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Tandem 1,4-Diaza,3-oxa-Cope Rearrangement - Nucleophilic Addition Reaction. A Route to 2-Oxobenzimidazoles.

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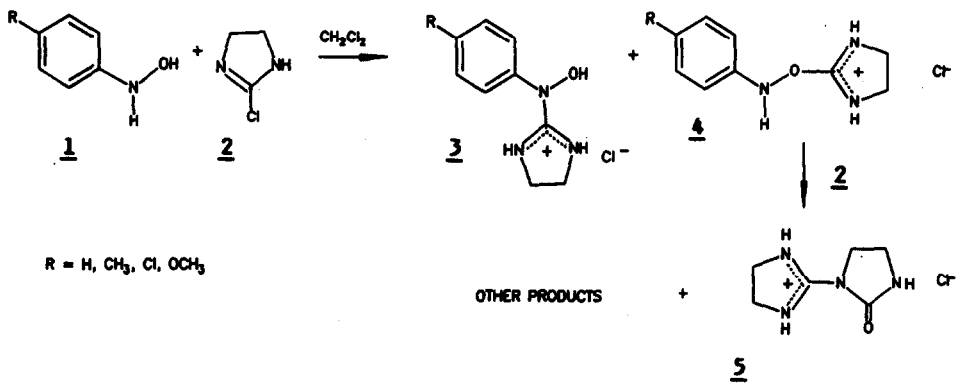
Abstract: *A novel tandem 1,4-diaza-3-oxa-Cope rearrangement - nucleophilic addition reaction has been deviced in which the formation of 2-oxobenzimidazoles* **2** *has been rationalized on the basis of an initial [3,3]sigmatropic rearrangement of the N-cyanato-anilines* **6**, *followed by an intramolecular nucleophilic addition in the intermediate isocyanates* **7**.

Polyhetero-Cope rearrangements, which differ in number, type and position of the heteroatom are well known and effective synthetic processes. In recent years increasing attention has been focussed on use of easily rearranging, non-isolable hetero-Cope systems bearing the central N-O bond. Thus, through 3-aza,4-oxa[1] [3,3] sigmatropic rearrangements of enolizable N-aryl-N,O-diacylhydroxylamines[2] or N-phenyl-O-acyl-hydroxylamine[3], the regiospecific syntheses of anilines having carbonyl- or carboxyl-functionalized alkyl groups in the *ortho* position may be accomplished. Of synthetic importance is the introduction of amino substituents into the *ortho* position of phenols or amines using N-alkyl-N'-phenoxyureas[4] or N-phenylhydroxamic acids[5] respectively. A similar aromatic rearrangements of O-aryloximes[6] or O-phenyl-N-acetoacetylhydroxylamines[7] to benzofurans, N-phenyl-O-vinylhydroksylamines to indoles[8,9] or N-aryl-O-acyl-hydroxamic acids to oxoindoles[10] were also succesfully applied in the field of heterocyclic and natural products chemistry[11].

In our attempt to prepare heterocyclic compounds of biological interest, we found that 2-oxobenzimidazoles **2** can now be prepared under mild reaction conditions starting from aromatic hydroxylamines **3** and cyanogen bromide.

Treatment of the readily available N-arylhydroxylamines **1** with 2-chloro-4,5-dihydroimidazole **2** in methylene chloride at room temperature gave the corresponding N-(4,5-dihydro-1H-imidazol-2-yl)-hydroxylamine hydrochlorides **3** as major products in 42-51% yields after purification by single recrystallization from ethanol. The crude ^{1}H-NMR spectrum of the products showed the presence of imidazolidinone **5**, which can be envisioned to be formed by an intermolecular reaction of the unstable O-substituted hydroxylamine **4** with a second molecule of **2** (scheme 1).



