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TBAF-Assisted Copper-Catalyzed *N*-Arylation and Benzylation of Benzazoles with Aryl and Benzyl Halides under the Ligand/Base/ Solvent-Free Conditions

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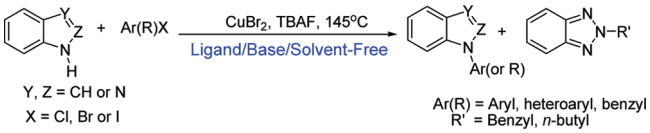

TBAF-assisted *N*-arylation and benzylation of benzazoles such as 1*H*-benzimidazole, 1*H*-indole, and 1*H*-benzotriazole with aryl and benzyl halides have been demonstrated under the ligand/base/solvent-free conditions. In the presence of $CuBr_2$ and TBAF (*n*-Bu_4NF), the azoles underwent *N*-arylation and benzylation with aryl and benzyl halides smoothly in moderate to good yields. It is noteworthy that the reaction is conducted under the ligand/base/solvent-free conditions.

N-Arylazoles such as *N*-aryl-1*H*-benzimidazoles,[1] *N*-aryl-1*H*-indoles,[1a−1c,1m,1n,2] and *N*-aryl-1*H*-benzotriazoles[1a−1c,1o,3] play an important role as structural and functional units in many biological active compounds, natural products, and useful synthons. In spite of these interests, the preparation of *N*-arylazoles is severely restricted because nitrogen heterocycles are not good substrates for the traditional arylation reagents. Thus, the Ullmann reaction[4] can only be performed using activated aryl halides, which require a ligand and harsh reaction conditions and very often give low yields. Although recent developments like efficient conditions,[3b,5,6] novel ligands,[1k,1l,2a] and additives[2b,3c] have been reported, the Ullmann and related reactions suffer still from economy and efficacy of the ligand. Therefore, we attempted the development of a convenient and efficient method for *N*-arylation of benzazoles.

According to the literature,[7] the tetrabutylammonium fluoride (TBAF) decomposes to tetetrabutylammonium bifluoride, tributylamine, and 1-butene at 77 °C. Therefore, TBAF may play concurrently two roles as the ligand and the base under the Ullmann reaction conditions.

As a continued interest in developing efficient and greener processes, we expected to apply TBAF as the ligand and the base in the *N*-arylation of azoles. As expected, *N*-arylation of 1*H*-benzimidazole (**1**) with 2-bromopyridine and TBAF without the ligand and the solvent at 145 °C gave *N*-(pyridin-2-yl)-1*H*-benzimidazole in the preliminary reaction.

In this paper, we report the TBAF-assisted Cu-catalyzed *N*-arylation and benzylation of azoles under ligand, base, and solvent-free conditions (Scheme 1).

Using a model reaction based on 1*H*-benzimidazole (**1**) and 2-bromopyridine (**4a**), five tetrabutylammonium salts (TBAX) and five Cu catalysts have been screened. When tetrabutylammonium fluoride (TBAF) and Cu calaysts except for CuI were used, 1-(pyridin-2-yl)-1*H*-benzimidazole (**5a**) was obtained in 61−85% yields (entries 1, 6, 11, and 16 in Table 1), whereas compound **5a** was obtained in low yields when four other salts such as tetrabutylammonium bromide (TBAB), tetrabutylammonium iodide (TBAI), tetrabutylammonium nitrate (TBAN), and tetrabutylammonium hydrosulfate (TBAS) were used (Table 1). Among the five Cu catalysts, $CuBr_2$ also showed the best results. Reaction of 1*H*-benzimidazole, however, with 2-bromopyridine without Cu catalyst give only **5a** in very low yield (entry 12 in Table 2). We next optimized the amount of Cu catalyst and TBAF required for the *N*-arylation of 1*H*-benzimidazole. The following system proved to be the best: azole (1 equiv), aryl

