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Synthesis of (2-methyl-6,7-dihydro-*5H*-benzo[6,7] Cyclohepta[1,2-*b*]pyridin-3-yl)(4-phenylpiperazin-1-yl)Methanone

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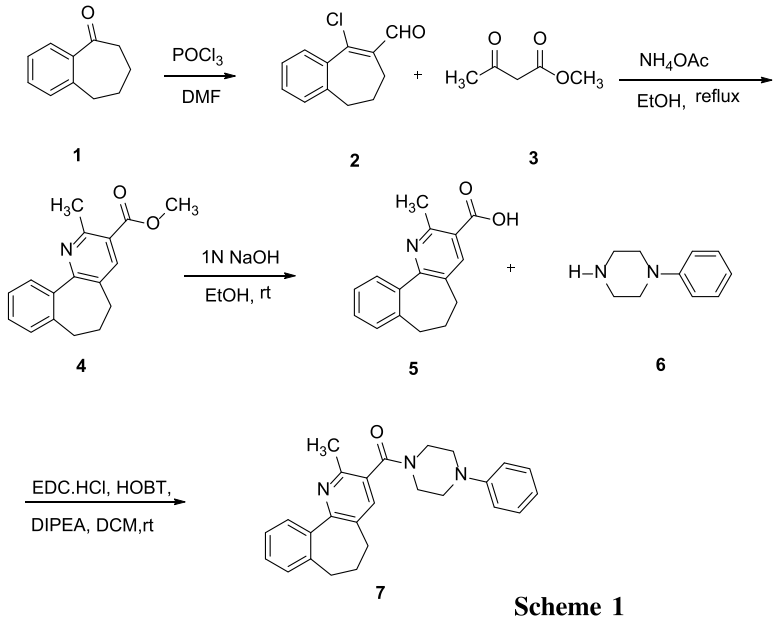
ABSTRACT

A novel approach for the synthesis of benzo[6,7]cyclohepta[1,2-*b*]pyridine derivatives has been developed using peptide reagents with phenyl piperazine at room temperature. The products obtained were of high yields.

Key words: Benzocylcoheptanone, phenyl piperazine, Vilsmeir-Haack reaction, ammonium acetate.

Introduction

Benzocycloheptanone and its derivatives are an important class of heterocyclic compounds, which constitute the key core of various natural products and play a unique role in drug discovery programme. They exhibit a wide range of biological activities such as cytotoxic, anticancer agents,[1-4] as high CB1 receptors,[5] and have very potent antagonistic activity.[5] In addition, these derivatives are widely used in diverse pharmaceutical applications, such as tricyclic antidepressants containing dibenzosuberone moieties mostly effecting the autonomic and central nervous systems and as traditional anti-depressants, like amitriptyline,[6] imipramine,[7] and noxiptiline[8] which continue to be used as first-line drugs in treating depressive disorders (Fig1). Pyridyl compounds are of interest to organic chemists in recent years owing to their wide spectrum of physiological activity.[9a-f] The condensed derivatives of pyridines play significant role in bioactive molecules, especially in the form of benzo[5,6] cyclohepta[1,2-*b*]pyridines which are structural analogues to benzocycloheptanone. The benzo[5,6]cyclohepta[1,2-*b*] pyridine is an important core biologically active compound with diverse biological activities, such as antihistamine as well as antitumor and anti-inflammatory activities. It is a highly potent pharmacophore and widely used in drugmolecular design. Derivatives containing this group such as loratadine, desloratadine, rupatadine and lonafarnib could exhibit enhanced biological profile with fore-mentioned biological activities. Because of the important aforementioned properties of benzocyclohepta[1,2-*b*] pyridines derivatives, preparation of this heterocyclic nucleus has gained great importance in organic synthesis.



Scheme 1

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EXPERIMENTAL

General

All reactions requiring anhydrous conditions were performed in oven-dried glassware under argon. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on Varian Gemini 200, 400 or Bruker WH 300 MHz spectrometers, using tetramethylsilane (TMS) as the internal standard. Chemical shifts were expressed in (ppm) down field from TMS. IR spectra were recorded on Perkin-Elmer model 683 or 1310 spectrometers with sodium chloride optics or KBr pellets. EI mass spectra were recorded on a VG Micromass-7070Hz 70eV using a direct inlet system. ESI MS were recorded on Thermo Finigan LCQ ion trap mass spectrometer equipped with electron spray ionization. High Resolution Mass spectra were recorded on Q STAR mass spectrometer (Applied Biosystems) at 5 or 7K resolution using polyethyelene glycol as an internal reference compound. All reactions were monitored by thin layer chromatography (TLC) employing 0.25 mm silica gel 60 plates (F_{254}, Merck). Column chromatography was performed using Acme silica gel (60-120 mesh). Visualization of the spots on TLC plates was achieved either by exposure to UV light, iodine vapor and by dipping the plates in Phosphomolybdic acid-ceric (IV) sulphate-sulphuric acid solution (PMA solution) and heating the plates at 120 °C.

9-Chloro-6,7-dihydro-5*H*-benzo[7]annulene-8-carbaldehyde (2):

Phosphorusoxychloride (0.9 g, 8.1 mmol) was added to a flask containing *N*, *N*-dimethylformamide (5 mL) in an ice bath and stirred for 10 min. The ice bath was replaced with an ambient temperature water bath and stirred for an additional 10-15 min. The benzocycloheptanone (**1**, 1.0 g, 6.2 mmol) was added and stirred for 15 min. The reaction mixture was heated to 80 ºC and stirred for an additional 3 h. The orange solution was diluted with ice water and neutralized with 20% sodium acetate solution and with diethyl ether (3 × 10-20 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (50 mL), brine 50 mL, and water (3 × 50 mL). The organic layer was dried with sodium sulphate and concentrated in vacuum to yield a red liquid. The product was purified by column chromatography (hexane/ EtOAc). Yield: 84%; IR (NEAT, ν cm^{-1}): 2936, 2860, 1671, 1580, 1448, 1262, 919, 750. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.00-2.20 (m, 4H, $2CH_2$), 2.62 (t, J = 6.4, 6.9 Hz, 2H, CH_2), 7.20-7.50 (m, 4H, Ar-H), 10.36 (s, 1H, CHO). EI-MS: m/z = 207 $[M+H]^+$, 229 $[M+Na]^+$.

