# 3-Bromoimidazo[1,2-*b*]pyridazine-Bromine and 3-Bromo-6-chloroimidazo[1,2-*b*]pyridazine-Bromine Complexes; New Brominating Agents for Organic Compounds

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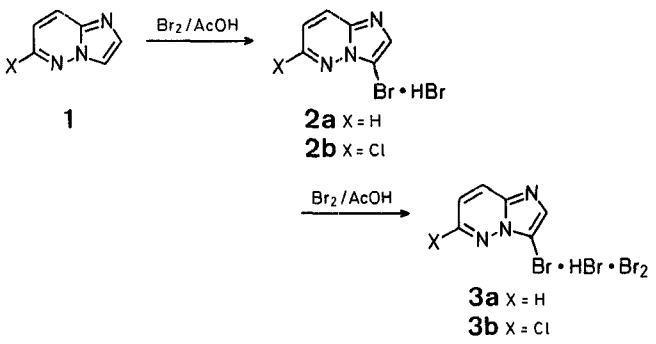
Among the many brominating agents used in organic chemistry, *N*-bromo compounds and organic bromine complexes are of special importance for the selective bromination of sensitive organic compounds under mild conditions[1]. In the course of our investigations on the chemistry of azolo-azines[2,3], we observed that some imidazo[1,2-*b*]pyridazine derivatives form stable, well-defined complexes with bromine.

We have recently described a new and improved bromination of $\alpha$-ergocryptine and some other ergot alkaloids using 3-bromo-6-chloro-2-methylimidazo[1,2-*b*]pyridazine-bromine complex, a new brominating agent, to give the corresponding 2-bromo derivatives in pure form in yields up to 81%[4]. Since this new brominating agent is advantageous as compared to other brominating agents previously used for this purpose[5,6], e.g., bromine, pyridine hydrobromide perbromide, *N*-bromosuccinimide, *N*-bromophthalimide, and others, 3-bromo-6-chloro-2-methylimidazo[1,2-*b*]pyridazine-bromine complex and similar bromine complexes might also be used for the bromination of other classes of organic compounds.

We report here the preparation of 3-bromo-imidazo[1,2-*b*]pyridazine hydrobromide-bromine complex **(3a)** and 3-bromo-6-chloroimidazo[1,2-*b*]pyridazine-bromine complex **(3b)** and their application as brominating agents for a variety of organic compounds. The complexes can be prepared from imidazo[1,2-*b*]pyridazine **(1a)** or 6-chloroimidazo[1,2-*b*]pyridazine **(1b)** by bromination with bromine in acetic acid. First, the corresponding 3-bromo derivatives **2** are formed as hydrobromide salts which are then converted into the complexes **3a** and **3b**, respectively, by excess bromine.

Representative brominations using complexes **3a** and **3b** were performed with some alkenes, ketones, 3-oxoalkanoic esters, and monocyclic and polycyclic *N*-heterocyclic compounds.




1,2-*trans*-Dibromocyclohexane was obtained from cyclohexene and $\alpha$-bromo derivatives were obtained from alkyl ketones and 3-oxoalkanoic esters. The bromination of 2-aminopyridine and 2-aminopyrimidine takes place at positions 5, and of imidazo[1,2-*b*]pyridazine derivatives at position 3. It has been reported, that the direct bromiation of 2-aminopyrazine fails so that its 5-bromo derivative could only be obtained by the readily proceeding bromination of 2-amino-3-methoxycarbonylpyrazine followed by hydrolysis and decarboxylation[7]. However, using complexes **3a** or **3b** either 2-amino-5-bromo- or 2-amino-3,5-dibromopyrazine can be prepared by direct bromination of 2-aminopyrazine, the reaction conditions and the ratio substrate to brominating agent determining which of the two products is formed.

Bromination with equimolar amounts of **3a** or **3b** proceeds smoothly to completion either at room temperature or on gentle heating. $^1$H-N.M.R. analysis of the crude products indicates that the conversion is practically quantitative in all cases and that the monobrominated compounds are the only products unless other conditions are used (see Table). The crude products obtained according to isolation procedure A are contaminated only with trace amounts (<2%) of the 3-bromoimidazo[1,2-*b*]pyridazine derivative **2a** or **2b** and, in some cases, with trace amounts (<1%) of starting material. On the other hand, the crude products obtained according to isolation procedure B are mixtures of the brominated product and the 3-bromoimidazo[1,2-*b*]pyridazine derivative **2a** or **2b** in approximately equimolar ratio, and, in some instances, starting compound in trace amounts (<1%). However, the yields are moderate only in spite of the practically complete conversion, due to losses during the chromatographic separation.

