Reaction of α-halo- and α,α-dihalo-β-oxoaldehydes with *o*- and *m*-phenylenediamines

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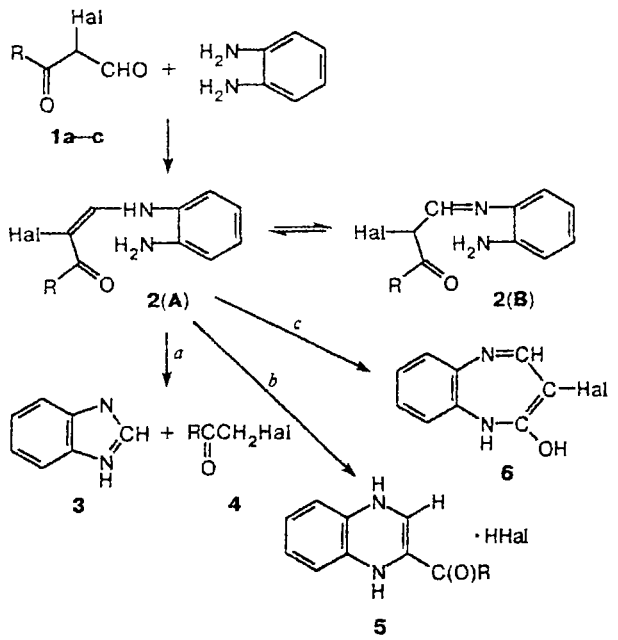
α-Halo-β-oxoaldehydes react with *o*- and *m*-phenylenediamines to give α-halo-β-oxoenamines. In the case of *o*-phenylenediamine, the initially formed monoenamine undergoes concurrent intramolecular cyclization to give benzimidazole and a halocarbonyl compound. α,α-Dihalo-β-oxoaldehydes react with *o*- and *m*-phenylenediamines according to the haloformic decomposition scheme involving formylation of amino groups.

Key words: α-halo-β-oxoaldehydes, phenylenediamines, intramolecular nucleophilic reaction, heterocyclization, benzimidazole.

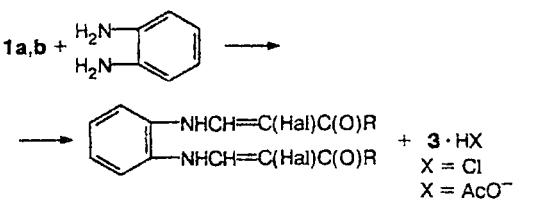
We have shown previously[1] that α-halo-β-oxoaldehydes (**1**) react with primary aromatic amines to give stable α-halo-β-oxoenamines. One might anticipate that the reaction of aldehydes **1a—c** with *o*-phenylenediamine would result in intermediate compounds of the type **2**, which can exist in the enamine (**A**) and imine (**B**) tautomeric forms. An analysis of available literature data on compounds with related structure makes it possible to assume several variants of subsequent stabilization of intermediates **2** through intramolecular nucleophilic reactions to give benzimidazole (**3**) and a halocarbonyl compound **4** (breaking of a C—C bond)[2] (pathway *a*); 2-acyl-1,4-dihydrobenzopyrazine hydrohalides (**5**)[3] (pathway *b*); or substituted benzodiazepines (**6**)[4,5] (pathway *c*).



R = Me, Hal = Br (**a**); R = Ph, Hal = Cl (**b**);
R = EtO, Hal = Cl (**c**)

We were unable to carry out reactions of aldehydes **1** with *o*-phenylenediamines in a number of solvents (CCl_4, $CHCl_3$, acetone—$CHCl_3$ (1 : 2), ether) at low temperatures (−5 to 0 °C) because of the extremely low rate of the process. An increase in temperature to ~20 °C results in strong resinification of the reaction mixture, and only the corresponding benzimidazole hydrohalide can be isolated therefrom. In addition, the ^{1}H NMR spectrum of the reaction mixture contains an intense signal at δ 4.20—4.50 characteristic of the $C(O)CH_2Hal$ group. This signal can be assigned to a halocarbonyl compound **4**. Unfortunately, we were unable to isolate pure compounds **4**.

A similar reaction pattern (at ~20 °C) is observed when the process is carried out in AcOH. The only difference is that the imidazole is formed as a mixture of two salts, a hydrohalide and an acetate. Decreasing the temperature to −5 to 0 °C (the reaction was carried out in an AcOH—Et_2O mixture) makes it possible to identify a functionally substituted bis-enamine **7** and benzimidazole salts **3** · HX in the reaction mixture.



