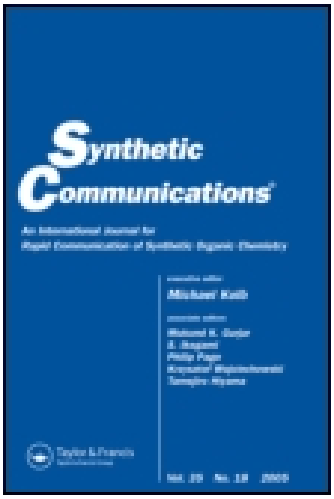

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Highly Efficient and Simple Catalytic System for the N-Arylation of Some Hindered Aza-Heterocycles in Water

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Accepted author version posted online: 19 Dec 2011.Published online: 09 Apr 2012.

To cite this article: Chhanda Mukhopadhyay & Pradip Kumar Tapaswi (2012) Highly Efficient and Simple Catalytic System for the N-Arylation of Some Hindered Aza-Heterocycles in Water, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:15, 2217-2228, DOI: 10.1080/00397911.2011.555219

To link to this article: http://dx.doi.org/10.1080/00397911.2011.555219

Synthetic Communications®, 42: 2217–2228, 2012

ISSN: 0039-7911 print/1532-2432 online
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HIGHLY EFFICIENT AND SIMPLE CATALYTIC SYSTEM FOR THE N-ARYLATION OF SOME HINDERED AZA-HETEROCYCLES IN WATER

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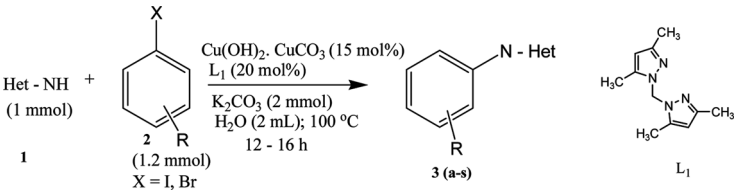
Department of Chemistry, University of Calcutta, Kolkata, India

GRAPHICAL ABSTRACT



Abstract *A highly efficient and simple protocol for the N-arylation of some hindered aza-heterocycles in water has been developed with readily available basic copper carbonate as the catalyst using bis(3,5-dimethyl-1H-pyrazol-1-yl)methane as ligand. This mild catalytic system possesses excellent tolerance for a large variety of functional groups. A total of 11 previously unknown coupling products have been synthesized by this methodology.*

Keywords Aqueous medium; basic copper carbonate; bis(3,5-dimethyl-1*H*-pyrazol-1-yl)methane; hindered aza-heterocycles; N-arylation

INTRODUCTION

N-arylazoles are important compounds that have extensive applications in biochemical, pharmaceutical, and material fields.[1] Traditionally, these moieties were prepared by nucleophilic aromatic substitution of azoles with activated aryl halides or the classical Ullmann-type coupling reactions.[2] For both these cases, the reactions suffered from several shortcomings such as high reaction temperature, use of stoichiometric copper reagents, moderate yields, and poor substrate generality, thereby limiting their applications.[3] The development of a mild, ecofriendly, and highly efficient protocol for the synthesis of N-arylazoles over the classical Ullmann-type or nucleophilic aromatic substitution reactions has recently gained considerable interest both in academia and industry.[4] Because of the economic attractiveness of copper[5] and by using N,N- and N,O-bidentate compounds as ligands, many copper-catalyzed C–N,[6] C–O,[7] C–S,[8] and C–C[9] bond-formation reactions have received growing

Received October 8, 2010.

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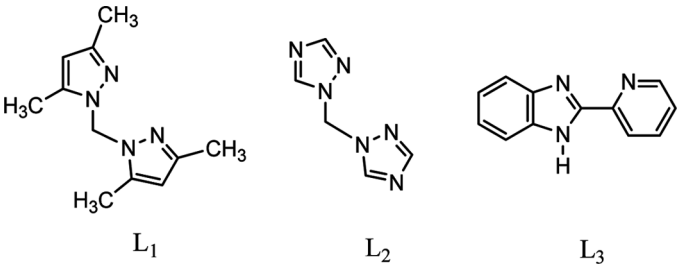


