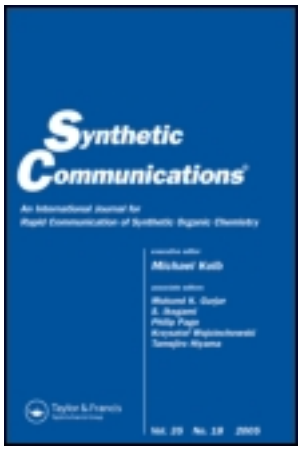

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Synthesis of *C*-Aryl-*N*-cyclopropylnitrones

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ABSTRACT

Synthesis of *C*-aryl-*N*-cyclopropylnitrones is described. Preparations were performed either by condensation of the appropriate aldehyde with *N*-cyclopropyl-hydroxylamine, or oxidation of *N*-substituted *N*-cyclopropylamines with sodium tungstate/hydrogen peroxide.

Free radicals are involved in many neurodegenerative diseases, such as cerebral ischemia and reperfusion, stroke, Alzheimer's disease, and aging.[1,2] Free radicals and other reactive oxygen or nitrogen species, such as hydroxyl radical ($^{\cdot}OH$), superoxide anion ($O_2^{-\cdot}$), hydrogen peroxide (H_2O_2), nitric oxide (NO), peroxynitrite ($ONOO^-$), generated during oxidative stress or ischemia and reperfusion, cause cell damage via lipid peroxidation, oxidation of proteins, and nucleic acids. Therefore, antioxidant therapy has an important role in the treatment of the above mentioned diseases.

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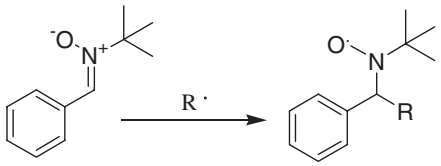
Free radical scavenging activity of *N*-*t*-butyl-α-phenylnitrone (PBN, **1**) was discovered in the 1970's.[3–5] Nitrone compounds can bind free radicals on their α carbon atom resulting in a nitroxyl radical **2** which is more stable and detectable by electron spin resonance spectroscopy (ESR) as well.



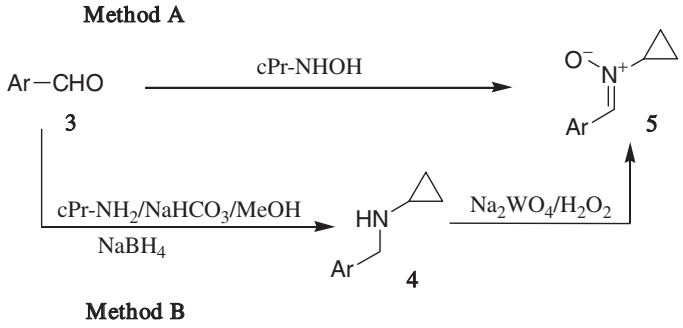
1 **2**

Stability of nitrone compounds as well as the corresponding nitroxyl radicals is highly influenced by the *N*-alkyl group. Various substituents on the nitrone nitrogen are described in the literature, however, we have found that no *N*-cyclopropylnitrone was reported yet, except two examples mentioned in a US patent[6] without any physical, spectroscopic, or activity data.

Our approach was to substitute the *t*-butyl group in PBN with a cyclopropyl moiety whose olefin-like character can effectively stabilize the nitrone, and moreover, the unpaired electron in the nitroxyl radical can overlap the molecule orbitals of the cyclopropyl ring resulting in an improvement of the free radical scavenging activity. Therefore, we aimed at the syntheses of new α-aryl- and hetaryl-*N*-cyclopropylnitrones **5**.

Preparations were performed using established methods for the syntheses of nitrones, either by direct condensation of the appropriate aldehyde **3** with *N*-cyclopropyl-hydroxylamine (Method A) or by oxidation of *N*-cyclopropylamines **4** (Method B). *N*-Cyclopropyl-hydroxylamine[7] was obtained from nitrocyclopropane by reduction with zinc in the presence of ammonium chloride in water. As *N*-cyclopropyl-hydroxylamine is not stable under normal conditions, the majority of *N*-cyclopropylnitrones were synthesized through the corresponding *N*-cyclopropylamines **4** via Method B. They were obtained from the appropriate aldehyde reacting with cyclopropylamine and then reducing the Schiff base obtained with sodium borohydride. *N*-Cyclopropylamines (**4**) were oxidized directly to the corresponding nitrones (**5**) by sodium tungstate/hydrogen peroxide (Table 1). Structures of *N*-cyclopropylnitrones **5** were characterized by IR and ^{1}H NMR spectroscopic methods. In addition to the standard ^{1}H NMR

experiments, structures of compounds **5** were verified by homonuclear ^{1}H-^{1}H NOE experiments, and each nitrone **5** prepared proved to be *Z*-isomer.