7a: R = Me; Hal = Br
7b: R = Ph; Hal = Cl

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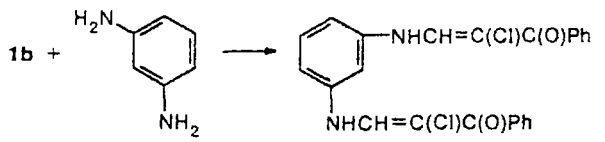
Undoubtedly, the formation of products **7** and **3** · HX occurs through the common intermediate **2**, which has several possibilities for subsequent stabilization. The spatial proximity of the amino group at the *ortho*-position to the enamine fragment facilitates a nucleophilic attack of the former to the highly-electrophilic imine carbon atom. This intramolecular process results in the formation of the structures of benzimidazole **3** and halocarbonyl compound **4**. Another possible direction of stabilization of intermediate **2** is the reaction of the free amino group with aldehydes **1** to give bis-enamine **7**. Judging by the amount of products formed (**7** and **3** · HX), the rates of these two processes are approximately equal.

Because of resinification of the reaction mixture, it is impossible to account for the total material balance of the reactions under study, and in particular, to determine the source of the hydrogen halide which converts benzimidazole into the corresponding hydrohalide. A specially conducted experiment showed that neither the starting substrates **1** nor halocarbonyl compounds **4** undergo dehydrohalogenation by benzimidazole. In addition, it is known[6] that the reaction of benzimidazole and other nitrogen-containing heterocyclic bases with halocarbonyl compounds results in quaternization of the nitrogen atom without further transformations. Most likely, the conversion of benzimidazole into its hydrohalide results from dehydrohalogenation of mono- (**2**) and bis-enamines (**7**), which are potentially capable of such transformations.

In the case of the reaction of aldehyde **1b** with *m*-phenylenediamine, the intramolecular reactions noted above are impossible. The process occurs unidirectionally to give enamines on two amino groups; as a result, *m*-bis-enamine **8** is formed.



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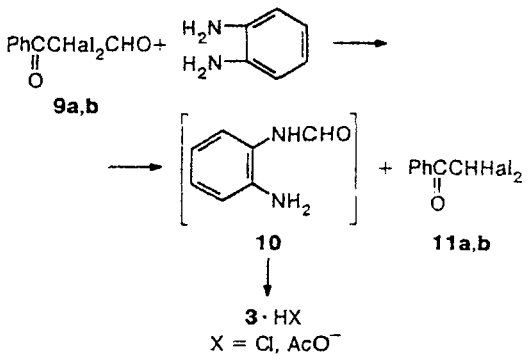
Reactions of α,α-dihalo-β-oxoaldehydes (**9**) with *o*- and *m*-phenylenediamines occur as formylation of amino groups (breaking of the C—CHO bond in aldehyde **9**). In the case of *o*-phenylenediamine, the monoformyl derivative **10** formed initially undergoes intramolecular cyclization into benzimidazole. Haloformic decomposition of oxoaldehydes **9** affords dihaloketone **11**.

A similar reaction with *m*-phenylenediamine occurs in a much more complex way to give a crystalline compound in a high yield. We were unable to determine the structure of this compound.

The structures of reaction products **3**, **7a,b**, **8**, and **11a,b** were confirmed by IR and NMR (^{1}H and ^{13}C) spectroscopic data.

Thus, the reactions of β-oxoaldehydes **1** and **9** with phenylenediamines occur regioselectively: in all cases,



Hal = Cl (**a**), Br (**b**)

the aldehyde carbon atom participates in the process, while the second carbonyl group is not involved.

Experimental

IR spectra were recorded on a UR-20 spectrometer in Vaseline oil. ^{1}H and ^{13}C NMR spectra were recorded in acetone-d_6 or in DMSO-d_6 on a Tesla B-567 spectrometer (100 MHz for ^{1}H and 25 MHz for ^{13}C) using HMDS as the internal standard. The starting monohaloaldehydes **1a—c** and dihaloaldehydes **10a,b** were prepared according to the known procedure.[7]

Reaction of aldehydes 1a—c with *o*-phenylenediamine. A solution of *o*-phenylenediamine (0.02 mol) in 20 mL of a solvent (CCl_4, $CHCl_3$, acetone—$CHCl_3$ (1 : 2), or Et_2O) was added dropwise with stirring (at −5 to 0 °C) to a solution of aldehyde **1a—c** (0.02 mol) in the corresponding solvent (20 mL). The reaction mixture was kept for 1 h at ~20 °C, the solvent was evaporated, and acetone was added to the residue. The solution obtained was added dropwise to ether. The crystals of benzimidazole hydrohalide (3 · HX) that formed were filtered off and treated with 5% $NaHCO_3$. Chloroform (15 mL) was added, the organic layer was separated, and the aqueous layer was extracted with chloroform (2×10 mL). The combined extracts were dried with $MgSO_4$, the solvent was evaporated, and the resulting crystals of benzimidazole **3** were dried. Yield 20%, m.p. 169—170 °C (in agreement with literature data[7]). ^{1}H NMR ($(CD_3)_2CO$), δ: 3.40 (br.s, 1 H, NH); 7.15 (q, 2 H, Ph); 7.55 (q, 2 H, Ph); 8.00 (s, 1 H, CH).

