A Practical Synthesis of Azobenzenes through Oxidative Dimerization of Aromatic Amines Using *tert*-Butyl Hypoiodite

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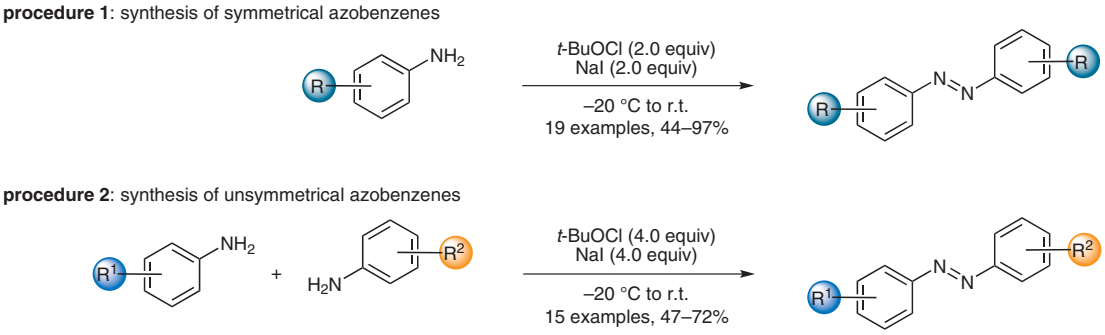
Abstract: A straightforward, convenient, and efficient synthetic method of azobenzenes through oxidative dimerization of aromatic amines using a unique and cost-effective iodinating reagent is described. This new method allows for easy access to both of symmetrical and unsymmetrical azobenzenes under extremely mild conditions.

Key words: amines, azo compounds, dimerization, iodine, oxidation



Scheme 1 General procedures for the synthesis of symmetrical (Procedure 1) and unsymmetrical (Procedure 2) azobenzenes from anilines

Introduction

Aromatic azo compounds, namely, azobenzenes constitute a large class of organic dyes in industry.[1] Additionally, light-sensitivity of azobenzenes (i.e., photoisomerization between *trans*- and *cis*-isomers)[2] offers the opportunities for the creation of photoresponsive soft materials such as smart polymers, liquid crystals, and photoswitches in biological systems.[3] From a synthetic viewpoint, among the conventional methods used for symmetrical azobenzenes,[4] the oxidative homodimerization of aromatic amines is a straightforward approach and advantageous in terms of availability of starting materials. However, these methods suffer from the use of environmentally unfriendly heavy-metal salts as an oxidant, such as $BaMnO_4$,[5a] $Pb(OAc)_4$,[5b] and HgO.[5c] On the other hand, for the preparation of unsymmetrical azobenzenes, diazonium coupling[6] and the Mills reaction[7] have been extensively used. Nevertheless, in these reactions, explosive or toxic starting materials must be prepared from commercially available compounds. More specifically, the main issue lies in the substrate scope, which is exclusively restricted to the combination of electron-rich and -deficient aromatic substrates. In this regard, recently, two catalytic oxidative dimerization reactions of aromatic amines have been independently developed by García[8] and Jiao groups.[9] Although both methods succeeded in preparing a series of unsymmetrical azobenzenes, there still remains considerable room for improving the reaction conditions, such as lowering the reaction temperature or reducing the use of excess amounts of reagents. As a part of our program to develop efficient synthetic methods of nitrogen-containing compounds by utilizing a unique iodinating reagent, *tert*-butyl hypoiodite (*t*-BuOI),[10] we have recently reported an efficient, less-energy-consuming, and metal-free synthetic method of azobenzenes through oxidative dimerization of aromatic amines (Scheme 1).[11] The method allows for synthesizing not only symmetrical azoben-

