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Oxygen as moderator in the zinc-mediated reduction of aromatic nitro to azoxy compounds

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Dedicated to Professor Dr. Hans-Ulrich Reissig on the occasion of his 60th birthday

ABSTRACT

A simple and useful protocol for the reduction of nitro arenes to their corresponding azoxy derivatives by employing zinc and NH_4Cl in a mixture of [bmim][BF_4] and water is described. The selective reduction of nitro to azoxy is attributed to the hitherto unknown moderating effect of oxygen on zinc metal.

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Aromatic azoxy compounds are of immense importance as materials for electronic devices because of their liquid crystalline properties.[1] 'Williams domain', an important phenomenon describing the electrooptic property of liquid crystals, was established with azoxyarenes by Williams.[2] Azoxyarenes have also been utilized as dyes, analytical reagents, reducing agents, stabilizers, and polymerization inhibitors.[3] Azoxy compounds can be prepared from their corresponding amines,[4] hydroxylamines,[5] nitroso hydroxylamine ammonium salts,[6] and azo,[7] nitro,[8–10] and nitroso compounds.[11,12] The aforementioned methods require reducing agents, oxidizing agents, or UV light.

Methods to obtain azoxyarenes from nitroarenes include heating with alcoholic KOH,[13] sodium alkoxide,[14] or Zn/NaOH,[15] reduction with $NaBH_4$,[16] $LiAlH_4$,[17] or sodium arsenite,[18] treatment with magnesium,[19] samarium,[20] or thallium metal[21] in alcohol, catalytic reduction over palladium,[22] alkaline reduction with phosphine[23] or glucose,[24] and electrochemical reduction.[25] Of all the methods known for the reduction of nitroarenes to their corresponding azoxy derivatives, a few involve interesting plausible mechanistic explanations.[26,8b,c]

In continuation of our work on zinc-mediated reductions of nitroarenes in ionic liquids,[27] we herein disclose an efficient methodology for the conversion of nitro compounds to their corresponding azoxy derivatives. Based on the observation from the previous work that the ionic liquids be completely free from dissolved oxygen during the zinc-mediated reduction of nitro arenes to corresponding amines,[27] we carried out the reduction of nitro compounds in ionic liquids under an atmosphere of oxygen. These conditions selectively yielded the azoxy compounds in excellent yields.

When no efforts were made to remove the dissolved oxygen in the ionic liquids during the zinc-mediated nitro reductions, we obtained a mixture of products: azoxy, azo, and hydrazoarenes, wherein azoxyarenes were the major products. The reactions were found to be more sensitive in [bmim][BF_4] than in [bmim][PF_6] (bmim = 1-butyl-3methylimidazolium). We found this effect of oxygen on the outcome of the reaction very interesting. Although the deleterious effects of oxygen on the metal-mediated reactions are well known,[28] we did not come across any report in the literature wherein oxygen is known to moderate zinc metal-mediated reductions.[29] This observation interested us to check if we could use oxygen to obtain exclusively the azoxyarenes without the formation of azo, hydrazo, or amine derivatives.

To select a solvent system that would facilitate the exclusive formation of azoxyarenes from aromatic nitro compounds, various solvent systems were screened. The reduction of *p*-nitrotoluene was carried out using zinc metal (3 equiv) and NH_4Cl (3 equiv) in a mixture of solvent–H_2O (10:1). From these experiments (Table 1), [bmim][BF_4] emerged as the solvent of choice for the formation of azoxyarenes upon the zinc-mediated reduction of nitroarenes. Using other solvents (Table 1, entries 4–8) resulted in the formation of a mixture of products. After the selection of a solvent, we wanted to check if other metals were better than zinc in affording azoxy arenes from nitroarenes under similar reaction conditions. The reduction of *p*-nitrotoluene was carried out with various metals, and the results are illustrated in Table 2.

