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EFFICIENT HETEROCYCLISATION VIA 2-AZA-COPE REARRANGEMENTS OF α-ACYLIMINIUM INTERMEDIATES. FORMATION OF PYRROLIZIDINES AND SOME THIA-ANALOGUES

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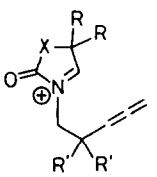
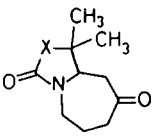
Abstract: HCOOH-ring closures of OH-lactams 7 possessing an allyl substituted alkene function solely afford pyrrolizidines 8 and 9 in high yield via 2-aza-Cope rearrangement and ensuing α-acyliminium cyclisation.

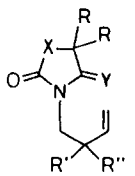
α-Acyliminium ions have proved previously to be versatile intermediates for π-cyclisation[2]. So far mostly 6-ring formation by intramolecular capture of π-nucleophiles has been observed[3]. Other types of ring closure, notably the preferential formation of pyrrolidines, are also documented[4], both with α-acyl-iminium initiating centres[5] as well as iminium[6] and nitrilium[7] and α-acyl-α-thia-carbocation[8] intermediates. Similar types of reaction in the carbocyclic series leading to the cyclopentane skeleton have also come to development[9].

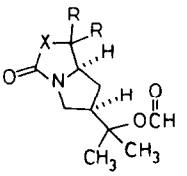


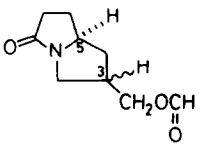


1 X = CH_2 , R=R'=H
2 X = CH_2 , R = H , R' = CH_3
3 X = CH_2 , R = CH_3 , R' = H
4 X = S , R = CH_3 , R' = H

5 X = CH_2
6 X = S







6 Y = O
7 Y = H,OH

a X = CH_2 , R = H , R' = R'' = CH_3
b X = CH_2 , R = R' = H , R'' = OCH_3

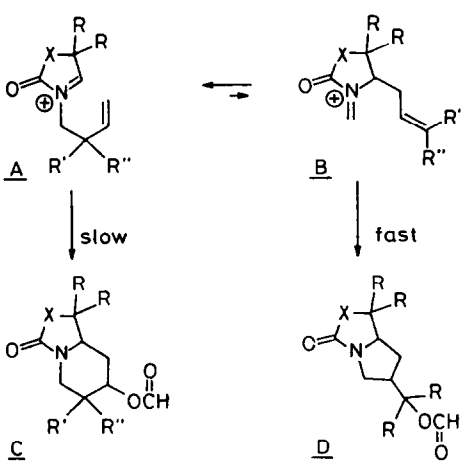
8 a X = CH_2 , R = H
b X = S , R = CH_3

9 a α-H_3
b β-H_3

Recently the behaviour of the allene moiety as a terminator was discussed[10] which was shown to yield products derived from aza-Cope rearrangements. Whereas the monosubstituted allene 1 gave rise to partial formation of ring-opened products the introduction of Me groups at the allyl position (e.g. 2) led to high yields of pyrrolizidines formed in an ensuing α-acyliminium cyclisation. To determine the behaviour of the allene moiety in ring substituted α-acyliminium compounds 3 and 4 a similar ring closure was carried out which surprisingly only afforded the seven membered ketones 5 and 6. Presumably the gem-diMe function effectively hinders the initial C-C bond formation on the central carbon atom of the rigid allene function thereby initiating the formation of secondary products derived from a reaction at the terminal methylene of the allene moiety followed by solvent capture of the intermediate vinyl cation[11]. In view of the unique behaviour of 2 in the aza-Cope rearrangement a decisive role of the substitution pattern on the allylic carbon of the π-nucleophile could also be envisaged. This was confirmed experimentally by the following sequence of reactions.

