A Short and General Synthesis of 1,3-Dihydro-6-heteroaryl-5-perfluoroalkyl-2*H*-imidazo[4,5-*b*]pyridin-2-ones

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Trifluoro- or pentafluoroacylation of heteroaryl-enamines **2a,b** gave the corresponding perfluoroacylated heteroaryl-enamines **3a-c**. Heating the latter compounds with diethyl iminomalonate gave 2-amino-3-pyridinecarboxylates **4a-c**. Hydrolysis to the free acids **5a-c**, and reaction with diphenylphosphoryl azide afforded the desired 1,3-dihydro-6-heteroaryl-5-perfluoroalkyl-2*H*-imidazo[4,5-*b*]pyridin-2-ones **6a-c**.

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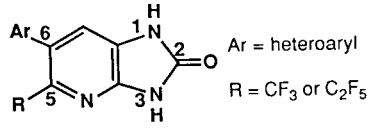
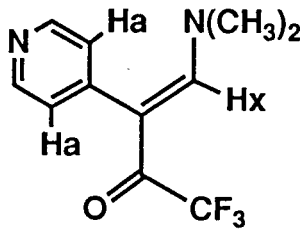
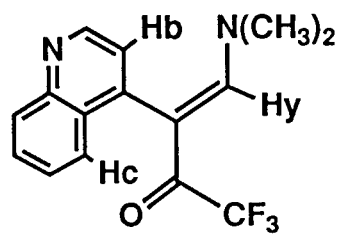
The preparation of fluorinated analogues of biologically active compounds has long been of interest to the pharmaceutical and agricultural industry [2]. In support of our cardiovascular program, we needed to prepare some 6-heteroaryl-5-perfluoroalkyl imidazo[4,5-*b*]pyridines. While selective substituted imidazo[4,5-*b*]pyridines are known compounds [3,4], 6-heteroaryl-5-perfluoroalkyl imidazo-[4,5-*b*]pyridines have not been reported. We now report our discovery of a short and general synthesis of these novel 1,3-dihydro-6-heteroaryl-5-perfluoroalkyl-2*H*-imidazo[4,5-*b*]pyridin-2-ones [5].



Treatment of the commercially available 4-picoline **1a** and 4-methylquinoline **1b** with Brederick's reagent, 1-(1,1-dimethylethoxy)-*N,N,N',N'*-tetramethyl-methanediamine, in dimethylformamide at 140° afforded the *N,N*-dimethyl-2-(4-pyridinyl)ethenamine **2a** (80%) [6] and *N,N*-dimethyl-2-(4-quinolinyl)ethenamine **2b** (80%) [6], respectively. Further treatment of **2a,b** with trifluoroacetic or pentafluoropropionic anhydride [7] in dichloromethane in the presence of triethylamine provided the corresponding trifluoro or pentafluoroacylated enamines **3a-c** in high yields (75-92%). In contrast, attempts to prepare **3a** employing the procedure reported for the preparation of acetyl enamine **3** [8] (Ar = 4-pyridinyl, R = methyl) afforded **2a** as the only isolated product (60%). The assignment of the *E* isomers **3a-c** were based upon the NOE experiments of **3a** and **3b**. A NOE study of **3a** showed that irradiation of the methyl groups enhanced both H_x (17%) and Ha (8%) in agreement with the *cis* relationship of the dimethylamino group and the pyridine. Similarly, irradiation of the methyl groups of **3b** enhanced H_y (18%), H_b (6%) and H_c (3%). Interestingly, the attempted acetylation of **2a,b** with acetic anhydride was unsuccessful although the acetylation of enamines was documented [9].



