ON THE REACTIVITY OF HYDROXIMOYL CHLORIDES PREPARATION OF 2-ARYL IMIDAZOLINES

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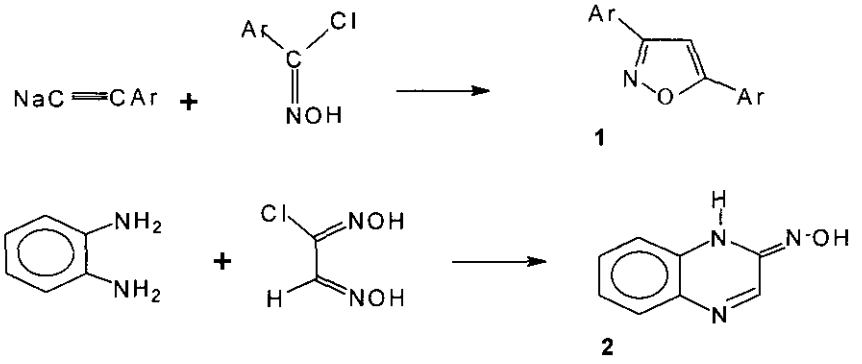
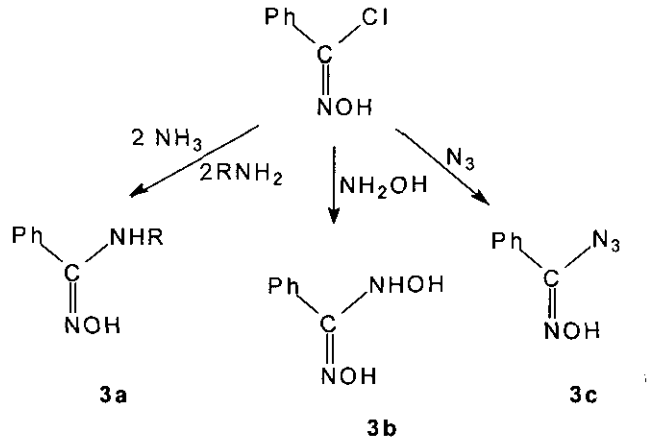
Abstract - Elimination of the hydroxylamino portion in arylhydroximoyl chlorides upon nucleophilic addition of ethylenediamine rendered an alternative procedure for 2-arylimidazolines preparation.

The imidazole nucleus, in its various oxidation states has shown to be an oustanding source of compounds which possess therapeutic value.[1] 2-Imidazolines on their own are often associated with drugs acting as adrenergic agents.[2] The 2-imidazoline nucleus is available from the interaction of diamines with carboxylic acids, esters, amides, imino ethers and nitriles.[3] In recent studies, base catalysed addition of hydrogen sulfide to nitriles [4] and acid catalysis by cuprous bromide [5] also on nitriles have been used to improve imidazoline formation. Surprisingly no imidazoline synthesis has been informed from hydroximoyl halides.

The halides of hydroximic acids have considerable interest in organic synthesis, since they are stable and frequently used precursors for the generation of important 1,3-dipoles (nitrile oxides).[6] In these and other reactions of hydoximoyl halides the C-N-O linkage is preserved. Thus, the condensation of hydroximic acid chlorides with sodium arylacetylides constitutes one of the oldest isoxazole (**1**) synthesis.[7] Later, ethynyl Grignard reagents replaced the arylacetylides sodium salts giving general validity to the method, which has been specially useful in the building of di- and polyisoxazole derivatives.[8] Similarly, glyoxalhydroximoyl

chloride reacted with *o*-phenylenediamine to yield quinoxalinone oxime (**2**).[9] The replacement of chlorine in benzohydroximoyl chloride by ammonia or amine to give benzamidoxime[10a] (**3a**), by hydroxylamine to give benzhydroxamidoxime[10b] (**3b**) and by azides to benzohydroximoyl azide[10c] (**3c**) is also known.

