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

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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-halogenoalkanols via ring-opening of epoxides, in the past 15 years.[1] Recently, we found an interesting paper[2] 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]

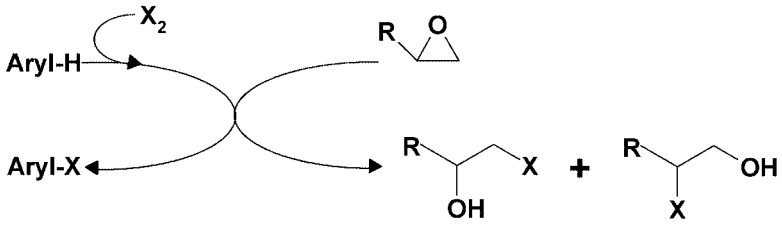
(c) Therefore, the only effect of the application of phenylhydrazine in this protocol[2] is the generation of hydrogen halogenide 'in situ'; the phenylhydrazine and molecular halogen is just a 'generator' of hydrogen halogenide in this reaction.[8]

(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-



Scheme 1

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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 iodohydrins 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 Mróž, and the mass spectra were measured with a HP8542 mass detector coupled with 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. The molecular structures of all known compounds were confirmed by taking their NMR spectra. The required epoxides were acquired from a local manufacturer. All reagents and solvents were of commercial quality and purchased from a local supplier (POCh Gliwice). The procedures described in this paper were not optimized.

Reaction of Bromine with Methyloxirane in the Presence of Phenylhydrazine

Methyloxirane (5.8 g, 0.10 mol) was added to a stirred solution of phenylhydrazine (3.2 g, 0.030 mol)[8] in CH_2Cl_2 (25 mL) at 10 °C (ice–H_2O bath). Then, a solution of bromine (16.0 g, 0.10 mole) in CH_2Cl_2 (25 mL) was added dropwise (30 min) to the mixture at the same temperature. The reaction mixture was stirred to reach a temperature of about 25 °C and kept additionally for 1 h at the same temperature. The solvent and unreacted bromine were evaporated, then the dark-brown products were distilled off under reduced pressure from a water bath to give 13.9 g of a distillate boiling at 65–72 °C/14 Torr, which contains 1-bromopropan-2-ol and 2-bromopropanol in a 80:20 ratio (calculated from the NMR spectra), and traces of aromatic compounds from which only bromobenzene was identified by GC/MS.

1-Bromopropan-2-ol

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

NMR ($CDCl_3$): δ = 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, *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_3H_7BrO], 123 (9), 125 (10) [M – CH_3], 93 (5), 95 (5) [CH_2Br], 59 (23) [M – Br], 45 (100) [C_2H_5O].

2-Bromopropanol

NMR ($CDCl_3$): δ = 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 δ = 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_6H_5Br], 79 (32), 81 (36) [Br], 77 (100) [C_6H_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, 1227, 1054, 860, 732, 707, 674, 548 cm^{-1}.

NMR (acetone-d_6): δ = 3.22 (s, 3 H, $NHNH_2$), 7.52 (s, 2 H, ArH_2).

MS (EI, 70 eV): *m*/*z* (%) = 327 (28), 329 (100), 331 (90), 333 (30) [$C_6H_4Br_3N$, M – NH], 248 (12), 250 (22), 252 (10) [$C_6H_4Br_2N$, M – NH – Br], 168 (32), 170 (32) [C_6H_4BrN, M – NH –2 Br], 90 (29) [C_6H_4N, 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.

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

Epoxide	Aromatic	Halogen	Yield (%) (ratio) of halohydrins	Yield of halogenoaromatics	Ref.
oxirane	anisole	Br_2	90	78 (4-)	[13a]
methyloxirane	anisole	Br_2	88 (69:31)	79 (4-)	[13a]
methyloxirane	acetanilide	Br_2	87 (79:21)	79 (4-)	[13b]
methyloxirane	naphthalene	Br_2	85 (69:31)	69 (1-)	[13c]
methyloxirane	2-naphthol	Br_2	79 (73:27)	73 (1,2-)	[13d]
ethyloxirane	anisole	Br_2	82 (69:31)	69 (4-)	[13a]
ethyloxirane	anisole	Cl_2	78 (76:24)	77 (4-)	[13e]

Acetone 2,4,6-Tribromophenylhydrazone
GC/MS: t_R 20.4 min.

MS (EI, 70 eV): *m*/*z* (%) = 367 (10), 369 (18), 371 (20), 373 (7) [$C_8H_6Br_3N_2$, M – CH_3], 352 (33), 354 (100), 356 (82), 358 (28) [$C_7H_3Br_3N_2$, M – 2 CH_3],

232 (8), 234 (18), 236 (9) [$C_6H_2Br_2$], 153 (18), 155 (16) [C_6H_2Br], 74 (32) [C_6H_2] (no molecular ion at 382/384/386/388).

The collected filtrates were evaporated to leave an oily dark residue (2.5 g), which was analyzed by means of NMR and GC/MS. No phenylhydrazine was found. The oil is a mixture of more than 12 compounds, mainly brominated phenylhydrazines and products, which could be derived from brominated phenyldiazonium salts, such as brominated benzenes and brominated phenylazophenylhydrazines.[4,5]

NMR ($CDCl_3$): there are more than 20 signals in the NMR spectrum, the most intense in the aromatic region are: δ = 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.

GC/MS (EI, 70 eV) (t_R 13.8 min): *m*/*z* (%) = 197 (8), 199 (7) [$C_6H_4BrN_3$], 169 (25), 171 (24) [C_6H_4BrN], 90 (100) [C_6H_4N] (no molecular ion).