In summary, we synthesized and characterized *N*-cyclopropylnitrones by simple chemical reactions in good or moderate yields. Their free radical scavenging activity will be published elsewhere.

Table 1. Preparation of *N*-cyclopropylamines **4** and *N*-cyclopropylnitrones **5**.

Ar	Amines (**4**)	Yield (%)	Nitrones (**5**)	Method of preparation	Yield (%)
Phenyl	**4a**	93	**5a**	A	43
				B	63
4-F-Phenyl	**4b**	95	**5b**	B	50
4-Cl-Phenyl	**4c**	99	**5c**	B	53
4-Br-Phenyl	**4d**	97	**5d**	B	66
2-Hydroxy-phenyl	**4e**	99	**5e**	B	52
3,4-Methylenedioxy-phenyl	**4f**	95	**5f**	B	62
3,4-Dimethoxy-phenyl	**4g**	97	**5g**	B	59
4-Etoxycarbonyl-phenyl	**4h**	88	**5h**	B	39
3,5-Di-*t*-butyl-4-hydroxy-phenyl	**4i**	62 (HCl-salt)	**5i**	B	38
4-F_3C-Phenyl	**4j**	93	**5j**	B	44
2-Pyrrol	**4k**	95	**5k**	B	41
3-Pyridyl	**4l**	96	**5l**	B	65

EXPERIMENTAL

Solvents and reagents were obtained from commercial sources. Spectra were recorded in DMSO-d_6 at 30°C on a Varian Inova-300 spectrometer (operating at 300 MHz for ^{1}H) using a ^{1}H{^{13}C} PFG double-resonance 5 mm probe. Chemical shifts are given relative to the reference: $\delta_{TMS} = 0.00$ ppm. For NOE measurements the gDPFGSE-NOE sequence as part of the standard spectrometer software package was used. We used *i*Burp2 selective 180° inversion pulses and 1 sec mixing time for the gDPFGSE-NOE experiments. Infrared data were recorded on a PERKIN ELMER 1000 spectrophotometer, phase: KBr pellet, resolution: 4 cm^{-1}. MS measurements were performed on Finigan MAT 95XP spectrometer using perfluoro-tributylamine as reference, EI, 70 eV. Gas chromatographic measurements were performed on a FISONS MD-800 GC-MS apparatus using Supelco MDN-5S column (30 m × 0.25 mm × 0.1 μm), helium gas, 50 kPa, 240°C, in EI mode. Melting points were determined on a Büchi melting point apparatus.

***N*-Cyclopropyl-hydroxylamine.**[7] To a two-phase emulsion of 1.31 g (15 mmol) of nitrocyclopropane,[8] 0.64 g (12 mmol) of ammonium chloride and 15 mL of water, 1.96 g (30 mmol) of zinc powder was added in portions in 3 h during stirring at 15°C. Stirring was continued overnight at room temperature. The mixture was filtered, then washed with warm water. The pH of the filtrate was set to 9 with potassium carbonate and extracted twice with diethyl ether. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated in vacuum. Zero point seven two gram (65%) of title compound was obtained as white powder, that was used in the next step without further purification.

Preparation of *N*-cyclopropyl-α-phenylnitrone (5a). Method A. Zero point three six gram (4.9 mmol) of *N*-cyclopropyl-hydroxylamine and 0.25 mL (2.5 mmol) of benzaldehyde in 8 mL of methanol were stirred under reflux for 3 h. The solvent was evaporated in vacuum, then dichloromethane and water were added to the residue. The layers were separated and the organic layer was washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated in vacuum. After crystallization from *n*-hexane 0.17 g (43%) of title compound **5a** was obtained as pale yellow crystals. M.p.: 87–88°C. IR (KBr): 1560, 1342, 1166, 1100, 941, 764, 697. ^{1}H NMR: 0.70–0.84 (m, 2H, *c*-Pr-CH$_2$), 1.18–1.27 (m, 2H, *c*-Pr-CH$_2$), 3.91–4.02 (m, 1H, *c*-Pr-CH), 7.36–7.45 (m, 3H, Ar-CH), 8.07 (s, 1H, =CH), 8.19–8.25 (m, 2H, Ar-CH). HRMS: calcd. for $C_{10}H_{11}NO$: 161.0835. Found: 161.0837.

