Tetrahedron Letters,Vol.26,No.14,pp 1761-1764,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

FORMATION OF FUSED BI- AND TRI-CYCLIC β-LACTAMS BY RADICAL RING CLOSURE

Athelstan L.J. Beckwith* and Douglas R. Boate

Research School of Chemistry, Australian National University, Camberra, A.C.T. 2601 AUSTRALIA.

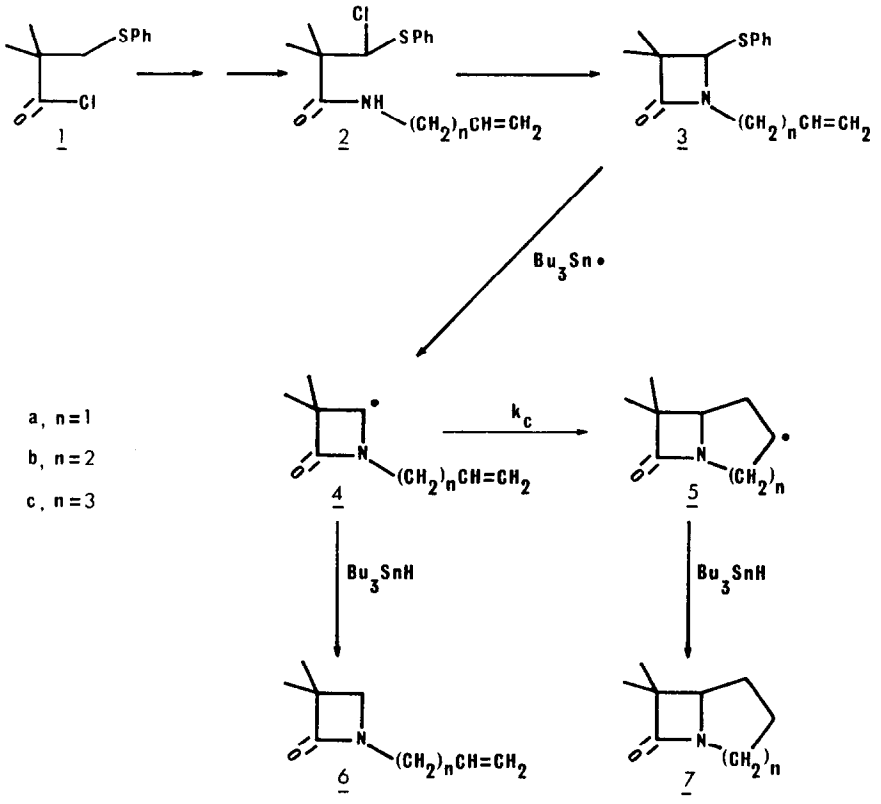
Summary: Methods involving intramolecular homolytic addition or intramolecular S_H2 processes in suitably constituted radicals provide convenient routes to bi- and tri-cyclic systems containing the azetidinone moiety.

Numerous recent examples[1-3] have demonstrated the utility of ring closure of suitably constituted alkenyl radicals and related species for the synthesis of both mono- and poly-cyclic systems. A notable feature of such processes is their propensity, in accord with stereoelectronic considerations,[4] to occur in the exo mode to give the smaller possible ring.[4-7] Although ring formation by an intramolecular S_H2 process at a heteroatom has been much less extensively studied it appears also to be subject to stereoelectronic control.[5,6,8] In this communication we describe the application of both types of reaction to the formation of fused β-lactams.

Radical precursors were readily prepared from appropriately substituted propanoyl chlorides (1) by consecutive treatment with N-chlorosuccinimide in carbon tetrachloride and with an unsaturated amine to give chloroamides (2) capable of affording azetidinones (3)[9] by base promoted intramolecular nucleophilic substitution. Overall yields from 1 were in the range 55-90%.

