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One-pot preparation of azobenzenes from nitrobenzenes by the combination of an indium-catalyzed reductive coupling and a subsequent oxidation

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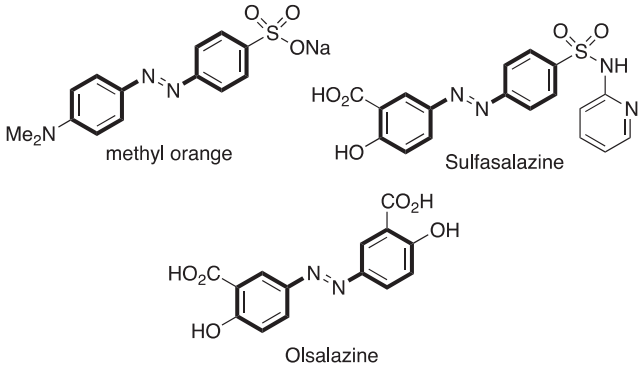
ABSTRACT

We demonstrated how a reduction step with a reducing system comprised of $In(OTf)_3$ and Et_3SiH and a subsequent oxidation that occurred under an ambient (oxygen) atmosphere allowed the highly selective and catalytic conversion of aromatic nitro compounds into symmetrical or unsymmetrical azobenzene derivatives. This catalytic system displayed a tolerance for the functional groups on a benzene ring: an alkyl group, a halogen, an acetyl group, an ester, a nitrile group, an acetyl group, an ester moiety, and a sulfonamide group.

1. Introduction

Azobenzene derivatives constitute important and central building blocks in functional materials, as well as in biologically active substances. For example, aryl azobenzene derivatives, which emit a variety of colors, have been widely utilized as the coloring matters, such as azo dyes or pigments, or as the photoresponsive functional materials, such as liquid crystals.[1] Also, because enzymes, such as azoreductase are known to selectively metabolize an azo moiety on azobenzenes for the release of a selected drug, which may show efficacy as a medicine, an azo moiety is often embedded in the drug structures.[2] Based on this biological action, sulfasalazine,[3] which treats rheumatoid arthritis, and olsalazine,[4] which is effective against inflammatory bowel disease, were developed as prodrugs (Scheme 1). Therefore, the development of a highly selective preparation for aromatic azobenzenes would be as valuable as their functions.

The substitution of diazonium salts with electron-rich benzenes under basic conditions and the coupling reaction of nitrosobenzenes with anilines (Mills reaction)[5] are considered as the classical methods that are used to prepare azobenzenes; along with those, other procedures[6] have also been disclosed.[7] Recently, a catalytic oxidation of anilines with a variety of oxidizing reagents, such as MnO_2 ($KMnO_4$),[8] $KMnO_4$–$CuSO_4 \cdot 5H_2O$,[9] HgO–I_2,[9a,10] or



Scheme 1. Functional materials containing an azobenzene skeleton.

$NaBO_3 \cdot 4H_2O$–$B(OH)_3$,[11] was developed. In their breakthrough study, Corma and Garcia reported that gold nanoparticles immobilized on TiO_2 catalyzed the aerobic oxidative coupling of anilines, producing azobenzenes.[12] Moreover, Jiao and co-workers have reported the development of a Cu(I)–pyridine system under an O_2 atmosphere, and Shi co-workers have detailed the Cu(I)–diaziridinone catalyzed oxidative dehydrogenative coupling of anilines.[13] As a reaction system without a metal catalyst, Minakata and co-workers disclosed that *tert*-butyl hypoiodite (*t*-BuOI) promoted the oxidative dimerization of aromatic amines, leading to a convenient preparation of unsymmetrical azobenzenes.[14]

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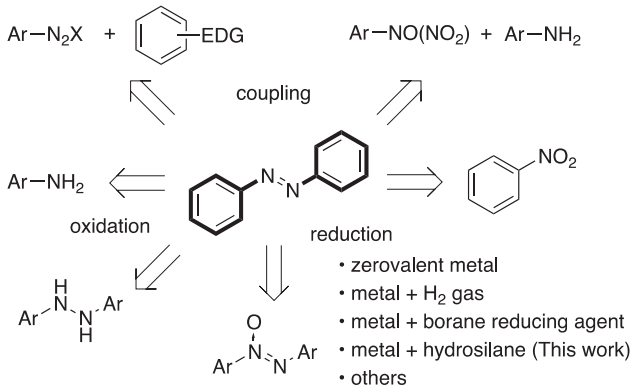
Likewise, the preparation of azobenzenes through a reduction of nitrobenzenes with reducing reagents has also been developed by several groups, but the typical approach was limited to operations that required more than stoichiometric amounts of a metal catalyst either the use of a Zn metal under strong basic conditions[15] or the use of a Pb metal in the presence of HCO_2H and Et_3N.[16] Also, compared with the catalytic preparation of azobenzenes via the oxidation of anilines, the catalytic preparation of azobenzenes by reduction of nitrobenzenes has thus far been limited to specific procedures using hydrogen gas in the presence of either a nano-Pd, a Pt-nanowire, a Ru-nanoparticle,[17] or another system.[18] As far as we could ascertain, the use of a hydrosilane as a reducing source for these transformations is unique (Scheme 2). Thus, the development of a catalytic and simple preparation for azobenzenes via the reduction of aromatic nitro compounds seems to have remained unexplored.



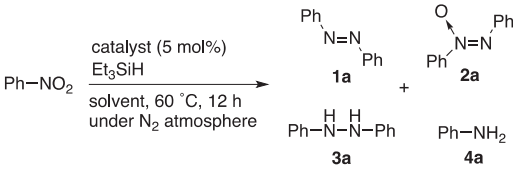
Scheme 2. Diverse approaches to azobenzenes.

