Synthesis of Alkynyl-Substituted Pyrrolidin-1-yloxyl Radicals from 1-Pyrroline *N*-Oxide Nitrones and Alkynylmagnesium Bromides

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The reaction of 1-pyrroline *N*-oxides with propargyl- and alkynylmagnesium bromides proceed to give alkynyl functionalized pyrrolidin-1-oxyls without the formation of isoxazolines by a dipolar cycloaddition reaction.

The readiness of nitrones to undergo 1,3-dipolar cycloaddition with alkenes and alkynes under mild conditions is well documented.[1] We reported earlier the *C*-alkylation of various 1-pyrroline *N*-oxides with alkyl and alkenyl Grignard reagents. The reactions of alkenyl compounds proceeded without dipolar cycloaddition, to give higher substituted nitrones and ultimately 1-oxyl-2,2,5,5-substituted pyrrolidine radicals.[2]

Aurich et al. recently reported the reaction of 2-alkyl-5,5-dimethyl-1-pyrroline *N*-oxides with electron-withdrawing group activated monoalkynes to give isoxazolines.[3] The present paper describes what we believe to be the first examples of the synthesis of alkynyl-substituted 1-oxypyrrolidine free radicals by the reaction of a nitrone with an alkynylmagnesium bromide.

The reaction of propargylmagnesium bromide with 2,5,5-trimethyl-1-pyrroline *N*-oxide **(1)** in anhydrous diethyl ether resulted in the formation of 2,5,5-trimethyl-2-propargylpyrrolidinoxy radical **(2)**; further reaction of **2** with **1** led to the formation of 3- and 4-[(2,5,5-trimethyl-1-oxylpyrrolidin-2-yl)methyl]-5,8,8-trimethyl-2-oxa-1-azabicyclo[3.3]oct-3-ene monoradicals **(3, 4)**[4] as byproducts (Scheme 1). The latter step probably requires an activation of **2** by an in situ formed acetylenic magnesium compound since isolated **2** did not react with **1** even when the reaction mixture was heated. The reaction of **1** with phenylacetylene in toluene at 110 °C led to **5** without the formation of significant amounts of radical **6**.

Various alkynylmagnesium bromides were prepared by the reaction of ethylmagnesium bromide with the corresponding alkyne in anhydrous THF,[5] and reacted with **1** to give **6a–e**. However, the reaction of **1** with BrMg–C≡C–Ph led to the formation of radical **6a** and the diamagnetic isoxazoline **5** as a minor product. Compound **5** was probably formed from the unstable hydroxylamine intermediate (Scheme 1).

Cycloaddition of the hydroxylamine intermediate can be effectively suppressed by the use of active MnO_2 as a stronger oxidant to form radical **6a**. Compound **6c** was deprotected in acidic media to **6e**. Compound **6e**, which was easily oxidizable to the aldehyde **6f**, was a key synthetic intermediate for the conversion to bromide **6g** and then to carboxylic acid **6i** via malonic ester **6h**. Compound **6g** could be converted with the sodium salt of methanesulfonothioic acid to **6j**, a propargyl group activated analogue of the previously prepared thiol specific allylic thiosulphonate ester, 2,5-dihydro-2,2,5,5-tetramethyl-4-methanethiosulfonylmethyl-1*H*-pyrrol-1-yloxy radical.[6] The propargylic alcohol was easily reduced with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) to allylic alcohol **7a**, and by the same routes as applied for the transformation of **6e**, we prepared bromide **7c** and the acid **7e** via malonester derivative **7d**, and with the sodium salt of methanesulfonothioic acid, the thiosulphonate ester **7f** (Scheme 1).

