RJC

RASĀYAN *J. Chem.*
Vol. 5 | No.4 | 496-499 | October-December | 2012
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESIS OF SMALL PYRIDINE BUILDING BLOCKS

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ABSTRACT

A number of pyridine derivatives have been synthesized. The main target pyridines in this study were 4-cyano-2-picoline, 4-methylamino-2-picoline and 4-(*N*-acetamidomethyl)-2-pyridine aldehyde. In addition, other pyridines have also been synthesized throughout the synthetic sequence. These compounds could be very useful as building blocks in organic synthesis and could have biological activities. The general synthetic pathway has been clearly described.

Keywords: Pyridine derivatives, synthesized, building blocks, organic synthesis

INTRODUCTION

1-(5-carboxy-1*H*-benzimidazol-2-ylmethyl)pyridinium chloride and 1-(6-carboxy-1*H*-benzimidazol-2-ylmethyl)pyridinium chloride have shown satisfactory capability in inhibiting the growth of human cancer cells[1]. Pyridine derivatives such as 2-hydroxypyridine, 2-aminopyridine and picolinic acid have been found to give complexes with copper, which evaluated for superoxide dismutase and antimicrobial activities[2]. Other pyridine-containing molecules were found to control phytopathogenic fungi[3]. The stable complexes of Eu^{3+} with the ligands 3-dodecanoylaminopicolinic acid and 3-dodecanoylaminopicolinic acid *N*-oxide show high levels of solubility in most commonly used solvents and have great impact on luminescence and spectroscopic properties in which they could be used as molecular devices for light-conversion either in solid or in liquid phase[4].

EXPERIMENTAL

Materials

2-Picoline *N*-oxide, iodoethane, potassium cyanide, 5% palladium on charcoal, acetic anhydride, selenium oxide, pyridine, fuming nitric acid, ethanol and ammonium hydroxide were purchased from Sigma-Aldrich and used without any further purification.

Instrumentation

Melting points were measured on a Gallenkamp apparatus and are uncorrected. 1H and 13C NMR spectra were recorded on a Bruker AC-250 or a Bruker Avance 300 spectrometer or JEOL 600 MHz spectrometer. Residual proton signals from the deuteriated solvents were used as references 3 Synthesis of some aminopicolinic acids [chloroform (1H, 7.25 ppm; 13C, 77 ppm) and D_2O (1H, 4.81 ppm]. Coupling constants were measured in Hz. All infrared spectra were recorded on Perkin–Elmer Spectrum RX/FT-IR system. Mass spectra were recorded on a Micromass Autospec M spectrometer.

The Preparation of 4-Cyano-2-picoline[5]

Iodoethane (58 cm^3, 721.23 mmol) was added dropwise to 2-picoline *N*-oxide (21.17 gm, 194.22 mmol) while stirring to ensure that the 2-picoline *N*-oxide was completely dissolved. The resulting clear solution was left standing overnight at room temperature. The resulting beige solid of 2-picoline *N*-ethoxy iodide was collected by filtration, washed with diethyl ether (3 x 30 cm^3) and air-dried. An aqueous solution of KCN (24.58 gm, 378.15mmol) in H_2O (72 cm^3) was added dropwise to a stirred solution of 2-picoline *N*-

ethoxy iodide (48.78 gm, mmol) in a mixture of EtOH/H_2O (232 cm^3; 7:3 v/v) at 48 – 50 °C. The reaction mixture was stirred at the same temperature for further 1 h, cooled to room temperature, extracted with DCM (4 x 50 cm^3), washed with brine (1 x 60 cm^3), dried over Na_2SO_4, filtered and the solvent evaporated *in vacuo* to give dark brown oil, which was purified by distilling off the impurity (impurity was colourless oil) affording a thick dark brown oil, which solidifies on standing (15.76 gm, 133.56 mmol, 69%), mp 43 – 46 °C (lit.[5] mp 45.5 – 46.5°C; from petroleum ether); ν_{max} (NaCl)/cm^{-1} 3064 (w), 2931 (w), 2240 (m), 1602 (s); δ_H [300 MHz, CDCl3] 8.57 (1H, s, ArC*H*), 7.29 (2H, d, *J* 14.8, 2 x ArC*H*), 2.51 (3H, s, CH_3); *m/z* EI^+ ($C_7H_6N_2$; 118.14) 118.06 (100), 91.04 (100), 78.03 (15), 64.04 (25), 51.02 (10), 39.03 (10).

