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Cascade Radical Reactions in Synthesis. A New Radical Mediated Double Ring Expansion-Cyclisation Process with Oxime Ethers

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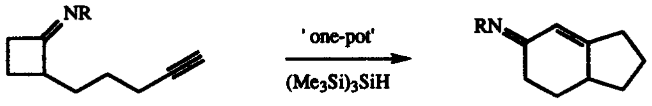
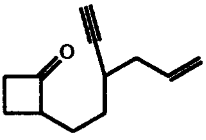
Abstract: Treatment of the acetylene substituted cyclobutanone oxime ether (**1**) with $(Me_3Si)_3SiH$ leads, in one pot, to the bicycle (**2**, 70%) by way of a novel double ring expansion-cyclisation process involving aminyl radical intermediates.

Radical mediated cyclisation processes, including those leading to polycycle constructions *via* consecutive ring forming reactions, are now embedded in the annals of contemporary organic synthesis method and design. In recent investigations in this area we have highlighted the scope for a number of cascade radical macrocyclisation-transannular processes,[1] and cascade radical fragmentation-transannular-cyclisation reactions[2] in the elaboration of a range of novel ring-fused carbocycles. In developments of this research program we have examined the intramolecular free radical reactions of terminal acetylenes with cycloalkanone oxime ethers,[3] and the subsequent radical chemistry of the aminyl radical intermediates.[4] From these studies, we now highlight a remarkable method for fused ring construction which depends on the 'one-pot' radical mediated double ring expansion-cyclisation of a cyclobutanone oxime *via* aminyl radical intermediates *viz* (**1**) → (**2**).

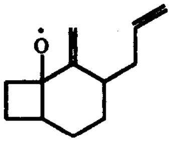


(**1**) $R = OCH_2Ph$

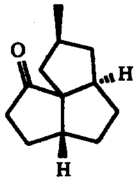
(**2**)



(**3**)



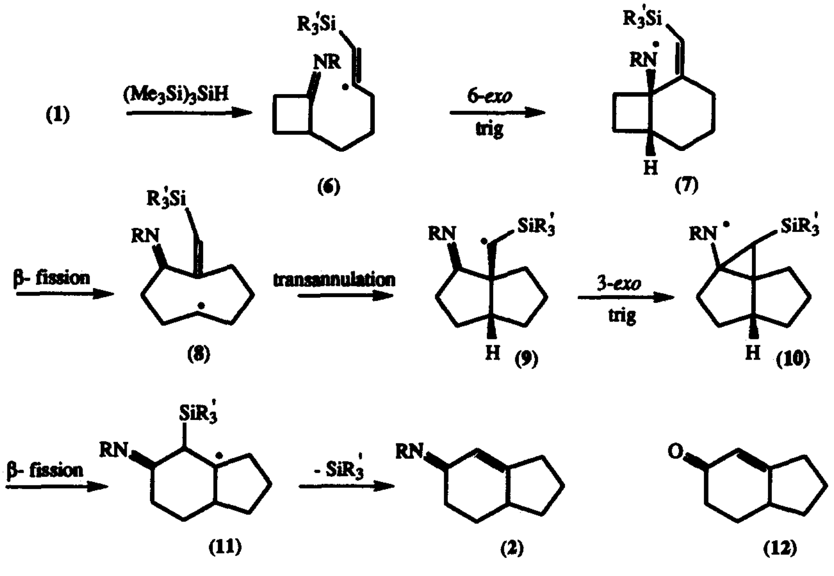
(**4**)



(**5**)

The initial focus of our study was the elaboration of angular-fused triquinanes by way of an oxy-radical fragmentation-radical transannulation-cyclisation sequence *i.e.* (**3**) → (**4**) → (**5**).[2] In the event, treatment of substrates like (**3**) with either Bu_3SnH or $(Me_3Si)_3SiH$ was found to lead to only the products of hydrostannylation or hydrosilylation of the acetylenic unit in (3),[5] and no compounds resulting from any cyclisation were observed. When the acetylenic oxime ether (1), corresponding to (3) however, was treated with $(Me_3Si)_3SiH$ [6] (hexane, sunlamp, 2h), a remarkable sequence of radical reactions ensued leading to the preparation of the bicyclic oxime (2) in 70% preparative yield. The oxime (2) could be separated as *Z*- and *E*-isomers (93:7) whose constitutions followed from spectroscopic data.[7] Furthermore, hydrolysis of the oxime (2) (dilute HCl, THF, 2h) led to the bicyclic enone (12) which was identical in every respect with an authentic sample produced by a Robinson annulation between cyclopentanone morpholine enamine and methyl vinyl ketone.[8]

