Comments on a Conversion of Epoxides to Halohydrins with Elemental Halogen Catalyzed by Phenylhydrazine: Tandem Electrophilic Halogenation of Aromatic Compounds and Epoxide Ring Opening to Halohydrins

Miroslaw Soroka,* Waldemar Goldeman, Piotr Malysa, Monika Stochaj
Politechnika Wroclawska, Instytut Chemii Organicznej, Biochemii i Biotechnologii, Wybrzeże Wyspińskiego 27, 50370 Wroclaw, Poland
Fax +48(71)3284064; E-mail: soroka@kchf.ch.pwr.wroc.pl
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Abstract: The halogenation of aromatic compounds by bromine or chlorine in the presence of an epoxide gives the corresponding halogenated aromatics and 2-halohydrins, both with good yields.

Key words: epoxides, halogenation, chlorohydrins, bromohydrins, arenes, bromine

The ring-opening reaction of epoxides to halohydrins seems to be still a current problem in preparative organic chemistry. Searching in common databases gives more than fifty papers concerning the preparation of 2-haloalkanols via ring-opening of epoxides, in the past 15 years.1 Recently, we found an interesting paper2 published in this journal, describing a conversion of epoxides to halohydrins with elemental halogens ‘catalyzed by phenylhydrazine.’ The authors proposed a four-step mechanism for this reaction to explain their findings, where the phenylhydrazine plays an essential role as a ‘catalyst.’ Since the authors did not isolate the ‘catalyst’ (unreacted phenylhydrazine) after the reaction from the reaction mixture,3 and because it is unlikely that phenylhydrazine – a very reactive aromatic compound and reducing agent – could survive in the presence of epoxide and in contact with molecular chlorine, bromine, or iodine, we decided to analyse and reinvestigate this reaction. The results of our investigation can be summarized as follows.

(a) We found that the phenylhydrazine is a reagent but not a catalyst. When we repeated the reaction described by Sharghi and Eskandari,2 we found no phenylhydrazine in the reaction products but only many halogenated aromatic compounds (from monobromo to tetrabromo), identified by GC/MS (see experimental part).

(b) The phenylhydrazine reacts with molecular halogen via electrophilic halogenation and redox reaction giving a mixture of products.4–7

(c) Therefore, the only effect of the application of phenylhydrazine in this protocol2 is the generation of hydrogen halogenide ‘in situ’; the phenylhydrazine and molecular halogen is just a ‘generator’ of hydrogen halogenide in this reaction.8

(d) Finally, the intermediate hydrogen halogenide reacts instantly with the epoxide present in the reaction mixture to give 2-halohydrin as the sole isolated product.9

During the reinvestigation of the paper by Sharghi and Eskandari,2 we realized that it is possible to combine any halogenation reaction with the ring opening of epoxides.10,11 Moreover, the evolution of hydrogen halogenide as a side product is one of the main problems in many halogenation reactions. It causes not only loss of about 50% of the halogen in the form of HX, but also causes some practical and environmental concerns, amongst them the necessity of neutralization of these very acidic by-products.

In this paper, we describe a few examples of a useful tandem electrophilic halogenation and ring opening of epoxides by hydrogen halogenide generated in situ (Scheme 1).

When we applied this concept to the reactions, well known from basic organic chemistry, namely the bromination of acetanilide, anisole, 2-naphthol and naphthalene, in the presence of a typical epoxide (ethylene, propylene, and butylene oxide), we observed in all cases almost quantitative yields of bromoarenes and corresponding bromohydrins (assayed by NMR). Both compo-
nents could be very easily isolated, by simple or fractional distillation of the reaction mixture, without the necessity for any chromatographic separations. In all cases, we obtained reasonable yields of the desired products with the expected regioselectivity. Also, the chlorination gave similar results.

