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

Vadim K. Khlestkin,* Vladimir A. Reznikov, Dmitrii G. Mazhukin, Aleksei Ya. Tikhonov and Leonid B. Volodarsky

Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 383 235 4752; e-mail: root@nitrox.nsk.su
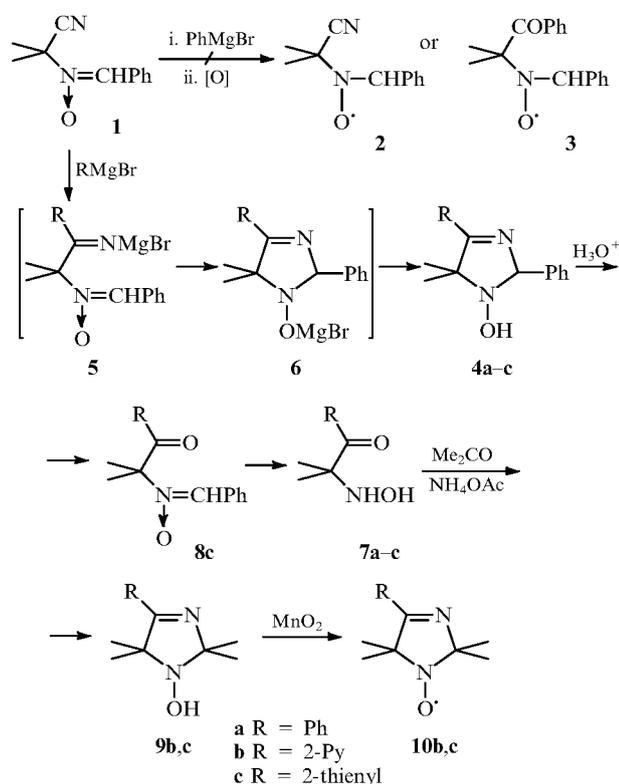
The reaction of N-(1-cyano-1-methylethyl)-α-phenylnitrone with phenyl-, 2-pyridyl- and 2-thienyl magnesium bromides affords 3-imidazolines which hydrolyse to alkylaromatic α-hydroxyaminoketones, synthons for stable nitroxides.

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

Scheme 1

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.

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

---

§ All new compounds give satisfactory analytical data and were characterised by UV, IR and ¹H 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); ¹H NMR ([²H₆]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); ¹H NMR ([²H₆]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 (CCl₄) 3600, 3260 (NH, OH) and 1695 (CO); ¹H NMR ([²H₆]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); ¹H NMR ([²H₆]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); ¹H NMR (CD₃OD) 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); ¹H NMR ([²H₆]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); ¹H NMR (CD₃OD) 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).

---

† 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 NH₄Cl 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%.

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.

References

1 M. Masui, K. Suda, M. Yamauchi and C. Yijima, *Chem. Pharm. Bull.*, 1973, **21**, 1605.
2 M. Masui, K. Suda, M. Yamauchi and C. Yijima, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1955.
3 K. Suda, H. Fuke, F. Hino and C. Yijima, *Chem. Lett.*, 1985, 1115.
4 M. Masui and M. Nakanishi, *Jpn Pat.*, 7326 740, C 07bcd, 1973 (*Chem. Abstr.*, 1973, **79**, 136548y).
5 M. Masui, C. Yijima and K. Suda, *Chem. Pharm. Bull*, 1971, **19**, 865; M. Masui, K. Suda and C. Yijima, *Chem. Pharm. Bull.*, 1972, **19**, 2150.
6 M. Masui and C. Yijima, *J. Chem. Soc. (C)*, 1967, 2022.
7 G. Zinner and U. Kruger, *Chem.-Zeit.*, 1977, **101**, 154.
8 Yu. G. Putsykin and L. B. Volodarsky, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1968, **9**, 101 (in Russian).
9 V. A. Reznikov, I. A. Gutorov, Yu. V. Gatilov, T. V. Ribalova and L. B. Volodarsky, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 400 (in Russian).
10 T. K. Sevastyanova and L. B. Volodarsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1972, 2339 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1972, **21**, 2226).
11 V. A. Reznikov, L. A. Vishnivetskaya and L. B. Volodarsky, *Izv. Akad. Nauk., Ser. Khim.*, 1994, 899 (*Russ. Chem. Bull.*, 1994, **43**, 844).
12 L. B. Volodarskii, A. S. Lapik, V. V. Russkikh, V. S. Kobrin, E. F. Lavretskaya, L. I. Volkova, D. A. Sarkisyan and M. M. Borisov, *USSR Pat.* 657 016, C 07c, 1979 (*Chem. Abstr.*, 1979, **91**, 68767q).
13 L. B. Volodarsky and T. K. Sevastyanova, *Zh. Org. Khim.*, 1971, **7**, 1687 [*J. Org. Chem. USSR (Engl. Transl.)*, 1971, **7**, 1752].
14 L. B. Volodarsky, V. A. Reznikov and V. I. Ovcharenko, *Synthetic Chemistry of Stable Nitroxides*, CRC Press, Boca Raton–Ann Arbor–London–Tokyo, 1994, p. 159.
15 F. Hintermaier, L. B. Volodarsky, K. Polborn and W. Beck, *Liebigs Ann.*, 1995, 2189.