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1,4-Diazabicyclo [2.2.2] octanium diacetate: As an effective, new and reusable catalyst for the synthesis of benzo[*d*]imidazole☆

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ABSTRACT

A general synthetic route to benzo[*d*]imidazoles has been developed using 1,4-diazabicyclo [2.2.2] octanium diacetate as a new bis ionic liquid under thermal and solvent free condition. The union of two fragments including one equivalent of various aldehydes and one equivalent of 1,2-phenylenediamine was accomplished by an efficient and convenient protocol enabling the synthesis of benzo[*d*]imidazoles in excellent yields. The major advantages of the present method are: less reaction times, high yields, and easy purification of the products, solvent-free conditions, environmental friendliness, and convenient operation.

1. Introduction

Compounds with imidazole nucleus are a common and important substructures found in natural products and pharmacologically active compounds. They act as glucagon receptor antagonists, [1] inhibitors of P38 MAP kinase, [2] β-Raf kinase, [3] transforming growth factor b1 (TGF-b1) type 1 activin receptor-like kinase (ALK5), [4] cyclooxygenase-2 (COX-2), [5] CB1 cannabinoid receptor antagonists, [6] modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR), biosynthesis of interleukin-1 (IL-1) [7].

Many functionalized imidazoles behave as antibacterial, [8] antibiotics, [9] antiulceretics, [10] fungicides, [11] antidiabetic, antihypertensive and anti-inflammatory agents [12,13].

In 1822, Japp and Radziszewki reported the first three component cyclocondensation synthesis of the imidazole nucleus from 1,2-dicarbonyl compounds, aldehydes and ammonia to obtain 2,4,5-triphenyl-1*H*-imidazole [14,15]. In addition, they can also be accessed by the hetero-cope rearrangement, [16] cycloaddition reaction of mesoionic-1,3-oxazolium-5-olates with *N*-(arylmethylene)-benzenesulfonamides, [17] four component condensation of aryl glyoxals, primary amines, carboxylic acids and isocyanides on Wang resin, [18] condensation of a 1,2-diketone with an arylnitrile and primary amine under microwave irradiation, [19] and reaction of *N*-(2-oxo)-amides with ammonium trifluoroacetate [20]. Another method for the synthesis of these compounds is the reaction of 1,2-phenylenediamine with aldehydes in the presence of acidic catalysts under various reaction conditions [21–29]. However, many of these methods suffer from acidic media, unsatisfactory yields, long reaction times, difficult work up, excessive use of reagents and catalyst. It is therefore important to find more convenient methods for the preparation of these compounds.

2. Experimental

Chemicals were purchased from Merck and Fluka. All solvents used were dried and distilled according to standard procedures. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were determined on a Shimadzu FT-IR 8600 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 400 DRX Avance instrument at 400 and 100 MHz.

2.1. Preparation of 1,4-diazabicyclo [2.2.2] octanium diacetate, [DABCO] dihydroacetate, as a novel bis ionic liquid

A mixture of 1,4-diaza-bicyclo [2.2.2] octane (10 mmol) and wet acetic anhydride (20 mmol) was irradiated with laboratory microwave equipped with thermometer (180 W) for 2 min at 100 °C three times. After completion of the reaction, the mixture was washed with diethyl ether (3 × 10 mL). The organic product was extracted from liquid phase and evaporated under vacuum to produce desired ionic liquid.

Analytical data for DABCO-dihydroacetate: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.16$ (s, 6H), 3.01 (s, 12H), 14.11 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.0, 44.5, 175.9$ ppm.

☆ Dr. Zare is submitting this paper for publication in the journal of molecular liquids.