Only iodine, which is a not a sufficiently electrophilic reagent for the iodination of aromatics, gave neither iodoaromatics nor iodoxydrines in our hands.\(^{12}\)

In conclusion, for the preparation of 2-halohydrins from epoxides we advise to combine this process with any useful halogenation of an organic compound, mainly aromatics, instead of using phenylhydrazine as was described by Sharghi and Eskandari.\(^2\) Such a tandem reaction gives high yields of both products with a good ‘atom economy’ and is consistent with modern trends towards ‘green chemistry.’ Some results of our investigations are presented in Table 1.

NMR spectra were recorded by Mr Paweł Dąbrowski on a Bruker Avance 300 MHz spectrometer locked on deuterium. Chemical shifts [δ (ppm)] were calculated from the chemical shift of the deuterium lock and are not calibrated. FTIR spectra were measured with a Perkin-Elmer 2000 spectrometer using KBr pellets (1/200) by Mrs Elżbieta Mróz, and the mass spectra were measured with a HP8542 gas chromatograph by Dr Andrzej Nosal (both from our institute). Mps were determined on a Boetius microscope with electrical hot plate and are corrected. Dr Andrzej Nosal (both from our institute). Mps were determined on a Boetius microscope with electrical hot plate and are corrected.

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**Table 1** Results of a Tandem Halogenation and Concomitant Epoxide Ring Opening

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Aromatic</th>
<th>Halogen</th>
<th>Yield (%) (ratio) of halohydrins</th>
<th>Yield of halogenoaromatics</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxirane</td>
<td>anisole</td>
<td>Br(_2)</td>
<td>90</td>
<td>78 (4-)</td>
<td>13a</td>
</tr>
<tr>
<td>methyloxirane</td>
<td>anisole</td>
<td>Br(_2)</td>
<td>88 (69:31)</td>
<td>79 (4-)</td>
<td>13a</td>
</tr>
<tr>
<td>methyloxirane</td>
<td>acetonilide</td>
<td>Br(_2)</td>
<td>87 (79:21)</td>
<td>79 (4-)</td>
<td>13b</td>
</tr>
<tr>
<td>methyloxirane</td>
<td>naphthalene</td>
<td>Br(_2)</td>
<td>85 (69:31)</td>
<td>69 (1-)</td>
<td>13c</td>
</tr>
<tr>
<td>methyloxirane</td>
<td>2-naphthol</td>
<td>Br(_2)</td>
<td>79 (73:27)</td>
<td>73 (1,2-)</td>
<td>13d</td>
</tr>
<tr>
<td>ethyloxirane</td>
<td>anisole</td>
<td>Br(_2)</td>
<td>82 (69:31)</td>
<td>69 (4-)</td>
<td>13a</td>
</tr>
<tr>
<td>ethyloxirane</td>
<td>anisole</td>
<td>Cl(_2)</td>
<td>78 (76:24)</td>
<td>77 (4-)</td>
<td>13e</td>
</tr>
</tbody>
</table>

1-Bromopropan-2-ol

GC/MS (column HP-1, 25 m, temperature program 60/1-8-280): \(t_r\) 10.8 min.

NMR (CDCl\(_3\)): \(\delta = 1.25\) (d, 3 H, CH\(_3\)), \(J = 6.3\), 3.29 (dd, 1 H, CH\(_2\)), \(J = 10.3, 6.7\), 3.41 (dd, 1 H, CH\(_2\)), \(J = 10.3, 3.9\), 3.95 (ddq, 1 H, CH\(_2\)), \(J = 6.7, 6.3, 3.9\), 4.4 (br s, OH).

MS (EI, 70 eV): \(m/z\) (%) = 138 (2), 140 (2) [M, M + 2, C\(_3\)H\(_7\)BrO], 123 (9), 125 (10) [M – CH\(_3\)], 93 (5), 95 (5) [CH\(_2\)Br], 59 (23) [M – Br], 45 (100) [C\(_2\)H\(_4\)O].

2-Bromopropanol

NMR (CDCl\(_3\)): \(\delta = 1.60\) (d, 3 H, CH\(_3\)), \(J = 6.8\), 3.62 (dd, 1 H, CH\(_2\)), \(J = 12.2, 6.9\), 3.70 (dd, 1 H, CH\(_2\)), \(J = 12.2, 4.6\), 4.14 (ddq, 1 H, CH, \(J = 6.9, 6.8, J = 4.6\), 4.4 (br s, OH). The ratio of the integrals of methyl groups (at \(\delta = 1.25\) and 1.60) is 80:20.