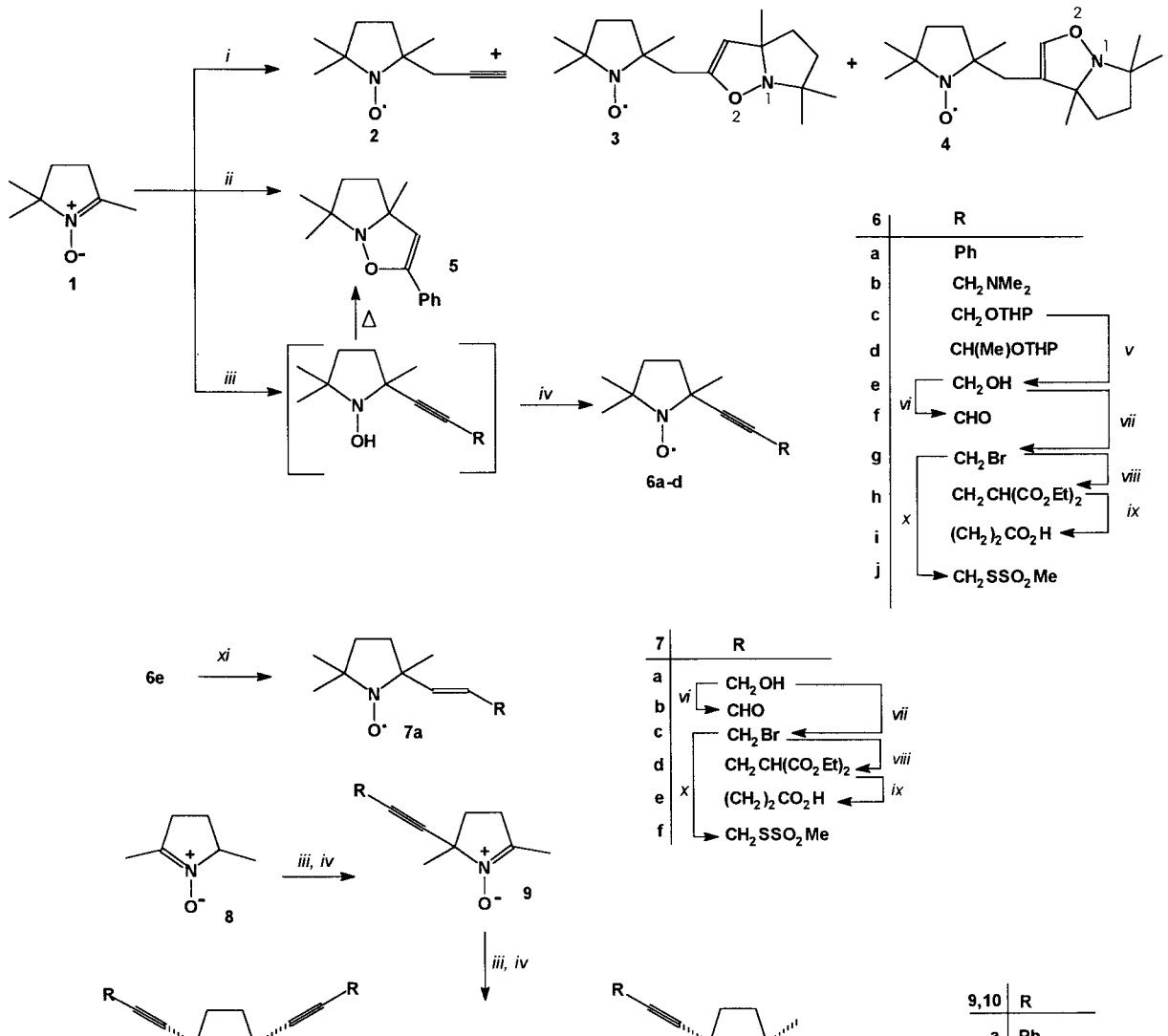
The reaction of another nitrone, 2,5-dimethyl-1-pyrroline *N*-oxide **(8)**, with alkynylmagnesium bromides in two consecutive steps via **9** allowed the preparation of the *Z,E*-stereoisomers of symmetrical 2,5-dialkynyl-2,5-dimethylpyrrolidin-1-yloxy radicals **(10a–c)** (Scheme 1).

Previous studies demonstrated that functionalization of a molecule containing the nitroxide free radical moiety is possible with Grignard reagents without an irreversible loss of the paramagnetic N–O centre (i.e. without *O*-alkylation).

The oxidation of olefins to ketones by a RuO_2 catalyzed reaction is widespread in organic syntheses.[7] Unfortunately, this method can be useful in the case of nitroxides only if the *N*-oxyl function is protected first with *O*-acetylation, e.g., **12** and after oxidation the protecting group is removed with hydrolysis giving nitroxide ketone **14**. An easily accessible method for the preparation of ketone **14** is the mercury salt catalyzed addition of water to the triple bond of acetylene **2** which does not require the protection of *N*-oxy function (Scheme 2).

