Tetrabutylammonium Bromide-Promoted Metal-Free, Efficient, Rapid, and Scalable Synthesis of N-Aryl Amines

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Supporting Information

ABSTRACT: A rapid, transition metal-free, high-yielding, tetrabutylammonium bromide-promoted method of N-arylation is reported within. The optimized conditions tolerated a wide range of secondary amines and was equally effective with bromo- and chlorobenzene-including substituted aryl halides. The developed method is found to be effective for N-arylation when compared to earlier methods which involved harsh conditions, transition metals, lack of scalability, and long reaction times. Our method utilizes conventional heating only; it is readily scalable; and the products are facile to purify.

INTRODUCTION

Recent advancements in N-aryl bond formation have motivated medicinal chemists to synthesize biologically important N-arylated compounds, which earlier proved difficult to prepare.1 Because of the abundance of natural products, drugs of pharmaceutical importance, pesticides, and color pigments containing N-arylated amines, efficient methods have been developed, including Buchwald−Hartwig and Ullmann couplings, among others.2 Copper or palladium metals, with or without other ligands, are generally required for the synthesis of C−N bonds in these well-known reactions.3

Though these reactions are widely used for the synthesis of aryl amines, some suffer several drawbacks as they require the use of a metal, harsh reaction conditions, and costly reagents. Because contamination of the product with the transition metal is of concern, much effort has been devoted toward the development of metal-free N-arylation reactions.5

Recently, Huang et al. reported the metal-free synthesis of N-aryl tertiary amines in which they reacted methyl and ethyl-derivatized tertiary amines with various aryl halides with excess potassium tert-butoxide to obtain the N-arylated product.6 Fang and co-workers also used aliphatic tertiary amines for the synthesis of arylated amines by using potassium hydroxide as a base.7 Shi et al. developed a rapid microwave-assisted synthesis of secondary and tertiary aryl amines in dimethyl sulfoxide (DMSO) and excess potassium tert-butoxide in good yields.8 Although the above methods were effective in generating the N-arylated products, the method of Fang et al. required 24 h to obtain moderate yields. Shi’s method requires the use of a microwave reactor, making scalability a challenge. In an attempt to identify a simple, efficient, and scalable method for the synthesis of N-aryl amines, we report rapid, metal-free tetrabutylammonium bromide (TBAB)-promoted arylation of secondary amines using bromo- and chlorobenzene.

RESULTS AND DISCUSSION

Bromobenzene (0.20 mL, 2 mmol) and morpholine (0.26 mL, 3 mmol) were chosen as substrates for reaction optimization (Scheme 1) with potassium tertiary butoxide (KO’Bu) as the base in DMSO (2 mL). We first studied the protocol of Shi et al. for large-scale synthesis by simply heating for 12 h with no microwave (Scheme 1).9 The method was successful in generating the N-arylated product, but only in 65% yield. Prolonged reaction time (greater than 12 h), increasing the temperature, or increasing the amount of base failed to increase the yields. After reviewing the literature, we found that TBAB has been successfully used in several carbon−heteroatom and carbon−carbon bond formation reactions, halogenation, and oxidation reactions. Johnson et al. utilized TBAB to efficiently alkylate sulfoximines;7 Wang et al. employed TBAB to rapidly alkylate acridone in a high yield;8 Majumdar et al. reported a TBAB-promoted S-alkylation of 4-mercapto-6-methyl-2-pyrene with allyl and propargyl halides under mild conditions with moderate to high yields;9 and Lebel et al. reported the synthesis of a complex polydentate phosphine ligand by utilizing TBAB-catalyzed P-alkylation of phosphine borane in excellent yields.10

Encouraged by the successful alkylations noted above under phase-transfer conditions, we also searched the literature for examples of TBAB being used under nonphase transfer
conditions. Li et al. and Tang et al. noted that TBAB could serve as an activator/additive to promote both substitution and cross-coupling reactions, respectively. On the basis of these findings, we attempted to utilize TBAB under nonphase transfer conditions. We were encouraged to see that complete consumption of the starting material occurred after 30 min with an isolated yield of 85% when 50 mol % (161 mg) TBAB was used. Hoping to further optimize the reaction conditions, we increased the loading of TBAB but were met with decreased yields. TBAB loading was then lowered systematically until it was found that 5 mol % was optimal (Figure 1).