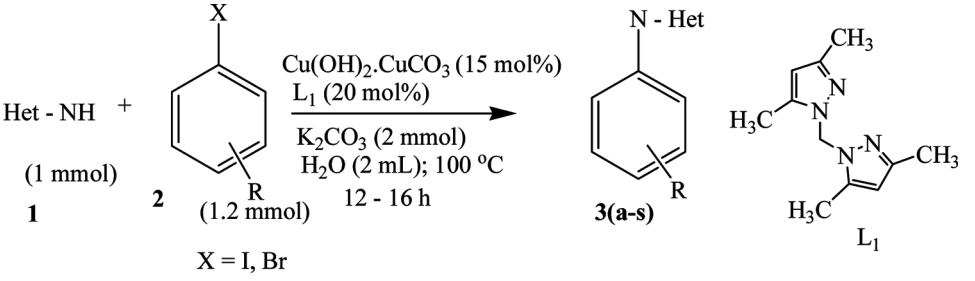
Figure 1. Proposed ligands for the N-arylation of azoles in water.

interest in carbon–heteroatom coupling reactions, and their applications seem to possess more importance[10,11] in the present scenario.

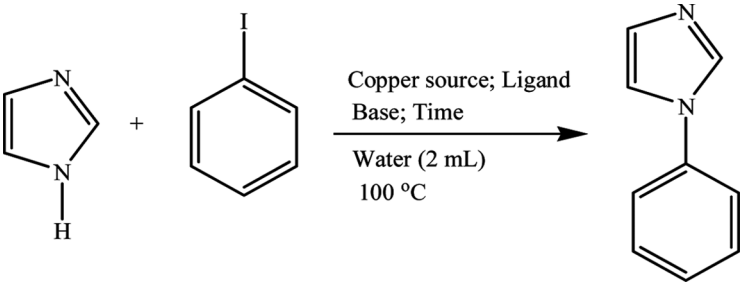
Recently, N-arylation has been carried out with various N-containing heterocycles using diverse organic ligands such as diamine derivatives,[12] amino acids,[13] N-hydroxyimides,[14] phosphine oxides,[15] imidazole derivatives,[16] diketones or diphenols,[17] fluoraphite,[18] per-6-amino-β-cyclodextrin,[19] and even pyridine N-oxides.[20(a)] On the other hand, several N-heterocycles such as bis(3,5-dimethyl-1-*H*-pyrazol-1-yl)methane,[21] bis(1,2,4-triazol-1*H*-yl)methane,[22] and 2-(2-pyridyl) benzimidazole[23] long have been recognized as ligands in coordination chemistry (Fig. 1), but applications of these N-heterocyclic ligands for copper-catalyzed N-arylation of aza-heterocycles have not yet been reported.

Despite significant progress in the copper-catalyzed N/O-arylation with aryl halides, very few reports are available describing N-arylation of azoles in aqueous medium.[20] Therefore, enough room for exploration of an efficient ligand-assisted catalytic system in the aqueous medium still remains open.

In general, almost all the organic-solvent-mediated syntheses of organic compounds have the inherent problem of pollution. In recent years, water-mediated organic synthesis without using organic solvents has become one of the most important developments in present-day organic chemistry to meet the environmental demands.[24] Carrying out organic synthesis in water is extremely challenging both from synthetic and environmental viewpoints. Additional problems of N-arylation of azoles in aqueous medium are the water tolerance for the catalyst and solubility of the substrates and ligands in the aqueous phase. In this regard, the development



Scheme 1. N-arylation of aza-heterocycles in water.



Scheme 2. Optimization of N-arylation of imidazole with iodobenzene in water.

of less expensive and more sustainable catalysts in water remains an attractive goal in modern synthetic organic chemistry.

RESULTS AND DISCUSSION

In continuation of our endeavors toward the synthesis and functionalization of biologically important N-containing heterocycles,[25] we herein describe N-arylation of azoles with aryl halides catalyzed by readily available $Cu(OH)_2 \cdot CuCO_3$ with N-heterocyclic ligands in water (Scheme 1).

