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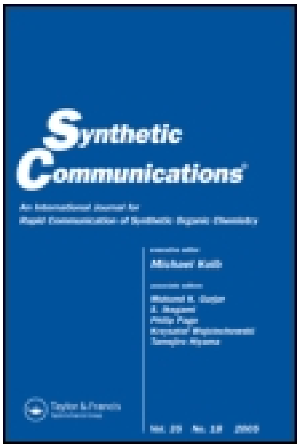

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Copper(II) Bromide: A Simple and Selective Monobromination Reagent for Electron-Rich Aromatic Compounds

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Copper(II) Bromide: A Simple and Selective Monobromination Reagent for Electron-Rich Aromatic Compounds

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Abstract: Copper(II) bromide was found to be a simple and efficient reagent for monobromination of electron-rich aromatic compounds at room temperature. The reaction proceeded smoothly with phenols, aryl alkyl ethers, and aromatic amines to afford the corresponding monobrominated product selectively in moderate to good yields.

Keywords: anilines, aryl alkyl ethers, bromination, copper(II) bromide, phenols

Although $CuBr_2$ had been extensively used for the α-bromination of carbonyl compounds[1] and bromination of alkenes and alkynes,[2] very little work has been carried out on its use as a brominating agent in aromatic systems.[3] During the development of a new protocol for tetrahydroquinoline synthesis with $CuBr_2$ as a catalyst, we observed the formation of a trace amount of brominated anilines.[4] This prompted us to investigate the use of $CuBr_2$ as a brominating agent for electron-rich aromatics.

The bromination of phenol with 2.1 equivalents of $CuBr_2$ (corresponds to 1.05 eq of bromine) in acetonitrile at ambient temperature gave 4-bromophenol in 63% yield, which was improved to 82% when 4 eq of $CuBr_2$ were employed. Interestingly, neither 2-bromophenol nor polybrominated phenols were detected (Table 1, entry 1) in the reaction. Our literature survey revealed only two reports[3a,b] on the use of alumina-supported $CuBr_2$ for

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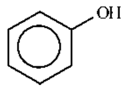
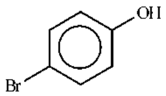
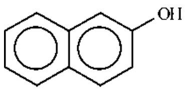
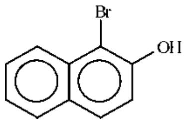
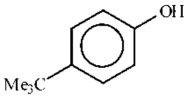
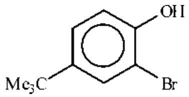
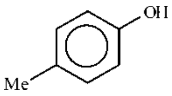
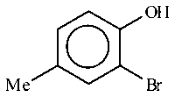
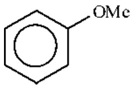
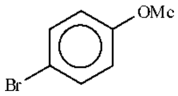
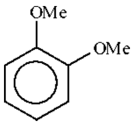
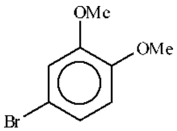
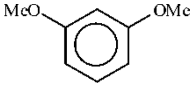
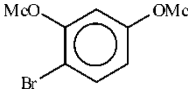
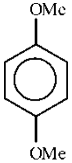
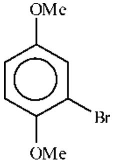
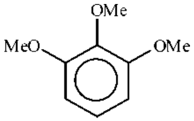
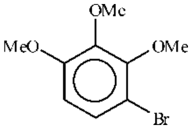
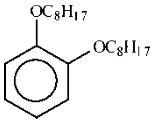
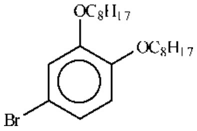
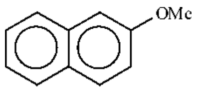
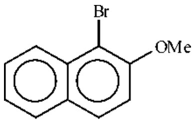
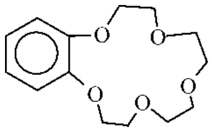
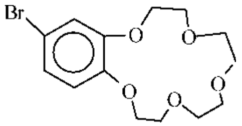
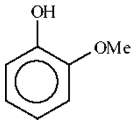
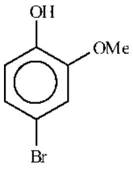
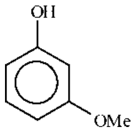
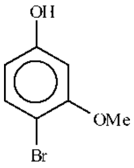
Table 1. Bromination of electron-rich aromatics with copper(II) bromide in acetonitrile[a]