The one-pot conversion of the cyclobutanone oxime (1) into the bicyclic oxime (2), in the presence of $(Me_3Si)_3SiH$, most likely occurs *via* sequential: (i) hydrosilylation[5] of the acetylene group in (1); (ii) 6-*exo*-trig cyclisation of the resulting vinyl radical intermediate (6) into the proximate oxime ether electrophore, leading to (7);[3] (iii) fragmentation (β-fission) from the aminyl radical centre in (7) to give (8);[4] (iv) 5-*exo*-trig transannular cyclisation of (8) producing (9);[9] and finally (v) a 5 → 6 ring expansion, involving a second aminyl radical (10) leading to the 5,6-ring-fused product radical (11).[10] Elimination of the $(Me_3Si)_3Si$-residue in (11), which occurs *in situ* then produces the observed product (2) (Scheme 1).

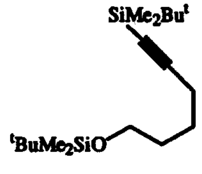


R = OCH$_2$Ph ; R' = SiMe$_3$

Scheme 1

With a view to developing some of the aforementioned chemistry towards the construction of angular triquinanes, we synthesised the propenyl substituted acetylenic cyclobutanone oxime (17). This oxime was prepared in a similar manner to that used in the synthesis of (1), starting from 5-hexynol. Thus, double protection of 5-hexynol as the corresponding *bis*-TBDMS derivative (13), followed by allylation (nBuLi, $CH_2{=}CHCH_2Br$) and mono-deprotection ($AcOH$-H_2O) first led to the enynol (14) (78% overall). Oxidation of (14) (PCC; 65%) to the corresponding aldehyde, and reaction with cyclopropyl phenyl sulphide (*n*-BuLi, -78°C) next gave the substituted cyclopropylmethanol (15; 62%), which on treatment with acid (*p*-TSA, H_2O, C_6H_6, Δ) gave rise to the cyclobutanone (16; 50%) as an oil.[11] After conversion of (16) into the corresponding oxime benzyl ether ($BnONH_2.HCl$, NEt_3, THF, $MgSO_4$), deprotection (TBAF) finally gave the enyne oxime (17) (66% over two steps).

When a solution of (17) in hexane was irradiated (sunlamp) in the presence of $(Me_3Si)_3SiH$, the major product isolated was the corresponding vinylsilane (18; 70%) (*cf.* 3), whose formation was accompanied by the allyl-substituted 5,6-ring fused oxime (19; 10%). We were unable to detect the co-formation of the triquinane oxime product (20), resulting from a radical cascade sequence, similar to that highlighted in our contemporaneous studies with related oxy-centred radicals,[2] from the reaction. Whether this feature is associated with the particular ring size in (17/20), the nature of the aminyl radical intermediate, or the stereochemical requirements of the reaction centres involved in the sequence leading from (17) to (20), remains unclear. Further work is in progress to examine these features, and also to explore further the scope for the novel double ring expansion-cyclisation depicted in (1) → (2).



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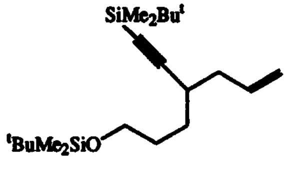

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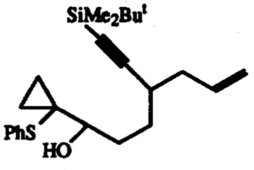

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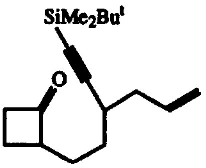

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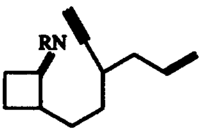

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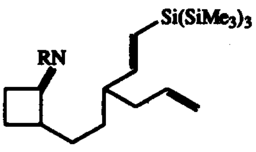

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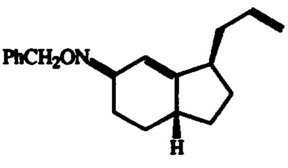

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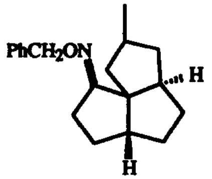

(20)

