Bromination of 1-Hydroxyimidazoles. Synthesis and Crystal Structures

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Bromination of 1-hydroxyimidazole 3-oxide and 1-hydroxy-2-methylimidazole 3-oxide using bromine in acetic acid gave 2-bromo-1,3-dihydroxyimidazole hydrobromide and 4,5-dibromo-1,3-dihydroxy-2-methylimidazole hydrobromide, respectively. In contrast, bromination in aqueous mixture (acetic acid, methanol, dimethylformamide, tetrahydrofuran) yielded 2,4,5-tribromo-1-hydroxyimidazole. Crystal structures of four compounds were determined by X-ray diffraction.

Key words: Bromination, Crystal Structure, Imidazole, *N*-Oxide

Introduction

Bromination of imidazole, first described in 1877 [1], gives 2,4,5-tribromoimidazole [2, 3]; the fully brominated derivative is also obtained from 1-methylimidazole [4, 5]. Different brominating agents and systems are known to effect this transformation [6 – 9]. Dibromo and monobromo compounds have been obtained by selective reduction of tribromo compounds using sodium sulfite [2, 3] or butyllithium [3]. Removal of the most reactive bromine atom in position 2 by a Grignard reagent gave 4,5-dibromo-1-methylimidazole in good yield [5]. These compounds are valuable building blocks for the synthesis of polysubstituted imidazoles [10 – 12]. Polybrominated imidazolium salts are also of interest as constituents of high-density ionic liquids [13]. It is also noteworthy that 2,4,5-tribromoimidazole is a natural product [14] and that trihaloimidazoles possess insecticidal activity [15]. Only a limited number of pertinent crystal structures have been published [16].

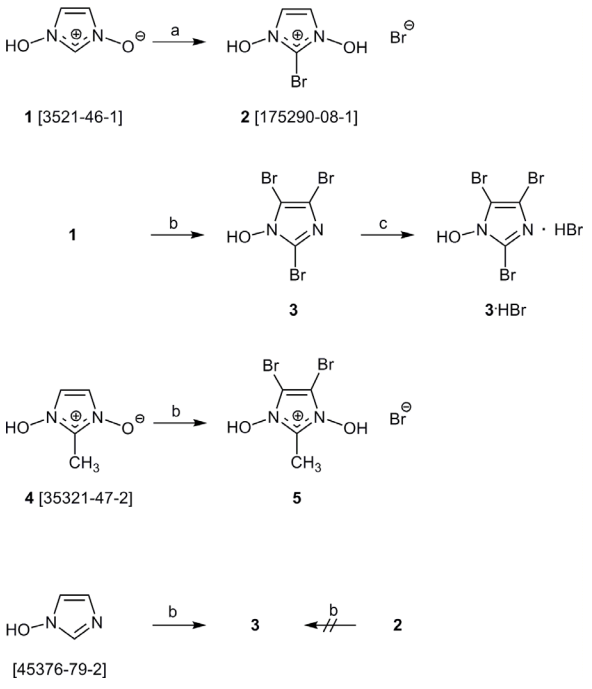
In contrast, oxidation of imidazoles by bromine has been observed in aqueous solution [17] resulting in complete fragmentation of the heterocyclic ring.

1-(Benzyloxy)imidazole, a rare example of an imidazole bearing an *N*-heteroatom substituent, was brominated at all available positions [18]. We have recently reported selective bromination in position 2 of quaternary 1,3-(dialkyloxy)imidazolium salts [19, 20]. The bromination of related 1-hydroxyimidazole-3-oxides has been described [21], but attempts to repeat these experiments gave, in our hands, different results. In our opinion, this situation demanded more research.

Results and Discussion

We examined the bromination of 1-hydroxyimidazole-3-oxides in several solvents. The choice of solvents was limited by the solubility of these very polar compounds. We confirmed that the reported bromination of **1** in acetic acid occurs solely at the 2-position to give crystalline 2-bromo-1,3-dihydroxyimidazolium bromide (**2**) as the sole product (Scheme 1). The yield improved when the reaction was carried out in a more concentrated solution and a longer reaction time was allowed. Perbromination was not observed, even with an excess of bromine. We found no difference when glacial acetic acid was used instead of 96 % acetic acid. Treatment of the 2,4,5-triphenyl derivative with bromine "in alkaline medium" [21] reportedly gave stable radicals [22]. However, the situation in the unsubstituted parent compound **1** can be expected to be quite different.