Imidazole and iodobenzene were chosen as model substrates (Scheme 2) to optimize the reaction conditions such as amount of ligands, base, copper source, and reaction temperature. Imidazole (1 mmol), iodobenzene (1.2 mmol), base (2 mmol), Cu source (15 mol%), and ligand (20 mol%) in water were taken for initial optimization. After thorough screening several combinations, the best result was obtained after 12 h of reflux using bis(3,5-dimethyl-1*H*-pyrazol-1-yl)methane (L_1) as ligand and $Cu(OH)_2 \cdot CuCO_3$ as copper source in aqueous medium. It should be mentioned here that when $Cu(OH)_2 \cdot CuCO_3$ (1.2 equivalents) was used both as

Table 1. Optimization of reaction condition for the N-arylation of imidazole in water

Entry	Copper source (15 mol%)	Ligand (20 mol%)	Base (2 eqv.)	Time (h)	Yield (%) (isolated)
1	—	—	K_2CO_3	24	Nil
2	$CuCO_3 \cdot Cu(OH)_2$	—	—	24	Nil
3	$CuCO_3 \cdot Cu(OH)_2$	—	K_2CO_3	24	55
4	$CuCO_3 \cdot Cu(OH)_2$	L_1	K_2CO_3	12	92
5	$CuCO_3 \cdot Cu(OH)_2$	L_2	K_2CO_3	12	82
6	$CuCO_3 \cdot Cu(OH)_2$	L_3	K_2CO_3	12	46
7	$CuCO_3 \cdot Cu(OH)_2$	L_1	Cs_2CO_3	12	88
8	$CuCO_3 \cdot Cu(OH)_2$	L_1	K_3PO_4	12	70
9	$CuCO_3 \cdot Cu(OH)_2$	L_1	DABCO	12	50
10	$Cu(OH)_2$	L_1	K_2CO_3	12	75
11	$CuSO_4$	L_1	K_2CO_3	12	65
12	CuI	L_1	K_2CO_3	12	60
13	$Cu(OAc)_2$	L_1	K_2CO_3	12	50
14	$CuCl_2$	L_1	K_2CO_3	12	55

Table 2. N-Arylation of aza-heterocycles in water

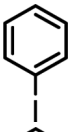
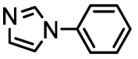
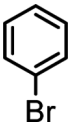
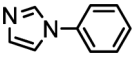
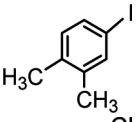
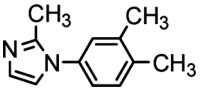
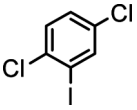
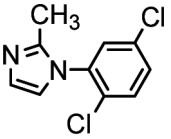
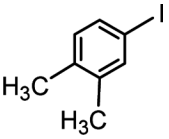
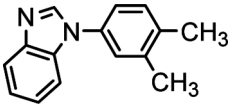
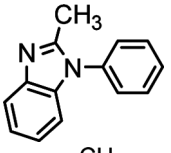
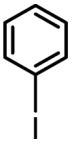
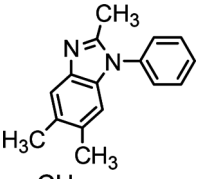
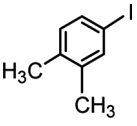
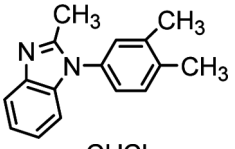
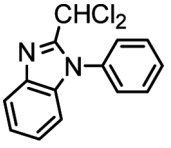
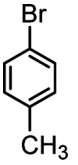
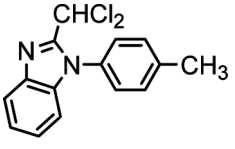
Entry	Aryl halides	Product no.	Products	Time (h)	Yields (%) (isolated)	References
1		**3a**		12	92	19
2		**3a**		14	88	19
3		**3b**		14	91	26
4		**3c**		15	85	—
5		**3d**		13	92	—
6		**3e**		13	92	27
7		**3f**		15	82	27
8		**3g**		13	86	—
9		**3h**		14	82	—
10		**3i**		16	82	—

