



Research Article

SYNTHESIS OF 1, 2 DISUBSTITUTED BENZIMIDAZOLES USING SODIUM ACETATE AS CATALYST

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ABSTRACT

Benzimidazoles are the fused bicyclic aromatic systems containing nitrogen as heteroatom. The usage of these compounds as medicinal drugs is abundantly increasing as they possess wide range of biological functions. In present method, condensing diaminobenzene with benzoic acid in presence of sodium acetate, methyl alcohol produced 2-phenyl benzimidazole and further reaction with 4-piperazine benzyl chloride afforded 1, 2 disubstituted benzimidazoles. The method was proved to be easy, efficient, and produced products in good yield.

Key Words: Benzimidazole, Benzyl chloride, Heteroatom, Infrared, Piperazine, Spectroscopy.

INTRODUCTION

The development of benzimidazoles has attained major importance in the recent years because of their tremendous biological importance. The anthelmintic, antifungal, antiprotozoal, antiulcer, anti-inflammatory, analgesic and anticancer properties of benzimidazoles have been reported¹. Many synthetic approaches were reported for the synthesis of benzimidazoles using aldehydes and acids in presence of catalysts such as boric acid², monobasic acids (Hydrochloric acid, acetic acid, and ethyl alcohol)³ by varying solvents (dimethyl formamide, acetonitrile, and nitrobenzene)⁴ and temperature conditions⁵. The biological significance of benzimidazoles can be enhanced by substituting 1 and 2 positions with various alkyl, aryl, and heterocyclic groups and was reported⁶. Among them piperazines are the groups possessing good biological activity and are being substituted to various important fused heterocyclic systems⁷. In present methodology benzimidazole derivatives were prepared by treating diaminobenzene with benzoic acid in presence of sodium acetate, methyl alcohol and 4-piperazine benzyl chloride⁸⁻¹¹. Because of its mild nature, easily availability and comfortable handling together with its low price made it a good catalyst for use in the synthesis of benzimidazole derivatives¹².

MATERIALS AND METHODS

Chemicals grade AR used in present investigation were procured from Aldrich chemicals, Hychem laboratories. Infrared spectra were recorded on Perkin Elmer Model 283B FT-IR instrument and values are given in cm^{-1} . Proton magnetic resonance spectra were recorded on Avance-300 MHz Bruker UX-NMR instrument. The samples were made in CCl_4 /chloroform-d (1:1) or DMSO-d_6 using tetra methyl silane (Me_4Si) as the internal standard and are given in the δ scale. Analytical thin layer chromatographic (TLC) was performed on pre coated silica gel-60 F_{254} (0.5mm) glass plates. Visualization of the spots on TLC plates was achieved by exposing to iodine vapours and ultraviolet

light. All solvents used for gel column chromatography were distilled prior to use. Silica gel used was 100-200 mesh & 60-120 mesh.

Procedure for synthesis of 2-phenyl benzimidazole^{13, 14}

A mixture of (0.25mol) substituted diaminobenzene, (0.34ml) of benzoic acid, sodium acetate (0.15g) and methyl alcohol (4ml) were stirred for 1h at 80-90°C. The crude form of 2-phenyl benzimidazole obtained was filtered, washed and recrystallised with pure ethanol to obtain it in pure form.

Procedure for synthesis of 1(4-piperazinylbenzyl), 2-phenyl benzimidazole¹⁵⁻¹⁷

A mixture of 2-phenyl benzimidazole (0.05 mol) is treated with 4-piperazine benzyl chloride (0.05mol) to get crude form of compound. It was washed and purified to obtain it in pure form. Developed design for the synthesis of benzimidazoles was shown in figure 1.

RESULT AND DISCUSSION

Two pot synthesis of benzimidazole derivatives (**5i-5v**) was achieved by treating aromatic diamines with benzoic acid, sodium acetate, methyl alcohol and substituted piperazines illustrated in table 1. The reactions were preceded precisely in presence of sodium acetate, methyl alcohol and produced reaction products in good yield. By utilising various catalysts and solvents, reaction conditions were optimised at different temperatures. Among them the utilisation of sodium acetate as catalyst and methyl alcohol as solvent has proved more efficient and simple for the development of 1, 2 disubstituted benzimidazole derivatives.