The Preparation of 4-Methylamino-2-picoline

A literature procedure[6] was adapted using aq. ammonia to assist reducing the cyano group. 4-Cayano-2-pcoline (15.54 gm, 131.70 mmol) was dissolved at room temperature in EtOH (150 cm^3). To the resulting clear solution, ammonium hydroxide (40 cm^3) was added. The resulting mixture was poured into the hydrogenation reactor followed by the addition of Pd/C (7.21 gm, 5% Pd). The reaction mixture was stirred at room temperature for 20 h under hydrogen and pressure of 60 PSI. The reaction mixture was filtered through a short pad of Celite and the solvent was removed *in vacuo*. The residual oil was dissolved in DCM (30 cm^3) and washed with water (1 x 25 cm^3) and brine (1 x 20 cm^3), dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The resulting oil was purified by distilling off the impurity (impurity was colorless oil) to afford the title compound as reddish-yellow oil (15.06 gm, 123.44 mmol, 94%). ν_{max} (NaCl)/cm^{-1} 3378 – 3303 (br), 2925 (m), 2212 (m), 1665 (s), 1608 (s); δ_H [600 MHz, $CDCl_3$] 8.63 (1H, s, ArC*H*), 7.30 (2H, s, ArC*H*), 4.01 (2H, s, CH_2), 2.74 (3H, s, CH_3); δ_C [150 MHz, $CDCl_3$] 156.1 (Ar*C*MeN), 150.6 (Ar*C*HN), 146.8 (Ar*C*), 119.3 (Ar*C*H), 117.1 (Ar*C*H), 43.1 (*C*H_2NH_2), 22.2 (*C*H_3); m/z EI^+ ($C_7H_{10}N_2$; 122.17) 122.09 (80), 121.08 (100), 118.07 (10), 117.06 (5).

The Preparation of 4-(*N*-Acetamidomethyl)-2-picoline

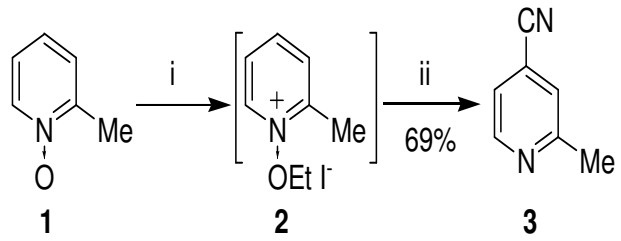
Acetic anhydride (48.0 cm^3, 508.71 mmol) was added dropwise at room temperature to a stirred solution of 4-methylamino-2-picoline (7.53 gm, 61.72 mmol) in water (40 cm^3) and MeOH (60 cm^3) in a two-necked round-bottomed flask equipped with a condenser in a reflux position. The resulting mixture was refluxed for 24 h, cooled to room temperature and extracted with DCM (4 x 30 cm^3). The aqueous layer was transferred into a 500 cm^3 beaker equipped with a stirring bar and then basified with a solid Na_2CO_3, extracted with DCM (4 x 30 cm^3), washed with brine (1 x 25 cm^3), dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo* to give the desired compound as red oil (5.06 gm, 30.85 mmol, 50%). ν_{max} (NaCl)/cm^{-1} 3151 – 2975 (vbr), 1657 (s), 1610 (s), 1556 (m); δ_H [300 MHz, $CDCl_3$] 8.87 (1H, s, N*H*), 8.62 (1H, s, ArC*H*), 7.30 (2H, d, *J* 17.3, 2 x ArC*H*), 4.62 (2H, s, CH_2), 2.76 (3H, s, CH_3CO), 2.30 (3H, s, CH_3); *m/z* EI^+ ($C_9H_{12}N_2O$; 164.20) 164.07 (100), 122.09 (70), 107.07 (40), 93.07 (45), 65.03 (15).

