DMD Oxidation of *in-Situ*-Generated σ^H Adducts Derived from Nitroarenes and the Carbanion of 2-Phenylpropionitrile to Phenols: The First Direct Substitution of a Nitro by a Hydroxy Group

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The dimethyldioxirane (DMD) oxidation of σ^H adducts derived from nitroarenes and the carbanion of 2-phenylpropionitrile yields unexpectedly the phenols **5** as the major products, while the usually observed nitroarenes **4** are formed in very little amounts, if any. The phenol yield was much improved when a small quantity (0.5−1.0 equiv.) of water was added at the start of the reaction. This novel oxidation of Meisenheimer complexes provides the first direct synthesis of phenols from nitroarenes, an unprecedented transformation.

Nucleophilic reagents react with nitroarenes in a variety of ways. The initial step of these reaction is usually reversible addition in the unsubstituted ortho and para positions to result in the anionic σ^H adducts (Meisenheimer complexes).[1] These σ^H adducts may be converted into products of hydrogen-atom replacement in several ways; the most important are oxidation and vicarious nucleophilic substitution.[2] For example, recently we have shown[3] that the carbanion of 2-phenylpropionitrile (**1**) adds quantitatively to nitrobenzenes **2** in liquid ammonia to give σ^H adducts **3**, which at −70 °C are relatively long-lived intermediates. Treatment of the σ^H adducts with KMnO$_4$ leads to rapid oxidation to give the so-called ONSH (oxidative nucleophilic substitution of hydrogen) products **4**, as shown in eq 1.[3]
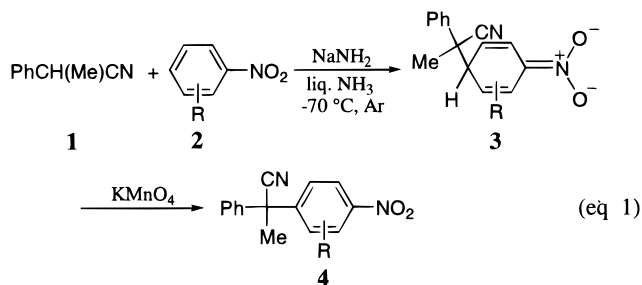
This ONSH reaction proceeds selectively in the position para to the nitro group, and the nitroarenes may possess a variety of substituents ortho and meta to the nitro group. Some substitutents, however, hinder or totally inhibit the oxidation. For example, the σ^H adduct **3b** derived from 3,5-dichloronitrobenzene (**2b**) is not oxidized by KMnO$_4$, and upon hydrolysis with aqueous NH$_4$Cl in liquid ammonia, both **1** and **2b** are recovered essentially quantitatively.[3]

Since anionic σ^H adducts **3** can be regarded as cyclohexadienenitronate anions, application of other strong carbanion-oxidizing agents was of interest. Among the strong oxidants used for the oxidation of carbanions, enolate anions, and related species, of particular interest is dimethyldioxirane (DMD), one of the most powerful and convenient oxygen-transfer agents.[4] Isolated DMD is readily available[5] as an acetone solution (ca. 0.1 M) and has been extensively employed for the oxidation of a variety of enolates to afford α-hydroxy ketones, esters, etc., a process of significant practical value.[6]

Since DMD cannot be employed in liquid ammonia, the σ^H adducts were produced and oxidized with DMD in a 1:20 DMF/THF mixture at −70 °C. The results are summarized in Table 1. In the first experiment (Table 1, entry 1), to a solution of the σ^H adduct **3a** of nitrobenzene (**2a**) and the carbanion of **1**, a solution of DMD in acetone was added in slight excess. After standard workup, ca. 50% of the nitrobenzene (**2a**) and the nitrile (**1**) were converted to afford 6% of the ONSH product **4a** and 47% of the phenol 2-(4-hydroxyphenyl)-2-phenylpro-

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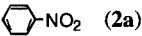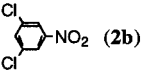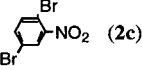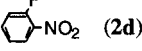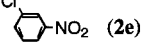
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Table 1. DMD Oxidation of σ^H Adducts[a]

entry	nitroarene 2	H$_2$O (equiv.)	yield (%)[b] 4	5
1		0	6	47
2[c]		0	traces	traces
3[d]	(2a)	0.5	5	71
4[e]		1.0	4	77
5[f]		1.0	6	83
6		1.0[g]	6	70
7[e]	(2b)	1.0	0	77
8[f]		1.0	0	69
9[e]	(2c)	1.0	traces	72
10[f]	(2d)	1.0	7	81
11[f]	(2e)	1.0	3	87

