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Cyclization of β-allenyloximes as a novel method for nitrone preparation

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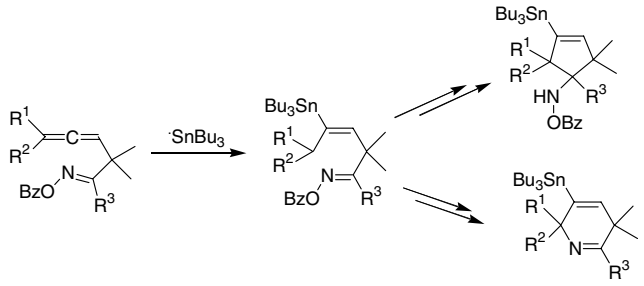
Abstract—Two different procedures for β-allenyloxime cyclization are described. One leads to substituted 1-hydroxypyrrolidines and the other represents a new route to pyrroline-*N*-oxides.

1. Introduction

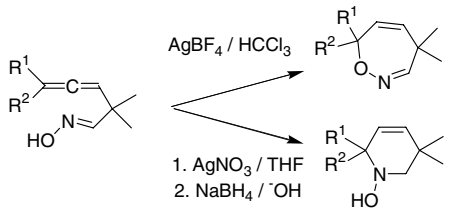
We present here a novel method for nitrone preparation, which was discovered during our study of the behaviour of 2,2-dimethylpenta-3,4-dienal oxime (**2**).

In the literature, there are only a few types of β-allenyloxime cyclization. Thus, under tin-mediated free-radical conditions, when a wide range of substituted β-allenyloximes were treated with tributyltin hydride the reaction occured at the allenic sp-carbon atom (Scheme 1). Depending on the type of substitution at the carbon atom of the oxime function, the reaction led to either cyclopentene derivatives or 2,5-dihydropyridines, both bearing a tributyltin group.[1,2]

Other attempts were carried out under metal catalysis. When $AgBF_4$ in chloroform was used, 4,7-dihydro-1,2-oxazepines were isolated in good yields (Scheme 2).[3] Applying $AgNO_3$ as catalyst in THF, the cyclization proceeded at the nitrogen atom to give a six membered ring and when the reaction mixture was subsequently treated with $NaBH_4$ in a basic medium, 1-hydroxy-1,2,3,6-tetrahydropyridines were formed.[4] The results are explained by the ambident character of the oxime and the function of the counter-anion.



Scheme 1. Examples of tin promoted cyclizations.



Scheme 2. Examples of Ag^+ catalyzed cyclizations.

In this letter we report that β-allenyloximes unsubstituted at position 5 undergo cyclization reactions, under specific conditions, to form new 5-membered heterocycles.

2. Results and discussion

β-Allenyloxime **2** was prepared according to the literature[1] from the corresponding allenylaldehyde[5] **1** by reaction with hydroxylamine hydrochloride in the presence of pyridine. The purified oxime was then used in cyclization reactions (Scheme 3).

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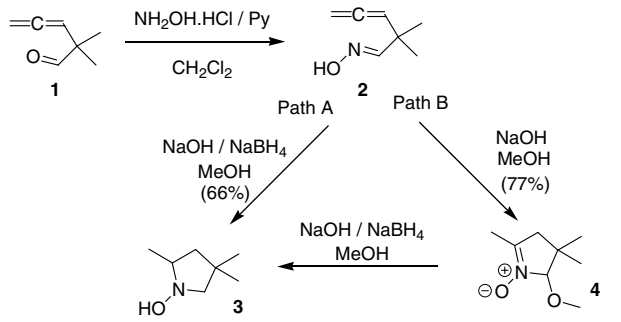
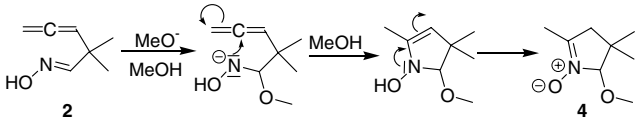


Scheme 3. General cyclization reaction scheme.