In conclusion, we have demonstrated that the synthesis of alkynyl-substituted pyrrolidine nitroxide free radicals can be carried out from pyrroline 1-oxide nitrones and certain alkynylmagnesium bromides, without dipolar cycloaddition to isoxazoline. Furthermore, propargylic alcohols exhibit high versatility to form alkynic acids and thiosulphonate spin label reagents. Exploration of the scope and limitations of these reactions is in progress in our laboratory.

Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were performed on Heraeus Micro U/E apparatus or (Hal) were carried out titrimetrically by Schöniger's method. The IR (Specord 75) spectra of the compounds were in each case consistent with the assigned structure. Mass spectra were taken on a Finnigan MAT 8430 mass spectrometer/SS300 data acquisition system. Operating conditions: U_{acc} = 3 kV, R = 1250, EI: E_{el} = 70 eV, I_{el} = 0.5 mA, $T_{ion\ source}$ = 250 °C. Samples were introduced via the direct insertion

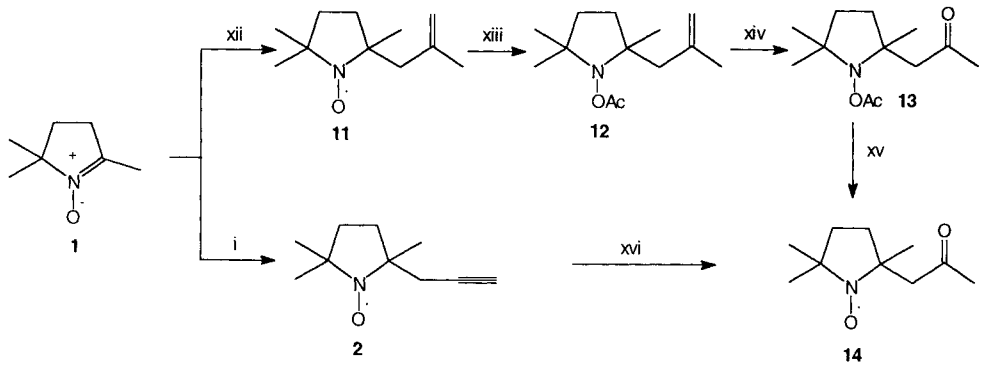


Scheme 1. *i)* HC≡C—CH_2MgBr (1 equiv.), Et_2O, 0 °C, 1 h, NH_4Cl, $CHCl_3$, MnO_2, **2** (54%), **3** (30%), **4** (10%); *ii)* Ph—C≡CH (1 equiv.), reflux, toluene, 3 h, 35%; *iii)* R—C≡CMgBr (1.2 equiv.) THF, -10 °C, 1 h, NH_4Cl; *iv)* cat. MnO_2, $CHCl_3$, 40 °C, 3 h, **6a** (75%) and **5** (15%); **6b** (46%); **6c** (72%), **6d** (68%), from **8**: **10a** [68%, (*Z*, 28%)(*E*, 40%)], **10b**[56%, (*Z*,20%), (*E*,36%)], **10c** [52% (*Z* +*E*)]; *v)* oxalic acid/aq. dioxane, 40 °C, 3 h, 62%; *vi)* MnO_2 (3.0 equiv.), $CHCl_3$, reflux, 3 h, **6f** (74%), **7b** (72%); *vii)* $MeSO_2Cl$ (1.2 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, washed (5% $NaHCO_3$, 5% H_2SO_4), then LiBr (1.5 equiv.), anhyd. acetone, reflux, 1 h, **6g** (72%), **7c** (67%); *(viii)* $CH_2(CO_2Et)_2$, K_2CO_3, 18-crown-6 (as PHT cat.), dioxane, reflux, 3 h, **6h** (84%), **7d** (75%); *ix)* 10 % NaOH (3.0 equiv.), aq. EtOH, 3 h, **6i** (80%), **7e** (73%); *x)* $NaSSO_2Me$ (1.5 equiv), EtOH, reflux, 1 h, **6j** (74%), **7f** (82%); *xi)* SMEAH (70% in toluene), Et_2O, reflux, 2 h, 5 % H_2SO_4, extr., airated cat. PbO_2, 45%.

probe. Assignments were corroborated by high-resolution mass measurements made at R = 10000 by the peak matching technique, with perfluorokerosene 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 × 20 × 0.2 cm) coated with Merck Kieselgel GF_{254}.