Reaction of aldehydes 1a,b with *o*-phenylenediamine in acetic acid. A solution of *o*-phenylenediamine (2.9 g, 0.03 mol) in AcOH (15 mL) was added dropwise at 0 °C to a mixture of aldehyde **1a** (5 g, 0.03 mol), AcOH (30 mL), and Et_2O (10 mL). The reaction mixture was stirred for 1 h with cooling (−5 to 0 °C) and for 0.5 h at ~20 °C. The crystals of compound **7** that precipitated were filtered off, washed with chloroform, and dried. The filtrate was poured into water, the mixture was extracted with chloroform (2×20 mL), and the extract was dried with $MgSO_4$. The solvent was evaporated, and the resulting crystals of two benzimidazole salts were filtered off and worked up as described above to give compound **3**. The physicochemical characteristics of compound **3** were identical to those presented above.

1-Di(2-bromo-3-oxobut-1-enylamino)benzene (7a). Yield 50%, m.p. 148—150 °C. Found (%): Br, 39.49; N, 7.34. $C_{14}H_{14}Br_2N_2O_2$. Calculated (%): Br, 39.74; N, 6.97.

IR, ν/cm^{-1}: 3230 (NH); 1640 (C=C). ^{1}H NMR (DMSO-d_6), δ: 2.42 (s, 6 H, Me); 7.26 (m, 2 H, Ph); 7.59 (m, 2 H, Ph); 8.00 (s, 1 H, CH); 8.32 (s, 1 H, CH); 8.84 (br.s, 2 H, NH).

1,2-Di(2-chloro-3-oxo-3-phenylprop-1-enylamino)benzene (7b). Yield 60%, m.p. 174—175 °C. Found (%): Cl, 16.30; N, 6.50. $C_{24}H_{18}Cl_2N_2O_2$. Calculated (%): Cl, 16.41; N, 6.41. IR, ν/cm^{-1}: 3210 (NH); 1620 (C=C). ^{1}H NMR (DMSO-d_6), δ: 7.10 (s, 4 H, H_{arom}); 7.60 (m, 10 H, H_{arom}); 7.65 (d, 2 H, 2 CH_2, ^3J = 12.5 Hz); 9.30 (d, 2 H, 2 NH_2, ^3J = 12.5 Hz).

1,3-Di(2-chloro-3-oxo-3-phenylprop-1-enylamino)benzene (8). A solution of *m*-phenylenediamine (0.03 mol) in AcOH (15 mL) was added dropwise at 3 °C to a mixture of aldehyde **1b** (0.03 mL), AcOH (30 mL), and Et_2O (10 mL). The reaction mixture was kept for 1 h with cooling and for 1 h at ~20 °C. The crystals of compound **8** that precipitated were filtered off, washed with Et_2O, and dried. Yield 80%, m.p. 240—242 °C. Found (%): Cl, 16.30; N, 6.70. $C_{24}H_{18}Cl_2N_2O_2$. Calculated (%): Cl, 16.41; N, 6.41. IR, ν/cm^{-1}: 3280 (NH); 1640 (C=C). ^{1}H NMR (DMSO-d_6), δ: 7.05 (s, 4 H, H_{arom}); 7.52 (m, 10 H, H_{arom}); 7.75 (d, 2 H, 2 CH, J = 12.5 Hz); 9.45 (d, 2 H, NH, J = 12.5 Hz). ^{13}C NMR (DMSO-d_6), δ: 110.2 (CCl); 121.3 (=CH—N); 131.2, 131.4, 133.6, 139.4, 142.1, 146.2 (C_{arom}); 189.7 (C=O).

Reaction of aldehydes 9 with o-phenylenediamine. *o*-Phenylenediamine (0.046 mol) was added in portions with stirring to a solution of aldehyde **9** (0.046 mol) in CCl_4 (20 mL). The reaction mixture was kept for 0.5 h with cooling and for 1 h at ~20 °C. The solvent was removed, and $CHCl_3$ was added to the residue. The solution obtained was added dropwise to benzene. The benzimidazole salt (**3** · HX) that precipitated was filtered off and worked up as described above to give compound **3** (the characteristics of the product were identical to those presented above). The filtrate was concentrated, and compound **11** was isolated by fractional distillation.

α,α-Dichloroacetophenone (11a). Yield 30%, b.p. 76 °C (0.09 Torr), n_D^{20} 1.5680 (in agreement with literature data[1]). ^{1}H NMR ($(CD_3)_2CO$), δ: 7.10 (s, 1 H, $CHCl_2$); 7.50 (m, 3 H, Ph); 8.10 (dd, 2 H, Ph).

α,α-Dibromoacetophenone (11b). Yield 28%, b.p. 138—140 °C (10 Torr), m.p. 36 °C (in agreement with literature data[7]).

When the reaction was carried out in AcOH, salts **3** · HX were isolated along with product **11**. The former compound was worked up as described above to give benzimidazole (**3**).

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