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A facile synthesis of 6-Chloro-2-methoxy-7-(trifluoromethyl) imidazo[1,5-a]pyrido[3,2-e]pyrazine

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Abstract

Ethyl 4-(trifluoromethyl)-1H-imidazole-5-carboxylate **(1)** and 2-Chloro-3-nitro-6-methoxypyridine react each other to offer Ethyl 4-(trifluoromethyl)-1-(6-methoxy-3-nitropyridin-2-yl)-1H-imidazole-5-carboxylate **(2)**. Compound **2** cyclised with Sodiumdithionate to form 2-Methoxy-7-(trifluoromethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one**(3)** which on chlorination offers 6-Chloro-2-methoxy-7-(trifluoromethyl) imidazo[1,5-a]pyrido[3,2-e]pyrazine**(4)**. The structures of all synthesized compounds were confirmed by IR, NMR and mass spectral data.

Introduction

Imidazoles are an important class of heterocycles and include many substances of both biological and chemical interest. Insertion of the imidazole nucleus is an important synthetic strategy in drug discovery. Imidazole drugs have broad applications in many areas of clinical medicine. These are currently used as tools in pharmacological studies. The important therapeutic properties of imidazole related drugs have encouraged the medicinal chemists to synthesize and test a large number of novel molecules.

Compounds with an imidazole ring system have many pharmacological properties and play important roles in biochemical processes.[1] Many of the substituted imidazoles are known as inhibitors of fungicides and herbicides, plant growth regulators and therapeutic agents.[2] Recent advances in green chemistry and organometallic chemistry have extended the boundary of imidazoles to the synthesis and application of a large class of imidazoles as ionic liquids and imidazole related N-heterocyclic carbenes.[3]

Generally, condensation of 1,2-dicarbonyl compounds with aryl 1,2-diamines affording pyridopyrazines is an interesting target in modern organic chemistry.[4-6] These compounds have great synthetic potential due to applications in many aspects of pharmaceutical and medicinal chemistry such as antibiotic,[7] potent inhibitors,[8,9] binding to DNA,[10] antimicrobial,[11-13] receptor antagonists,[14,15] activities.

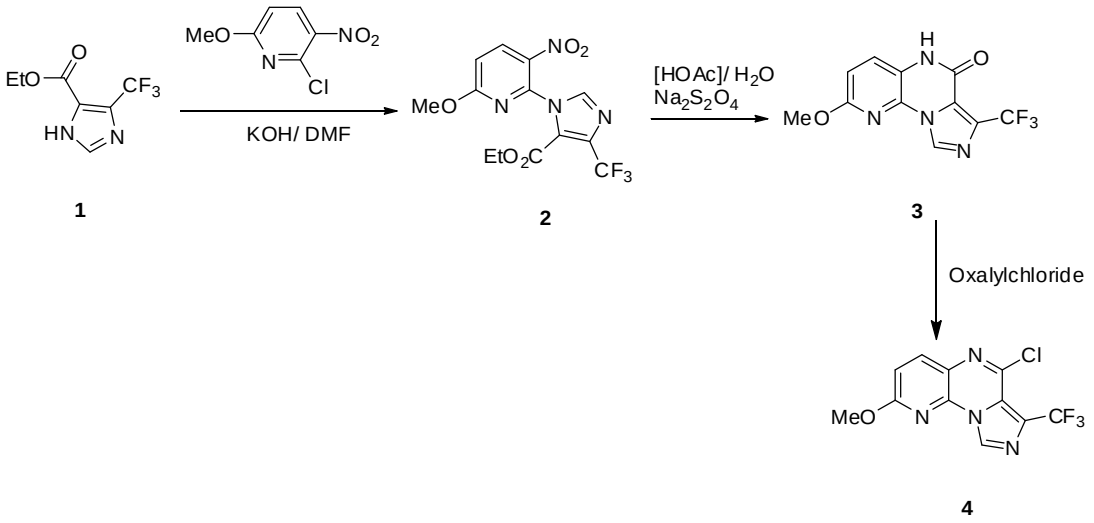
Many of the synthetic protocols reported so far suffer from one or more disadvantages such as harsh reaction conditions, poor yields, prolonged time period, use of hazardous and often expensive acid catalysts. Moreover, the synthesis of these heterocycles has been

usually carried out in polar solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. These processes also generate waste containing catalyst and solvent, which have to be recovered, treated and disposed off. In view of the importance of these compounds, herein we repot synthesis of title compounds.