2,5,5-Trimethyl-2-propargylpyrrolidin-1-yloxy Radical (2) and 3- and 4-[(2,5,5-Trimethyl-1-oxylpyrrolidin-2-yl)methyl]-5,8,8-trimethyl-2-oxa-1-azabicyclo[3,3]oct-3-enes (3, 4):

To Mg turnings (0.36 g, 0.015 mol) in anhyd. Et_2O (30 mL) was added $HgCl_2$ (15 mg) and the mixture was stirred for 30 min under Ar atmosphere at r.t. Then the flask was cooled to 0 °C and propargyl bromide (1.43 g, 0.012 mol) was added dropwise. After stir-



Scheme 2. *xii*) $CH_3C(CH_2)CH_2MgCl$, Et_2O, 1 h, then NH_4Cl, MnO_2, 73 %; *xiii*) 1. aq. dioxane, ascorbic acid, 30 min. 2. Et_3N, $CHCl_3$, 0 °C, AcCl, 1 h, 67 % ; *xiv*) $CCl_4/CH_3CN/H_2O$, $NaIO_4$, cat. $RuCl_3$, cat. 18-crown-6, 0 °C then r.t., 3 h; *xv*) 10 % NaOH, EtOH, 1 h, 48 %; xvi) 5 % H_2SO_4, cat. $Hg(OAc)_2$, 30 min., 69 %.

Table 1. Compounds **2–14** Prepared[a]

Product[b]	Yield (%)	IR (neat/Nujol) ν (cm^{-1})	MS *m/z* (%)
2	54	3290 (≡C–H), 2110 (C≡C)	166 (M^+, 100), 128 (20), 112 (24), 56 (26), 55 (28), 41 (30)
3+4	40	–	293 (M^+, 16), 182 (16), 166 (38), 151 (43), 128 (100), 112 (65)
5	35, 15	–	229 (M^+, 4), 214 (42), 127 (100)
6a	75	1600 (C=C, arom)	228 (M^+, 14), 142 (100), 141 (38), 77 (6), 74 (7)
6b	46	–	210 (M^+, 20), 82 (42), 58 (100)[c]
6c	72	–	266 (M^+, 8), 236 (4), 85 (100)
6d	68	–	280 (M^+, 8), 164 (24), 93 (35), 85 (100)
6e	62	3250–3450 (OH)	182 (M^+, 44), 167 ($M^+ - CH_3$, 10), 137 ($M^+ - CH_3 - NO$, 100), 119 ($M^+ - CH_3 - NO - H_2O$, 30), 95 (55), 81 (44)
6f	74	1670 (C=O)	180 (M^+, 1.5), 166 ($M^+ + H - CH_3$, 8), 165 ($M^+ - CH_3$, 3), 152 ($M^+ - CO$, 20), 128 ($M^+ - C_2CO$, 40), 127 ($M^+ - C_2CHO$, 40), 95 (18)
6g	72	–	244/246 (M^+, 29/29), 214/216 (35/35), 55 (100)
6h	84	1730 (C=O)	324 (M^+, 30), 379 (50), 219 (50), 165 (100)
6i	80	3000–3500 (OH), 1715 (C=O)	225 (M^+, 20), 210 (50), 179 (17.5), 110 (100)[c]
6j	74	–	276 (M^+, 55), 262 (100), 247 (80), 197 (50)
7a	45	3400 (OH), 1660 (C=C)	184 (M^+, 80), 154 (57), 41 (100)
7b	72	1690 (C=O), 1630 (C=C)	182 (M^+, 33), 123 (83), 97 (100)
7c	67	–	246/248 (M^+, 15/15), 167 (10), 160/162 (15/15), 81 (100)
7d	75	1730 (C=O)	326 (M^+, 100), 309 (41), 281 (29), 266 (47), 240 (94), 194 (94), 166 (77)
7e	73	2900–3450 (OH), 1720 (C=O)	226 (M^+, 1), 208 (3), 182 (70), 123 (80), 97 (95), 71 (100)
7f	82	–	278 (M^+)
(*Z*)-**10a**	28	–	314 (M^+, 46), 142 (100)
(*E*)-**10a**	40	–	314 (M^+, 30), 142 (100)
(*Z*)-**10b**	20	–	390 (M^+, 10), 360 (6), 85 (100)
(*E*)-**10b**	36	–	390 (M^+, 6), 360 ($M^+ - NO$, 40), 85 (100)
(*E*/*Z*)-**10c**	52	–	418 (M^+, 9), 388 (3), 334 (5), 234 (6), 85 (100)
11	73	1620 (C=C)	182 (M^+, 86), 128 ($M^+ - CH_2C(CH_2)CH_2$, 46), 81 (100), 69 (82), 55 (52), 41 (78)
12	67	1760 (C=O), 1630 (C=C)	182 ($M^+ - COCH_3$, 3), 170 ($M^+ - C_4H_7$, 36), 128 (170 $- CH_2CO$, 100), 69 (11), 55 (9), 41 (11)
14	48, 69	1690 (C=O)	185 (M^+, 44), 170 ($M^+ - CH_3$, 95), 128 ($M^+ - CH_2COCH_2$, 100), 69 (45), 43 (76)[c]