Nitro reductions were carried out using a metal (3 equiv), NH_4Cl (3 equiv) in [bmim][BF_4]:H_2O (10:1) at room temperature in an atmosphere of oxygen (bubbling). Reduction with zinc over 26 h (Table 2, entry 1) afforded a mixture of azoxy and azo compounds (95:5). Reducing the time to 12 h resulted in the exclusive formation of an azoxy compound but with 80% conversion of the starting material (Table 2, entry 2). When samarium, tin, and indium were used for the reduction of *p*-nitrotoluene, the conversions were very

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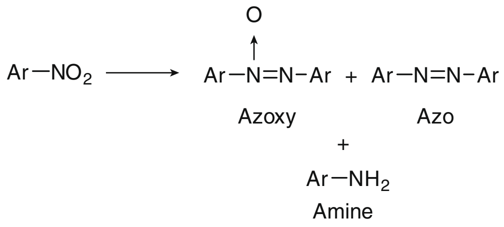
Table 1

Product distribution during zinc-mediated reduction of *p*-nitrotoluene in different solvents



Entry	Solvent	Temperature, time (°C, h)	Product distribution (azoxy/azo/amine)	Yield[a] (%)
1	$bmimBF_4$	10, 12	100/0/0	90 (80)
2	$bmimBF_4$	0, 2 then 25, 9	100/0/0	91 (70)
3	$bmimBF_4$	−10, 12	100/0/0	88 (50)
4	$bmimPF_6$	15, 24	79/0/21	95 (40)
5	THF	10, 12	60/10/30	86 (60)
6	DMSO	10, 3	70/20/10	91
7	MeCN	10, 13	70/30/0	84 (30)
8	Acetone	10, 15	90/10/0	92 (55)

Reactions were carried out with 3 equiv of Zn and 3 equiv of NH_4Cl in solvent–H_2O (10:1) under an atmosphere of oxygen.

[a] Numbers in parentheses are the percentage conversions of nitroarenes.

low (Table 2, entries 3, 4, and 6) and using lead as the metal for nitro reduction resulted in a complete recovery of the starting material without any conversion of the nitroarene (Table 2, entry 5). Using 4 equiv of zinc resulted in the exclusive formation of azoxyarene with a complete conversion of the nitro compound.

The optimized condition, that is, Zn (4 equiv), NH_4Cl (3 equiv) in $[bmim][BF_4]$:H_2O (10:1) at room temperature in an atmosphere of oxygen, was employed for a variety of nitroarenes which yielded azoxyarenes in good to excellent yields (Table 3). The reaction conditions were tolerant to various functional groups such as chloro, iodo, acetate, *O*-allyl, and *O*-benzyl. After the completion of the reaction, products were separated by extracting with 30–50% EtOAc in hexane. The crude products thus obtained were pure and did not require any further purification in general. However, the azoxyarenes were filtered through a short pad of silica gel before recording their NMR spectra. The products were confirmed by comparing the ^1H NMR spectra (400 MHz) with those reported in the literature.[8] The ionic liquids used for the reaction were recycled. After the extraction of the product, CH_2Cl_2 was added to the reaction mixture containing $[bmim][BF_4]$ and inorganic impurities. The suspension was filtered through a Whatman filter paper to remove the insoluble impurities, and the ionic liquids were reused after removing CH_2Cl_2 completely on a rotavapor followed by vacuum drying.

Table 2

Comparison of product distribution during reduction of *p*-nitrotoluene with various metals

Entry	M	Time (h)	Product distribution (azoxy/azo/hydrazo)	Yield[a] (%)
1	Zn	26	95/5/0	96
2	Zn	12	100/0/0	93 (80)
3	Sm	12	100/0/0	85 (20)
4	Sn	72	69/0/39[b]	81 (25)
5	Pb	72	—	—
6	In	68	100/0/0	62 (40)
7	Zn	16	100/0/0	94[c]

3 equiv of metal and 3 equiv of NH_4Cl were used.

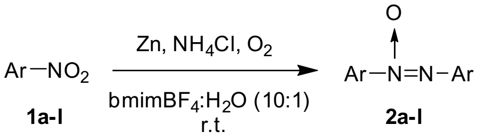
[a] Numbers in parentheses are the percentage conversions of nitroarenes.

[b] Hydrazo = Ar–NH–NH–Ar.

[c] 4 equiv of Zn was used.