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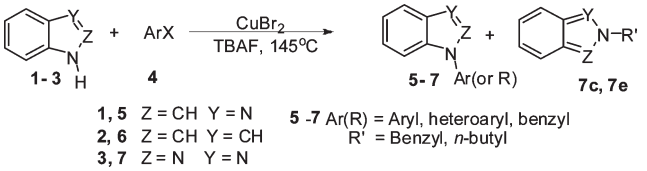
TABLE 1. Screening of Copper Halides and Tetrabutylammonium Salts[a]

entry	catalyst	TBAX[b]	**5a** (isolated yield, %)
1	CuBr	TBAF	61
2	CuBr	TBAB	3
3	CuBr	TBAI	10
4	CuBr	TBAN	3
5	CuBr	TBAS	12
6	$CuBr_2$	TBAF	85
7	$CuBr_2$	TBAB	30
8	$CuBr_2$	TBAI	18
9	$CuBr_2$	TBAN	three spot
10	$CuBr_2$	TBAS	30
11	CuCl	TBAF	64
12	CuCl	TBAB	12
13	CuCl	TBAI	42
14	CuCl	TBAN	6
15	CuCl	TBAS	trace
16	$CuCl_2$	TBAF	61
17	$CuCl_2$	TBAB	45
18	$CuCl_2$	TBAI	15
19	$CuCl_2$	TBAN	3
20	$CuCl_2$	TBAS	trace
21	CuI	TBAF	trace
22	CuI	TBAB	trace
23	CuI	TBAI	trace
24	CuI	TBAN	trace
25	CuI	TBAS	trace

[a]Reaction conditions: **1** (1 equiv), **4a** (1 equiv), Cu-catalyst (10 mol %), TBAX (3 equiv), 145 °C (±2 °C), 24 h in sealed tube. [b]TBAF = tetrabutylammonium fluoride, TBAB = tetrabutylammonium bromide, TBAI = tetrabutylammonium iodide, TBAN = tetrabutylammonium nitrate, TBAS = tetrabutylammonium hydrosulfate.

SCHEME 1



halide (1 equiv), $CuBr_2$ (10 mol %), and TBAF (5 equiv) (entry 10 in Table 2).

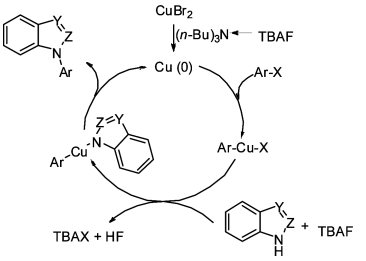
1*H*-Benzimidazole (**1**) was reacted with some aryl and benzyl halides under the optimized conditions to give the corresponding 1-arylated or benzlated 1*H*-benzimidazoles **5** except for 4-methoxyhalobenzene (**4e**, **4f**, and **4g**) in 69−90% yields. Reaction of **1** with **4e** or **4g** under the same conditions gave 1-arylated compound **5e** (8% for **4e**, 18% for **4g**) and 1-*n*-butyl-1*H*-benzimidazole (**5f**, 69% for **4e**, 17% for **4g**). Compound **1** was also treated with **4f** under the same conditions to afford only 1-*n*-butyl derivative **5f** in 15% yield. On the other hand, 1*H*-indole (**2**) was reacted with **4b**, **4d**, **4g**, or **4h** under the same conditions to give *N*-aryl-1*H*-indoles **6a** (61%), **6b** (58% for **4d**, 64% for **4h**), or **6c** (**47%**), whereas reaction with 4-methoxybromobenzene (**4e**) under the same conditions did not give any product. 1*H*-Benzotriazole (**3**) was reacted with **4b**, **4c**, **4d**, **4g**, or **4h** in the presence of $CuBr_2$ (10 mol %)/TBAF (5 equiv) under the ligand/base/solvent-free conditions to give 1-aryl(or benzyl) benzotriazoles [**7a** (76% for **4b**), **7b** (72% for **4c**) and **7f** (38% for **4d**, 35% for **4h**)], 2-aryl(or benzyl)benzotriazoles [**7c** (23% for **4c**) and **7g** (30% for **4d**, 25% for **4h**)], and/or 1-(*n*-butyl)benzotriazole [**7d** (14% for **4d**, 13% for **4h**)] except for 4-methoxyhalobenzenes **4f** and **4g**. It is interesting that the reactions of **4b** and **4c** show very high selectivity for N-1 substitution of the benzotriazole, although N-1 arylation of benzotriazole is more favorable than N-2 arylation.[1o,8] Bletskaya et al.[3b] also reported *N*-arylation of 1*H*-benzotriazole (**3**) with activated aryl halide using copper 2-phenylcyclopropane carboxylate/K_2CO_3/$C_{16}H_{33}Me_3NBr$ in toluene. Reaction of **3** with **4f** or **4g** under the same conditions, however, gave 1- and 2-*n*-butyl-1*H*-benzotriazoles **7d** (38% for **4f**, 28% for **4g**) and **7e** (21% for **4f**, 22% for **4g**) instead of the corresponding *N*-aryl (or benzyl) derivatives. The formation of *N*-*n*-butylazoles may be due to 1-butene, which is the decomposition product of TBAF. In the case of less reactive halides like 4-methoxybromobenzene (**4e**) and 4-methoxychlorobenzene (**4f**), the *N*-alkylation of the azoles may be more favorable then the corresponding *N*-arylation under our conditions.

