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Synthetic Methods

Oxidative Dimerization of Aromatic Amines using tBuOI: Entry to Unsymmetric Aromatic Azo Compounds**

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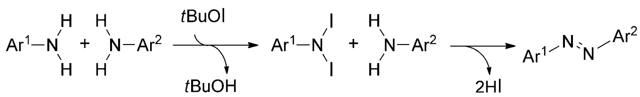
Aromatic azo compounds have found tremendous applications in industry as organic dyes, pigments, food additives, indicators, and therapeutic agents.[1] Furthermore, by taking advantage of their unique photochemical responsivity, the potential applications of azo compounds have been extended to a wide range of light-responsive functional materials (e.g., liquid crystals,[2] molecular photoswitches,[3] and photochromic ligands for optochemical genetics[4]) over the past few decades. Of the myriad of synthetic methods for aromatic azo compounds,[5] conventional methods for symmetric aromatic azo compounds involve reductive homodimerization of nitroarenes[6] and oxidation of aromatic amines.[5,7] Nevertheless, these methods suffer from the stoichiometric use of environmentally unfriendly transition-metal oxidants (e.g., Mn,[7a] Pb,[7b] and Hg[7c,d] salts), or from difficulty in controlling product distribution (e.g., the azo-/azoxybenzene ratio in the reductive methods). In addition to these problems, great challenges remain in the synthesis of unsymmetric aromatic azobenzenes. Representative protocols for unsymmetric aromatic azo compounds involve diazo coupling[8] and the Mills reaction.[9] These methods require the preparation of reactive intermediates, that is, diazonium salts and nitroso compounds, from commercially available compounds. More specifically, the main issue of these approaches lies in the substrate scope, which is limited to the combination of electron-rich and electron-deficient aromatic amines because of their intrinsic reaction mechanism. In this regard, a recent catalytic oxidation of aromatic amines using oxygen as an oxidant has been developed.[10,11] While Grirrane, Corma, and García developed an oxidative dimerization of aniline derivatives utilizing a Au/TiO_2 catalyst,[10] Jiao and co-workers reported a copper-catalyzed aerobic oxidative coupling of aromatic amines.[11] Both succeeded in synthesizing a series of unsymmetric azobenzenes by using their methods. Nonetheless, the former method requires high pressures of O_2 (5 bar) and high temperatures (100 °C), and the latter requires excess amounts (5 equiv) of the electron-deficient aromatic amines to attain sufficient yields of the unsymmetric azo products relative to the symmetric products. Therefore, there still remains considerable room for the development of synthetic methods for unsymmetric aromatic azo compounds. Herein, we present an efficient oxidative homo- and cross-dimerization reaction of aromatic amines utilizing the organic oxidant *tert*-butyl hypoiodite (*t*BuOI)[12] under mild reaction conditions (room temperature or below), thus leading to a variety of symmetric and unsymmetric aromatic azo compounds having high functional-group tolerance (Scheme 1).



Scheme 1. Oxidative dimerization of aromatic amines using *t*BuOI.

As part of our research project to develop efficient synthetic methods for heterocycles utilizing Q-halogen-containing reagents (Q = O, N),[13] we have demonstrated that *t*BuOI is a powerful iodinating reagent for compounds bearing acidic hydrogen atoms, such as oximes, carboxamides, and sulfonamides, to generate unique species having Q–I bonds; such species serve as the key intermediates in the synthetic reactions.[14] On the basis of this background, we envisioned that oxidative dimerization of anilines, which have two relatively weakly acidic hydrogen atoms, would be feasible by utilizing *t*BuOI. Namely, the treatment of anilines with *t*BuOI would generate $ArNI_2$ through a hydrogen–iodine exchange process, and the subsequent elimination of 2 HI from $ArNI_2$ and unreacted $ArNH_2$ should produce symmetric aromatic azo compounds (Scheme 1). Specifically, given that two different anilines are used, the aniline having the more acidic hydrogen atoms (Ar^1NH_2) should undergo iodination prior to the other (Ar^2NH_2). We hypothesized that nucleophilic substitution at the nitrogen atom of Ar^1NI_2 with the remaining Ar^2NH_2 would selectively give the unsymmetric azo product over the homodimer.