[a] All products are oils except **6a**; mp 47–48 °C
[b] Satisfactory microanalyses obtained: C ± 0.23, H ± 0.16, N ± 0.18.
[c] Mass spectra of N–OH form of the compound.

ring for 2 h, 2,5,5-trimethyl-1-pyrroline 1-oxide (1.27 g, 0.01 mol) was added dropwise at 0 °C. After an additional 1 h sat. NH_4Cl solution (40 mL) was added and the mixture extracted with Et_2O (3 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was dissolved in $CHCl_3$ (40 mL), a catalytic amount of MnO_2 was added and O_2 was bubbled for 30 min and then filtered. The yellow residue obtained on evaporation of $CHCl_3$ was chromatographed on silica gel with hexane/Et_2O to give yellow oils of **2** (0.90 g, 54%); **3** (0.44 g, 30%), and **4** (0.15 g, 10%).

5,8,8-Trimethyl-3-phenyl-2-oxa-1-azabicyclo[3.3]oct-3-ene (5):
Phenylacetylene (1.02 g, 0.01 mol) and 2,5,5-trimethyl-1-pyrroline 1-oxide (**1**; 1.27 g, 0.01 mol) was refluxed in toluene (50 mL) for 3 h. The solvent was evaporated and the residue chromatographed on silica gel with hexane/Et_2O giving **5**; yield: 0.80 g (35%).

Alkylation of Nitrone 1 with Alkynylmagnesium Bromides to Compounds 6a–d and 10a–c; General Procedure:
To a solution of EtMgBr (0.012 mol) in anhyd. THF (25 mL) was

added the appropriate alkyne (0.012 mol) over 15 min while heating the reaction mixture at 50 °C. After heating at 50 °C for 1 h, nitrone **1** (1.27 g, 0.01 mol) was added at −10 °C. After stirring for an additional 1 h at r.t., sat. NH_4Cl solution was added. The organic phase was separated, dried and evaporated to dryness. The residue was dissolved in $CHCl_3$ (40 mL) and stirred with a catalytic amount of active MnO_2 in $CHCl_3$ at 40 °C for 3 h, then filtered and evaporated. The crude product was purified by flash chromatography to give acetylene derivatives of nitroxides; yield **(6a)**: 1.71 g (75%); **(6b)**: 0.96 g (46%); **(6c)**: 1.92 g (72%); **(6d)**: 1.91 g (68%).

For the preparation of 2,5-dialkyl-2,5-dimethylpyrrolidin-1-yloxy radicals the same procedure as above was applied using 2,5-dimethyl-1-pyrroline *N*-oxide nitrone **(8)**. Compounds **9a–c** were used in the second Grignard reaction without purification; yield **(10a)**: 2.13 g [68%, *Z*: 0.88 g (28%), *E*: 1.26 g (40%]; **(10b)**: 2.19 g [56%, *Z*: 0.78 g (20%), *E*: 1.41 g (36%)]; **(10c)**: 2.18 g (52%).

