A NOVEL SYNTHESIS OF BENZIMIDAZOLINONES§

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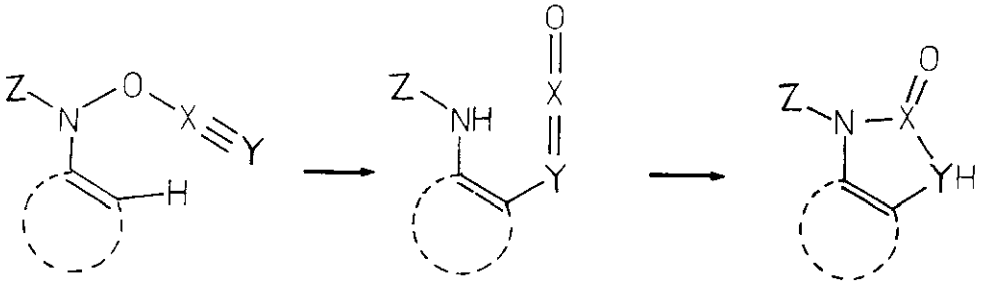
Abstract - A new route to N-monosubstituted benzimidazolinones, involving an hetero-oxy Cope rearrangement, consists in the reaction of hydroxamic acids with cyanogen bromide.

N-Monoarylhydroxylamines are particularly prone to a variety of reactions such as rearrangements, radical formation and disproportionation. Their N-acyl derivatives while moderating this reactivity still permit the inherent weakness of the N-O bond to be exploited for a wealth of chemical applications, ranging from the generation of disciplined carbon centered radicals[1] to the synthesis of natural products.[2]

We describe in this paper our results in the domain of the general rearrangement depicted in Scheme 1, where Z is an acyl or aroyl group, X is a carbon atom and Y a nitrogen atom, and further show that such a reaction provides an excellent method for the synthesis of imidazolinones fused to aromatic rings.



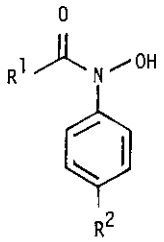
Scheme 1

§ This paper is dedicated to Professor Sir Derek Barton on the occasion of his 70th anniversary.

Table - 1: Compounds 2(a-f), 3, 5(a,b) and 7 prepared

Starting material	Product[a]	Yield[b] (%)	mp[c] (^{o}C)	^{1}H-Nmr ($CDCl_3$/TMS)[d] δ (ppm)
1a	2a	65	199-200 (lit.[3] 198-200)	8.99[e](1H, bs), 7.87(1H, d, J=8.0 Hz), 7.80(2H, d, J=7.5Hz) 7.62(1H, t, J=7.5 Hz), 7.49(2H, t, J=8.0 Hz), 7.16 (1H, m), 6.99(2H, t, J=7.5 Hz)
1b	2b	59	155.5-156.5 (lit.[4] 158-160)	9.98[e](1H, bs), 7.81(1H, d, J=8.0 Hz), 7.26-7.09 (3H, m), 4.56 (2H, q, J=7.0 Hz), 1.50(3H, t, J=7.0 Hz)
1c	2c	52	215.5-216.5	9.00[e](1H, bs), 7.80(2H, d, J=7.5 Hz), 7.71(1H, d, J=8.0 Hz), 7.60(1H, t, J=7.5 Hz), 7.48(2H, t, J=7.5 Hz), 6.94(1H, d, J=8.0 Hz), 6.70(1H, s), 2.37(3H, s)
1d	2d	72	153-153.5	9.71[e](1H, bs), 7.59(1H, d, J=8.5 Hz), 6.69(1H, s), 6.66 (1H, d, J=8.5 Hz), 4.47(2H, q, J=7.0 Hz), 2.30(3H, s), 1.43(3H, t, J=7.0 Hz)
1e	2e	81	227-228	7.91[e](1H, bs), 7.80-7.76(3H, m), 7.62(1H, t, J=7.5 Hz), 7.49(2H, t, J=7.5 Hz), 7.30(1H, d, J=7.0 Hz), 7.18 (1H, s)
1f	2f	77	170-171	9.66[e](1H, bs), 7.68(1H, d, J=8.5 Hz), 7.29(1H, s), 7.25 (1H, d, J=8.5 Hz), 4.55(2H, q, J=7.0 Hz), 1.50(3H, t, J=7.0 Hz)
1g	3[f]	64[g]	308-310 (lit.[5] 308-310)	9.75[e](2H, bs), 6.99(4H, m)
4a	5a	69	208.5-209	9.11[e](1H, bs), 8.13(2H, d, J=8.0 Hz), 7.87(1H, d, J=8.0 Hz), 7.74-7.66(3H, m), 7.56(2H, t, J=8.0 Hz), 7.47-7.37 (2H, m), 7.20(1H, d, J=8.0 Hz)
4b	5b	63	146-147	10.23[e](1H, bs), 7.98(1H, d, J=8.5 Hz), 7.87(1H, d, J=8.5 Hz), 7.74(1H, d, J=8.5 Hz), 7.52(1H, t, J=8.5 Hz), 7.43-7.36(2H, m), 4.66(2H, q, J=7.0 Hz), 1.53 (3H, t, J=7.0 Hz)
6	7	99[g]	316-318 (dec.)	7.78 (1H, s), 7.86(1H, s), 7.80(1H, d, J=7.5 Hz), 7.32 (1H, t, J=7.5 Hz), 7.09(1H, d, J=7.5 Hz), 6.25(2H, s)[h]

