Redox-Neutral Selenium-Catalysed Isomerisation of para-Hydroxamic Acids into para-Aminophenols

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Abstract: A selenium-catalysed para-hydroxylation of N-aryl-hydroxamic acids is reported. Mechanistically, the reaction comprises an N–O bond cleavage and consecutive selenium-induced [2,3]-rearrangement to deliver para-hydroxyaniline derivatives. The mechanism is studied through both 18O-crossover experiments as well as quantum chemical calculations. This redox-neutral transformation provides an unconventional synthetic approach to para-aminophenols.

The para-aminophenol motif, epitomized by the century-old analgesic paracetamol, is an important structural feature in pharmaceuticals and materials. Numerous methods for the preparation of para-aminophenols have been reported ever since Eugen Bamberger discovered the first practical synthesis employing the rearrangement of N-arylhydroxylamine in aqueous sulfuric acid (Scheme 1 a).[1] This process presumably involves the heterolytic cleavage of the N–O bond and subsequent intermolecular addition of water to a nitrenium intermediate. Besides strong Brønsted acids, these N–O bond cleavage/rearrangement events have also been triggered by Lewis acids,[2] thermal activation[3] or transition metals.[4] Pioneering work using Lewis acid-mediated ortho-migration of a methoxy group was reported by Kikugawa (Scheme 1b).[2] Later, the same group disclosed the PBu3/CCl4-induced ortho-migration of the hydroxyl group in N-acyl-N-phenylhydroxylamines (Scheme 1c); minor amounts of the para-isomer were also observed.[5] Ngai described the elegant ortho-trifluoromethoxylation of aniline through a thermal rearrangement process (Scheme 1d).[3] Recently, Terada reported an in-depth study of the elegant cobalt-catalysed [1,3]-migration of alkoxycarbonyloxyl groups (Scheme 1e).[1] Interestingly, the large majority of these N–O bond cleavage processes lead to the formation of new C–O bonds with ortho-selectivity. The few approaches achieving para-hydroxylation either require relatively harsh conditions or produce a mixture of ortho- and para-regioisomers.[5,6] To the best of our knowledge, a mild and practical method for regioselective para-hydroxylation still has not emerged.[7]

Selenium is an essential oligoelement, perhaps best known for its occurrence in selenocysteine.[8–10] Within organic synthesis, organoselenium reagents have also emerged as unique catalysts for oxidation,[11] reduction,[12] C–C/C–X bond formation and rearrangements.[13–15] The heavier selenium shows distinct properties when compared to the other chalcogens.[16] Herein we present a new selenium-catalysed, redox-neutral para-selective hydroxylation starting from hydroxamic acids via consecutive [2,3]-rearrangements to form para-aminophenols (Scheme 1 f).

In initial efforts, we treated hydroxamic acid $A$ with one equivalent of PhSeBr. Gratifyingly, the para-aminophenol $B$ was obtained in 72% isolated yield (Table 1, entry 1). Encouraged by this early result, we realized that reducing the loading of phenylselenyl bromide to 10 mol% still afforded para-aminophenol $B$ initially in 66% yield (entry 2). It is noteworthy that the catalytic process, while requiring increased reaction time to reach full conversion, resulted in only a slight decrease in yield. We noted that para-hydroxylation catalysed by PhSeCl gave almost the same yield as with PhSeBr (entry 3). Changing the catalyst to N-(phenylselenyl)-phthalimide or 2-nitrophenyl selenocyanate led to 40% and 35% yields of para-aminophenol $B$, respectively (entries 4 and 5). To increase the electrophilicity of the selenium reagent, a combination of PhSeCl and AgOTf was employed but gave only 25% yield of $B$ (entry 6). PhSeSePh was ineffective and resulted in recovery of starting material. After these initial observations we elected phenylselenyl bromide as the catalyst for further investigations. In subsequent experiments, several solvents were examined. Dichloromethane, acetonitrile and ethereal solvents were all found to be suitable for this reaction (Table 1, entry 8–12). 1,4-dioxane was eventually elected as the best system, since its
Table 1: Investigation of selenium catalysts. [a] Reactions were carried out at 0.2 M concentration. [b] Yields were determined by NMR using trimethoxybenzene as internal standard. [c] isolated yield.

| Entry | Reagent           | Solvent[1] | Temperature | Time | Yield[1, c] |
|-------|-------------------|------------|-------------|------|-------------|
| 1     | PhSeBr (1 equiv) | 1,4-dioxane| rt          | 1 h  | 72%         |
| 2     | PhSeBr (10 mol%) | 1,4-dioxane| rt          | 3 h  | 66%         |
| 3     | PhSeCl (10 mol%) | 1,4-dioxane| rt          | 6 h  | 67%         |
| 4     | N-Phenyldialkyl-phthalimide (10 mol%) | 1,4-dioxane| rt          | 12 h | 40%         |
| 5     | 2-nitrophenyl selenocyanate (10 mol%) | 1,4-dioxane| rt          | 18 h | 35%         |
| 6     | PhSeCl (10 mol%) | AgOTf (10 mol%) | 1,4-dioxane| rt    | 18 h | 25%         |
| 7     | PhSeBr (10 mol%) | MeCN       | rt          | 18 h | 0%          |
| 8     | PhSeBr (10 mol%) | MeOH       | rt          | 3 h  | 79% (76%)   |
| 9     | PhSeBr (10 mol%) | CH₂Cl₂     | rt          | 3 h  | 29%         |
| 10    | PhSeBr (10 mol%) | MeCN       | rt          | 3 h  | 73%         |
| 11    | PhSeBr (10 mol%) | THF        | rt          | 3 h  | 76%         |
| 12    | PhSeBr (10 mol%) | 1,4-dioxane| rt          | 3 h  | 81%         |

