Novel Synthesis of 2-Amino-1,4-benzoquinone-4-phenylimides from Anilines via Dess–Martin Periodinane Oxidation

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Abstract: A synthetic investigation on oxidation of anilines to 2-amino-1,4-benzoquinone-4-phenylimides via Dess–Martin periodinane (DMP) was carried out. This facile protocol offered the advantage of short reaction times, mild reaction conditions, high yields and compatibility with a wide range of functional groups.

Key words: iminoquinone, periodinane, oxidation

Iminoquinone is an important moiety of a large number of antineoplastic drugs and plays a significant role in the nucleus of actinomycins, which are powerful, highly toxic natural antibiotics. The antineoplastic activity of these drugs is the result of a strong interaction with DNA in the target cells, which causes degradation of the nucleic acid and, consequently, terminates its biological functions. The planar structure of these drugs facilitates intercalation between the DNA base pairs. At the same time, the quinone moiety of these agents can also undergo enzymatic reduction.[1] Several iminoquinone-based compounds related to the actinoymcin chromophore have already been synthesized as new anticancer intercalating drugs.[2]

In recent years, Dess–Martin periodinane [DMP, 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one] has emerged as the reagent of choice for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively.[3] Its unique oxidizing properties and convenience of use make DMP a common oxidizing reagent employed in the synthesis of biologically important natural products. For examples, DMP was used in the key oxidation steps in the total syntheses of cyclotheonamide B,[4] (±)-deoxypreussomerin A,[5] (±)-brevioxime,[6] erythromycin B,[7] (+)-discodermolide,[8] (+)-cephalostatin 7,[9] (+)-cephalostatin 12,[9] (+)-ritterazine K,[9] 3-*O*-galloyl-(2*R*,3*R*)-epicatechin-4β,8-[3-*O*-galloyl-(2*R*,3*R*)-epicatechin],[10] fredericamycin A,[11] indolizidine alkaloids (–)-205A, (–)-207A, and (–)-235B,[12] 1,19-aza-1,19-desoxyavermectin B_{1a},[13] angucytcline antibiotics,[14] tricyclic β-lactam antibiotics,[15] and the platelet aggregation-inhibiting γ-lactam PI-091.[16] In this paper, we report a new approach for the preparation of iminoquinones **1b** by reaction of anilines **1a** with DMP in CH_2Cl_2.

The reaction conditions were optimized by examining the oxidation of 4-methylaniline with DMP under various conditions (Table 1). It was found that benzene, toluene, CH_3CN, $CHCl_3$, and CH_2Cl_2 were all suitable solvents. Interestingly, addition of water accelerated the reaction (entries 3–6). After optimization, we found that using 2.2 equivalents of DMP and two equivalents of water provided the highest product yield (entry 6).

Table 1 Optimization of Reaction Conditions[a]

1a **1b**

Entry	DMP (equiv)	Conditions	Time (min)	Yield (%)
1	1.5	anhyd CH_2Cl_2, open air	40	73
2	2.0	anhyd CH_2Cl_2, N_2	40	65
3	2.0	CH_2Cl_2, H_2O (1.0 equiv), N_2	20	72
4	2.0	CH_2Cl_2, H_2O (2.0 equiv), N_2	15	93
5	2.0	CH_2Cl_2, H_2O (2.0 equiv), open air	15	92
6	2.2	CH_2Cl_2, H_2O (2.0 equiv), open air	15	96

[a] All reactions were run on a 1.5-mmol scale at r.t.

The DMP oxidation reaction was extended to anilines with various substituents under the optimal conditions (Table 2). A variety of functional groups were tolerated on the aryl residue, ranging from the electron-donating methoxy (entry 4) to the synthetically fertile halides (entries 6–12). Remarkably, even an *ortho*-substituted phenylaniline, **14a**, afforded the corresponding iminoquinone **14b** in 80% yield (entry 14). However, the presence of the strong electron-withdrawing nitro group completely retarded the reaction (entry 18). In the case of 2-aminothiophenol, the oxidation reaction led to a tricyclic compound **16b** in 90% yield with the formation of a S–S bond (entry 16). In another particular case, oxidation reaction of 1,4-phenylenediamine (**17a**) gave 4,4′-diazenediylbisaniline (**17b**), but only in the absence of water (entry 17).

