Synthesis of Novel Bicyclic Nitroxides Using Partial Favorskii Rearrangement

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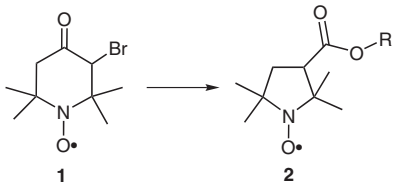
Abstract: 3-Bromo-2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl was reacted with several *C*-nucleophiles to give novel bicyclic pyrrolidine nitroxides through partial Favorskii rearrangement. Further reduction with sodium borohydride gave spin probes with free hydroxyl groups and under harsh reduction conditions allowed the Favorskii rearrangement to proceed to completion.

Key words: bicyclic compounds, rearrangements, nitroxide free radicals, spin probes, ring opening

Favorskii rearrangement has been known for over 100 years and it is still often used in synthetic organic chemistry; for example, in the synthesis of A-norsteroids,[1] amides from α-haloketimines,[2] and cyclic analogues of proline.[3] It was important in the field of nitroxide chemistry from the very beginning, since it allows for the convenient preparation of pyrroline and pyrrolidine nitroxides[4–6] which are more resistant to acidic media and redox conditions in vitro and in vivo.[6,7] Recent advances in low-frequency electron paramagnetic resonance imaging have created a need for spin probes that can provide specific data in real time.[8–10] Nitroxides are very well suited for this task and novel synthetic approaches that could provide molecular tools with tailored properties for spin probing are welcome.[11] Existing synthetic approaches to pyrroline nitroxides are multistep processes which mostly start from 3,5-dibromo-2,2,6,6-tetramethyl-4-oxopiperidine.[4,6] The rearrangement of 3-bromo-2,2,6,6-tetramethyl-4-oxopiperidin-1-oxyl (3-Br-TEMPONE, **1**) with O-nucleophiles gives the corresponding esters of 2,2,5,5-tetramethyl-pyrrolidin-1-oxyl-3-carboxylic acid (**2**) in one reaction step, as depicted in Scheme 1. This approach is a good alternative to tedious multistep syntheses.[12]

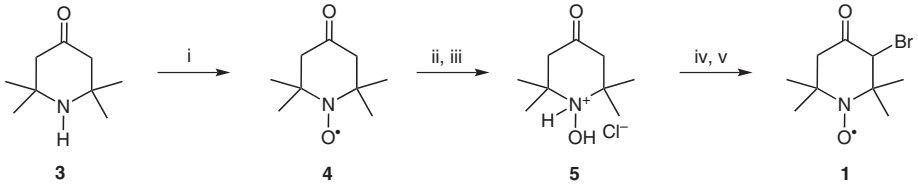
Favorskii rearrangement of α-haloketones is usually carried out with N- or O-nucleophiles, although several authors have demonstrated that a similar rearrangement can also proceed in the presence of C-nucleophiles.[13–18] The classical mechanism of Favorskii rearrangement involves a cyclopropanone intermediate which reacts with another nucleophile/base molecule to yield a carboxylic acid or its derivative. The reaction is subjected to the influence of solvent, acidity of substrate, structure of cyclopropanone intermediate, carboanion stability, and base structure.[19,20] We describe the reaction of 3-Br-TEMPONE with selected C-nucleophiles and present a convenient route to new nitroxyl spin probes.



Scheme 1 Favorskii rearrangement with an O-nucleophile

Compound **1**, the key reagent for the Favorskii rearrangement, was synthesized from triacetoneamine according to known procedures in five reaction steps as outlined in Scheme 2.[4,5,12] Scheme 3 presents the conversion of 3-Br-TEMPONE (**1**) to **6a–h** under the conditions of Favorskii rearrangement. However, contrary to N- and O-nucleophiles the reaction evidently stops on the tetrahydric intermediate stage, which is a tertiary alcohol when C-nucleophiles are used. The O- and N-nucleophiles convert to semiketals and semiazaketals, respectively, which are unstable under normal reaction conditions and give proper Favorskii products which, in our case, would be pyrrolidine nitroxides.

The partial Favorskii reaction was carried out by slowly adding appropriate sodium salts, prepared in the usual



Scheme 2 Synthesis of 3-Br-TEMPONE. *Reaction conditions*: (i) H_2O_2, Na_2WO_4, Na_2EDTA, H_2O, r.t.; (ii) H_2, Pd/C, MeOH, r.t.; (iii) $HCl_{(aq)}$, (iv) Br_2, $CHCl_3$, r.t.; (v) $NaNO_2$, $CHCl_3$, r.t.

