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Discussion

Comments on a facile conversion of epoxides to halohydrins with elemental halogen using isonicotinic hydrazide (isoniazide) as a new catalyst—a reinvestigation

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Abstract

The reaction of epoxides with bromine or iodine in the presence of isonicotinic hydrazide gives in fact the corresponding 2-halohydrins with reasonable yields, but contrary to the literature statement [H. Sharghi, M.M. Eskandari, R. Ghovami, J. Mol. Catal. A: Chem. 215 (2004) 55–62] the isonicotinic hydrazide is not a catalyst—it is just a stoichiometric reagent which reacts with 2 mol of halogene to give quantitatively the nitrogen, and to generate the hydrogen halogenide, which is a real epoxide ring opening compound.

Keywords: Oxiranes; Ring opening; Halohydrins; Bromohydrins; Hydrazide oxidation by halogens

The ring-opening reaction of epoxides to halohydrins is still a current problem in preparative organic chemistry. Searching databases brings more than 50 papers concerning the preparation of 2-halogenoalkanols via ring-opening of epoxides, most of them by means of catalysts, in last years [1]. Lately, we found a paper [2] published in this journal, describing a conversion of epoxides to halohydrins with bromine or iodine catalyzed by isonicotinic hydrazide. Authors proposed a four steps mechanism for this reaction, in which the isonicotinic hydrazide plays an essential role as a catalyst. Their conclusion was supported by citing the literature precedents, measurement of UV spectra, and some kinetic data. Additionally, they described the isolation of the products as well as the catalyst. For example, the authors stated in their paper that: "The catalysts were easily recovered and could be reused several times". They also described the recovery of catalyst by "crystallization in diethyl ether, then after cooling the catalyst was filtered off and washed with cold ether". However, the structure of the "recovered catalyst" (unreacted isonicotinic hydrazide) was not confirmed.

Since it is unlikely that isonicotinic hydrazide—a very reactive compound and also reducing agent, could survive in the presence of epoxide, and in contact with oxidizing reagents like molecular bromine or iodine [3], we decided to reinvestigate this reaction. The results of our investigation are summarized below:

1. When we repeated the reaction of methyloxirane [4] with iodine in tetrahydrofuran, in the presence of 10 mol% of isonicotinic hydrazide as described by Sharghi et al. [2] we found in fact the iodohydrin, but no isonicotinic hydrazide in the reaction mixture after reaction. Instead, we observed a vigorous nitrogen evolution, and some derivatives of isonicotinic acid, namely polytetrahydrofuran [5] isonicotinate, identified and assayed by means of H NMR (see Section 1.1). Therefore, the isonicotinic hydrazide is not a catalyst but just a stoichiometric reagent.
2. By simple titration of residual iodine, we estimated the stoichiometry of the reaction as 2 mol of iodine per mol of isonicotinic hydrazide. Our observation is in opposition to that described in the paper [2] where a 10 mol% of catalyst was used [6].
3. When we replaced tetrahydrofuran by dichloromethane (to avoid a polymerisation of tetrahydrofuran), and

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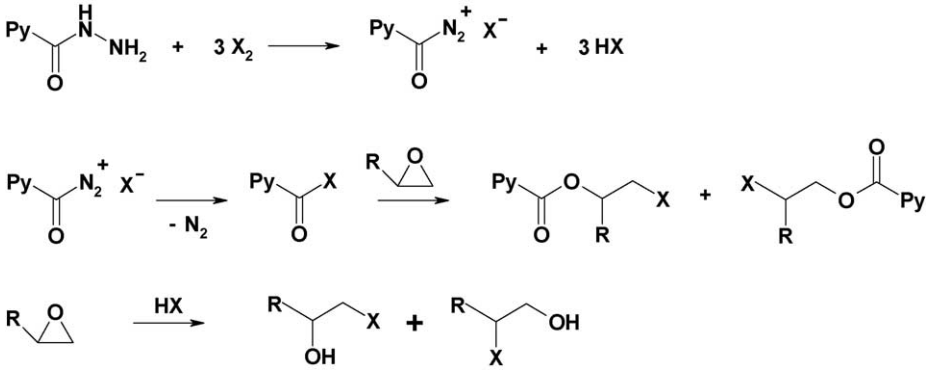
applied stoichiometrical amount of iodine, and stoichiometrical amount of isonicotinic hydrazide (Section 1.2), we observed almost quantitative yield of nitrogen, and iodohydrins, and iodohydrins isonicotinates in about 5:1 molar ratio.