[a] With 1.0 mmol of **1**, 1.0 mmol of **2**, 1.1 mmol of *t*-BuOK, and 1.2 mmol of DMD in DMF/THF (1 mL/20 mL) under argon gas unless otherwise indicated. DMD solution (predried two times over fresh molecular sieves for 2 days each), precooled at −70 °C and added in one portion. [b] Yields of isolated materials after column chromatography on silica gel. [c] DMD solution dried over P$_2$O$_5$ (3 h) and K$_2$CO$_3$ (2 h). [d] H$_2$O was added first to the DMD solution and the wet solution to the reaction mixture. [e] H$_2$O was added first to the reaction mixture and 5 min later the dry DMD solution. [f] DMD was added first to the reaction mixture and 5 min later the H$_2$O. [g] aqueous 2 N NaOH solution added.

$$1 + 2 \xrightarrow[\substack{\text{DMF/THF} \\ -70\ °C,\ Ar}]{^t\text{BuOK}} 3 \xrightarrow{\substack{O \\ \diagup\diagdown \\ O}, H_2O} \xrightarrow{\text{aq. NH}_4\text{Cl}}$$

Ph—C(CN)(Me)—(ring, R)—OH + 4   (eq 2)

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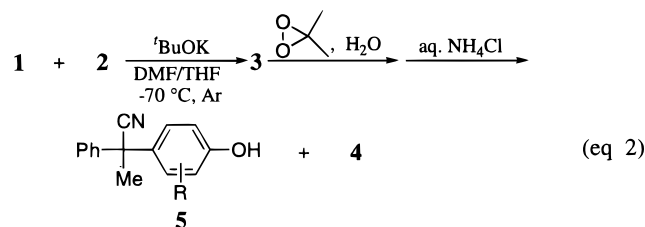
pionitrile (**5a**). This unexpected reaction offers the first direct method for the synthesis of phenols from nitroarenes.

Since the conversion of the σ^H adduct into phenol was only around 50%, the reaction was studied in detail to optimize the yield of the phenol **5a**. In view of the fact that DMD solutions dried over molecular sieves contain traces of water, presumably the σ^H adduct **3** was hydrolyzed back to the starting materials. Therefore, to exclude this possiblity, the DMD solution was rigorously dried over P$_2$O$_5$ and subsequently over solid K$_2$CO$_3$, the latter to remove possible traces of acids. Surprisingly, with such a rigorously dried DMD solution, only traces of the phenol **5a** were formed (Table 1, entry 2). Consequently, water (0.5 equiv relative to **2**) was intentionally added to the DMD solution, and a much better yield (71%) of the phenol **5a** was obtained (Table 1, entry 3). In fact, water may be added separately, either before or after the oxidation by DMD, to produce the phenol **5a** in good yields, i.e., 77% (Table 1, entry 4) before the addition of the DMD solution and 83% (Table 1, entry 5) after.

Similar results were obtained with nitroarene **5b** (Table 1, entries 7 and 8).

The difference between entries 1 and 5 (Table 1) is that in the former, aq NH$_4$Cl (pH ca. 5) was used in the workup, which suggests that acidic conditions disfavor the oxidation to achieve high yields of phenol **5a**. Indeed, when 1 equiv of 2 N NaOH solution was employed in the workup instead of aq NH$_4$Cl, again a good yield (70%) of phenol **5a** was obtained (Table 1, entry 6). This suggests that the oxidation occurs, at least partially, upon addition of water. Similarly, when σ^H adducts **3c**, **3d**, and **3e**, derived from nitroarenes **2c**, **2d**, and **2e**, were treated with DMD and subsequently worked up with water, the corresponding phenols were obtained in 72, 81, and 87% yields (Table 1, entries 9, 10, and 11). Moreover, all the nitroarenes **2** studied here gave the phenolic products **5** as the major products, while only small amounts, if any, of the ONSH products **4** were detected (Table 1).

Mechanistically, this unprecedented oxidation of σ^H adducts by DMD is akin to the Nef reaction.[7] For example, the formation of 4,4-disubstituted cyclohexadienones was already observed when para σ^H adducts of MeMgBr or BuMgBr to *p*-nitrotoluene were acidified with aqueous HCl.[8] Similarly, the addition of an alkylmagnesium halide to 10-alkyl-9-nitroanthracene and oxidation of the resulting σ^H adducts by Pb(OCOCH$_3$)$_4$ gave 10,10-dialkylanthrones.[9] Although the normal Nef reaction is a hydrolysis, the present case (Table 1) is an oxidation process because DMD is essential. For instance, acidification of the σ^H adduct **3a** with 27% aqueous HCl led only to the corresponding nitroso compound. An attempt to oxidize **3a** by 70% H$_2$O$_2$ resulted in its reversion to the starting materials. It is most likely that the phenols arise from the corresponding dienenones, but the details of the oxidation mechanism by DMD require a more elaborate scrutiny.

In conclusion, the DMD oxidation of σ^H adducts, generated in situ from the 2-phenylpropionitrile carbanion and nitroarenes gives the corresponding phenols **5** in very good yields. This unprecedented oxidation provides the first direct way to prepare phenols from nitroarenes.

Supporting Information Available: Experimental details for the DMD oxidation of σ^H adducts **3** and the data for the characterization of the phenols **5** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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