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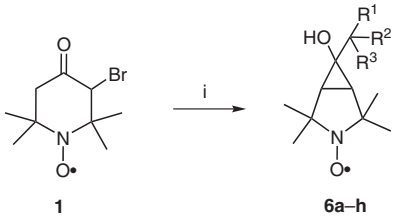
Table 1 Partial Favorskii Rearrangement Products **6a–h**, Reaction Conditions, and Yields

Compd	R^1	R^2	R^3	Solvent	Na salt (equiv)	Temp (°C)	Time (h)	Yield (%)[a]
6a	COMe	CO_2Et	H	Et_2O	2.0	34	24	65
6b	COMe	CO_2Me	H	THF	1.4	50	1.5	81
6c	COMe	CO_2t-Bu	H	THF	1.4	50	1.5	71
6d	COMe	COMe	H	THF	2.5	30	24	31
6e	CO_2Me	CO_2Me	H	THF	1.4	50	1.5	75
6f	COPh	CO_2Et	H	THF	1.4	50	1.5	81
6g	CN	CO_2Me	H	THF	4.0	50	1.5	37
6h	CO_2Et	CO_2Et	Me	THF	1.05	50	1.5	60

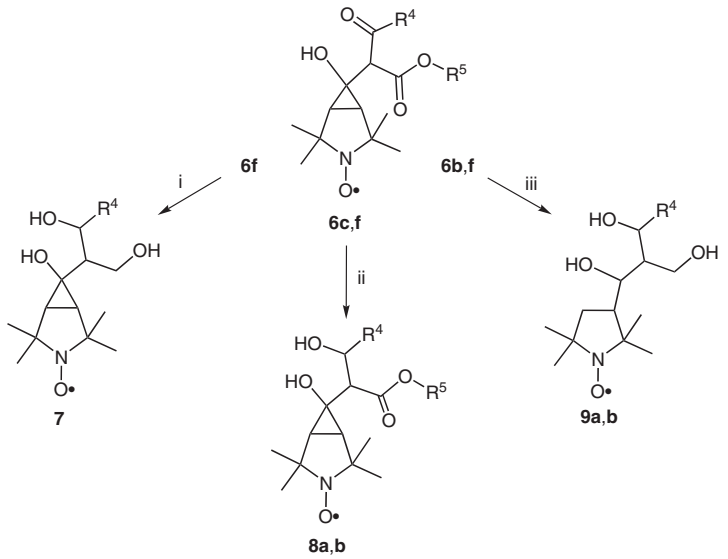
[a] Isolated yields.



Scheme 3 Partial Favorskii rearrangement with C-nucleophiles. *Reaction conditions*: (i) $R^1R^2R^3$-C$^-$Na$^+$, THF, reflux.

manner,[21] to a stirred solution of **1** in dry solvent under conditions listed in Table 1. Diethyl ether and THF were found to be suitable solvents for these reactions and, due to the higher boiling point of THF, reactions in this solvent were faster. Furthermore, the higher solubility of sodium salts in THF also contributed to increased reaction rate. It is noteworthy, however, that **6a** could also be obtained in good yield in diethyl ether. The optimal reaction temperature proved to be 50 °C and reaction times were no longer than 1.5 h, which makes the reaction highly practical for spin-probe synthesis.[22] Even though the rearrangement mechanistically requires minimal excess of base/nucleophile, it was advantageous to use up to 1.4 equivalents of sodium salts. The yields of **6d** and **6g**[23] could not be improved, even with bigger excess of base, indicating an important influence of the nucleophile/base on the outcome of the reaction. It is noteworthy to add that the bicyclic structure was unambiguously confirmed by indirect ^{1}H NMR and ^{13}C NMR spectroscopy of reduced form of **6e**,[24] which clearly showed cyclopropane protons and carbon atoms, respectively. Since **6e** was a nitroxide free radical and was therefore paramagnetic it had to be reduced to its hydroxylamine derivative prior to all NMR experiments.[25] The reaction products, conditions, and yields are summarized in Table 1.

Scheme 4 outlines the further reaction steps used to obtain new spin probes and Table 2 presents reaction conditions and yields. Compounds **6f** and **6c** were partially reduced at 0 °C in methanol using $NaBH_4$, giving esters **8a** and **8b**,[26] respectively, as four diastereomers. At low tempera-



Scheme 4 Sodium borohydride reduction products. *Reaction conditions*: (i) $NaBH_4$, MeOH, 0–25 °C; (ii) $NaBH_4$, MeOH, 0 °C; (iii) $NaBH_4$, THF–MeOH, 40 °C.