Experimental Section :

Chemicals and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E. Merck AL silica gel 60 F254 plates and visualized under UV light. IR spectra were recorded as KBr pellet with a Perkin-Elmer Spectrum GX FTIR instrument and only diagnostic and/or intense peaks are reported. ^{1}H NMR spectra were recorded in DMSO-d_6 with a Varian Mercury plus 400 MHz instrument. ^{13}C NMR spectra were recorded in DMSO-d_6 with a Varian Gemini 100 MHz instrument. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling constants (*J*) corresponds to the order of multiplicity assignment. Mass spectra were recorded with a PE Sciex model API 3000 instrument. All the reactions were carried out under argon atmosphere.

Scheme



1 **2** **3** **4**

Ethyl-4-(trifluoromethyl)-1-(6-methoxy-3-nitropyridin-2-yl)-1H-imidazole-5-carboxylate (2)

Ethyl 4-(trifluoromethyl)-1H-imidazole-5-carboxylateand 2-Chloro-3-nitro-6-methoxypyridine (0.01 mole) was dissolved in DMF (25 mL).To this freshly powdered NaOH (0.01 mole)was added and heated to reflux for overnight. After completion of reaction (monitored by TLC), the solvent was removed by distillation and diluted with water then extracted from ethyl acetate.The separated the organic layer, dried over Na_2SO_4 and concentrated under vacuum to afford crude compd-**2**.The crude compound was purified bycolumn chromatographyusing 106% ethyl acetate in pet ether.

IR (KBr):3029, 2933, 1655, 1611, 1595, 1507, 1491, 1394, 1374, 1349, 1319, 1305, 1256, 1236, 1215, 1197, 1178, 1116, 1012, 980, 901, 844, 817, 790, 766, 747, 717, 683, 602 cm^{-1}; ^{1}H NMR (*400 MHz, CDCl$_3$*):δ = 8.39 (d 1H),7.90 (s, 1H), 7.02 (d, 1H), 4.20 (q, 2H),4.00 (s, 3H), 1.28 (t, 3H).

MS: m/z 361 (m+1).

2-Methoxy-7-(trifluoromethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one (3)

Ethyl-4-(trifluoromethyl)-1-(6-methoxy-3-nitropyridin-2-yl)-1H-imidazole-5-carboxylate**(2)**(0.01 mole) was dissolved in acetic acid and addedwater (50mL) followed by sodium dithionite (0.07 mole). The reaction washeated to 100°C for overnight.The reaction mass was cooled to room temperature and then diluted with water .The solid product was filtered and washed with water followed by hexane to afford crude compound 3.

IR (KBr): 3444, 3182, 3075, 3064, 2934, 2904, 2844, 2832, 2050, 1613, 1575, 1434, 1400, 1373, 1349, 1312, 1296, 1271, 1160, 1125, 1114, 1027, 1010, 969, 933, 782, 748, 696, 531, 509, 414 cm^{-1}; ^1H NMR (*400 MHz, DMSO-d_6*):δ = 11.89 (brs, 1H), 9.00 (s, 1H),7.65 (d, 1H), 7.00 (d, 1H), 4.01 (s, 3H)
MS: m/z 285 (m+1)

6-Chloro-2-methoxy-7-(trifluoromethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazine (4)

2-Methoxy-7-(trifluoromethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one **(3)** (0.01mole) was suspended in oxalyl chloride 35 (mL) and was heated to 110°C for 24h.Excess oxalyl chloride was distilled off under reduce pressure then quenched with iceandne-utralised with solid $NaHCO_3$. The resulting solids were filtered. The crude compound was purified by column chromatography over silica gel(60-120 mesh) using 6% ethyl acetate in pet ether.
IR (KBr): 3086, 2939, 2920, 2902, 1620, 1567, 1530, 1490, 1451, 1305, 1279, 1262, 1241, 1216, 1148, 1135, 1113, 1090, 1065, 1011, 903, 877, 850, 819, 803, 788, 780, 759, 737, 713, 687, 677, 656, 608, 571, 527, 501, 482, 455 cm^{-1};
Mass 302.9

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