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References

1. Hitchcock, S.A.; Pattenden, G. *Tetrahedron Lett.*, **1992**, *33*, 4843.
2. Mowbray, C.E.; Pattenden, G. *Tetrahedron Lett.*, **1993**, *34*, 127; Ellwood, C.W.; Pattenden, G. *Tetrahedron Lett.*, **1991**, *32*, 1591.
3. For other cyclisations involving oxime ethers, see Corey, E.J.; Pyne, S.G. *Tetrahedron Lett.*, **1983**, *24*, 2821; Bartlett, P.A.; McLaren, K.L.; Ting, P.C. *J. Am. Chem. Soc.*, **1988**, *110*, 1633; Enholm, E.J.; Burroff, J.A.; Jaramillo, L.M. *Tetrahedron Lett.*, **1990**, *31*, 3727.
4. For some examples of the chemistry of aminyl radicals, see Bowman, W.R.; Clark, D.N.; Marmon, R.J. *Tetrahedron Lett.*, **1991**, *32*, 6441 and references cited therein.

5. Neumann, W.P. *Synthesis,* **1987**, 665; Ramaiah, M. *Tetrahedron,* **1987**, *43*, 3541; Curran, D.P. *Synthesis,* **1988**, 417 and 489; Hart, D.J. *Science,* **1984**, *223*, 883; Kopping, B; Chatgilialoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.,* **1992**, *57*, 3994 ; Kraus, G.A.; Liras, S. *Tetrahedron Lett.,* **1990**, *31*, 5265.
6. Chatgilialoglu, C. *Acc. Chem. Res.,* **1992**, *25*, 188.
7. Satisfactory spectroscopic data, together with microanalytical and/or mass spectrometry data were obtained for all new compounds. The major 5,6 bicyclic unsaturated *O*-benzyl oxime ether (**2**, R=OCH_2Ph) showed υ_{max} (neat) 3064, 3032, 1652 cm.$^{-1}$; δ_H 1.08-1.33 (m, CH_2), 1.55-1.71 (m, C*H*H), 1.78-1.92 (m, CH*H*), 1.98-2.21 (m,4H), 2.34 (dd, *J* 16.3 and 8.0Hz, C*H*H-C=NOBn), 2.57 (dd, *J* 16.3 and 9.0Hz, CH*H*-C=NOBn), 3.16 (dd, *J* 16.0 and 4.5Hz, C*H*-C=C), 5.13 (s, PhCH_2-0), 6.00 (dd, *J* 2.0 and 1.0Hz, -C=CH), 7.30-7.48 (m, ArH); δ_C 23.4 (t), 24.0 (t), 27.7 (t), 31.1 (t), 33.2 (t), 42.0 (d), 75.7 (t), 115.5 (d), 127.6 (d), 127.9 (d), 128.3 (d), 138.0 (s), 157.6 (s), 158.5 (s) p.p.m. λ_{max} (EtOH) 207.3, 248.4, 253.5. MS *m/e* (rel. intensity) 241 (22.0, M^+), 224 (12.5), 201 (4.4), 163 (5.5), 151 (11.1), 113 (8.1), 105 (8.8), 91 (100), 77 (11.0), 59 (10.6), 51 (21.1), (HRMS calculated for $C_{16}H_{19}NO$ 241.1467. Found 241.1465), whereas the minor oxime ether isomer of (**2**) displayed δ_H 1.07 (t, *J* 7.6Hz, C*H*H), 1.07 (dd, *J* 19.1 and 11.9Hz, C*H*H), 1.21 (dd, *J* 11.9 and 7.6Hz, CH_2), 1.25-2.6 (m, 7H), 5.08 (s, PhCH_2-0), 6.65 (dd, *J* 1.6 and 1.0Hz, -C=CH-), 7.27-7.43 (m, ArH); δ_C 23.7 (t), 28.5 (t), 29.0 (t), 31.2 (t), 32.9 (t), 43.3 (d), 75.4 (t), 109.8 (d), 127.5 (d), 127.9 (d), 128.2 (d), 138.2 (s), 154.6 (s), 162.6 (s) p.p.m.