Table 2 $NaBH_4$ Reduction Products, Conditions, and Yields

Compd	Starting compound	R^4	R^5	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
7	**6f**	Ph	–	MeOH	0–25	12	73
8a	**6f**	Ph	Et	MeOH	0	3	73
8b	**6c**	Me	*t*-Bu	MeOH	0	3	93
9a	**6f**	Ph	–	THF–MeOH	40	3	21
9b	**6b**	Me	–	THF–MeOH	40	3	34

[a] Isolated yields.

ture the reaction proceeded stereoselectively with the ratio between the two enantiomeric pairs of 4.8 and 6.2 for **8a** and **8b**, respectively, determined by HPLC. Carbonyl group as well as the ester moiety of **6f**, however, could also be fully reduced to bicyclic triol **7**[27] by adding an excess of $NaBH_4$ several times, allowing the reaction temperature to raise and prolonging the reaction time which also resulted in the drop of the ratio between enantiomeric pairs to 3.0. The products of the reduction reactions **7**, **8a**, and **8b** were also indirect proofs that Favorskii rearrangement indeed proceeded only partially.

Interestingly, **9a**[28] was first observed as a side product, present in very small amounts, in the synthesis of **7**. Modification of reaction conditions lead to a slight increase in yield of **9a** and **9b**. The harsh reduction conditions, with the addition of methanol producing sodium methylate in situ, opened the cyclopropane ring and therefore allowed the final step of the Favorskii rearrangement to take place. This gave a pyrrolidine type of spin labels, **9a** and **9b** as a mixture of several diastereomers.

In summary, we present a convenient route to new bicyclic nitroxides, using a partial Favorskii rearrangement of 3-bromo-TEMPONE with C-nucleophiles. The cyclopropane ring of bicyclic nitroxides remains intact under mild reduction conditions while, at elevated temperatures, it was possible to obtain classical products of Favorskii rearrangement. This gave new nitroxides with multiple functional groups applicable for spin labeling or used alone as spin probes.

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(21) Becker, H. G. O. *Organikum*; Wiley-VCH: Weinheim, **2001**, 608.
(22) **Typical Procedure for the Synthesis of Products 6a–h**
3-Bromo-2,2,6,6-tetramethyl-1-oxyl-piperidine-4-one (**1**, 400 mg, 1.61 mmol) was dissolved in anhyd THF (20 mL). The sodium salt of the appropriate *C*-nucleophile was dissolved in anhyd THF (5 mL) and added dropwise to the stirred solution of **1** over a period of 5 min under argon. The reaction mixture was refluxed at 50 °C for 1.5 h. After that time the solvent was evaporated under reduced pressure and the yellow solid dissolved in cold citric acid (10 mL, pH 3.5). The aqueous phase was immediately extracted with EtOAc. The organic phase was washed with brine, dried with Na_2SO_4, and the solvent evaporated under reduced pressure. The crude product was purified using circular chromatography (Et_2O–hexane, 3:1). A bright yellow solid was obtained.

(23) **Methyl 2-Cyano-2-{6-hydroxy-3-oxyl-2,2,4,4-tetramethyl-3-azabicyclo[3.1.0]hex-6-yl}acetate (6g)**
Yield 37%; yellow solid; mp 120–124 °C. IR (KBr): 3213, 2984, 2257, 1738, 1442, 1306, 1220, 1016, 928, 712 cm^{-1}. MS (EI): *m/z* = 267 $[M]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 2 H, CH), 1.32 (s, 12 H, CH_3), 3.30 (s, 1 H, CH), 3.84 (s, 3 H, $COOCH_3$) ppm. EPR: a_N = 1.55 mT. Anal. Calcd for $C_{13}H_{19}N_2O_4$ (%): C, 58.41; H, 7.19; N, 10.48. Found: C, 58.17; H, 7.33; N, 10.71.

(24) **Dimethyl 2-{6-Hydroxy-3-oxyl-2,2,4,4-tetramethyl-3-azabicyclo[3.1.0]hex-6-yl} Malonate (6e)**
Yield 75%; yellow solid; mp 146–150 °C. IR (KBr): 3442, 2981, 1742, 1438, 1253, 1179, 1011, 914, 715, 624 cm^{-1}. MS (EI): *m/z* = 300 $[M]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 12 H, CH_3), 1.30 (s, 2 H, CH), 3.15 (s, 1 H, CH), 3.67 (s, 6 H, $COOCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.21, 25.36, 31.58, 52.89, 58.09, 61.71, 65.92, 168.32 ppm. EPR: a_N = 1.55 mT. Anal. Calcd for $C_{14}H_{22}NO_6$ (%): C, 55.98; H, 7.38; N, 4.66. Found: C, 55.78; H, 7.57; N, 4.69.

(25) NMR spectra were obtained after reduction with phenyl hydrazine. The compound was dissolved in perdeuterated solvent, transferred into a NMR tube, and flushed with argon. Phenyl hydrazine (2 equiv) was added and the NMR tube shaken to allow the reduction to proceed to completion prior to the NMR spectroscopic analysis.

