Tetrahedron Letters No. 11, pp 939 - 942, 1977. Pergamon Press. Printed in Great Britain.

ACETYLENE CYCLISATIONS OF α-ACYLIMMONIUM IONS
EFFICIENT SYNTHESIS OF BRIDGEHEAD NITROGEN BICYCLIC KETONES

by
Tj. Boer-Terpstra, J. Dijkink, H.E. Schoemaker[1] and W.N. Speckamp*,
Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

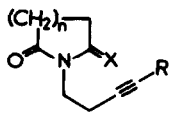
(Received in UK 5 January 1977; accepted for publication 5 February 1977)

Participation of triple bonds in solvolyses proceeding through carbenium ion intermediates leads to the formation of cyclic products. This type of reaction has been studied extensively both in mechanistic[2] and synthetic[3] respect. The analogous process in heterocyclic chemistry is less well-known and usually leads to 1,3-oxazines in α-amido alkylation reactions[4]. Recently two examples of efficient intramolecular ring closures of acetylenic ω-ethoxylactams were reported[5,6] and we now wish to emphasize the high versatility of the cyclic α-acylimmonium ion induced C–C bond formation in this class of unsaturated compounds.

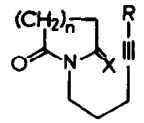
As model compounds the N-substituted ω-ethoxylactams 1-4 were selected in which both the effects of ringsize variations and terminal acetylene substitution could be investigated. Preparation of the starting materials was easily accomplished via the oxidation-reduction coupling[7] of the imide and the appropriate acetylene alcohol followed by $NaBH_4/H^{\oplus}$ reduction of the N-substituted imide to the ω-ethoxylactam. All of the so-obtained materials were chromatographed prior to use in cyclisation studies.

HCOOH-cyclisation (72 h/r.t.) of 1a and 1b (1 mmole in 4 ml HCOOH) afforded ketones 5a and 5b in near-quantitative yield[5]. The formation of small amounts of the dimerization product 6 in the cyclisation of 1b [12% yield, ^{1}H-NMR δ ($CDCl_3$): 6·01 s (=CH); 4·3-3·9 m (2H); 3·7-3·5 m (2H)] could be completely suppressed by working under higher dilution conditions (1 mmole of 1b in 40 ml HCOOH). The latter conditions were also applied in all other experiments.

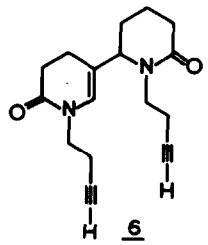
HCOOH-cyclisation of 2a (72 h/r.t.) proceeded quantitatively to a 9:1 mixture



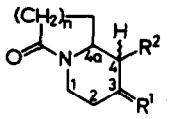
1a,1b; X = H,OEt ; R = H
2a,2b; X = H,OEt ; R = CH_3



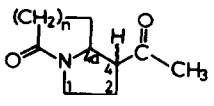
3a,3b ; X = H,OEt ; R = H
4a,4b ; X = H,OEt ; R = CH_3



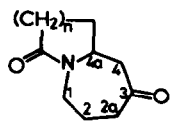
6



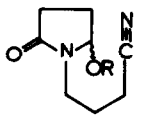
5a,5b; R^1 = O ; R^2 = H
7a,7b; R^1 = O ; R^2 = CH_3
10a,10b; R^1 = H_2 ; R^2 = $-COCH_3$



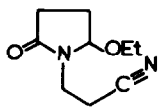
8a,8b



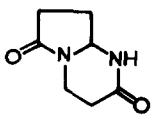
9a,9b



11c R = Et
11d R = H



12



13

a: n=1 ; b: n=2

of 7a and 8a. Only one epimer of 7a was found, ^{1}H-NMR δ($CDCl_3$): 4·3-4·6 m (H_1-eq); 3·22-3·52 m (H_{4a}); 1·05 d (CH_3), m.p. 2,4 DNP 218-220°C.

On the contrary, cyclisation of 2b (HCOOH/r.t./72 h) produced a 16:84 mixture of 7b and 8b in quantitative yield in which 8b was present as a mixture of two C_4-$COCH_3$ epimers. The latter result most probably reflects the difference in stability of the corresponding N-bridgehead azabicyclics. The preferential formation of 7a vs 8a is rationalized on the basis of ring-strain effects while the reversed outcome in the cyclisation of 2b can be explained via the observed order

./.

of stability of exo- and endo-vinylcations[8]. Attempts to capture the latter type of intermediate by carrying out experiments in CH_2Cl_2-CF_3COOH[9] were not successful. Therefore the effect of extending the alkenyl N-substituent with one carbon atom was also investigated.