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Table 2. Continued

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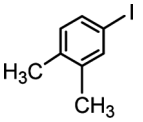
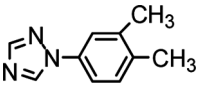
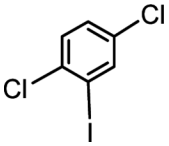
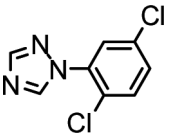
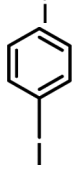
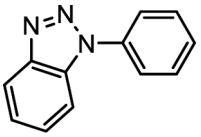
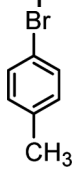
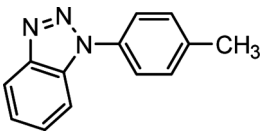
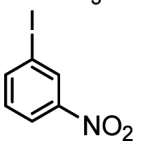
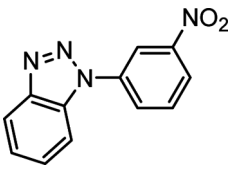
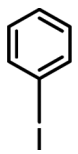
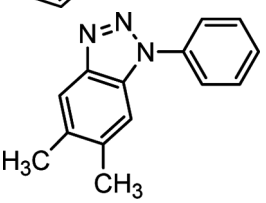
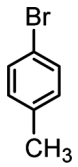
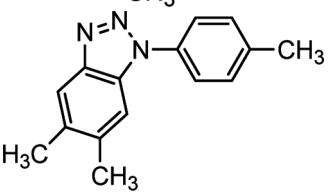
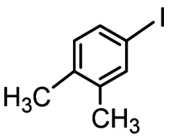
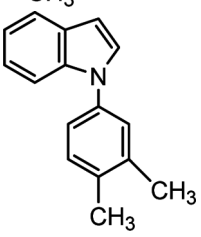
11		**3j**		14	92	—
12		**3k**		15	88	—
13		**3l**		12	92	25 (d)
14		**3m**		14	85	25 (d)
15		**3n**		12	90	25 (d)
16		**3o**		16	86	—
17		**3p**		16	84	—
18		**3q**		12	90	—

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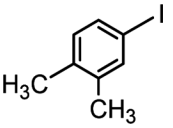
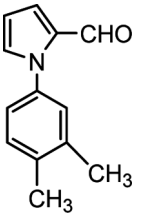
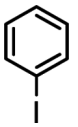
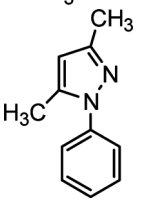
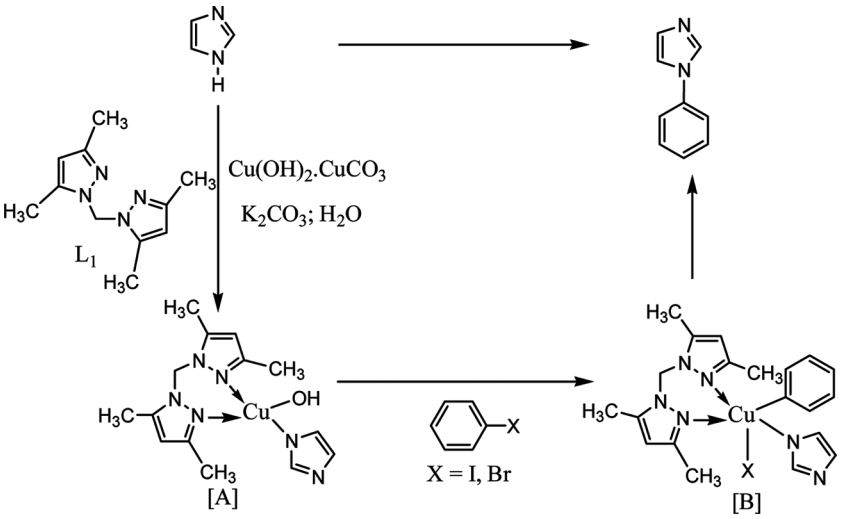
Table 2. Continued

Entry	Aryl halides	Product no.	Products	Time (h)	Yields (%) (isolated)	References
19		**3r**		13	88	—
20		**3s**		12	90	12(a)

source of metal and as base, almost complete conversion of imidazole to 1-phenylimidazole occurred after 16 h of reflux in aqueous conditions. However, the isolated yield was poor (50%), which may be due to the partial conversion of imidazole to corresponding Cu(ii) complex of imidazole. Then we decided to use $Cu(OH)_2 \cdot CuCO_3$ as the metal source only and not as a base. Under this condition, the product yield was better than in the previous case. The arylation reaction is highly sensitive to reaction temperature and time. With lower temperature (below 90 °C) and shorter reaction time (less than 12 h), rate of conversion of imidazole to 1-arylimidazole decreases sharply. Therefore, the optimized conditions for the N-arylation of imidazole in water are the combination of $Cu(OH)_2 \cdot CuCO_3$ (15 mol%), L_1 (20 mol%), and K_2CO_3(2 mmol) at 100 °C for 12 h in air. The results are listed in Table 1.

