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SELECTIVE REDUCTION OF NITRONES AND NITROXIDES TO FUNCTIONALIZED SECONDARY AMINES

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Abstract: Nitrones and nitroxides were selectively reduced with Fe/AcOH to secondary amines in the presence of different functional groups (aldehyde, nitrile, carboxylic ester, activated and nonactivated double or triple bonds).

The synthetic route through reductive cyclization of γ-nitroketones obtained from Michael addition of a nitroalkane to an α,β-unsaturated carbonyl compound allows the preparation of a great variety of dipolarofil nitrones[1] and nitroxide spin label reagents.[2,3]

Searching for new antiarrhythmic compounds we found that sterically hindered amines, such as 2,2,5,5-tetramethyl-3-pyrroline derivatives exhibited the highest activity.[4]

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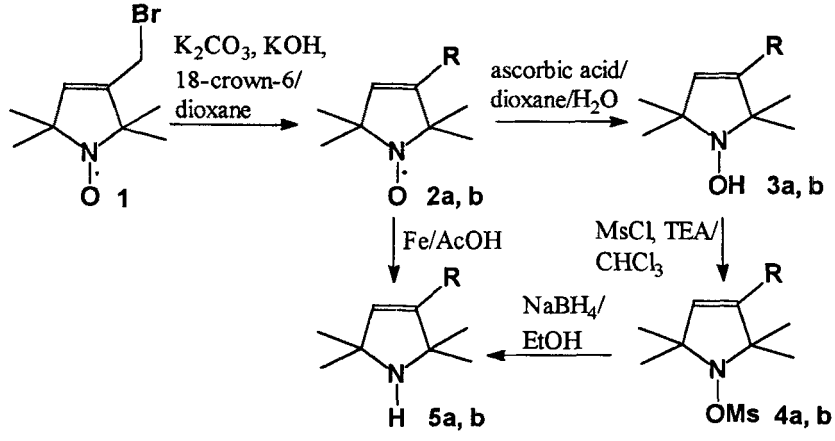
These findings forced us to investigate the methods for selective reduction of nitrones and nitroxides to secondary amines without the involvement of other functions, such as unsaturated bond, aldehyde, carboxylic ester, nitrile.

Several methods have already been used to reduce nitrones to imines by phosphines or phosphites,[5] to hydroxylamines by $LiAlH_4$, $NaBH_4$[6,7] and to amines by catalytic reduction with Raney-Ni or Pt.[8] The reduction of hydroxylamines with carbon disulfide was also described.[9] The reduction of nitroxides to amines by several methods was reported.[10]

Cyclic nitrones are preferentially prepared by Zn/NH_4Cl or Zn/AcOH reduction[11] of γ-nitroketone but sometimes overreduction was observed to 2-pyrroline instead of 1-pyrroline-*N*-oxide.