Astoundingly, bromination of **1** in aqueous mixtures of acetic acid or other solvents (methanol, dimethylformamide, tetrahydrofuran) yielded 2,4,5-tribromo-1-hydroxyimidazole **3** in approximately 10 % yield. Acetic acid procured the best yield (up to 17 %). In pure water, a violent reaction was observed, and the yield of **3** was very low (7 %). Severe degradation of the molecule occurred under these conditions. Ammonium bromide and oxalic acid were identified as the final products (by ^{13}C NMR, IR, reduction of $KMnO_4$,



Scheme 1. a) Br_2, AcOH; b) 3 Br_2, AcOH/H_2O (1 : 2); c) HBr, MeOH.

and X-ray diffraction). Therefore, the modest yield is understandable. The starting material, however, is inexpensive, and the procedure is simple and yields **3** as a crystalline product. Separation of main product and byproducts was straightforward due to their complementary solubilities.

It is assumed that the first step of the reaction involves oxidative cleavage of the N–O bond leading to 1-hydroxyimidazole, which is subsequently perbrominated. This is principally a new synthesis of 1-hydroxyimidazole, but not a practical one. This hypothesis is supported by the fact that, under these conditions, the parent compound 1-hydroxyimidazole, but not the monobromo *N*-oxide **2**, gives the deoxygenated and perbrominated product **3** (Scheme 1). The observation, that half an equivalent of bromine yielded the crystalline hydrobromide of the starting material, was surprising at first but corroborates the picture of the mechanism. The protonated form of **1** did not react at all.

Furthermore, we disproved the reported [21] monobromination of 1-hydroxy-2-methylimidazole 3-oxide (**4**). When treated with one equivalent of bromine in acetic acid, this compound rather gave a mixture of di-brominated product and unchanged starting material. This mixture, perfidiously, cannot be recognized

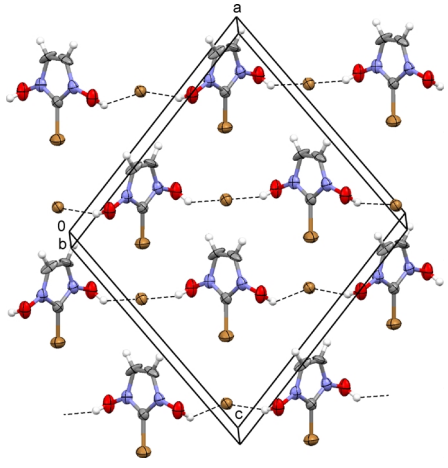


Fig. 1 (color online). Hydrogen bonding in the crystal structure of **2**.

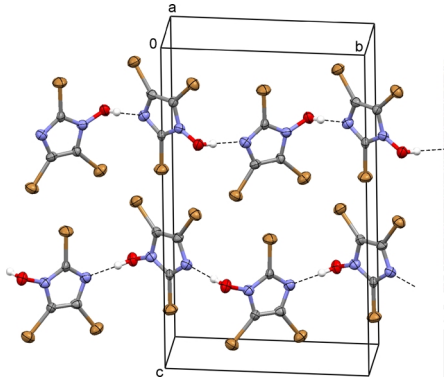


Fig. 2 (color online). Hydrogen bonding in the crystal structure of **3**.

by ^{1}H NMR (at least not in the solvent reported) or elemental analysis. With both methods, the mixture appeared to be a mono-brominated product. The authors of the previous work therefore interpreted their result as a mono-brominated product. We identified the components, however, by ^{13}C NMR spectroscopy. Two equivalents of bromine yielded pure 4,5-dibromo-1,3-dihydroxyimidazolium bromide (**5**), isolated in acceptable yield. When water was used as the solvent, again decomposition of the heterocyclic ring was observed.