General procedure for the preparation of *N*-cyclopropylnitrone (5a–l) through the corresponding *N*-cyclopropylamine (4a–l). Method B. **a**. Twelve point five millimoles of aldehyde, 1.4 mL (15 mmol) of cyclopropylamine and 1.58 g (19 mmol) of sodium hydrogencarbonate were suspended in 15 mL of methanol. The mixture was stirred under reflux for 4 h, then it was cooled to 0°C and 0.57 g (15 mmol) of sodium borohydride was added portion wise in 1 h. Then the mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated in vacuum, then dichloromethane and water were added to the residue. The layers were separated and the organic layer was washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated in vacuum. Yield: 90–99% as an oil. Crude amines were used in the next step without further purification, however, hydrochloride salts could be isolated in crystalline form from ethanol as well.

4a. M.p.: 159–160°C. **4b.** M.p.: 186°C. **4c.** M.p.: 196°C. **4d.** M.p.: 198°C. **4e.** M.p.: 175–176°C. **4f.** M.p.: 118–119°C. **4g.** M.p.: 166–167°C. **4h.** M.p.:°C. **4i.** M.p.: 200–202°C. **4j.** M.p.: 205–207°C. **4k.** M.p.: 119–120°C. **4l.** M.p.: 216–217°C.

b. Ten millimoles of amine **4a–l** prepared as described above and 0.82 g (2.5 mmol) of sodium tungstate dihydrate were suspended in 9 mL of methanol. One point six milliliters of hydrogen peroxide was added drop-wise in 1 h at 0°C. The mixture was allowed to warm to room temperature and stirred for 3 h. Then it was cooled to 0°C and 1.6 mL of hydrogen peroxide was added. The mixture was stirred at room temperature for 2 h. Then the solvent was evaporated in vacuum, and dichloromethane and water were added to the residue. The layers were separated and the organic layer was washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated in vacuum. Nitrones **5a–l** were isolated from diethyl ether/*n*-hexane, 1:1 in crystalline form. Purity by GC: 98+%.

5b. M.p.: 68°C. IR (KBr): 1604, 1503, 1346, 1167, 1087, 847, 521. ^{1}H NMR: 0.70–0.85 (m, 2H, *c*-Pr-CH_2), 1.17–1.30 (m, 2H, *c*-Pr-CH_2), 3.89–4.00 (m, 1H, *c*-Pr-CH), 7.20–7.32 (m, 2H, Ar-CH), 8.10 (s, 1H, =CH), 8.26–8.38 (m, 2H, Ar-CH). HRMS: calcd. for $C_{10}H_{10}NOF$: 179.0741. Found: 179.0738.

5c. M.p.: 107°C. IR (KBr): 1551, 1335, 1164, 1086, 943, 849, 519. ^{1}H NMR: 0.75–0.83 (m, 2H, *c*-Pr-CH_2), 1.19–1.26 (m, 2H, *c*-Pr-CH_2), 3.93–4.02 (m, 1H, *c*-Pr-CH), 7.46–7.52 (m, 2H, Ar-CH), 8.14 (s, 1H, =CH), 8.23–8.28 (m, 2H, Ar-CH). HRMS: calcd. for $C_{10}H_{10}NOCl$: 195.0451. Found: 195.0450.

5d. M.p.: 123–124°C. IR (KBr): 1565, 1417, 1165, 1094, 1066, 847, 514. ^{1}H NMR: 0.76–0.82 (m, 2H, *c*-Pr-CH_2), 1.20–1.25 (m, 2H, *c*-Pr-CH_2), 3.94–4.00 (m, 1H, *c*-Pr-CH), 7.60–7.64 (m, 2H, Ar-CH), 8.11 (s, 1H, =CH), 8.16–8.20 (m, 2H, Ar-CH). HRMS: calcd. for $C_{10}H_{10}NOBr$: 238.9940. Found: 238.9975.

5e. M.p.: 92°C. IR (KBr): 1580, 1487, 1285, 1166, 1054, 937, 754. ^{1}H NMR: 0.82–0.90 (m, 2H, *c*-Pr-CH_2), 1.24–1.31 (m, 2H, *c*-Pr-CH_2), 4.02–4.11 (m, 1H, *c*-Pr-CH), 6.80–6.90 (m, 2H, Ar-CH), 7.32–7.39 (m, 1H, Ar-CH), 7.53–7.57 (m, 1H, Ar-CH), 8.37 (s, 1H, =CH), 12.14 (m, 1H, -OH). HRMS: calcd. for $C_{10}H_{11}NO_2$: 177.0784. Found: 177.0790.

5f. M.p.: 114–115°C. IR (KBr): 1502, 1345, 1245, 1167, 1042, 921, 822. ^{1}H NMR: 0.71–0.79 (m, 2H, *c*-Pr-CH_2), 1.16–1.23 (m, 2H, *c*-Pr-CH_2), 3.83–3.92 (m, 1H, *c*-Pr-CH), 6.07 (s, 2H, O-CH_2-O), 6.98 (d, $J = 8.4$ Hz, 1H, Ar-CH), 7.61 (dd, $J = 8.4$, 1.5 Hz, 1H, Ar-CH), 7.98 (s, 1H, =CH), 8.07 (d, $J = 1.5$ Hz, 1H, Ar-CH). HRMS: calcd. for $C_{11}H_{11}NO_3$: 205.0733. Found: 205.0740.

