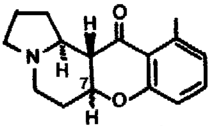
Tetrahedron Letters Vol. 21, pp 1373 - 1374
0040-4039/80/0401-1373$02.00/0

VINYLOGOUS URETHANES IN ALKALOID SYNTHESIS: FORMAL SYNTHESES OF ELAEOCARPUS ALKALOIDS

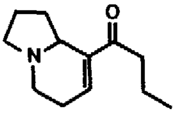
Arthur S. Howard*, Graeme C. Gerrans* and Clive A. Meerholz
Department of Chemistry, University of the Witwatersrand, Johannesburg, South Africa

Abstract: The substituted dehydroindolizidine **8** has been prepared from the exocyclic vinylogous urethane **7** via an acylative ring closure. The specific formation of the enolate required for further elaboration to Elaeocarpus alkaloid precursors has been achieved by making use of the vinylogous amide **12**.

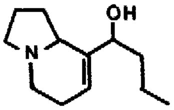
In a previous communication[1] we reported on the use of the nucleophilic properties of a vinylogous urethane in the synthesis of the quinolizidine alkaloid, lupinine. We now report the further use of compounds of this type in the syntheses of indolizidine alkaloids. Inspection of the structures of the Elaeocarpus alkaloids[2] reveals that acylation at C(8) of a 7-oxygenated indolizidine system should present a general approach to their synthesis. The sequence outlined in Scheme I represents our development of this idea resulting in the formal syntheses of elaeocarpine(**1**), isoelaeocarpine(**2**) and elaeokanines A, B and C(**3**, **4** and **5**).



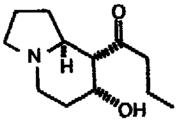
1, C(7)αH **2**, C(7)βH



3



4

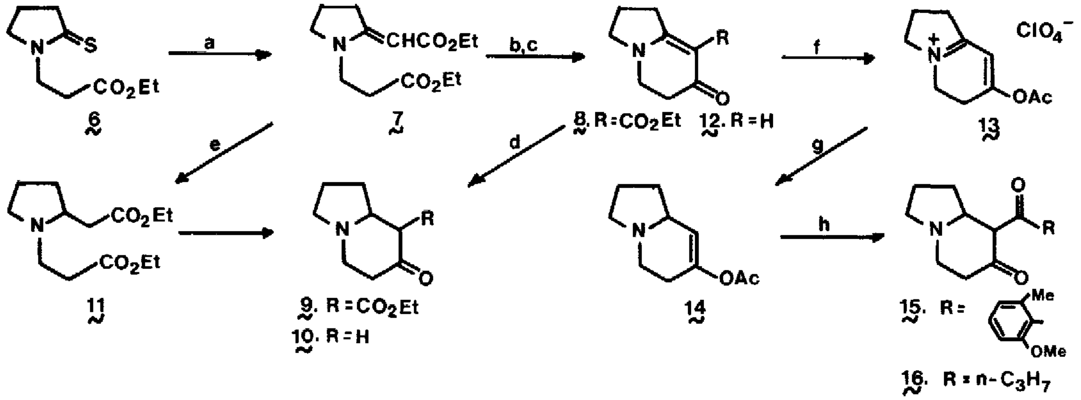


5

Pyrrolidine-2-thione[3] was alkylated on N to yield **6** ($CH_2{=}CHCO_2Et$, THF, NaOH cat, 55°C, 3.5h; 98%, 141°/0,5 torr)[4,5] which was converted to the vinylogous urethane **7** (79%, 31-3°C) using the sulphide contraction sequence.[6] Attempts to cyclise **7** directly were unsuccessful so it was converted via the sodium salt to a mixed anhydride which, without isolation, was cyclised to **8** (71%, 74.5 - 75.5°C). Selective reduction of **8** to the β-keto ester **9** (53%, 56°C) followed by decarbalkoxylation (1,8M H_2SO_4 reflux) yielded 7-oxoindolizidine **10** (68%).[7] Alternatively this ketone could be prepared by the catalytic reduction of **7** to **11** (90%)[7] which other workers have converted to **10**.[7] Not surprisingly it was found that under conditions of either kinetic or thermodynamic control the enolate mixture produced from **10** was very largely that leading to further reaction at C(6).[8] Furthermore direction of acylation to C(8) by use of the β-keto ester **9** could not be achieved. The most common result was acylation at N and cleavage of the C(9)-N bond.