8. The bicyclic unsaturated ketone (**12**) exhibited: υ_{max} (neat) 3030, 1662cm.$^{-1}$; δ_H 1.26 (ddd, *J* 23.8, 12.5 and 6.9Hz, C*H*H), 1.67-1.83 (m, CH_2), 1.85-2.03 (m, C*H*H), 2.18 (dt, *J* 11.5 and 6.9Hz, C*H*H), 2.25-2.90 (m, 6H), 5.91 (dd, *J* 1.5 and 1.0Hz, -C=CH); δ_C 23.9 (t), 29.3 (t), 31.8 (t), 32.8 (t), 37.5 (t), 43.1 (d), 122.2 (d), 175.6 (d), 199.8 (s) p.p.m.; MS *m/e* (rel. intensity) 136 (42.7, M^+), 121 (6.8), 108 (100), 97 (46.3), 84 (36.1), 79 (29.9), 68 (10.1), 55 (20.2), 51 (20.8), (HRMS calculated for $C_9H_{12}O$ 136.0888. Found 136.0850); see Bestmann, H.J.; Schade, G.; Lutke, H.; Monius, T. *Chem. Ber.,* **1985**, *118*, 2640; Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.,* **1963**, *85*, 207.
9. See: Nishida, A; Takahashi, H.; Takeda, H.; Takada, N.; Yonemitsu, O. *J. Am. Chem. Soc.,* **1990**, *112*, 902.
10. *cf.* Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.,* **1987**, *109*, 3493 and 6548; Baldwin, J.E.; Adlington, R.M.; Robertson, J. *Tetrahedron,* **1989**, *45*, 909; Beckwith, A.L.J.; Kazlauskas, R.; Syner-Lyons, M.R. *J.Org.Chem.,* **1983**, *48*, 4718; Suginome, H.; Yamada, S. *Tetrahedron Lett.,* **1987**, *28*, 3963; See also ref. 2.
11. *cf.* Trost, B.M.; Keeley, D.E.; Arndt, H.C.; Rigby, J.H.; Bogdanowicz, M.J. *J. Am. Chem. Soc.,* **1977**, *99*, 3080; Trost, B.M.; Keeley, D.E.; Arndt, H.C.; Bogdanowicz, M.J. *J. Am. Chem. Soc.,* **1977**, *99*, 3088.
12. The vinyl silane (**18**) showed relevant data: υ_{max} (neat) 3065, 3031, 1640 cm.$^{-1}$; δ_H 0.02 (s, $(TMS)_3Si$–) 0.8-1.8 (m, CH_2, 6H), 2.03-2.11 (m, CH_2), 2.22 (m, C*H*-CH=CH-Si), 2.81 (td, 8.1 and 1Hz, -CH_2-C=NO), 3.08-3.16 (m, C*H*-C=NO), 4.97 (m, CH_2=C), 5.02 (s, ArCH_2-ON), 5.46 (d, *J* 18.8Hz, Si-C*H*=C), 5.63-5.77 (m, -C*H*=CH_2, -C*H*=CH-Si), 7.27-7.39 (m, ArH); δ_C 0.8 (q), 21.4 (t), 28.54 (t), 30.9 (t), 31.7 (t), 39.8 (t), 45.4 (d), 47.6 (d), 75.5 (t), 115.6 (t), 121.2 (d), 127.6 (d), 128.1 (d), 128.1 (d), 128.3 (d), 128.3 (d), 137.0 (d), 138.0 (s), 152.6 (d), 163.0 (s) p.p.m.; (HRMS calculated for $C_{25}H_{46}NOSi_4$ 488.2656. Found 488.2629). The allyl substituted bicyclic *O*-benzyl oxime ether (**19**) showed: υ_{max} (neat) 3074, 3028, 1641cm.$^{-1}$; δ_H 1.1-2.0 (m, 6H), 1.98-2.12 (m, CH_2-CH=CH_2), 2.29-2.50 (m, C*H*-C=CH), 2.60-2.74 (m, C*H*H-C=NO), 2.76 (ddd, *J* 22.9, 14.3 and 8.6Hz, CH*H*-C=NO), 3.06-3.20 (m, C*H*-C=CH), 4.91-5.08 (m, CH_2=CH-), 5.12 (s, ArCH_2-ON), 5.80 (ddt, *J* 15.7, 10.0 and 7.1Hz, CH_2-C*H*=CH_2), 5.98 (dd, *J* 1.4 and 1.4Hz, N=C-C*H*=C), 7.27-7.43 (m, ArH) p.p.m.; (MS *m/e* (rel. intensity) 240 (8.1) 149 (7.0), 133 (7.6), 129 (4.4), 117 (8.7), 105 (5.6), 91 (100), 81, (6.1), 79 (7.6), 77 (10.0), 73 (44.7), 59 (46.5). HRMS calculated for $C_{16}H_{18}NO$ 240.1388. Found 240.1368).

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