The Preparation of 4-(*N*-Acetamidomethyl)-2-pyridine Aldehyde

A literature procedure[7] was adapted using pyridine as a solvent. SeO_2 (4.91 gm, 44.23 mmol) was added at room temperature as a solid to a stirred solution of 4-(*N*-Acetamidomethyl)-2-picoline (4.84 gm, 29.51 mmol) in freshly distilled pyridine (35 cm^3). The resulting mixture was stirred at 50 – 60 °C for 2 h, then the temperature was raised to 80 – 85 °C and the mixture stirred at this temperature for 3.5 h. The reaction mixture was stirred at room temperature overnight, filtered through a pad of celite, evaporated and the residual was dissolved in DCM (30 cm^3) and washed with brine (25 cm^3), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give the title compound as thick brown oil (1.99 gm, 11.18 mmol, 38 %). ν_{max} (NaCl)/cm^{-1} 3373 (vbr), 1752 (m), 1675 (m), 1560 (w), 1510 (m); δ_H [300 MHz, $CDCl_3$] 9.86 (1H, s, C*H*O), 8.39 (1H, s, Ar-C*H*), 7.31 (2H, s, 2 x Ar-C*H*), 2.30 (2H, s, CH_2), 2.28 (3H, s, CH_3); *m/z* EI^+ ($C_9H_{10}N_2O_2$; 178.19) 178.04 (100), 163.03 (99), 150.10 (32), 136.08 (100), 120.08 (100).

RESULTS AND DISCUSSION

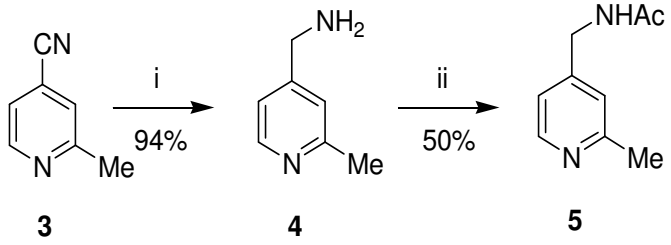
The synthesis of 4-cyano-2-picoloine **3** required the treatment of 2-picoline *N*-oxide **1** by iodoethane at room temperature to form 2-picoline *N*-ethoxy iodide **2**. The latter *N*-ethoxy iodide derivative **2** was treated directly, without any further purification, with potassium cyanide at about 50° C to give the desired 4-cyano-2-picoline **3** in good yield (Scheme-1).



Reagents and Conditions: (i) EtI, rt, overnight; (ii) KCN, EtOH/H_2O (7:3 v/v), 48 - 50 ^oC, 1 h

Scheme-1

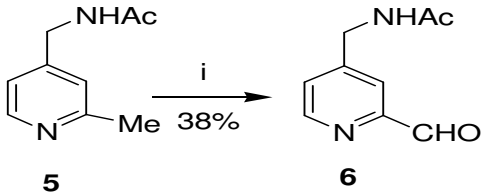
The resulting 4-cyano-2-picoline **3** was reduced using catalytic hydrogenation to the corresponding primary amine **4** in excellent yield after which the amino group was protected by converting it into an *N*-acyl group forming the 4-(*N*-acetamidomethyl)-2-picoline **5** (Scheme-2).



Reagents and Conditions: (i) H_2, Pd/C, EtOH, NH_4OH, 60 PSI, rt, 20h; (ii) Ac_2O, H_2O, reflux, 24h

Scheme-2

The *N*-protected 2-picoline derivative **5** was oxidized to the corresponding aldehyde **6** in moderate yield, using SeO_2 in pyridine. An attempt to further oxidize the aldehyde **6** to the corresponding carboxylic acid by employing fuming nitric acid was unsuccessful (Scheme-3).



Reagents and Conditions: (i) SeO_2, pyridine, 50-60^oC then 80-85^oC, stirring at rt overnight

Scheme-3

CONCLUSION

A number of substituted 2-picolines have been synthesized economically in moderate to excellent yields by adapting various synthetic methods.

ACKNOWLEDGMENTS

Authors would like to thank the Department of Chemistry at Mississippi State University, ACS-PRF and NSF-REU, Mississippi State RIP for funding.

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[RJC-987/2012]