Finally, the structure of the new product was confirmed by X-ray diffraction. The crystal structures of the new brominated imidazoles show the expected interionic and intermolecular interactions (Figs. 1 – 4). Thus, the 1,3-dihydroxyimidazolium bromides **2** and **5** exhibit O–H···Br···H–O hydrogen bonds, 1-hydroxyimidazole hydrobromide **3**·HBr shows O–H···Br···H–N, and 1-hydroxyimidazole **3**

Table 1. Hydrogen bonding geometries (Å, deg) with estimated standard deviations in parentheses.

Compound	Interaction	D–H	H···A	D···A	D–H···A	Symmetry code (A)
2a	O1–H···Br2	0.84(9)	2.4(1)	3.106(7)	139(10)	$1/2+x, 1/2-y, 1/2+z$
	O2–H···Br2	0.83(8)	2.28(8)	3.080(6)	162(8)	–
3a	O1–H···Br4	0.84(6)	2.30(6)	3.127(7)	168(6)	–
	N2–H···Br4	0.90(6)	2.43(9)	3.184(9)	143(7)	$x, 1+y, z$
3	O1–H···N2	0.85(2)	1.83(2)	2.681(7)	180(9)	$1-x, -1/2+y, 1/2-z$
5a	O1–H···Br1	0.83(3)	2.29(3)	3.108(4)	170(5)	$1-x, 1/2+y, 1/2-z$
	O2–H···Br1	0.84(6)	2.25(6)	3.060(4)	163(6)	–

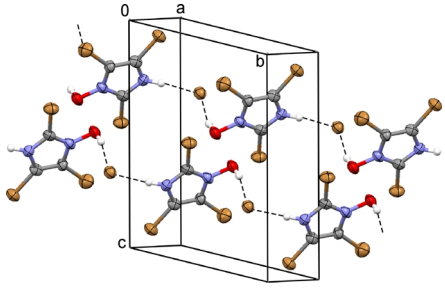


Fig. 3 (color online). Hydrogen bonding in the crystal structure of **3**·HBr.

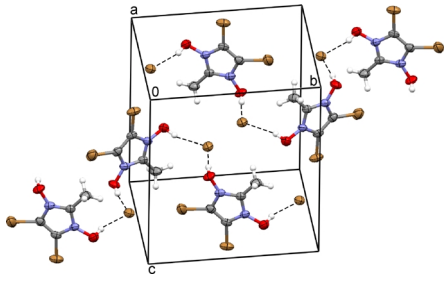


Fig. 4 (color online). Hydrogen bonding in the crystal structure of **5**.

O–H···N contacts. The hydrogen bonding parameters are listed in Table 1.

Conclusion

The choice of solvent was found to be crucial for the outcome of the bromination of 1-hydroxyimidazole 3-oxides. In aqueous solution, N–O bond cleavage and severe degradation of the heterocyclic ring was observed. Oxalic acid and ammonium bromide were identified as the final products. The new tri- and dibromo derivatives are expected to open up interesting pathways in further imidazole chemistry.

Experimental Section

NMR spectra were recorded with a Bruker AC 300 spectrometer. IR spectra were obtained with a Nicolet 5700 FT instrument.

*1,3-Dihydroxyimidazolium bromide (**1**·HBr)*

For spectroscopic comparison, this compound was prepared from **4** and 48 % HBr. M. p., ^{1}H NMR, IR and crystal structure: see ref. [23]. – ^{13}C NMR (75 MHz, [D$_4$]MeOH): δ = 119.6 (2C), 129.9 ppm.

*2-Bromo-1,3-dihydroxyimidazolium bromide (**2**)*

Bromine (5.1 mL, 100 mmol) was added dropwise to a solution of 1-hydroxyimidazole-3-oxide (10.0 g, 100 mmol) in glacial acetic acid (100 mL). The mixture was stirred at ambient temperature for 24 h. The precipitate was filtered off, washed with acetic acid (2 mL), twice with Et_2O (2 × 10 mL), and dried. Yield: 50 %. Single crystals were obtained from MeOH at −20 °C. M. p. 180 °C (181 °C [21]). – ^{1}H NMR (300 MHz, [D$_4$]MeOH): δ = 7.97 (s, 2 H) ppm. – ^{13}C NMR (75 MHz, [D$_4$]MeOH): δ = 117.4, 120.8 (2C) ppm. – IR (neat): ν = 3155 (w), 3136 (w), 2911 (w), 2850 (w), 2767 (m), 2688 (m), 2634 (br m), 1544 (w), 1515 (w), 1418 (w), 1316 (w), 1041 (m), 762 (w), 702 (m), 615 (s) cm^{-1}. – $C_3H_4Br_2N_2O_2$ (259.88): calcd. C 13.86, H 1.55, N 10.78; found C 13.66, H 1.25, N 10.76.

