Tetrahedron Letters,Vol.23,No.26,pp 2619-2622,1982 0040-4039/82/262619-04$03.00/0
Printed in Great Britain

THE KETENE THIOACETAL GROUP AS A CATIONIC CYCLIZATION TERMINATOR. A SYNTHESIS OF THE PYRROLIZIDINE RING SYSTEM.

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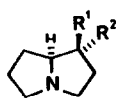
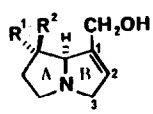
Summary: A cationic cyclization to the pyrrolizidine ring system is reported in which a ketene thioacetal group serves as an efficient terminator for 5-membered ring formation. (±)-Supinidine is prepared using this methodology.

The pyrrolizidines are a group of alkaloids which exhibit an incredible range of biological activity, including antitumor, hypotensive, local anesthetic, anti-spasmotic, anti-inflammatory, carcinogenic, and (especially) hepatotoxic action.[1,2] Syntheses of the deceptively simple aza-[3.3.0]octane ring system common to these alkaloids have focused mainly on the fully saturated derivatives 1,[3] while the unsaturated ones such as 2 have received relatively little attention[4] in spite of their more profound physiological activity.[1] We report in this communication a new cyclization-isomerization sequence which efficiently produces the skeleton 2, illustrated by a straightforward synthesis of supinidine (2a).



1A, R^1=H, R^2=CH_2OH (TRACHELANTHAMIDINE)
B, R^1=CH_2OH, R^2=H (ISORETRONECANOL)

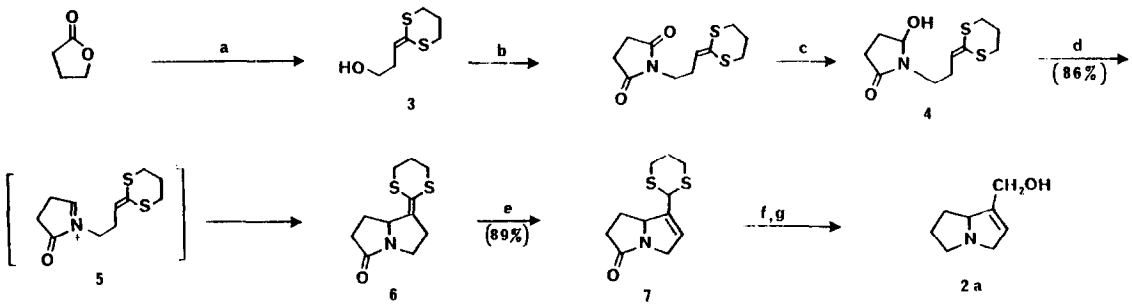


2A, R^1=R^2=H (SUPINIDINE)
B, R^1=H, R^2=OH (RETRONECINE)
C, R^1=OH, R^2=H (HELIOTRIDINE)

We chose to investigate a cationic cyclization which would close the B-ring onto a preformed A ring. The selection of an electrophilic partner for this ring closure was based on the extensive work on acyliminium ion cyclizations by Speckamp,[5] whose group has utilized such a reaction in conjunction with electronically-biased acetylenic terminators to prepare saturated pyrrolizidines such as 1a.[6] We have developed a new cationic cyclization terminator, the ketene thioacetal group,[7] which not only results in very efficient 5-membered ring formation,[8] but also produces upon cyclization another ketene thioacetal moiety capable of controlling the placement of an endocyclic double bond in the final product.

The cyclization precursor (4) required for the synthesis of 2a was prepared in three steps by treatment of γ-butyrolactone with bis-(dimethylaluminum)-1,3-

propanedithiolate[9] (CH_2Cl_2, -78°C → 20°, then reflux 20 hr), Mitsunobu coupling[10] of the resulting ketene thioacetal alcohol 3[11] with succinimide (Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, 20°C, 15 hr), and $NaBH_4$ reduction of the imide group (excess $NaBH_4$, MeOH -5°C, 45 min) to give 4[12] in an overall yield of 49%. It is noteworthy that reduction of the imide to the hydroxy lactam 4 proceeds cleanly (89% isolated yield) without added acid[13] if methanol is used as solvent rather than ethanol.



A. $Me_2AlSCH_2CH_2SAlMe_2$, CH_2Cl_2, -78°C → 20°C then reflux 20 hr, 93% crude.
B. Succinimide, Ph_3P, Diethyl azodicarboxylate, 20°C, 15 hr, 61% after flash chromatography.
C. Excess $NaBH_4$, MeOH, -5°C, 1 hr, 87% after flash chromatography.
D. CH_3SO_2Cl, pyridine, Et_3N, -30°C → 20°C, 86% after flash chromatography.
E. 4 equiv LDA, 4 equiv HMPT, -78°C → 20°C, then MeOH, 89% after flash chromatography.
F. $BF_3{\cdot}OEt_2$, HgO, THF/H_2O 85/15, 20°, 3 hr, 85% crude yield.
G. $LiAlH_4$, THF reflux, 2 hr, 60%.

The key step of the synthesis, cyclization of 4 to 6, required generating the acyliminium ion (5) under non-acidic conditions because of the presence of the acid-labile[14] ketene thioacetal group. The usual conditions for acyliminium ion formation (HCOOH or HCl/EtOH)[5] were presumed to be unsatisfactory in this regard, but we reasoned that the conversion of 4 to its mesylate[15] should allow acyliminium ion formation under conditions to which the ketene thioacetal would be stable. Indeed, treating 4 with 1.1 equiv each of mesylchloride, triethylamine, and pyridine at -30°C in dichloromethane followed by warming to 20°C leads directly to the pyrrolizidine 6 in 86% yield. The proposed structure of 6 was supported by spectral data,[16] particularly the ^{13}CMR and ^{1}HMR spectra,[17] and by subsequent transformation to the known alkaloid 2a.

