Tetrahedron Letters, Vol.22, No.28, pp 2693 - 2694, 1981
Printed in Great Britain

0040-4039/81/282683-02$02.00/0

FREE-RADICAL ANNELATION IN THE SYNTHESIS OF BICYCLIC β-LACTAMS. 2. ALTERNATIVE USE OF CHLORO-, PHENYLSELENO-, AND PHENYLTHIO-FUNCTIONALITIES AS FREE-RADICAL PRECURSORS

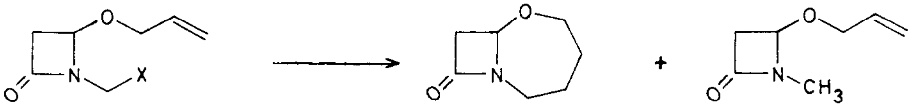
Mario D. Bachi* and Christian Hoornaert
Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Abstract: The tributyltin hydride-azobisisobutyronitrile induced cyclization of N-chloromethyl-, N-phenylselenomethyl-, and N-phenylthiomethyl-4-allyloxy-2-azetidinones to 9-oxo-6-oxa-1-aza-bicyclo[5.2.0]nonane is described.

In the preceding communication,[1] we have described a new method for the synthesis of fused bicyclic β-lactams by free radical annelation. The radical precursors were N-chloroalkyl β-lactams such as (1) which, due to their instability, were used in their crude form immediately after their preparation. For the further extention of the scope of this method, more stable free-radical precursors were sought. We examined the suitability of the phenylseleno-, and phenylthio- groups as possible substitutes to the chlorine atom. Neither of these groups have been previously used for the purpose of free-radical cyclization of unsaturated compounds. However, it has been reported that some phenylselenides,[2] and phenylsulfides,[3] were reduced by tributyltin hydride in a presumabely homolytic mechanism. The β-lactams (2) and (3) were thus selected as substrates for the annelation study.

The N-phenylselenomethyl- and N-phenylthiomethyl β-lactams (2) and (3) were prepared in a phase-transfer reaction of the N-chloromethyl β-lactam (1)[1] with phenylselenol and phenylthiol respectively (NaOH, C_6H_6, H_2O, 5% n-Bu_4NBr, 10°C, 30 min, 64-66%). These compounds appeared stable on silica gel chromatography and on storage at 5°C.[4,5]

Treatment of each of the β-lactams (1), (2), and (3) with 1.1 equivalent of Bu_3SnH and 2-4 molar % AIBN in benzene afforded, depending on the reaction conditions, variable yields of the annelation product (5) and the reduction product (6).[4] These experiments are summarized in the table.



(1) X=Cl (3) X=SPh (5) (6)
(2) X=SePh (4) X=Unpaired electron

Comparison of entries 1, 4, and 6 in the table indicates that the reaction courses of the phenylseleno-compound (2) and the phenylthio-compound (3) were very similar to that of the chloro-derivative (1), giving about the same ratio of annelation to hydrogenation products. These results indicate the involvement of a common radical intermediate (4).[6] Increasing dilution

Entry	S.m.	X	Conc. mM	Temp. °C	Time h	Ratio[a] (5):(6)	Yield (%)[b] (5)	(6)
1[c]	(1)	Cl	20	80	44	1.3:1	34	31
2	(1)	Cl	5	80	44	9:1	57	-
3	(1)	Cl	5	80	96	9:1	56	-
4	(2)	SePh	20	80	44	1.4:1	38	27
5	(3)	SPh	20	15[d]	44	-	22	42
6	(3)	SPh	20	80	44	1.3:1	41	30
7	(3)	SPh	20	140	44	1.5:1	40	24
8	(3)	SPh	5	80	44	-	37	-[e]
9	(3)	SPh	5	80	120	9:1	56	-[f]

[a] Ratio estimated by n.m.r. of the crude product. [b] Yield of product isolated by column chromatography. [c] This experiment is a relay to the experiments described in ref. 1. [d] Reaction initiated with four 40 Watts sunlamps. [e] 37% Recovered starting material. [f] 17% Recovered starting material.

of the reaction mixtures, of the chloro-compound (entries 1, 2) and of the phenylthio-compound (entries 6, 9) resulted in the same increment (ca. 7 fold) of the annelation versus hydrogenolysis ratio. However, the reaction with the sulfur derivative was somewhat slower. A more moderate (3-4 fold) increase in the ratio of annelation versus hydrogenolysis was observed on increasing the temperature from 15°C to 140°C in the reactions with the phenylthio-derivative (entries 5, 7).

The observed dependance of the ratio of annelation versus hydrogenolysis, on temperature and concentration, is a known trend in free-radical cyclization.[7] The endo addition mode, which was observed in all the experiments, was not diverted to an exo mode even at 15°C.[8]

The phenylthio-compound (3) is much more stable than the corresponding chloro-derivative (1). Since it, and similar compounds, could possibly be prepared by other straightforward methods, the phenylthio-grouping appears to be a potentially useful functionality for the generation of free radicals in the synthesis of bicyclic β-lactams by the radical annelation process.[1]

Acknowledgements: We thank Professor Y. Kishi for useful discussions and the United States-Israel Binational Science Foundation for financial support.

References and Notes

1. M.D. Bachi and C. Hoornaert, Tetrahedron Lett., preceding paper.
2. K.C. Nicolaou, R.L. Magolda, W.J. Sipio, W.E. Barnette, Z. Lysenrko and M.M. Joullie, J.Am. Chem.Soc., 102, 3784 (1980) and references cited therein.
3. J.M. McIntosh and C.K. Schram, Canad.J.Chem., 55, 3755 (1977); C.G. Gutierrez, R.A. Stringkan, T. Nitasaka and K.G. Glasscock, J.Org.Chem., 45, 3393 (1980) and references cited therein.
4. The structure of the compounds were determined by I.R., N.M.R. , and high resolution mass spec spectra.
5. A slow formation of (PhSe)$_2$ or (PhS)$_2$ was observed (TLC) on prolonged storage at r.t.
6. The formation of free-radical from chloro-compounds under these condidions is well documented see H.G. Kuivila, Synthesis, 499 (1970).
7. a) C. Walling and A. Cioffari, J.Am.Chem.Soc., 94, 6059, 6044 (1972); b) M. Julia, Acc.Chem. Res., 4, 386 (1971).
8. For the dependance of the mode of cyclization of certain alkenyl radicals on the temperature, see ref. 7b.

(Received in UK 23 April 1981)