In principle, two regioisomeric products could be formed from the coupling of the aniline **1** to the oxidized quinone. It was difficult to ascertain which regioisomer was formed just by ^1H and ^{13}C NMR spectroscopy. Unfortunately, we were unable to isolate any crystals suitable for X-ray crystal structure analysis. However, it was found that

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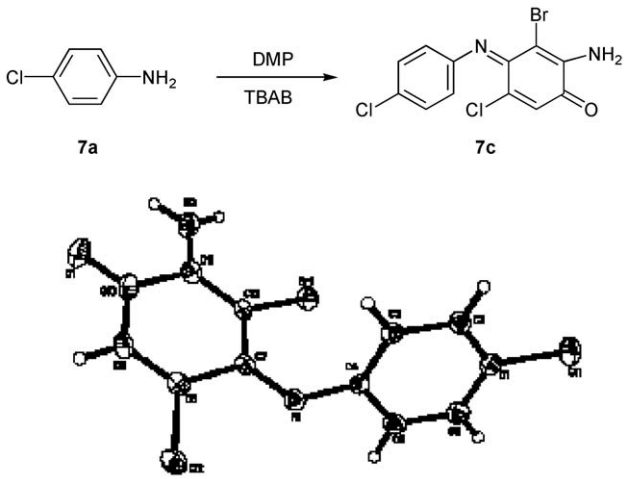


Scheme 1 Preparation and X-ray crystal structure of **7c**

addition of tetrabutylammonium bromide as an additive in the reaction of **7a** led to the formation of the corresponding bromination product **7c** that could be subjected to X-ray crystallography diffraction analysis (Scheme 1),[17] and thus the product regiochemistry was determined.

In brief, we have conducted a synthetic investigation on the oxidation of anilines via DMP in metal-free systems and developed a facile protocol for the synthesis of iminoquinones. As a result of its mildness and good functional group compatibility, this method might find application in the synthesis of polycyclic targets and natural products consisting of iminoquinone moieties. The possible mechanism is still under investigation and extension of this preliminary work is now under way in our laboratory.

Table 2 Oxidation of Anilines with DMP[18]