HCOOH-cyclisation of 3a (72 h/r.t.) afforded a quantitative yield of the ketone 9a: m.p. 81-83°, ^{1}H-NMR δ($CDCl_3$): 4·52-4·28 m ($\underline{H}_1$-eq); 3·95-3·65 m ($\underline{H}_{4a}$). Similarly, HCOOH-cyclisation (72 h/r.t.) of 3b gave a complete conversion to 9b; ^{1}H-NMR δ($CDCl_3$): 4·85-4·60 m ($\underline{H}_1$-eq); 3·92-3·60 m ($\underline{H}_{4a}$), m.p. 2,4 DNP 200-201°C. Thus this type of cyclisation of a terminal acetylene moiety constitutes a method of choice in the synthesis of a variety of azabicyclic ketones composed of combinations of varying ringsizes.

On the contrary, cyclisation of 4a and 4b gave exclusively the acetyl cyclisation products 10a and 10b in yields up to 90%. Thus 10a was isolated as an oil which according to GLC and spectral analysis consisted of 2 stereoisomers in a ratio of 95:5. The major isomer showed the following ^{1}H-NMR data: δ($CDCl_3$): 4·26-4·05 m ($\underline{H}_1$-eq); 3·78-3·48 m ($\underline{H}_{4a}$); 2·20 s ($CO\underline{CH}_3$). Product 10b which consisted of 2 stereoisomeric acetylderivatives in a ratio of 85:15 showed for its major isomer: δ($CDCl_3$): 4.95-4.69 m ($\underline{H}_1$-eq); 3·63-3.30 m ($\underline{H}_{4a}$); 2·15 s ($CO\underline{CH}_3$), m.p. tosylhydrazone 250° (dec). Neither treatment of 10b with alkali nor with acid changed the observed ratio of stereoisomers to a significant extent. Presumably in both 10a and 10b the equatorial isomer is formed predominantly.

The preferred formation of 6-membered rings vs 7-membered rings can be understood in terms of the stability of the linear methylsubstituted vinylcation. Yet the exclusive formation of 7-membered rings upon reaction of unsubstituted acetylenes is notable in particular when compared with the sluggish reaction of the corresponding terminal ethylene analogues[10]. Of major synthetic interest is the overall high reactivity of the cyclic α-acylimmonium ion towards triple bonds.

Finally, in order to test the versatility of the method further the two alkylnitriles 11c and 12 were investigated as model compounds possessing a different electron distribution in a triple bond combined with a terminal nucleophilic centre. In contrast to the acetylene result HCOOH-cyclisation of 11c (72h, r.t.) gave only conversion of the ω-ethoxylactam in the ω-hydroxylactam 11d no single trace of cyclized material being detected[11]. At the other hand, HCOOH-

cyclisation of 12 gave a smooth reaction (75 h/r.t.) to the bicyclic dilactam 13 (50% yield), m.p. 164-166° (EtOH); ^{1}H-NMR δ($CDCl_3$): 3·15 m, $W_{½}$=29 c/s (H_1-ax); 4·18 m (H_1-eq); 5·13 m, $W_{½}$=9 c/s (H_{4a}). In addition some polymeric material was formed.

The aforementioned data emphasize the usefulness of α-acylimmonium intermediates in cyclisation reactions with triple unsaturated bonds. Further extensions in this field are actively pursued.

REFERENCES AND NOTES

1) Part of the forthcoming Ph.D. thesis of H.E. Schoemaker, University of Amsterdam.

2a) P.J. Stang, Prog.Phys.Org.Chem., 10, 205 (1973).

b) M. Hanack, Acc.Chem.Res., 9, 364 (1976).

3) W.S. Johnson, Bioorg.Chem., 5, 51 (1976).

4) H.E. Zaugg, Synthesis, 49 (1970).

5) J. Dijkink, H.E. Schoemaker and W.N. Speckamp, Tetrahedron Letters, 4043 (1975).

6) Preceding communication.

7) O. Mitsunobu, M. Wada and T. Sano, J.Amer.Chem.Soc., 94, 679 (1972).

8) P.E. Peterson and R.J. Kamat, J.Amer.Chem.Soc., 91, 4521 (1969).

9) W.S. Johnson, M.B. Gravestock, R.J. Parry and D.A. Okorie, J.Amer.Chem.Soc., 94, 8604 (1972).

10) H.E. Schoemaker, unpublished observations.

11) CF_3COOH result.
Upon carrying out the cyclisation of 11c in CF_3COOH (0.5 h/r.t.) the reaction product consisted of 11d, N-cyanopropyl-3-pyrrolin-2-one[12] and a dimer of the latter compound[13].

12) J.C. Hubert, J.B.P.A. Wijnberg and W.N. Speckamp, Tetrahedron, 31, 1437 (1975).

13) J.B.P.A. Wijnberg, W.N. Speckamp and J.J.J. de Boer, Tetrahedron Letters, 4077 (1974).

++++++++++++++++