4. Also the reaction with bromine in tetrahydrofuran in the presence of 10 mol% of isonicotinic hydrazide (Section 1.3) gave us almost quantitative amount of nitrogen, bromohydrins and a huge amount of polytetrahydrofuran which contains the isonicotinyl groups.
5. A similar reaction with stoichiometric amounts of bromine, isonicotinic hydrazide and methyloxirane in dichloromethane (Section 1.4), gave almost quantitative yield of nitrogen, bromohydrins and their isonicotinates in about 5:2 molar ratio.
6. In the independent experiment (Section 1.5) we confirmed that the isonicotinic hydrazide reacts with molecular bromine via redox reaction giving nearly stoichiometric amount of nitrogen, 3 mol of hydrogen bromide, and about 1 mol of isonicotinyl bromide hydrobromide—products which could be derived from intermediate isonicotinylium cation. Addition of methanol to this reaction mixture containing isonicotinyl bromide hydrobromide gave us methyl isonicotinate with good yield. Obviously, an addition of methyloxirane to the reaction mixture after bromination of isonicotinic hydrazide (Section 1.6) gave the same products as in experiment 4, namely bromohydrins, and their isonicotinates, in about 6:1 molar ratio, with a similar ratio of regioisomers.

Therefore, the only effect of application of isonicotinic hydrazide in the Sharghi et al. protocol [2] is "in situ" generation of hydrogen halogenide. In other words, the isonicotinic hydrazide is not the catalyst but stoichiometric reagent, which reduces molecular halogen to the hydrogen halogenide. The hydrogen halogenide reacts instantly with epoxide present in the reaction mixture to give 2-halohydrin as a sole isolated product described [2]. Also the acylium cation derived from isonicotinic hydrazide opens the oxirane as well as tetrahydrofuran, to give, respectively, esters of both isomers of halohydrin, and polytetrahydrofuran nicotinate—the products missed by Sharghi et al.

Our findings could be illustrated by scheme:



Some times ago [7] we combined halogenation reactions with epoxide ring opening. In many cases we observed almost quantitative yields (assayed by NMR) of halogenated product and corresponding halohydrins. However, there is no reason to use the isonicotinic hydrazide nor any hydrazide, in a similar reaction, since they gave additional side products.

In conclusion, since we found that the isonicotinic hydrazide (isoniazide) reacts with elemental bromine or iodine to give 1 mol of isonicotinyl halogenide hydrohalogenide (via isonicotinyldiazonium halogenide), 1 mol of nitrogen, and 3 mol of hydrogen halogenide, all authors measurements, discussion, and conclusions concerning the catalytic effect of isonicotinic hydrazide must be simply wrong. The only role the isonicotinic hydrazide plays in this protocol is just generating of hydrogen halogenide which in situ reacts with epoxide present in the reaction mixture. However, we do not recommend this protocol, because theoretically as much as 25% of halogene (and epoxide) is lost as side products, namely the halohydrins isonicotinates.

WARNING! We would also like to warn readers about dissolving bromine in tetrahydrofuran (sic!), what causes a very energetic reaction [8], sometimes with splashing of the reaction mixture, especially when it is not cooled and stirred enough. Generally, using the tetrahydrofuran as a solvent for any reaction with a strong electrophilic reagent should be avoided.

1. Experimental

NMR spectra were recorded by Mr. Rafał Kozicki on a Bruker Avance 300 MHz spectrometer locked on deuterium. Chemical shifts (δ [ppm]) were calculated from chemical shift of deuterium lock and were not calibrated. FTIR spectra were measured on Perkin Elmer 2000 spectrometer in KBr pellets (1/200) by Mrs. Elżbieta Mróź. The mass spectra were measured on HP8542 mass detector coupled with HP8542 gas chromatograph, by Dr. Andrzej Nosal. Elemental analyses were done by Mrs. Czesława Andrzejewska. Melting points were determined on the Boetius microscope with electrical hot plate and were corrected. The structures of all compounds were derived from H NMR spectra. The evolution of nitrogen was assayed by means of a gas burette. The methyloxi-

rane was acquired from local manufacturer. All reagents and solvents were of commercial quality and purchased from local supplier (POCh Gliwice).