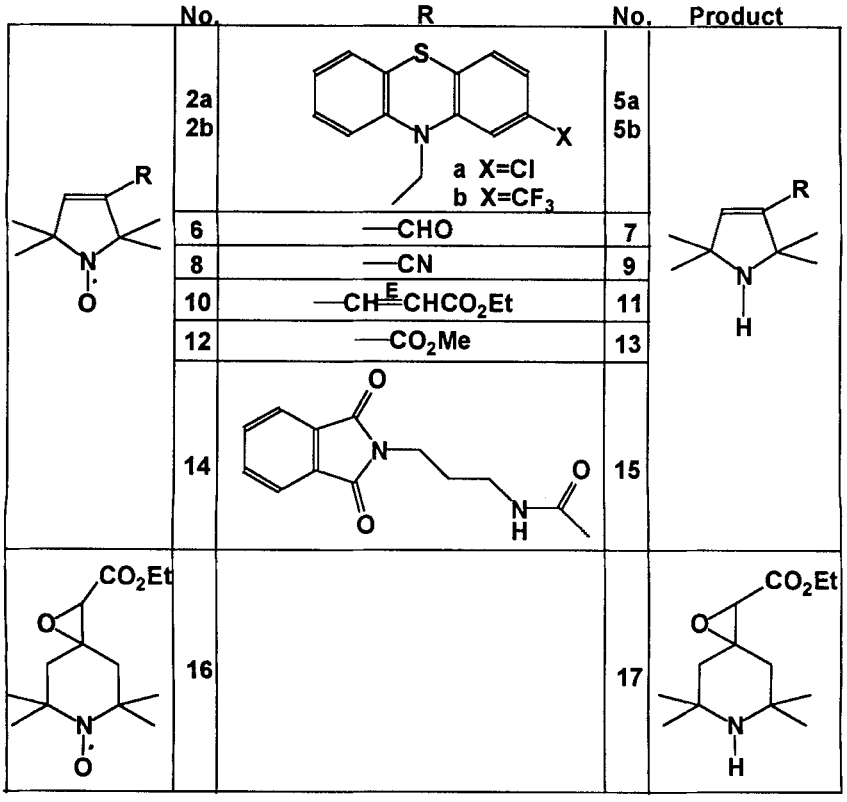
This route was not feasible in the case of nitroxides **2a,b** but these compounds could be reduced by ascorbic acid to a labile *N*-hydroxyl compound[12] which is spontaneously reoxidized in the presence of air. *N*-Hydroxyl compounds **3a,b** react with methanesulfonyl chloride to mesylates **4a,b** and these mesylate compounds were reduced with $NaBH_4$ to amines **5a,b**.

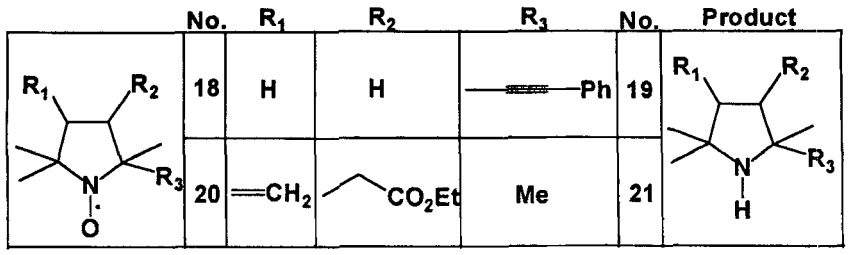


After the acylation or alkylation of paramagnetic nitroxide reagents the removal of *O*-alkyl or -acyl protecting group by reduction could provide the appropriate amine compound.

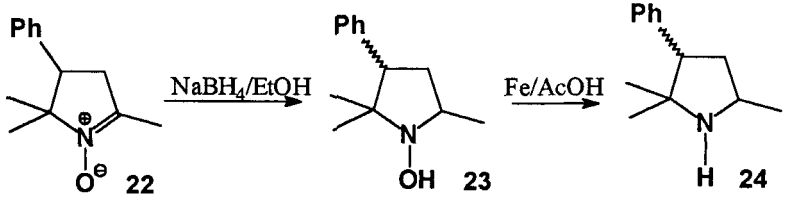
The disadvantage of this method is the separation of the labile, spontaneously reoxidizing *N*-hydroxyl compound, and the low yield due to the multiple steps.

Conjugated indolinone nitroxide radical was reduced with Fe powder in AcOH to amine earlier.[13] We found this reagent also suitable for the reduction of nitroxides **2a, 2b, 6, 8, 10, 12, 14, 16, 18, 20** in the presence of isolated and activated double bond, carboxylic ester, aldehyde and nitrile groups.





Reduction of nitrone **22** with Fe/AcOH failed to occur even at longer reaction times. However, when nitrone **22** was first reduced to *N*-hydroxylamine **23** with $NaBH_4$, it could be transformed to secondary amine **24** in acetic acid with Fe powder.



This simple reaction can increase the synthetic potential of nitroxides and nitrones, because they can be precursors of a variety of substituted hindered secondary amines which are difficult to obtain by other means.

Experimental

Melting points were determined on a Boetius micro-mp apparatus and are not corrected. Elemental analyses (C, H, N) were performed on a Heraeus Micro U/E apparatus or (Hal) were carried out titrimetrically by Schöniger's method. IR (Specord 75) spectra of the compounds were in each case consistent with the assigned structures.

