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Ferric chloride immobilized on neutral alumina: an efficient catalyst for the solvent-free selective synthesis of 1, 2-disubstituted benzimidazoles

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A B S T R A C T

Synthesis of 1,2-disubstituted benzimidazoles from o-phenylenediamine and aromatic aldehydes in an excellent yield (86-95%)in presence of $FeCl_3$–Al_2O_3 using microwave (MW) irradiation under solvent-free conditions. The present protocol shows some specific advantages such as mildness, short reaction times and enhanced selectivity under solvent-free conditions.

Keywords: Benzimidazoles, microwave assisted synthesis, Lewis acid

A R T I C L E I N F O

CONTENTS

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1. Introduction

Benzimidazole derivatives have occupied a prominent place in medicinal chemistry. Benzimidazoles have a long and distinguished history extending from the days of their discovery as important heterocycle to their current use in the chemotherapy of AIDS. During the last two decades, several Benzimidazole derivatives have been developed as chemotherapeutic agents and have found wide clinical applications. Benzimidazole derivatives have been reported to have a wide range of pharmacological and biochemical activity. It consider to be CNS depressant, anti-Parkinson, antiviral activity [1-4], anti ulcerative, antihypertensive, antifungal, antitumor, antihistaminic, anti-bacterial and

antihelminthes agents. The optimization of benzimidazole derivatives based on their structures has resulted in various potent drugs that are now being currently practiced in the market, like albendazole, omeprazole, mebendazole, etc. Several compounds from this class have been used as inhibitors of hepatitis C virus NS5B polymerase [5], thrombopoietin receptor agonists [6], selective inhibitors of 1KK-ε kinase [7] and non steroidal antiandrogen [8], currently predominantly used for the treatment of androgen dependent prostate cancer in mature rats.

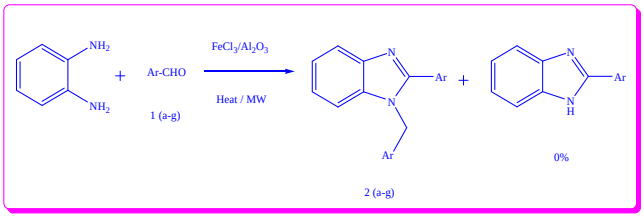
Synthesis of benzimidazole derivatives has been a developing field within heterocyclic chemistry for the past several decades because of their ready accessibility through synthesis. The major drawbacks of several reported methods were low yields and formation of inseparable mixture of mono and disubstituted benzimidazoles. Therefore, this reaction continues to be the focus of the researchers striving to find milder and more efficient procedures for the synthesis substituted benzimidazoles. This has led to the development of several synthetic methodologies synthesis of benzimidazole. These involves the condensation of *o*-phenylenediamine and aryl carboxylic acid or their derivatives such as amidates, orthoesters, nitriles in presence of strong acid such as polyphosphoric acid or mineral acid [9-12] and the thermal or acid promoted cyclization of N- (N-arylbenzimidoyl))-1,4-benzoquinone-imines [13]. Another protocol for the synthesis of these compounds involves the reaction of o-phenylenediamine and aldehyde in presence of acid catalysts under various reaction conditions [14-17].

However there are still some limitations with the existing protocols such as drastic reaction conditions, tedious work-up procedures, poor selectivity, low yields. Recently, several reports [18-19] that have applied MW technology in solid-phase synthesis are now widely reported because of its faster chemistry and formation of cleaner products compared with conventional heating. In continuation of our recent efforts [20-24] into the applications of $FeCl_3$ adsorbed on inorganic support as a post transitional Lewis acid in organic synthesis, we wished to explore the usage of $FeCl_3/Al_2O_3$ for the selective synthesis of 1,2-disubstitued benzimidazoles by the application of MW technology. To the best of our knowledge, the $FeCl_3/Al_2O_3$ catalyst-system has not been used earlier for the synthesis of benzimidazoles.

2. Experimental

Melting points were measured by using the capillary tube method with an electrothermal method 9200 apparatus. ^{1}H NMR spectra were recorded on BRUKER ADVANCE II 400 NMR Spectrometer using TMS as internal standard. The mass spectra were obtained on a JEOL 5x102/DA-6000 mass spectrometer. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-*d* or DMSO-*d*6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm)

General procedure for the synthesis of benzimidazoles (2a-g): Freshly distilled aromatic aldehyde (20 mmol), *o*-phenylenediamine (10 mmol) and 3.1 g of catalyst (5 mol% with respect to $FeCl_3$) were mixed thoroughly in a beaker with glass rod and then irradiated in the MW oven for about 10 min at power level 800 W with 30 sec pause after every one min. Upon completion of the reaction (TLC), the reaction mixture was cooled at room temperature, ethyl acetate was added, and stirred well followed by filtration through celite under suction. The organic layer was washed with water (2×30 ml) and brine (30 ml). After drying over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue upon column chromatography affords the pure product. All the products were identified by spectral (IR, ^{1}H NMR, ^{13}C NMR and mass) and analytical data.