The following commercially not available compounds were prepared according to literature procedures: imidazo[1,2-*b*]pyridazine[8], 6-chloroimidazo[1,2-*b*]pyridazine[9], 6-chloro-2-methylimidazo[1,2-*b*]pyridazine[10], 6-chloro-2-phenylimidazo[1,2-*b*]pyridazine[10], and 3-bromo-6-chloroimidazo[1,2-*b*]pyridazine hydrobromide[9].

**3-Bromoimidazo[1,2-*b*]pyridazine Hydrobromide-Bromine Complex (3a):**

*Preparation from Imidazo[1,2-b]pyridazine* **(1a):** *To a stirred solution* of imidazo[1,2-*b*]pyridazine (**1a**; 1.19 g, 1 mmol) in glacial acetic acid (20 ml), an excess of bromine (4.0 g, 2.5 mmol) is added dropwise at room temperature. The precipitate, which is formed immediately, is collected by filtration and washed with glacial acetic acid, recrystallized from acetic acid, washed with diethyl ether, and dried in vacuo at 30°C for 1 h; yield: 3.51 g (80%). At temperatures above ~160°C, complex **3a** decomposes into **2a** and bromine.

| | | | | |
|---|---|---|---|---|
| $C_6H_5Br_4N_3$ | calc. | C 16.42 | H 1.15 | N 9.58 |
| (438.7) | found | 16.66 | 1.36 | 9.39 |

$^1$H-N.M.R. (DMSO-$d_6$/TMS$_{int}$): $\delta$ = 8.90 (dd, 6-H); 8.35 (dd, 8-H); 8.31 (s, 2-H); 8.89 ppm (s, HBr); $J_{6,7}$ = 4.5 Hz, $J_{6,8}$ = 1.5 Hz, $J_{7,8}$ = 9.6 Hz.

*Regeneration from 3-Bromoimidazo[1,2-b]pyridazine Hydrobromide* **(2a):** A stirred solution of 3-bromoimidazo[1,2-*b*]pyridazine hydro-

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bromide (**2a**; 1.98 g, 0.7 mmol) in glacial acetic acid (20 ml) is treated dropwise with an excess of bromine (2.4 g, 1.5 mmol). Work-up is as described above; yield: 2.65 g (85%).

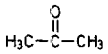
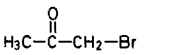
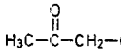
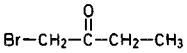
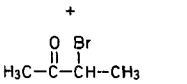
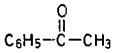
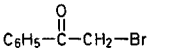
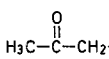
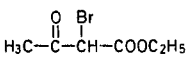
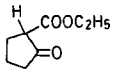
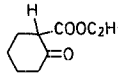
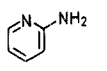
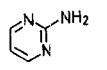
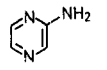
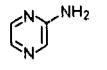
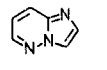
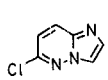
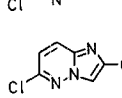
**3-Bromo-6-chloroimidazo[1,2-*b*]pyridazine Hydrobromide-Bromine Complex (3b):**

Complex **3b** is prepared either from 6-chloroimidazo[1,2-*b*]pyridazine (**1b**) or from 3-bromo-6-chloroimidazo[1,2-*b*]pyridazine hydrobromide (**2b**) as described above for **3a**; yield of **3b**: 90%. At temperatures above ~160°C, complex **3b** decomposes into **2b** and bromine.

| | | | | |
|---|---|---|---|---|
| $C_6H_4Br_4ClN_3$ | calc. | C 15.23 | H 0.85 | N 8.88 |
| (472.8) | found | 15.12 | 0.83 | 9.08 |

$^1$H-N.M.R. (DMSO-$d_6$/$TMS_{int}$): $\delta = 10.07$ (s, HBr); 9.12 (dd, 6-H); 8.52 (s, 2-H); 8.49 (dd, 8-H); 7.79 ppm (dd, 7-H); $J_{6,7} = 4.5$ Hz, $J_{6,8} = 1.5$ Hz, $J_{7,8} = 9.5$ Hz.