After optimizing the reaction condition, it was tested with different azaheterocycles. The scope of this coupling reaction was further expanded to diverse aryl bromides, and the overall yields were little bit lower with aryl bromides than with the aryl iodides. The results indicate clearly that this methodology is quite general and applicable for the reaction of a wide variety of imidazoles, benzimidazoles, triazoles, benzotriazoles, indoles, pyrroles, and pyrazoles. Substrates possessing electron-rich groups such as 4-bromotoluene, 3,4-dimethyliodobenze, and 2,5-dichloroiodobenzene afford coupling products in good yields but with larger reaction time than 3-nitroiodobenzene. The reaction is also less sensitive to steric factors and gives good yields, as is evident in the case of the reaction of 2,5-dichloroiodobenzene with 2-methylimidazole. This methodology also provides good results in the case of the reaction of sterically hindered 5,6-dimethylbenzimidazole and benzotriazoles. The complete results are shown in Table 2.

To our delight, most of the imidazole and triazole derivatives afforded the corresponding arylated products in good yields. Notably, 2-methylimidazole (Table 2, entries 3 and 4), 2-methylbenzimidazole (Table 2, entries 6 and 8), and even more bulkier 2-dichloromethylbenzimidazole (Table 2, entries 10 and 11) gave satisfactory



Scheme 3. Probable mechanism for N-arylation of nitrogen-containing heterocycles (imidazole) with basic copper carbonate.

yields under the present reaction conditions. All the coupling products were well characterized by ^{1}H NMR, ^{13}C NMR, and infrared (IR) spectroscopic data.

A probable mechanism for the basic copper carbonate–catalyzed N-arylation of nitrogen-containing heterocycles has been proposed in Scheme 3, in which the first step is the rapid coordination of copper hydroxide and the ligand (L_1) with the N-containing heterocycles such as imidazole to form a four-coordinated copper(ii) complex A. The second step involves the oxidative addition of the aryl halide to form the five-coordinated complex (intermediate B). Complex B subsequently undergoes reductive elimination to form the N-aryl products.

CONCLUSION

In summary, we have utilized cheap and commercially available $Cu(OH)_2 \cdot CuCO_3$ as an efficient catalyst for the N-arylation of aza-heterocycles with wide a range of aryl iodides and aryl bromides in aqueous medium using bis(3,5-dimethyl-1-*H*-pyrazol-1-yl)methane (L_1) as the ligand. This methodology avoids the use of hazardous, toxic organic solvents and an inert atmosphere, which are common requirements in previous methods. Therefore, this methodology is very simple for N-arylation of aza-heterocycles.

EXPERIMENTAL

All solvents were distilled before use. All the chemicals were purchased from Aldrich Chemical Company and Spectrochem, Pvt. Ltd. (Mumbai, India). Silica gel G with binder from Spectrochem, Pvt. Ltd., Mumbai, India, was used for thin-layer chromatography (TLC). ^{1}H and ^{13}C NMR spectra were obtained on a Bruker

300-MHz instrument at 300 and 75 MHz, respectively. $CDCl_3$ was purchased from Aldrich Chemical Company. Melting points were determined on an electrical melting-point apparatus with an open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer RX/FT-IR system. The elemental-analyses were carried out on a 2400 series II CHNS analyzer, Perkin-Elmer, USA.

General Experimental Procedure

Azole (1 mmol), aryl halide (1.2 mmol), $Cu(OH)_2 \cdot CuCO_3$ (15 mol%), ligand (L_1) (20 mol%), K_2CO_3 (2 mmol), and water (2 mL) were mixed in an Erlenmeyer flask (5 mL) fitted with a reflux condenser and refluxed on an oil bath for the stipulated period of time. After the completion of the reaction (monitored by TLC), 20 mL of EtOAc was added to the reaction mixture after transfer to a beaker (50 mL) and stirred for several minutes. The mixture was then filtered through a bed of celite, and the organic layer was separated by the separating funnel, which was washed successively with water (2×10 mL) and brine (2×10 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated by reduced pressure in a rotary evaporator. Finally, the products were purified by column chromatography using neutral alumina as the column material and EtOAc and petroleum ether (60–80 °C) as eluant. The IR, ^{1}H NMR, ^{13}C NMR, and analytical data of all previously unknown compounds are given.

