 3.87 (s, 3H, OCH_3); 5.0 (s, 2H, OCH_2); 7.07 and 7.32 (br., s, 2H, NH_2); 7.10 (d, 2H, aromatic H); 8.08 (s, 1H, C–H(5)); 8.25 (d, 2H, aromatic H) ppm. IR (Nujol) (cm^{-1}):3400; 3200; 2220; 1650. MS M^+, *m/z*: 351, 307; 293 (base peak). Analysis: Calc. for $C_{16}H_{12}F_3N_3O_3$: C, 54.71; H, 3.44; N, 11.96%. Found: C, 54.68; H, 3.41; N, 11.90%.

2-*O*-Acetamido-3-cyano-4-trifluoromethyl-6-*p*-chlorophenylpyridine (**2d**): ^{1}H NMR (DMSO-d_6) δ: 5.11 (s, 2H, OCH_2); 7.08 and 7.32 (br., s, 2H, NH_2); 7.65 (d, 2H, aromatic H); 8.20 (s, 1H, C–H(5)); 8.29 (d, 2H, aromatic H) ppm. IR (Nujol) (cm^{-1}): 3380; 3190; 2220; 1665. MS M^+, *m/z*: 355; 311; 297 (base peak). Analysis: Calc. for $C_{15}H_9ClF_3N_3O_2$: C, 50.65; H, 2.55; N, 11.81%. Found: C, 50.61; H, 2.57; N, 11.77%.

2-Amino-3-cyano-4-trifluoromet yl-6-substituted pyridines (4a–d): general procedure

The 2-*O*-acetamido-3-cyano-4-trifluoromethyl-6-substituted pyridines (0.001 mol) were suspended in *N,N*-dimethylformamide (6 ml) and treated with potassium carbonate (0.276 g, 0.002 mol) at 110–120 °C for 2 h. The dark reaction mixture was cooled and poured into crushed ice. The separated solid was filtered, washed with water and dried. The isolated compound was purified by passing through alumina in chloroform.

2-Amino-3-cyano-4-trifluoromethyl-6-phenylpyridine (**4a**): ^{1}H NMR ($CDCl_3$) δ: 5.50 (s, 2H, NH_2); 7.35 (s, 1H, H–C(5)); 7.47 (m, 3H, aromatic H); 7.95 (m, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 3450; 3370; 2215; 1575; 1360; 1130. MS M^+, *m/z*: 263 (base peak); 236; 244. Analysis: Calc. for $C_{13}H_8F_3N_3$: C, 59.32; H, 3.06; N, 15.96%. Found: C, 59.30; H, 3.02; N, 15.89%.

2-Amino-3-cyano-4-trifluoromethyl-6-*p*-tolylpyridine (**4b**): ^{1}H NMR ($CDCl_3$) δ: 2.42 (s, 3H, CH_3); 5.53 (s, 2H, NH_2); 7.22 (s, 1H, H–C(5)); 7.40 (d, 2H, aromatic H); 7.83 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 3445; 3360; 2210; 1570; 1350; 1135. MS M^+, *m/z*: 277; 115; 91 (base peak). Analysis: Calc. for $C_{14}H_{10}F_3N_3$: C, 60.65; H, 3.63; N, 15.15%. Found: C, 60.61; H, 3.62; N, 15.09%.

2-Amino-3-cyano-4-trifluoromethyl-6-*p*-anisylpyridine (**4c**): ^{1}H NMR ($CDCl_3$) δ: 3.85 (s, 3H, OCH_3); 5.51 (s, 2H, NH_2); 6.95 (d, 2H, aromatic H); 7.29 (s, 1H, H–C(5)); 7.93 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 3440; 3360; 2215; 1560; 1340; 1130. MS M^+, *m/z*: 293 (base peak); 250. Analysis: Calc. for $C_{14}H_{10}F_3N_3O$: C, 57.34; H, 3.43; N, 14.33%. Found: C, 57.29; H, 3.40; N, 14.31%.

