

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.

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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

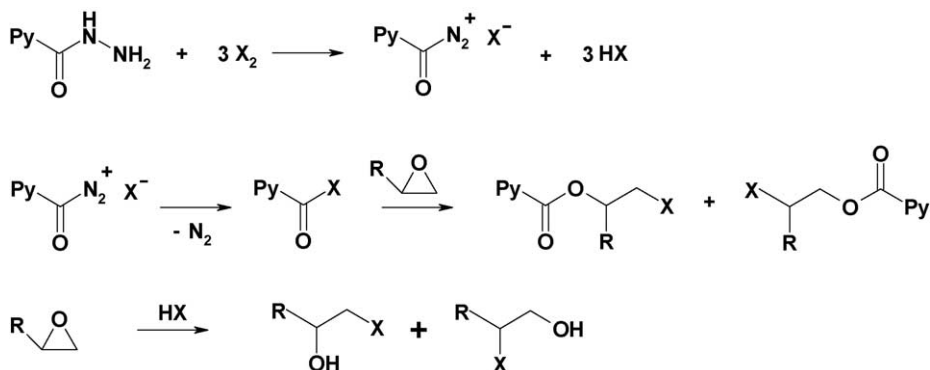
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applied stoichiometrical amount of iodine, and stoichiometrical amount of isonicotinic hydrazide (Section 1.2), we observed almost quantitative yield of nitrogen, and iodohydrins, and iodohydrins isonicotinates in about 5:1 molar ratio.

- 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.
- 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.
- 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 isonicotinylum 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 isonicotinylum cation 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 Mróz. 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 ^1H NMR spectra. The evolution of nitrogen was assayed by means of a gas burette. The methyloxi-

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