1-(2,5-Dichlorophenyl)-2-methyl-1*H*-imidazole (3c, Table 2, Entry 4)

White crystalline solid, mp 60–62 °C (EtOAc); IR (KBr): 3052, 2980, 2926, 2213, 1609, 1517, 1448, 1392, 1279 and 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (dd, $J = 9.0$ and 3.6 Hz, 1H), 7.22–7.15 (m, 2H), 6.87 (s, 1H), 6.70 (s, 1H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.4, 136.1, 133.4, 131.4, 130.7, 130.5, 129.1, 127.3, 120.5, 12,9. Anal. calcd. for $C_{10}H_8N_2Cl_2$: C, 52.89: H, 3.55: N, 12.34%. Found: C, 52.76: H, 3.65: N, 12.37%.

1-(3,4-Dimethylphenyl)-1*H*-benzimidazole (3d, Table 2, Entry 5)

Pale yellow low-melting solid; IR (KBr): 3042, 2923, 1605, 1504, 1452, 1293, 1210 and 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (s, 1H), 7.88–7.82 (m, 1H), 7.48–7.43 (m, 1H), 7.29–7.23 (m, 2H), 7.20 (d, $J = 7.7$ Hz, 2H), 7.14 (d, $J = 7.7$ Hz, 1H), 2.24 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.6, 141.9, 138.1, 136.2, 133.5, 133.4, 130.5, 124.6, 123.0, 122.1, 120.8, 120.0, 110.1, 19.4, 19.0. Anal. calcd. for $C_{15}H_{14}N_2$: C, 81.05: H, 6.35: N, 12.60%. Found: C, 80.92: H, 6.44: N, 12.64%.

1-(3,4-Dimethylphenyl)-2-methyl-1*H*-benzimidazole (3g, Table 2, Entry 8)

Pale yellow solid; mp 84–86 °C (EtOAc); IR (KBr): 3029, 2934, 1598, 1466, 1289, 1225 and 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, $J = 7.8$ Hz, 1H), 7.25 (d, $J = 7.8$ Hz, 1H), 7.19 (t, $J = 7.8$ Hz, 1H), 7.12 (t, $J = 7.8$ Hz, 1H), 7.08–6.98

(m, 3H), 2.39 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.5, 141.4, 138.5, 137.7, 136.3, 133.2, 130.9, 127.8, 124.2, 122.7, 122.5, 118.5, 110.1, 19.8, 19.5, 14.1. Anal. calcd. for $C_{16}H_{16}N_2$: C, 81.32: H, 6.82: N, 11.85%. Found: C, 81.19: H, 6.93: N, 11.87%.

2-Dichloromethyl-1-phenyl-1*H*-benzimidazole (3h, Table 2, Entry 9)

Oil; IR (neat): 2935, 1577, 1499, 1381, 1278 and 1088 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.90–7.87 (m, 1H), 7.59–7.42 (m, 6H), 7.36–7..25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.2, 136.3, 130.0, 128.0, 124.0, 123.6, 122.7, 120.5, 118.1, 110.4. Anal. calcd. for $C_{14}H_{10}N_2Cl_2$: C, 60.67: H, 3.64: N, 10.11%. Found: C, 60.58: H, 3.70: N, 10.14%.

2-Dichloromethyl-1-(4-methylphenyl)-1*H*-benzimidazole (3i, Table 2, Entry 10)

Oil; IR (neat): 3033, 2928, 1601, 1467, 1288, 1221 and 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.80–7.77 (m, 1H), 7.42–7.39 (m, 1H), 7.29–7.16 (m, 6H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.5, 142.1, 138.0, 133.7, 133.5, 130.4, 123.8, 123.5, 122.6, 120.2, 110.4, 20.9. Anal. calcd. for $C_{15}H_{12}N_2Cl_2$: C, 61.87: H, 4.15: N, 9.62%. Found: C, 61.79: H, 4.22: N, 9.63%.

1-(3,4-Dimethylphenyl)-1*H*-[1,2,4]triazole (3j, Table 2, Entry 11)

Pale white solid; mp 52–54 °C (MeOH); IR (KBr): cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.45 (s, 1H), 8.01 (s, 1H), 7.38 (s, 1H), 7.31–7.25 (m, 1H), 7.15 (d, $J = 8.1$ Hz, 1H), 2.25 (s, 3H), 2.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.1, 140.6, 138.2, 136.7, 134.7, 130.4, 121.1, 117.2, 19.7, 19.2. Anal. calcd. for $C_{10}H_{11}N_3$: C, 69.34: H, 6.40: N, 24.26%. Found: C, 69.25: H, 6.47: N, 24.28%.