2-Amino-3-cyano-4-trifluoromethyl-6-*p*-chlorophenylpyridine (**4d**): ^{1}H NMR ($CDCl_3$) δ: 5.50 (s, 2H, NH_2); 7.60 (s, 1H, H–C(5)); 7.62 (d, 2H, aromatic H); 8.10 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 3490; 3370; 2215; 1560; 1320; 1130. MS M^+, *m/z*: 297; 270; 69 (base peak). Analysis: Calc. for $C_{13}H_7ClF_3N_3$: C, 52.45; H, 2.37; N, 14.11%. Found C, 52.43; H, 2.36; N, 14.09%.

2-O-Ethoxy-3-cyano-4-trifluoromethyl-6-phenylpyridine (6)

The 2-*O*-ethylacetoxy-3-cyano-4-trifluoromethyl-6-phenylpyridine (0.350 g, 0.001 mol) was dissolved in absolute ethanol (5 ml) and potassium hydroxide (0.2 g) was added. The reaction mixture was refluxed for 2 h and the product diluted with water. On cooling in ice, the white solid which separated was collected and dried (0.28 g, 96%). ^{1}H NMR ($CDCl_3$) δ: 1.44 (t, 3H, CH_3); 4.60 (q, 2H, CH_2); 7.53 (m, 3H, aromatic H); 7.78 (s, 1H, H–C(5)); 8.16 (m, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 2200; 1570; 1355; 1130. MS M^+, *m/z*: 292; 277; 264 (base peak). Analysis: Calc. for $C_{15}H_{11}F_3N_2O$: C, 61.64; H, 3.79; N, 9.58%. Found: C, 61.52; H, 3.73; N, 9.51%.

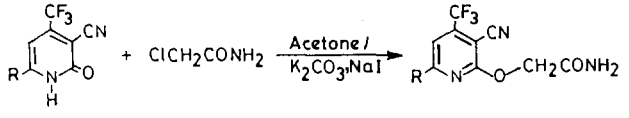
2-Ethoxyethyleneamino-3-cyano-4-trifluoromethyl-6-phenylpyridine (7)

The 2-amino-3-cyano-4-trifluoromethyl-6-phenylpyridine (0.263 g, 0.001 mol) was taken up in triethyl orthoacetate (4 ml) and acetic acid (0.2 ml). The reaction

mixture was heated to reflux for 2 h, cooled and concentrated under vacuum. Water was added to the residue, and the latter was extracted with $CHCl_3$ and dried over anhydrous Na_2SO_4. On concentration, the final product was obtained (0.28 g, 85.6%). ^1H NMR ($CDCl_3$) δ: 1.42 (t, 3H, CH_3); 2.15 (s, 3H, CH_3); 4.41 (q, 2H, CH_2); 7.55 (m, 3H, aromatic H); 7.76 (s, 1H, H–C(5)); 8.07 (m, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 2215; 1570; 1200. MS M^+, *m/z*: 333; 318; 290 (base peak). Analysis: Calc. for $C_{17}H_{14}F_3N_3O$: C, 61.26; H, 4.23; N, 12.60%. Found: C, 61.31; H, 4.27; N, 12.57%.

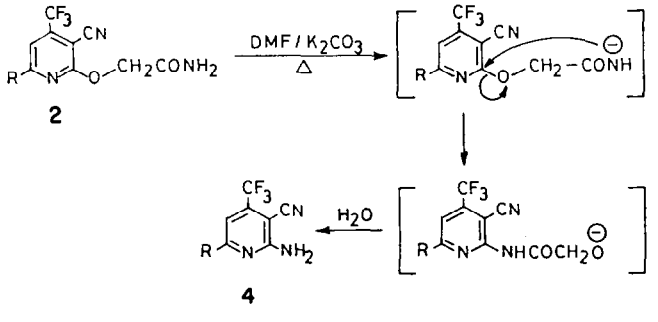
Results and discussion

When 3-cyano-4-trifluoromethyl-6-substituted 2(1*H*)-pyridones (**1**) were reacted with 2-chloroacetamide, the 2-*O*-acetamido-3-cyano-4-trifluoromethyl-6-substituted pyridines (**2**) formed exclusively. This is in concurrence with an earlier report which indicated that when an *ortho* substituent offers steric hindrance, only *O*-alkylation takes place [3].