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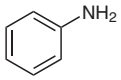
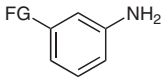
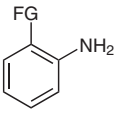
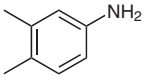
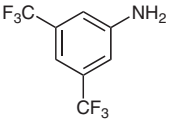
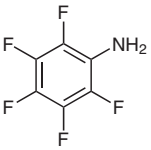
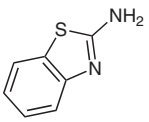
zenes (Procedure 1 in Scheme 1) but also unsymmetrical types in a selective manner (Procedure 2 in Scheme 1). Herein we wish to describe our practical procedures for preparing a series of azobenzenes using the combination of inexpensive and easy to handle reagents, *tert*-butyl hypochlorite (*t*-BuOCl) and NaI as the precursors of *t*-BuOI.

Scope and Limitations

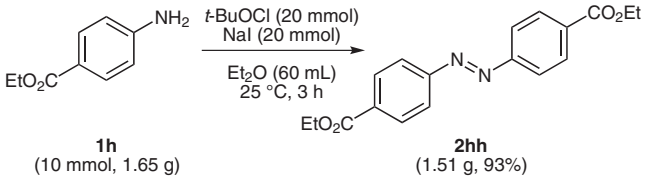
A typical procedure for the homodimerization (Procedure 1 in Scheme 1) of aromatic amines is as follows: *t*-BuOCl (1.0 mmol) was added to a solution of aromatic amine (0.5 mmol) and NaI (1.0 mmol), and the resulting mixture was stirred for the time indicated in Table 1. The simplest aromatic amine, aniline (**1a**), was efficiently converted into azobenezne (**2aa**) in one hour at room temperature (entry 1). Symmetrical azobenzenes bearing the 4,4′-difunctionalities were synthesized in high to excellent yields from *para*-substituted anilines **1b**–**1k**, regardless of their electronic structures (entries 2–11). It should be noted that aromatic iodination did not occur, even though electronically rich aniline **1c** was used in the presence of iodonium cation (I^+) equivalent reagent. Anilines that have a *meta*-substituent **1l** and **1m** also afforded the corresponding azobenzenes **2ll** and **2mm** in high yields (Table 1, entries 12 and 13). Remarkably, aniline **1n** bearing a sterically demanding substituent at the *ortho*-position was also converted into the corresponding azobenzene **2nn**, albeit in moderate yield (entry 14). Using this method, a variety of symmetrical azobenzenes **2oo**–**2rr** were successfully prepared in high yields (entries 15–18). Notably, heteroaromatic amine **1s** also served as a substrate for the oxidative homodimerization to afford the multiple heteroatom-incorporated azo product **2ss** in 72% yield (entry 19).

Table 1 Synthesis of Symmetrical Azobenzenes **2**[a]

Entry	$ArNH_2$ **1**	Conditions	Product **2**	Yield (%)[b]
1	 **1a**	MeCN 25 °C, 1 h	**2aa**	95
2	**1b** FG = Me	Et_2O 25 °C, 1 h	**2bb**	97
3	**1c** FG = OMe	MeCN 25 °C, 0.25 h	**2cc**	87
4	**1d** FG = F	acetone 25 °C, 6 h	**2dd**	95
5	**1e** FG = Cl	Et_2O –20 °C, 12 h	**2ee**	96
6	**1f** FG = Br	acetone 25 °C, 3 h	**2ff**	83
7	**1g** FG = I	Et_2O –20 °C, 12 h	**2gg**	88
8	**1h** FG = CO_2Et	Et_2O 25 °C, 3 h	**2hh**	95
9	**1i** FG = Ac	Et_2O –20 °C, 12 h	**2ii**	91
10	**1j** FG = CN	THF 25 °C, 12 h	**2jj**	89
11[c]	**1k** FG = NO_2 	THF 25 °C, 6 h	**2kk**	79
12	**1l** FG = Cl	acetone 25 °C, 3 h	**2ll**	86
13	**1m** FG = NO_2 	THF –20 °C, 12 h	**2mm**	78
14	**1n** FG = Ph	Et_2O –20 °C, 36 h	**2nn**	44
15	**1o** FG = CN	Et_2O 25 °C, 24 h	**2oo**	73
16	 **1p**	Et_2O 25 °C, 1 h	**2pp**	89
17	 **1q**	THF 25 °C, 12 h	**2qq**	94
18	 **1r**	Et_2O 25 °C, 12 h	**2rr**	67
19	 **1s**	MeCN 25 °C, 48 h	**2ss**	72