**Table.** Bromination of Organic Compounds with 3-Bromoimidazo[1,2-*b*]pyridazine Hydrobromide-Bromine Complex (**3a**) and 3-Bromo-6-chloroimidazo[1,2-*b*]pyridazine Hydrobromide-Bromine Complex (**3b**)

| Substrate | Product | Reaction time[a] [min] | Method of isolation | Yield[b] [%] with **3a** | Yield[b] [%] with **3b** | Yield[b] [%] reported | m.p. or b.p./torr [°C] found | m.p. or b.p./torr [°C] reported |
|---|---|---|---|---|---|---|---|---|
|  |  | 30 | A | 98 | 92 | 95[11] | b.p. 96–98°/12 | b.p. 99–103°/16[11] |
|  |  | 30 | A | 67 | 76 | 43–44[12] | b.p. 40–42°/12 | b.p. 40–42°/13[12] |
|  |  | | | 17 | 19 | — | b.p. 42–43°/12 | b.p. 145–146°/760[13] |
| |  | 30 | A | | | | | |
| | | | | 52 | 58 | | b.p. 36–37°/12 | b.p. 133–134°/760[13] |
|  |  | 30 | A | 78 | 96 | 64–66[14] | m.p. 49° | m.p. 49–51°[14] |
|  |  | 30 | A | 80 | 92 | 17[15] | b.p. 78–80°/12 | b.p. 79–82°/13 |
|  |  | 60 | A | 82 | 89 | 60–65[16] | b.p. 87–88°/12 | b.p. 89–90°/14[16] |
|  |  | 90 | A | 89 | 94 | 55[17] | b.p. 102–104°/12 | b.p. 101–104°/12 |
|  |  | 90 | A | 60 | 74 | — | b.p. 110–112°/4 | b.p. 104–106°/1.5[18] |
|  |  | 90 | A | 42 | 60 | 50[16] | b.p. 140–142°/12 | b.p. 144°/13[16] |
|  |  | 120 | B | 47 | 53 | 46[19] | m.p. 135–137° | m.p. 137–138°[19] |
|  |  | 90 | B | 32 | 44 | 41[20] | m.p. 240–242° | m.p. 242–244°[20] |
|  |  | 90 | B[c] | 35 | 36 | — | m.p. 112–114° | m.p. 113.6°[7] |
|  |  | 90 | B[d] | 26 | 31 | — | m.p. 118° | m.p. 116°[21] |
|  |  | 30 | B | — | 70 | 80[8] | m.p. 159° | m.p. 163°[8] |
|  |  | 30 | B | 50 | — | 92[9] | m.p. 155° | m.p. 156°[9] |
|  |  | 90 | B | 62 | 67 | 74[22] | m.p. 190° | m.p. 190°[22] |

[a] At room temperature.

[b] Yield of purified product; yields reported in the literature were obtained with other brominating agents. The products were identical in all respects (M.S., I.R., $^1$H-N.M.R.) with the compounds prepared according to literature procedures.

[c] A 1:1 molar ratio of substrate to brominating agent was used.

[d] A 1:2.5 molar ratio of substrate to brominating agent was used.

**Bromination of Organic Compounds with Bromine Complexes 3a or 3b; General Procedure:**

*Bromination:* To a stirred solution of the substrate (2 mmol) in chloroform or acetic acid (15 ml) is added a suspension of the brominating agent **3a** or **3b** in 10% excess, unless otherwise stated, in the same solvent (5–10 ml). The mixture is stirred at room temperature or heated at reflux temperature until the starting compound disappears from the solution (15–20 min). The reaction is followed by T.L.C. [Merck DC-Fertigplatten Kieselgel 60 $F_{254}$ or Aluminiumoxid 150 $F_{254}$ and chloroform/methanol (9/1 or 5/1) as solvent are used].

*Isolation:*

Method A, for compounds which are soluble in the reaction solvents and which do not form hydrobromides: The reaction mixture is cooled and the respective 3-bromoimidazo[1,2-*b*]pyridazine hydrobromide **(2a, b)** and unreacted brominating agent **(3a, b)** are filtered off. The filtrate is washed with water (2 × 20 ml) and dried with sodium sulfate. The solvent is evaporated in vacuo and the residue purified by crystallization or distillation.

Method B, for products which form hydrobromides: The reaction mixture is evaporated in vacuo, the residue suspended in water (10 ml), and neutralized with concentrated aqueous ammonia. The precipitate is collected by filtration and the filtrate extracted with chloroform (3 × 15 ml). The combined extracts are dried with sodium sulfate and chloroform is evaporated in vacuo. The precipitate collected by filtration and the solid residue obtained by evaporation of chloroform is a mixture of brominated product, 3-bromoimidazo[1,2-*b*]pyridazine derivative and, in some instances, starting compound in trace amounts. This mixture is separated by T.L.C. [Merck PSC Fertigplatten Kieselgel 60 $F_{254}$, and chloroform/methanol (5/1) as solvent are used].

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