**Bromobenzene**

\(t_r\) 6.2 min.

MS (EI, 70 eV): \(m/z\) (%) = 156 (71), 158 (70) [M, M + 2, C\(_6\)H\(_5\)Br], 79 (32), 81 (36) [Br], 77 (100) [C\(_6\)H\(_5\)].

2,4,6-Tribromophenylhydrazine

The semi-solid residue after distillation was treated with CCl\(_4\) (15 mL), then the crystalline precipitate was filtered off, washed with CCl\(_4\) (3 × 10 mL), and dried. A crystalline product was obtained, identified as 2,4,6-tribromophenylhydrazine.

Yield: 4.0 g (33%); an analytical sample had mp 119–121 °C (with faint recrystallization before melting); GC/MS \(t_r\) 22.9 min.

FTIR: 3413, 3285, 3073, 1615, 1562, 1541, 1456, 1349, 1289, 1260, 1237, 1233, 1166, 1152, 1054, 860, 732, 707, 674, 548 cm\(^{-1}\).

NMR (acetone-\(d_6\)): \(\delta = 3.22\) (s, 3 H, NH\(_2\)NH\(_2\)), 7.52 (s, 2 H, Ar\(_2\)).

MS (EI, 70 eV): \(m/z\) (%) = 327 (28), 329 (100), 331 (90), 333 (30) [C\(_6\)H\(_4\)BrN, M – NH – Br], 248 (12), 250 (22), 252 (10) [C\(_6\)H\(_4\)BrN, M – NH – Br], 168 (32), 170 (32) [C\(_6\)H\(_4\)BrN, M – NH – Br], 90 (29) [C\(_6\)H\(_4\)N, M – NH – 3 Br].

MS: no molecular ion. Since the MS spectrum was identical with that of 2,4,6-tribromoaniline, we prepared on a column the corresponding hydrazone of acetone with this 2,4,6-tribromophenylhydrazine to confirm the structure.
Acetone 2,4,6-Tribromophenylhydrazine

GC/MS: 7,0 eV; m/z (%): 367 (10), 369 (18), 371 (20), 373 (7) [C₆H₂Br₂N₂, M – CH₃], 352 (33), 354 (100), 356 (82), 358 (28) [C₆H₄Br₂N₂, M – 2 CH₃].

GC/MS (EI, 70 eV): there are more than 20 signals in the NMR spectrum, the most intense in the aromatic region are: 7.18 (s), 6.82 (d), 7.37 (d), 7.42 (s) and 7.63 (s), but there are no peaks of phenylhydrazine at δ = 7.21 (t), 6.76 (d + t).

GC/MS: there are more than 20 peaks. However, there are no peaks from phenylhydrazine. Since most of the MS spectra show no signal of molecular ions, we were not able to find the exact structures, so we present only the most representative fragments derived from the highest peaks on the total ion chromatogram.

NMR (CDCl₃): there are more than 20 signals in the NMR spectrum, the most intense in the aromatic region are: 7.18 (s), 6.82 (d), 7.37 (d), 7.42 (s) and 7.63 (s), but there are no peaks of phenylhydrazine at δ = 7.21 (t), 6.76 (d + t).

GC/MS (EI, 70 eV) (τg, 13.8 min): m/z (%) = 197 (8), 199 (7) [C₆H₂Br₂N₂], 169 (25), 171 (24) [C₆H₄Br₂N₂, M – CH₃], 90 (100) [C₆H₆N] (no molecular ion).

GC/MS (EI, 70 eV) (τg, 20.9 min): m/z (%) = 292 (6), 294 (9), 296 (4) [C₆H₄Br₂N₂], 172 (100), 174 (96) [C₆H₄Br₂N₂] (no molecular ion).