^{1}H-NMR spectra of amines have been recorded with a Bruker AC-250 spectrometer in $CDCl_3$ solution unless otherwise stated.

ESR spectra were obtained from 10^{-5} molar solution, using a Zeiss ER 9 spectrometer. All the monoradicals exhibit three equidistant lines, with a_N=14.8-15.2 G.

Mass spectra were taken on a Finnigan MAT 8430 mass spectrometer/ SS300 data acquisition system. Operation conditions: EI: U_{acc}=3 kV, E_{el}=70 eV, I_{el}= 0.5 mA, $T_{ion\ source}$= 250°C, R= 1250. Samples were introduced via the direct insertion probe. The evaporation temperatures of the samples varied between 50 and 250°C, and were each controlled within ±1°C accuracy. Assignments were corroborated by high-resolution mass measurements made at R=10000 by the peak matching technique, with PFK as the reference material.

Flash column chromatography on silica gel was performed with Merck Kieselgel 60 (0.040-0.063 mm). Qualitative TLC was carried out on commercially prepared plates (20 x 20 x 0,2 cm) coated with Merck Kieselgel GF_{254}.

The starting materials 2-chlorophenothiazine and 2-(trifluoromethyl)-phenothiazine were commercially available products and were used without purification. Compounds **1**,[14] **6**,[15] **8**,[16] **10**,[17] **12**,[18] **14**,[4] **16**,[19] **18**,[20] **20**,[21] **22**[22] were prepared according to published procedures. Compound **15**[4] was identical in all respects with the compound that have been described in the literature earlier. Compound **13** was prepared analogously to saturated methyl ester.[23]

N-Alkylation of 2-chlorophenothiazine and 2-(trifluoromethyl)phenothiazine with bromomethyl nitroxide (**1**) to compounds **2a** and **2b**:

To a solution of phenothiazine (0.01 mol) in dioxane (20 mL) K_2CO_3 (2.76 g, 0.02 mol), KOH (catalytic amount, ~100 mg), 18-crown-6 (catalytic amount, 200 mg) and 3-bromomethyl-2,5-dihydro-2,2,5,5-

tetramethyl-1*H*-pyrrol-1-yloxyl radical (**1**; 2.33 g, 0.01 mol) were added. The mixture was stirred and refluxed for 3 h then filtrated and evaporated. The residue was dissolved in $CHCl_3$ and washed with brine, dried ($MgSO_4$) and evaporated. The product was purified by flash column chromatography on silica gel using hexane/EtOAc as eluent.

Compound **2a**: Yield: 2.43 g (63%); mp 201-202°C; Anal. calcd. for $C_{21}H_{22}N_2OSCl$ (385.93); C 65.36; H 5.75; N 7.26; S 8.31; Cl 9.19; Found: C 65.36; H 5.57; N 7.30; S 8.20; Cl 9.24 %.

MS, *m/z*(%): 385/387 (M^+, 28.5/11.4), 233/235 ($C_{12}H_8NSCl^{+\bullet}$, 69.4/25.2), 232/234 (M^+- O-py[24], 100/45.1), 122 ($C_9H_{14}^+$, 16.3)

Compound **2b**: Yield: 2.85 g (68%); mp 159-160°C; Anal. calcd. for $C_{22}H_{22}N_2OSF_3$ (419.48); C 62.99; H 5.29; N 6.68; S 7.64; Found: C 62.91; H 5.24; N 6.70; S 7.59 %.

MS *m/z*(%): 419 (M^+, 55.3), 266 (M^+ - py, 100), 123 ($C_9H_{15}^+$, 41)

Reduction and O-mesylation of nitroxides (**2a, b**) to compounds **4a** and **4b**: To a mixture of nitroxide phenothiazine (**2a** or **2b**; 0.01 mol) in dioxane/H_2O (2:1; 30 mL) ascorbic acid (5.28 g, 0.03 mol) was added and warmed up to 40°C. After decolorization $CHCl_3$ (2 x 10 mL) was added and the mixture was extracted, the organic phase was dried ($MgSO_4$) under N_2 and filtered. Under N_2 Et_3N (1.51 g, 0.015 mol) was added to the filtrate and $MeSO_2Cl$ (1.38 g, 0.012 mol) was added dropwise at 0-5°C. After stirring for 1 h the mixture was evaporated and the residue was extracted with Et_2O (20 mL), washed with brine (2 x 10 mL), dried and evaporated to dryness. The residue was purified by flash column chromatography using hexane/EtOAc as eluent to give the pure product.

