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o-Phenylenediamine as a New Catalyst in the Highly Regioselective Conversion of Epoxides to Halohydrins with Elemental Halogens – A Reinvestigation

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Summary. In contrast to a previous report, *o*-phenylenediamine is not a catalyst in the ring opening reaction of epoxides by means of bromine or iodine. The *o*-phenylenediamine is just a reactant which reacts with iodine to give phenazine-2,3-diamine and hydrogen iodide, or with bromine to give a mixture of brominated and polymerized products as well as hydrogen bromide. The hydrogen halogenides are in fact the real epoxide ring opening reactants.

Keywords. Oxiranes; Ring Opening; Halogenation; Bromohydrins; Iodohydrins.

Introduction

In 2004 a paper has been published [1] describing the ring opening reaction of epoxides to halohydrins by means of bromine or iodine in the presence of *o*-phenylenediamine as a catalyst. The authors also discussed the mechanistic details of this reaction and proposed a four-step mechanism, where *o*-phenylenediamine and its complexes with iodine or bromine play an essential role. Their mechanistic proposal was supported by UV and *Raman* spectra, and by literature precedents. The authors neither isolated nor confirmed the presence of the catalyst, namely *o*-phenylenediamine, in the reaction mixture after reaction. Anyway, the authors stated in their paper that: "The catalyst was easily recovered and could be reused several times."

We could not reproduce the experiments described by *Eshghi et al.* [1]. Moreover, it is unlikely that *o*-phenylenediamine, a strong nucleophilic and reducing agent, could survive in the presence of strong oxidizing and electrophilic

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reagents like bromine or iodine, therefore it could not be a catalyst in the reaction described in this paper. Under such circumstances, we decided to reinvestigate this reaction.

Results and Discussions

First, we analyzed the literature data and found that in fact the reaction of *o*-phenylenediamine with iodine is well-known. It has been described for the first time by *Richter* [2] in 1911, and by *Knoevenagel* [3] in 1914 as a preparative method of oxidation of *o*-phenylenediamine to phenazine-2,3-diamine. Although a similar reaction with bromine has never been described in literature, the high reactivity of aromatic amines towards bromine is well known. *E.g.*, 2-methyl-1*H*-benzimidazol, a compound very closely related to *o*-phenylenediamine, has been easily perbrominated [4].

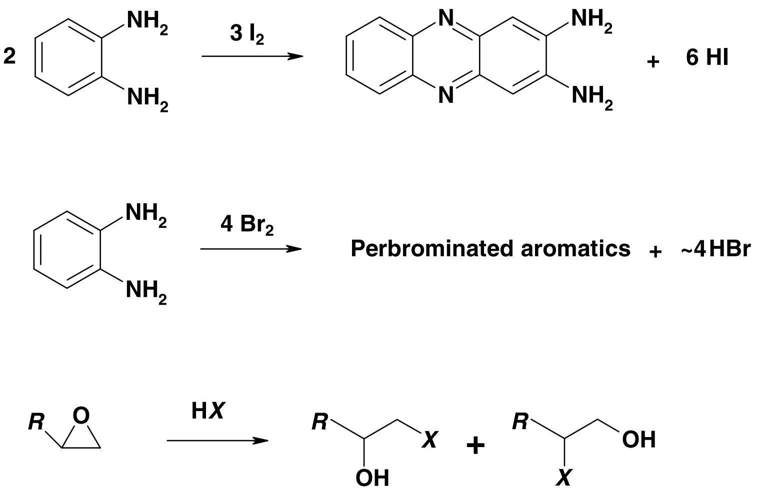
When we repeated the reaction of 1-chloro-2,3-epoxypropane with iodine in the presence of 20 mol% of *o*-phenylenediamine [5] as described by *Eshghi et al.* (*cf.* Ref. [1], table 2, entry 25), we identified the corresponding iodohydrin by means of ^{1}H NMR spectroscopy (Experiment 1), but with rather low yield (only about 60%), unreacted 1-chloro-2,3-epoxypropane (about 40%) and almost quantitative yield of phenazine-2,3-diamine identified by their ^{1}H NMR spectra. This means that *o*-phenylenediamine is not a catalyst, but just a stoichiometric reagent.

When we applied the same conditions for the reaction with methyloxirane (we chose methyloxirane for this demonstration because it gives products in which all of the methyl groups are separated and easily visible in the ^{1}H NMR spectra), we also identified the iodohydrins (Experiment 2), with rather low yield (only about 50%), and a considerable amount of phenazine-2,3-diamine (about 95%) identified by ^{1}H NMR spectra. These results also confirm that *o*-phenylenediamine is not a catalyst but a reagent.

