Communication

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Synthesis of (Z)-N-aryl-C-(pyrid-3-yl)-nitrones

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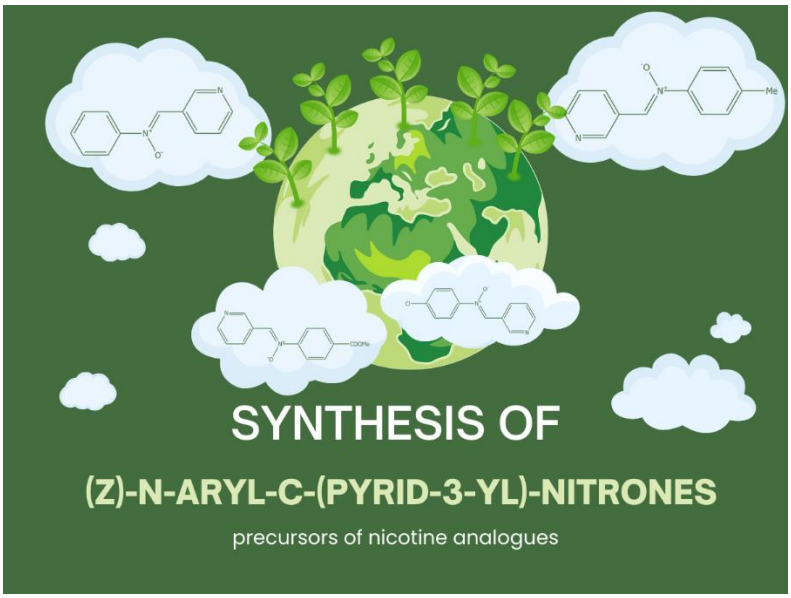

Abstract: In this work, new nitrones, derived from nicotinaldehyde and N-aryl-N-hydroxylamines are described, and methods for their synthesis, and purification are presented. Spectral characterisation of said nitrones is also presented.

Keywords: nitrones, heterorganic chemistry

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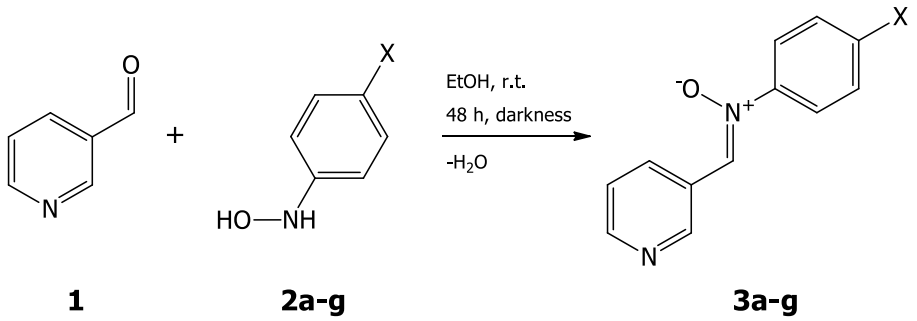
Nitrones constitute a group of heterorganic compounds that have vast application in both industry among many: as antioxidants [1], polymer chemistry [2] and agriculture [3].

Some nitrones are also patented for medical applications e.g., in treating tinnitus [4] and radiologically-dense breasts [5]. Considering the broad applicational potential of nitrones, their synthesis seems an interesting field of development. Furthermore, nitrones of C-(pyrid-3-yl) type can be, and have successfully been, used in synthesis of nicotine analogues [6,7]. Those nicotine analogues can be useful in industry [8]. Furthermore the group of reactions used to synthetise those nicotinoids is well described in terms of computational chemistry, which largely accelerates development of processes involving nitrones as feedstock [9-11]. By describing new nitrones we hope to simplify the work of future synthetic chemists looking for solutions for problems contemporary to them.

For synthesis of nitrones **3a-g** we decided to use condensation between N-aryl-N-hydroxylamines **2a-g** and 3-pyridylaldehyde (**1**) (Scheme 1.) The method we applied for synthesis of nitrones has been widely and successfully used for synthesis of various nitrones [12,13]. Via the described route we have managed to synthesise seven N-aryl-C-(pyrid-3-yl) nitrones, for of which are newly synthesised compounds. Structure of compounds was identified by ^{1}H-NMR and^{13}C-NMR spectra analysis. Further confirmation came with the analysis of IR spectroscopy and mass spectrometry results.



1 **2a-g** **3a-g**

X = Me (**a**), H (**b**), F (**c**), I (**d**), Br (**e**), Cl (**f**), COOMe (**g**)

Scheme 1. Condensation of 3-pyridylaldehyde (**1**) and 4-substituted analogues of N-hydroxyl-N-phenylamine **2a-g** leading to nitrones **3a-g**

The key signals present in spectra of **3b** are listed and assigned below (see Experimental). For signal to be recognised as key it had to be specific nitrone moiety and easily observable, so that future synthesis of this group of compounds is facilitated.

By cross reference of the spectra with reference data [14] in ^{1}H-NMR the singlet at 7.99 ppm with unitary integral is assigned to the hydrogen nucleus of the atom in the C-position in the nitrone moiety. The singlet has additional advantage over multiplets, namely it is easily observable even on the low-resolution NMR.