Compound **4a**: Yield: 3.44 g (74%); mp 123-126°C; Anal. calcd. for $C_{22}H_{25}N_2S_2O_3Cl$ (465.03); C 56.82; H 5.42; N 6.02; S 13.79; Cl 7.62;

Found: C 56.88; H 5.30; N 5.84; S 13.92; Cl 7.51%.

^{1}H-NMR (δ, ppm): 7.2 - 6.7 (m, 7H, Ar), 5.3 (s, 1H, pyrroline 4-H), 4.4 (bs, 2H, CH_2), 3.2 (s, 3H, SO_2CH_3), 1.6, 1.35 (2bs, 12H, 2,5-C($C\underline{H}_3$)$_2$).

Compound **4b**: Yield: 3.29 g (66%); mp 147-148°C; Anal. calcd. for $C_{23}H_{25}N_2S_2O_3F_3$ (498.58); C 55.41; H 5.05; N 5.62; S 12.86; Found: C 55.58; H 4.97; N 5.49; S 12.73%.

^{1}H-NMR (δ, ppm): 7.15 - 6.75 (m, 7H, Ar), 5.3 (s, 1H, pyrroline 4-H), 4.45 (m, 2H, CH_2), 3.15 (s, 3H, SO_2CH_3), 1.55, 1.4 (2bs, 12H, 2,5-C($C\underline{H}_3$)$_2$).

Reduction of N-mesylates (**4a,b**) *to amines* (**5a,b**):

To a mixture of the mesylate (**4a,b**; 0.01 mol) in EtOH (20 mL) $NaBH_4$ (0.76 g, 0.02 mol) was added. After 30 min the solvent was evaporated. The residue was dissolved in $CHCl_3$ (20 mL) and washed with H_2O (2x10 mL). The product was purified by flash column chromatography using *$CHCl_3$/MeOH* as eluent.

Compound **5a**: Yield: 2.19 g (59 %); mp 154-155°C; Anal. calcd. for $C_{21}H_{23}N_2SCl$ (370.94); C 68.00; H 6.25; N 7.55; S 8.64; Cl 9.56; Found: C 67.89; H 6.11; N 7.47; S 8.53; Cl 9.56 %.

^{1}H-NMR (δ, ppm): 7.15 - 6.75 (m, 7H, Ar), 5.35 (s, 1H, pyrroline 4-H), 4.35 (m, 2H, CH_2), 1.45, 1.25 (2bs, 12H, 2,5-C($C\underline{H}_3$)$_2$).

MS *m/z*(%): 370/372 ($M^{+\bullet}$, 35/14), 355/357 ($M^{+\bullet}$ - $^{\bullet}CH_3$, 7/2.6), 231/233 ($C_{12}H_6NSCl^{+\bullet}$, 100/38).

Compound **5b**: Yield: 2.30 g (57 %); mp 136-138°C; Anal. calcd. for $C_{22}H_{23}N_2SF_3$ (404.49); C 65.33; H 5.73; N 6.93; S 7.93; Found: C 65.48; H 5.59; N 6.77; S 8.00 %.

^{1}H-NMR (DMSO-d_6, δ, ppm): 7.45 - 6.95 (m, 7H, Ar), 5.47 (s, 1H, pyrroline 4-H), 4.70 (m, 2H, CH_2), 1.7, 1.4 (2s, 12H, 2,5-C(CH_3)$_2$).

MS *m/z*(%): 404 ($M^{+\bullet}$, 12), 389 ($M^{+\bullet}$ - $^{\bullet}CH_3$, 7), 280 ($C_{14}H_9NSF_3^+$, 12), 266($M^{+\bullet}$ - py[25], 100), 123 ($C_8H_{13}N^{+\bullet}$, 26).