The cyclisation to the pyrrolidine ring is assumed to occur via the primary α-acyliminium ion B (scheme I) possessing the electron-rich diMe-alkene function. A plausible mode for the generation of B could start with an aza-Cope rearrangement of the first-formed secondary α-acyliminium ion A. If the latter process A ⇄ B and the ensuing ring closure B → D are fast compared to the normal mode of cyclisation A → C the formation of the pyrrolizidines D could be achieved in a controlled manner. Moreover the result would provide additional information on the irreversible trapping of less stable primary α-acyliminium ions by incorpor-

Scheme I



ating latent stabilizing functionalities[12].

The starting lactams 7 are obtained via $NaBH_4/H^{\oplus}$ reduction[13] of the corresponding imides[14]. Subsequent HCOOH cyclisation of 7a proceeded fast and exothermally (5 min, r.t.) and led to a quantitative formation of pyrrolizidine 8a in a stereocontrolled fashion. The structure of 8a was evident from 250 MHz ^{1}H-NMR and ^{13}C-NMR-analysis. The relative stereochemistry at C-3 could unambiguously be established by NOE-Difference-spectroscopy. 8a: m.p. 58.5-60.5°C (diisopropylether, dipe); ^{1}H-NMR ($CDCl_3$): δ 7.90 (s, OOCH); 3.88 (m, H_5); 3.40 (d of d, β-H_2, J = 8.6 and 11.0 Hz); 3.08 (t, α-H_2, J = 10.6 Hz); 2.72 (m, H_3); 1.97 (m, α-H_4); 1.45 (s, 6H, CH_3); 1.29 (q, β-H_4, J = 10.5 Hz). IR($CHCl_3$): 1720 and 1675 cm^{-1} (C = O). In extending the methodology the 2-oxo-thiazolidine carbinol 7c in the same manner stereoselectively afforded the bicyclic product 8b in 66% isolated yield (HCOOH, r.t. 1.75 hr). 8b: m.p. 100.0-102.0°C (dipe); ^{1}H-NMR($CDCl_3$): δ 8.00 (s, OOCH); 4.00 (d of d, H_5, J = 7.0 and 10.0 Hz). 3.42 (m, 2H, H_2); 2.83 (m, H_3); 1.50-1.55 (4s, 12H, CH_3). IR($CHCl_3$): 1720 and 1665 cm^{-1} (C = O). From this result it follows that the presence of a gem-diMe function at the ring carbon next to the iminium site does not raise a steric barrier to the aza-Cope process as was found in the cyclisation of the allenes 3 and 4.

In a similar fashion the lactam 7b was cyclized in HCOOH (18 hr, r.t.) to furnish after hydrolysis a 5:1 mixture of epimers 9 in 55% total yield (not optimized). Tentative assignment of stereochemistry of the epimeric aldehydes 9a and 9b occurred on the basis of 250 MHz ^{1}H-NMR analysis and upon comparison with other results (vide supra). Thus the major compound of the C-3 epimer mixture consisted of isomer 9a. In addition only small amounts (ca 3%) of 5/6 fused bicyclic formate were produced, probably resulting from a 6-endo-trig cyclisation. (A → C, Scheme I). 9a: ^{1}H-NMR($CDCl_3$): δ 9.53 (d, CHO), J = 1.5 Hz); 3.95 (m, H_5); 3.87 (d of d, β-H_2, J = 4.4 and 10.9 Hz); 3.10-3.30 (m, 2H, α-H_3 and α-H_2); 1.59 (m, β-H_4). 9b: ^{1}H-NMR($CDCl_3$): δ 9.62 (br.s, CHO); 1.08 (m, β-H_4).

From the present results it may be concluded that certain types of allylic substitution of a butenyl N-substituent can change the usually observed pattern of N-acyliminium olefin cyclisations. It has to be kept in mind, however, that a single allylic alkyl substituent leads to normal type of ring closure without

a trace of aza-Cope derived products[16]. In view of the importance to develop novel methods for the controlled synthesis of substituted pyrrolizidines other types of allylic substituents are currently under investigation.

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