2,4,6-Tribromophenylhydrazine

GC/MS (EI, 70 eV) (τg 22.6 min): m/z (%) = 327 (35), 329 (100), 331 (98), 333 (32) [C₆H₄Br₂N₂, M – NH], 248 (17), 250 (30), 252 (16) [C₆H₄Br₂N₂, M – NH – Br], 168 (34), 170 (34) [C₆H₄Br₂N₂, M – NH – 2 Br], 90 (46) [C₆H₄N, M – NH – 3 Br] (no molecular ion).

GC/MS (EI, 70 eV) (τg, 28.3 min): m/z (%) = 445 (3), 447 (9), 449 (13), 451 (9), 453 (2) [C₆H₄Br₂N₂], 352 (40), 354 (100), 356 (92), 358 (29) [C₆H₄Br₂N₂] (no molecular ion).

All fragments of mass spectra clearly indicate the presence of brominated compounds.

Tandem Halogenation and Epoxide Ring Opening; General Procedure

To a stirred solution of epoxide (0.10 mol) and aromatic compound (0.10 mol) in CH₂Cl₂ (25 mL), a solution of bromine (16.0 g, 0.10 mol) in CH₂Cl₂ (25 mL) was added dropwise (about 30 min) at 10 °C (ice–H₂O bath was necessary since the reaction was exothermic). The reaction mixture was stirred to reach a temperature of about 25 °C, then kept for a further 1 h the same temperature. The solvent was evaporated, then the products were distilled off or fractionated under reduced pressure. All compounds prepared according to this procedure are known and were identified by means of NMR.

In the case of chlorination, an analogous procedure was applied except that gaseous chlorine was bubbled through a cooled and stirred solution of the epoxide (0.10 mol) and aromatic compound (0.10 mol) in CH₂Cl₂ (50 mL).

References

(1) Since citation of more than 50 papers in this short article is not appropriate, we are ready to send a copy of a text file with the citations to interested readers.
(3) For concluding that the phenylhydrazine is a catalyst, it is necessary to find it, or better to isolate it, or much better to use it again, after reaction.
(6) The substitution of the NH₂ moiety by iodine was described by Joshi, as well as by: (a) Brady, O. L.; Bowman, J. H. J. Chem. Soc. 1921, 119, 896. (b) Meyer, E. J. Prakt. Chem. 1887, 36, 115.
(8) Sharghi and Eskandari concluded that 10 mol% of phenylhydrazine is enough to obtain optimum yields of halohydrins. This is inconsistent with the stoichiometry of the total possible bromination and oxidation of phenylhydrazine which could give only eight HBr molecules (PhNH₂ + 7 Br₂ = C₆H₄Br₃ + N₂ + 8 HBr). However, we did not observe more than tetrabrominated products in the reaction mixture. Since the main product is 2,4,6-tribromophenylhydrazine, the proper stoichiometry should be at least one mole of phenylhydrazine per three moles of bromine (and respectively 3 mol of epoxide).
(9) If our conclusion is correct, Sharghi and Eskandari2 should observe the same or similar regioselectivity in their reaction as in a common ring opening by hydrogen halogenides. However, some of the results described in Table 2 of ref.2 are hard to understand, since in many cases the regioselectivities recorded are opposite those indicated by the mechanism of the ring opening reaction of epoxides and, therefore, should be re-analysed.
(10) There are many examples of using epoxides as hydrogen halogenide scavengers or a specific kind of ‘terminating’ base. The side products of those reactions are usually halohydrins. For example, epoxides were extensively used for the precipitation of amino acids from their hydrochlorides or hydrobromides, see: (a) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. J. Org. Chem. 1990, 55, 3068. (b) Jackson, R. F. W.; Turner, D.;

(12) Since phenylhydrazine is oxidized by iodine into phenyldiazonium iodide and HI as a side product, it is hard to understand the stoichiometry of the reaction described: there are only three molecules of hydrogen iodide per mole of phenylhydrazine (PhNHNH₂ + 2 I₂ = PhN₂I⁻ + 3 HI).