3a

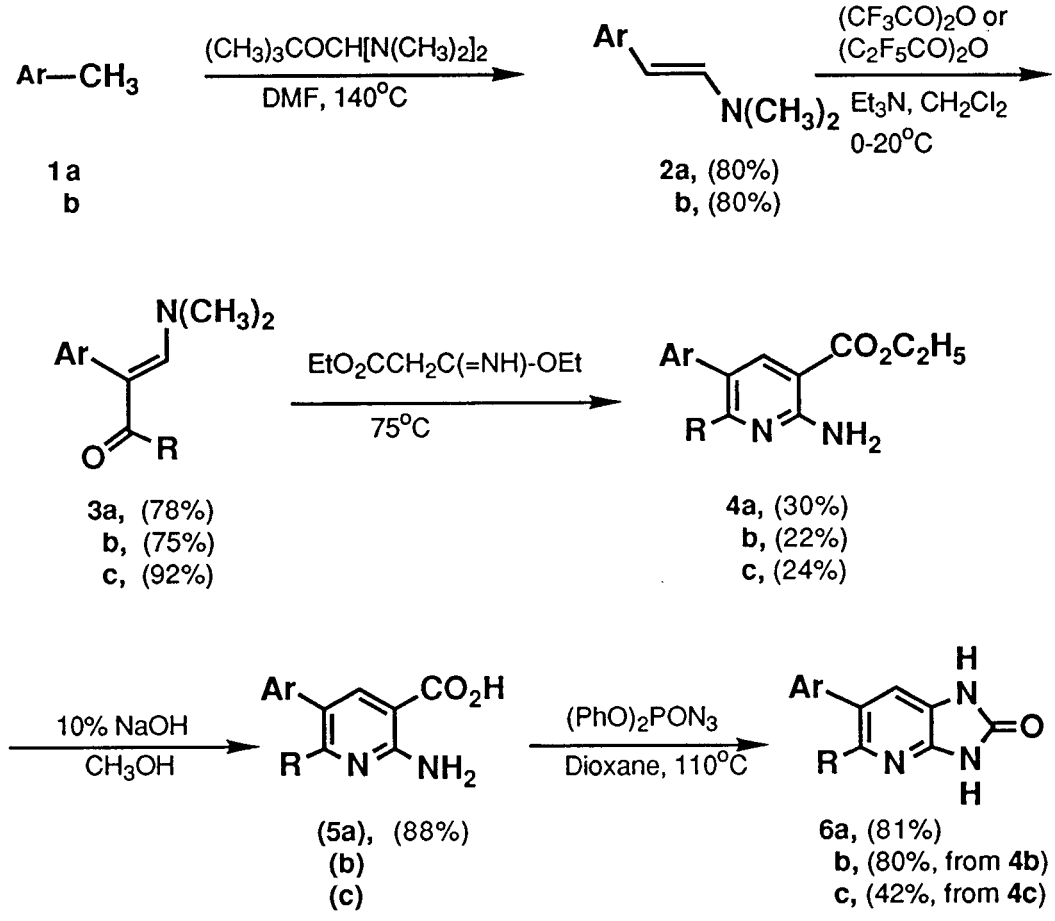


3b

Reaction of **3a-c** with the easily prepared diethyl iminomalonate [10] gave the desired 2-amino-3-pyridinecarboxylates **4a-c** directly, albeit in low yields (22-30%) [11]. This single step transformation avoids an alternative three-step sequence normally used for the preparation of related 2-aminopyridines, *i.e.* conversion of the acetyl enamines to pyridinones, chlorination of pyridinones to 2-chloropyridines and a high pressure amination of 2-chloropyridines to 2-aminopyridines [12,13]. Carboxylates **4a-c** were readily hydrolyzed with 10% aqueous sodium hydroxide to the 2-amino-3-pyridinecarboxylic acids **5a-c** which were used for the next step directly without purification. A Curtius rearrangement [14] was effected by the reaction of **5a-c** with diphenylphosphoryl azide in dioxane at 110° to give the corresponding isocyanate intermediates which underwent intramolecular cyclization with the 2-amino group to afford the desired imidazo[4,5-*b*]pyridin-2-ones **6a-c** in good yields (42-81%) (Scheme I).

In summary, considering the easy accessibility of heteroarylenamines **2** [6] and fluorinated alkanoic anhydrides, and the mild reaction conditions, the five-step synthetic route depicted in Scheme I represents a general method for the preparation of novel 1,3-dihydro-6-heteroaryl-5-perfluoroalkyl-2*H*-imidazo[4,5-*b*]pyridin-2-ones.

Scheme I



1, 2	Ar	3, 4, (5), 6	Ar	R
a	4-pyridinyl	a	4-pyridinyl	CF_3
b	4-quinolinyl	b	4-quinolinyl	CF_3
		c	4-pyridinyl	C_2F_5

EXPERIMENTAL

All reagents were commercially available and used without further purification. Dichloromethane, *p*-dioxane and DMF were dried over 4 A molecular sieves prior to use. Melting points were obtained on a Thomas-Hoover melting point apparatus, and are uncorrected. The ir spectra were obtained using a Nicolet 20 SX spectrometer. The ^{1}H nmr spectra were recorded on a GE QE 300 (300 MHz) spectrometer. Mass spectra were obtained using a Nermag R 10-10C spectrometer. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN.

