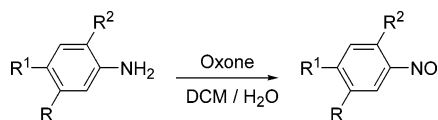# Efficient Preparation of Nitrosoarenes for the Synthesis of Azobenzenes[†]

Beate Priewisch and Karola Rück-Braun*

Technische Universität Berlin, Institut für Chemie, Strasse des 17. Juni 135, D-10623 Berlin, Germany

krueck@chem.tu-berlin.de

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Reaction conditions are described for the oxidation of anilines furnishing nitrosoarenes and the synthesis of unsymmetrically substituted azobenzenes. In a comparative study, the catalytic oxidation of methyl 4-aminobenzoate by hydrogen peroxide was investigated, and SeO_2 proved to be superior or equal to methyl trioxorhenium (MTO) and Na_2WO_4, respectively. Nevertheless, the application of the inexpensive, environmentally friendly, Oxone in a biphasic system proved to be more efficient, and a variety of useful nitrosoarenes for the synthesis of azo compounds were prepared in high yield and purity on a large scale.

Nitroso compounds undergo a variety of transformations of great potential such as nitroso aldol reaction,[1] nitroso ene reaction,[2] [2 + 2][2] and [4 + 2][3] cycloadditions, additions of Grignard reagents,[4] and coupling with amines to yield azobenzenes.[5] They are also used as spin traps[6] and were even studied as anti-retroviral agents and antitumor agents.[7]

During our efforts to synthesize unsymmetrically substituted azobenzenes from anilines and nitrosoarenes, we became aware of a lack of simple high-yielding procedures for the large-scale synthesis of nitrosoarenes containing electron-withdrawing groups. We herein report on catalytic oxidations by hydrogen peroxide and the application of Oxone in a biphasic system.

For the synthesis of nitrosoarenes from anilines a number of suitable oxidation methods have been published in recent years employing, e.g., the oxidizing agents Caro's acid (peroxomonosulfuric acid), peracetic acid, 3-chloroperoxybenzoic acid (*m*-CPBA), or potassium permanganate.[8] The application of hydrogen peroxide in the presence of rhenium,[9] tungsten,[10] or molybdenum[11] catalysts was reported to give high yields of the nitroso compounds on a 1−10 mmol scale. Side reactions during the oxidation of anilines **1** are the formation of nitro derivatives **6** due to further oxidation of the nitroso compounds **2** and condensation reactions yielding azobenzenes **3** from the nitrosoarenes **2** and anilines **1** or azoxybenzenes **4** from the *N*-arylhydroxylamine intermediates **5** and anilines **1** (Scheme 1). General observa-

SCHEME 1
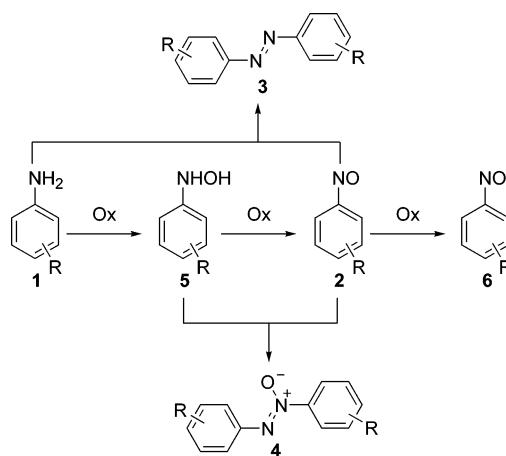
tions and achievements can be summarized as follows: Side reactions were commonly observed to a greater extent for less reactive anilines with an electron-withdrawing group in the para or meta position, especially during prolonged reaction times. Often, complex reaction mixtures were obtained in larger quantity under homogeneous reaction conditions as under heterogeneous in catalytic oxidations with hydrogen peroxide. Two-phase heterogeneous systems were found to secure the separation of the generally less water-soluble nitroso compounds **2** from the *N*-arylhydroxylamine intermediates **5** and the aniline precursors **1,** and thus to prevent condensation reactions. Reaction time, temperature, and the pH value are of importance in order to optimize the reaction conditions and product ratios.