Table 3

Zinc-mediated reduction of various nitroarenes to azoxyarenes



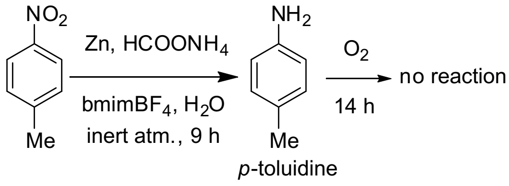
Entry	Substrate	R	Time (h)	Yield (%)
1	**1a**	*p*-Me	16	96
2	**1b**	*p*-OMe	16	91
3	**1c**	*o*-Me	18	88
4	**1d**	*p*-Cl	15	90
5	**1e**	*m*-Cl	16	86
6	**1f**	*p*-OAc	17	78
7	**1 g**	H	16	94
8	**1 h**	*p*-I	16	82
9	**1i**	*o*-OMe	18	92
10	**1j**	*o*-OBn	20	90
11	**1 k**	*p*-O-allyl	16	86
12	**1 l**	*m*-Me	16	94

4 equiv of Zn and 3 equiv of NH_4Cl were used.

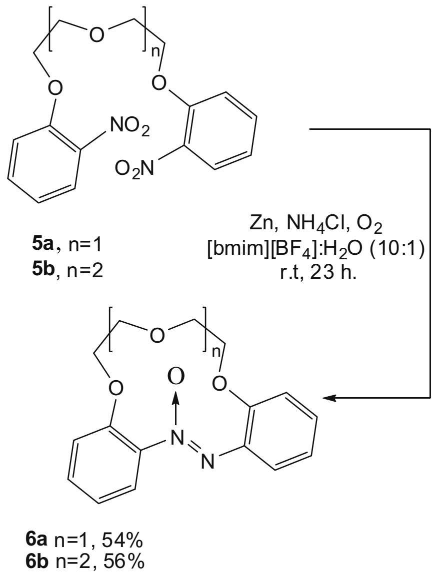
At the outset, we thought that the reason for the selective formation of azoxy derivatives under an oxygen atmosphere could be attributed to the moderating effect of oxygen on zinc metal. We wanted to rule out other possibilities wherein nitro is first reduced to amino and then oxidized to azoxy. To check on this possibility, two experiments were carried out. Subjecting *p*-toluidine to the conditions that were used for the conversion of nitroarenes to their azoxy derivatives resulted in the complete recovery of the starting material. In the second control experiment, *p*-nitrotoluene was reduced to *p*-toluidine following the protocol reported previously.[27] Once the conversion to *p*-toluidine was complete, oxygen was bubbled through the reaction mixture, but *p*-toluidine did not undergo any oxidation (Scheme 1). This observation rules out the possibility that a reagent system generated in situ during the reduction of nitro to amino can be responsible for the selective formation of azoxy derivatives. Based on these results, the selective formation of the azoxy derivatives was attributed to the moderating effect of oxygen on zinc.

The methodology was extended to the synthesis of azoxycrowns. Crowns, wherein the azoxy moiety is part of the crown, are known to be ion carriers. The existing methods for the synthesis of these compounds would require a tedious chromatography to separate the products from the mixture.[30] Applying the present procedure for the cyclization of bis-nitro derivatives **5a**,**b** resulted in the selective formation of azoxy crowns **6a**,**b** (Scheme 2) in yields better or comparable to that reported.[30]

In summary, we have described a novel, efficient method for the conversion of nitro compounds to their corresponding azoxy derivatives. This method was applied to the preparation of a variety of aromatic azoxy arenes including azoxy crowns. The ionic liquid used $[bmim][BF_4]$ was recycled without any effect on the outcome of the reaction.



Scheme 1.



Scheme 2.

General procedure for the synthesis of azoxy compounds: To an oxygen purged solution of nitroarene (0.5 mmol) in [bmim][BF_4] (1 mL), zinc metal (2 mmol) NH_4Cl (1.5 mmol) and water (0.1 mL) were added and vigorously stirred at room temperature for the specified time (Table 3) under an oxygen atmosphere. After the consumption of the starting material, as monitored by TLC, 30–50% EtOAc in hexane (3 × 5 mL) was added to the reaction mixture with vigorous stirring for 5 min. The mixture was allowed to stand for 2 min, and the clear supernatant liquid was decanted. The combined organic extracts were concentrated to dryness, and the crude product was found to be pure enough from the 400 MHz ^1H NMR spectrum. The crude product was further purified by being passed through a small silica gel column for calculating the yield.

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