![Figure 1. TBAB optimization graph.](image)

Using these conditions, N-phenylmorpholine (Table 1, entry 9) was obtained in 95% yield in only 8 min. When the reaction was conducted at 100 °C, the reaction furnished the N-arylated product in excellent yield but required greater than double the time interval for completion. Below 100 °C, the reaction was sluggish and required several hours to complete.

We then screened different solvents such as tetrahydrofuran, EtOH, dimethylformamide, and N-methylpyrrolidone (NMP) to assess if further optimization was possible. NMP proved to be the only other suitable solvent for our reaction conditions, but produced lower yield than that obtained from DMSO. After the solvent, time, and TBAB loading conditions were established, we carried out multiple N-arylation reactions with several different secondary amines. This method was equally effective with all secondary amines tested, and the products were furnished in good to excellent yields (Table 1). Bromobenzenes substituted with electron-donating or -withdrawing groups were also found to be as effective as unsubstituted bromobenzene, yielding the mixture of isomers in their expected ratios5,6 (Table 1). To test the scalability, unsubstituted bromobenzene, yielding the mixture of isomers (Table 1, entry 10, yield 76%), 1,2,3,4-tetrahydroquinoline (Table 1, entry 12, yield 91%), even the sterically crowded dicyclohexylamine (Table 1, entry 6, yield 82%), and diphenylamine (Table 1, entry 14, yield 79%) all proceeded in good to excellent yields in short reaction times.

It is accepted that the reaction proceeds mechanistically through the generation of a benzyne intermediate (slow) followed by its rapid quenching via the desired nucleophile (fast), as explained by the mixture of isomers obtained from 1-bromo-4-fluorobenzene, 4-bromotoluene, and 4-bromoanisole with morpholine (entries 21, 22, and 23).5,6 The reactions were completed within 15 min, and isomers of the products were formed in a 1:1 ratio, as indicated by nuclear magnetic resonance (NMR) spectroscopy (see the Supporting Information).

### CONCLUSIONS

C=N-aryl bond formation is one of the most challenging tasks in medicinal chemistry, with scalability and metal contamination being major concerns with the current approaches. Herein, we have detailed a scalable, high-yielding, and efficient TBAB-promoted N-arylation of several secondary amines. Future studies will focus on determining the mechanism through which TBAB promotes this reaction.

### EXPERIMENTAL SECTION

#### General Information

Reagents and solvents were of ACS grade and purchased from Sigma-Aldrich or Alfa Aesar. Inert atmosphere (N2 or argon) is not required. Anhydrous solvents were used as provided without further purification. Reactions were monitored by thin-layer chromatography (TLC), visualizing with an ultraviolet lamp and I2. Flash column chromatography was performed on RediSep Rf Gold columns with a Whatman Purisil 60A silica gel (230–400 mesh) loading column on a Teledyne Isco CombiFlash Rf. 1H NMR spectra were recorded on a Varian INOVA 400 MHz NMR spectrometer at 25 °C. All synthesized compounds were characterized by 1H NMR and electrospray ionization (ESI) mass spectrometry analysis (in the case of 1-bromo-4-fluorobenzene). Chemical shifts are reported in parts per million. The residual solvent peak was used as the internal reference: CDCl3. Mass spectra were obtained on an ESI time-of-flight mass spectrometer (Bruker amaZon X).