Signals in the IR spectra were identified in accordance with results presented by H. Shindo et al. [15]. Special focus is also given to nitrone moiety as the most characteristic part

of the molecules. According to the reference material [15] C=N bond of a C,N-diarylnitrone vibrates between 1488 and 1596 cm^{-1}, C-H bond falls around 3000 cm^{-1}, while N-O stretching of C,N-diarylnitrones falls between 1058 and 1088. Vibrations of aryl rings are alco cross-referred with the same data.

Experimental

Instruments and methods

All melting points are uncorrected and have been measured on Boetius apparatus. Mass spectrometry was conducted with Shimadzu LCMS, with chemical ionization. IR spectra were obtained with Thermo FT-IR NICOLET 6700, using ATR, spectra were registered between 400 cm^{-1} and 4000 cm^{-1}, and were analysed with OMNIC spectra 8.2. All NMR spectra were registered in $CDCl_3$ with BRUKER ASCEND 500 apparatus, ^{1}H-NMR was registered with 500 MHz frequency, while ^{13}C-NMR used 125 MHz; and were analyzed with Bruker TopSpin 4.2 software. UV-Vis spectra were recorded using Macherey-Nagel Nanocolor UV/VIS apparatus in methanol solutions.

Reagents

N-Aryl-N-hydroxylamines **2a-g** were prepared fresh via reduction of respective nitroarenes according to the procedure described in the literature .

General procedure for synthesis of N-phenyl-C-(pyrid-3-yl) nitrone (**3b**)

4.64 g of N-phenyl-N-hydroxylamine (42.5 mmol, 1.2 eq) was mixed with enough ethyl alcohol to dissolve all the solids in room temperature (10 cm^3), to the sollution 1 g of anhydrous sodium sulphate(VI) was added, followed by 3.80 g of 3-pirydylaldehyde (35.5 mmol, 1 eq). Reaction was stirred for 48 hours in absence of light. After that time, solids were filtered and washed with diethyl ether. The filtrate was evaporated and product recrystalised from equivolume mixture of cyclohexane and dichloromethane (CyH:DCM 1:1 v/v).

All other nitrones **3a,c-g** were prepared in an analogous manner, the solvent used for recrystallisation is specified for every compound.

(Z)-N-(4-methylphenyl)-C-(pyrid-3-yl) nitrone (**3a**)

Brutto formula: $C_{13}H_{12}N_2O$; m.p.: 118-122 ^{o}C (DCM); ^{1}H-NMR: 2.43 (s, 3H), 7.30 (d, 2H, J=8,1 Hz), 7.43 (dd, 1H, J_1=8.2 J_2=4.9 Hz), 7.67-7.69 (m, 2H), 7.97 (s, 1H), 8.64 (dd, 1H, J_1=4.9 J_2=1.7 Hz), 9.08 (d, 1H, J=2.0 Hz), 9.21 (dt, 1H, J_1=8.1 J_2=1.8 Hz) ppm; ^{13}C-NMR: 21.21, 121.40, 123.68, 127.40, 129.79, 130.99, 134.79, 140.79, 146.49, 150.34, 150.81 ppm; IR v: 3040 (C-H nitrone), 1555 (C=N nitrone) 1077 (N-O nitrone), 824, 705 (aryl) cm^{-1}; UV-Vis: $\lambda_{max\ MeOH}$ 317.8 nm; MS: 213($[M+H]^+$) m/e.

N-phenyl-C-(pyrid-3-yl) nitrone (**3b**)

Brutto formula: $C_{12}H_{10}N_2O$; m.p.: 111-115 °C (Cyclohexane:DCM 1:1 v/v); ^{1}H-NMR: 7.44 (dd, 1H, J_1=8.2 J_2=4.9 Hz), 7.50-7.54 (m, 3H), 7.78-7.80 (m, 2H), 7.99 (s, 1H), 8.66 (dd, 1H, J_1=4.9 J_2=1.7 Hz). 9.10 (d, 1H, J=2.0 Hz), 9.22 (dt, 1H, J_1=8.1 J_2=1.7 Hz) ppm; ^{13}C-NMR:121.68, 123.70, 127.29, 129.33, 130.44, 134.84, 148.77, 150.39, 150.96 ppm; IR v: 3057 (C-H nitrone), 1552 (C=N nitrone), 1071 (N-O nitrone), 705, 688 (aryl) cm^{-1}; UV-Vis: $\lambda_{max\ MeOH}$ 315.5 nm; MS: 199([M+H]$^+$) m/e.