We first started a comparative study and investigated the ability of methyl trioxorhenium (MTO), Na_2WO_4, and SeO_2 to catalyze the oxidation of methyl 4-aminobenzoate **1a** by H_2O_2 furnishing **2a** (Table 1). Espenson et al. described the oxidation of donor-substituted anilines (~10

[†] Dedicated to Prof. Horst Kunz on the occasion of his 65th birthday.
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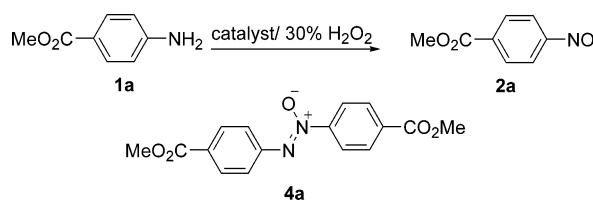(9) Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 1326−1332.
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mmol scale) by H_2O_2 in methanol at room temperature in 2 h furnishing nitrosobenzenes in good yields with methyl rhenium trioxide (MTO, 0.02 equiv), a homogeneous catalyst in both organic solvents and water.[9] The nitro compounds and azobenzenes were observed as byproducts. In these studies, an electron-withdrawing group was found to inhibit the reaction resulting in lower yields compared to compounds bearing an electron-releasing group. The same reaction conditions applied to the oxidation of aniline **1a** (0.6 mmol scale) in either methanol or dichloromethane (DCM) at room temperature were not effective in our hands (Table 1, entries 1 and 2), yielding only a mixture of the corresponding azoxybenzene **4a**[12] and the nitro compound after complete consumption of the starting material (19 h, TLC monitoring).

TABLE 1. Oxidation of Methyl 4-aminobenzoate 1a by H_2O_2

| entry	catalyst/additives	solvent	time (h)	conv (%)	ratio[a] 2a	ratio[a] 4a
1	0.2 MTO	MeOH	19	100	0	b
2	0.2 MTO	DCM	19	100	0	b
3	0.02 Na$_2$WO$_4$	DCM	22	56	43	13
4	0.02 Na$_2$WO$_4$	CHCl$_3$	20	63	20	43
5	0.02 Na$_2$WO$_4$	pentane/DCM 1:1.7	20	75	26	49
6	0.1 Na$_2$WO$_4$	DCM	18	97	51	46
7	0.1 Na$_2$WO$_4$/TBABr	DCM	18	16	0	16
8	0.1 Na$_2$WO$_4$/TBABr/ H$_3$PO$_4$	pentane/DCM 1:1	18	100	84	16
9	0.05 SeO$_2$	MeOH	19	100	0	100
10	0.1 SeO$_2$	DCM	22	100	80	20
11	0.1 SeO$_2$/TBABr/ H$_3$PO$_4$	pentane/DCM 1:1	22	100	82	18

[a] Ratio as determined by ^{1}H NMR spectroscopy. [b] A mixture of **4a** and **6a** was obtained.

The application of sodium tungstate (Na$_2$WO$_4$) as described in a patent was investigated next using chloroform, DCM, and DCM/pentane (Table 1).[10a] Treatment of aniline **1a** with 0.02 equiv of Na$_2$WO$_4$/3 equiv of H$_2$O$_2$ at room temperature after 20 h furnished a nitrosoarene content in the range of 20−43% (Table 1, entries 3−5). Almost complete conversion of the starting material was detected in the presence of 0.1 equiv of Na$_2$WO$_4$, and the percentage of nitroso compound **2a** formed increased to 51% (entry 6). The application of the phase-transfer catalyst tetrabutylammonium bromide (TBABr) in DCM was found to lower the reaction rate and resulted only in the formation of the azoxybenzene **4a** (entry 7). However, under identical conditions in the presence of H$_3$PO$_4$ according to Mel'nikov et al.[10b] complete conversion and an 84% nitrosoarene content was obtained (entry 8). Obviously, in the presence of an acid in a

biphasic mixture the formation of the azoxybenzene side product is suppressed.