(26) **Preparation of *tert*-Butyl 3-Hydroxy-2-{6-hydroxy-3-oxyl-2,2,4,4-tetramethyl-3-azabicyclo[3.1.0]hex-6-yl)butanoate} (8)**
tert-Butyl 2-{6-hydroxy-3-oxyl-2,2,4,4-tetramethyl-3-azabicyclo[3.1.0]hex-6-yl}-3-oxobutanoate (**6c**) (200 mg, 0.61 mmol) was dissolved in MeOH (10 mL) and cooled to 0 °C. Sodium borohydride (24 mg, 0.61 mmol) was added with stirring. The temperature was maintained at 0 °C for 2 h, after which the reaction was quenched with citric acid and the pH adjusted to 6. The solvents were evaporated under reduced pressure and citric acid (10%) was added to adjust the pH to 3. The water phase was extracted with EtOAc. The organic phase was washed with brine, dried with Na_2SO_4, and the solvent evaporated under reduced pressure. The crude product was purified using circular chromatography (Et_2O–hexane, 3:1). A bright yellow solid was obtained; yield 93%; mp 101–108 °C. IR (KBr): 3460, 2976, 1702, 1477, 1375, 1160, 993, 646 cm^{-1}. MS (EI): *m/z* = 328 $[M]^+$. MS–FAB: *m/z* = 330 $[M + 2]^+$. HRMS (EI): *m/z* calcd for $C_{17}H_{30}N_1O_5$: 328.212398 $[MH]^+$; found: 328.213250.

(27) **Preparation of 2-{6-Hydroxy-3-oxyl-2,2,4,4-tetramethyl-3-azabicyclo[3.1.0]hex-6-yl}-1-phenyl-propane-1,3-diol (7)**
Ethyl 2-{6-hydroxy-3-oxyl-2,2,4,4-tetramethyl-3-azabicyclo[3.1.0]hex-6-yl}-3-oxo-3-phenylpropanoate (**6f**, 170 mg, 0.47 mmol) was dissolved in MeOH (10 mL) and cooled to 0 °C. While being stirred, $NaBH_4$ (42 mg, 1.06 mmol) was added. The same amount of $NaBH_4$ (42 mg, 0.53 mmol) was again added after 1 h and 2 h. After the third addition the reaction mixture was allowed to warm to ambient temperature. Then, 12 h later, citric acid was added and the pH adjusted to 6. The solvents were evaporated under reduced pressure and citric acid (10%) was added to adjust the pH to 3. The water phase was extracted with EtOAc. The organic phase was washed with brine, dried with Na_2SO_4, and the solvent evaporated under reduced pressure. The crude product was purified using circular chromatography (CH_2Cl_2–MeOH, 15:1). A bright yellow solid was obtained; yield 73%; mp 147–157 °C. IR (KBr): 3421, 2978, 1649, 1457, 1287, 1174, 1032, 705 cm^{-1}. MS (EI): *m/z* = 320 $[M]^+$. HRMS (EI): *m/z* calcd for $C_{18}H_{26}N_1O_4$: 320.186184 $[MH^+]$; found: 320.187330.

(28) **Preparation of 1-(1-Oxyl-2,2,5,5-tetramethylpyrrolidine-3-yl)-2-hydroxymethyl-3-phenylpropane-1,3-diol (9a)**
Ethyl 2-{6-hydroxy-3-oxyl-2,2,4,4-tetramethyl-3-azabicyclo[3.1.0]hex-6-yl}-3-oxo-3-phenylpropanoate (**6f**, 300 mg, 0.83 mmol) was dissolved in THF (10 mL), and $NaBH_4$ (148 mg, 3.72 mmol) was added. The reaction mixture was refluxed at 40 °C and MeOH (0.5 mL) was added over 0.5 h. Following the addition of MeOH the temperature was maintained at 40 °C for another 2.5 h. Several drops of H_2O were then added and the solvents evaporated under reduced pressure, giving a bright yellow foam. Citric acid (10%, 10 mL) was added and the water phase extracted with EtOAc after the evolution of hydrogen stopped. The organic phase was washed with brine, dried with Na_2SO_4, and the solvent evaporated under reduced pressure. The crude product was purified using circular chromatography (CH_2Cl_2–MeOH, 15:1). A bright yellow solid was obtained; yield 21%; mp 157–163 °C. IR (KBr): 3290, 2976, 1474, 1411, 1367, 1295, 1257, 1050, 763, 706 cm^{-1}. MS (EI): *m/z* = 322 $[M]^+$. MS–FAB: *m/z* = 322 $[M]^+$, 324 $[M + 2]^+$. HRMS (EI): *m/z* calcd for $C_{18}H_{28}N_1O_4$: 322.201834 $[M]^+$; found: 322.202650.