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Ecofriendly one pot synthesis of 2-substituted benzimidazole

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ABSTRACT

Various 2-substituted benzimidazole derivatives have been prepared from o-phenylene diamine and substituted aldehyde in presence of ammonium bromide as catalyst at room temperature. This method was proved to be simple, facile and ecofriendly with good yield.

Keywords: Ecofriendly synthesis, Substituted aldehyde, o-Phenylene diamine, benzimidazole, ammonium bromide.

INTRODUCTION

Benzimidazole scaffold have received considerable attention in pharmaceutical chemistry [1-3], due to their wide applications as antiulcer, antihypertensive, antiviral, antifungal, anticancer, antitumor, anti-inflammatory and antihistamine activities [2].They are important intermediates in many organic reactions [3]. In addition, these compounds also seen as ligands in biological model [4].

Various classical method for benzimidazole synthesis involve coupling of o-phenylene diamine with acids, acid chlorides, nitriles, amides. They usually require strong acidic condition such as Polyphospheric acid [5] or mineral acid [6]. In the alternative approach benzimidazole have been prepared from o-phenylene diamine and substituted benzaldehyde in presence of $Sc(OTf)_3$ or $Yb(OTf)_3$[7,8], H_2O_2-HCl[9], Sulphanic acid[10], Silica-Sulphuric acid[11], NH_4Cl[12] were reported. However the reported methods suffering from number of drawbacks like prolonged reaction time, high temperature, hazardous chemicals, and expensive catalyst.

By knowing importance of green methodology, we reported an ecofriendly synthesis of 2-substituted benzimidazole by using Ammonium bromide as catalyst. Synthesized compounds are conformed by spectral study and by comparing physical constant with reported one.

MATERIAS AND METHODS

All the reagents & chemicals used were of analytical grade. Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded in DMSO on Broker Avalce-400MHz using TMS as internal standard. Mass spectra were recorded on Micro mass Q-T micro (TOF MS ES+). Electronic spectra were recorded on Shimadzu UV-3600 using DMSO.

General procedure for synthesis of benzimidazole:
To a mixture of o-phenylene diamine (0.100g, 0.92mmol) and various substituted aldehyde(0.100g, 0.92mmol) in 5 ml ethanol was added NH4Br (0.05 g, 10 mol%). The resulting mixture was stirred for 2 h at room temperature. Completion of reaction mixture was confirmed by TLC (ethyl acetate : hexane, 1:2). The reaction mixture was poured in ice cold water and the product was precipitated as yellow solid. The content was filtered and product was washed with water and then purified by recrystallization from ethanol.

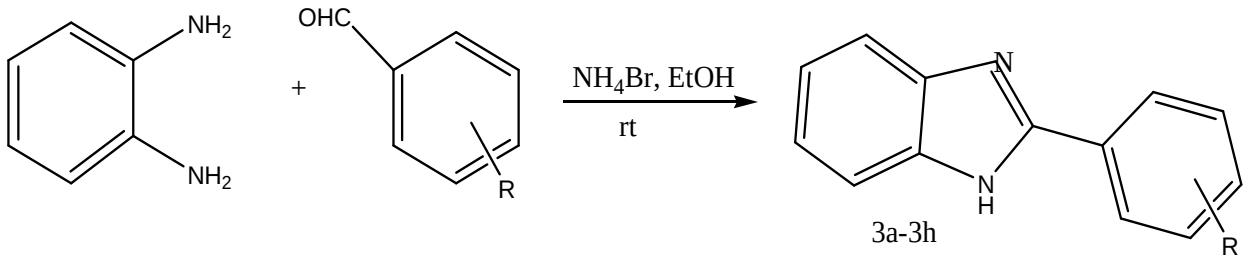
Compound 3f: 2-(furan-2-yl)-1H-benzo[d]imidazole:
1H NMR (400 MHz, $CDCl_3$, d ppm): 12.87 (s, 1H), 8.07 (d, 1H, J = 1.19 Hz), 7.47 (d, 2H, J = 1.50 Hz), 7.15–7.19 (m, 3H), 6.78 (m, 1H); **IR (KBr)**: 3442 (-NH), 3093, 1625 (C-N) 1521, 1438, 1355, 973 cm^{-1}; **MS: m/z:** 185.1; **Anal. Calcd** for C11H8N2O: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.68; H, 4.39; N, 15.48

Compound 3h: 2-(4-nitrobenzyl)-1H-benzo[d]imidazole:
1H NMR (400 MHz, CDCl3, d ppm): 12.98 (s, 1H) 8.41 (d, 2H, J = 8.05 Hz), 8.02 (d, 2H, J = 8.1 Hz), 7.92–7.95 (m, 2H), 7.51–7.55 (m, 2H); **IR (KBr)**: 3447 (–NH), 3083, 2961, 1631 (C N) 1506, 1372, 972 cm^{-1}; **MS: m/z:** 240.1; **Anal. Calcd** for C13H9N3O2: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.48; H, 3.74; N, 15.58

RESULTS AND DISCUSSION

In continuation of our research work on the development of useful synthetic methodologies, we have observed that benzimidazole derivatives were prepared by reaction between o-phenylene diamine and various substituted aldehydes using catalytic amount of NH_4Br in ethanol at room temperature. The completion of reaction mixture was monitored by TLC (1:2, ethyl acetate: hexane). This methodology was applied for synthesize library of 2-substituted benzimidazole.

The electronic effect of the different substituted aldehyde has been investigated and it was observed that aldehyde with electron withdrawing group afford good yield with shorter reaction time compared to aldehyde having electron donating groups. Similar to this, aliphatic aldehyde and aryl ketones reacted very slowly with lower yield. The products were isolated in high yields (82–90%). Maximum number of products was purified by using 60–120 mesh size silica gel for column chromatography with acetone in hexane. The structures of the products were determined from their spectral (^{1}H NMR, IR and MS) data.



O-phenyl diamine **Aldehyde** **Benzimidazole**

TableI: Synthesis of 2-substituted benzimidazole (3a-3h) by using ammonium bromide

Entry	Aryl aldehyde	Time (min)	Isolated yield	M.P. in ^oC observed	M.P.(reported) in ^oC
3 a	Ph	40	88	292–293	292
3 b	4-MeC_6H_4	60	82	274-276	275
3 c	4-$MeOC_6H_4$	55	80	227–228	226
3 d	1-Naphthyl	60	80	264–265	266
3 e	2-Pyridyl	55	85	245-247	245-248
3 f	2-Furyl	60	82	295-297	296
3 g	4-BrC6H4	50	87	291–292	291–294
3 h	4-$NO_2C_6H_4$	45	90	311–312	316

CONCLUSION

We have developed a simple, efficient and green method for synthesis of 2-substituted benzimidazole derivatives by using easily available and efficient catalyst ammonium bromide. The method offers several advantages like simple reaction conditions, short reaction time, high yields of products and simple experimental operation, which leads to a useful and attractive process for synthesis of benzimidazole derivatives.

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