Then we turned our attention toward the use of selenium dioxide, a well-established catalyst for the oxidation of secondary amines by hydrogen peroxide yielding nitrones.[13] To the best of our knowledge this reagent has never been reported for the oxidation of aromatic amines to nitroso compounds. Treatment of **1a** with 0.05 equiv of SeO$_2$/H$_2$O$_2$ in methanol at room temperature (20 h, TLC monitoring) furnished exclusively the azoxybenzene **4a** (entry 9). By conducting the oxidation in DCM with 0.1 equiv of SeO$_2$ a nitrosoarene content of 80% was obtained, and in the presence of TBABr/H$_3$PO$_4$ in DCM/pentane similar results were observed (entries 10 and 11). In the oxidation of **1a**, SeO$_2$ as catalyst gives results similar to Na$_2$WO$_4$. The data obtained so far were encouraging but still far from optimal with respect to reaction time and side-product formation. Therefore, our next approach toward nitrosobenzenes of higher purity focused on Oxone, a stable triple salt (2KHSO$_5$·KHSO$_4$·K$_2$SO$_4$).

TABLE 2. Oxidation of Aromatic Amines by Oxone
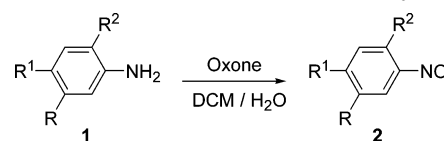
entry	1/2	R	R^1	R^2	time (h)	yield[a] (%)
1	**a**	H	CO$_2$Me	H	0.5	quant
2	**b**	H	CO$_2$H	H	1	quant
3	**c**	CO$_2$Me	H	H	3	quant
4	**d**	CO$_2$H	H	H	3.5	96
5	**e**	CN	H	H	3	96
6	**f**	H	Br	H	3.5	70
7	**g**	H	Et	H	12	65
8	**h**	H	SO$_3$H	H	4	b
9	**i**	H	SO$_3$NBu$_4$	H	0.5	97[b]
10	**j**	H	CH$_2$OH	H	1	b
11	**k**	H	CH$_2$CO$_2$H	H	4	b
12	**l**	H	CH$_2$NHBoc	H	9.5	60
13	**m**	CO$_2$Me	H	Me	3.5	96

[a] Isolated yield. [b] See text.

Caro's acid (H$_2$SO$_5$) was first reported to oxidize anilines to nitrosobenzenes.[14] Later, Oxone was investigated, e.g., in MeOH/water at pH 11 under homogeneous reaction conditions.[15] The oxidation of **1a** with Oxone (1−2 equiv) in water at room temperature led to 79% conversion of the starting material in 7 h and gave a nitrosoarene content of 73% accompanied by 6% of the azoxybenzene. Fortunately, in a mixture of water and DCM complete consumption of the starting material was observed within 30 min and the nitrosoarene **2a** was isolated quantitatively in 94% purity (Table 2, entry 1).[16] Since these results proved to be superior to those shown in Table 1, we examined the application of Oxone in

(12) The azoxybenzenes were identified by ^{1}H NMR and HR-MS.

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(16) The synthesis of this compound was reported previously by oxidation with MoO$_3$/H$_2$O$_2$/KOH (1 mmol scale) in comparable yield with a reaction time of 4 d (see ref 11b).

water/DCM for the synthesis of a number of other substituted nitrosoarenes **2** (Table 2).

A broad variety of compounds (**2a**–**e,m**: 1–73 mmol scale) were obtained in high yields and purities after workup in 0.5–12 h at room temperature (Table 2). Scale-up of the oxidation of **1a** (5 g, 33 mmol) gave 98% of **2a** in 95% purity. The nitroso compounds **2f**, **2g**, and **2l** were purified by either sublimation, distillation, or recrystallization.