We have reported that a reducing system comprised of an indium (III) compound and a hydrosilane was highly effective for the reduction of reducible agents, such as an aldehyde, a ketone, an acetal, and a carboxylic acid.[19,20] However, the conversion from a nitrobenzene to an azobenzene in our previous work was limited to several substituents.[21] Herein, we report the full details of the catalytic and reductive preparation of azobenzenes from a variety of nitrobenzenes via the $In(OTf)_3$—Et_3SiH reducing system. We also detail how this system was applied in the preparation of asymmetrical azobenzene derivatives and in an intramolecular manner.

2. Results/discussion

Based on our previous study,[21] when we initially examined the reduction of nitrobenzene with $InBr_3$ and Et_3SiH under $CHCl_3$ reflux conditions, most of the nitrobenzene was recovered, and four types of reductive products involving azobenzene (**1a**), azoxybenzene (**2a**), hydrazobenzene (**3a**), and aniline (**4a**) were formed with low selectivity (entry 1 in Table 1). Thus, to improve the product selectivity, the effect from relatively high polar solvents, such as THF, MeOH, and DMF, was investigated. As a result, THF and MeOH selectively gave azoxybenzene (**2a**) and hydrazobenzene (**3a**), respectively (entries 2 and 3). Also, when DMF was used, the corresponding hydrazobenzene was obtained in an almost quantitative yield (entry 4). Then, when the effect of a counterion on the indium compound in DMF was tested, neither $InCl_3$ nor $In(OAc)_3$ improved either the reactivity or the selectivity, but $InCl_3$ gave a small amount of azobenzene (entries 5 and 6). It is noteworthy that when the equivalent of Et_3SiH was reduced to 3 equiv in the presence of $InBr_3$ in DMF, the yield of azobenzene (**1a**) was increased to a 59% yield (entry 7). This was probably due to controlling the over-reduction of the azobenzene. Moreover, $In(OTf)_3$ further improved both the chemical yield and the product selectivity (entry 8). After several optimizations of the reaction conditions, we finally settled on the following procedure. The mixtures that involved azobenzene (**1a**) and hydrazobenzene (**3a**) that were produced by the first reduction step, were treated with oxidation under an ambient atmosphere to directly convert the corresponding azobenzene derivative (entry 9). When the second oxidation step was carried out under an O_2 atmosphere, the reaction time was drastically shortened (entry 10). During the search for optimal conditions, we also found that the indium compound catalyzed the dehydrogenate conversion from a hydrazobenzene to an azobenzene.[22] However, the use of other group 13 metals, such as $AlCl_3$ and $GaCl_3$, did not catalyze the reduction as well as $In(OTf)_3$, and neither did $ZnCl_2$ nor $BiCl_3$ (entries 11–14).

Table 1
Examinations of reaction conditions



Entry	InX_3	Silane (equiv)	Solv	Yield (%)[a]			
				1a	**2a**	**3a**	**4a**
1	$InBr_3$	4	$CHCl_3$	2	15	10	9
2	$InBr_3$	4	THF	Trace	96	Trace	ND
3	$InBr_3$	4	MeOH	Trace	ND	75	ND
4	$InBr_3$	4	DMF	ND	ND	94	ND
5	$InCl_3$	4	DMF	19	2	65	ND
6	$In(OAc)_3$	4	DMF	ND	48	ND	4
7	$InBr_3$	3	DMF	59	12	20	ND
8	$In(OTf)_3$	3	DMF	66	Trace	25	ND
9[b]	$In(OTf)_3$	3	DMF	(81)	ND	Trace	Trace
10[c]	$In(OTf)_3$	3	DMF	84	ND	Trace	Trace
11	$AlCl_3$	4	DMF	ND	ND	ND	ND
12	$GaCl_3$	4	DMF	3	34	Trace	3
13	$BiCl_3$	4	DMF	ND	ND	ND	ND
14	$ZnCl_3$	4	DMF	ND	ND	ND	ND

[a] GC (Isolated) yield.
[b] After the first reduction, the resultant mixture was stirred for 20 h under an ambient atmosphere.
[c] After the first reduction, the resultant mixture was stirred for 3 h under an O_2 atmosphere.

With the optimal conditions in hand, the generality of this coupling was examined using a variety of nitrobenzenes (Table 2).[23] The use of a substrate with a methyl group, with no relation to the location, afforded the desired azobenzene derivatives **1b**–**d** in moderate to good yields. However, when the reaction was carried out using a nitrobenzene with a methoxy group, the azobenzene **1e** was obtained in only a 10% yield, and most of the starting nitrobenzene was recovered. This was probably due to the fact that the indium catalyst coordinated the methoxy group rather than the nitro group. Unexpectedly, the substrate with a dimethylamino group produced the azobenzene derivative **1f** in a practical yield, and seemed to more strongly coordinate with the indium catalyst than the substrate with a methoxy group. The use of nitrobenzenes, which have a halogen atom and a trifluoromethyl group at the *para* position, underwent the coupling reaction to give the corresponding azobenzene derivatives **1g**–**i** in relatively good yields. In contrast, using nitrobenzenes with an *ortho*-substituted halogen atom gave the azobenzenes **1j**–**l** in moderate yields, which was probably caused by a steric repulsion. Also, a cyano group, which directly bonded to a benzene ring, was sensitive to this reducing system, leading to a decrease in the yield. However, when using the substrate with a cyano group, which sandwiched a methylene chain, the corresponding azobenzene **1n** was obtained in a relatively good yield. It is worth noting that the nitrobenzenes with either an acetyl