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A route to the synthesis of previously unknown α-heteroatom substituted nitrones

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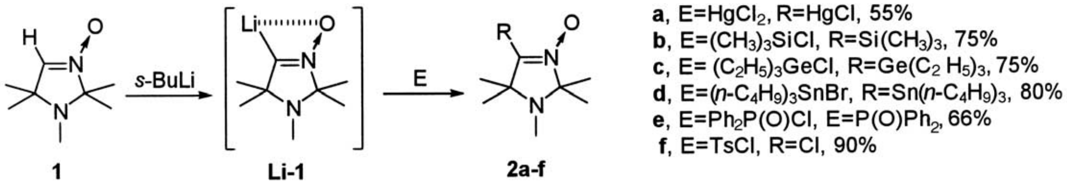
Abstract—α-Heteroatom substituted nitrones have been synthesized for the first time by the reaction of α-lithiated cyclic aldonitrone 1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide with $HgCl_2$, $(CH_3)_3SiCl$, $(C_2H_5)_3GeCl$, $(n\text{-}C_4H_9)_3SnBr$ and $Ph_2P(O)Cl$. α-Chloronitrone was prepared for the first time by direct chlorination of α-lithiated aldonitrone using TsCl. © 2002 Elsevier Science Ltd. All rights reserved.

During the last decades nitrones have attracted the attention of investigators as compounds with a wide spectrum of biological activity,[1] light-sensitive materials,[2] polymer stabilizers,[3] as well as useful starting compounds in different synthetic strategies.[4] Due to the synthetic potential and practical application of these compounds, considerable efforts have consequently been applied to the preparation of interesting new derivatives, in particular those containing α-heteroatom substituents. However, among the many known nitrones, only a few examples bearing a heteroatom adjacent to the nitrone group carbon atom have been reported, namely aminonitrones,[5] alkoxynitrones,[5b,c,6] mercaptonitrones,[5b,c,7] a phosphononitrone[8] and chloronitrones.[9] The narrow range of α-heteroatom containing nitrones seems to result from restrictions which current synthetic methods impose on the variety of substituents at the α-carbon of a nitrone.[10] Only two methods for the synthesis of α-heteroatom substituted nitrones, based on the direct transformation of an aldonitrone group, have been reported.[6,8]

As part of our investigation aimed at the development of a procedure for chemical modification of compounds, containing the aldonitrone group, we have shown,[11,12] that the lithiation-electrophilic substitution sequence in the series of cyclic aldonitrones provides a new route to the synthesis of nitrones diversely substituted at the α-carbon. Here the synthesis of hitherto unknown α-heteroatom substituted nitrones of the 3-imidazoline 3-oxide series via this approach[11,12] is described.

Results and discussion

The metalation of 1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide **1** with *s*-BuLi leads to the dipole-stabilized organolithium intermediate **Li-1**.[13] The **Li-1** reacted with $HgCl_2$, $(CH_3)_3SiCl$, $(C_2H_5)_3GeCl$, $(n\text{-}C_4H_9)_3SnBr$ and $Ph_2P(O)Cl$ to give nitrones **2a**–**e** in good yields (Scheme 1). The reaction of **Li-1** with $(C_2H_5)_3SnCl$ afforded a product, which underwent decomposition so rapidly, that it could not be isolated and characterized.



Scheme 1.

Keywords: nitrones; synthesis; α-lithiation of aldonitrones; dipole-stabilized organolithiums; α-heteroatom substituted nitrones; IR; ^{13}C NMR spectroscopy.

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The reaction of **Li-1** with TsCl afforded the α-chloronitrone **2f** (cf. Ref. 9).