*2,4,5-Tribromo-1-hydroxyimidazole (**3**)*

Bromine (15.4 mL, 300 mmol) was added dropwise to a solution of 1-hydroxyimidazole-3-oxide (10.0 g, 100 mmol) in a mixture of acetic acid (50 mL) and water (100 mL). The mixture was stirred at ambient temperature for 24 h, then kept at 5 °C for 1 h. The precipitate was filtered off, washed with H_2O (50 mL), and dried to constant weight. Yield: 5.3 g (17 %). Single crystals were obtained from acetone/H_2O. M. p. 154 °C. – ^{13}C NMR (75 MHz, [D$_4$]MeOH): δ = 105.5, 112.9, 115.8 ppm. – IR (neat): ν = 2344 (br m), 1653 (w), 1527 (m), 1505 (s), 1378 (s), 1314 (s), 1226 (s), 1127 (m), 995 (s), 863 (m), 746 (m), 599 (m) cm^{-1}. – $C_3HBr_3N_2O$ (320.76): calcd. C 11.23, H 0.31, N 8.73; found C 11.53, H 0.27, N 8.75.

*2,4,5-Tribromo-1-hydroxyimidazole hydrobromide (**3**·HBr)*

This compound was prepared from **3** and 48 % HBr in MeOH. Hygroscopic single crystals were obtained from H_2O. M. p. 199 °C. – ^{13}C NMR (75 MHz, [D$_4$]MeOH):

Table 2. Crystal data and numbers pertinent to data collection and structure refinement of **2**, **3**, **3**·HBr, and **5**.

Compound	**2**	**3**	**3**·HBr	**5**
Formula	$C_3H_4Br_2N_2O_2$	$C_3HBr_3N_2O$	$C_3H_2Br_4N_2O$	$C_4H_5Br_3N_2O_2$
M_r	259.90	320.76	401.71	352.83
Crystal size, mm^3	$0.3 \times 0.05 \times 0.04$	$0.12 \times 0.04 \times 0.04$	$0.25 \times 0.11 \times 0.03$	$0.31 \times 0.15 \times 0.05$
Crystal system	monoclinic	orthorhombic	triclinic	monoclinic
Space group	*Cc*	$P2_12_12_1$	$P\bar{1}$	$P2_1/c$
a, Å	13.4290(2)	3.9509(2)	6.0964(4)	7.4026(4)
b, Å	4.2773(4)	10.1324(4)	7.1078(5)	10.7990(4)
c, Å	12.8093(8)	17.0987(7)	11.3449(7)	11.8247(6)
α, deg	90	90	76.010(4)	90
β, deg	102.818(4)	90	89.610(4)	104.733(3)
γ, deg	90	90	70.580(4)	90
V, Å^3	717.43(8)	684.50(5)	448.42(5)	914.20(8)
Z	4	4	2	4
D_{calcd}, g cm^{-3}	2.41	3.11	2.98	2.56
μ, mm^{-1}	11.2	21.2	17.9	13.2
F(000), e	488	584	364	656
T, K	233	173	233	233
Radiation	MoK_α	CuK_α	MoK_α	MoK_α
hkl range	±15, $-5 \rightarrow 4$, ±15	±4, $-10 \rightarrow 12$, ±20	±7, ±8, ±13	$-8 \rightarrow 9$, ±13, $-14 \rightarrow 10$
Refl. measured	2077	4238	2633	5260
Refl. independent	1224	1212	1537	1765
R_{int}	0.042	0.032	0.055	0.063
Refl. observed	1160	1180	1339	1539
Restraints / parameters	4 / 91	1 / 85	2 / 100	2 / 109
R_1 / wR_2 [$I \geq 2\sigma(I)$]	0.034 / 0.076	0.030 / 0.074	0.066 / 0.184	0.043 / 0.111
R_1 / wR_2 (all data)	0.037 / 0.078	0.031 / 0.075	0.072 / 0.192	0.050/ 0.114
x (Flack)	0.48(3)	−0.01(7)	–	–
Goodness of fit	1.04	1.11	1.06	1.07
$\Delta\rho_{max\,/\,min}$, e Å^{-3}	0.87 / −0.46	1.39 / −0.50	1.64 / −1.73	0.86 / −1.47
CCDC number	864100	864099	864101	864102