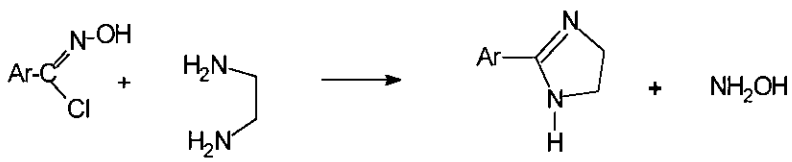




It is interesting to note that in any of these reported experiments, a double addition of the reacting nucleophile was observed.[11] Functionalised hydroximoyl chlorides are readily prepared from aldoximes and recently from nitro-olefines.[12] Thus, formation of the imidazoline nucleus from hydroximoyl halides and ultimately from aldehydes should be a convenient alternative.

Reactions of hydroximoyl halides (**4**) (prepared from the corresponding aromatic aldoximes by the

conventional protocol), with freshly distilled ethylenediamine in the presence of solvents such as methanol, dry DMF or dry dioxane did not give satisfactory results. Cuprous bromide catalysis did not improve reaction performance. Therefore it was decided to use excess ethylenediamine on the hydroximic acid halide in the absence of solvent. Then after heating at 90 °C for an average period of 4 h, the starting hydroximoyl chloride disappeared and usual work of the mixture gave the desired 2-arylimidazoline in the yields shown in Table1. When purification of crude products was needed, it was made by percolation through a silica precolumn.



4 5

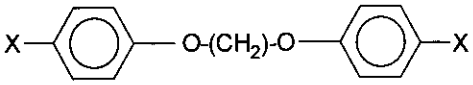
Table 1. 2-Arylimidazolines 5 from hydroxyminoyl chlorides 4

Entry	Aryl	mp (° C)	Lit. mp (° C)	Yield (%)
a	C_6H_5	101 - 102	102 - 103[13]	70
b	4-MeC_6H_4	182 - 183	183[14]	85
c	4-$MeOC_6H_4$	138 - 140	140[15]	60
d	3,4-di$MeOC_6H_3$	157 - 159	158.5[15]	55
e	4-FC_6H_4	147 - 148[a]	-	68
f	4-ClC_6H_4	185 - 187	187[15]	43
g	4-BrC_6H_4	179 - 180[a]	-	48
h	2-$NO_2C_6H_4$	97 - 99	98[15]	40

[a] See experimental section.

A further application of the procedure was made to the synthesis of the *bis*imidazoline (**8**), an analogue of the drug 1,5-*bis*(4-amidinophenoxy)pentane (pentamidine).[16] As usual, preparation of the required *bis*hydroximoyl chloride (**7**) was made from the corresponding dialdoxime (**6**), following Liu conditions.[17]

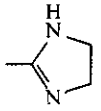
Reaction of **7** with ethylenediamine used as solvent, afforded compound (**8**), which was isolated in 86% yield and gave similar spectroscopic data as the product obtained from the corresponding *bis*iminoether.[18]



6; HC=NOH

X = **7**; -CCl=NOH

8;



Overall the result might appear simple, however it becomes quite interesting if one considers the strong basicity of ethylenediamine (pKa_1= 6.90, pKa_2= 9.95)[19] yet, it preferred to react nucleophilically with the hydroximic acid chloride, under conditions where no solvent was present. It may be argued that the process involved an intramolecular nucleophilic addition and thus it was facilitated. Previously, hydroximoyl chlorides have been used as synthons in the preparation of 2-arylbenzoxazoles, 2-arylbenzothiazoles and 2-arylbenzimidazoles by reaction with *ortho* substituted aromatic amines. [20,21]

In conclusion, the nucleophilic addition of ethylenediamine to arylhydroximoyl chlorides represents another application of these intermediates in organic synthesis, in this case for the preparation of the imidazoline nucleus.

