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# An efficient synthesis of novel cyclohexylmethyl-*1H*- imidazolo carboxamide

**[1] Boyina Gopala Rao[a], [1] Venkateswara Rao P, [2] Venkatnarayana P and [2] Bethanamudi. Prasanna [*].**

[1] Department Of Chemistry, Nizam College (Autonomous), Hyderabad, Andhra Pradesh, India

[2] Research Centre, Department of Chemistry, Chaitanya Post Graduate College (Autonomous), Hanamkonda, Warangal, Andhra Pradesh, India.

[*] **Corresponding Author:** E-Mail: prasschem@gmail.com

**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, $^{1}$H NMR, $^{13}$ C NMR and Mass spectral data.

**Keywords:** Cyclohexyl methyl bromide, Sodium cyanide, 2-chloroethylacetoacetate, Potassium tertiary butoxide and Diphenyl phoshorylamide.

## 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 monoamineoxidase (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 $Y_5$ (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 Trifenagrel [18] is a 2, 4, 5-triaryl-1*H*-imidazole that reduces platelet aggregation in several animal species and humans. Some of the aryloxycyclohexyl 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.

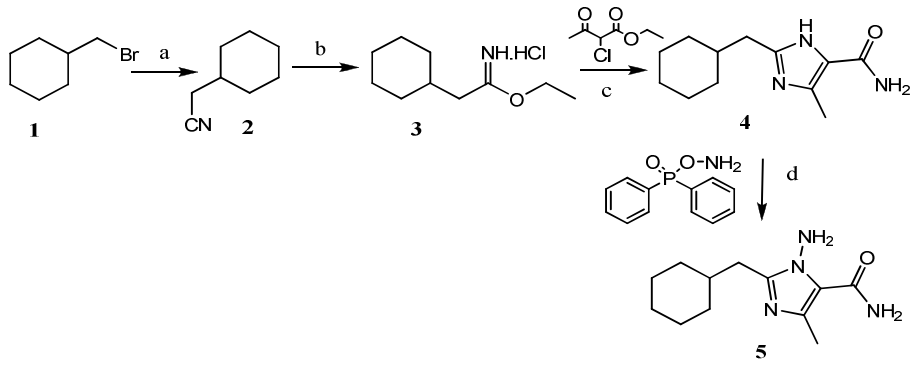
## 2. MATERIALS AND METHODS

### 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 60$F_{254}$ purchased from Merck. IR spectra (KBr) were obtained using Baker WM-4(X) spectrometer (577model). $^{1}$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Bruker WM-400 spectrometer in DMSO-$d_6$ 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)




**Scheme - 1: Preparation of 1-amino-2-cyclohexylmethyl)-4-methyl-1H-imidazol-5-carboxamide.**

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 $Na_2SO_4$ 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; $^1$H NMR (400MHz, DMSO-$d_6$):$\delta$ 1.35-1.38 (t, 1H, -CH), 1.52-1.62 (m,10H, 5x-$CH_2$), 2.10-2.12 (t, 2H,-$CH_2$), $^{13}$C NMR (100MHz, DMSO-$d_6$): $\delta$ 22.4, 25.8, 26.4, 27.2, 32.1, 116.2; MS(*m/z) 124.2* (M+1)+.Anal. Calcd for $C_8H_{13}N$: 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$^0$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-cyclohexylacetamiditate hydrochloride 3 was dried under vacuo.

Yield:80%;IR(KBr,$cm^{-1}$): 3013.36, 2938.24, 2829.25, 1582.23; $^1$H NMR (400MHz, DMSO-$d_6$):$\delta$ 0.88-0.97(m,3H,-$CH_3$), 1.39 (m,1H,-CH), 1.58-1.65 (m,10H,5x-$CH_2$), 2.16-2.18 (t,2H,-$CH_2$), 4.01-4.07(q,2H,-$CH_2$); $^{13}$C NMR (100MHz, DMSO-$d_6$): $\delta$ 14.8, 24.2, 25.4, 26.7, 27.2, 32.0, 60.4, 170.8; MS(*m/z)* 206.0 (M+H).Anal. Calcd for $C_{10}H_{20}ClNO$: 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-chloroethylacetoacete (0.01 mol) and liquid ammonia were added at -70 $^0$ C under $N_2$ atmosphere. Then the reaction slowly heated up to 100 $^0$C for 20 h, around 20 kg/$cm^2$ 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 $Na_2S0_4$ .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; $^1$H NMR (400MHz, DMSO-$d_6$):$\delta$ 1.12-1.26 (m,4H,2x-$CH_2$), 1.59-1.70 (m,6H,3x-$CH_2$), 1.65-1.75 (m,1H,-CH), 2.33 (s,3H,-$CH_3$), 2.39-2.49 (m,2H,-$CH_2$); $^{13}$C NMR (100MHz, DMSO-$d_6$): $\delta$ 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. Calcd for $C_{12}H_{19}N_3O$: 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 O-diphenylphosphinylhydroxylamine (81.44 mmol) lot wise about 30 min. The progress of the reaction was monitored by TLC (9:1: $CH_2Cl_2$: MeOH). After completion of reaction, the mixture was quenched with water (500 mL) and extracted trice with ethylaetate (2X100 mL). Combined organic layers were washed with brine, dried over anhydrous $Na_2S0_4$ 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 $^0$C IR (KBr,$cm^{-1}$): 3351.38, 3185.32, 2914.54, 2844.25, 1668.69,

1500.57; $^1$H NMR (400MHz,DMSO-$d_6$): $\delta$ 1.11-1.13 (m,2H, -$CH_2$), 1.55-168 (m, 8H, 4x-$CH_2$), 1.81-1.84 (m, 1H, -CH), 2.46 (s, 3H, -$CH_3$), 2.81-2.83(dd, 2H, -$CH_2$). $^{13}$C NMR (100MHz, DMSO-$d_6$): $\delta$ 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 $C_{12}H_{20}N_4O$: 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 $NH_3$; d) t-BuOK in NMP and $P(Ph)_2O_2NH_2$.

**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. the treatment of compound 2 by passing of HCl gas in ethanol to form the compound 3 then which was treated with 2-chloroethyl acetoacetate in the presence of liquid $NH_3$ in tertiary butanol as solvent around 20 kg/cm$^2$ pressure was developed during the reaction in autoclave. Heating of compound 4 with O-diphenylphosphinyl hydroxylamine in potassium tertiary 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.

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