A typical procedure is as follows: *s*-BuLi hexane solution (2.3×10^{-3} mol) was placed under argon in a three-necked flat-bottomed flask fitted with a magnetic stirrer, dropping funnel and thermometer, and cooled to −70°C. Then, a solution of **1** (1.9×10^{-3} mol in 3 ml of THF) was added dropwise over 15 min with vigorous stirring. After this, a solution of the electrophile (2.1×10^{-3} mol in 3 ml of THF) was added all at once, then the mixture stirred for 5 min at −70°C, allowed to warm-up to 0°C, and evaporated under reduced pressure. The residues were chromatographed on Al_2O_3 ($CHCl_3$ as eluent). The synthesized compounds were characterized with IR, UV, NMR, mass spectra (M^+) and microanalyses.[†]

The nitrones **2a** and **2e** are stable crystalline solids. Nitrone **2b** is a moisture-sensitive viscous oil that decomposes within 1 week even when stored in the refrigerator. Nitrone **2c** is a low-melting (about 28°C) crystalline compound, **2d** is a fluid liquid. The chloronitrone **2f** is a crystalline solid, which turns yellow upon storage at room temperature. Nitrones **2c**, **2d** and **2f** can be stored in the refrigerator (−5°) for weeks without any trace of decomposition.

In conclusion, the α-heteroatom substituted nitrones, including those containing an α-carbon–metal bond, were synthesized from a 3-imidazoline 3-oxide by a lithiation–electrophilic substitution sequence. Our further experiments have shown that the described approach could be successfully applied to the aldonitrones of pyrroline-1-oxide, dihydroisoquinoline-2-oxide and 2*H*-imidazol-1-oxide as well. In view of this, the reaction sequence described here can be considered as being a general method for the synthesis of cyclic α-heteroatom substituted nitrones.