General procedure for reduction of nitroxides (**2a,b, 6, 8, 10, 12, 14, 16, 18, 20**) *to amines* (**5a,b, 7, 9, 11, 13, 15, 17, 19, 21**):

To a solution of nitroxide (0.01 mol) in cc. AcOH (10 mL) Fe powder (2.79 g, 0.05 mol) was added and the mixture was warmed up to 50°C until the reaction started. The mixture was stirring at room temperature for 3 h, then diluted with water (30 mL) decanted and alkaline to pH 9-10 by adding solid K_2CO_3. The mixture was filtered off, the filtrate was extracted with $CHCl_3$, dried ($MgSO_4$) and flash chromatographed on silica gel with $CHCl_3$/MeOH as eluent.

Compound **5a**: Yield: 2.15 g (58 %).

Compound **5b**: Yield: 2.22 g (55 %). Compounds **5a** and **5b** are identical in all respect with compounds prepared with the previous method.

Compound **7**: Yield: 0.75 g (49 %); oil; Anal. calcd. for $C_9H_{15}NO$ (153.22); C 70.55; H 9.87; N 9.14; Found: C 70.39; H 9.81; N 9.20 %.

^{1}H-NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 9.4 (s, 1H, C<u>H</u>=O), 6.3 (s, 1H, pyrroline 4-H), 0.94, 0.91 (2s, 12H, 2,5-C(C<u>H</u>$_3$)$_2$)

MS *m/z* (%): 153 ($M^{+\bullet}$, 0.9), 138 ($M^{+\bullet}$ - $^{\bullet}CH_3$, 39), 110 ($M^{+\bullet}$ - $^{\bullet}CH_3$ - CO, 100), 95 ($C_6H_7O^+$, 32).

Compound **9**: Yield: 0.93 g (62 %); oil; Anal. calcd. for $C_9H_{14}N_2$ (150.22); C 71.96; H 9.39; N 18.65; Found: C 71.81; H 9.50; N 18.72 %.

^{1}H-NMR (δ, ppm): 6.5 (s, 1H, pyrroline 4-H), 1.4, 1.3. (2s, 12H, 2,5-C(C<u>H</u>$_3$)$_2$);

MS *m/z*(%): 150 ($M^{+\bullet}$, 1.3), 135 ($M^{+\bullet}$ - $^{\bullet}CH_3$, 100), 120 ($M^{+\bullet}$ - 2 $^{\bullet}CH_3$, 57), 119 ($M^{+\bullet}$ - 2x $M^{+\bullet}$ - $^{\bullet}CH_3$- $^{\bullet}H$, 35), 42 ($C_2H_6N^+$, 19)