N,N-Dimethyl-2-(4-pyridinyl)ethenamine (**2a**).

Compound **2a** was prepared according to the literature procedure [6].

N,N-Dimethyl-2-(4-quinolinyl)ethenamine (**2b**).

Compound **2b** was prepared according to the literature procedure [6].

4-(Dimethylamino)-1,1,1-trifluoro-3-(4-pyridinyl)-3-buten-2-one (**3a**). General Procedure.

A mixture of **2a** (9.45 g, 63.9 mmoles) and triethylamine (12.9 g, 128 mmoles) in dichloromethane (100 ml) was cooled to 0°, and a solution of trifluoroacetic anhydride (14.7 g, 70.2 mmoles) in dichloromethane (5 ml) was added dropwise over 30 minutes. The reaction mixture was allowed to warm to 20° and stirred for 16 hours. The solvent was removed and the oily residue extracted with ether (4 x 200 ml). Silica gel (6 g) and magnesium sulfate (5 g) was added to the ether solution which was stirred and filtered. The filtrate was concentrated *in vacuo* and the residue solidified at 0° to give a yellow-orange oily solid (27 g). This crude oily solid

was used directly in the next reaction. The crude oily solid of another run starting with **2a** (4.3 g, 29 mmoles) was further purified by flash chromatography on silica gel (dichloromethane/acetone, 4:1) and then crystallized from dichloromethane/hexane to give **3a** as yellow crystals, yield 5.5 g (78%), mp 82-84°; ir (potassium bromide): ν 1591, 1410, 1177, 1126 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.46 (br s, 3 H), 3.22 (br s, 3 H), 7.13 (d, 2 H, J = 5.8 Hz), 7.69 (s, 1 H), 8.55 (d, 2 H, J = 5.7 Hz); ms: (CI) m/z 245 (M + 1, s).

Anal. Calcd. for $C_{11}H_{11}N_2F_3O$: C, 54.10; H, 4.54; N, 11.47; F, 23.34. Found: C, 54.02; H, 4.52; N, 11.43; F, 23.37.

4-(Dimethylamino)-1,1,1-trifluoro-3-(4-quinolinyl)-3-buten-2-one (**3b**).

The same procedure described for **3a** was followed for the reaction of **2b** with trifluoroacetic anhydride. The product was purified by flash chromatography on silica gel (dichloromethane/acetone, 1:2) and crystallized from dichloromethane/hexane to give **3b** as light-yellow crystals, yield 75%, mp 135-137°; ir (potassium bromide): ν 1589, 1504, 1435, 1404, 1245, 1180 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.18 (br s, 3 H), 3.21 (br s, 3 H), 7.33 (d, 1 H, J = 4.3 Hz), 7.56 (br t, 1 H, J = 7.3 Hz), 7.73 (br t, 1 H, J = 7.7 Hz), 7.82 (d, 1 H, J = 8.1 Hz), 7.99 (s, 1 H), 8.15 (d, 1 H, J = 8.4 Hz), 8.90 (d, 1 H, J = 4.3 Hz); ms: (CI) m/z 295 (M + 1, s).

Anal. Calcd. for $C_{15}H_{13}N_2OF_3$: C, 61.22; H, 4.45; N, 9.52; F, 19.31. Found: C, 60.98; H, 4.40; N, 9.46; F, 19.35.

1-(Dimethylamino)-4,4,5,5,5-pentafluoro-2-(4-pyridinyl)-1-penten-3-one (**3c**).

The same procedure described for **3a** was followed for the reaction of **2a** with pentafluoropropionic anhydride. The product was purified by flash chromatography on silica gel (ether/dichloromethane, 1:1) and crystallized from ethyl acetate/hexane to give **3c** as light-yellow crystals, yield 92%, mp 105-106°; ir (potassium bromide): ν 2984, 2942, 1582, 1490, 1359, 1195 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.44 (br s, 3 H), 3.19 (br s, 3 H), 7.13 (d, 2 H, J = 6.2 Hz), 7.73 (s, 1 H), 8.55 (d, 2 H, J = 6.2 Hz); ms: (CI) m/z 295 (M + 1, s).