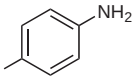
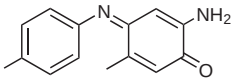
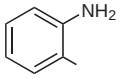
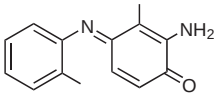
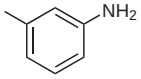
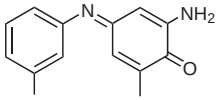
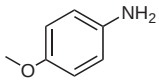
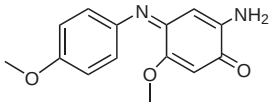
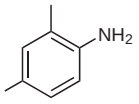
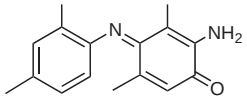
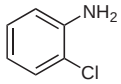
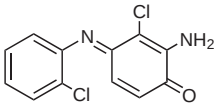
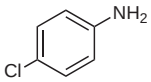
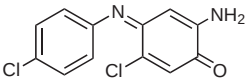
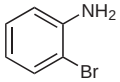
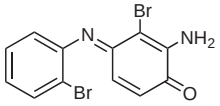
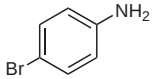
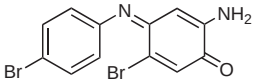
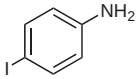
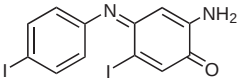
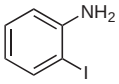
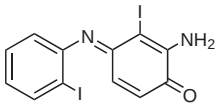
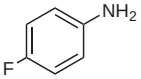
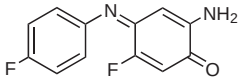
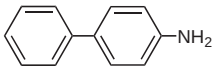
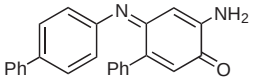
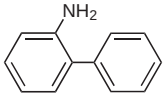
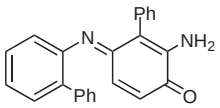
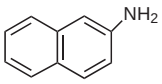
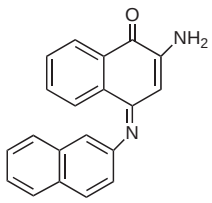
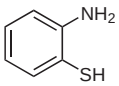
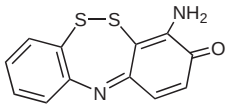
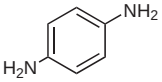
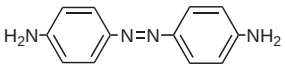
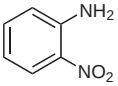
Entry	Substrate[a]	Time (min)	Product	Yield (%)[b]
1	 **1a**	10	 **1b**	96
2	 **2a**	10	 **2b**	89
3	 **3a**	15	 **3b**	87
4	 **4a**	15	 **4b**	79
5	 **5a**	15	 **5b**	94
6	 **6a**	10	 **6b**[19]	93
7	 **7a**	10	 **7b**	85
8	 **8a**	25	 **8b**	88

Table 2 Oxidation of Anilines with DMP[18] (continued)

Entry	Substrate[a]	Time (min)	Product	Yield (%)[b]
9	 **9a**	25	 **9b**	84
10	 **10a**	25	 **10b**	86
11	 **11a**	20	 **11b**	81
12	 **12a**	30	 **12b**	79
13	 **13a**	25	 **13b**	77
14	 **14a**	25	 **14b**	80
15	 **15a**	30	 **15b**	86
16	 **16a**	30	 **16b**	90
17[c]	 **17a**	40	 **17b**	84
18	 **18a**	overnight	none	

[a] Substrates **13a** and **14a** were prepared according to ref. 20. Others were commercially available and used without further purification. Reactions were run on a 1.5-mmol scale using DMP (2.2 equiv) and H_2O (2.0 equiv) in CH_2Cl_2 (8 mL) at r.t.
[b] Isolated yield after column chromatography.
[c] The reaction was run without H_2O.

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(17) CCDC 643540 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(18) **General Procedure**: H_2O (54 mg, 3.0 mmol) and aniline (1.5 mmol) were added to a solution of DMP (1.3 g, 2.64 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred at r.t. until complete consumption of the aniline (observed by TLC). The solution was washed with H_2O (5 × 8 mL) and the organic phase was dried over anhyd Na_2SO_4. After filtration, the solvent was removed and the residue was purified by silica gel column chromatography to afford the final compound.

(19) 2-Amino-3-chloro-1,4-benzoquinone-4-(2-chloro)phenylimide (**6b**): bright red-orange solid; mp 128–130 °C. IR (KBr): 3475, 3370, 1653, 1623, 1598, 1562, 1392, 1338, 838, 766, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 5.0 Hz, 1 H), 7.25 (t, *J* = 4.8 Hz, 1 H), 7.10 (t, *J* = 4.8 Hz, 1 H), 6.76–6.82 (m, 2 H), 6.44 (d, *J* = 6.3 Hz, 1 H), 5.10 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.95, 153.72, 146.74, 140.81, 129.89, 129.49, 129.04, 126.93, 126.02, 124.77, 121.48, 111.99. MS (FAB): *m*/*z* = 266.8 [M + H^+]. Anal. Calcd for $C_{12}H_8Cl_2N_2O$: C, 53.96; H, 3.02; N, 10.49. Found: C, 53.92; H, 2.98; N, 10.52.

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