Reaction of *N*-(1-cyano-1-methylethyl)-α-phenylnitrone with phenyl-, 2-pyridyl- and 2-thienyl magnesium bromides: a new approach to alkylaromatic α-hydroxyaminoketones

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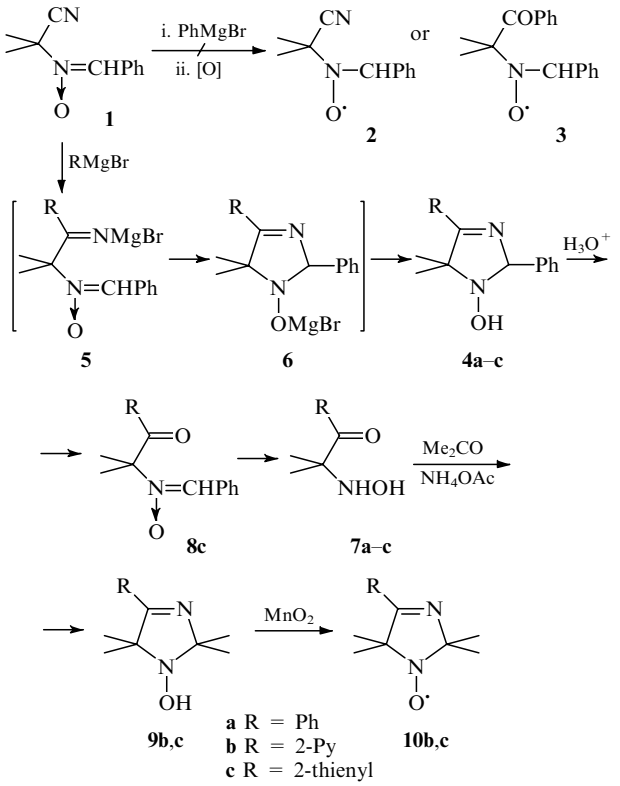
The reaction of *N*-(1-cyano-1-methylethyl)-α-phenylnitrone with phenyl-, 2-pyridyl- and 2-thienyl magnesium bromides affords 3-imidazolines which hydrolyse to alkylaromatic α-hydroxyaminoketones, synthons for stable nitroxides.

N-(1-Cyanoalkyl)aldonitrones (CAN) bearing nitrile and nitrone groups have attracted the attention of scientists as synthons in the synthesis of heterocycles[1–3] including biologically active[4] compounds. The availability of two electrophilic centres in CAN enables it to react with nucleophilic nitrone and nitrile groups.[2–6] There are no reported data on the reaction of CAN with organomagnesium compounds.

One might expect that the reaction of CAN **1**[7†] with PhMgBr would proceed with hydroxyl amine derivative formation. Subsequent oxidation would lead to unknown compounds **2** or **3** with a hydrogen atom at the α-carbon of the nitroxyl group,[9] bearing a nitrile group after the addition of 1 mol of PhMgBr, or a ketone group after the addition of 2 mol of PhMgBr.



Scheme 1

We found that only 1 mol of the reagent is added in the reaction of CAN **1** with an excess of PhMgBr. Hydrolysis results in 1-hydroxy-3-imidazoline **4a** in 65% yield. This may be rationalized by initial PhMgBr addition to the nitrile group, intermediate iminonitrone **5** cyclization and hydrolysis of **6** to give 3-imidazoline **4a**.[10] No subsequent reagent addition to imidazoline **6** was found, as in the case of 2,2,5,5-tetramethyl substituted 3-imidazoline (Scheme 1).[11] This result is of interest for the synthesis of both 1-hydroxy-3-imidazoline derivatives and α-hydroxyaminoketones, synthons for nitroxyl

† CAN **1** was obtained by the dehydration of *N*-(2-hydroxyimino-1,1-dimethylethyl)-α-phenylnitrone.[8] Its synthesis will be reported elsewhere.

‡ Typical procedure: 10.6 mmol (2.0 g) of CAN **1** was quickly added to a solution of 21.3 mmol of Grignard reagent in 20 ml of absolute ether. The mixture was stirred for 10–15 min, then a saturated solution of NH_4Cl was added. In the case of compounds **4a**,**b** the resultant imidazoline precipitate was filtered off. In the case of compound **4c** an ether layer was separated, ether was concentrated by evaporation up to 5 ml, kept for 3 h at +5 °C, and the resulting imidazoline precipitate was filtered off. The yields of compounds **4a–c** were 45–70%.

§ All new compounds give satisfactory analytical data and were characterised by UV, IR and ^{1}H NMR spectroscopy. For **4b**: mp 210–212 °C; UV λ_{max}/nm (log ε) (EtOH) 235 (3.91) and 270 (3.77); IR ν_{max}/cm^{-1} (KBr) 1610, 1580 and 1565 (C=C, C=N); ^{1}H NMR ([$^2H_6$]DMSO) δ 1.44 (s, 3 H, Me), 1.48 (s, 3 H, Me), 5.56 (s, 1 H, 2-H), 7.28–7,56 (m, 6 H, Ph, Py), 7.89 (m, 2 H, Py, OH), 8,02 (d, 1 H, Py, *J* 8.0 Hz) and 8.67 (m, 1 H, Py).

For **4c**: mp 178–179 °C; UV λ_{max}/nm (log ε) (EtOH) 258 sh (4.04), 264 (4.05) and 287 (4.03); IR ν_{max}/cm^{-1} (KBr) 1580 (C=N); ^{1}H NMR ([$^2H_6$]DMSO) δ 1.35 (s, 3 H, Me), 1.49 (s, 3 H, Me), 5.46 (s, 1 H, 2-H), 7.18 (dd, 1 H, thienyl, *J* 4.0, 5.0 Hz), 7.29–7.45 (m, 5 H, Ph), 7.71 (d, 1 H, thienyl, *J* 4.0 Hz), 7,75 (d, 1 H, thienyl, *J* 5.0 Hz) and 7.91 (s, 1 H, OH).