Functional groups such as carboxylic acid, ester, nitrile, and bromine and alkyl substituents are well tolerated. However, nitroso compounds with functional groups having high water solubility or being unstable in the presence of the redox-active nitroso functionality led to somewhat inferior results (entries 8, 10, and 11, Table 2). These substances may persist in the aqueous phase and thus are prone to further oxidation to the corresponding nitro compounds. In a first attempt, oxidation of 4-(hydroxymethyl)aniline **1j** in dichloromethane at room temperature gave a mixture of the nitro and nitroso compound (2:1) in 40% isolated yield in 1 h. When the oxidation was carried out at 0 °C using a mixture of chloroform and ethanol,[17] 45% **2j** were obtained with a purity of 75% in 1.5 h. Attempts to purify **2j** by column chromatography failed due to the instability of this nitroso compound. For compound **1k** solely the nitro compound was isolated in 85% yield. In the case of the sulfonic acid **1h** the problems were solved by simply converting the free acid to the tetrabutylammonium salt **1i**,[18] being soluble in organic solvents such as DCM (entries 8 and 9).[19] Therefore, compound **2i** was isolated in 97% yield with a purity of 85%. Attempts to purify the compound by chromatography on silica gel and Florisil resulted in partial decomposition. Interestingly, during the oxidation of **1l** the protecting group was not removed.

In the synthesis of the unsymmetrically substituted azobenzenes **3a**–**c** according to Chart 1 small impurities of nitro compounds or azoxybenzenes from amine oxidation do not interfere. Hence, purification of the less stable nitroso compounds before condensation is generally avoided since the purification of the resulting azobenzenes proved to be less troublesome.[20] The couplings were achieved in acetic acid or a mixture of acetic acid and DMSO at room temperature. Azobenzene **3a** was prepared from crude nitrosoarene **2a** and 4-bromoaniline **1f** and isolated in 98% yield by chromatography, while **3b** was obtained from **2f** and *tert*-butyl 4-aminobenzoate in

CHART 1

89% yield after recrystallization. Coupling of *N*-(4-aminobenzyl)carbamic acid 9*H*-fluorenylmethyl ester with **2b** gave the protected ω-amino acid Fmoc-AMPB-OH **3c**[5b,21] after crystallization from acetone/water in quantitative yield.

In summary, we have developed a simple, high-yielding synthesis of nitrosoarenes bearing different functional groups for the direct preparation of azobenzenes. SeO$_2$ was shown to be suitable for the catalytic oxidation of anilines by hydrogen peroxide, which represents a valuable extension to the known catalysts. Nevertheless, the use of Oxone proved to be superior to the catalytic methods tested in terms of reaction time, purity, and yield. The direct preparation of three azobenzenes from the crude nitroso compounds obtained by amine oxidation with Oxone was successfully demonstrated.

Supporting Information Available: Experimental procedures and spectral and analytical data are described. For new compounds (**1i**, **2l,m**, **3a,b**) ^{1}H NMR, ^{13}C NMR, IR, and HR-MS data are reported. For known compounds (**2a**,[11b] **2b**,[10b] **2c**,[22] **2d**,[22] **2e**,[22] **2f**,[11b] **2g**,[11a] **3c**[5b]) generally only ^{1}H NMR and HR-MS data are reported. This material is available free of charge via the Internet at http://pubs.acs.org.
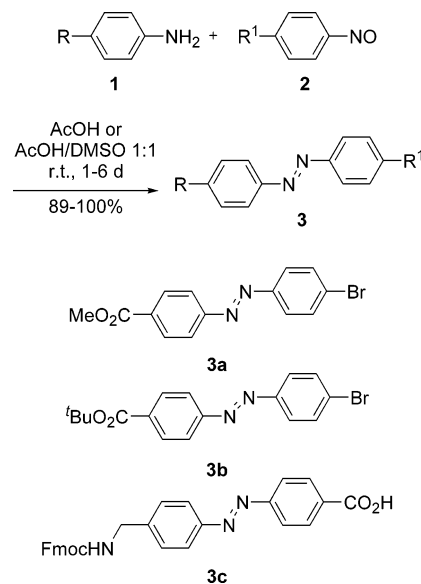
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(17) As ethanol is soluble both in organic solvents and water this mixture is known to be excellent for the extraction of very water-soluble compounds from the aqueous phase; see: Leonard, J.; Lygo, B.; Procter, G. *Praxis der Organischen Chemie*; VCH Verlagsgesellschaft: Weinheim, 1996.

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