[a] Reaction conditions: aromatic amine **1** (0.5 mmol), *t*-BuOCl (1.0 mmol), NaI (1.0 mmol), and solvent (3 mL).
[b] Isolated yield.
[c] *t*-BuOCl (2 mmol) and NaI (2 mmol) were used.

To demonstrate the power of this synthetic method, a large-scale preparation of azobenzene **2hh** was performed (Scheme 2). From a 10 mmol (1.65 g) of ethyl 4-aminobenzoate (**1h**), the desired product **2hh** was successfully synthesized in gram-scale (1.51 g, 93%) without any significant loss of reaction efficiency, compared with the small-scale (0.5 mmol) preparation (Table 1, entry 8,).



Scheme 2 Large-scale synthesis of **2hh**

The notable feature of this oxidative dimerization method is the feasibility of selective synthesis of unsymmetrical azobenzenes (Procedure 2 in Scheme 1). The scope of the cross-dimerization of aromatic amines is shown in Table 2. When an equimolar THF solution of *p*-toluidine (**1b**; 0.25 mmol) and ethyl 4-aminobenzoate (**1h**; 0.25 mmol) was treated with *t*-BuOCl (1.0 mmol) in the presence of NaI (1.0 mmol) at 0 °C, cross-dimerized product **2bh** was formed in a selective manner (62%) over the homodimers **2bb** and **2hh** (Table 2, entry 1).[12] These azobenzenes were easily separated by silica gel column chromatography. Cross-dimerization of **1b** with anilines bearing electron-deficient functionalities proceeded smoothly, affording unsymmetrical azobenzenes **2bk**–**2bq** in good yields (entries 2–6). Notably, this method allowed for the efficient access to unsymmetrical azobenzenes possessing electron-deficient moieties on the phenyl ring that are otherwise difficult to prepare by conventional method (entries 7–14). Furthermore, unsymmetrical azobenzenes that has a heteroaromatic component was also selectively synthesized in moderate yield (entry 15). In the case of the combination of electron-rich anilines, cross-dimerization failed, and homodimers were the major products. Although the precise mechanism of the oxidative dimerization is unclear at present, a tentative mechanism is as follows: 1) the electronically richer aniline is doubly N-iodinated through the agency of halogen bonding between *t*-BuOI and Ar^1NH_2; 2) nucleophilic substitution on the N-center of Ar^1NI_2 by the remaining Ar^2NH_2 proceeds to form the N–N single bond; 3) then HI is eliminated from the resulting *N*,*N*′-diarylhydrazine to give azo products. The limitation in the cross-dimerization of electron-rich anilines might be ascribed to the existence of equilibrium between $ArNH_2$ and $ArNI_2$, leading to the scrambling of homo-dimers.

Table 2 Synthesis of Unsymmetrical Azobenzenes **2**[a]