Heating of the thioether (3b) with tributylstannane (0.05M) and a trace of azobis-isobutyronitrile (AIBN) as initiator in benzene at 80° gave some starting material (22%), the direct reduction product[9] (6b, 48%), and the bicyclic compound (7b,26%) identified by its spectral characteristics: ^{1}H n.m.r. ($CDCl_3$), δ 1.16 (3H, s, Me), 1.23-1.46 (2H, m, $NCH_2CH_2\underline{CH_2}$), 1.32 (3H, s, Me), 1.54-1.96 (4H, b.m, $NCH_2\underline{CH_2}$, and $CH.\underline{CH_2}$), 2.60-2.80 (1H, m, NCH), 3.02-3.13 (1H, m, NCH), 3.71-3.86 (1H, m, $C(Me)_2\underline{CH}$); ^{13}C n.m.r. ($CDCl_3$), δ 16.6, 21.9, 22.8, 24.7, 26.1, 38.0, 54.0, 59.6, 172.1. The fact that no other cyclised product could be detected indicates that the radical undergoes ring closure exclusively in the endo mode. The higher homolog (3c) behaved similarly on treatment with tributylstannane (0.05M) and gave the direct reduction product (6c, 25%), starting material (19%) and only one cyclised product (7c, 55%): ^{1}H n.m.r. ($CDCl_3$), δ 1.12 (3H, s, Me), 1.18-1.70 (4H, m, $N(CH_2)_2\underline{CH_2CH_2}$), 1.27 (3H, s, Me), 1.78-2.07 (4H, m, $NCH_2\underline{CH_2}$, and $CH\underline{CH_2}$), 3.18-3.49 (3H, m, $N\underline{CH_2}$, and $C(Me)_2\underline{CH}$); ^{13}C n.m.r. ($CDCl_3$), δ 16.6, 22.4, 26.5, 28.9, 29.5, 31.2, 42.7, 50.8,

65.0, 173.4. As expected the N-allyl-azetidinone (3a) did not afford any cyclised product; the inability of 4-pentenyl radical and similar species such as (4a) to undergo ring closure is well known.[5-7]

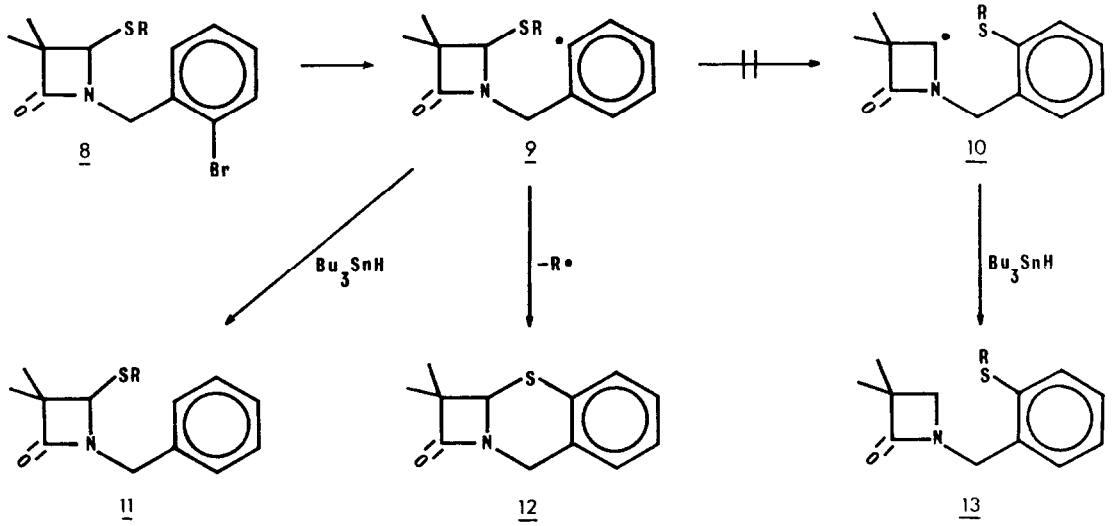


Since no value is available for the rate constant for direct reaction of azetidinonyl radicals (e.g. 4) with tributylstannane it is not possible to determine the rate constants for ring closure. However, comparison of the relative yields of cyclised and uncyclised products, 7, and 6, respectively, show that ring closure of 4c to afford the seven membered ring of 5c is faster than ring closure of 4b to give the six-membered ring of 5b. We believe that this unusual behaviour and the unexpected[5-7] preference for endo ring closure reflect strain in the exo transition structures engendered by the azetidinonyl ring. It is noteworthy that other radical ring closures leading to fused β-lactam systems behave similarly,[3] whereas pyrollidinonyl radicals give both exo and endo products.[2]

Suitable precursors (8)[9] for intramolecular S_H2 reactions were readily prepared in good yield as described above from appropriate acid chlorides. When the t-butyl thioether (8a) was treated with tributylstannane (0.03M) in boiling benzene it afforded a mixture of direct reduction product (11a, 16%), starting material (17%), and the tricyclic compound (12, 42%): ^{1}H n.m.r. ($CDCl_3$), δ 1.27 (3H, s, Me), 1.45 (3H, s, Me), 4.13 (1H, d, J 16Hz,

NCH), 4.70 (1H, s, CHS), 4.72 (1H, d, J 16Hz, NCH), 7.10-7.38 (4H, m, ArH); ^{13}C n.m.r. ($CDCl_3$), δ 16.8, 22.2, 41.7, 56.4, 62.8, 126.0, 127.9, 128.2, 129.5, 130.5, 131.3, 173.5. The methyl thioether (8b) gave the same cyclised product (12) upon similar treatment but in less yield (21%); in this case 11b[9] was the major product (46%). Treatment of the phenylthioether (8c) with tributylstannane gave no cyclised product. Only starting material (42%) and direct reduction product (11c, 40%) could be isolated from the reaction mixture.

