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FREE-RADICAL ANNELATION IN THE SYNTHESIS OF BICYCLIC β-LACTAMS. 1. SYNTHESIS OF 8-OXO-5-OXA-1-AZABICYCLO[4.2.0]OCTANE AND 9-OXO-6-OXA-1-AZABICYCLO[5.2.0]NONANE DERIVATIVES

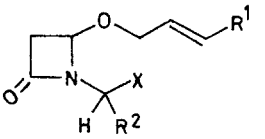
Mario D. Bachi* and Christian Hoornaert
Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Abstract: A new method for the synthesis of some fused bicyclic β-lactams based on the completion of the molecular backbone by a free-radical C-C bond forming reaction is described.

Many of the synthetic approaches to the fused bicyclic molecular backbone of β-lactam antibiotics are based on the annelation of non-fused β-lactams bearing the appropriate appendages.[1,2] In most cases this transformation is performed by a ionic-reaction.[3] Considering the high sensitivity of some fused bicyclic β-lactams to nucleophilic reagents we have developed a new methodology which is based on annelation by a free-radical rather than by a ionic mechanism.[4] The key step in this approach involves the generation of a radical species (1) and its conversion into a bicyclic β-lactam of type (2), where R' represents an unsaturated side chain and Y represents a heteroatom or a methylene unit. In the present publication compounds in which Y is an oxygen atom will be considered. Bicyclic β-lactams of this type are structurally related to antibacterial agents like oxa-dethiacephalosporins and to β-lactamase inhibitors like the clavulanic acid, and may exhibit an interesting biological activity.

(1) (2)

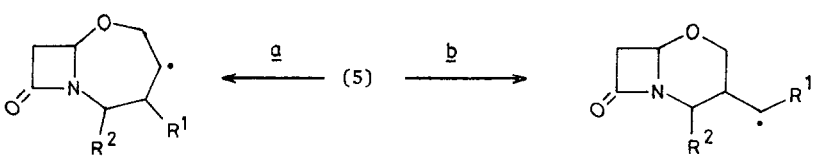
The N-chloromethyl β-lactams (4a)-(4d) were chosen as substrats for the study of the radical annelation. These compounds were obtained in three straightforward steps from 4-acetoxy-2-azetidinone via the corresponding N-hydroxymethyl derivative (3).[5,6] Thus, on boiling for 44 h under argon, a 0.02 M solution of a chloro-compound (4), 1.1 equiv. of n-Bu_3SnH and 2-4 molar % AIBN in benzene, a mixture of products deriving from annelation and hydrogenation of the intermediate free-radical species (5)[7] was obtained and separated by chromatography. The structures and yield of formation of these products are displayed in the table.[8,9]



			R^1	R^2
(3)	X=OH	a.	H	H
(4)	X=Cl	b.	H	CO_2Bu^t
(5)	X=unpaired electron	c.	CO_2Me	CO_2Bu^t
(6)	X=H	d.	Ph	CO_2Bu^t

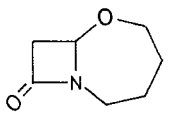
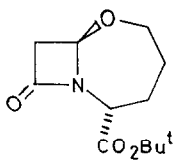
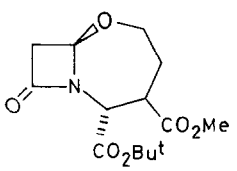
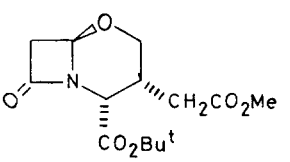
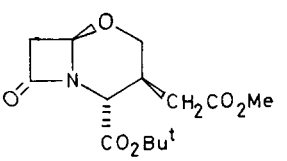
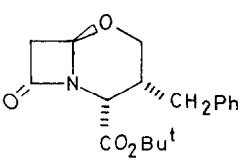
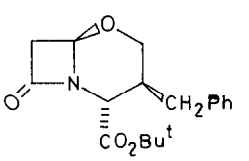
The course of the reactions proved to be highly influenced by the nature of the substituent R^1 on the unsaturated side chain. Thus, compounds (4a) and (4b) bearing a side chain with a terminal double bond gave regiospecifically the corresponding 9-oxo-6-oxa-1-azabicyclo[5.2.0]nonanes (7) and (8). The formation of these endo addition products of the free-radical intermediates (5a) and (5b) is in sharp contrast with the few reported[10] cyclization of hept-6-enyl radicals which afforded exclusively six-membered ring products deriving from an exo addition mode. This mode of addition was however predominant in the annelation of the carbomethoxy derivative (4c) which afforded the 9-oxo-6-oxa-1-azabicyclo[5.2.0]nonane (9) and the 8-oxo-5-oxa-1-azabicyclo-[4.2.0]octanes (10) and (11) in ca. 1:16 ratio, and exclusive in the annelation of the phenyl derivative (4d) which gave the 8-oxo-5-oxa-1-azabicyclo[4.2.0]octanes (12) and (13). The introduction of free-radical stabilizing groups R^1 and R^2 in compounds (4) favoured the annelation process relatively to the competing reduction.