TABLE 2. Optimization for TBAF-Assisted Copper-Catalyzed Arylation of 1 with 2-Bromopyridine (4a)[a]

entry	TBAF (equiv)	$CuBr_2$ (mol %)	time (h)	**5a**[b] (%)
1	1	20	24	36
2	2	20	24	64
3	3	20	24	87
4	5	20	4	85
5	7	20	4	86
6	5	0.5	18	67
7	5	1	18	61
8	5	2	18	55
9	5	5	18	73
10	5	10	4	90
11	5	15	6	73
12	5		6	13

[a]Reaction conditions: **1** (1 equiv), **4a** (1 equiv), Cu-catalyst (0−20 mol %), TBAF (1−7 equiv) 145 ± 2 °C in sealed tube. [b]Isolated yield.

SCHEME 2. Plausible Mechanism of TBAF-Assisted *N*-Arylation of Benzazoles



As described in Scheme 2, we have formulated a working mechanism for the TBAF-assisted *N*-arylation and benzylation. The $(n\text{-Bu})_3N$ may be act as the ligand. The fluoride ion of TBAF may also act as the base. The structures of compounds **5**−**7** were established by IR, NMR, and elemental analyses.

In summary, we have reported the TBAF-assisted Cu-catalyzed *N*-arylation, and benzylation of azoles such as 1*H*-benzimidazole, 1*H*-indole, and 1*H*-benzotriazole with aryl, benzyl, and heteroaryl halides providing moderate to good yields. It is noteworthy that the present reaction is conducted under ligand, solvent, and base-free conditions and is of great value to the research and development efforts in the chemical industry. Further work including the applications of the TBAF/Cu catalyst system in the formation of other C−N bond transformations is currently underway in our laboratory.

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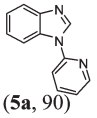
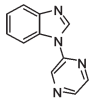
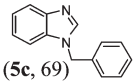
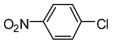
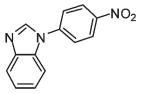
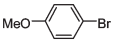
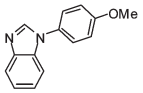
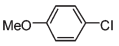
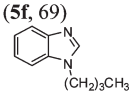
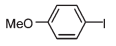
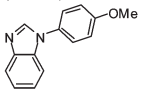
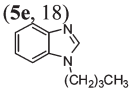
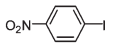
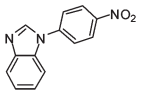
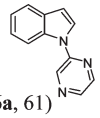
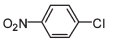
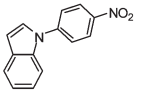
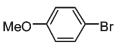
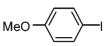
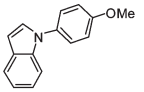
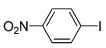
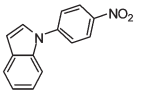
TABLE 3. TBAF-Assisted Copper-Catalyzed N-Arylation and Benzylation of Benzazoles with Aryl Halides Using the $CuBr_2$/TBAF System[a]

entry	azole	halide	time (h)	product (%)[b]
1	 (**1**)	 (**4a**)	4	 (**5a**, 90)
2	 (**1**)	 (**4b**)	1	 (**5b**, 76)
3	 (**1**)	 (**4c**)	1.5	 (**5c**, 69)
4	 (**1**)	 (**4d**)	3	 (**5d**, 81)
5	 (**1**)	 (**4e**)	24	 (**5e**, 8)
6[c]	 (**1**)	 (**4f**)	15	 (**5f**, 15)
7	 (**1**)	 (**4g**)	24	 (**5e**, 18)  (**5f**, 17)
8	 (**1**)	 (**4h**)	4.5	 (**5d**, 86)
9	 (**2**)	 (**4b**)	2.5	 (**6a**, 61)
10	 (**2**)	 (**4d**)	2.5	 (**6b**, 58)
11	 (**2**)	 (**4e**)	24	No Reaction
12	 (**2**)	 (**4g**)	24	 (**6c**, 47)
13	 (**2**)	 (**4h**)	4	 (**6b**, 64)
14	 (**3**)	(**4b**)	10	(**7a**, 76)
15	(**3**)	(**4c**)	0.5	(**7b**, 72) (**7c**, 23)
16	(**3**)	(**4f**)	4	(**7d**, 38) (**7e**, 21)
17	(**3**)	(**4g**)	7.5	**7d** (28) **7e** (22)
18	(**3**)	(**4d**)	15	(**7f**, 38) (**7g**, 30)
19	(**3**)	(**4h**)	10	**7d** (14) (**7f**, 35) (**7g**, 25) **7d** (13)