#### General Procedure for the Synthesis of Tertiary Amines

To a dry round-bottom flask (or pressure vial for low boiling amines) was added bromobenzene/chlorobenzene (2.0 mmol) and secondary amine (3.0 mmol) in 3 mL of DMSO, followed by TBAB (32.0 mg, 5 mol %) and 1.5 equiv potassium tert-butoxide (337.0 mg, 3.0 mmol). The reaction was heated at 130 °C and monitored by TLC at frequent time intervals. The reaction mixture was allowed to cool, diluted with water, and extracted with ethyl acetate (4×). The organic layers were combined, washed with brine, dried over MgSO4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by column chromatography (0–20% ethyl acetate/hexanes) to provide the desired tertiary amines. All resulting products were verified by NMR (directly compared with the result from previously published literature).

**N,N-Diethyl-aniline (1).** 263 mg, 88% yield, clear to light yellow liquid; 1H NMR (CDCl3, 400 MHz, ppm): δ 7.24–7.18 (m, 2H), 6.70–6.63 (m, 2H), 3.36–3.32 (m, 6H), 1.18–1.13 (m, 6H).

**N,N-Diisopropyl-aniline (2).** 301 mg, 85% yield, light brown liquid; 1H NMR (CDCl3, 400 MHz, ppm): δ 7.20–7.16 (m, 2H), 6.70–6.63 (m, 2H), 3.36–3.32 (m, 6H), 1.18–1.13 (m, 6H).

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Table 1. TBAB-Promoted Reaction of Bromo/Chlorobenzene with Secondary Amines

| Entry | ArX | Amine | Product | Time | Yield | Reference |
|-------|-----|-------|---------|------|-------|-----------|
| 1     | PhBr | (CH₃CH₂)₂NH | (CH₃CH₂)₂NPh | 12   | 88    | 6         |
| 2     | PhBr | (CH₃CH₂)₂NH | (CH₃CH₂)₂NPh | 12   | 85    | 5         |
| 3     | PhBr | (i-Pr)₂NH | (i-Pr)₂NPh | 15   | 90    | 6         |
| 4     | PhBr | (CH₃CH₂)₂NH | (CH₃CH₂)₂NPh | 10   | 86    | 6         |
| 5     | PhBr | (CH₃CH₂)₂NH | (CH₃CH₂)₂NPh | 10   | 80    | 12        |
| 6     | PhBr | (Cy)₂NH | (Cy)₂NPh | 12   | 82    | 6         |
| 7     | PhBr | 1-Phenylpiperazine | 1,4-Diphenylpiperazine | 10   | 87    | 13        |
| 8     | PhBr | Piperidine | 1-Phenylpiperidine | 10   | 85    | 5         |
| 9     | PhBr | Morpholine | 1-Phenylmorpholine | 8    | 95    | 6         |
| 10    | PhBr | Indole | 1-Phenylindole | 18   | 76    | 6         |
| 11    | PhBr | 1,2,3,4-Tetrahydropyridine | 1-Phenyl-1,2,3,4-tetrahydropyridine | 14   | 86    | 6         |
| 12    | PhBr | 1,2,3,4-Tetrahydroisoquinoline | 2-Phenyl-1,2,3,4-tetrahydroisoquinoline | 12   | 91    | 14        |
| 13    | PhBr | 1-Methylpiperazine | 1-Methyl-4-phenylpiperazine | 10   | 85    | 13        |
| 14    | PhBr | Diphenylpiperazine | Triphenylamine | 10   | 79    | 6         |
| 15    | PhCl | (i-Pr)₂NH | (i-Pr)₂NPh | 15   | 87    | 6         |
| 16    | PhCl | (CH₃CH₂)₂NH | (CH₃CH₂)₂NPh | 14   | 90    | 6         |
| 17    | PhCl | Piperidine | 1-Phenylpiperidine | 12   | 82    | 5         |
| 18    | PhCl | Morpholine | 1-Phenylmorpholine | 10   | 92    | 6         |
| 19    | PhCl | Indole | 1-Phenylindole | 20   | 72    | 6         |
| 20    | PhCl | Tetrahydropyridine | 1-Phenyltetrahydropyridine | 15   | 84    | 6         |
| 21    | PhCl | morpholine | 1-Morpholine | 12   | 92    | 15        |
| 22    | PhCl | morpholine | 1-Morpholine | 10   | 82    | 6         |
| 23    | PhCl | morpholine | 1-Morpholine | 14   | 88    | 5         |
| 24    | PhBr | (CH₃CH₂)₂NH | (CH₃CH₂)₂NPh | 16   | 80    | 6         |
| 25    | PhBr | Piperidine | 1-Phenylpiperidine | 18   | 76    | 5         |
| 26    | PhBr | Morpholine | 1-Phenylmorpholine | 16   | 89    | 6         |

