Tetrahedron Letters, Vol. 34, No. 33, pp. 5325-5326, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Mercury(II) oxide Oxidation of 2-Substituted-*N*-hydroxypiperidine: A Solution to the Regiochemical Problem

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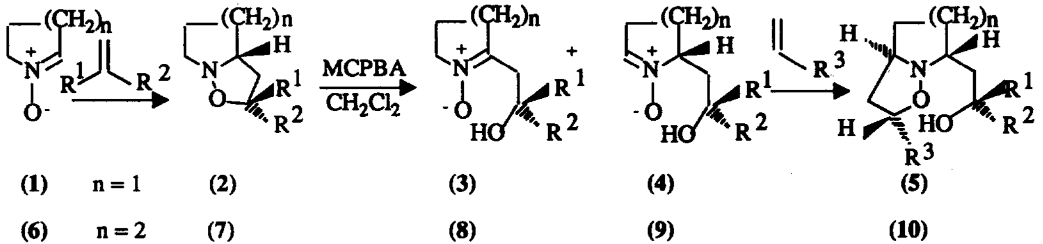
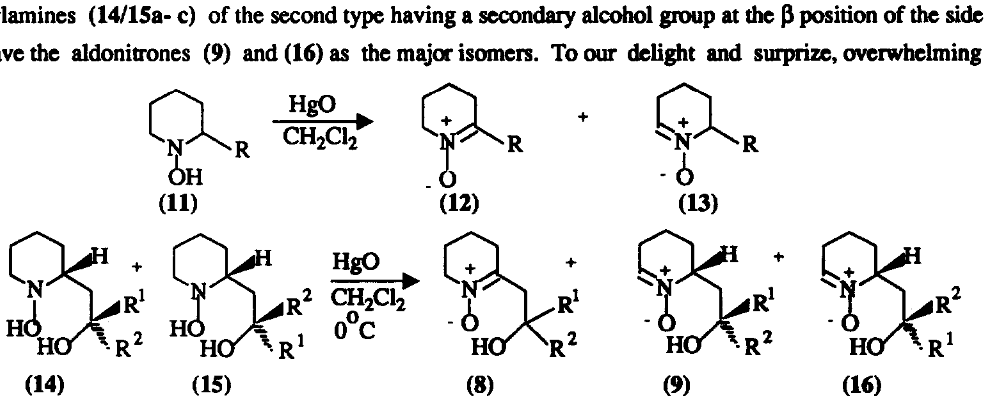
Abstract: *Mercury(II) oxide oxidation of N-hydroxypiperidines having tertiary alcohol group at the β position of the C(2) side chain gave aldonitrones in a highly regioselective manner.*

The aldonitrones (4), obtained exclusively by m-chloroperbenzoic acid (MCPBA) oxidation of the nitrone (1)-alkene adducts (2), upon undergoing a second sequence of cycloaddition afford the adducts (5).[1,2] However, in the piperidine series the application of this sequence has been hampered by the lack of selectivity in the oxidation[1a,3] of the isoxazolidines (7)[4] which lead to the ketonitrones (8) either as the major or the sole isomers. In order to pursue our goal in preparing the aldonitrones (9), we choose to investigate the oxidation of *N*- hydroxypiperidines having three types of C(2) side chain. While the hydroxylamines (11) on oxidation with HgO or p-benzoquinone afforded the ketonitrones (12) as the predominant isomer, the hydroxylamines (14/15a- c) of the second type having a secondary alcohol group at the β position of the side chain gave the aldonitrones (9) and (16) as the major isomers. To our delight and surprize, overwhelming



Scheme 1.



Scheme 2.

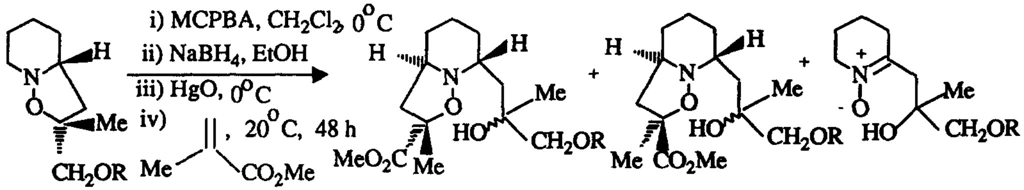
Table. Regiochemistry of Mercury(II) oxide oxidation of hydroxylamines (**11**), (**14**) and (**15**)

Hydroxylamine[a]	Ketonitrone (12)	Aldonitrone (13)
(**11a**), R = Me	75	25
	82[b]	18
(**11b**), R = CH_2Ph	75	25
	80[b]	20
	(8)	**(9) + (16)**
(**14a**),(**15a**), $R^1 = CH_2OH$; $R^2 = H$	35	65
(**14b**),(**15b**), $R^1 = Ph$; $R^2 = H$	30	70
(**14c**),(**15c**), $R^1 = CH_2CH_2OH$; $R^2 = H$	40	60
(**14d**),(**15d**), $R^1 = Me$; $R^2 = Ph$	7	93
(**14e**),(**15e**), $R^1 = Me$; $R^2 = CH_2OH$	10	90
(**14f**),(**15f**), $R^1 = Me$; $R^2 = CH_2OSi^tBuMe_2$	5	95
(**14g**),(**15g**), $R^1 = Me$; $R^2 = CH_2CH_2OH$	5	95
(**14h**),(**15h**), $R^1 = CH_2CH_2OH$; $R^2 = CH_2OH$	10	90

[a]mixture of (**14**) and (**15**) is obtained by $NaBH_4$ reduction of nitrones (**8**) and (**9**); [b]using p-benzoquinone

preference for the formation of the aldonitrones (**9**) and (**16**) was observed in the oxidation of the hydroxylamines (**14/15d-h**) of the third type having a tertiary alcohol at the β position.

The efficiency of this methodology is illustrated with the synthesis of the second-adducts (**17**) and (**18**). Thus, the adduct (**7f**)[4] upon undergoing the sequence of reactions as shown in Scheme 3 afforded, after chromatography (silica, ether), (**17**) and (**18**) in an overall yield of 83%; the ketonitrone (**8f**) remained unreacted under the experimental conditions. In most of the nitrones, the presence of vicinal hydroxyl groups, which can be cleaved by $NaIO_4$, provide an excellent handle for further manipulation of the side chain.



(**7f**) (**17**) (**18**) (**8f**)

R = OSi^tBuMe_2

Scheme 3.

Experimental: *Mercury(II) oxide oxidation of the Hydroxylamines (11), (14), (15)*.- To a solution of the hydroxylamine (1.0 mmol) in CH_2Cl_2 (10 cm^3) at 0°C was added yellow HgO (3.5 mmol) and stirred for 1 h. The resulting greyish mixture was filtered through a small bed of $MgSO_4$. Evaporation of the solvent gave the nitrones in almost quantitative yield.

Financial support provided by King Fahd University of Petroleum and Minerals, Dhahran under grant CY/NITRONES/151 is gratefully acknowledged.

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(Received in UK 23 June 1993; accepted 25 June 1993)