To verify our hypothesis, we examined an oxidative homodimerization of aniline (**1a**) in the presence of *t*BuOI.[15] When 0.5 mmol of **1a** was treated with *t*BuOI (1.0 mmol) in acetonitrile at room temperature for 1 hour, oxidative homodimerization to form a N=N bond smoothly proceeded to give *trans*-azobenzene (**2aa**) in 95 % yield (Table 1).[16]

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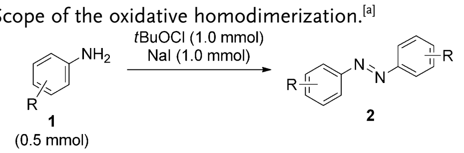
To confirm the superiority of the system, we tested the reaction with other halogen-containing oxidants using *p*-toluidine (**1b**) as a substrate (see Table S1 in the Supporting Information). Whereas the use of *t*BuOI resulted in the homocoupled product **2bb** in 97% yield, other iodine-containing oxidants such as I_2 and IPy_2BF_4 failed to provide the azo product. The employment of *t*BuOCl and *N*-iodosuccinimide (NIS) resulted in rather low yields of **2bb** (4% and 10%, respectively). The order of the addition of the reagents also turned out to be an important factor: no dimerized products were produced when *t*BuOCl was added before NaI; only a monochlorinated amine was obtained. Taken together, the results show that in situ generation of *t*BuOI would be much faster than the reaction of amines with *t*BuOCl.

Having identified a suitable reagent, we explored the substrate scope of the homodimerization reaction (Table 1). Aniline derivatives having an electron-donating group in the *para* position were readily dimerized to produce the corresponding azo products **2bb** and **2cc** in high yields (entries 2 and 3). Halo-substituted anilines were also applicable to the reaction (entries 4–7). The reaction of electron-deficient aromatic amines proceeded smoothly to give the corresponding azobenzenes in excellent yields, albeit with extended reaction times when compared to those of electron-donating anilines (entries 2 and 3 versus entries 8–11). *Meta* substitution on the benzene ring did not significantly affect the product yield (entries 12 and 13). Although *ortho*-substituted aromatic amines required prolonged reaction times, presumably because of the steric bulk, the corresponding azobenzenes **2nn** and **2oo** were successfully obtained in 44% and 73% yield, respectively (entries 14 and 15). Multiply substituted aromatic amines were converted into the corresponding azo compounds **2pp–rr** in moderate to high yields (entries 16–18).

Table 1: Scope of the oxidative homodimerization.[a]



Entry	1	R	Conditions	2	Yield [%][b]
1	**1a**	H	MeCN, RT, 1 h	**2aa**	95
2	**1b**	*p*-Me	Et_2O, RT, 1 h	**2bb**	97
3	**1c**	*p*-OMe	MeCN, RT, 0.25 h	**2cc**	87
4	**1d**	*p*-F	acetone, RT, 6 h	**2dd**	95
5	**1e**	*p*-Cl	Et_2O, −20°C, 12 h	**2ee**	96
6	**1f**	*p*-Br	acetone, RT, 3 h	**2ff**	83
7	**1g**	*p*-I	Et_2O, −20°C, 12 h	**2gg**	88
8	**1h**	*p*-CO_2Et	Et_2O, RT, 3 h	**2hh**	95
9	**1i**	*p*-C(O)Me	Et_2O, −20°C, 12 h	**2ii**	91
10	**1j**	*p*-CN	THF, RT, 12 h	**2jj**	89
11[c]	**1k**	*p*-NO_2	THF, RT, 6 h	**2kk**	79
12	**1l**	*m*-Cl	acetone, RT, 3 h	**2ll**	86
13	**1m**	*m*-NO_2	THF, −20°C, 12 h	**2mm**	78
14	**1n**	*o*-Ph	Et_2O, −20°C, 36 h	**2nn**	44
15	**1o**	*o*-CN	Et_2O, RT, 24 h	**2oo**	73
16	**1p**	3,4-Me_2	Et_2O, RT, 1 h	**2pp**	89
17	**1q**	3,5-$(CF_3)_2$	THF, RT, 12 h	**2qq**	94
18	**1r**	2,3,4,5,6-F_5	Et_2O, RT, 12 h	**2rr**	67