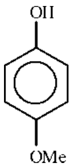
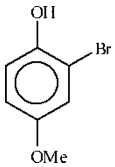
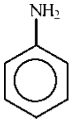
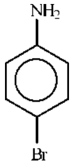
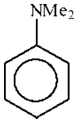
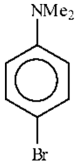
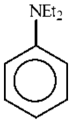
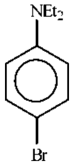
Entry	Substrate	Reagent and conditions	Product	Time (h)	Yield (%)[b]
1		i) $CuBr_2$ (4.2 eq)/CH_3CN/rt ii) alumina supported $CuBr_2$ (3.3 eq)/CCl_4/reflux		i) 0.5 ii) 1.0	i) 82 ii) 23
2		$CuBr_2$ (2.1 eq)/CH_3CN/rt		12.0	80
3		$CuBr_2$ (4.2 eq)/CH_3CN/rt		0.03	91
4		$CuBr_2$ (4.2 eq)/CH_3CN/rt		0.5	50
5		i) $CuBr_2$ (4.2 eq) /CH_3CN/rt ii)alumina supported $CuBr_2$ (3.3 eq)/CCl_4/reflux		i) 2.0 ii) 1.0	i) 50 ii) 43

6		$CuBr_2$ (2.1 eq)/CH_3CN/rt		0.5	83
7		$CuBr_2$ (2.1 eq)/CH_3CN/rt		0.5	54
8		$CuBr_2$ (2.1 eq)/CH_3CN/rt		0.5	48
9		$CuBr_2$ (2.1 eq)/CH_3CN/rt		3.0	74
10		$CuBr_2$ (2.1 eq)/CH_3CN/rt		3.0	64

(*continued*)

Table 1. Continued

Entry	Substrate	Reagent and conditions	Product	Time (h)	Yield (%)[b]
11		$CuBr_2$ (2.1 eq)/CH_3CN/rt		1.0	86
12		$CuBr_2$ (2.1 eq)/CH_3CN/rt		4.0	55
13		$CuBr_2$ (2.1 eq)/CH_3CN/rt		12.0	76
14		$CuBr_2$ (2.1 eq)/CH_3CN/rt		12.0	70

15		$CuBr_2$ (2.1 eq)/CH_3CN/rt		12.0	68
16		$CuBr_2$ (2.1 eq)/CH_3CN/rt		0.03	61
17		$CuBr_2$ (2.1 eq)/CH_3CN/rt		0.03	60
18		$CuBr_2$ (2.1 eq)/CH_3CN/rt		0.03	78

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[a] All the reactions were carried out in acetonitrile (5 mL per mmol) at ambient temperature.

[b] Isolated and unoptimized yields.

the nuclear bromination of alkylbenzenes in CCl_4 under reflux. Therefore, a comparative study on the efficiency of an alumina-supported $CuBr_2/CCl_4$ system with the present protocol ($CuBr_2/CH_3CN$) was undertaken. For example, phenol and alumina-supported $CuBr_2$ (3.3 eq)/CCl_4 under reflux yielded a mixture of mono- and polybrominated products from which 4-bromophenol was isolated in 23% yield after preparative thin-layer chromatography (TLC). This established $CuBr_2$ (2.1 eq)/CH_3CN as a superior and efficient brominating agent for the nuclear monobromination of phenols.

To see the generality of this reaction, bromination of several phenols and aryl alkyl ether were investigated (Scheme 1, Table 1, entries 2–15).

To extend the scope of the reaction, bromination of aniline and $CuBr_2$ (2.1 eq) in acetonitrile for 5 min afforded 4-bromoaniline as the sole product in 61% yield (Table 1, entry 16). Similarly, *N,N*-dimethylaniline and *N,N*-diethylaniline underwent smooth bromination to yield 4-bromo-*N,N*-dimethylaniline and 4-bromo-*N,N*-diethylaniline in 60% and 78% yields respectively (Table 1, entries 17 and 18).

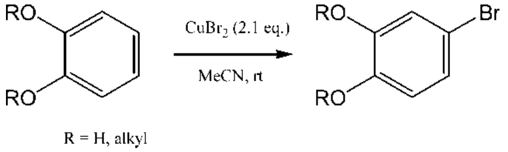
In conclusion, we have developed a simple reagent system: $CuBr_2$ as an efficient nuclear brominating agent for electron-rich aromatic compounds such as phenols, aryl alkyl ethers, and anilines at ambient temperature.

EXPERIMENTAL

Melting points were determined using Fisher-Johns melting-point apparatus and are uncorrected. IR spectra were scanned with a Jasco FT/IR 4100 spectrophotometer. The ^{1}H NMR spectra were recorded with a Bruker AC 200 (200-MHz) spectrometer. Mass spectra were recorded with a Shimadzu mass spectrometer. Microanalysis was performed with Carlo Erba elemental analyzer (model 1110). $CuBr_2$ was purchased from Aldrich Chemical Co. and used without further purification. Acetonitrile was dried and distilled over P_2O_5. All reactions were carried out under an argon atmosphere.