A noteworthy feature of these reactions is their failure to afford aryl thioethers (13) *via* intramolecular homolytic displacement of the azetidinonyl substituent from sulfur to give the radical (10). If the reaction were under thermodynamic control such a pathway should be favoured through conjugative stabilisation of azetidinonyl radicals (10) by interaction of the free spin with the adjacent nitrogen lone pair. We conclude that the reaction is under stereoelectronic control and proceeds by interaction of the semi-occupied orbital with a lobe of the σ^* orbital of the bond undergoing fission.[5,6,8] The optimal colinear arrangement is readily attainable for fission of the S-R bond in 9 but not for fission of the bond to the azetidinone moiety.



Within this constraint the usual thermochemical factors appear to be effective. Thus the data indicate that the S-Me bond undergoes fission less rapidly than the weaker S-Bu^t bond, while the essentially thermoneutral transformation, 9c → 12, is not observed. Since a value for the rate constant of hydrogen atom transfer from tributylstannane to aryl

radicals is now available[10] it is possible to determine the rates of competing processes. We obtain values of k_c of 4 x 10^7 s^{-1} for ring closure of 9a and of 2 x 10^6 s^{-1} for ring closure of 9b[11] at 80°.

Acknowledgement: We thank Dr C. Easton for helpful discussions.

REFERENCES AND NOTES

1. See for example G. Stork and P.M. Sher, J. Am. Chem. Soc., 1983, 105, 6765; S. Danishefsky and E. Tanijama, Tetrahedron Lett., 1983, 24, 15; E.J. Corey and S.G. Pyne, Tetrahedron Lett., 1983, 24, 2821; A.L.J. Beckwith, D.M. O'Shea and D.H. Roberts, J. Chem. Soc., Chem. Commun., 1983, 1445-1446; A.L.J. Beckwith, G. Phillipou and A.K. Serelis, Tetrahedron Lett., 22, 2811-2814.
2. J.K. Choi, D.J. Hart and Y.M. Tsai, Tetrahedron Lett., 1982, 23, 4765; D.J. Hart and Y.M. Tsai, J. Am. Chem. Soc., 1982, 104, 1430.
3. M.D. Bachi, F. Frolow and C. Hoornaert, J. Org. Chem., 1983, 48, 1841; M.D. Bachi and C. Hoornaert, Tetrahedron Lett., 1981, 22, 2689, 2693; 1982, 23, 2505.
4. A.L.J. Beckwith in "Essays on Free Radical Chemistry", Chem. Soc. Spec. Publ. No. 24, p.239, Chem. Soc. London, 1970.
5. A.L.J. Beckwith and K.U. Ingold in "Rearrangements in Ground and Excited States" (ed. P. De Mayo) Vol. 1, p.161, Academic Press, New York, 1980.
6. A.L.J. Beckwith, Tetrahedron, 1981, 37, 3073.
7. A.L.J. Beckwith, C.J. Easton and A.K. Serelis, J. Chem. Soc., Chem. Commun, 1980, 482.
8. J.A. Kampmeier, R.B. Jordan, M.S. Liu, H. Yamanaka and D.J. Bishop in "Organic Free Radicals" (ed. W.A. Pryor) ACS Symposium Series No. 69, p.275. Am. Chem. Soc., Washington, D.C., 1978; J.E. Baldwin and T.S. Wan, J. Chem. Soc. Chem. Commun, 1979, 249.
9. All new compounds gave correct microanalytical and spectral data.
10. L.J. Johnston, J. Lusztyk, D.D.M. Wayner, A.N. Abeywickrema, A.L.J. Beckwith, J.C. Scaiano and K.U. Ingold, J. Am. Chem. Soc., 1985, 107, 0000.
11. This value for 9b is based on the assumption that all of 11b arises by direct reduction. If formation of 11b involves 1,8 hydrogen atom transfer, the value of k_c might be greater.

(Received in UK 23 January 1985)