Scheme I: The synthetic route was depicted in scheme I

3. Results and Discussion

Spectral data for selected compounds:

1-Phenylmethyl-2-phenyl-1*H*-benzimidazole (2a): White solid, mp 131-133ºC. IR (cm^{-1}, KBr): 3392, 1602, 1508, 1460, 1388, 1264, 1161, 1129, 1073, 776, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, *J* = 8.1 Hz, 1H), 7.68 (m, 2H), 7.47 (m, 3H), 7.22-7.34 (m, 6H), 7.11 (d, *J* = 7.4 Hz, 2H), 5.46 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 153.5, 142.4, 136.2, 135.5, 129.5, 129.6, 128.8, 128.6, 128.4, 127.2, 125.5, 122.8, 122.3, 119.4, 110.4, 47.8.

1-(4-Methylphenylmethyl)-2-(4-methylphenyl)-1*H*-benzimidazole (2b): White Solid, mp 128-130ºC; IR (cm^{-1}, KBr): 3545, 1683, 1610, 1441, 1248, 1183, 1119, 983 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.45 (d, *J* = 7.9 Hz, 1 H), 7.58 (d, *J* = 8.1 Hz, 2 H), 7.28-7.31 (m, 2 H),.20-7.24 (m, 3 H), 7.13 (d, *J* = 7.9 Hz, 2 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 5.41 (s, 2 H), 2.40 (s, 3 H), 2.33 (s, 3 H).

1-(4-Methoxyphenylmethyl)-2-(4-methoxyphenyl)-1*H*-benzimidazole (2c): White Solid, mp 129-130ºC. IR (cm^{-1}, KBr): 3529, 1608, 1586, 1228, 1291, 1284, 1291, 1244, 1170, 1107, 1082, 1011 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, *J* = 8.0 Hz, 1 H), 7.60 (t, *J* = 8.3 Hz, 3 H), 7.21-7.29 (m, 3 H), 6.84-7.04 (m, 6H), 5.38 (s, 2H), 3.83 (s, 3 H), 3.75 (s, 3 H).

1-(4-Chlorophenylmethyl)-2-(4-chlorophenyl)-1*H*-benzimidazole (2d):

White Solid, mp 136ºC. IR (cm^{-1}, KBr): 3447, 1601, 1493, 1384, 1291, 1249, 1160, 765 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, *J* = 6.6 Hz, 1 H), 7.59 (d, *J* = 6.7 Hz, 2 H), 7.43 (d,

J = 6.8 Hz, 2 H), 7.30-7.36 (m, 3 H), 7.19 (t, *J* = 7.8 Hz, 2 H), 7.02 (d, *J* =7.0 Hz, 2 H), 5.36 (s, 2 H).

1-(4-Bromophenylmethyl)-2-(4-bromophenyl)-1*H*-benzimidazole (2e): White Solid, mp =140-141ºC. IR (cm^{-1}, KBr): 3035, 2890, 1618, 1592, 1052 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.88 (d, *J* = 7.92 Hz, 1 H), 7.60 (d, *J* = 7.52 Hz, 2 H), 7.53(d, *J* = 8.36 Hz, 2 H), 7.48-7.46 (m, 2 H), 7.34 (t, *J* = 7.24 Hz, 1 H), 7.27 (t, *J* = 8.36 Hz, 1H), 7.20 (d, *J* = 7.96 Hz, 2 H), 6.96 (d, *J* = 7.88 Hz, 2 H), 5.38 (s, 2 H).

1-(4-Trifluoromethylphenylmethyl)-2-(4-(trifluoromethyl) phenyl)-1*H*-benzimidazole (2f): White Solid, mp 145-147ºC. IR (cm^{-1}, KBr): 3025, 1609, 1589, 1108, 1058 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.88 (d, *J* = 7.96 Hz, 1 H), 7.61 (d, *J*= 8.48 Hz, 2 H), 7.54-7.46 (m, 4 H), 7.36-7.33 (m, 2 H), 7.29-7.26 (m, 1 H), 7.20 (d, *J* = 7.96 Hz, 2 H), 6.97 (d, *J* = 8.32 Hz, 2 H), 5.38 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ 152.4, 143.1, 140.0, 135.9, 131.9, 130.5, 129.5, 127.8, 126.2, 126.1, 125.9, 125.1, 125.0, 123.9, 123.3, 122.4, 119.7, 119.6, 110.3, 48.0.

1-(4-Phenylmethyloxyphenylmethyl)-2-(4-benzyloxy-phenyl)-1*H*-benzimidazole (2g): White Solid, mp 127 ºC. IR (cm^{-1}, KBr): 3434, 1610, 1511, 1455, 1384, 1246, 1175, 1024 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.83 (d, *J* = 7.5 Hz, 2 H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.29-7,42 (m, 9H), 7.21 (d, *J* = 2.8 Hz, 4H), 7.06 (dd, *J* = 2.9 Hz, 4H), 6.92 (d, *J* = 8.2 Hz, 2H), 5.38 (s, 2H), 5.11 (s, 2H), 5.03 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 160.64, 158.90, 137.04, 136.59, 131.28, 129.20, 128.68, 128.61, 128.04, 127.80, 123.32, 123.11, 120.26, 115.90, 115.66, 110.98, 70.63, 48.44.

4. Conclusion

The present work concludes that, $FeCl_3/Al_2O_3$ has been employed as a novel and efficient catalyst for the synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles. The present methodology is very simple, cheap and shows some specific advantages such as mildness, short reaction times and enhanced selectivity under solvent-free conditions.

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