The structural characterisation of series of synthesised compounds was achieved by IR and ¹HNMR spectroscopic methods and developed characteristic absorption peaks. The spectral data of the synthesised derivatives clearly show that aromatic diamines can be easily converted into benzimidazoles by utilising benzoic acid, sodium acetate and methyl alcohol.

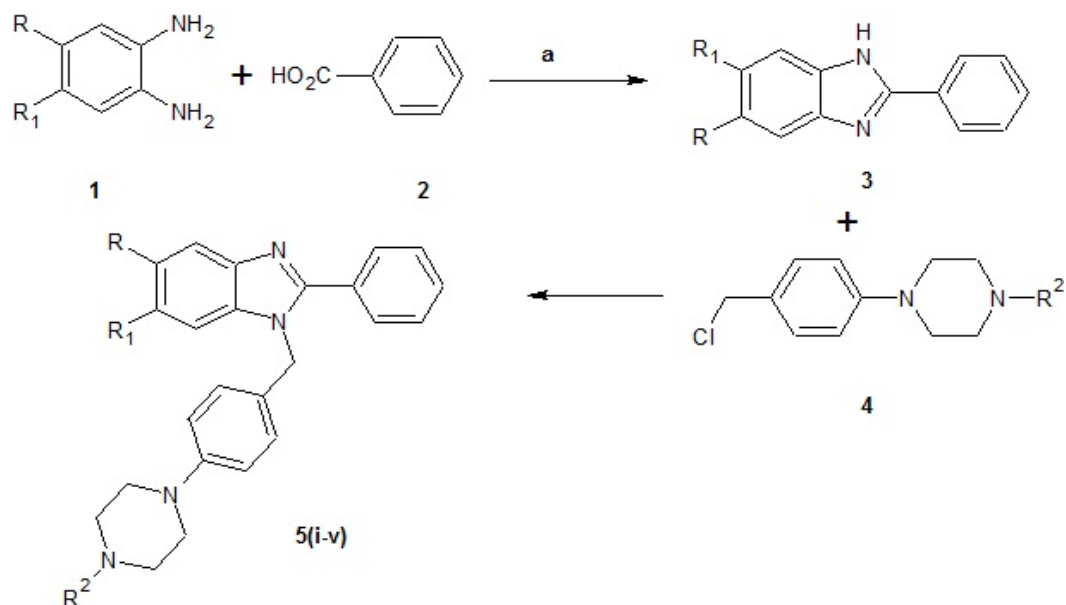


Figure 1: Schematic Representation Of Synthetic Route
 1. Diaminobenzene 2. P- Benzoic acid 3. 2-phenyl Benzimidazole.
 4. 4-piperazine benzyl chloride
 5(i-v). 1, 2 disubstituted Benzimidazoles
 a. NaOAc (sodium acetate), CH₄O (methyl alcohol), 80^oC

Table 1: Synthesised Benzimidazole Derivatives

Entry	Substituents	Compound ^a	Molecular Formula	Time ^b	Yield ^c
1(5i)	R=CH ₃ , R ¹ =H R ² =H		C ₂₅ H ₂₆ N ₄	60	72
2(5ii)	R=CH ₃ , R ¹ =H R ² =CH ₃		C ₂₆ H ₂₈ N ₄	60	70
3(5iii)	R=CH ₃ , R ¹ =H R ² =CH ₂ CH ₃		C ₂₇ H ₃₀ N ₄	60	65

4 (5iv)	R=Cl, R ¹ =H R ² =CH ₂ CH ₃		C ₂₆ H ₂₇ ClN ₄	60	72
5 (5v)	R=Cl, R ¹ =CH ₃ R ² =CH ₂ CH ₃		C ₂₇ H ₂₉ ClN ₄	60	72

a. Synthesised benzimidazole derivative b. Provided reaction time (min)
c. Isolated yield (%)

Spectral data of synthesised compounds (5i-v)

5i:1-(4-piperazinyl benzyl) 2-phenyl 5-methyl benzimidazole.
(IR (cm⁻¹): 3066(Ar-C-H), 2920, (alkyl-C- H), 1600-1420 (C-C), 1634(C=N).

