Synthesis and reactivity of α-allenylhydroxylamines: a new efficient access to 3,6-dihydro-1,2-oxazines

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SmI_2-promoted reduction of α-allenyl nitro derivatives 2a–f using controlled conditions provides either 3-amino-4-vinylidenetetrahydrofuran 3a or 3-hydroxylamino-4-vinylidenetetrahydrofurans 4b–f, which undergo intramolecular cyclization consistent with a reverse Cope elimination to afford 3,6-dihydro-1,2-oxazines 5b–f.

The *C*-nitroso group (R–N=O) acts as a heterodienophile in hetero-Diels–Alder reactions with 1,3-dienes to afford regioselectively 3,6-dihydro-1,2-oxazines.[1] The intramolecular variant Diels–Alder reaction has received some attention since resulting 3,6-dihydro-1,2-oxazines are involved in strategies for the synthesis of indolizidine alkaloids.[2] The most useful synthetic application of these cycloadditions is the easy cleavage of the N–O bond in the adduct to generate 1,4-bifunctional groups.[3]

Despite their synthetic potential, 3,6-dihydro-1,2-oxazines have exclusively been prepared by [4 + 2] cycloaddition.[4] Nevertheless, the well documented electrophilic-catalyzed intramolecular cyclizations of β-allenyl alcohols into dihydropyrans[5] suggest that cyclic derivatives of hydroxylamines, namely 3,6-dihydro-1,2-oxazines, should alternatively be provided by related cyclization of α-allenylhydroxylamines.

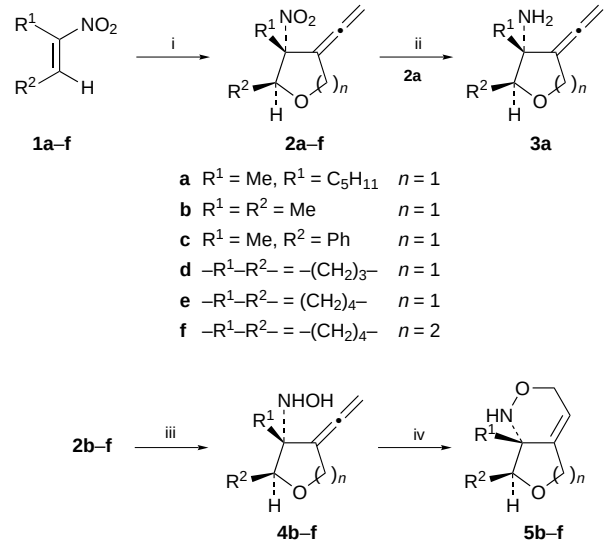
Although a number of methods are available for the synthesis of allenic amines,[6] to the best of our knowledge, among nitrogen related derivatives with higher oxidation state, allenylhydroxylamines have never been described. Nevertheless, addition of alkylhydroxylamines to allenyl carbonyl compounds provides allenyl nitrones which have been postulated as intermediates[7] in 1,3-dipolar cycloadditions leading to bicyclic isoxazolidines. Moreover, a diastereoselective synthesis of nitroallenes has recently been reported.[8]

We disclose here the efficient reduction of nitroallenes **2b**–**f** upon treatment with SmI_2 to the corresponding hydroxylamines **4b**–**f**, which are subsequently converted into 3,6-dihydro-1,2-oxazines **5b**–**f** by remarkably facile cyclization (Scheme 1).

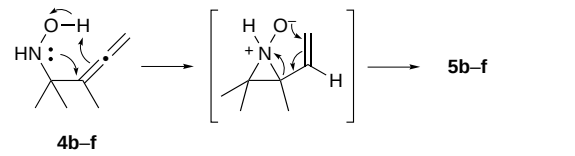
3-Nitro-4-vinylidenetetrahydrofurans **2a**–**e** were prepared[8] by tandem oxa-Michael addition–S_N2' substitution of 4-chlorobut-2-yn-1-ol with nitroalkenes **1a**–**e**, while the same sequence with **1f** afforded 3-nitro-4-vinylidenetetrahydropyran **2f** when 5-chloropent-3-yn-1-ol was used as nucleophile. Reduction of nitro compounds has been used for a long time as a routine method for the preparation of various nitrogen derivatives such as amines and hydroxylamines;[9] however, in many cases over reduction occurs and further reduction to amines is difficult to avoid. Since the previous work of Kagan and co-workers on the reactivity of SmI_2 with nitrogen compounds,[10] alkylhydroxylamines and alkylamines have been prepared selectively from nitroalkanes and SmI_2 under mild conditions.[11]

According to this procedure, allenyl amine **3a**† was obtained by treatment of **2a** with 6 equiv. of SmI_2 in THF–Bu^{t}OH, while reaction of **2b**–**f** with 4 equiv. of SmI_2 allowed the isolation of the corresponding hydroxylamines **4b**–**f** in 60–65% yield.‡§