The reaction of 1-chloro-2,3-epoxypropane with bromine in the presence of 20 mol% *o*-phenylenediamine [6] (Experiment 3) gave in fact as much as 82% yield of bromohydrins but also a large amount of a dark residue. However, when we analyzed the reaction mixture directly after reaction by means of ^{1}H NMR, we found no absorption in the aromatic area on the spectrum. This obviously means that *o*-phenylenediamine was not present in the reaction mixture after the reaction.

Methyloxirane with bromine, under the same reaction conditions, gave 74% yield of bromohydrins and a large amount of a dark residue (Experiment 4). When we analyzed the reaction mixture directly after the reaction by means of ^{1}H NMR, we found again no absorption in the aromatic area on the spectrum. Therefore, *o*-phenylenediamine was not present in the reaction mixture after reaction.

Eshghi et al. described also ring opening reactions of several 1-aryloxy-2,3-epoxypropanes by bromine (*cf.* Ref. [1], table 2, entries 14, 16, 18, and 20). However, it is well known, that in these cases a bromination of the highly activated aromatic ring should occur [7]. When we reinvestigated the reaction of 1-phenoxy-2,3-epoxypropane with bromine (Experiment 5), we found no necessity of any catalyst. The reaction proceeds smoothly without *o*-phenylenediamine to give 1-bromo-3-(4-bromophenoxy)propan-2-ol as the sole product, but not 1-bromo-



Scheme 1

3-phenoxypropan-2-ol as stated [1]. Our findings are illustrated by the sequence in Scheme 1.

In conclusion, we could not reproduce the *Eshghi et al.* [1] protocol. When we reinvestigated this reaction we found that the *o*-phenylenediamine reacts with molecular iodine or bromine to give hydrogen iodide or hydrogen bromide. Therefore, the only role *o*-phenylenediamine plays in their protocol is to generate the hydrogen halogenide, which reacts *in situ* with the epoxide. This is very close to our procedure based on the generation of hydrogen halogenide in the halogenation of active aromatics, developed some time ago and described recently [8]. It appears that the author's extensive discussion and the final conclusions concerning the catalytic effect of *o*-phenylenediamine are in error.

Experimental

All reagents and solvents were of commercial quality. The authentic phenazine-2,3-diamine was available from Synchem (www.synchem.de). The properties of this compound are described in Merck Index 13th ed. p. 3002, Merck & Co., Inc. 2001. ^{1}H NMR spectra were recorded by Mr. *R. Kozicki* on a Bruker Avance 300 MHz spectrometer locked on D from the solvent. Chemical shifts (δ/ppm) were calculated from the chemical shift of the D lock and were not calibrated. FTIR spectra were measured on a Perkin Elmer 2000 spectrometer in KBr pellets (1/200) by Mrs. *E. Mróź*. Melting points were determined on a Boetius microscope with an electrically heated plate. The structures of all compounds were derived from their ^{1}H NMR spectra.

Experiment 1. The Reaction of Iodine with 1-Chloro-2,3-epoxypropane in Dichloromethane in the Presence of 20 mol% o-Phenylenediamine

1-Chloro-2,3-epoxypropane (2.3 g, 25 mmol) was added to a stirred mixture of 0.54 g *o*-phenylenediamine (5 mmol) in 25 cm^3 CH_2Cl_2 at about 20°C (water bath). Next, a solution of 6.4 g I_2 (25 mmol) in 30 cm^3 CH_2Cl_2 was added dropwise (30 min) to the above mixture at the same temperature. The reaction mixture darkened and a dark crystalline material precipitated. Then, the reaction mixture was stirred 3 h at the same temperature. A sample of 0.15 cm^3 of the reaction mixture was taken, evaporated in *vacuo* from a warm water bath (below 30°C), dissolved in 0.50 cm^3 $CDCl_3$, and its ^{1}H NMR spectrum was measured. From this the ratio of unreacted 1-chloro-2,3-epoxypropane (multiplets at 2.61, 2.90, 3.25, and 3.57), to the corresponding iodohydrin, 1-chloro-3-iodopropan-2-ol (multiplets at 2.43, 3.91, 3.69, and 3.82), was estimated as 40 to 60 (based on integrals of these multiplets). There were no peaks in the aromatic region on this spectrum indicating on the presence of *o*-phenylenediamine. Then, the whole reaction mixture after reaction was titrated by 47.0 cm^3 of a 1.00 *M* solution of $Na_2S_2O_3$ in H_2O, what corresponds with yield of iodohydrin. The precipitate from inhomogenous mixture was separated by suction, washed with 2×10 cm^3 H_2O, 5×10 cm^3 of saturated solution of $Na_2S_2O_3$ in H_2O, 3×10 cm^3 H_2O, and dried on air to obtain 0.7 g of a dark red-brown solid identified as crude phenazine-2,3-diamine by comparison of its FTIR and ^1H NMR spectra with pure compound. The organic phase from collected filtrates was evaporated to leave 2.2 g of oily residue identified as a mixture of unreacted 1-chloro-2,3-epoxypropane and iodohydrin, as mentioned before.