Having efficiently cyclized to the pyrrolizidine skeleton, the next step undertaken was a controlled migration of the double bond to the proper endocyclic position. To accomplish this transformation, we exploited the propensity of lithiated ketenethioacetals to protonate α to sulfur;[18] hence, formation of the dianion[19] of 6 (3LDA, HMPT, THF, -78°C → -20°C, 30min) followed by methanol quench at -78°C gives 7[20] in 89% yield. Conversion of 7 into supinidine (2a)

was accomplished by dithiane hydrolysis[21] ($BF_3 \cdot OEt_2$, THF-H_2O, HgO, 20°C, 1 hr, 85% crude yield) followed by reduction of both the resulting aldehyde and the lactam carbonyls (LAH, THF, 20° → reflux, 2 hr, 60%). The product was identical with authentic supinidine in all respects.[22]

The synthesis of (±)-supinidine described in this communication clearly illustrates the value of the ketenethioacetal group both as an internal nucleophile in cationic cyclization and as a control element for the regioselective placement of an endocyclic double bond. The methodology appears promising as an entry into the more highly oxygenated pyrrolizidines such as 2b and 2c. These and other studies are in progress.

Acknowledgements: We wish to thank the Cancer Research Coordinating Committee of the University of California, the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (Grant No. GM 30073) for financial support. The high pressure liquid chromatograph used in this work was purchased with funds supplied by Research Corporation, to which we are grateful. NMR and mass spectra were obtained with spectrometers purchased with the assistance of N.S.F. instrumentation grants.

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11. The ketene thioacetal 3 was isolated in 93% crude yield: 80 MHz ^{1}HMR ($CDCl_3$): δ 5.95 (t, J = 7.3 Hz, 1H), 3.64 (t, J = 6.6 Hz, 2H), 2.8-3.0 (m, 4H), 2.47 ("q", J ≈ 7 Hz, 2H), 2.0-2.3 (m, 2H), ~ 2.7 (s, 1H, D_2O exchangable). It was used in the next step without purification.

12. The reduction product 4 was purified by flash chromatography on silica (87% yield): m.p. 98-100°C; 250 MHz ^{1}HMR ($CDCl_3$) δ 5.89 (t, J = 7.4 Hz, 1H), 5.23 (m, 1H), ~ 4.0 (br s, 1H, D_2O exchangable), 3.55 (dt, J = 14, 7 Hz, 1H), 3.22 (dt, J = 14, 7 Hz, 1H), 2.86 (t, J = 6.3 Hz, 4H), 1.8-2.7 (m, 8H); IR (thin film) 3360, 1670, 1585 cm^{-1}.

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14. Carey, F.A.; Court, A.S. J. Org. Chem. 1972, 37, 1926. For other examples where ketene thioacetals react with electrophiles, see references 7a,b,c.

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16. The crystaline cyclized product 6, purified by flash chromatography on silica, was isolated in 86% yield: m.p. 107-109°C; 250 MHz ^{1}HMR ($CDCl_3$) δ 4.58 (br t, J = 6.7 Hz, 1H-8), 4.05 (t, J = 10.0 Hz, 1βH-3), ^{17} 2.25-3.05 (m, 9H), 2.15 (m, 2H), 1.75 (m, 2H); ^{13}CMR ($CDCl_3$) δ 175.7 (C-5), 142.5 (C-9), 119.4 (C-1), 64.1 (C-8), 41.6 (C-3), 33.7, 33.2, 29.7, 29.6, 28.9, 24.6; IR ($CDCl_3$) 1690, 1615 cm^{-1}; MS m/e 241 (M^+, 100%), 167 ($M^+ - C_3H_6S$, 73%), 123 ($M^+ - C_4H_6S_2$, 46%); HPLC (μ-Porasil, EtOAc/hexane 5/1) >99% pure based on detection at 254 nm.

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19. In this step the amide is almost certainly enolized, but this occurrence does not affect ketene thioacetal deprotonation. The lactam carbonyl can be reduced prior to double bond migration (LAH, THF reflux, 45 min, 89%) but it is more efficient to postpone this step so that it may be carried out at the same time as enal reduction.

20. The product 7 was purified by flash chromatography, 89% yield. 250 MHz ^{1}HMR ($CDCl_3$) δ 5.92 (br s, 1 H-2), 4.75 (m, 1 H-8) 4.67 (Brs, 1 H-9), 4.35 (dm, J = 16.2, ~ 1.9, 1β-H-3^{17}) 3.70 (dm, J = 16.2, ~ 1.8, 1α-H-3^{17}), 1.6-3.0 (m, 11H); IR ($CDCl_3$) 1690, 1630 cm^{-1}; NMR also shows ~ 5% of the ketene thioacetal 6, which does not separate from 7 chromatographically; otherwise >99% pure by HPLC (μ-Porasil, EtOAc:hexane 4:1.)

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22. The 250 MHz ^{1}HMR, ^{13}CMR, IR, and MS(EI) spectra of our synthetic 2a were virtually identical to those of an authentic sample, and comparable to values reported in the literature.[4d] The samples also co-chromatographed by TLC (SiO_2, $CHCl_3$/MeOH/conc. NH_3 10/4/1). Authentic supinidine was obtained by the hydrolysis of supinine (3N H_2SO_4 reflux, 24 h), which was graciously provided by Dr. Matthew Suffness (Nat. Prod. Branch, Div. of Cancer Treatment, NCI).

(Received in USA 16 March 1982)