5g. M.p.: 85–86°C. IR (KBr): 1597, 1519, 1263, 1166, 1131, 1020, 858. ^{1}H NMR: 0.70–0.79 (m, 2H, *c*-Pr-CH_2), 1.18–1.25 (m, 2H, *c*-Pr-CH_2), 3.76 (s, 3H, -OCH_3), 3.80 (s, 3H, -OCH_3), 3.85–3.93 (m, 1H, *c*-Pr-CH), 7.02 (d, $J = 8.4$ Hz, 1H, Ar-CH), 7.67 (dd, $J = 8.4$, 1.5 Hz, 1H, Ar-CH), 7.96 (s, 1H, =CH), 8.15 (d, $J = 1.5$ Hz, 1H, Ar-CH). HRMS: calcd. for $C_{12}H_{15}NO_3$: 221.1046. Found: 221.1045.

5h. M.p.: 91–94°C. IR (KBr): 1714, 1420, 1261, 1163, 1091, 944, 768. ^{1}H NMR: 0.79–0.87 (m, 2H, *c*-Pr-CH_2), 1.21–1.29 (m, 2H, *c*-Pr-CH_2), 1.33 (t, $J = 6.9$ Hz, 3H, -CH_3), 4.00–4.09 (m, 1H, *c*-Pr-CH), 4.32 (q, $J = 6.9$ Hz, 2H, -OCH_2), 7.96–8.02 (m, 2H, Ar-CH), 8.24 (s, 1H, =CH), 8.30–8.36 (m, 2H, Ar-CH). HRMS: calcd. for $C_{13}H_{15}NO_3$: 233.1052. Found: 233.1055.

5i. M.p.: 169–170°C. IR (KBr): 2952, 1586, 1220, 1161, 1070, 941, 893. ^{1}H NMR: 0.67–0.75 (m, 2H, *c*-Pr-CH_2), 1.16–1.23 (m, 2H, *c*-Pr-CH_2), 1.38 (s, 18H, *t*-Bu), 3.79–3.89 (m, 1H, *c*-Pr-CH), 7.34 (s, 1H, -OH), 7.92 (s, 1H, =CH), 8.11 (s, 2H, Ar-CH). HRMS: calcd. for $C_{18}H_{27}NO_2$: 289.2036. Found: 289.2049.

5j. M.p.: 97–98°C. IR (KBr): 1581, 1326, 1170, 1126, 1068, 944, 855. ^{1}H NMR: 0.80–0.88 (m, 2H, *c*-Pr-CH_2), 1.23–1.30 (m, 2H, *c*-Pr-CH_2), 4.01–4.09 (m, 1H, *c*-Pr-CH), 7.75–7.81 (m, 2H, Ar-CH), 8.28 (s, 1H, =CH), 8.39–8.46 (m, 2H, Ar-CH). HRMS: calcd. for $C_{11}H_{10}NOF_3$: 229.0709. Found: 229.0720.

5k. M.p.: 72–74°C. IR (KBr): 3321, 1607, 1416, 1333, 1152, 1037, 932. ^{1}H NMR: 0.68–0.77 (m, 2H, *c*-Pr-CH_2), 1.15–1.22 (m, 2H, *c*-Pr-CH_2), 3.78–3.87 (m, 1H, *c*-Pr-CH), 6.16–6.20 (m, 1H, CH), 6.53–6.57

(m, 1H, CH), 6.89–6.93 (m, 1H, CH), 7.95 (s, 1H, =CH), 11.81 (s, br, 1H, -NH). HRMS: calcd. for $C_8H_{10}N_2O$: 150.0793. Found: 150.0798.

5l. M.p.: 103–104°C. IR (KBr): 1553, 1423, 1164, 1093, 942, 826, 698. ^{1}H NMR: 0.78–0.86 (m, 2H, *c*-Pr-CH_2), 1.21–1.28 (m, 2H, *c*-Pr-CH_2), 3.99–4.08 (m, 1H, *c*-Pr-CH), 7.42–7.48 (m, 1H, CH), 8.20 (s, 1H, =CH), 8.55 (dd, $J = 4.8$, 3.0 Hz, 1H, CH), 8.72–8.77 (m, 1H, CH), 9.19 (d, $J = 2.1$ Hz, 1H, CH). HRMS: calcd. for $C_9H_{10}N_2O$: 162.0793. Found: 162.0791.

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