1 **2**

When the 2-*O*-acetamido compounds **2** were treated with potassium carbonate in *N*,*N*-dimethylformamide at 110–120 °C, the proton from NH_2 was abstracted preferentially by the base. The nucleophile formed attacked the 2-position of the pyridine ring in a similar manner to that found by us [5] for other systems, thus introducing an interesting rearrangement. The final products were formed by subsequent *in situ* hydrolysis. No nucleophilic addition to the nitrile was observed, since product **3** was not isolated.

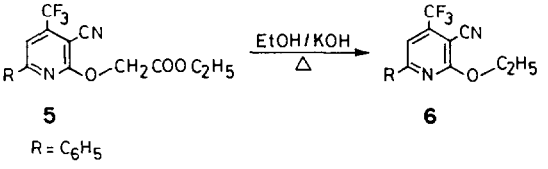


2 **4**

The susceptibility of the 2-position towards nucleophilic attack is further exemplified in the formation of 2-ethoxy-3-cyano-4-trifluoromethyl-6-phenylpyridine (**6**) from 2-*O*-ethylacetoxy-3-cyano-4-trifluoromethyl-6-phenylpyridine (**5**) when the latter was treated with potassium hydroxide in refluxing ethanol.

TABLE 1.

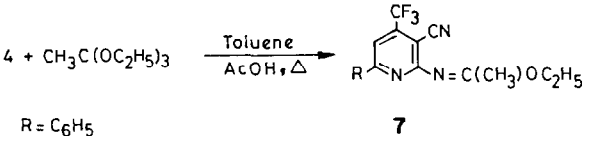
Product No.	R	Yield (%)	M.p. (°C)
2a	C_6H_5	86.4	241
2b	*p*-$CH_3C_6H_4$	83.6	219
2c	*p*-$OCH_3C_6H_4$	96.4	214
2d	*p*-ClC_6H_4	98.0	230
4a	C_6H_5	83.6	162
4b	*p*-$CH_3C_6H_4$	88.2	212
4c	*p*-$OCH_3C_6H_4$	93.8	193
4d	*p*-ClC_6H_4	94.2	198
6	C_6H_5	96.0	119
7	C_6H_5	85.6	115



5 **6**

R = C_6H_5

The structure of product **4** has been confirmed by its reaction with triethyl orthoacetate in which only the addition product **7** was formed.



R = C_6H_5 **7**

The results of the various reactions are listed in Table 1.

Spectra

The infrared spectra of products **4** demonstrate the presence of the nitrile (C≡N) function as a sharp peak at 2210 cm^{-1}, that of the amine (NH_2) function as two doublet shoulders at 3370 and 3450 cm^{-1} and the absence of the carbonyl (C=O) function which is present in compounds **2** at 1680 cm^{-1}. The ^1H NMR spectra of products **4** show the absence of active methylene protons at δ 5.05 ppm, which are present as a singlet in compounds **2**. The NH_2 protons appeared as a broad singlet at δ 5.6 ppm in compounds **4** and are exchangeable with D_2O. The mass spectra show the molecular ion with a characteristic fragmentation. Elemental analyses gave satisfactory results.

Conclusions

A series of new fluorinated intermediates (except **4a**) having active functional groups in the *ortho* positions have been obtained readily in good yield. These compounds can be further utilized in the synthesis of many fluorinated heterocycles of biological interest.

Acknowledgement

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