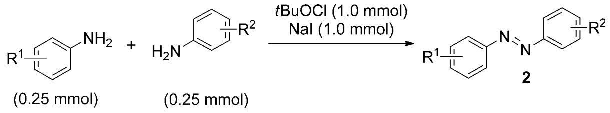
[a] Reaction conditions: aromatic amine **1** (0.5 mmol), *t*BuOCl (1.0 mmol), NaI (1.0 mmol), and solvent (3 mL). [b] Yields of isolated product. [c] 2 mmol of *t*BuOCl and NaI were used. THF = tetrahydrofuran.

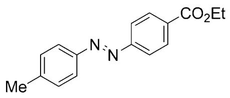
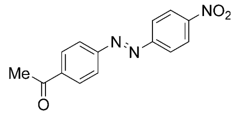
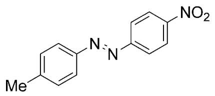
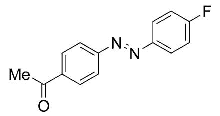
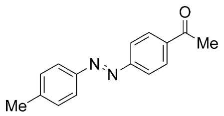
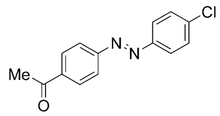
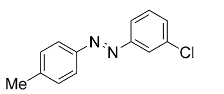
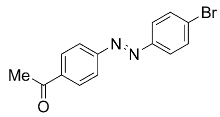
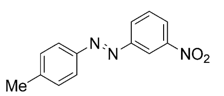
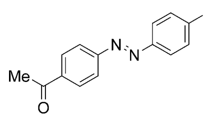
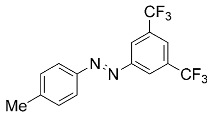
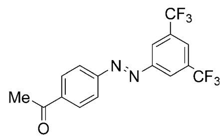
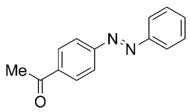
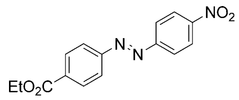
The success in the homodimerization prompted us to investigate the cross-dimerization reaction (Table 2). Initially, we examined the reaction of *p*-toluidine (**2b**) with an equimolar amount of ethyl 4-aminobenzoate (**1h**) to find that the corresponding unsymmetric azo product **2bh** was selectively furnished in 62% yield over the production of homocoupled azo products (entry 1).[17] Considering the difficulty in achieving the oxidative cross-dimerization of aromatic amines,[18] this result demonstrated the validity of the present method. When **1b** was treated with electron-deficient anilines at low temperature, the push–pull-type azobenzenes **2bk** and **2bi**, which constitute an industrially important class of organic dyes, were produced in good yields (entries 2 and 3). The cross-dimerization with anilines substituted at the *meta* position also proceeded to give the corresponding unsymmetric azobenzenes **2bl**, **2bm**, and **2bq** in moderate to good yields (entries 4–6). Then, the cross-coupling reaction of the electron-deficient aniline **1i** with various anilines was examined (entries 7–13). The simplest aromatic amine **1a** was applicable to the reaction with **1i**, thus affording the monoacetylated azobenzene **2ai** in good yield, albeit with a relatively long reaction time (entry 7). Anilines containing electron-withdrawing and halogen groups selectively reacted with **1i**, thus leading to the corresponding cross-coupled products in high yields (entries 8–13). The reaction of the aniline **1h** with *p*-nitroaniline (**1k**) gave the unsymmetrical azo compound **2hk** (entry 14). Because the unsymmetric azo compounds having two electron-deficient aromatic rings are difficult to synthesize by conventional methods, these results highlight the superiority of our method. In all cases, unsymmetric azo products were selectviely formed over homodimers, and they were easily separated by column chromatography.[19]

The present reaction was also applicable to heteroaromatic amines (Scheme 2). When 2-aminobenzothiazole (**1s**) was treated with *t*BuOI at room temperature for 48 hours, the azo product bearing two heteroarenes, **2ss**, was obtained in good yield. Moreover, the reaction of **1s** with **1b** gave the corresponding unsymmetric coupling product **2bs** in 47% yield. Recently, unsymmetric heteroaromatic azo compounds have attracted increasing attention as nonlinear optical (NLO) materials.[20]