General Procedure for Bromination

A solution of phenol/arylalkylether/aniline (2.0 mmol) and $CuBr_2$ (4.2 mmol, 1.0 g, 2.1 eq) in dry acetonitrile (10 mL) was stirred at room



Scheme 1.

temperature for an appropriate time (see Table 1). After completion of the reaction, as indicated by tlc, the reaction mixture was concentrated, quenched with water and ethyl acetate (10 mL), and passed through a bed of Celite®. The Celite bed was thoroughly washed with ethyl acetate (10 mL). The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent followed by preparative TLC (silica gel; hexane/ethyl acetate = 9/1) afforded the monobrominated product. The spectroscopic and analytical data for the unknown compounds are given next.

Data

2-Bromo-4-*tert*-butylphenol (entry 3): solid; mp 37–38°C; IR (neat): $\nu = 3521$, 3155, 2975, 1604, 1508, 1177, 820 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.46$ (d, 1H, $J = 2.2$ Hz), 7.24 (dd, 1H, $J = 2.2$, 8.5 Hz), 6.96 (d, 1H, $J = 8.5$ Hz), 5.47 (bs, 1H, OH), 1.30 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 149.8$, 145.0, 128.8, 126.1, 115.5, 109.8, 34.1, 31.3; anal. calcd. for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72; found C, 52.59; H, 5.52.

1-Bromo-3,4-dioctyloxybenzene (entry 10): oil; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.7$ (d, 1H, $J = 9.0$ Hz), 7.0 (m, 2H), 3.96 (t, 4H, $J = 6.6$ Hz), 1.8 (m, 4H), 1.3 (m, 20H), 0.9 (bt, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 149.9$, 148.3, 123.3, 116.8, 115.0, 112.7, 69.4, 69.2, 31.8, 29.2, 25.9, 22.6, 14.0; EIMS: m/z = 414, 412, 302, 300, 190, 188, 71, 69, 57, 55; anal. calcd. for $C_{22}H_{37}BrO_2$: C, 63.91; H, 9.02; found C, 64.11; H, 9.17.

4′-Bromobenzo-15-crown-5 (entry 12): oil; IR (neat): $\nu = 2929$, 2869, 1508, 1257, 1137, 931, 725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.99$ (m, 2H), 6.72 (d, 1H, $J = 8.3$ Hz), 4.08 (t, 4H, $J = 4.1$ Hz), 3.88 (t, 4 H, $J = 4.1$ Hz), 3.73 (s, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 149.7$, 148.1, 123.6, 116.8, 115.0, 112.8, 71.0, 70.7, 70.1, 69.9, 69.3, 69.2, 68.9, 68.7; EIMS: m/z = 348, 346, 216, 214, 201, 199, 160, 158, 79; anal. calcd. for $C_{14}H_{19}BrO_5$: C, 48.43; H, 5.52; found C, 48.31; H, 5.41.

4-Bromo-3-methoxyphenol (entry 14): oil; IR (neat): $\nu = 3502$, 2944, 2838, 1603, 1483, 1207, 1021 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.3$ (d, 1H, $J = 8.8$ Hz), 6.59 (d, 1H, $J = 2.8$ Hz), 6.4 (dd, 1H, $J = 2.8$, 8.8 Hz), 5.55 (bs, 1H, OH), 3.76 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 156.4$, 152.5, 134.4, 102.4, 100.5, 100.2, 56.4; EIMS: m/z = 204, 202, 189, 173, 161, 159, 150, 108, 93, 79, 65; anal. calcd. for $C_7H_7BrO_2$: C, 41.41; H, 3.48; found C, 41.59; H, 3.66.

2-Bromo-4-methoxyphenol (entry 15): solid, mp 59–60°C IR (neat): $\nu = 3421$, 2924, 1654, 1498, 1207, 1031, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.0$ (d, 1H, $J = 2.8$ Hz), 6.93 (d, 1H, $J = 8.9$ Hz), 6.8 (dd, 1H,

$J = 2.8, 8.9$ Hz), 5.20 (bs, 1H, OH), 3.70 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 153.7$, 146.5, 116.8, 116.3, 115.3, 110.0, 55.9; EIMS: m/z = 204, 202, 189, 187, 161, 141, 131, 108, 91, 79, 53; anal. calcd. for $C_7H_7BrO_2$: C, 41.41; H, 3.48; found C, 41.62; H, 3.66.

4-Bromo-*N*,*N*-diethylaniline (entry 18): oil; IR (neat): $\nu = 2975$, 2929, 1589, 1498, 1262, 1197, 805 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.65$ (d, 2H, $J = 8.9$ Hz), 6.54 (d, 2H, $J = 8.8$ Hz), 3.31 (q, 4H, $J = 7.1$ Hz), 1.14 (t, 6H, $J = 7.1$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 146.7$, 131.8, 113.4, 106.9, 44.4, 12.4; EIMS: m/z = 230, 228, 216, 213, 200, 199, 187, 185, 168, 149, 135, 130, 115, 86, 84, 58; anal. calcd. for $C_{10}H_{14}BrN$: C, 52.65; H, 6.19; N, 6.14; found C, 52.48; H, 6.11; N, 6.02.

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