¹H NMR (DMSO-d₆) δ ppm: δ 6.82 (d, 2H, aromatic), 6.98 (d, 2H, aromatic), 7.06 (t, 1H, aromatic), 7.28 (m, 2H, aromatic), 7.52 (m, 2H, aromatic), 5.5 (s, 2H, - benzyl -CH₂), 2.32 (s, 3H, Ar-CH₃).

5ii.1-{4-(N-methyl piperazinyl) benzyl} 2-phenyl 5-methyl benzimidazole.

(IR (cm⁻¹):3066(Ar-C-H), 2920(alkyl-C- H), 1600-1420 (C-C), 1634(C=N).

¹H NMR (DMSO-d₆) δ ppm: δ 6.82 (d, 2H, aromatic), 6.98 (d, 2H, aromatic), 7.06 (t, 1H, aromatic), 7.28 (m, 2H, aromatic), 7.52 (m, 2H, aromatic), 5.5 (s, 2H, -CH₂-benzyl), 2.32 (s, 3H, Ar-CH₃).

5iii.1-{4-(N-ethyl piperazinyl) benzyl} 2-phenyl 5-methyl benzimidazole.

(IR (cm⁻¹):3066(Ar-C-H), 2920(alkyl-C- H), 1600-1420 (C-C), 1634(C=N).

¹H NMR (DMSO-d₆) δ ppm: δ 6.82 (d, 2H, aromatic), 6.98 (d, 2H, aromatic), 7.06 (t, 1H, aromatic), 7.28 (m, 2H, aromatic), 7.52 (m, 2H, aromatic), 5.5 (s, 2H, -CH₂-benzyl), 2.32 (s, 3H, Ar-CH₃).

5iv. 1-{4-(N-ethyl piperazinyl) benzyl} 2-phenyl 5-chloro benzimidazole.

(IR (cm⁻¹):3066(Ar-C-H), 2920(alkyl-C- H), 1600-1420 (C-C), 1634(C=N), 790(C-Cl)

¹H NMR (DMSO-d₆) δ ppm: δ 6.82 (d, 2H, aromatic), 6.98 (d, 2H, aromatic), 7.06 (t, 1H, aromatic), 7.28 (m, 2H, aromatic), 7.52 (m, 2H, aromatic), (s, 2H, -CH₂-benzyl).

5v.1-{4-(N-ethyl piperazinyl) benzyl} 2-phenyl 5-chloro 6-methyl benzimidazole.

(IR (cm⁻¹):3066(Ar-C-H), 2920(alkyl-C- H), 1600-1420 (C-C), 1634(C=N), 790(C-Cl)

¹H NMR (DMSO-d₆) δ ppm: δ 6.82 (d, 2H, aromatic), 6.98 (d, 2H, aromatic), 7.06 (t, 1H, aromatic), 7.28 (m, 2H, aromatic), 7.52 (m, 2H, aromatic), (s, 2H, -CH₂-benzyl), 2.32 (s, 3H, Ar-CH₃).

CONCLUSION

In present methodology we have developed a simple, short and efficient method for the synthesis of 1, 2 disubstituted benzimidazole derivatives from aromatic amines and benzoic acid in a two-step procedure using sodium acetate as catalyst and achieved reaction products in good yield. Sodium acetate served as a good catalyst by providing mild reaction conditions, good yield of products and was easily removed from the reaction mixture. 5 benzimidazole derivatives were prepared and characterisation of synthesised compounds was achieved by IR and ¹H NMR spectroscopic methods. In future, the synthesised derivatives may serve as potent medicinal agents with significant biological activity.

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