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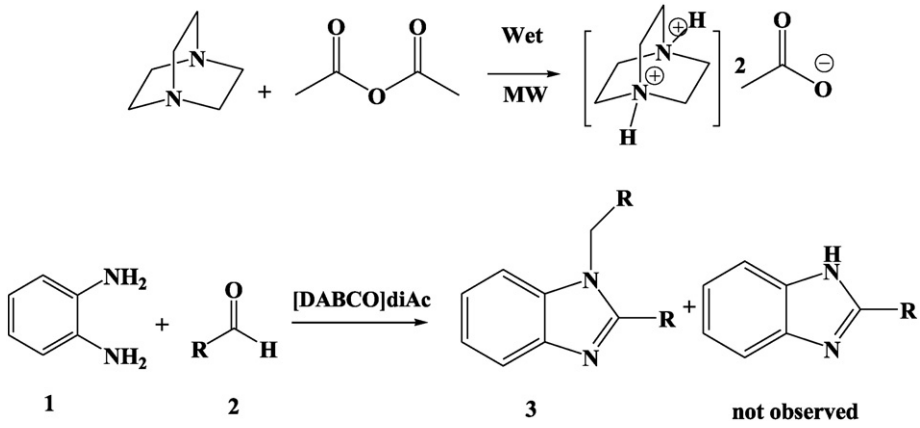

Scheme 1. Synthesis of DABCO-dihydroacetate and benzimidazoles.

2.2. General procedure for the preparation of 3a-l

A mixture of aldehyde (1 mmol), 1,2-phenylenediamine (1 mmol) and [DABCO] dihydroacetate (0.5 mmol) was heated at 80 °C for the required reaction time according to Table 2. After completion of reaction, as indicated by TLC, the reaction product was extracted by $CHCl_3/H_2O$. After evaporation of organic solvent, the crude product was released and recrystallized from EtOH and dried to afford the powdery compounds of **3a–l**.

The aqueous phase was concentrated under reduced pressure, washed with diethyl ether, and evaporated under reduced pressure to recover the ionic liquid for subsequent use.

2.2.1. Analytical data for selected compounds

1-Benzyl-2-phenyl-1*H*-benzo[*d*]imidazole (**3a**). FT-IR (KBr): 2924 (aliphatic C—H stretch), 1625 (C═N stretch), 3041 (aromatic C—H stretch), 1555, 1458 (aromatic C═C stretch), 1317 (C═N stretch), 1163 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 5.79$ (s, 2H), 7.19 (d, $J = 7.6$ Hz, 1H), 7.30–7.39 (m, 2H), 7.50–7.66 (m, 3H), 7.69–7.84 (m, 4H), 7.87–7.96 (m, 3H), 8.50 (d, $J = 7.6$ Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 47.2$, 110.6, 118.6, 122.0, 126.2, 127.8, 128.4, 128.9, 129.1, 129.6, 135.1, 135.8, 143.0, 149.1, 152.9. Anal Calc. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.50; H, 5.69, N, 9.81.

4-(1-(4-(Dimethylamino)benzyl)-1*H*-benzo[*d*]imidazol-2-yl)-*N*,*N*-dimethylbenzenamine (**3b**). FT-IR (KBr): 1612 (C═N stretch), 1521, 1911 (aromatic C═C stretch), 1376 (C—N stretch), 1219, 1043 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 2.73$ (s, 6H), 2.85 (s, 6H), 5.41 (s, 2H), 6.58–7.12 (m, 12H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.2$, 40.5, 48.1, 110.6, 111.1, 112.7, 117.2, 119.1, 122.5, 124.6, 126.2, 130.5, 135.6, 142.6, 149.4, 151.4, 155.7. Anal Calc. for $C_{24}H_{26}N_4$: C, 77.80; H, 7.07; N, 15.12. Found: C, 77.75; H, 7.10, N, 15.14.

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole (**3c**). FT-IR (KBr): 1628 (C═N stretch), 1279, 1095 (C—Cl stretch), 1406 (aromatic C═C stretch) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 5.61$ (s, 2H), 7.20–7.25 (m, 3H), 7.30–7.40 (m, 1H), 7.52–7.61 (m, 4H), 7.69–7.76 (m, 2H), 8.20–8.23 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta =$ 46.7, 110.6, 120.4, 122.4, 123.5, 126.5, 127.7, 128.6, 129.5, 130.1, 133.9, 133.2, 135.0, 135.7, 142.1, 152.1. Anal Calc. for $C_{20}H_{14}Cl_2N_2$: C, 68.00; H, 3.99; N, 7.93. Found: C, 68.08; H, 3.95, N, 7.89.

