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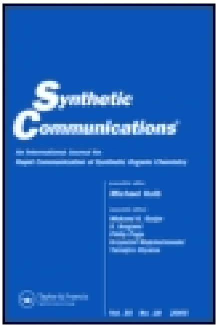

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Regioselective Bromination of Aromatic Amines and Phenols Using N-Benzyl-DABCO Tribromide

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Regioselective Bromination of Aromatic Amines and Phenols Using *N*-Benzyl-DABCO Tribromide

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Abstract: *N*-Benzyl-DABCO tribromide, a stable, solid organic ammonium tribromide, has been used as a bromine source for the regioselective and high-yielding bromination of aromatic amines and phenols. Mono-bromination proceeds well in the presence of a stoichiometric amount of bromine source at room temperature.

Keywords: *N*-Benzyl-DABCO tribromide, bromination, mono-bromoarenes, organic ammonium tribromides

INTRODUCTION

Bromoaromatics are widely used in the synthesis of a variety of biologically active compounds, and they are the key intermediates in the preparation of organometallic reagents. Also, they play significant roles in organic syntheses by functionalization through carbon–carbon bond and transition metal–mediated coupling reactions such as Heck, Stille, Sonogashira, and Suzuki reactions and formation of diarenes, ethylenic, or actylenic condensation.[1–4]

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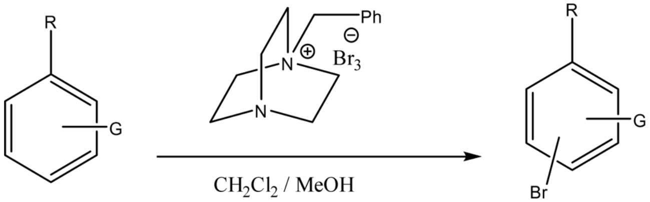
The traditional electrophilic bromination reaction involves toxic elemental bromine in the presence of a metal catalyst under harsh reaction conditions with generation of corrosive hydrobromic acid. Moreover, handling of hazardous liquid bromine, difficulties in separation, the production of by-products from side reactions, and the lack of regioselectivity are disadvantages of classical bromination methods. To overcome the problems in this context, numerous attempts at bromoaromatic synthesis have been developed, and several methods have been reported.[5–11] A variety of brominating agents under various reaction conditions have been used, which include Br_2–Lewis acids,[12] Br_2–zeolite or clay-supported $ZnBr_2$,[13,14] BDMS (bromodimethylsulfonium bromide),[15] NBS (*N*-bromosuccinimide),[16] Br_2–heteropolyacid cesium salt,[17] Br_2/SO_2Cl_2,[18] hexamethylenetetramine–bromine,[19] and organic ammonium tribromides (OATBs).[7,20,21]

Solid OATBs such as Bu_4NBr_3[21a] have good stability, ease of handling, and ability to maintain the desired stoichiometry and thus are finding increasing applications as an alternative to molecular bromine in various organic reactions.

Over the past few years, we have synthesized *N*-benzyl-DABCO-tribromide (NBDTB) as a new, solid OATB, and we have applied it for the synthesis of benzothiazols,[22] deprotection of dithioacetals,[23] and oxidative coupling of benzyl cyanides.[24]

Following our continued interest in NBDTB, herein we report a new and useful application of NBDTB as a reagent for easier, inexpensive, high-yielding, and highly regioselective bromination of aromatic compounds within a short reaction time (Scheme 1).

NBDTB[22] is an efficient, stable, and cheap solid-form reagent, which is quite soluble in methanol, dichloromethane, and dimethylsulfoxide but insoluble in most nonpolar or less-polar solvents such as *n*-hexane and diethyl ether. A series of aromatic compounds was subjected to bromination to furnish the corresponding bromoarenes (Table 1).



Scheme 1. Regioselecive mono-bromination of aromatic compounds using NBDTB. R: OH, NMe_2, NH_2, OMe; G: H, electron-releasing or -withdrawing substituent.

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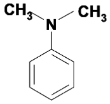
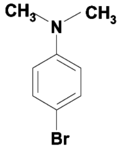
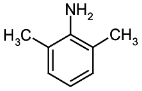
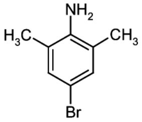
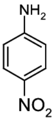
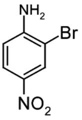
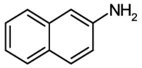
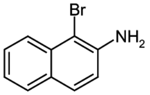
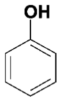
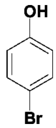
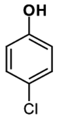
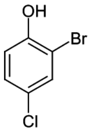
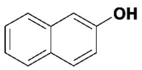
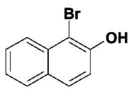
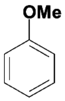
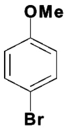
Table 1. Results of bromination of phenols and amines using NBDTB

Entry	Substrate	T (°C)	Time (min)	Product	Yield (%)^a	Mp/bp (°C)	Mp/bp (°C)[lit.]
1		rt	Immediately		98	53–54	55–56[9]
2		rt	Immediately		90	47–50	48–51[19]
3		rt	45		91	102–104	104.5[19]
4		rt	5		77	63–66	63[25]
5		rt	Immediately		82	61–63	61–64[19]
6		rt	30		80	32–34	33–34[9]
7		rt	Immediately		96	82–84	84[9]
8		40	10		85	223	223[7]

(*Continued*)

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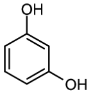
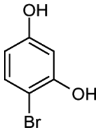
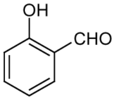
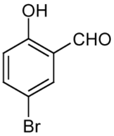
Table 1. Continued

Entry	Substrate	T (°C)	Time (min)	Product	Yield (%)[a]	Mp/bp (°C)	Mp/bp (°C)[lit.]
9		rt	Immediately		63	99–101	100–102[9]
10		rt	30		80	102–104	105[25]

[a]Yields refer to the isolated products.