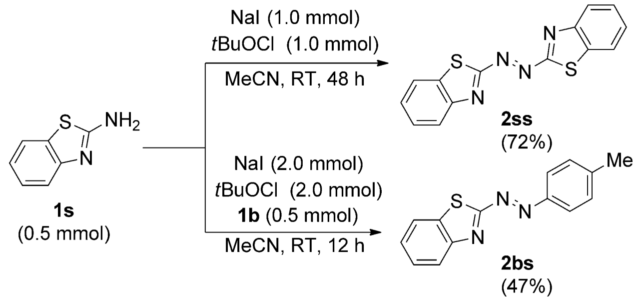
To gain insight into the reaction mechanism, several experiments were conducted. The addition of stoichiometric amounts of TEMPO or Galvinoxyl, which are representative radical scavengers, did not retard the dimerization reaction. Furthermore, the reaction proceeded efficiently even under an O_2 atmosphere or in the dark, thus giving the corresponding azo products in comparable yields to those obtained under the optimal reaction conditions (see Table S3 in the Supporting Information). These results exclude the radical reaction pathways. For obtaining further information, the reactions of anilines with *t*BuOI were monitored using ^{1}H NMR techniques. Upon the addition of two equivalents of *t*BuOI into

Table 2: Scope of the oxidative cross-dimerization of aromatic amines.[a]



Entry	Conditions	2[b]		Entry	Conditions	2[b]	
1	THF, 0°C, 6 h		**2bh** (62%)	8	MeCN, −20°C, 24 h		**2ik** (72%)
2	THF, 0°C, 3 h then, RT, 1 h		**2bk** (64%)	9	DME, RT, 3 h		**2di** (61%)
3[c]	THF, −20°C, 24 h		**2bi** (58%)	10	MeCN, 0°C, 18 h		**2ei** (65%)
4	acetone, 0°C, 3 h		**2bl** (52%)	11	DME, −20°C, 24 h		**2fi** (58%)
5	THF, −20°C, 24 h		**2bm** (60%)	12	THF, RT, 12 h		**2gi** (53%)
6	THF, RT, 12 h		**2bq** (66%)	13	MeCN, −20°C, 24 h		**2iq** (63%)
7	THF, RT, 12 h		**2ai** (54%)	14[d]	MeCN, 0°C, 24 h		**2hk** (66%)

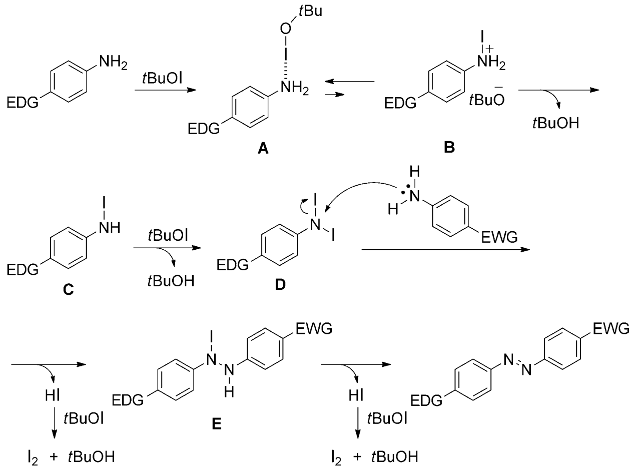
[a] Reaction conditions: Ar^1NH_2 (0.25 mmol), Ar^2NH_2 (0.25 mmol), *t*BuOCl (1.0 mmol), NaI (1.0 mmol), and solvent (3 mL). [b] The values in parentheses indicate the yields of the isolated unsymmetric azo products. [c] **1b** (0.5 mmol), **1i** (0.25 mmol), *t*BuOCl (1.5 mmol), and NaI (1.5 mmol) were used. [d] **1h** (0.25 mmol), **1k** (0.5 mmol), *t*BuOCl (1.5 mmol), and NaI (1.5 mmol) were employed. DME = dimethoxyethane.