GC/MS (EI, 70 eV) (t_R 20.9 min): *m*/*z* (%) = 292 (6), 294 (9), 296 (4) [$C_6H_6Br_2N_4$], 172 (100), 174 (96) [C_6H_7BrN] (no molecular ion).

2,4,6-Tribromophenylhydrazine
GC/MS (EI, 70 eV) (t_R 22.6 min): *m*/*z* (%) = 327 (35), 329 (100), 331 (98), 333 (32) [$C_6H_4Br_3N$, M – NH], 248 (17), 250 (30), 252 (16) [$C_6H_4Br_2N$, M – NH – Br], 168 (34), 170 (34) [C_6H_4BrN, M – NH – 2 Br], 90 (46) [C_6H_4N, M – NH – 3 Br] (no molecular ion).

GC/MS (EI, 70 eV) (t_R 28.3 min): *m*/*z* (%) = 445 (3), 447 (9), 449 (13), 451 (9), 453 (2) [$C_6HBr_4N_2$], 352 (40), 354 (100), 356 (92), 358 (29) [$C_6HBr_3N_3$] (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 CH_2Cl_2 (25 mL), a solution of bromine (16.0 g, 0.10 mol) in CH_2Cl_2 (25 mL) was added dropwise (about 30 min) at 10 °C (ice–H_2O 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 CH_2Cl_2 (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.
(2) Sharghi, H.; Eskandari, M. M. *Synthesis* **2002**, 1519.
(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.
(4) There are two possibilities: electrophilic halogenation of phenylhydrazine, and the oxidation of phenylhydrazine by halogen. Both reactions give hydrogen halogenide as a side product. Therefore, the reaction of arylhydrazines with chlorine or bromine gave a mixture of chlorination/bromination and oxidation products, mainly aryldiazonium salts, and the products thereof. We found some precedents in the literature. For examples, see: (a) Chattaway, F. D.; Hodgson, G. D. *J. Chem. Soc.* **1916**, 583. (b) Chattaway, F. D. *J. Chem. Soc.* **1908**, 852. (c) Chattaway, F. D. *J. Chem. Soc.* **1909**, 862. (d) Michaelis, L. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2190. (e) Vaubel, W. *J. Prakt. Chem.* **1894**, *49*, 540.
(5) The oxidation of arylhydrazines to diazonium salts by bromine were exploited as a preparative way for substitution of the $NHNH_2$ moiety by bromine. For examples, see: (a) Callander, D. D.; Coe, P. L.; Tatlow, J. C. *Tetrahedron* **1966**, *22*, 419. (b) Field, L. D.; Hambley, T. W.; Pierens, G. K. *Tetrahedron* **1990**, *46*, 7069. (c) Joshi, S. S.; Deorha, D. S. *J. Chem. Soc.* **1957**, 2414.
(6) The substitution of the $NHNH_2$ moiety by iodine was described by Joshi,[5c] 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.
(7) Also, the application of halogens for the oxidation of N,N′-disubstituted hydrazines to azo compounds is a well-documented fact. See for example: (a) Overberger, C. G.; Pao-Tung, H.; Berenbaum, M. B. *Org. Synth. Coll. Vol. IV*; Wiley: London, **1966**, 66. (b) Rabjohn, N. *Org. Synth. Coll. Vol. III*; Wiley: London, **1966**, 375.
(8) Sharghi and Eskandari[2] 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 ($PhNHNH_2 + 7\ Br_2 = C_6Br_6 + N_2 + 8\ HBr$). 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 Eskandari[2] 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 to 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.;

Block, M. H. *J. Chem. Soc., Chem. Commun.* **1995**, 2207. (c) Chambers, J. R.; Isbell, A. F. *J. Org. Chem.* **1964**, *29*, 832.

(11) For other, more sophisticated examples, see: (a) Sato, K.; Kojima, Y.; Sato, H. *J. Org. Chem.* **1970**, *35*, 2374. (b) Isaacs, N. S.; Kirkpatrick, D. *Tetrahedron Lett.* **1972**, 3869. (c) Hartshorn, M. P.; Jones, E. R. H. *J. Chem. Soc.* **1962**, 1312. (d) Kirk, D. N.; Patel, D. K.; Petrow, V. *J. Chem. Soc.* **1956**, 627. (e) Hunsberger, I. M.; Tien, J. M. *Chem. Ind.* **1959**, 88. (f) Buddrus, J. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 536; *Angew. Chem.* **1968**, *80*, 535. (g) Buddrus, J. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1041; *Angew. Chem.* **1972**, *84*, 1173. (h) Weyerstahl, P.; Klamann, D.; Finger, C.; Nerdel, F.; Buddrus, J. *Chem. Ber.* **1967**, *100*, 1858.

(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 [2] – there are only three molecules of hydrogen iodide per mole of phenylhydrazine ($PhNHNH_2 + 2\ I_2 = PhN_2^+I^- + 3\ HI$).

(13) (a) *Organikum*; Fichte, B., Ed.; VEB Deutscher Verlag der Wissenschaften: Berlin, **1977**, 384. (b) Vogel, A. I. *Textbook of Practical Organic Chemistry*; Longman: London, **1978**, 585. (c) Clarke, H. T.; Brethen, M. R. *Org. Synth. Coll. Vol. I*; Wiley: London, **1966**, 121. (d) Koelsch, C. F. *Org. Synth. Coll. Vol. III*; Wiley: London, **1966**, 132. (e) Barber, H. J.; Fuller, R. F.; Green, M. B. *J. Appl. Chem.* **1953**, *3*, 409.