Abstract

Compound 1-amino-2-(cyclohexylmethyl)-4-methyl-1H-imidazol-5-carboxamide 5 has been synthesized via a facile four step reaction sequence with involving, cyanation, imine formation, cyclization and amination starting from commercially available cyclohexyl methyl bromide. The structures of newly synthesized compounds have been established on the basis of elemental analysis, IR, 1H NMR, 13C NMR and Mass spectral data.

Keywords: Cyclohexyl methyl bromide, Sodium cyanide, 2-chloro ethylacetoacetate, Potassium tertiary butoxide and Diphenyl phosphorylamide.

1. INTRODUCTION

Imidazoles are probably the most well known heterocyclics which is common and important feature of a variety of natural products and medicinal agents these are known to possess biological activity [1-3]. Compounds with an imidazole rings have many pharmacological properties and play important roles in biochemical processes [4] and these are known as inhibitors of fungicides and herbicides, plant growth regulators and therapeutic agents [5]. These are also a major component of a variety of drugs such as angiotensin II receptor antagonists, anti-inflammatory agents and protein kinase inhibitors [6]. The derivatives of imidazole possess a broad spectrum of pharmacological activities such as anticonvulsant [7], anti-Parkinson [8] and monoamine oxidase (MAO) inhibitory [9] activities and these are also widely applied as N-ligands coordinating transition metals [10-11]. The application of imidazoles in medicinal chemistry [12], natural products [13, 14] and some of 1,3-disubstituted imidazolium salts are act as ionic liquids [15, 16] are also well known.

Generally the substituted 2-cyclohexyl-4-phenyl-1H-imidazole derivatives are modulators of mammalian neuropeptide Y5 (NPY5) receptors [17], and also useful for treatment of various physiological disorders associated with NPY5 receptor activation, such as feeding disorders, psychiatric disorders and cardiovascular diseases. Compound Trifenaqrel [18] is a 2, 4, 5-triaryl-1H-imidazole that reduces platelet aggregation in several animal species and humans. Some of the aryl oxycyclohexyl imidazoles have been shown antileishmanial agents [19]. In continuation of our interest towards the synthesis of biologically potent heterocycles, we report herein the synthesis of novel cyclohexylmethyl-1H-imidazolocarboxamide 5.

2. MATERIALS AND METHODS

2.1. Materials

Melting points were measured in open capillary and were uncorrected. Column chromatography was performed using silica gel (100-200 mesh size) purchased from Thomas Baker and Thin Layer Chromatography (TLC) was carried out using aluminum sheets pre-coated with silica gel F254 purchased from Merck. IR spectra (KBr) were obtained using Baker WM-4(X) spectrometer (577model). 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded on a Bruker WM-400 spectrometer in DMSO-d6 with TMS as an internal standard. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrometer. CHN analysis was done by Carlo Erba EA 1108 automatic analyzer. Combustion analyses were found to be within the limits permissible errors. The chemicals and solvents used were of commercial grade and used without further purification unless otherwise stated.

2.2. General methods

2.2.1. Synthesis of 2-cyclohexyl acetonitrile (2)
Compound cyclohexyl methyl bromide 1 (0.005 mol) was dissolved in dry DMF at room temperature for 20 minutes then added NaCN (0.005 mol) slowly. The reaction mixture was stirred at room temperature for 30 h. After completion of the reaction (monitored by TLC), reaction mass was poured into ice cold water, extracted with ethyl acetate, then collected ethyl acetate layers were washed with cold water, dried over anhydrous Na₂SO₄ and concentrated under vacuum to get oily compound.

Yield:85%; IR(KBr,cm⁻¹): 3073.58, 2932.33, 2840.85, 2223.90, 1597.11, 1515.52; ¹H NMR (400MHz, DMSO-d₆): δ 1.35-1.38 (t, 1H, -CH₂), 1.52-1.62 (m,10H, 5x-CH₂), 2.10-2.12 (t, 2H, -CH₂), 13C NMR (100MHz, DMSO-d₆): δ 22.4, 25.8, 26.4, 27.2, 32.1, 116.2; MS(m/z) 124.2 (M+1). Anal. Calc'd for C₇H₁₃N: C, 77.99; H, 10.64; N, 11.37. Found: C, 77.92; H, 10.47; N, 11.24 %.

2.2.2. Synthesis of ethyl-2-cyclohexylacetimidate hydrochloride (3)

Dry HCl gas passed through the solution of 2-cyclohexyl acetonitrile 2 (0.01 mol) in dry ethanol for 50h by maintaining the temperature at 0-5°C. After completion of the reaction (monitored by TLC), the mixture was concentrated under vacuo, then triturated with diethyl ether, and the resulting compound ethyl-2-cyclohexylacetimidate hydrochloride 3 was dried under vacuo.