"Optimized conditions: 2.0 mmol aryl halide, 3.0 mmol amine, 3.0 mmol KO‘Bu, and 5 mol % TBAB in 3 mL of DMSO. Time in minutes. Isolated yield.

2H), 6.64–6.61 (m, 3H), 3.23–3.20 (m, 4H), 1.62–1.57 (m, 4H), 0.93–0.89 (m, 6H). N,N-Diisopropylaniline (3). 320 mg, 90% yield, clear liquid; 1H NMR (CDCl₃, 400 MHz, ppm): δ 7.24–7.16 (m, 2H), 6.89–6.76 (m, 3H), 3.77–3.74 (m, 2H), 1.20–1.18 (d, J = 6.5 Hz, 12H).

N,N-Dibutylaniline (4). 353 mg, 86% yield, light yellow liquid; 1H NMR (CDCl₃, 400 MHz, ppm): δ 7.20–7.16 (m, 2H), 6.64–6.60 (m, 3H), 3.77–3.74 (m, 2H), 1.57–1.53 (m, 4H), 1.35–1.31 (m, 4H), 0.96–0.92 (t, J = 7.6 Hz, 6H).

N,N-Diisobutylaniline (5). 328 mg, 80% yield, clear to light yellow liquid; 1H NMR (CDCl₃, 400 MHz, ppm): δ 7.19–7.16 (m, 2H), 6.64–6.59 (m, 3H), 3.13–3.11 (d, J = 7.2 Hz, 4H), 2.08–2.05 (m, 2H), 0.89–0.87 (d, J = 6.4 Hz, 12H).

N,N-Dicyclohexylaniline (6). 422 mg, 82% yield, light yellow liquid; 1H NMR (CDCl₃, 400 MHz, ppm): δ 7.24–7.14 (m, 2H), 6.93–6.78 (m, 3H), 3.25–3.19 (m, 2H), 1.75 (m, 8H), 1.63–1.48 (m, 6H), 1.35–1.24 (m, 6H), 1.31–1.08 (m, 2H).

1,4-Diphenylpiperazine (7). 414 mg, 87% yield, yellow to light brown solid, mp 159–160 °C; 1H NMR (CDCl₃, 400 MHz, ppm): δ 7.33–7.29 (m, 4H), 7.01–6.99 (d, J = 7.6 Hz, 4H), 6.92–6.89 (t, J = 7.2 Hz, 2H), 3.35 (s, 8H).

1-Phenylpiperidine (8). 274 mg, 85% yield, light yellow liquid; 1H NMR (CDCl₃, 400 MHz, ppm): δ 7.26–7.22 (m,
2H), 6.94−6.92 (m, 2H), 6.83−6.81 (m, 1H), 3.15−3.13 (t, \( J = 5.2 \) Hz, 4H), 1.71−1.69 (m, 4H), 1.59−1.56 (m, 2H).5

1-Phenylmorpholine (9). 310 mg, 95% yield, brown crystalline chunks, mp 51−53 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta = 7.71−7.69 \) (d, \( J = 8 \) Hz, 1H), 7.59−7.56 (d, \( J = 8.4 \) Hz, 1H), 7.52−7.51 (d, \( J = 4 \) Hz, 4H), 7.36−7.34 (m, 2H), 7.25−7.17 (m, 2H), 6.69−6.68 (d, \( J = 3.2 \) Hz, 2H).6