1-(4-Bromobenzyl)-2-(4-bromophenyl)-1*H*-benzo[*d*]imidazole (**3d**). FT-IR (KBr): 1629 (C═N stretch), 1526, 1403 (aromatic C═C stretch) 1068 (C—Br stretch) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 5.57$ (s, 2H), 7.28 (s, br, 2H), 7.41 (s, br, 1H), 7.47 (s, br, 1H), 7.62 (s, br, 2H), 7.75 (s, br, 2H), 7.84 (d, $J = 8.0$ Hz, 2H), 8.18 (d, $J =$ 8.0 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 45.9$, 110.2, 120.8, 122.2, 123.8, 126.1, 127.3, 128.6, 129.0, 131.2, 132.8, 133.0, 134.5, 135.2, 142.6, 151.6. Anal Calc. for $C_{20}H_{14}Br_2N_2$: C, 54.33; H, 3.19; N, 6.34. Found: C, 54.27; H, 3.31, N, 6.37.

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole (**3e**). FT-IR (KBr): 1410, 1246 (C—O stretch), 1511, 1452 (aromatic C═C stretch), 1625 (C═N stretch) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 3.72$ (s, 3H), 3.81 (s, 3H), 5.41 (s, 2H), 6.85–7.69 (m, 12H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 46.7$, 55.5, 55.9, 110.8, 114.0, 114.5, 119.2, 122.7, 123.0, 127.4, 128.7, 130.0, 135.4, 143.7, 154.4, 159.6, 159.3. Anal Calc. for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.41; H, 6.37, N, 7.43.

1-(2-Chlorobenzyl)-2-(2-chlorophenyl)-1*H*-benzo[*d*]imidazole (**3f**). FT-IR (KBr): 2956 (aliphatic C—H stretch), 1623 (C═N stretch), 3017 (aromatic C—H stretch), 1562, 1462 (aromatic C═C stretch), 1382 (C—N stretch), 1221, 1048 (C—Cl stretch) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 5.41$ (s, 2H), 6.52–7.87 (m, 12H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 45.9$, 110.6, 120.4, 122.9, 123.4, 126.0, 127.2, 127.8, 128.1, 129.6, 129.7, 130.5, 131.3, 132.5, 132.9, 133.5, 134.5, 134.9, 142.0, 151.8. Anal Calc. for $C_{20}H_{14}Cl_2N_2$: C, 68.00; H, 3.99; N, 7.93. Found: C, 68.05; H, 4.01, N, 7.98.

2-((2-(2-Hydroxyphenyl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)phenol (**3g**). FT-IR (KBr): 1503, 1462 (Aromatic C═C stretching), 1621 (C═N stretching), 1408, 1241 (C—O stretching), 1159 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 5.53$ (s, 2H), 6.21–7.28 (m, 12H), 9.52 (s, br., 1H), 10.08 (s, br., 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 45.8$, 110.2, 120.7, 121.7, 123.5, 125.7, 126.3, 127.4, 128.2, 129.0, 129.6, 130.5, 131.5, 132.8, 133.2, 133.8, 134.7, 135.0, 142.3, 151.2. Anal Calc. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.89; H, 5.12, N, 8.89.

Table 1
Effect of acidic catalyst on the reaction of benzaldehyde and diaminophenylene.

Entry	Catalyst	Catalyst amount/1 mmol of substrate	Reaction condition	Time (min)	Yield (%)
1	H_2SO_4	5 drops	Reflux	7200	15
2	*p*-TsOH	0.1 mmol	Reflux	3600	33
3	Montmorillonite K10	0.1 g	Reflux	60	73
4	HY-zeolite	0.1 g	Reflux	45	79
5	I_2	0.1 mmol	Reflux	120	53
6	l-Proline	0.1 mmol	Reflux	60	75
7	Nano particle Fe_3O_4	0.05 g	Reflux	45	89
8	DBU-Ac	0.5 mmol	Heat, 80 °C	10	80
9	DABCO-dihydroAc	0.5 mmol	Heat, 80 °C	10	90
10	DABCO-dihydroAc	0.3 mmol	Heat, 80 °C	10	78
11	DABCO-dihydroAc	0.1 mmol	Heat, 80 °C	30	57
12	DABCO-dihydroAc	0.7 mmol	Heat, 80 °C	9	91