Experiment 2. The Reaction of Iodine with Methyloxirane in Dichloromethane in the Presence of 20 mol% o-Phenylenediamine

Methyloxirane (2.9 g, 50 mmol) was added to a stirred mixture of 1.08 g *o*-phenylenediamine (10 mmol) in 50 cm^3 CH_2Cl_2 at about 20°C (water bath). Next, a solution of 12.7 g I_2 (50 mmol) in 100 cm^3 CH_2Cl_2 was added dropwise (30 min) to the above mixture at the same temperature. The reaction mixture darkened and a dark crystalline material precipitated. Then, the reaction mixture was stirred overnight at the same temperature. A sample of 0.15 cm^3 of the reaction mixture was taken, evaporated in *vacuo* from a warm water bath (below 30°C), dissolved in 0.50 cm^3 $CDCl_3$, and its ^1H NMR spectrum was measured. From this the corresponding iodohydrins, 1-iodopropan-2-ol and 2-iodopropanol, in a 72/28 ratio (based on integrals of the corresponding methyl groups at 1.31 and 1.90 ppm) were identified and assayed. There were no peaks in the aromatic region on this spectrum indicating on the presence of *o*-phenylenediamine. Then, the whole reaction mixture after reaction was titrated by means of a 1.00 *M* solution of $Na_2S_2O_3$ in H_2O. About 74 cm^3 of this solution were necessary to titrate the excess of iodine. Thus, as much as about 37 mmol of the iodine remained unreacted. Accordingly, the stoichiometry of the reaction of *o*-phenylenediamine to iodine is about 2:3.

The precipitate from inhomogenous mixture was separated by suction, washed with 2×10 cm^3 H_2O, and dried on air to obtain 1.0 g (95%) of a red-brown solid identified as phenazine-2,3-diamine by means of IR and ^1H NMR spectra. ^1H NMR (acetone-d_6): $\delta = 5.61$ (bs, 4H, NH_2), 7.17 (s, 2H), 7.58 (dd, 2H, $J = 3.4$, 6.6 Hz), 7.97 (dd, 2H, $J = 3.4$, 6.6 Hz).

The organic phase from the collected filtrates was separated and dried over Na_2SO_4 (20 g), filtered, and evaporated in *vacuo* from a warm water bath (below 30°C) to leave an oily residue (4.7 g, 50%) identified by means of its ^1H NMR as the mixture of iodohydrins, 1-iodopropan-2-ol and 2-iodopropanol. No other peaks were observed on the spectrum.

Experiment 3. The Reaction of Bromine with 1-Chloro-2,3-epoxypropane in Dichloromethane in the Presence of 20 mol% o-Phenylenediamine

1-Chloro-2,3-epoxypropane (23.1 g, 250 mmol) was added to a stirred mixture of 5.4 g *o*-phenylenediamine (50 mmol) in 250 cm^3 CH_2Cl_2 at about 20°C (water bath). Next, a solution of 12.8 cm^3 Br_2 (250 mmol) in 50 cm^3 CH_2Cl_2 was added dropwise (30 min) to the above mixture. The reaction was slightly exothermic. The reaction mixture darkened and dark precipitate appeared. Then, the reaction mixture was stirred 2 h at the same temperature, a sample of 0.15 cm^3 of the reaction mixture was withdrawn, evaporated in *vacuo* from a warm water bath (below 40°C), dissolved in 0.50 cm^3 $CDCl_3$, and its ^1H NMR spectrum was measured. Except of peaks from the corresponding bromohydrin, 1-bromo-3-chloropropan-2-ol (at 2.49, 3.58, 3,70, and 4.04), there were no other peaks, especially in the aromatic region on the spectrum. Thus, no *o*-phenylenediamine was present in the reaction mixture after reaction. Then, the reaction mixture was evaporated in *vacuo* from a warm water bath (below 40°C) to leave a dark oily residue, which was treated with 100 cm^3 ethyl ether. The dark precipitate was separated by suction, washed with 3×10 cm^3 ethyl ether, and dried on air to obtain 19.5 g of a dark solid insoluble in organic solvents or water containing huge amounts of Br_2 (*Beilstein* test). The collected filtrates were evaporated in *vacuo* from a warm water bath (below 40°C) to leave a dark oily residue, which was distilled "bulb to bulb" to give 35.5 g (82%) of 1-bromo-3-chloropropan-2-ol and about 4.0 g of a dark solid residue after distillation.