Methyl-2-methyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridine-3-carboxylate (4):

A mixture of β-chloroacroleins (**2,** 0.42 mmol), methyl acetoacetate (**3,** 0.42 mmol) and ammonium acetate (0.84 mmol) was heated at reflux in ethanol for 8 h. The completion of the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice cold water and extracted with ethyl acetate. The organic layer was washed with brine and water and dried over Na_2SO_4. After evaporation of the solvent, the crude products were purified by column chromatography on silica gel (60-120 mesh, Merck) using the solvent system (petroleum ether-ethyl acetate, 9.8:0.2) to afford benzo[6,7]cyclohepta[1,2-*b*] pyridine **4**. White solid: m.p. 95-97 °C; IR (neat): ν_{max} 2925, 2856, 1721, 1592, 1543, 1426, 1259, 1240, 1178, 1089, 765, 738, 620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.18-2.29 (m, 2H), 2.48-2.57 (m, 4H), 2.89 (s, 3H), 3.95 (s, 3H), 7.22-7.26 (m, 1H), 7.33-7.43 (m, 2H), 7.73-7.77 (m, 1 H), 8.06 (s, 1H); ESI-MS: *m/z* 268 (M+H).

2-Methyl-6,7-dihydro-5*H*-benzo[6,7] cyclohepta[1,2-*b*] pyridine-3-carboxylic acid (5):

The intermediate benzo[6,7]cyclohepta[1,2-*b*]pyridine **4** was converted into its corresponding carboxylic acid **5** by treating with 1N KOH : EtOH (30 mL, 1:1) under reflux condition for 1h. After completion of the reaction (TLC analysis), the solution was allowed to cool to room temperature and ethanol was removed under vacuum, the obtained solid was filtered to 2-methyl-6,7-dihydro-5*H*-benzo[6,7] cyclohepta[1,2-*b*]pyridine-3-carboxylic acid (**5**) as white solid., m.p. 108-110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20-2.30 (m, 2H), 2.50-2.60 (m, 4H), 2.90 (s, 3H), 7.20 (d, 1H), 7.40-7.43 (m, 2H), 7.80 (d, 1 H), 8.20 (s, 1H); ESI-MS: *m/z* 254 (M+H).

(2-Methyl-6,7-dihydro-*5H*-benzo[6,7]cyclohepta[1,2-*b*] pyridin-3-yl)(4-phenylpiperazin-1-yl) methanone (7):

To the stirred solution of 2-methyl-6,7-dihydro-5*H*-benzo[6,7] cyclohepta[1,2-*b*]pyridine-3-carboxylic acid (0.1 g, 0.0005 mol) in DMF, *N*-phenyl piperzine (0.0005 mol) was added at room temperature, followed by the addition of EDC· HCl (0.0006 mol) and HOBt (0.0006 mol) and the mixture was stirred for 1h. After completion of the reaction (TLC analysis), small amount of ice cold water (10 mL) was added to the reaction mixture and then extracted with chloroform (2 x 10 mL). The chloroform layer was separated, dried over Na_2SO_4 and evaporated under vacuum to give corresponding (2-methyl-6,7-dihydro-*5H*-benzo[6,7] cyclohepta[1,2-*b*] pyridin-3-yl) (4-phenylpiperazin-1-yl) methanone. Yield: 78%; m.p. 93-95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20-2.28 (m, 2H), 2.47 (t, 2H), 2.55-2.59 (t, 2H), 2.60 (s, 3H), 3.15(t, 2H) 3.30(t, 2H) 3.50(t, 2H) 4.01(t,2H) 7.20-7.40 (m, 8H),7.70(s, 1H).

RESULTS AND DISCUSSION

Benzocycloheptanone (**1**) undergoes Vilsmeyer Haack Arnold reaction in the presence of phosphorous oxychloride to give 5-chloro-8, 9-dihydro-7*H*-benzocycloheptene-6-carbaldehyde (**2**) which has been treated with methyl acetoacetate (**3**) and ammonium acetate to give methyl-2-methyl-6,7-dihydro-5*H*-benzo[6,7] cyclohepta[1,2-*b*] pyridine-3-carboxylate (**4**)[10] followed by treatment with 1N KOH : EtOH (1:1) for 1h to produce 2-methyl-6,7-dihydro-5*H*-benzo[6,7] cyclohepta[1,2-*b*]pyridine-3-carboxylic acid (**5**). The acid reacts with phenyl piperazine in the presence

of coupling reagent DIPEA,HOBT, EDC.HCl in DMF under room temperature for 1h to give corresponding (2-methyl-6,7-dihydro-*5H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-3-yl) (4-phenylpiperazin-1-yl)methanone (**7**) respectively, as shown in Scheme 1.

Conclusions

In conclusion, we have successfully synthesized a novel analogue of benzocycloheptenone based phenyl piperazine. This simple procedure is efficient and can be applied for the synthesis of secondary amines. The ambient reaction conditions, shorter reaction times, good to excellent product yields gives us an efficient approach for synthesis of substituted benzocycloheptenones.

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