EXPERIMENTAL

All reactions were carried out under nitrogen. Melting pointa were measured on a electrothermal melting point apparatus and are uncorrected. IR spectral data were obtained from a Perkin Elmer FT 1600 infrared spectrophotometer. ^{1}H NMR spectral data were obtained using a Bruker DPX 300 MHz NMR spectrometer. Chemical shifts are given in ppm downfield from TMS (δ_H = 0). MS were obtained with a Hewlett Packard Vectra 486S/20 instrument. Column chromatography was carried out with silica gel (Merck 60, 70-230 mesh)

as the adsorbent. Ethylenediamine and dioxane were dried with sodium under nitrogen and distilled prior to use.

4,5-Dihydro-2-(4'-fluorophenyl)-1H-imidazole (5e). 4-Fluorophenylhydroximoyl chloride (0.2 g, 1.15 mmol), was cooled in an ice bath. Ethylenediamine (5 mL, 74.8 mmol) was added dropwise, under nitrogen and keeping the temperature at 0 °C. The reaction mixture was then heated under a gentle reflux (90 °C), progress of the reaction was monitored by tlc (EtOH/EtOAc 1:1). After 4 h , the reaction mixture was allowed to cool to ambient temperature and poured into iced water. The mixture was extracted with methylene chloride (4 x 30 mL). The organic layer was dried (anh. Na_2SO_4) and solvent removed under reduced pressure. The residue was packed in a Varian (Bond Elut S1) precolumn and eluted with dry hexane to get the title compound as needles,129 mg (68 % yield), mp 147-148 °C. IR (KBr, νmax) 1600, 1555 cm^{-1}. ^1H NMR (DMSO-d_6), 3.8 (s, 4H), 7.2 (t, 2H, J= 8 Hz), 7.6 (dd, 2H, J=3 Hz, J= 8 Hz). MS m/z; 164 (M^+), 136 (M^+- 28, 100%). Anal. Calcd for $C_9H_9N_2F$; C, 65.85; H, 5.48; N, 17.073. Found; C, 65.61; H, 5.55; N, 17.31.

4,5-Dihydro-2-phenyl-1H-imidazole (5a). Obtained in 70% yield from phenylhydroximoyl chloride and ethylenediamine following the procedure described above, mp 101 - 102 °C (lit.,[13] 102 - 103 °C).

4,5-Dihydro-2-(4'-tolyl)-1H-imidazole (5b). Obtained in 85% yield from 4-tolylhydroximoyl chloride and ethylenediamine following the procedure described above, mp 182 - 183 °C (lit.,[14] 183 °C).

4,5-Dihydro-2-(4'-methoxyphenyl)-1H-imidazole (5c). Obtained in 60% yield from 4-methoxyphenyl-hydroximoyl chloride and ethylenediamine following the procedure described above, mp 138 - 140 °C (lit.,[15] 140 °C).

4,5-Dihydro-2-(3,4-dimethoxyphenyl)-1H-imidazole (5d). Obtained in 55% yield from 3,4-dimethoxy-phenylhydroximoyl chloride and ethylenediamine following the procedure described above, mp 157 - 159 °C (lit.,[15] 158.5 °C).

4,5-Dihydro-2-(4-chlorophenyl)-1H-imidazole (5f). Obtained in 43% yield from 4-chlorophenyl-

hydroximoyl chloride and ethylenediamine following the procedure described above, mp 185 - 187 °C (lit ,[15] 187 °C).

4,5-Dihydro-2-(4-bromophenyl)-1H-imidazole (5g). Obtained in 48% yield from 4-bromophenyl-hydroximoyl chloride and ethylenediamine following the procedure described above, mp 179 - 180 °C. IR (KBr, vmax), 1600, 1550 cm^{-1}. ^1H NMR ($CDCl_3$) 3.79 (s, 4H), 7.53 (d , 2H, J= 8 Hz), 7.65 (d, 2H, J = 8 Hz). MS m/z; 227 (M^+ + 2), 226 (M^+ + 1), 225 (M^+), 197 (M^+- 28, 100%). Anal. Calcd for $C_9H_9N_2Br$; C, 48; H, 4; N, 12.45.Found; C, 47.98; H, 4.19; N, 12.51.