Yield:80%; IR(KBr,cm⁻¹): 3013.36, 2938.24, 2829.25, 1582.23; ¹H NMR (400MHz, DMSO-d₆): δ 0.88-0.97(m,3H,-CH₃), 1.39 (m,1H,-CH), 1.58-1.65 (m,10H,5x-CH₂), 2.16-2.18 (t,2H,-CH₂), 4.01-4.07(q,2H,-CH₃); 13C NMR (100MHz, DMSO-d₆): δ 14.8, 24.2, 25.4, 26.7, 27.2, 32.0, 60.4, 170.8; MS(m/z) 206.0 (M+H). Anal. Calc'd for C₁₀H₂₀CINO: C, 58.38; H, 9.80; N, 6.81. Found: C, 58.30; H, 9.64; N, 6.78 %.

2.2.3. Synthesis of 2-(cyclohexylmethyl)-4-methyl-1H-imidazol-5-carboxamide (4):

To a stirred solution of compound 3 (0.01 mol) in tertiary butanol, 2-chloroethylacetocate (0.01 mol) and liquid ammonia were added at -70 °C under N₂ atmosphere. Then the reaction slowly heated up to 100 °C for 20 h, around 20 kg/cm² pressure was developed during the reaction in autoclave. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and extracted with ethyl acetate (2x50 mL) and dried over anhydrous Na₂SO₄. The collected ethyl acetate was concentrated under vacuo to get the compound 2-(cyclohexylmethyl)-4-methyl-1H-imidazol-5-carboxamide 4 as viscous liquid.

Yield:40%; IR (KBr,cm⁻¹): 3437.72, 2917.58, 2848.47, 1661.34, 1590.11; ¹H NMR (400MHz, DMSO-d₆): δ 1.12-1.26 (m,4H,2x-CH₂), 1.59-1.70 (m,6H,3x-CH₃), 1.65-1.75 (m,1H,-CH), 2.33 (s,3H,-CH₃), 2.39-2.49 (m,2H,-CH₂); 13C NMR (100MHz, DMSO-d₆): δ 21.8, 25.4, 25.6, 32.1, 36.3, 41.2, 117.0, 150.6, 151.2, 160.5; MS(m/z) 222.2 (M+1)+. Anal. Calc'd for C₁₀H₁₅N₃O: C, 65.13; H, 8.65; N, 18.99. Found: C, 65.10; H, 8.59; N, 18.92 %.

2.2.4. Synthesis of 1-amino-2-(cyclohexylmethyl)-4-methyl-1H-imidazol-5-carboxamide (5)

Potassium tertiary butoxide (113.12 mmol) was added to a stirred solution of compound 4 (45.24 mmol) in N-methyl pyrrolidone (100 mL) at 0°C. Further Stirring was continued from 0°C to room temperature for 30 min followed by addition of 0-diphenylphosphinylhydroxylamine (81.44 mmol) lot wise about 30 min. The progress of the reaction was monitored by TLC (9:1; CH₂Cl₂ : MeOH). After completion of reaction, the mixture was quenched with water (500 mL) and extracted trice with ethylactate (2X100 mL). Combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ filtered and concentrated under reduced pressure to get the crude which was purified by flash column chromatography to get desired compound as off-white solid.

Yield: 35%; mp: 78-80 °C IR (KBr,cm⁻¹): 3351.38, 3185.32, 2914.54, 2844.25, 1668.69,
1500.57; 1H NMR (400MHz,DMSO-d6): δ 1.11-1.13 (m,2H, -CH3), 1.55-1.68 (m, 8H, 4x-CH2), 1.81-1.84 (m, 1H, -CH), 2.46 (s, 3H, -CH3), 2.81-2.83(dd, 2H, -CH2). 13C NMR (100MHz, DMSO-d6): δ 21.9, 25.4, 25.6, 28.4, 32.8, 39.6, 126.2, 152.6, 158.4, 159.4; MS (m/z) 237.0 (M+1) +. Anal. Calcd for C13H20N2O: C, 60.99; H, 8.53; N, 23.71. Found: C, 60.92.; H, 8.48; N, 23.64 %.

Reaction conditions: a) NaCN / DMF; b) Dry HCl gas in EtOH, c) α-chloroethylacetoacetate in tertiary-BuOH / liq NH3; d) t-BuOK in NMP and P(Ph)3.O,NH2.

3. RESULTS AND DISCUSSION

The synthetic route for the preparation of 1-amino-2-cyclohexylmethyl)-4-methyl-1H-imidazol-5-carboxamide 5 is outlined in Scheme-1. In the present investigation, cyclohexyl methyl bromide 1 was dissolved in DMF and added sodium cyanide at room temperature to afford compound 2. The compound 4 was obtained via heating of compound 2 with O-diphenylphosphinyl hydroxylamine in potassium tert-butoxide as a catalyst resulted in the formation of the cyclohexylmethyl-1H-imidazolocarboxamide 5. The structures of all the synthesized compounds were established on the basis of elemental and spectral analysis.

4. CONCLUSION

In conclusion, we have developed a simple and efficient method for the preparation of cyclohexyl-1H-imidazolecarboxamide starting form cyclohexylmethyl bromide through cyanation, imine formation, cyclization and amination as key steps. Further research and applications of the reactions are in progress in our laboratories. We believe that this method is highly useful for the synthesis of biologically potent highly substituted imidazole derivatives.

5. REFERENCES

13. Bara PS, O Malley DP and Zografos AL. Sceptrin as a potential biosynthetic precursor to complex pyrrole – imidazole alkaloids: The