Acylation of tertiary vinylogous amides has been reported to occur at either C or O[9] and hence **8** was decarbethoxylated to the vinylogous amide **12** (aq. KOH reflux 1h; acidify, reflux 1h.; 93%, 110/0.1 torr). This compound could not be induced to acylate at C8 and in most cases only unchanged **12** was obtained. Reaction with acetyl perchlorate produced the O-acetyl salt **13**[10] which was converted to the required enol acetate **14** by selective reduction of the iminium group. Several hydride reductants (LAH, $NaBH_4$, $NaBH_3CN$) were tried using a variety of conditions. The cleanest reaction was obtained using $NaBH_4$ in acetonitrile but the product isolated contained boron(ν(B-H) 2370, 2325, 2270 cm^{-1}).11) Purification of this boron complex before decomposition according to the method of Johnson12) permitted the isolation of 14 in high purity (130°/0.1 torr) but caused substantial losses of material. Enol acetate of satisfactory purity for the final stage could be obtained without purification of the boron complex (45% from vinylogous amide 12). The enolate generated from 14 by treatment with MeLi reacted with the appropriate acyl cyanide13) to produce the β-diketones 15 (73%,14) 102-4°C, picrate 180-2°C, lit.15) 181-3°C) and 16 (23%,14) 52-55°C, lit.16) 52-54°C). The general usefulness of this approach is apparent since compound 15 has previously been converted to 1 and 215) and 16 to 5 which in turn has been converted to 3 and 416).

SCHEME I



(a) $BrCH_2CO_2Et$, CH_3CN, r.t., 16 h; Ph_3P, Et_3N, CH_3CN, r.t., inst. (b) Aq. NaOH (0.4M, 1 equiv.), Reflux 0.5 h. (c) Ac_2O, CH_3CN, r.t., 40 h. (d) $LiAlH_4$ (2/3 molar equiv.) Et_2O, r.t., 1 h. (e) H_2/PtO_2, glac. HOAc (f) CH_3COCl, $AgClO_4$, CH_3CN, N_2, dark, r.t., 1 h. (g) $NaBH_4$, CH_3CN, r.t., 1 h; glac. HOAc, Reflux 1 h. (h) MeLi (2 equiv), THF, N_2, 0°C, 0.25 h; RCOCN, THF, N_2, 0°C, 0.25 h.

References

1. G.C. Gerrans, A.S. Howard and B.S. Orlek, Tetrahedron Letters, 4171 (1975).
2. S.R. Johns and J.A. Lamberton in "The Alkaloids Vol. XIV" Ed. R.H.F. Manske, Academic Press, 1973.
3. J. Tafel and P. Lawaczek, Chem. Ber., 40, 2842 (1907).
4. Distillation data are for bulb-to-bulb distillations.
5. All known compounds had physical properties in agreement with reported values. All new compounds gave satisfactory combustion analyses and/or accurate masses of the molecular ions. The spectra (IR, UV, MS, ^{1}H NMR and in many cases ^{13}C NMR) in all cases are in accord with the structures shown.
6. M. Roth, P. Dubs, E. Götschi and A. Eschenmoser, Helv. Chem. Acta., 54, 710 (1971).
7. R.T. Holden and R. Raper, J. Chem. Soc., 2545 (1963).
8. Analysis of the enolate mixture was done by gas chromatography of the enol acetates.
9. J.V. Greenhill, Chem. Soc. Reviews, 6, 277 (1977).
10. Compound 13 was not normally purified but used immediately reaction was complete (tlc).
11. A. Meller, Organometal. Chem. Rev., 2, 1 (1967).
12. J.A. Marshall and W.S. Johnson, J. Org. Chem., 28, 421 (1963).
13. A.S. Howard, C.A. Meerholz and J.P. Michael, Tetrahedron Letters, 1339 (1979).
14. Considerable loss of material occurred during purification. The spectral data of 15 agreed with published data15); the spectra of 16 were identical with those kindly provided by Dr S.R. Johns.
15. T. Tanaka and I. Iijima, Tetrahedron, 29, 1285 (1973).
16. N.K. Hart, S.R. Johns and J.A. Lamberton, Aust. J. Chem., 25, 817 (1972).

(Received in UK 21 January 1980)