N-(4-fluorophenyl)-C-(pyrid-3-yl) nitrone (**3c**)

Brutto formula: $C_{12}H_9N_2OF$; m.p.: 145-149 °C (EtOAc); ^{1}H-NMR: 7.17-7.22 (m, 2H), 7.44 (dd, 1H, J_1=8.1 J_2=4.9 Hz), 7.79-7.83 (m, 2H), 7.95 (s, 1H), 8.66 (dd, 1H, J_1=4.9 J_2=1.7 Hz), 9.09 (d, 1H, J=2.1 Hz), 9.19 (dt, 1H, J_1=8.1 J_2=2.1 Hz) ppm; ^{13}C-NMR: 116.15, 116.34, 123.64, 123.72, 127.15, 131.44, 134.83, 144.94, 150.38, 151.08, 162.34, 164.34 ppm ;IR v: 3054 (C-H nitrone), 1558 (C=N nitrone), 1075 (N-O nitrone), 706 (aryl) cm^{-1}; UV-Vis: $\lambda_{max\ MeOH}$ 313.0 nm; MS: 217([M+H]$^+$) m/e.

N-(4-iodophenyl)-C-(pyrid-3-yl) nitrone (**3d**)

Brutto formula: $C_{12}H_9N_2OI$; m.p.: 163-175 °C (THF); ^{1}H-NMR: 7.44 (dd, 1H, J_1=8.1 J_2=4.9 Hz), 7.54-7.57 (m, 2H), 7.84-7.87 (m, 2H), 7.97 (s, 1H), 8.66 (dd, 1H, J_1=4.9 J_2=1.7 Hz), 9.09 (d, 1H, J=2,1 Hz), 9.19 (dt, 1H, J_1=8.1 J_2=2.1 Hz) ppm; ^{13}C-NMR: 96.16, 123.29, 123.76, 127.09, 131.44, 138.45, 148.27, 150.41, 151.14 ppm; IR v: 3045 (C-H nitrone), 1582 (C=N nitrone), 1074 (N-O nitrone), 697 (aryl) cm^{-1}; UV-Vis: $\lambda_{max\ MeOH}$ 323.3 nm; MS: 325([M+H]$^+$).

N-(4-bromophenyl)-C-(pyrid-3-yl) nitrone (**3e**)

Brutto formula: $C_{12}H_9N_2OBr$; m.p.: 143-150 °C (Cyclohexane:DCM 1:1 v/v); ^{1}H-NMR: 7.44 (dd, 1H, J_1=8.1 J_2=4.9 Hz), 7.64 (d, 2H, J=8,7 Hz), 7.70 (d, 2H, J=8.6 Hz), 7.97 (s, 1H), 8.67 (d, 1H, J=4.7 Hz), 9.10 (s, 1H), 9.19 (d, 1H, J=8.1 Hz) ppm; ^{13}C-NMR: 123.20, 123.74, 124.46, 127.08, 131.48, 132. 47, 134.91, 147.57, 150.44, 151.19 ppm; IR v: 3045 (C-H nitrone), 1548 (C=N nitrone), 1075 (N-O nitrone), 700 (aryl) cm^{-1}; UV-Vis: $\lambda_{max\ MeOH}$ 318.0 nm; MS: 277([M_{Br-79}+H]$^+$), 279([M_{Br-81}+H]$^+$) m/e.

N-(4-chlorophenyl)-C-(pyrid-3-yl) nitrone (**3f**)

Brutto formula: $C_{12}H_9N_2OCl$; m.p.: 133-139 °C (EtOAc); ^{1}H-NMR: 7.44 (dd, 1H, J_1=8.1 J_2=4.9 Hz), 7.47-7.51 (m, 2H), 7.46-7.78 (m, 2H), 7.97 (s, 1H), 8.67 (dd, 1H, J_1=4.8 J_2=1.6 Hz), 9.09 (d, 1H, J=1.9 Hz), 9.19 (dt, 1H, J_1=8.1 J_2=1.7 Hz) ppm; ^{13}C-NMR: 122.97, 123.74, 127.08, 129.48, 131.50, 134.50, 136.37, 147.08, 150.43, 151.17 ppm; IR v: 3048 (C-H nitrone), 1551 (C=N nitrone), 1075 (N-O nitrone), 700 (aryl) cm^{-1}; UV-Vis: $\lambda_{max\ MeOH}$ 321.0 nm; MS: 233([M_{Cl-35}+H]$^+$) m/e.

N-(4-carbomethoxyphenyl)-C-(pyrid-3-yl) nitrone (**3g**)

Brutto formula: $C_{14}H_{12}N_2O_3$; m.p.: 166-173 °C (n-hexanol); ^{1}H-NMR: 3.97 (s, 3H), 7.46 (dd, 1H, J_1=8.1 J_2=4.9 Hz), 7.87-7.90 (m, 1H), 8.04 (s, 1H), 8.15-8.23 (m, 3H), 8.68 (dd, 1H, J_1=4.8 J_2=1.7 Hz), 9.12 (d, 1H J=2.0 Hz), 9.22 (dt, 1H, J_1=8.1 J_2=1.8 Hz) ppm; ^{13}C-NMR: 52.59, 121.77, 122.58, 123.76, 125.35, 127.01, 130.22, 130.40, 130.85, 132.15, 135.02, 150.54, 151,31 ppm; IR ν : 3047 (C-H nitrone), 1550 (C=N nitrone), 1074 (N-O nitrone), 698 (aryl) cm^{-1}; UV-Vis: $\lambda_{max\ MeOH}$ 323.0 nm; MS: 257([M+H]$^+$) m/e.

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