Our method is based on the in situ generation of Br^+ using NBDTB. Simply by adding NBDTB to a solution of aromatic amines and phenols, rapid complete conversion and regioselective mono-bromination was delivered.

Initially, bromination of *N,N*-dimethylanilin as a model compound using NBDTB in various solvents was examined. The solvents examined were dichloromethane, chloroform, and methanol. Chloroform was an inferior solvent compared to dichloromethane and methanol. Next, the effect of the amount of the NBDTB was examined in a mixture of dichloromethane and methanol. The optimum molar ratio of *N,N*-dimethylanilin to NBDTB (1:1) in dichloromethane and methanol (50:50 v/v) was found to be ideal for complete conversion.

In our investigation, electron-rich aromatics such as substituted anilines, phenols, and β-naphthol were found to be the most reactive, and in those examples where both *ortho*- and *para*-substitution was possible, bromination occur only in *para*-position and the *para*-substituted product was the only isomer isolated. The *para*-substituted aromatics were brominated in the *ortho*-position (Table 1, Entries 3 and 6).

According to our investigation on the series of aromatics in Table 1, the best results in terms of good yield and short reaction time were *N,N*-dimethylanilin (Entry 1) and β-naphthol (Entry 7). However, pyridine, indole, quinoline, and coumarins could not be brominated by NBDTB at ambient temperature or even after a prolonged reaction time.

To demonstrate the advantage of this reagent, its activity was compared with different OATBs[7,20b,21] in the bromination reaction. Table 2 shows the results, and it was found that compound NBDTB as

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Table 2. Comparison of the effect of NBDTB with three different OATBs

OATB	Substrate	Solvent/condition	Time	Product	Yield (%)
PHP[a]	Anisole	$H_2O/AcOH/Et_2O$	4 h	4-Bromoanisol	94[7]
NBDTB	Anisole	$CH_2Cl_2/MeOH$ (1:1), 40°C	10 min	4-Bromoanisol	85
TBATB[b]	phenol	$CH_2Cl_2/MeOH$ (1:1)/$CaCO_3$	1 h	4-Bromophenol	60[21a]
NBDTB	phenol	$CH_2Cl_2/MeOH$ (1:1), rt	Immediately	4-Bromophenol	82
PBC[c]	β-naphthol	AcOH, heat	20–45 min	α-Bromo-β-naphthol	85[21b]
NBDTB	β-naphthol	$CH_2Cl_2/MeOH$ (1:1), rt	Immediately	α-Bromo-β-naphthol	96

[a] Pyridinium hydrobromide perbromide (PHP).
[b] Tetrabutylammonium tribromide (TBATB).
[c] Pyridinium bromochromate (PBC).

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brominating reagent for anisole, phenol, and β-naphthol gives the best yield in shorter reaction time under mild reaction conditions.

In conclusion, we have developed a novel and efficient brominating reagent using NBDTB as an interesting alternative to liquid brominating reagents for mono-bromination of phenols and substituted anilines at room temperature with good yield. The mild reaction conditions, rapid conversion, excellent yields, and high regioselectivity are the impressive advantages of the present protocol.

EXPERIMENTAL

The compounds all gave satisfactory spectroscopic data. A Bruker (DRX-500 Avance) NMR instrument was used to record the ^{1}H NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature. Melting points were determined on a Buchi B540 apparatus.

Procedure for Bromination of Aromatic Compounds

NBDTB[22–24] (0.44 g, 1 mmol) was added to a stirred solution of phenol or amine (1 mmol) in CH_3OH–CH_2Cl_2 (50:50, 6 mL), and the reaction mixture was stirred at room temperature for the required time (see Table 1). Upon the completion of reaction (monitored by thin-layer chromatography), the reaction mixture was washed with two portions of water (15 mL). The organic layer was separated and dried over $MgSO_4$. Evaporation of the solvent gave the desired pure product.

Spectral Data of the Selected Products

N,N-Dimethyl-4-bromoaniline (Entry 1, Table 1)

^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 2.98 (s, 6H), 6.66 (d, $J = 8.9$ Hz, 2H), 7.37 (d, $J = 8.9$ Hz, 2H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 149.8, 132.1, 114.6, 109.1, 41.0.

2-Bromo-4-nitroaniline (Entry 3, Table 1)

^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 4.88 (s, 2H), 6.78 (d, $J = 8.9$ Hz, 1H), 8.07 (dd, $J = 6.5$ Hz, 2.5 Hz, 1H), 8.41 (d, $J = 2.5$ Hz, 1H).

4-Bromophenol (Entry 5, Table 1)

^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 5.45, (s, 1H), 6.77 (d, $J = 8.9$ Hz, 2H), 7.38 (d, $J = 8.9$ Hz, 2H).

1-Bromo-2-naphthol (Entry 7, Table 1)

^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 5.96 (s, 1H), 7.31 (d, $J = 8.8$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 1H), 7.62 (t, $J = 7.7$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, Hz, 1H), 7.83 (d, $J = 8.1$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 106.5, 117.5, 124.5, 125.7, 128.2, 128.6, 129.7, 130.1, 132.7, 151.0.

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