1.1. Experiment 1. The reaction of iodine with methyloxirane in tetrahydrofuran, in the presence of "catalytic" amount of isonicotinic hydrazide—a reinvestigation

Methyloxirane (2.9 g, 50 mmol) was added to a stirred solution of isonicotinic hydrazide (0.70 g, 5.0 mmol) in tetrahydrofuran (25 mL) at 10 °C (ice-water bath). Next, a solution of iodine (12.7 g, 50 mmol) in tetrahydrofuran (30 mL) was added dropwise (30 min) to the above mixture at the same temperature. At the beginning the iodine disappeared, then the solution remained dark. The gaseous nitrogen evolving from the reaction mixture was collected in gas burette connected to the reaction flask by silicon tube. The reaction mixture was stirred to reach the temperature about 25 °C and kept for 1 h more at the same temperature. A 100 mL of nitrogen was collected at temperature 27 °C (4.1 mmol, 82% yield). Then, the mixture after reaction was titrated by means of 1.00 M solution of $Na_2S_2O_3$ in water. About 72 mL of this solution was necessary to titrate an excess of iodine, thereafter as much as 36 mmol of iodine remained inreacted, so the stoichiometry of the reaction of isonicotinic hydrazide to iodine is about 1:2. The mixture was extracted with dichloromethane (1×100 mL, then 3×20 mL), organic phases were collected and dried over Na_2SO_4 (20 g), filtered and evaporated under vacuo from warm water bath (below 40 °C) to give oily residue (7.0 g) identified and assayed by means of NMR as the mixture of iodohydrins—1-iodopropan-2-ol and 2-iodopropanol in 84/16 ratio (based on integrals of the corresponding methyl groups at 1.21 and 1.84 ppm), and polytetrahydrofuran (at 1.5–1.6 and 3.3–3.5 ppm, for CH_2 and CH_2–O moieties, respectively). The molar ratio of iodohydrins to polytetrahydrofuran (as a mer) is about 38/62, based on an NMR integrations.

1.2. Experiment 2. The reaction of iodine with methyloxirane in dichloromethane, in the presence of stoichiometric amount of isonicotinic hydrazide

Methyloxirane (2.6 g, 44 mmol) was added to a stirred mixture of isonicotinic hydrazide (1.4 g, 10 mmol) in dichloromethane (20 mL) at 10 °C (ice-water bath). Next, a solution of iodine (5.1 g, 20 mmol) in dichloromethane (100 mL) was added dropwise (30 min) to the above mixture at the same temperature. The gaseous nitrogen evolving from the reaction mixture was collected in gas burette connected to the reaction flask by silicon tube. The reaction mixture was stirred to reach the temperature about 25 °C and kept for 1 h more at the same temperature. About 210 mL of nitrogen was collected (9.4 mmol, 94% yield). Then a sample of 0.10 mL of the reaction mixture was taken, evaporated under vacuo from warm water bath (below 40 °C), dissolved in 0.50 mL of $CDCl_3$, and NMR spectrum was measured, from which the corresponding iodohydrins—1-iodopropan-2-ol and 2-iodopropanol in 76/24 ratio (based on integrals of the corresponding methyl groups at 1.32 and 1.91 ppm), and their isonicotinic acid esters in 69/31 ratio (based on the integrals of corresponding methyl groups at 1.99 and 1.32 ppm), were identified and assayed. The ratio of integrals of a total methyl groups of iodohydrins to their isonicotinates was determined as 84/16. The structure of the 2-iodopropanol was additionally confirmed by GC/MS.