Scheme 2. Oxidative dimerization of a heteroaromatic amine.

a [D$_6$]DMSO solution of *p*-fluoroaniline (**1d**), the signal corresponding to the two N-H hydrogen atoms (δ = 4.93 ppm) disappeared, and the aromatic hydrogen atoms (δ = 6.51 and 6.82 ppm) spontaneously shifted to lower field (δ = 6.65 and 6.87 ppm, respectively). In the case of the reaction of *p*-aminoacetophenone (**1i**) with *t*BuOI, a similar phenomena were observed (see Figures S1 and S2 in the Supporting Information). These results would indicate that both anilines were rapidly transformed into $ArNI_2$ species through a hydrogen–iodine exchange.[21] In contrast, when an equimolar mixture of **1d** and **1i** was treated with *t*BuOI (2 equiv), the ^{1}H NMR spectra indicated the exclusive generation of *p*-fluoro-*N*,*N*-diiodoaniline with **1i** remaining intact (see Figures S3 in the Supporting Information). Taking into account that the Hammett constants (σ_p) of F and Ac are 0.06 and 0.50,[22] respectively, the result suggests that the aniline having an electron-rich aromatic ring was preferentially doubly iodinated by *t*BuOI, at least on the NMR time scale.

Although the precise mechanism is unclear at present and the elucidation of the details require further study, a plausible mechanism is proposed in Scheme 3. The reaction would initiate from N iodination of the aniline having a more electron-donating group (EDG). The first iodination process would take place through a) halogen bond[23] formation between the aniline and *t*BuOI (**A**) and b) the following deprotonation of the resulting ammonium salt **B**, accompanied by the production of *t*BuOH as the by-product. Subsequent iodination of the monoiodinated aniline **C** in



Scheme 3. A plausible reaction mechanism.

a similar manner would afford the *N,N*-diiodoaniline **D**. These sequences can explain the results of the ^{1}H NMR experiments. It should be noted that the factor which governs the preference in the iodination processes is not be the acidity of N–H as assumed preliminarily, but the nucleophilicity of the anilines. Higher nucleophilicity would facilitate easier formation of halogen bonds (**A**), and thus allow the subsequent iodination processes. Notably, the second iodination of **C** was more predominant over the iodination of electron-deficient aromatic amines, thus indicating the higher nucleophilicity of the monoiodinated amine **C**, possibly because of the results of a slight pyramidalization of the N atom.[24] The next step would be N–N bond formation through nucleophilic attack of the iodinated nitrogen atom by the remaining aniline, accompanied by the liberation of HI. In the last step, another equivalent of HI would be eliminated from the *N*-iodohydrazine **E** to produce the unsymmetric azo product.[25] The role of another two equivalents of *t*BuOI could be to trap the liberated HI, thus resulting in *t*BuOH and I_2.[26]

In conclusion, we have developed an efficient, lower-energy-consuming, and metal-free synthetic method for symmetric and unsymmetric aromatic azo compounds. The methodology was applicable to a wide range of aromatic amines under mild reaction conditions. The additional investigation of the mechanistic aspects and the application of the *t*BuOI to other organic synthetic reactions are ongoing in our laboratory.

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[15] *t*BuOI was easily generated in situ from commercially available *tert*-butyl hypochlorite (*t*BuOCl) and NaI, see ref. [14].
[16] When the reaction was conducted with one equivalent of *t*BuOI, the azo product was obtained in less than 50% yield.
[17] The homodimerized products **2bb** and **2hh** were produced in 32% and 30% yields, respectively.
[18] For example, the reaction of aniline (**1a**) with *p*-iodoaniline (**1g**) under the reaction conditions reported in Ref. [7d] gives the homocoupling product **2gg** as a major product (32% yield) over the cross-coupled azo compound **2ag** (23% yield).
[19] For the detail information on the product distribution of the oxidative dimerization, see the Supporting Information.
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[25] The pH measurement of the water layer extracted after reaction completion indicated 4.75, thus implying the liberation of HI. For the details, see the Supporting Information.

[26] Supplementary experiments to examine the effect of base addition are described in the Supporting Information.