With suitable reaction conditions in hand, we turned our attention towards the scope of this selenium-catalysed hydroxylation (Scheme 2). As shown, the transformation tolerates a broad range of functionalities, including the sterically hindered pivalamide 4a and adamantylamide 4b, as well as the highly strained cyclobutane 4c. Notably, higher yields and shorter reaction times are achieved for substrates carrying an electron-deficient benzamide fragment (see 4d, 2, 4e). This appears to correlate with a correspondingly weaker N–O bond in those substrates. Also tolerated are cinnamylamide 4f and styrene-amide 4g, albeit with slightly diminished yields. Next, a variety of different substituents at the N-aryl ring were investigated. Naphthalene 3i reacted smoothly to give aminophenol 4i. Noteworthy, the congested 3,4-dimethyl-substituted substrate 3k and 2,6-dimethyl-substituted substrate 3l both led to the corresponding para-aminophenols. Furthermore, our protocol was also applicable towards various halogen-substituted substrates to afford the desired para-aminophenol (4o–4t). Electronic effects at the N-arene ring significantly affected the reaction yield: while the electron-rich 4-methoxyphenyl substrate 3m was high-yielding at room temperature, N-electron deficient hydroxamic acids (4n, 4p, 4q) required higher temperature to form the corresponding para-aminophenol in moderate yields.27

In order to elucidate the mechanism of the reported reaction, we carried out 18O-labelling studies, as well as quantum chemical calculations (see Supporting Information for additional details). In the event, upon reaction of 3h with PhSeBr and an internal proton transfer, in line with reported electrophilic selenium reactivity,28 the first step A→B is an exergonic [2,3]-sigmatropic rearrangement with N–O bond cleavage and ortho-attack of selenium, followed by a barrierless proton transfer B→C. Intermediate C then undergoes a second proton transfer, preceding the second [2,3]-sigmatropic rearrangement D→E. This step involves concerted Se–C bond cleavage and the formation of a new C–O bond leading to the para-O-aryl intermediate E. The fifth step E→F is the highly thermodynamically and kinetically favorable (ΔG° = −28 kcal mol⁻¹, ΔG°* = 7 kcal mol⁻¹) re-aromatization assisted by a second substrate molecule. The last step ultimately closes the catalytic cycle yielding the final product and regenerating intermediate A. Interestingly, the apparent activation energy of the cycle, ΔG° = 25 kcal mol⁻¹, is determined by the final step, the intermolecular proton transfer.

Scheme 2. Scope of selenium-catalysed para-hydroxylation. Yields refer to pure, isolated products.
The proposed mechanism highlights the critical role of the substrate itself in the deprotonation of intermediate E, in agreement with the base-free conditions that are employed. This redox-neutral, regioselective hydroxylation can be deployed in a number of synthetically relevant contexts (Scheme 5). Practolol (Scheme 5a, compound 5) is a known beta-adrenergic blocking agent, often used for the treatment of cardiovascular diseases, and it has been previously prepared by various routes.[19,20] In our gram-scale approach, hydroxamic acid 3h was exposed to selenium-catalysed para-hydroxylation providing 72% yield of para-aminophenol 4h. Ether synthesis with epichlorhydrin, followed by epoxide opening by isopropylamine gave practol 5 in 56% yield over two steps. Next, we targeted diloxanide furoate 8, a luminal amoebicide widely used as the treatment against amoeba infections (Scheme 5b).[21] Readily prepared dichloroacetyl hydroxamic acid 6 was subjected to selenium-catalysis to yield the corresponding para-dichloroacetyl aminophenol 7 in 57% yield. Introduction of the furoyl group and methyl-ation completed the synthesis of 8.

Finally, Paracetamol/para-acetaminophenol 4h, one of the most commonly used and produced drugs worldwide, is conventionally prepared by a few different methods. Representative approaches are depicted in Scheme 5c.[22] The first route involves a nitration of chlorobenzene 9 that also produces ortho-chloronitrobenzene as side product.[22] Processes using a Bamberger reaction also form significant amounts of ortho-aminophenol.[22] In contrast, our selenium-catalysed para-hydroxylation offers a highly regioselective, alternative solution as it generates para-aminophenol 4h from simple precursor 3h as the single regioisomer in excellent yield.

In conclusion, we have reported a catalytic method for the synthesis of para-aminophenols from the corresponding arylhydroxamic acids. The catalytic reaction proceeds via a unique electrophilic selenium-induced N/C0 bond cleavage event followed by a successive [2,3]-rearrangement to form the para-aminophenol assisted by another substrate molecule. The mechanism is supported by 18O-crossover experiments as well as quantum chemical calculations. This operationally easy process tolerates a broad range of functional groups and can easily be applied, for example, to prepare practol 5 and diloxanide furoate 8 in gram-scale.

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Conflict of interest

The authors declare no conflict of interest.

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