1.3. Experiment 3. The reaction of bromine with methyloxirane in tetrahydrofuran, in the presence of "catalytic" amount of isonicotinic hydrazide—a reinvestigation

Methyloxirane (5.8 g, 100 mmol) was added to a stirred suspension of isonicotinic hydrazide (1.4 g, 10 mmol) in tetrahydrofuran (50 mL) at 10 °C (ice-water bath). Next, a solution of bromine (5.0 mL, 100 mmol) in dichloromethane (20 mL) was added dropwise (30 min) to the above mixture at the same temperature. The gaseous products (mainly nitrogen) evolving from the reaction mixture were collected in gas burette connected to the reaction flask by silicon tube. The reaction mixture was stirred to reach the temperature about 25 °C, and after 15 min the reaction mixture spontaneously started boiling, and temperature reached about 60 °C (sic!). After stirring for 1 h more at the temperature about 25 °C, 0.10 mL of the reaction mixture was taken, dissolved in 0.50 mL of $CDCl_3$ and NMR spectrum was measured, on which only bromohydrins and polytetrahydrofuran were identified. The rest of the mixture after reaction was evaporated under vacuo from warm water bath (below 40 °C) to give oily residue (27.2 g) identified as a polytetrahydrofuran, and a mixture of bromohydrins—1-bromopropan-2-ol and 2-bromopropanol in a 70/30 ratio (based on the integrations of the methyl groups at 1.31 and 1.71 ppm).

1.4. Experiment 4. The reaction of bromine with methyloxirane in dichloromethane, in the presence of stoichiometric amount of isonicotinic hydrazide

Methyloxirane (2.6 g, 44 mmol) was added to a stirred mixture of isonicotinic hydrazide (1.4 g, 10 mmol) in dichloromethane (20 mL) at 10 °C (ice-water bath). Next, a solution of bromine (1.0 mL, 20 mmol) in dichloromethane (10 mL) was added dropwise (30 min) to the above mixture at the same temperature. The gaseous nitrogen evolving from the reaction mixture was collected in gas burette connected to the reaction flask by silicon tube. The reaction mixture was stirred to reach the temperature about 24 °C and kept for 1 h more at the same temperature. About 220 mL of nitrogen was collected (9.8 mmol, 98% yield). Then, a sample of 0.10 mL of the reaction mixture was taken, evaporated under vacuo from warm water bath (below 40 °C), dissolved in 0.50 mL of $CDCl_3$, and NMR spectrum was measured, from

which the corresponding bromohydrins—1-bromopropan-2-ol and 2-bromopropanol in 82/18 ratio (based on the corresponding methyl groups integrals at 1.32 and 1.72 ppm), and their isonicotinic acid esters in 58/42 ratio (at 1.82 and 1.55 ppm, respectively), were identified and assayed. The ratio of a sum of bromohydrins to their isonicotinates was determined as 72/28. Rest of the reaction mixture was filtered (the precipitate was identified as a crude isonicotinyl bromide hydrobromide), and washed with dichloromethane, then the collected filtrates were evaporated to give 4.8 g of semisolid residue, which was crystallized by addition of dichloromethane (5 mL) and ether (5 mL), and kept in the refrigerator overnight. Crystalline material was separated by suction, washed with dichloromethane/ether 1/1 (2×5 mL), and dried on air to give 1.0 g of crystalline product identified as a mixture of 1-bromopropan-2-ol and 2-bromopropanol isonicotinates in 18/82 ratio:

4-PyCOOCH(CH_3)CH_2Br: NMR ($CDCl_3$): 1.56 (d, 3H, CH_3, $J = 6.4$), 3.59 (dd, 1H, CH_2Br, $J = 5.9$, $J = 11.2$), 3.66 (dd, 1H, CH, CH_2Br, $J = 4.4$, $J = 11.2$), 5.43 (ddq, 1H, CH–O, $J = 4.4$, $J = 5.9$, $J = 6.4$), 8.56 (d, 2H, 2-, 6-Py-H, $J = 5.5$), 9.21 (d, 2H, 3-, 5-Py-H, $J = 5.5$). GC/MS: $R_t = 22.66$ min, (EI, 70 eV): *m*/*z* (%): 243 (2), 245 (2) [M, M + 2], 164 (54) [M−Br], 124 (34), 123 (15), 106 (100) [4-PyCO], 78 (59) [4-Py].