Compound **11**: Yield: 1.61 g (52 %); oil; Anal. calcd. for $C_{13}H_{21}NO_2$ (223.32); C 69.92; H 9.48; N 6.27; Found: C 70.03; H 9.56; N 6.20 %.
^{1}H-NMR (δ, ppm): 7.3 (d, 1H, $J_{1,3}$ = 16 Hz, -CH=CH-), 6.05 (d, 1H, ^3J = 16 Hz, -CH=CH-), 6.05 (s, 1H, pyrroline 4-H), 4.25 (qua, 2H, OCH_2CH_3), 1.4 (s, 6H, 2-$C(CH_3)_2$), 1.33 (t, 3H, OCH_2CH_3), 1.3 (s, 6H, 5-$C(CH_3)_2$)
MS *m/z*(%): 223 ($M^{+\bullet}$, 6), 208 ($M^{+\bullet}$ - $^\bullet CH_3$, 100), 178 ($M^{+\bullet}$ - $^\bullet$OEt, 16).
Compound **17**: Yield: 1.40 g (58 %); oil; Anal. calcd. for $C_{13}H_{23}NO_3$ (241.33); C 64.70; H 9.61; N 5.80; Found: C 64.83; H 9.57; N 5.88 %.
^{1}H-NMR (δ, ppm): 4.2 (m, 2H, OCH_2CH_3), 3.35 (s, 1H, CH), 1.6 (m, 4H, CH_2CCH_2), 1.3 (t, 3H, OCH_2CH_3), 1.22, 1.20 (2s, 12H, 2,6-$C(CH_3)_2$)
MS *m/z*(%): 241 ($M^{+\bullet}$, 1), 226 ($M^{+\bullet}$ - $^\bullet CH_3$, 100), 198 ($M^{+\bullet}$ - $^\bullet CH_3$ - CO, 19), ($M^{+\bullet}$ - $^\bullet CH_3$, 100), 120 ($M^{+\bullet}$ - $^\bullet CO_2Et$, 36), 58 ($C_3H_8N^+$, 58)
Compound **19**: Yield: 1.15 g (54 %); oil; Anal. calcd. for $C_{15}H_{19}N$ (213.32); C 84.46; H 8.98; N 6.57; Found: C 84.51; H 9.07; N 6.50 %.
^{1}H-NMR (δ, ppm): 7.45 – 7.30 (m, 5H, Ph), 2.35 – 1.6 (m, 4H, CH_2CH_2), 1.55, 1.35, 1.2 (3s, 9H, 2-$C(CH_3)$, 5-$C(CH_3)_2$)
MS *m/z*(%): 213 ($M^{+\bullet}$, 3), 198 ($M^{+\bullet}$ - $^\bullet CH_3$, 100)
Compound **21**: Yield: 1.33 g (59 %); oil; Anal. calcd. for $C_{13}H_{23}NO_2$ (225.33); C 69.29; H 10.29; N 6.22; Found: C 69.40; H 10.18; N 6.25 %.
^{1}H-NMR (δ, ppm): 4.9 (d, 1H, ^2J = 2.5 Hz, =CHH), 4.8 (d, ^2J = 2.5 Hz, =CHH), 4.19 (qua, 2H, OCH_2CH_3), 2.85 (m, 1H, pyrroline CH), 2.35 (m, 2H, CH_2CO), 1.3 (t, 3H, OCH_2CH_3), 1.3 (s, 6H, 2-$C(CH_3)_2$), 1.2, 0.93 (2s, 6H, 5-$C(CH_3)CH_3$)
MS *m/z*(%): 225 ($M^{+\bullet}$, 3), 210 ($M^{+\bullet}$ - $^\bullet CH_3$, 100), 122 ($M^{+\bullet}$ - $^\bullet$OEt - C_3H_8N, 19), 58 ($C_3H_8N^+$, 21).

Reduction of nitrone (**22**) *to secondary amine* (**24**):

To a solution of nitrone **22** (0.01 mol, 2.03 g) in EtOH (15 mL) $NaBH_4$

(0.02 mol, 0.76 g) was added. After 30 min the solvent was evaporated, the residue was dissolved in $CHCl_3$ (15 mL) and washed with brine (2 x 10 mL), dried ($MgSO_4$) and evaporated. The further procedure to reduce the N-OH compound with Fe/AcOH was the same as described above with nitroxide compounds.

Compound **24**: Yield: 1.21 g (62 %); oil; Anal. calcd. for $C_{13}H_{19}N$ (189.30); C 82.48; H 10.12; N 7.40; Found: C 82.42; H 10.20; N 7.49 %.

^{1}H-NMR (δ, ppm): 7.4 - 7.2 (m, 5H, Ph), 3.8 (m, 1H, 3-H), 3.3 (m, 1H, 5-H), 2.7 - 1.9 (m, 4-CH_2), 2.0 (s, 3H, 5-CH_3), 1.5, 1.05 (2s, 6H, 2-$C(CH_3)(CH_3)$.

MS *m/z*(%): 189 ($M^{+\bullet}$, 23), 174 ($M^{+\bullet}$ - $^\bullet CH_3$), 85 ($M^{+\bullet}$ - $PhCH{=}CH_2$, 100), 70 (85 - $^\bullet CH_3$, 34), 42 ($C_2H_3N^+$, 48).

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24., O-py : (2,2,5,5-tetramethylpyrrolin-1-yloxy-3-yl)methyl

25., py : (2,2,5,5-tetramethylpyrrolin-3-yl)methyl

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