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[†] **2a**: (mp 201–203°C, from EtOAc:$CHCl_3$, 1:2); IR (KBr, cm^{-1}): 1576 (C=N); UV ($CHCl_3$, λ_{max}) 265 nm ($\varepsilon=4194$); ^1H NMR (CCl_4) δ (ppm): 1.34 (6H, s, $2\times CH_3$), 1.50 (6H, s, $2\times CH_3$), 2.42 (3H, s, NCH_3), ^{13}C NMR: 24.71, 24.79 (CH_3), 28.04 (NCH_3), 67.60 (C5), 93.11 (C2), 172.18 (C=N). Anal. calcd for $C_8H_{15}N_2OHgCl$: C, 24.55; H, 3.84; N, 7.16. Found: C, 24.39; H, 3.59; N, 7.12. Mass spectrum (M^+): calcd for $C_8H_{15}N_2OHgCl$: 392.05792. Found: 392.05754. **2b**: oil, IR (CCl_4, cm^{-1}): 1525 (C=N); UV (EtOH, λ_{max}) 246 nm ($\varepsilon=6195$); ^1H NMR (CCl_4) δ (ppm): 0.47 (9H, s, $Si(CH_3)_3$), 1.41 (6H, s, $2\times CH_3$), 1.54 (6H, s, $2\times CH_3$), 2.53 (3H, s, NCH_3), ^{13}C NMR: −2.81 ($Si(CH_3)_3$), 23.92, 24.36 (CH_3), 26.82 (NCH_3), 65.22 (C5), 90.02 (C2), 144.54 (C=N). Anal. calcd for $C_{11}H_{24}N_2OSi$: C, 57.89; H, 10.52; N, 12.28. Found: C, 58.10; H, 10.52; N, 12.04. Mass spectrum (M^+): calcd for $C_{11}H_{24}N_2OSi$: 228.16578. Found: 228.16595. **2c**: oil, IR (CCl_4, cm^{-1}): 1533 (C=N); UV (heptane, λ_{max}) 257 nm ($\varepsilon=8008$); ^1H NMR (CCl_4) δ (ppm): 1.04 (15H, s, $Ge(C_2H_5)_3$), 1.16 (6H, s, $2\times CH_3$), 1.33 (6H, s, $2\times CH_3$), 2.32 (3H, s, NCH_3), ^{13}C NMR: 3.74, 9.00 ($Ge(C_2H_5)_3$), 24.45, 24.72 (CH_3), 26.99 (NCH_3), 65.07 (C5), 89.97 (C2), 146.64 (C=N). Anal. calcd for $C_{14}H_{30}N_2OGe$: C, 52.85; H, 9.53; N, 8.90. Found: C, 53.06; H, 9.87; N, 8.62. Mass spectrum (M^+): calcd for $C_{14}H_{30}N_2OGe$: 316.15699. Found: 316.15556. **2d**: liquid, IR (CCl_4, cm^{-1}): 1533 (C=N); UV (heptane, λ_{max}) 252 nm ($\varepsilon=4758$); ^1H NMR (CCl_4) δ (ppm): 0.88 (9H, t, $^3J_{H\text{–}H}=7.6$ Hz, $3\times CH_3$, Bu), 0.91 (6H, t, $^3J_{H\text{–}H}=7.0$ Hz, $3\times Sn\text{-}C\underline{H}_2\text{-}CH_2$), 1.32 (6H, tt, $^3J_{H\text{–}H}=7.0$ Hz, $^3J_{H\text{–}H}=6.4$ Hz, $3\times CH_2\text{-}C\underline{H}_2\text{-}CH_2$), 1.52 (6H, qt, $^3J_{H\text{–}H}=7.6$ Hz, $^3J_{H\text{–}H}=6.4$ Hz, $3\times CH_2\text{-}C\underline{H}_2\text{-}CH_3$), 1.15 (6H, s, $2\times CH_3$), 1.32 (6H, s, $2\times CH_3$), 2.32 (3H, s, NCH_3), ^{13}C NMR: 13.52 (CH_3, Bu), 10.08, 26.93, 28.99 (CH_2, Bu), 24.43, 24.89 (CH_3), 27.27 (NCH_3), 65.32 (C5), 89.84 (C2), 151.19 (C=N). Anal. calcd for $C_{20}H_{42}N_2OSn$: C, 53.97; H, 9.44; N, 6.29. Found: C, 54.13; H, 9.71; N, 6.06. **2e**: purified by chromatography on silica gel ($CHCl_3$), (mp 131–133°C, from hexane:benzene, 1:1); IR (KBr, cm^{-1}): 1543 (C=N); UV (EtOH, λ_{max}) 261 nm ($\varepsilon=7786$); ^1H NMR ($CDCl_3$) δ (ppm): 1.36 (6H, s, $2\times CH_3$), 1.57 (6H, s, $2\times CH_3$), 2.35 (3H, s, NCH_3), 7.42–7.47, 7.51–7.55, 7.79–7.85 (10H, m, Ph), ^{13}C NMR: 24.04, 24.56 (CH_3), 26.79 (NCH_3), 66.09 (C5, d, $^2J_{C\text{–}P}=10.2$ Hz), 92.09 (C2, d, $^3J_{C\text{–}P}=5.1$ Hz), 128.27 (*o*-Ph, d, $^2J_{C\text{–}P}=12.7$ Hz), 129.48 (*i*-Ph, d, $J_{C\text{–}P}=111.9$ Hz), 131.24 (*m*-Ph, d, $^3J_{C\text{–}P}=10.6$ Hz), 132.26 (*p*-Ph, d, $^4J_{C\text{–}P}=2.2$ Hz), 139.45 (C=N, d, $J_{C\text{–}P}=104.6$ Hz). ^{31}P NMR (rel. 85% H_3PO_4): 20.63 (P=O). Anal. calcd for $C_{20}H_{25}N_2PO_2$: C, 67.42; H, 7.02; N, 7.87; P, 8.71. Found: C, 67.48; H, 7.03; N, 7.48; P, 8.76. **2f**: purified by chromatography on Al_2O_3 (hexane:EtOAc 1:1), mp 82–83°C (from hexane). IR (KBr, cm^{-1}): 1578 (C=N); UV (CCl_4, λ_{max}) 260 nm ($\varepsilon=6020$); ^1H NMR (CCl_4) δ (ppm): 1.13 (6H, s, $2\times CH_3$), 1.27 (6H, s, $2\times CH_3$), 2.23 (3H, s, NCH_3), ^{13}C NMR: 23.44, 23.73 (CH_3), 27.25 (NCH_3), 63.28 (C5), 90.26 (C2), 132.46 (C=N). Anal. calcd for $C_8H_{15}N_2OCl$: C, 50.39; H, 7.93; N, 14.69; Cl, 18.59. Found: C, 50.38; H, 8.23; N, 14.71; Cl, 18.40. Mass spectrum (M^+): calcd for $C_8H_{15}N_2OCl$: 190.08728. Found: 190.08769.

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