2,5,5-Trimethyl-2-(3-hydroxyprop-1-ynyl)pyrrolidin-1-yloxy Radical (6e):

To a mixture of OTHP compound **6c** (5.32 g, 0.02 mol) in dioxane/water (50 mL, 1:1) was added oxalic acid (4.50 g, 0.05 mol) and stirred for 3 h at 40 °C. Then brine (20 mL) was added and the water layer was extracted with $CHCl_3$ (3 × 20 mL). The combined organic phase was dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by flash chromatography with $CHCl_3$/Et_2O to give the hydroxyl compound **6e**; yield: 2.26 g (62%).

Oxidation of Propargyl and Allyl Alcohols 6e, 7a to Aldehydes 6f, 7b; General Procedure:

Propargyl or allylic alcohol compound **6e, 7a** (5 mmol) was dissolved in $CHCl_3$ and refluxed with MnO_2 (3 equiv) for 3 h. The mixture was filtered, evaporated and purified by flash chromatography with hexane/Et_2O to give aldehyde; yield **(6f)**: 0.67 g (74%); **(7b)**: 0.66 g (72%).

Propargyl and Allylic Bromides 6g, 7c from Alcohols 6e, 7a; General Procedure:

To a solution of Et_3N (1.2 g, 0.012 mol) and alcohol **6e, 7a** (0.01 mol) in anhyd. CH_2Cl_2 (30 mL) was added $MeSO_2Cl$ (1.37 g, 0.012 mol) at 0 °C. The mixture was stirred for 30 min, washed with 5% $NaHCO_3$ solution, 5% H_2SO_4 solution, dried ($MgSO_4$) and evaporated. The oily residue was dissolved in anhyd. acetone (50 mL) and LiBr (1.30 g, 0.015 mol) was added. The mixture was refluxed for 1 h and the solvent was evaporated. The residue was dissolved in water and extracted with Et_2O, dried and evaporated. Flash chromatography of the residue with hexane/Et_2O provided the bromides; yield **(6g)**: 1.76 g (72%); **(7c)**: 1.66 g (67%).

Diethyl Malonate Derivatives 6h, 7d; General Procedure:

To a solution of propargyl or allylic bromide **6g, 7c** (0.02 mol) in dioxane were added diethyl malonate (3.20 g, 0.02 mol), powdered KOH (100 mg), K_2CO_3 (2.76 g, 0.02 mol) and 18-crown-6 (100 mg). The mixture was stirred and refluxed for 3 h, cooled to r.t. and filtered. After removal of the solvent under reduced pressure, the product was dissolved in $CHCl_3$ (20 mL) and washed with 5% H_2SO_4 (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), evaporated and the yellow oil was purified by flash column chromatography eluting with hexane/EtOAc to give diethyl malonate compounds; yield **(6h)**: 5.45 g (84%); **(7d)**: 4.90 g (75%).

Ester Hydrolysis and Decarboxylation of 6h and 7d to 6i and 7e:

To an EtOH solution (50 mL) of ester **6h** or **7d** (0.015 mol) was added 10% NaOH solution (18 mL), stirred for 3 h and then acidified with 5% H_2SO_4 solution. The mixture was extracted with $CHCl_3$ (3 × 20 mL), dried ($MgSO_4$) and evaporated in vacuo to dryness; yield **(6i)**: 2.69 g (80%); **(7e)**: 2.83 g (73%).

2,5,5-Trimethyl-2-(3-methanethiosulfonylmethylprop-1-ynyl)pyrrolidin-1-yloxyl Radical (6j) and 2,5,5-Trimethyl-2-(3-methanethiosulfonylmethylprop-1-enyl)pyrrolidin-1-yloxyl Radical (7f):

To a solution of the bromine compound **6g** or **7c** (5 mmol) in EtOH (20 mL) was added $NaSSO_2Me$ (1.01 g, 7.5 mmol) in water (4 mL) and the mixture was refluxed for 1 h. EtOH was evaporated, the residue was taken up in $CHCl_3$ (20 mL), washed with brine, dried ($MgSO_4$), evaporated and purified by flash column chromatography on silica gel; yield **(6j)**: 1.02 g (74%); **(7f)**: 1.14 g (82%).