Experiment 4. The Reaction of Bromine with Methyloxirane in Dichloromethane in the Presence of 20 mol% o-Phenylenediamine

Methyloxirane (5.8 g, 100 mmol) was added to a stirred mixture of 2.2 g *o*-phenylenediamine (20 mmol) in 100 cm^3 CH_2Cl_2 at about 20°C (water bath). Next, a solution of 5.1 cm^3 Br_2 (100 mmol) in 30 cm^3 CH_2Cl_2 was added dropwise (30 min) to the above mixture. The reaction was slightly exothermic. The reaction mixture darkened and dark precipitate appeared. Then, the reaction mixture was stirred overnight at the same temperature. A sample of 0.15 cm^3 of the reaction mixture was withdrawn, evaporated in *vacuo* from a warm water bath (below 40°C), dissolved in 0.50 cm^3 $CDCl_3$, and its ^{1}H NMR spectrum was measured. From this the corresponding bromohydrins, 1-bromopropan-2-ol and 2-bromopropanol, in a 67/33 ratio (based on integrals of the corresponding methyl groups at 1.30 and 1.70 ppm) were identified and assayed. There were no peaks in the aromatic region on the spectrum. Thus, no *o*-phenylenediamine was present in the reaction mixture after reaction. Then, the precipitate from the whole reaction mixture after reaction was separated by suction, washed with 3×10 cm^3 CH_2Cl_2, and dried on air to obtain 4.9 g of a dark solid insoluble in organic solvents or water containing huge amounts of Br_2 (*Beilstein* test). The collected filtrates were evaporated in *vacuo* from a warm water bath (below 40°C) to leave a dark oily residue, which was distilled "bulb to bulb" to give 10.3 g (74%) of a mixture of bromohydrins, 1-bromopropan-2-ol and 2-bromopropanol, identified by means of its ^{1}H NMR, and about 2.5 g of a dark solid residue after distillation. No other peaks were observed in the spectrum.

Experiment 5. The Reaction of Bromine with 1-Phenoxy-2,3-epoxypropane in Dichloromethane in the Presence of 20 mol% o-Phenylenediamine

Freshly distilled 1-phenoxy-2,3-epoxypropane (18.8 g, 125 mmol) was dissolved in 100 cm^3 CH_2Cl_2. Next, a solution of 6.4 cm^3 Br_2 (125 mmol) in 30 cm^3 CH_2Cl_2 was added dropwise (60 min) to the above mixture at about 20°C (water bath). The reaction was slightly exothermic, and the yellow-brown color disappeared immediately after addition of each drop of bromine. Then, the reaction mixture was stirred 2 h at the same temperature, a sample of 0.15 cm^3 of the reaction mixture was withdrawn, evaporated in *vacuo* from a warm water bath (below 40°C), dissolved in 0.50 cm^3 $CDCl_3$, and its ^{1}H NMR spectrum was measured. The spectrum clearly indicated on the presence of 1-bromo-3-(4-bromophenyl)propan-2-ol only. The rest of the reaction mixture was evaporated in *vacuo* from a warm water bath (finally about 100°C) to leave 38.4 g (99%) of a dense oily residue of crude 1-bromo-3-(4-bromophenyl)propan-2-ol. ^{1}H NMR ($CDCl_3$): $\delta = 2.54$ (bs, 1H, OH), 3.59 (dd, 1H, 1/2 CH_2Br, $J = 5.6$, 10.5 Hz), 3.64 (dd, 1H, 1/2 CH_2Br, $J = 5.1$, 10.5 Hz), 4.04 (dd, 1H, 1/2 CH_2O, $J = 5.4$, 8.0 Hz), 4.07 (dd, 1H, 1/2 CH_2O, $J = 3.8$, 8.0 Hz), 4.18 (dddd, quasi quinted, 1H, CH–OH, $J = 3.8$, 5.1, 5.4, 5.6 Hz), 6.80 (d, 2H, $J = 9.0$ Hz), 7.39 (d, 2H, $J = 9.0$ Hz).

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[5] 10 or even 20 mol% of *o*-phenylenediamine is obviously not enough for optimum yields of iodohydrins. First of all, this is inconsistent with stoichiometry of the oxidation of *o*-phenylenediamine by iodine, which could give only six hydrogen iodide molecules per two moles of *o*-phenylenediamine. According to the reaction described in Scheme 1, two moles of *o*-phenyl-

enediamine give six moles of hydrogen iodide, therefore the proper stoichiometry should be two moles of *o*-phenylenediamine per three moles of iodine (and respectively six moles of epoxide). It is not less than 33 mol%. Another question remains: if the *o*-phenylenediamine is only a catalyst but not a reagent, where the hydrogens came from?

[6] Since the reaction of *o*-phenylenediamine with bromine has never been described, the stoichiometry of this reaction is not known. However, it should not exceed 4 moles of Br_2 per mol of *o*-phenylenediamine.

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