1-Phenyl-1H-indole (10). 293 mg, 76% yield, yellow to brown liquid; \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta = 7.25−7.24 \) (m, 2H), 7.20−7.18 (m, 4H), 7.01−6.99 (m, 2H), 6.86−6.84 (m, 1H), 4.44−4.42 (m, 2H), 3.59−3.56 (m, 2H), 3.01−2.98 (m, 2H).13

1-Methyl-4-phenylpiperazine (13). 299 mg, 85% yield, clear liquid; \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta = 7.25−7.23 \) (m, 2H), 6.93−6.91 (d, \( J = 8 \) Hz, 3H), 3.21−3.18 (t, \( J = 5 \) Hz, 4H), 2.57−2.55 (t, \( J = 5 \) Hz, 4H), 2.37−2.33 (m, 2H).13

Triphenylamine (14). 387 mg, 79% yield, off-white crystalline solid, mp 125−127 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta = 7.32−7.28 \) (m, 6H), 7.17−7.15 (m, 6H), 7.08−7.04 (m, 4H).6

4-(Fluorophenyl)morpholine and 4-(3-Fluorophenyl)-morpholine (21). 333 mg, 92% yield, colorless liquid; P-isomer \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta = 6.98−6.94 \) (t, \( J = 8.8 \) Hz, 1H), 6.86−6.83 (dd, \( J = 4.8 \) Hz, 1H), 3.85−3.84 (t, \( J = 7.6 \) Hz, 2H), 3.07−3.05 (t, \( J = 5 \) Hz, 2H). m-isomer \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta = 7.19 \) (dd, \( J = 0.5 \) Hz, 6.64 (dd, \( J = 0.5 \) Hz, 6.55−6.54 (m, 1H), 3.83−3.82 (t, \( J = 5 \) Hz, 2H), 3.15−3.13 (t, \( J = 4.8 \) Hz, 2H).14 A 1:1 ratio was obtained; therefore, integration values should be multiplied by 2 to obtain the reported spectra in the literature of each individual isomer.15,16

4-(4-Methylphenyl)morpholine and 4-(3-Methylphenyl)-morpholine (22). 290 mg, yellow to brown solid, 82% yield. P-isomer \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta = 7.08−7.06 \) (d, \( J = 8 \) Hz, 1H), 6.83−6.81 (d, \( J = 8.8 \) Hz, 1H), 3.86−3.83 (t, \( J = 4.6 \) Hz, 2H), 3.10−3.08 (t, \( J = 5 \) Hz, 2H), 2.28 (s, 1.5H). m-isomer \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta = 7.15 \) (t, \( J = 4.4 \) Hz, 0.5H), 6.73−6.71 (m, 1.5H), 3.86−3.84 (t, \( J = 4.6 \) Hz, 2H), 3.14−3.12 (t, \( J = 4.8 \) Hz, 2H), 2.31 (s, 1.5H). A 1:1 ratio was obtained; therefore, integration values should be multiplied by 2 to obtain the reported spectra in the literature of each individual isomer.2

4-(4-Methoxyphenyl)morpholine and 4-(3-Methoxyphenyl)morpholine (23). 340 mg, clear liquid, 88% yield. P-isomer \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta = 6.89 \) (d, \( J = 9.6 \) Hz, 2H), 6.85−6.83 (d, \( J = 8 \) Hz, 1H), 3.86−3.84 (t, \( J = 6.4 \) Hz, 2H), 3.78 (s, 1.5H), 3.05−3.03 (t, \( J = 4.6 \) Hz, 2H). m-isomer \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta = 7.19−7.15 \) (m, 0.5H), 6.53−6.51 (d, \( J = 8 \) Hz, 0.5H), 6.44 (s, 0.5H), 3.82−3.80 (t, \( J = 6.4 \) Hz, 2H), 3.76 (s, 1.5H), 3.15−3.13 (t, \( J = 4.6 \) Hz, 2H). A 1:1 ratio was obtained; therefore, integration values should be multiplied by 2 to obtain the reported spectra in the literature of each individual isomer.3
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