a) Satisfactory microanalysis obtained for all new compounds reported. b) Refers to crystalline isolated products; the mother liquor consists essentially of the N-acylbenzimidazolinones and a small quantity of the corresponding N-acyl-N'-cyanobenzimidazolinones, and no attempt was made to isolate further quantities of the pure material from the mixture. c) From EtOH. d) 300 MHz. e) Exchange with D_2O. f) Product 2g gave 3 on boiling with water. g) Crude product. h) Solvent $CDCl_3$:DMSO (1:1).



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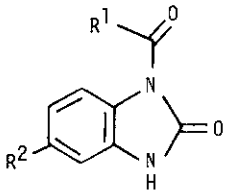

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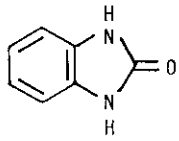

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a: $R^1 = C_6H_5$ $R^2 = H$

b: $R^1 = C_2H_5O$ $R^2 = H$

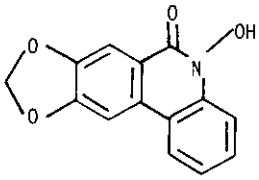
c: $R^1 = C_6H_5$ $R^2 = CH_3$

d: $R^1 = C_2H_5O$ $R^2 = CH_3$

e: $R^1 = C_6H_5$ $R^2 = Br$

f: $R^1 = C_2H_5O$ $R^2 = Br$

g: $R^1 = CF_3$ $R^2 = H$



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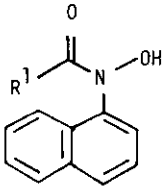

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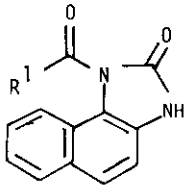
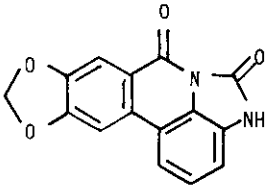


5

a: $R^1 = C_6H_5$

b: $R^1 = C_2H_5O$



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Thus when equimolecular quantities of N-phenylbenzohydroxamic acid (1a) and cyanogen bromide in dry tetrahydrofuran are treated with triethylamine at -40 °C to room temperature, a fast and clean reaction occurred and a crystalline solid (mp 199-200 °C; ir (KBr) 3185, 3100, 1730 and 1685 cm^{-1})was isolated in an analytically pure state in 65% yield. This compound was identified as N-benzoylbenzimidazolinone (2a) by comparison with an authentic sample[3] (mp, mmp, ir, ^1H nmr, tlc). Aqueous hydrolysis of 2b yielded benzimidazolinone (3).

Variation in the electronic character of either the hydroxylamine moiety or the acyl portion of of the hydroxamic acids (cf. Table - 1) did not significantly alter either the yield or the regiospecificity of the reaction. We therefore believe that, in the light of exclusive formation of benzimidazolinones and the high yield obtained in all cases, that the rearrangements are intramolecular and most probably concerted in nature.

This method, limited only by the availability of hydroxylamines, provides a smooth and a direct entry into substituted benzimidazolinones, without requiring an o-diamine as starting material,[6] and has the advantage of affording a product in which one of the nitrogen atoms is already protected, thus permiting further selective transformations. Application of this mehtod to the synthesis of imidazole alkaloids and use of the N-acylbenzimidazolinones as acyl transfer agents is under active study.

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