δ = 105.9, 112.4, 116.0 ppm. – IR (neat): ν = 2813 (w), 2750 (w), 2702 (m), 2667 (m), 2600 (s), 2569 (s), 2525 (s), 2465 (m), 2369 (m), 1704 (m), 1555 (s), 1308 (m), 826 (s), 753 (s) cm^{-1}.

*1,3-Dihydroxy-2-methylimidazolium bromide (**4**·HBr)*

For the purpose of spectroscopic comparison, this compound was prepared from **4** and 48 % HBr. M. p. 164 – 165 °C. – ^{1}H NMR (300 MHz, [D$_4$]MeOH): δ = 2.62 (s, 3 H), 7.66 (s, 2 H) ppm. – ^{13}C NMR (75 MHz, [D$_4$]MeOH): δ = 7.4, 118.0 (2C), 139.3 ppm. – IR (neat): ν = 3151 (w), 3111 (w), 3034 (w), 2958 (w), 2911 (w), 2805 (m), 2699 (s), 2647 (s), 2590 (s), 1595 (w), 1455 (m), 1356 (m), 1109 (s), 1053 (w), 1033 (w), 950 (w), 756 (m), 712 (s), 621 (s), 594 (s) cm^{-1}.

*4,5-Dibromo-1,3-dihydroxy-2-methylimidazolium bromide (**5**)*

Bromine (4.5 mL, 88 mmol) was added dropwise to a solution of 1-hydroxy-2-methylimidazole-3-oxide (10.0 g, 88 mmol) in acetic acid (100 mL). The mixture was stirred at ambient temperature for 27 h. The precipitate was filtered off, washed with acetic acid (2 mL), twice with Et$_2$O (2 × 10 mL), and dried. This crude product was dissolved in warm MeOH (*ca.* 12 mL) and kept at −20 °C overnight. The colorless product was collected by filtration, washed with Et$_2$O (10 mL), and dried to constant weight. Yield: 6.5 g (21 %). Single crystals were obtained from MeOH. M. p. 183 °C (dec). – ^{1}H NMR (300 MHz, [D$_4$]MeOH): δ = 2.68 (s, 3 H) ppm. – ^{13}C NMR (75 MHz, [D$_4$]MeOH): δ = 8.9, 106.4 (2C), 142.4 ppm. – IR (neat): ν = 2981 (w), 2916 (w), 2806 (m), 2674 (br s), 1569 (m), 1452 (m), 1302 (m), 1145 (m), 1016 (m), 840 (m), 807 (w), 604 (s), 587 (s) cm^{-1}. – $C_4H_5Br_3N_2O_2$ (352.81): calcd. C 13.62, H 1.43, N 7.94; found C 13.76, H 1.31, N 7.95.

Crystal structure determinations

The crystal structures were determined using Nonius KappaCCD and Oxford Diffraction Gemini-R Ultra diffractometers with MoK_α and CuK_α radiation, respectively. Several ϕ and ω scans were made to increase the number of redundant reflections, which were averaged previous to the refinement cycles. This procedure replaces in good approximation an empirical absorption correction. The structures were solved with direct methods and refined against F^2 [24]. The struc-

ture of **2** was refined as racemic (inversion) twin with a batch scale factor of 0.47 and checked for higher symmetry using the PLATON software [25]. The experimental conditions and crystallographic data are summarized in Table 2.

CCDC 864099–864102 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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