These preliminary observations seem to indicate that the relative stability of the radicals (14) and (15) which may be produced during the ring closure of the radical (5), is an important factor in determining the endo versus exo mode of addition. When R^1=H, the secondary radical (14) is more stable than the primary radical (15) and the reaction takes path a, while when R^1=CO_2Me or Ph, radical (15) becomes more stable than radical (14) and the reaction through path b is favored.



(14) (15)

Table: Reaction Products of Compounds (4a)-(4d) with n-Bu_3SnH and AIBN

S.m.	Products [Yield][a]		
	Oxa-azanonanes	Oxa-azaoctanes	Hydrogen products
(4a)	 (7) [34%]		(6a) [31%]
(4b)	 (8) [47%] (m.p. 59-60°C)		(6b) [22%]
(4c)	 (9)[b] [4%]	 (10)[c] [68%, ratio 3.3:1]  (11)[c]	(6c)[b] [16%]
(4d)		 (12)[c]  (13)[c] [68%, ratio 1:1]	(6d) [10%]

[a]Yields were based on compounds (3) assuming a quantitative conversion of compounds (3) into compounds (4).[6]

[b]Compounds (6c) and (9) were obtained as an inseparable mixture and their yields were estimated by nmr.

[c]The epimers (10)/(11) and (12)/(13) were not separated. A pure sample of (10) (m.p. 86°C) and of (12) (m.p. 121-2°C) were obtained by crystallization.

In addition to their remarkable regiospecificity, these reactions proved to be also highly stereospecific in regard to the orientation of the tert-butyl ester which acquired a cis orientation to the bridgehead hydrogen atom. The same relative configuration is observed also in all the naturally occuring β-lactam antibiotics.

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References and Notes

1. R.D.G. Cooper in "Topics in Antibiotics Chemistry", P.G. Sammes Ed., Ellis Horwood Ltd., Chichester, 1980, Vol. 3, p. 39.
2. F.A. Jung, W.R. Pilgrim, J.P. Poyser and P.J. Siret, in "Topics in Antibiotics Chemistry", P.G. Sammes Ed., Ellis Horwood Ltd., Chichester, 1980, Vol. 4, p. 13.
3. For annelation by a carbenoid insertion reaction into a N-H bond see: D.G. Melillo, I. Shinka, and T. Liu, Tetrahedron Lett., 21, 2783 (1980); R.W. Ratcliffe, T.N. Salzmann, and B.G. Christensen, Tetrahedron Lett., 21, 31 (1980).
4. For reviews on free-radical cyclizations of olefines see: M. Julia, Acc.Chem.Res., 4, 386 (1971); A.L.J. Beckwith, C.J. Easton, and A.L. Serelis, J.Chem.Soc.,Chem.Commun., 482 (1980); A.L.J. Beckwith, T. Lawrence, and A.K. Serelis, J.Chem.Soc.,Chem.Commun., 484 (1980).
5. 4-Acetoxy-2-azetidinone was treated with an alcohol $R^1CH=CHCH_2OH$ and $Zn(OAc)_2$ to give a 4-alkoxy-2-azetidinone which with R^2CHO afforded the corresponding adduct (3), in turn converted into the chloro-compound (4) with $SOCl_2$ and 2,6-lutidine. For related transformations see: C.L. Branch, J.H.C. Nayler and M.J. Pearson, J.Chem.Soc.Perkin Transaction I, 1450 (1978).
6. Compounds (4) are unstable and were used immediately in their crude form after their preparation.
7. The formation of free-radical under these conditions is well documented, see: H.G. Kuivila, Synthesis, 499 (1970).
8. The structure of all the products were determined by I.R., N.M.R. and, with the exception of compounds (6c) and (9), high resolution mass spectra. The stereochemistry of the bicyclic compounds (8)-(13) was established on the ground of decoupling experiments with a 270 MHz NMR instrument.
9. In addition to the compounds listed in the table, minute amounts of products deriving from the cleavage of the β-lactam ring, namely $R^2CH_2NHCO=CHOCH_2CH=CHR^1$ were also detected.
10. J.-M. Surzur, Bull.Soc.Chim.France, 3070 (1970); A.L.J. Beckwith and G. Moad, J.Chem.Soc., Chem.Comm., 472 (1974); H. Pines, N.C. Sih and D.B. Rosenfield, J.Org.Chem., 31, 2255 (1966).

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