[a] Reaction conditions: **1** (1 equiv), **4** (1 equiv), $CuBr_2$ (10 mol %), TBAF (5 equiv), 145 ± 2 °C in sealed tube. [b] Isolated yield. [c] Unreacted reagents were isolated.

Experimental Section

Typical Experimental Procedure for TBAF-Assisted *N*-Arylation and Benzylation of Azoles. A mixture of azole (**1**−**3**, 1.7 mmol), halide (**4**, 1.7 mmol), $CuBr_2$ (10 mol %), and TBAF (5 equiv) was stirred at 145 °C until the reaction stopped progressing. After the mixture was cooled and then ethyl acetate (10 mL) was added, the mixed solvent (ethyl acetate/water = 150 mL/80 mL) was added. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was

applied to an open-bed silica gel column (10 × 3 cm). The column was eluted with ethyl acetate/*n*-hexane (1/10, v/v). Fractions containing the product were combined, and the solvent was evaporated under reduced pressure to give the products **5**−**7**.

1-(Pyridin-2-yl)-1*H*-benzimidazole (5a): mp oil (lit.[1] mp 59−60 °C); IR (KBr) 3081, 3057, 3016, 1589, 1495, 1474, 1454, 1438, 1295, 1236, 1203 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.32−7.44(m, 3H), 7.76−7.79 (m, 1H), 7.91−7.94 (m, 1H), 8.03−8.08 (m, 1H), 8.26−8.29 (m, 1H), 8.61−8.64 (m, 1H), 8.95 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 114.4, 115.1, 120.3, 122.5, 123.5, 124.4, 132.3, 140.1, 142.1, 144.6, 149.4, 150.2. Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.85; H, 4.70; N, 21.56.

1-(4-Nitrophenyl)-1*H*-benzimidazole (5d): mp 181 °C (lit.[4] mp 175−178 °C); IR (KBr) 3088, 1595, 1453, 1347, 1199, 852 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.34−7.43 (m, 2H), 7.76−7.83 (m, 2H), 8.01−8.06 (m, 2H), 8.44−8.49 (m, 2H), 8.75 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 111.5, 120.7, 123.7, 124.3, 124.5, 126.0, 132.8, 141.8, 143.8, 144.6, 146.2. Anal. Calcd for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.30; H, 3.81; N, 17.58.

1-(Pyridin-2-yl)-1*H*-indole (6a): mp 73−74 °C; IR (KBr) 3106, 3070, 3052, 3017, 1584, 1522, 1488, 1450, 1419, 1363, 1251, 1212, 1135, 1018, 839 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.83 (d, 1H, J = 3.6 Hz), 7.17−7.32 (m, 2H), 7.66−7.68 (d, 1H, J = 7.7 Hz), 8.15−8.16 (d, 1H, J = 3.6 Hz), 8.42−8.46 (m, 1H), 8.51−8.52 (d, 1H, J = 2.6 Hz), 8.60−8.61 (m, 1H), 9.18 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 107.0, 114.8, 121.4, 122.3, 123.9, 126.4, 130.6, 135.1, 136.9, 140.6, 141.7, 142.8. Anal. Calcd for $C_{13}H_{10}N_2$:C,80.39; H, 5.19; N, 14.42. Found: C, 80.41; H, 5.23; N, 14.45.

1-Benzyl-1*H*-benzotriazole (7b): mp 114−115 °C (lit.[8] mp 114−115 °C); IR (KBr) 3085, 3065, 3029, 2975, 2943, 1497, 1456, 1365, 1325, 1262, 1225, 1162, 1095, 1070, 947 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 5.99 (s, 2H), 7.27−7.38 (m, 5H), 7.39−7.43 (m, 1H), 7.50−7.56 (m, 1H), 7.83−7.86 (m, 1H), 8.04−8.08 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 51.4, 111.1, 119.7, 124.5, 127.9, 128.2, 128.5, 129.3, 133.1, 136.3, 145.8. Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.65; H, 5.33; N, 20.10.

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Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR spectral data, CHN analyses and melting points for compounds **5**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.