2,5,5-Trimethyl-2-(3-hydroxyprop-1-enyl)pyrrolidin-1-yloxyl Radical (7a):

To a solution of **6e** (3.64 g, 0.02 mol) in anhyd Et_2O (100 mL) was added dropwise with stirring a 70% toluene solution of SMEAH (7 mL) in Et_2O (50 mL). The resulting mixture was stirred and refluxed under Ar for 20 h then cooled in an ice bath and cautiously decomposed by the dropwise addition of 10% NaOH (30 mL). The organic phase was washed with brine, dried ($MgSO_4$) and aerated for 30 min in the presence of PbO_2 as a catalyst to reoxidize the *N*-hydroxy compound to nitroxide. Evaporation of the solvent and purification by flash chromatography gave **7a** as yellow oil; yield: 1.66 g (45%).

2,5,5-Trimethyl-2-(2-methylprop-2-enyl)pyrrolidin-1-yloxy Radical (11):[2]

To a solution of 2-methylprop-2-enylmagnesium chloride (0.02 mol, prepared from 0.04 mol Mg turnings and 0.02 mol 3-chloro-2-methylpropene at 0 °C) under Ar in anhyd Et_2O (50 mL) was added nitrone **1** (1.905 g, 0.015 mol) at 0 °C in Et_2O (30 mL) dropwise and stirred for 1 h. Then aq sat. NH_4Cl (50 mL) was added dropwise at 0 °C and the organic layer was separated, washed with brine (30 mL), dried ($MgSO_4$) and evaporated. The residue was dissolved in $CHCl_3$ and aerated in the presence of a catalytic amount of MnO_2 for 30 min. After the *N*-hydroxy compound was oxidized to nitroxide, the solution was filtered and evaporated to give a reddish oil which was purified by flash column chromatography using hexane/Et_2O as eluent; yield: 2.00 g (73%).

1-Acetoxy-2,5,5-trimethyl-2-(2-methylprop-2-enyl)pyrrolidine (12):

To a solution of radical **11** (1.82 g, 0.01 mol) in dioxane (20 mL) was added a solution of ascorbic acid (8.80 g, 0.05 mol) in water (10 mL) and the mixture was stirred at 40 °C for 15 min. The colourless solution was extracted with $CHCl_3$ (3 × 20 mL) and dried ($MgSO_4$) under N_2. Then Et_3N (1.21 g, 0.012 mol) and AcCl (0.94 g, 0.012 mol) were added at 0 °C. The stirring was continued for 1 h at r.t., then the mixture was filtered and evaporated to dryness. The residue was dissolved in brine and extracted with Et_2O (3 × 20 mL). The organic layer was dried ($MgSO_4$), evaporated and the product was purified by flash column chromatography (hexane/Et_2O) giving the title compound as a colourless oil; yield: 1.51 g (67%).

2,5,5-Trimethyl-2-(2-oxopropanyl)pyrrolidin-1-yloxy Radical (14):

Step xv: To a well stirred solution of 1-acetoxyalkene **12** (1.13 g, 5 mmol) in CCl_4 (10 mL) and MeCN (10 mL) was added $NaIO_4$ (4.28 g, 20 mmol), then the mixture was cooled to 0 °C and water (15 mL), 18-crown-6 (10 mg) and $RuCl_3$ (10 mg) were added. The stirring was continued for 3 h at r.t. After the reaction was complete, Et_2O was added and the ethereal phase was decanted several times (5 × 10 mL) and filtered on Celite. The filtrate was evaporated to give 1-acetoxy ketone **13** as a pale yellow oil which was hydrolyzed without any purification. Compound **13** was dissolved in dioxane (10 mL), 10% NaOH solution (2 mL) was added and the mixture was stirred for 30 min. After acidifying with 5% H_2SO_4, brine (10 mL) was added and extracted with Et_2O (3 × 20 mL). The organic phase was dried, evaporated and purified on silica gel with hexane/Et_2O giving ketone **14**; yield: 0.45 g (48%).

Step xvi: To a solution of **2** (0.83 g, 5 mmol) in EtOH (10 mL) were added 5% H_2SO_4 (5 mL) and a catalytic amount of $Hg(OAc)_2$. The mixture was stirred for 30 min at r.t. After the reaction was complete, brine (10 mL) was added and the mixture extracted with Et_2O (3 × 15 mL). The organic phase was dried and evaporated. The crude product was purified by flash column chromatography to afford ketone **14**. The physical and spectroscopic data of this compound were identical with the compound prepared by the oxidation of **12** as described above; (step xv); yield: 0.63 g (69%).

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