When oxime **2** was heated in boiling methanol in the presence of sodium hydroxide (concn~2.5%) and the reducing agent $NaBH_4$ (Scheme 3, Path A), formation of pyrrolidine-1-ol **3** was observed. Surprisingly, no product containing a C=C bond was detected. The reaction without reducing agent (Path B) led to formation of nitrone **4** containing a methoxy group in the α position. It should be noted here that nitrone preparation based on allenyl synthons has not been reported previously and represents a completely new route to nitrone-type compounds.

Cleavage of the H_3CO–C bond and formation of product **3** when nitrone **4** was treated under the same conditions as in Path A could indicate that conversion of **2** to **3** may proceed via a step-wise mechanism (cyclization–reduction). A possible reaction mechanism is shown in Scheme 4.



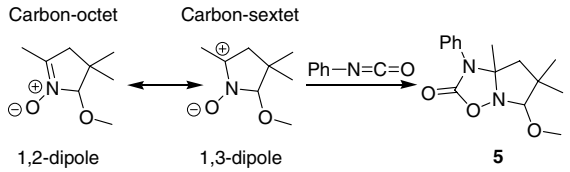
Scheme 4. Proposed mechanism for nitrone formation.

The process is started by methoxide anion addition to the polar C=N bond, which can initiate attack of the nitrogen atom on the central allenylic carbon atom. This attack leads to an enamine, which is stabilized by the protic solvent forming **4**.

The structures of compounds **3** and **4** were determined by NMR, MS and by X-ray analysis[6] of their corresponding picrates (Figs. 1 and 2).[7] Protonation of compound **3** occurs on the N-atom whilst compound **4** is protonated on the O-atom.

To verify the dipole-structure of nitrone **4** (nitrones are classified as 1,3-dipoles with internal octet-stabilization[8]), some experiments with dipolarophiles were carried out.

Compound **4** was shown to be a highly reactive species in 1,3-dipolar cycloadditions. The resonance structures of nitrone **4** and formation of a pyrrolidino[1,2-*b*]-[1,2,4] oxadiazole skeleton on reaction with phenylisocyanate are shown in Scheme 5.



Scheme 5. 1,3-Dipolar cycloaddition with nitrone **4**.

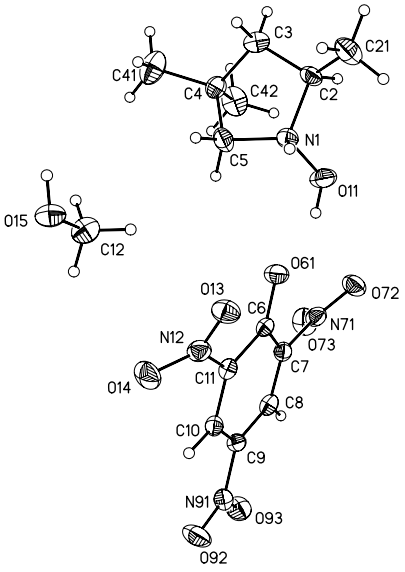


Figure 1. ORTEP representation of the structure of compound **3**: picrate.

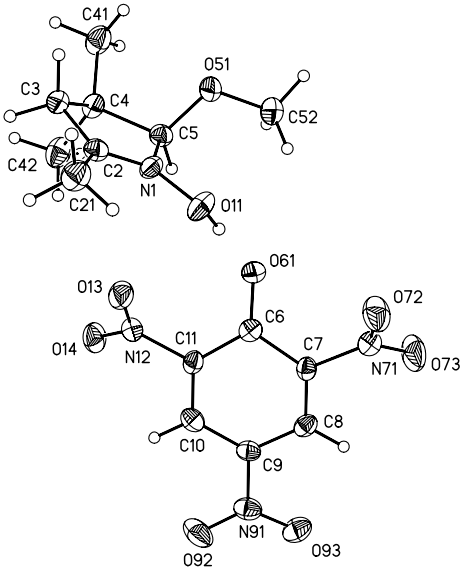


Figure 2. ORTEP representation of the structure of compound **4**: picrate.