Upon standing at room temperature without catalyst, **4b**,**c**,**e**,**f** (6 h) or **4d** (15 d) were converted into **5b**–**f**¶ in 62–92% yield. This non-catalyzed intramolecular cyclization of hydroxylamines is in contrast to the well-known electrophilic catalysis required for the cyclization of functionalized allenic derivatives.[5,12] Although intramolecular cyclization of α-allenyl amines proceeds according to a 5-*endo-trig* mode to afford pyrroline derivatives[13] the chemo- and regio-selectivities of the cyclization of **4b**–**f** allow the formation of **5b**–**f** *via* apparently exclusive intramolecular *O*-alkylation. Nevertheless, while it is premature to propose a definitive mechanism, the fact that the cyclizations proceed uncatalyzed at ambient temperature strongly suggests a pathway which features a reverse Cope elimination [eqn. (1)].[14]‖ Moreover, this pathway proceeds according to the usual reactivity of hydroxylamines, which undergo alkylation on nitrogen rather than on oxygen by addition to the activated double bond.[15]



Scheme 1 *Reagents and conditions*: i, **1** (1 equiv.), THF, Bu^{t}OK (1.5 equiv.), $ClCH_2C{\equiv}C(CH_2)_nOH$ (1.5 equiv.), 0 °C, 10 min, then room temp., 15–30 min, n = 1 (ref. 8), n = 2 (74%); ii, SmI_2 (6 equiv.), THF, Bu^{t}OH, 15 min, 42%; iii, SmI_2 (4 equiv.), THF, Bu^{t}OH, 15 min, 60–65%; iv, room temp., 6 h to 15 d, 62–92%



In conclusion, the SmI_2-controlled mild reduction of **2b**–**f** constitutes a new access to allenyl hydroxylamines **4b**–**f** which are precursors of 3,6-dihydro-1,2-oxazines **5b**–**f**, probably by reverse Cope elimination.

Notes and References

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† *Selected data* for **3a**: ν_{max}(neat)/cm^{-1} 3367, 2964, 1965, 1092, 1021; δ_H(400 MHz, $CDCl_3$) 0.90 (m, 3 H), 1.14 (s, 3 H), 1.19–1.81 (m, 8 H), 3.90

[t, *J* 1.8, 1 H ($C_5H_{11}CHO$–)], 4.35 [dt, *J* 12.3, 4.7, 1 H (OCH_AH_B)], 4.46 [dt, *J* 12.3, 4.2, 1 H (OCH_AH_B)], 4.73 [dt, *J* 9.8, 4.5, 1 H (=CH_AH_B)], 4.80 [dt, *J* 9.8, 4.5, 1 H (=CH_AH_B)]; δ_C(100.61 MHz, $CDCl_3$) 14.2, 22.6, 22.7, 26.7, 29.2, 32.1, 66.6 (OCH_2), 71.1 (C–N), 81.3 (=CH_2), 88.1 (C_5H_{11}–C–O), 103.9, 197.6; *m/z* (12 eV) 196 (M + 1), 194, 178, 123, 99, 95, 82 (100%).

‡ Bicyclic adducts **2d**–**f** are *cis* ring fused (refs. 8 and 16), and this stereochemistry is recovered in **4**, **5d**–**f**.

§ *Selected data* for **4c**: ν_{max}(neat)/cm^{-1} 3555, 3257, 3033, 2859, 2969, 1966, 1058; δ_H(400 MHz, C_6D_6) 0.79 (s, 3 H), 4.52 [dt, *J* 11.9, 5.0, 1 H (OCH_AH_B)], 4.60 [dt, *J* 11.9, 3.5, 1 H (OCH_AH_B)], 4.70 [ddd, *J* 10.3, 4.9, 3.4, 1 H (C=CH_AH_B)], 4.76 (ddd, *J* 10.3, 5.2, 3.6, 1 H), 5.20 [s, 1 H (PhCHO)], 7.12 (tt, *J* 7.4, 1.2, 1 H), 7.21 (t, *J* 7.4, 2 H), 7.50 (d, *J* 7.5, 2 H); δ_C(100.61 MHz, $CDCl_3$) 20.4, 68.6 (OCH_2), 71.4 (C–N), 81.2, 84.3 (PhCHO–), 106.9, 126.8, 127.6, 128.2, 139.8, 199.2.

¶ *Selected data* for **5e**: ν_{max}(neat)/cm^{-1} 3387, 3265, 3218, 2930, 1657, 1011; δ_H(400 MHz, $CDCl_3$) 1.33–1.61 (m, 6 H), 1.95–2.07 (m, 2 H), 3.44 [m, 1 H (C_6 ring CHO–)], 4.14 [ddd, *J* 16, 5.6, 3, 1 H (OCH_AH_B–C_6ring)], 4.21 [ddt, *J* 16, 3.1, 2.1, 1 H (OCH_AH_B–C_6ring)], 4.34 [ddd, *J* 12.6, 4.1, 2.3, 1 H (OCH_AH_B–C_5ring)], 4.53 [ddd, *J* 12.6, 5.4, 3.1, 1 H (OCH_AH_B–C_5ring)], 5.55 [tt, *J* 3.1, 2.0, 1 H (=CH)]; δ_C (100.61 MHz, $CDCl_3$) 20.0, 21.1, 27.0, 27.1, 60.3 (C–N), 66.2 (OCH_2, C_6ring), 68.2 (OCH_2, C_5ring), 79.1 (O–CH–), 114.9, 142.9; *m/z* (12 eV) 182, 181 (100%, M^+), 150, 149, 111, 96, 83.

‖ This pathway has been suggested by referees.

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