4-PyCOOCH_2CH(CH_3)Br: NMR ($CDCl_3$): 1.81 (d, 3H, CH_3, $J = 6.8$), 4.38 (tq, 1H, CHBr, $J = 6.0$, $J = 6.8$), 4.60 (d, 2H, CH_2O, $J = 6.0$), 8.54 (d, 2H, 2-, 6-Py-H, $J = 5.5$), 9.21 (d, 2H, 3-, 5-Py-H, $J = 5.5$). GC/MS: $R_t = 22.76$ min, (EI, 70 eV): *m*/*z* (%): 243 (0.3), 245 (0.3) [M, M + 2], 164 (71) [M−Br], 124 (33), 123 (32), 106 (100) [4-PyCO], 78 (65) [4-Py].

The FTIR of the mixture of both isomers also confirms the structure. The identities of both products were confirmed independently by their synthesis from isonicotinyl chloride hydrochloride and original mixture of 1-bromopropan-2-ol and 2-bromopropanol, as well.

1.5. Experiment 5. The reaction of bromine with isonicotinic hydrazide in dichloromethane

A solution of bromine (2.0 mL, 40 mmol) in dichloromethane (10 mL) was added dropwise (30 min) to a stirred mixture of isonicotinic hydrazide (2.7 g, 20 mmol) in dichloromethane (20 mL) at 10 °C (ice-water bath). The gaseous nitrogen evolving from the reaction mixture was collected in gas burette connected to the reaction flask by silicon tube. The reaction mixture was stirred to reach the temperature about 25 °C and kept for 1 h more at the same temperature. About 300 mL of nitrogen was collected (67% yield). The precipitate of isonicotinyl bromide hydrobromide was filtered of, washed with dichloromethane (4×10 mL), and then introduced to methanol (30 mL) under reflux condenser. After vigorous reaction, the mixture was refluxed for 1 h, then cooled, evaporated under vacuo, and residue was treated with water (100 mL), and neutralized by addition of solid $NaHCO_3$. Organic material was extracted with dichloromethane (1×20, then 3×10 mL), collected extracts were dried over Na_2SO_4 (20 g), filtered, and evaporated to give 1.7 g (63% yield) of methyl isonicotinate, which structure was confirmed by comparison of retention time and mass spectrum with those measured with authentic sample. MS (EI, 70 eV), *m*/*z* (%): 137 (81) [M], 106 (100) [4-PyCO], 78 (100) [4-Py].

1.6. Experiment 6. The reaction of bromine with isonicotinic hydrazide in dichloromethane, then with methyloxirane

A solution of bromine (1.0 mL, 20 mmol) in dichloromethane (10 mL) was added dropwise (30 min) to a stirred mixture of isonicotinic hydrazide (1.4 g, 10 mmol) in dichloromethane (40 mL) at 10 °C (ice-water bath). The gaseous nitrogen evolving from the reaction mixture was collected in gas burette connected to the reaction flask by silicon tube. The reaction mixture was stirred to reach the temperature about 25° C and kept for 1 h more at the same temperature. About 200 mL of nitrogen was collected (89% yield). Then, the mixture was cooled again to about 10 °C (ice-water bath), and methyloxirane (2.6 g, 44 mmol) was added dropwise, the reaction mixture was stirred for additional 1 h, the precipitate was filtered off, and the filtrate was evaporated to give 3.5 g of oily residue identified as a mixture of the corresponding bromohydrins—1-bromopropan-2-ol and 2-bromopropanol in 81/19 ratio (based on the integrals of the corresponding methyl groups at 1.30 and 1.69 ppm), and their isonicotinic acid esters in 65/35 ratio (base on the integrals of methyl groups at 1.79 and 1.51 ppm), were identified and assayed. The ratio of bromohydrins to their isonicotinates was determined as 87/13, also from the corresponding integrals.

References

[1] Since citation of more than 50 papers in this short article is nonsense, we are ready to send a copy of text file with the citations to interested readers.

[2] H. Sharghi, M.M. Eskandari, R. Ghovami, J. Mol. Catal. A: Chem. 215 (2004) 55–62.