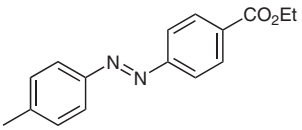
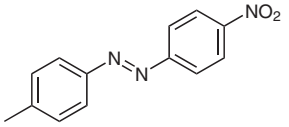
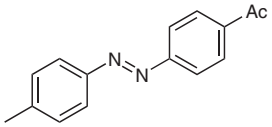
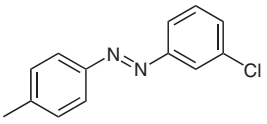
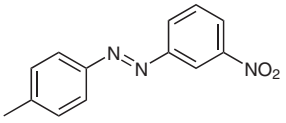
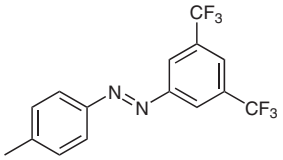
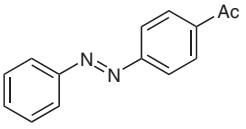
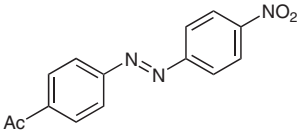
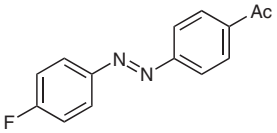
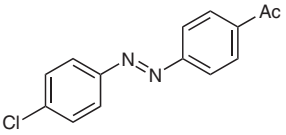
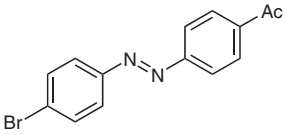
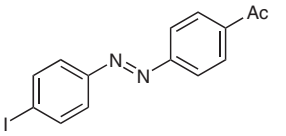
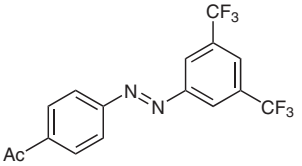
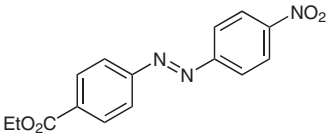
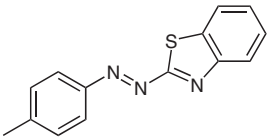
Entry	**1**	Conditions	Product **2**	Yield (%)[b]
1	**1b** + **1h**	THF 0 °C 6 h	 **2bh**	62
2	**1b** + **1k**	THF 0 °C, 3 h then 25 °C, 1 h	 **2bk**	64
3[c]	**1b** + **1i**	THF –20 °C 24 h	 **2bi**	58
4	**1b** + **1l**	acetone 0 °C 3 h	 **2bl**	52
5	**1b** + **1m**	THF –20 °C 24 h	 **2bm**	60
6	**1b** + **1q**	THF 25 °C 12 h	 **2bq**	66
7	**1a** + **1i**	THF 25 °C 12 h	 **2ai**	54
8	**1i** + **1k**	MeCN –20 °C 24 h	 **2ik**	72
9	**1d** + **1i**	DME 25 °C 3 h	 **2di**	61

Table 2 Synthesis of Unsymmetrical Azobenzenes **2**[a] (continued)

Entry	1	Conditions	Product 2	Yield (%)[b]
10	**1e** + **1i**	MeCN 0 °C 18 h	 **2ei**	65
11	**1f** + **1i**	DME –20 °C 24 h	 **2fi**	58
12	**1g** + **1i**	THF 25 °C 12 h	 **2gi**	53
13	**1i** + **1q**	MeCN –20 °C 24 h	 **2iq**	63
14[d]	**1h** + **1k**	MeCN 0 °C 24 h	 **2hk**	66
15[e]	**1b** + **1s**	MeCN 25 °C 12 h	 **2bs**	47

[a] Reaction conditions: two different aromatic amines **1** (0.25 mmol for each), *t*-BuOCl (1.0 mmol), NaI (1.0 mmol), and the solvent (3 mL).
[b] Isolated yield.
[c] Anilines **1b** (0.5 mmol) and **1i** (0.25 mmol), *t*-BuOCl (1.5 mmol), and NaI (1.5 mmol) were used.
[d] Anilines **1h** (0.25 mmol) and **1k** (0.5 mmol), *t*-BuOCl (1.5 mmol), and NaI (1.5 mmol) were used.
[e] Anilines **1b** (0.5 mmol) and **1s** (0.5 mmol), *t*-BuOCl (2.0 mmol), and NaI (2.0 mmol) were used.

In summary, a straightforward, efficient, and cost-effective synthetic procedure of azobenzenes has been developed. The method was successfully applied to a wide variety of readily available aromatic amines. Furthermore, by using this method, unsymmetrical azobenzenes were selectively synthesized over homodimerized products under mild conditions, which has been a synthetic challenge for a long time. Moreover, the practical utility of the method was further demonstrated by gram-scale synthesis.