Anal. Calcd. for $C_{12}H_{11}N_2F_5O$: C, 48.99; H, 3.77; N, 9.52. Found: C, 48.69; H, 3.75; N, 9.42.

6-Amino-2-(trifluoromethyl)-[3,4'-bipyridine]-5-carboxylic Acid Ethyl Ester (**4a**). General Procedure.

Diethyl iminomalonate hydrochloride (20 g, 102.3 mmoles) [10] was added slowly to an ice-cold mixture of sodium bicarbonate (17 g), water (100 ml) and ether (60 ml) with rapid stirring. The ether layer was separated and the aqueous layer extracted with ether (3 x 30 ml). The combined ether solution was dried (sodium sulfate) and concentrated to give diethyl iminomalonate (16.1 g) as a colorless oil. The colorless oil was mixed with the crude oily solid **3a** (20 g, 37 mmoles) and stirred at 75° for 16 hours. The reaction mixture was dissolved in water (250 ml), acidified with acetic acid and extracted with ether (3 x 100 ml), dried (sodium sulfate) and concentrated. The crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:5 to 1:3) and crystallized from dichloromethane/hexane to give **4a** as white crystals, yield 3.5 g (30%), mp 121-125°; ir (potassium bromide): ν 3440, 3315, 3240-3100, 1711, 1638, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.37 (t, 3 H, J = 7.2 Hz), 4.37 (q, 2 H, J = 7.2 Hz), 7.24 (d, 2 H, J = 4.0 Hz), 8.09 (s, 1 H), 8.66 (d, 2 H, J = 3.8 Hz); ms: (CI) m/z 312 (M + 1).

Anal. Calcd. for $C_{14}H_{12}N_3O_2F_3$: C, 54.02; H, 3.89; N, 13.50; F, 18.31. Found: C, 54.34; H, 4.07; N, 13.18; F, 18.23.

2-Amino-5-(4-quinolinyl)-6-(trifluoromethyl)-3-pyridinecarboxylic Acid Ethyl Ester (**4b**).

The same procedure described for **4a** was followed, but using **3b** instead of **3a**. The product was purified by flash chromatography on silica gel (ethyl acetate/hexane, 1:10 to 1:5) and crystallized from dichloromethane/hexane to give **4b** as white crystals, yield 22%, mp 204-206°; ir (potassium bromide): ν 3435, 3286, 1704, 1619, 1584, 1236 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.34 (t, 3 H, J = 7.0 Hz), 4.35 (m, 2 H), 7.30 (d, 1 H, J = 4.3 Hz), 7.52 (m, 2 H), 7.77 (m, 1 H), 8.14 (s, 1 H), 8.21 (d, 1 H, J = 8.5 Hz), 8.98 (d, 1 H, J = 4.3 Hz); ms: (CI) m/z 362 (M + 1, s).

Anal. Calcd. for $C_{16}H_{14}N_3O_2F_3$: C, 59.84; H, 3.91; N, 11.63; F, 15.77. Found: C, 59.73; H, 3.90; N, 11.50; F, 15.93.

6-Amino-2-(pentafluoroethyl)-[3,4'-bipyridine]-5-carboxylic Acid Ethyl Ester (**4c**).

The same procedure described for **4a** was followed, but using **3c** instead of **3a**. The product was purified by flash chromatography on silica gel (ether/hexane, 1:1) and crystallized from dichloromethane/hexane to give **4c** as white crystals, yield 24%, mp 125-127°; ir (potassium bromide): ν 3442, 3140-3053, 1698, 1628, 1309, 1249, 1228 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.36 (t, 3 H, J = 7.1 Hz), 4.37 (q, 2 H, J = 7.1 Hz), 7.21 (d, 2 H, J = 5.7 Hz), 8.04 (s, 1 H), 8.64 (d, 2 H, J = 5.7 Hz); ms: (CI) m/z 362 (M + 1, s).

Anal. Calcd. for $C_{15}H_{12}N_3O_2F_5$: C, 49.87; H, 3.35; N, 11.63; F, 26.29. Found: C, 49.67; H, 3.20; N, 11.53; F, 26.14.

6-Amino-2-(trifluoromethyl)-[3,4'-bipyridine]-5-carboxylic Acid (**5a**). General Procedure.