[3] (a) The halogenations of isonicotinic hydrazide and the oxidations of isonicotinic hydrazide by halogens were not described in the literature. However, we found some literature precedents concerning the reaction of some aromatic and aliphatic hydrazides with halogens, according to them the reaction of hydrazides with chlorine, bromine or iodine, gave mainly oxidation products, which could be derived from acyldiazonium salts. For example: T. Curtius, J. Prakt. Chem. 50 (1894) 275–294;
(b) T. Curtius, G. Struve, J. Prakt. Chem. 50 (1894) 295–310;
(c) R. Stolle, J. Prakt. Chem. 66 (1902) 332–338.;
(d) A closely related chemistry of substituted hydrazines were extensively reported in the literature. For example, the reactions of arylhydrazine with chlorine or bromine gave a mixture of oxidized and halogenated products: F.D. Chattaway, G.D. Hodgson, J. Chem. Soc. (1916) 582–587;
(e) F.D. Chattaway, J. Chem. Soc. (1908) 852–856;

(f) F.D. Chattaway, J. Chem. Soc. (1909) 862–870;
(g) L. Michaelis, Chem. Ber. 26 (1893) 2190–2197;
(h) W. Vaubel, J. Prakt. Chem. 49 (1894) 540–545;
(i) An oxidation of arylhydrazines to diazonium salts by bromine were applied for the substitution of $-NHNH_2$ moiety by bromine: D.D. Callander, P.L. Coe, J.C. Tatlow, Tetrahedron 22 (1966) 419–432;
(j) L.D. Field, T.W. Hambley, G.K. Pierens, Tetrahedron 46 (1990) 7069–7080;
(k) S.S. Joshi, D.S. Deorha, J. Chem. Soc. (1957) 2414;
(l) The substitution of $-NHNH_2$ moiety by iodine was also described by Joshi and Deorha [3](k) and by: O.L. Brady, J.H. Bowman, J. Chem. Soc. 119 (1921) 894–900;
(m) E. Meyer, J. Prakt. Chem. 36 (1887) 115–116;
(n) An application of halogens for oxidation of *N*,*N*′-disubstituted hydrazines, mainly diacylated hydrazines, to azocompounds is described in Organic Syntheses: C.G. Overberger, H. Pao-Tung, M.B. Berenbaum, Organic Syntheses, coll. vol. IV, pp. 66–67;
(o) N. Rabjohn, Organic Syntheses, coll. vol. III, pp. 375–377.

[4] We have chosen the methyloxirane because it gives products in which all of the methyl groups are separated and easily visible on the NMR spectra.

[5] (a) The polytetrahydrofuran derivatives are the products of ring opening polymerisation of tetrahydrofuran by electrophilic species present in the reaction mixture, namely the isonicotinyl halogenide hydrohalogenide and hydrogen halogenide. The cationic polymerisation of tetrahydrofuran is a very well known reaction, and polytetrahydrofuran itself is a commercially available product. See: P. Dreyfus, Poly(tetrahydrofuran), Gordon & Breach, 1982;
(b) Concise Encyclopedia of Chemical Technology, J. Wiley & Sons, 1985, p. 930.

[6] Sharghi et al. [2] concluded that 10 mol% of isonicotinic hydrazide is enough for optimum yields of halohydrins. This is inconsistent with stoichiometry of the reaction we found, which could give only three HBr molecules: $PyCONHNH_2 + 2X_2 = PyCOX + N_2 + 3HX$. The proper amount should be at least 1 mol of isonicotinic hydrazide per 2 mol of bromine, and respectively 3 mol of epoxide. Addition of a 4 mol of epoxide have to result in obtaining a mol of additional product which could be derived from epoxide ring opening reaction by isonicotinyl halogenide.

[7] M. Soroka, W. Goldeman, P. Małysa, M. Stochaj, Synthesis (2003) 2341–2344.

[8] (a) The reactions of halogens with THF were described many times in the literature. The reaction is usually a self-catalytic, therefore it is an extremely dangerous. For example, see: N.C. Deno, N.H. Potter, J. Am. Chem. Soc. 89 (1967) 3550–3554;
(b) Also the oxiranes could react with halogens, however usually there are no useful products described from such reactions. There are a lot of citations to these reactions, however we found only a few which are worth of note and related to the epoxide ring opening: J. Beger, H. Schiefer, D. Scheller, J. Prakt. Chem. 325 (1983) 719–728;
(c) M.I. Konaklieva, M.L. Dahl, E. Turos, Tetrahedron Lett. 33 (1992) 7093–7096.