For **7b**: mp 68–70 °C; UV λ_{max}/nm (log ε) (EtOH) 231 (3.82) and 270 (3.60); IR ν_{max}/cm^{-1} (CCl_4) 3600, 3260 (NH, OH) and 1695 (CO); ^{1}H NMR ([$^2H_6$]DMSO) δ 1.35 (s, 6 H, 2 Me), 7.27 (br s, 1 H, NH), 7.48 (s, 1 H, OH), 7.64 (ddd, 1 H, Py, *J* 1.5, 5.0, 7.5 Hz), 7.90 (ddd, 1H, Py, *J* 1.0, 1.5, 7.5 Hz), 7.99 (ddd, 1 H, Py, *J* 1.5, 7.5, 7.5 Hz) and 8.67 (ddd, 1 H, Py, *J* 1.0, 1.5, 5.0 Hz).

For **7c**: mp 98–100 °C , UV λ_{max}/nm (log ε) (EtOH) 266 (3.98) and 286 (3.95); IR ν_{max}/cm^{-1} (KBr) 1640 (CO); ^{1}H NMR ([$^2H_6$]DMSO) δ 1.26 (s, 6 H, 2 Me), 6.06 (br s, 1 H, NH), 7.16 (dd, 1 H, thienyl, *J* 3.5, 5.0 Hz), 7.18 (s, 1H, OH), 7.87 (d, 1 H, thienyl, *J* 5.0 Hz) and 8.21 (d, 1 H, thienyl, *J* 3.5 Hz).

For **8c**: mp 143–146 °C; UV λ_{max}/nm (log ε) (EtOH) 227 (3.96) and 233 (3.95), 266 sh (4.12), 298 (4.33); IR ν_{max}/cm^{-1} (KBr) 1665 (C=O); ^{1}H NMR (CD_3OD) δ 1.93 (s, 6 H, 2 Me), 7.10 (dd, 1 H, thienyl, *J* 3.9, 4.8 Hz), 7.47–7.61 (m, 3 H, Ph), 7.76 (dd, 1 H, thienyl, *J* 1.0, 3.9 Hz), 7.81 (dd, 1 H, thienyl, *J* 1.0, 4.8 Hz), 8.19 (s, 1 H, CH) and 8.36 (m, 2 H, Ph).

For **9b**: m. p. 165–166 °C; UV λ_{max}/nm (log ε) (EtOH) 232 (3.95) and 270 (3.72); IR ν_{max}/cm^{-1} (KBr) 1615, 1580 and 1570 (C=C, C=N); ^{1}H NMR ([$^2H_6$]DMSO) δ 1.34 (s, 6 H, 2 Me), 1.45 (s, 6 H, 2 Me), 7.44 (ddd, 1 H, Py, *J* 1.2, 4.8, 7.7 Hz), 7.58 (s, 1 H, OH), 7.84 (ddd, 1 H, Py, *J* 1.6, 7.5, 7.5 Hz), 8.02 (d, 1 H, Py, *J* 7.7 Hz) and 8.62 (m, 1 H, Py).

For **9c**: mp 138–143 °C; UV λ_{max}/nm (log ε) (EtOH) 263 (4.00) and 282 (3.97); IR ν_{max}/cm^{-1} (KBr) 1600 (C=N); ^{1}H NMR (CD_3OD) δ 1.43 (s, 6 H, 2 Me), 1.53 (s, 6 H, 2 Me), 7.18 (dd, 1 H, thienyl, J 3.6, 5.2 Hz) and 7.62–7.69 (m, 2 H, thienyl).

For **10b**: mp 75–77 °C; UV λ_{max}/nm (log ε) (EtOH) 236 (4.09) and 270 (3.82); IR ν_{max}/cm^{-1} (KBr) 1610, 1580 and 1565 (C=C, C=N).

For **10c**: mp 107–108 °C; UV λ_{max}/nm (log ε) (EtOH) 262 (4.02) and 287 (3.99); IR ν_{max}/cm^{-1} (KBr) 1590 (C=N).

radicals of the 3-imidazoline series[10] which also show a marked neurotropic activity.[12] Thus, 1-hydroxy-3-imidazoline **4a** is readily hydrolysed in 6% HCl solution to give the α-hydroxyaminoketone **7a**.[13]

The reaction of **1** with 2-pyridyl- and 2-thienyl magnesium bromides also proceeds predominantly at the nitrile group to give 3-imidazoline derivatives **4b**,**c**. The hydrolysis of compounds **4b**,**c** with 6% HCl results in the corresponding α-hydroxyaminoketones **7b**,**c** in high yield. This reaction is likely to proceed stepwise *via* nitronoketones **8** formation (Scheme 1). Thus, nitronoketone **8c** was isolated after the hydrolysis of imidazoline **4c** at room temperature. Heating of **8c** in 6% HCl results in α-hydroxyaminoketone **7c**.[§]

Condensation of α-hydroxyaminoketones **7b**,**c** with acetone in the presence of ammonium acetate (*cf*. ref. 10) gave 1-hydroxy-4-R-2,2,5,5-tetramethyl-3-imidazolines **9b**,**c** which when oxidised with MnO_2, gave nitroxides **10b**,**c**, respectively. Compound **10b** is of interest as a spin-labelled reagent capable of chelating phenanthroline analogues (*cf*. refs. 14 and 15). The transformation presented here is a convenient method for the synthesis of alkylaromatic α-hydroxyaminoketones, synthons for stable nitroxides of 3-imidazolines.

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