Scheme 1

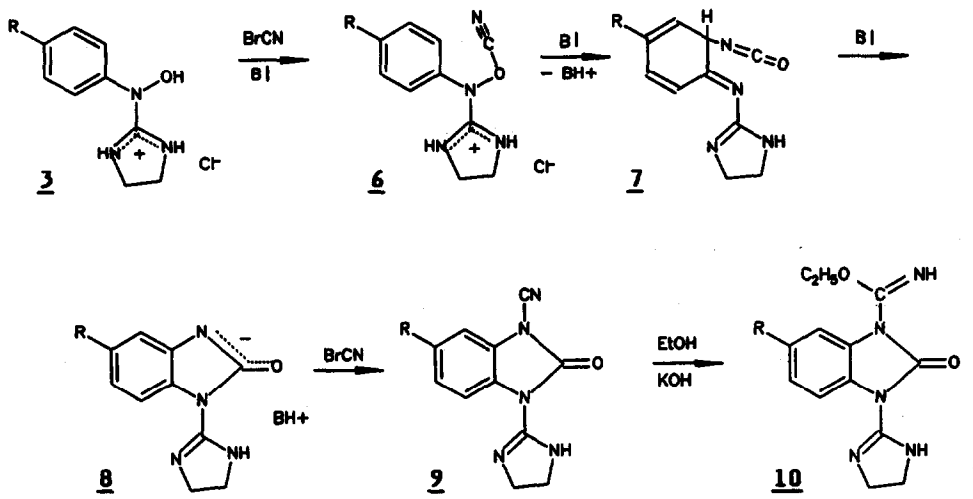
Reactions of the hydroxylamine hydrochlorides **3** with cyanogen bromide in the presence of triethylamine in polar aprotic solvents such as acetone or tetrahydrofuran at room temperature directly afforded the 3-(4,5-dihydro-1H-imidazol-2-yl)-2-oxo-2,3-dihydro-benzimidazole-1-carbonitriles **9** (scheme 2).

Mechanism for this reaction involves O-cyanation of the hydroxylamine **3**, rearrangement of the N-cyanato derivative **6**, prototropic rearomatization and internal nucleophilic addition in the resulting isocyanate **7**. This process is completed by reaction of the 2-oxobenzimidazole **8** with a second molecule of BrCN leading to the carbonitrile **9**. In no case were the intermediates **6**, **7** or **8** isolable. Whether the crucial step occurs by a concerted [3,3] sigmatropic rearrangement of **6**, homolysis to a diradical and recombination or by a heterolytic cleavage of the N-O bond cannot be stated with certainty. However, the absence of *para*-substituted product in case of **3a** as well as the lack of effect of light, air and m-dinitrobenzene may eliminate a possible hetero- or homolytic cleavage of N-O bond. The [3,3] step in these conversions is very likely a "charge-induced" pericyclic reaction as the preformed free base of **3** showed no sign of rearrangement in the reaction with cyanogen bromide.

It is pertinent to note that under the conditions so far investigated, the reaction could not be stopped at the stage of the intermediate **8**, which reacted further with cyanogen bromide and the benzimidazole-1-carbonitriles **9a-d** were isolated exclusively in 41-69% yields.

A list of hydroxylamines **3a-d** and 2-oxobenzimidazoles **9a-d** obtained is given in Table 1.

The assignment of the position of the cyano group in **9** was based on spectroscopic evidence[12]. Thus, IR spectrum of **9a** (mp. 159 - 160°C) exhibited absorption at 2272 cm^{-1} due to C≡N vibrations, and in ^{1}H-NMR spectrum run in DMSO-d_6, the signal of the imidazoline CH_2-CH_2 group appeared as a singlet at 3.65 ppm.



Scheme 2

Compound	R	mp. (°C)	Yield (%)
3a	H	182 - 185	48
3b	CH_3	188 - 190	45
3c	Cl	186 - 188	42
3d	OCH_3	183 - 185	51
9a	H	159 - 160	41
9b	CH_3	162 - 165	32
9c	Cl	170 - 172	69
9d	OCH_3	175 - 178	40
10	H	161 - 162	78

Table 1. Hydroxylamines 3 and 2-oxobenzimidazoles 9 and 10 obtained.

Although the products yields in these reactions are rather moderate, the method described herein constitutes an original way to utilize polyhetero-Cope rearrangement for the construction of 2-oxobenzimidazole ring. Moreover, as exampilfied by the facile, base-catalyzed addition of ethanol to the C≡N triple bond, compounds 9 represent the valuable precursors to a variety of novel functionalized 2-oxobenzimidazoles such as 1-(4,5-dihydro-1H-imidazol-2-yl)-3-ethoxycarbonimidoyl-1,3-dihydrobenzimidazol-2-one 10.

Acknowledgments.

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References and Notes

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12. Spectral data of **9a** - IR (KBr): 3385 cm^{-1} (N-H), 2272 (C≡N), 1750 (C=O), 1648, 1600, 1490, 1455, 1375, 1215, 1165; - ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.65 ppm (s, 4H,), 7.0 (s,1H, NH), 7.2-7.4 (m, 3H), 8.25 (m, 1H); - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 44.3 ppm, 52.3, 102.5, 109.9, 116.4, 124.4, 125.0, 126.2, 126.7, 149.8, 153.4; - MS (15 eV): m/z (%) = 227 (100%, M^+), 226 (95.4), 171 (20.5), 170 (17.6), 159 (20.5), 158 (10.6), 144 (11.8), 143 (18.6), 90 (12.2), 68 (48.6).

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