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt Automated Melting Point System. IR spectra were recorded on a Shimadzu IR Affinity-1 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol FT-NMR JNM EX 270 spectrometer (^{1}H NMR, 270 MHz; ^{13}C NMR, 68 MHz) using TMS as an internal standard. ^{19}F NMR spectra were recorded on a Bruker Avance III 400 spectrometer (^{19}F NMR, 376 MHz) using benzotrifluoride as an internal standard. Mass spectra were obtained on a Jeol JMS-DX303HF mass spectrometer. High-resolution mass spectra were obtained on a Jeol JMS-DX303HF mass spectrometer. Products were purified by chromatography on silica gel BW-300 (Fuji Silysia Chemical Ltd.) or Al_2O_3 (Merck, 90 active stage I, 0.063–0.200 mm). Analytical TLC was performed on pre-coated silica gel glass plates (Merck silica gel 60 F_{254}, 0.25 mm thickness). Compounds were visualized with UV lamp or treatment with an ethanolic solution of phosphomolybdic acid followed by heating.

(*E*)-1,2-Diphenyldiazene (2aa); Typical Procedure for Symmetrical Azobenzenes (Procedure 1 in Scheme 1)

To a mixture of aniline (**1a**; 46.6 mg, 0.5 mmol) and NaI (150.0 mg, 1.0 mmol) in MeCN (3 mL) was added *t*-BuOCl (108.6 mg, 1.0 mmol) under the N_2 atmosphere at 25 °C. The mixture was stirred for 1 h, quenched with aq $Na_2S_2O_3$ (1.0 M, 10 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane–EtOAc, 99:1) gave **2aa**[9] (43.0 mg, 95%) as a yellow solid; mp 67–68 °C; R_f = 0.53 (hexane–EtOAc, 9:1).

IR (ATR): 1580, 1481, 1450, 1298, 1068, 926, 773 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.41–7.53 (m, 6 H), 7.89–7.94 (m, 4 H).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 122.7, 129.0, 130.9, 152.5.

MS (EI, 70 eV): *m*/*z* (%) = 182 (57, $[M]^+$), 77 (100), 105 (26).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{10}N_2$: 182.0844; found: 182.0841.

Ethyl (*E*)-(*p*-Tolyldiazenyl)benzoate (2bh); Typical Procedure for Unsymmetrical Azobenzenes (Procedure 2 in Scheme 1)

To a mixture of *p*-toluidine (**1b**; 26.8 mg, 0.25 mmol), ethyl 4-aminobenzoate (**1h**; 41.3 mg, 0.25 mmol), and NaI (150.0 mg, 1.0 mmol) in THF (3 mL) was added *t*-BuOCl (108.6 mg, 1.0 mmol) under the N_2 atmosphere at 0 °C. The mixture was stirred for 6 h, quenched with aq $Na_2S_2O_3$ (1.0 M, 10 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane–EtOAc, gradient from 99:1 to 70:30) gave **2bh**[9] (41.3 mg, 62%) as a yellow solid; mp 100–101 °C; R_f = 0.43 (hexane–EtOAc, 9:1).

IR (ATR): 2922, 1715, 1601, 1265, 1103, 1094, 1008, 866, 822, 773, 709 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.0 Hz, 3 H), 2.45 (s, 3 H), 4.42 (q, *J* = 7.0 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.87 (d, *J* = 8.4 Hz, 2 H), 7.92 (d, *J* = 8.6 Hz, 2 H), 8.19 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 14.4, 21.6, 61.2, 122.4, 123.1, 129.7, 130.4, 131.8, 142.3, 150.6, 155.1, 165.9.

MS (EI, 70 eV): *m*/*z* (%) = 268 (53, $[M]^+$), 91 (100), 119 (33), 149 (25).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{16}N_2O_2$: 268.1212; found: 268.1214.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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