3. Experimental

3.1. 2,2-Dimethylpenta-3,4-dienal oxime (*2*)

To a stirred mixture of hydroxylamine hydrochloride (25.2 g, 0.363 mol) and pyridine (31.6 g, 0.399 mol) in CH_2Cl_2 (100 ml), 3 Å molecular sieves (~8 g) and 2,2-di-

methylpenta-3,4-dienal (20.0 g, 0.182 mol) were added. The reaction mixture was then stirred for 1 h. Then, the mixture was filtered, diluted with 250 ml of diethyl ether and washed with water (150 ml) and then six times with $CuSO_4$ (5% aqueous solution, 100 ml) to remove pyridine. The solvent was dried over $MgSO_4$ and removed under reduced pressure. The crude product was purified by vacuum distillation using a Kugelrohr apparatus to give **1** (72%, 16.4 g). δ_H ($CDCl_3$) 300 MHz: 1.22 (s, 6H, CH_3), 4.83 (d, $^4J_{H,H} = 6.6$, 2H, CH_2), 5.16 (t, $^4J_{H,H} = 6.6$, 1H, C=CH), 7.37 (s, 1H, N=CH), 8.90 (s, 1H, OH); δ_C ($CDCl_3$) 75.5 MHz: 25.9 ($2 \times CH_3$), 37.0 (H_3C–*C*–CH_3), 78.1 (CH_2), 97.4 (C=*C*H), 157.4 (N=C), 207.0 (=C=); IR (film) ν_{max}/cm^{-1} 849, 943, 1383, 1456, 1955 (=C=), 2870, 2931, 2972, 3320 (OH); MS *m*/*z* (%):[9] 126 (M^++1, 100), 110 (82), 81 (72), 67 (23), 53 (20), 41 (24).

3.2. 2,4,4-Trimethylpyrrolidine-1-ol (3)

Oxime **2** (2.5 g, 20 mmol) was added to a mixture of NaOH (0.35 g, 8.75 mmol) and $NaBH_4$ (2.26 g, 59.91 mmol) in methanol (15 g). The reaction mixture was heated under reflux for 2 h. Next, a small amount of concd HCl (~2–3 ml) was added to reach pH~3. The mixture was then concentrated under vacuum and 15 ml of water and solid NaOH pellets were added to make the mixture alkaline. The mixture was then extracted with CH_2Cl_2 (4×15 ml). The combined extracts were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified using a Kugelrohr apparatus (95 °C, 0.13 mbar) to give **2** (66%, 1.71 g). δ_H ($CDCl_3$) 300 MHz: 1.06 (s, 3H, H_3C–C–CH_3), 1.07 (s, 3H, H_3C–C–CH_3), 1.19 (d, $^3J_{H,H} = 6.0$, 3H, HC–CH_3), 1.22–1.31 (m, 1H, HC–CH_2–C), 1.73 (dd, $^2J_{H,H} = 12.9$, $^3J = 7.6$, 1H, HC–CH_2–C), 2.59 (d, $^2J_{H,H} = 9.6$, 1H, N–CH_2–C), 2.80–2.97 (m, 1H, CH), 3.06 (d, $^2J_{H,H} = 9.6$, 1H, N–CH_2–C), 8.26 (s, 1H, OH); δ_C ($CDCl_3$) 75.5 MHz: 18.5 (H_3C–CH), 30.1 (H_3C–C–CH_3), 31.3 (H_3C–C–*C*H_3), 33.7 (H_3C–*C*–CH_3), 45.8 (HC–*C*H_2), 63.9 (CH), 71.8 (N–CH_2); IR (film) ν_{max}/cm^{-1} 1379, 1451, 2867, 2957, 3222 (OH); MS *m*/*z* (%):[9] 130 (M^++1, 77), 114 (74), 69 (39), 56 (100), 41 (37).