4,5-Dihydro-2-(2-nitrophenyl)-1H-imidazole (5h). Obtained in 40% yield from 2-nitrophenylhydroximoyl chloride and ethylenediamine following the procedure described above, mp 97 - 99 °C (lit.,[15] 98 °C).

1,5-Bis(4-imidazolinophenoxy)pentane (8). 1,5*Bis*-(4-hydroximoylphenoxy)pentane chloride (0.15 g, 0.38 mmol) and ethylenediamine (4.5g , 75 mmol) were heated at 90 °C for 30 min. Work up of the reaction mixture as described before gave the title compound in 80% yield, mp 145 - 148 °C (hydrochloride) (lit.,[16] 147 °C).

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REFERENCES

1. D. Lednicer and L. A. Mitscher, "The Organic Chemistry of Drug Synthesis," Vol. 2, John Wiley & Sons Inc., New York, 1980, pp. 242-261.
2. A. F. Cosy, "The Steric Factor in Medicinal Chemistry", Plenum Press, New York, 1993, pp. 101-103.
3. R. J. Ferm and J. L. Riebsomer, ***Chem. Rev.***, 1954, **54**, 593.
4. G. Levesque, J. C. Gressier, and M. Proust, ***Synthesis***, 1981, 963.
5. G. Rouselet, P. Capdevielle, and M. Maumy, ***Tetrahedron Lett.***, 1993, **34**, 6395.
6. D. J. Miller, R. M. Scrowston, P. A. Kennewell, and R. Westwood, ***Tetrahedron***, 1994, **50**, 5159. P. Caramella and P. Grunanger, "1,3 Dipolar Cycloaddition Chemistry", ed. by A. Padwa, Wiley, NY, 1984. A. P. Kozikowski, ***Acc. Chem. Res.***, 1984, **17**, 410.
7. C. Weygand and E. Bauer, ***Ann. Chem.***, 1927, **459**, 123.
8. S. Cabiddu and V. Solinas, ***Gazz. Chim. Ital.***, 1969, **99**, 1107.
9. A. Koçak and Ö. Bekâroglu, ***Helv. Chim. Acta***, 1984, **67**, 1503.

10. a. A. Weiner and C. Bloch., ***Ber.***, 1899, **27**, 1975. 10b. H. Ley and M. Ulrich, ***Ber.***, 1914, **47**, 2941. 10c. F. Eloy, ***J. Org. Chem.***, 1961, **26**, 952.
11. R. J. Morath and G. W. Stacy, "The Chemistry of the Carbon-Nitrogen Double Bond", ed. by S. Patai, Interscience Publishers, London, 1970, pp. 327-342.
12. G. Kumaran and G. H. Kulkarni ***Tetrahedron Lett.***, 1994, **35**, 5517.
13. S. R. Aspinall, ***J. Org. Chem.***, 1941, **6**, 895.
14. A. J. Hill and S. R. Aspinall, ***J. Am. Chem. Soc.***, 1939, **61**, 822.
15. P. Oxley and W. F. Short, ***J. Chem. Soc.***, 1947, 497.
16. R. R. Tidwell, S. K. Jones, J. D. Geratz, K. A. Ohmeng, M. Cory, and J. E. Hall, ***J. Med. Chem.***, 1990, **33**, 1252. I. O. Donkor, R. R. Tidwell, and S. K. Jones, ***J. Med. Chem.***, 1994, **37**, 4554.
17. Ch. Liu, B.R. Shelton, and R.K. Howe, ***J. Org. Chem.***, 1980, **45**, 3916.
18. E. F. Elsanger, Final report, Department of the Army. 1970. Contract No DADA 49-193-MD-2754.
19. C. R. Bertsch, W. C. Fernelius, and B. P. Block, ***J. Phys. Chem.***, 1958, **62**, 444 .
20. T. Sasaki, T. Yoshioka, and Y. Suzuki, ***Bull. Chem. Soc. Jpn.***, 1969, **42**, 3335.
21. A. O. Abdelhamid, C. Párkányi, S. M. K. Rashid, and W. D. Lloyd, ***J. Heterocycl. Chem.***, 1988, **25**, 403.

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