A mixture of **4a** (2.2 g, 7.1 mmoles), 10% aqueous sodium hydroxide (12 ml) and methanol (20 ml) was stirred at 100° for 6 hours. The reaction mixture was concentrated *in vacuo* and the aqueous mixture was neutralized with dilute acetic acid to *p*H 4-5. The solid product was collected, washed with water, dichloromethane and dried to give **5a** as a white solid; yield: 1.76 g (88%); mp > 283° dec; ir (potassium bromide): ν 3502, 3338, 2432, 1919, 1701 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 8.30 (d, 2 H, J = 7.1 Hz), 8.91 (s, 1 H), 9.15 (d, 2 H, J = 7.1 Hz); ms: (CI) m/z 284 (M + 1).

No attempts were made to prepare an analytical sample.

1,3-Dihydro-6-(4-pyridinyl)-5-(trifluoromethyl)-2*H*-imidazo[4,5-*b*]-pyridin-2-one (**6a**). General Procedure.

A mixture of **5a** (1.5 g, 5.3 mmoles), diphenylphosphoryl azide (1.9 g, 6.9 mmoles) and triethylamine (1.5 ml) in *p*-dioxane (30 ml) was stirred at 110° for 6 hours. The reaction mixture was concentrated *in vacuo* and the residue treated with water (8 ml) and acetic acid (2 ml). The solid was collected, washed with water and air dried to give a yellowish white solid. The crude product was recrystallized from methanol to give **6a** as white crystals, yield 1.2 g (81%), mp > 300°; ir (potassium bromide): ν 3600-3000, 1725, 1600, 1480 cm^{-1}; ^1H nmr (acetone-d_6): δ 7.29 (s, 1 H), 7.38 (d, 2 H, J = 4.9 Hz), 8.65 (d, 2 H, J = 4.9 Hz); ms: (CI) m/z 281 (M + 1).

Anal. Calcd. for $C_{12}H_7N_4OF_3$: C, 51.44; H, 2.52; N, 19.99. Found: C, 51.56; H, 2.54; N, 19.90.

1,3-Dihydro-6-(4-quinolinyl)-5-(trifluoromethyl)-2*H*-imidazo[4,5-*b*]-pyridin-2-one (**6b**).

The same procedure described for **5a** was followed to prepare **5b** as a pale yellow solid. Compound **5b** was used directly without purification to prepare **6b** following the same procedure described for **6a**. Compound **6b** was purified by flash chromatography on silica gel (dichloromethane/methanol, 9:1) and crystallized from methanol to give **6b** as a white solid; yield 80% from **4b**, mp >300° dec; ir (potassium bromide): ν 3110-2708, 1722, 1248, 1199 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 7.90 (d, 1 H, J = 8.7 Hz), 7.91 (s, 1 H), 8.06 (t, 1 H, J = 7.9 Hz), 8.11 (d, 1 H, J = 5.8 Hz), 8.34 (t, 1 H, J = 7.9 Hz), 8.49 (d, 1 H, J = 8.7 Hz), 9.26 (d, 1 H, J = 5.8 Hz); ms: (CI) m/z 331 (M + 1).

Anal. Calcd. for $C_{15}H_9N_4OF_3 \cdot 0.25H_2O$: C, 57.41; H, 2.86; N, 16.74. Found: C, 57.53; H, 2.77; N, 16.40.

1,3-Dihydro-5-(pentafluoroethyl)-6-(4-pyridinyl)-2*H*-imidazo[4,5-*b*]pyridin-2-one (**6c**).

The same procedure described for **5a** was followed to prepare **5c** as a yellow solid. Compound **5c** was used directly without purification to prepare **6c** following the same procedure described for **6a**. Compound **6c** was purified by flash chromatography on silica gel (dichloromethane/methanol, 15:1) and crystallized from DMF to give **6c** as white crystals, yield 42% from **4c**, mp >290° (dec); ir (potassium bromide): ν 3500-3100, 1721, 1601 cm^{-1}; ^1H nmr (acetone-d_6): δ 7.27 (s, 1 H), 7.35 (br d, 2 H, J = 5.9 Hz), 8.63 (br d, 2 H, J = 5.9 Hz); ms: (CI) m/z 331 (M + 1, s).

Anal. Calcd. for $C_{13}H_7N_4OF_5$: C, 47.29; H, 2.14; N, 16.97; F, 28.77. Found: C, 47.36; H, 2.21; N, 16.67; F, 28.89.

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