1-(2,5-Dichlorophenyl)-1*H*-[1,2,4]triazole (3k, Table 2, Entry 12)

White crystalline solid, mp 102–104 °C (EtOAc); IR (KBr): 3099, 2927, 2374, 1581, 1513, 1477, 1141, 1091, 1029 and 820 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.66 (s, 1H), 8.16 (s, 1H), 7.65 (d, $J = 2.1$ Hz, 1H), 7.50 (d, $J = 8.7$ Hz, 1H), 7.39 (dd, $J = 8.7$ Hz and 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.4, 144.4, 135.5, 133.7, 131.6, 130.1, 127.4, 126.3. Anal. calcd. for $C_8H_5N_3Cl_2$: C, 44.89: H, 2.35: N, 19.63%. Found: C, 44.77: H, 2.44: N, 19.66%.

5,6-Dimethyl-1-phenyl-1*H*-benzotriazole (3o, Table 2, Entry 16)

Pale yellow crystalline solid; mp 88–90 °C (EtOAc): IR (KBr): 3046, 2965, 2373, 1590, 1498, 1455, 1063 and 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 7.74 (d, $J = 8.1$ Hz, 2H), 7.56 (t, $J = 8.7$ Hz, 2H), 7.46–7..41 (m, 2H), 2.39 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.6, 138.5, 137.2, 134.0, 131.1, 129.6, 128.7, 122.5, 119.1, 109.7, 20.8, 20.2. Anal. calcd. for $C_{14}H_{13}N_3$: C, 75.31: H, 5.87: N, 18.82%. Found: C, 75.22: H, 5.94: N, 18.84%.

5,6-Dimethyl-1-(4-methylphenyl)-1*H*-benzotriazole (3p, Table 2, Entry 17)

Pale yellow crystalline solid; mp 132–134 °C (EtOAc); IR (KBr): 2950, 2372, 1512, 1457, 1058, 996 and 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.71 (s, 1H), 7.50 (d, $J = 7.8$ Hz, 2H), 7.33 (s, 1H), 7.25 (d, $J = 7.8$ Hz, 2H), 2.32 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.4, 138.4, 138.3, 134.6, 134.0, 131.3, 130.1, 122.4, 119.0, 109.7, 21.0, 20.8, 20.2. Anal. calcd. for $C_{15}H_{15}N_3$: C, 75.92: H, 6.37: N, 17.71%. Found: C, 75.80: H, 6.47: N, 17.73%.

3,4-Dimethylphenyl-1*H*-indole (3q, Table 2, Entry 18)

Oil; IR (neat): 2954, 2934, 1601, 1487, 1243, 1190 and 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.48–7.35 (m, 6H), 6.86 (br. d, $J = 3.0$ Hz, 1H), 2.49 (s, 6H). Anal. calcd. for $C_{16}H_{15}N$: C, 86.84: H, 6.83: N, 6.33%. Found: C, 86.72: H, 6.92: N, 6.36%.

1-(3,4-Dimethylphenyl)-1*H*-pyrrole-2-carbaldehyde (3r, Table 2, Entry 19)

Dark brown semisolid; IR (KBr): 2923, 2853, 2376, 1657, 1383, 1040 and 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.54 (s, 1H), 7.21 (d, $J = 7.9$ Hz, 1H), 7.16–7.10 (m, 2H), 7.07 (d, $J = 7.9$ Hz, 1H), 7.03 (s, 1H), 6.37 (t, $J = 3.0$ Hz, 1H), 2.30 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 178.7, 137.2, 136.2, 136.1, 132.0, 131.6, 129.8, 126.7, 123.1, 121.5, 110.6, 19.2, 18.9. Anal. calcd. for $C_{13}H_{13}NO$: C, 78.36: H, 6.58: N, 7.03%. Found: C, 78.24: H, 6.67: N, 7.06%.

ACKNOWLEDGMENTS

One of the authors (P. K. T.) thanks the University Grants Commission (UCG), New Delhi, for a fellowship. We thank the CAS Instrumentation Facility, Department of Chemistry, University of Calcutta, for spectral data. We also acknowledge a grant received from UGC for Major Project F No. 37-398/2009 (S.R.).

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