3.3. 2-Methoxy-3,3,5-trimethyl-3,4-dihydro-2*H*-pyrrole-1-oxide (4)

Oxime **2** (2.5 g, 20 mmol) was added to a solution of NaOH (0.35 g, 8.75 mmol) in methanol (15 g) and the mixture was heated under reflux for 3 h. Then it was concentrated under reduced pressure and 15 ml of water was added. The mixture was extracted with CH_2Cl_2 (4×15 ml). The combined extracts were dried over $MgSO_4$ and concentrated under vacuum to give crude product **4** (2.43 g, 77%). The product could be further purified by distillation using a Kugelrohr apparatus (71 °C, 0.12 mbar), to give a colourless liquid (1.92 g, 61%). δ_H ($CDCl_3$) 300 MHz: 1.04 (s, 3H, H_3C–C–CH_3), 1.13 (s, 3H, H_3C–C–CH_3), 1.99 (s, 3H, H_3C–C=N), 2.27 (d, $^2J_{H,H} = 18.83$, 1H, CH_2), 2.49 (d, $^2J_{H,H} = 18.83$, 1H, CH_2), 3.83 (s, 3H, O–CH_3), 4.42 (s, 1H, CH); δ_C ($CDCl_3$) 75.5 MHz: 13.0 (H_3C–C=N), 22.0 (H_3C–C–CH_3), 27.5 (H_3C–C–*C*H_3), 36.7 (H_3C–*C*–CH_3), 45.7 (CH_2), 61.2 (O–CH_3), 107.6 (CH), 191.9 (H_3C–*C*=N); IR (film) ν_{max}/cm^{-1} 1115, 1178, 1215, 1244, 2848, 2873, 2931, 2964; MS *m*/*z* (%):[9] 158 (M^++1, 100), 127 (46), 112 (51), 86 (24), 71 (45), 56 (32), 41 (52).

3.4. 5-Methoxy-6,6,7a-trimethyl-1-phenylpyrrolidino-[1,2-*b*][1,2,4]oxadiazol-2(1*H*)-one (5)

Nitrone **4** (100 mg, 0.636 mmol) and phenylisocyanate (75.7 mg, 0.636 mmol) were refluxed in dry benzene (5 ml) for 3.5 h. The solvent was evaporated and the remaining crude product was crystallized from EtOH/Et_2O = 1:1. 107 mg (61%), mp 147.5–148.5 °C. δ_H ($CDCl_3$) 300 MHz: 1.12 (s, 3H, H_3C–C–CH_3), 1.15 (s, 3H, H_3C–C–CH_3), 1.68 (s, 3H, H_3C–C–CH_3), 1.87 (d, $^2J = 13.87$, 1H, CH_2), 2.32 (d, $^2J = 13.87$, 1H, CH_2), 3.65 (s, 3H, O–CH_3), 4.33 (s, 1H, HC–O), 7.51–7.30 (m, 5H, C_{Ar}–H). δ_C ($CDCl_3$) 75.5 MHz: 23.4 (C–CH_3), 27.5 (C–CH_3), 27.6 (C–CH_3), 37.7 (H_3C–*C*–CH_3), 48.1 (CH_2), 59.0 (OCH_3), 84.1 (N–C–N), 106.6 (HC–O), 125.7 (C_{Ar}H), 127.5 (C_{Ar}H), 129.7 (C_{Ar}H), 134.9 (C_{Ar}H), 155.6 (C=O). IR (film) ν_{max}/cm^{-1} 1124, 1213, 1373, 1496, 1762 (C=O), 2951, 2968. MS *m*/*z* (%):[9] 277 (M^++1, 10), 157 (69), 127 (100), 112 (57), 85 (21), 56 (31).

Acknowledgements

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5. Zachová, H.; Man, S.; Nečas, M.; Potáček, M. *Eur. J. Org. Chem.* **2005**, 2548.
6. Diffraction data were collected on a Kuma KM-4 four-circle CCD diffractometer and corrected for Lorentz and polarization effects. The structures were solved by direct methods and refined using the SHELXTL program package.The hydrogen atoms were placed in calculated idealized positions and refined as riding. Crystallographic data for compound **3** (CCDC deposition number 611904) and **4** (CCDC deposition number 611905) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
7. Compounds **3** and **4**, respectively, were mixed with 1 equiv of picric acid in methanol. The mixture was left to crystalyze at room temperature affording crystals suitable for X-ray analysis.
8. Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 365.
9. MS were measured on a Fisons Instruments Trio 100 with EI ionization (70 eV).