Tetrahedron Letters,Vol.27,No.24,pp 2695-2698,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

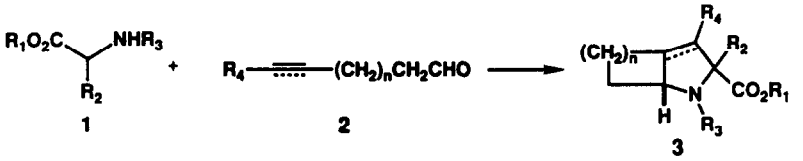
INTRAMOLECULAR [3+2] CYCLOADDITIONS OF FUNCTIONALIZED AZOMETHINE YLIDES

PAT N. CONFALONE * AND RICHARD A. EARL

CONTRIBUTION NUMBER 3995
CENTRAL RESEARCH AND DEVELOPMENT DEPARTMENT
E. I. DU PONT DE NEMOURS α COMPANY
EXPERIMENTAL STATION WILMINGTON, DELAWARE 19898

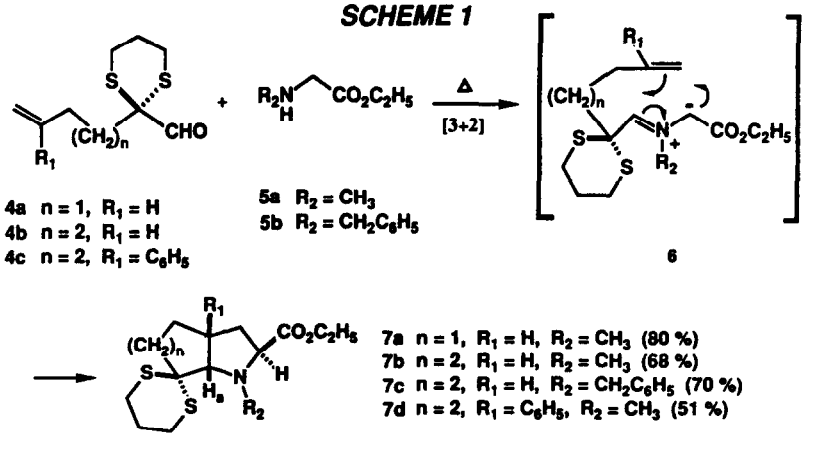
ABSTRACT: THE USE OF DITHIANE CHEMISTRY TO SYNTHESIZE FUNCTIONALIZED AZOMETHINE YLIDES WHICH ARE THEN EMPLOYED IN [3+2] CYCLOADDITION CHEMISTRY IS DESCRIBED. THE ADVANTAGES OF THIS METHODOLOGY AS WELL AS AN APPROACH TO THE LYCORENINE ALKALOID SYSTEM ARE PRESENTED.

A number of recent reports have described the use of amino acids and their alkyl or silyl esters as precursors to azomethine ylides, employing a condensation reaction with aldehydes for their genesis.[1-3] The dipoles thus formed are readily trapped by a C-C multiple bond to yield a variety of derivatives of pyrrolidine. Of particular utility is the reaction of amino esters of type 1 with an unsaturated aldehyde such as 2 to afford the bicyclic adducts 3, derived from an intramolecular reaction mode. This ring-forming transformation has been shown to proceed with a high degree of stereoselectivity about the newly formed C-C bonds as the process



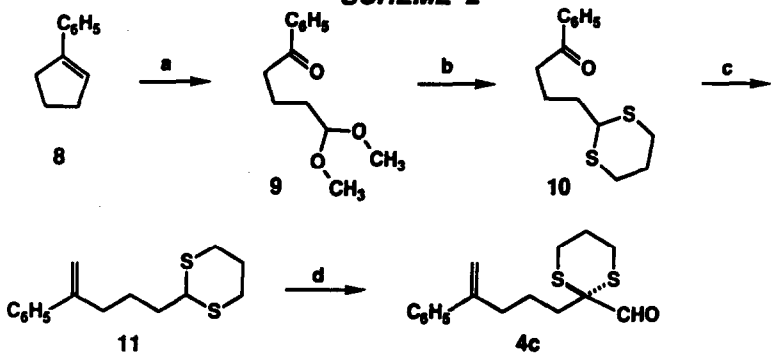
effectively annulates a pyrrolidine ring to an internal olefin. Reactions such as this, which construct two carbon-carbon bonds simultaneously, are relatively rare in organic synthesis and the few on record have found extensive application. We wish to report a further extension of this cycloaddition methodology to include functionalized olefin-aldehydes of general structure 4 (Scheme 1), possessing a dithiane group alpha to the carbonyl moiety and offering a number of advantages in their construction and subsequent transformations.

SCHEME 1



Aldehydes **4** condense with N-alkyl glycinates **5** to yield the annulated pyrrolidines **7**, products of an intramolecular [3+2] cycloaddition reaction of the presumed intermediate azomethine ylides **6**.[4] The substrate **4a** is readily prepared in a one-pot reaction by alkylation of 2-lithio-1,3-dithiane with 4-bromobut-1-ene followed by a subsequent deprotonation with n-butyllithium and formylation with dimethylformamide.[5] The aldehyde **4b** is prepared in a similar manner with 5-bromopent-1-ene. The synthesis of the styrene-derived dithiane aldehyde **4c** is shown in Scheme 2. Ozonolysis of 1-phenylcyclopentene (**8**), followed by treatment with tosic acid in methanol affords the corresponding aldehyde dimethyl acetal[6] **9**, which is converted into the desired crystalline dithiane **10** by 1,3-propanedithiol. Wittig methylenation of **10** and formylation of the dithiane anion of the resulting product provides the substrate **4c**.

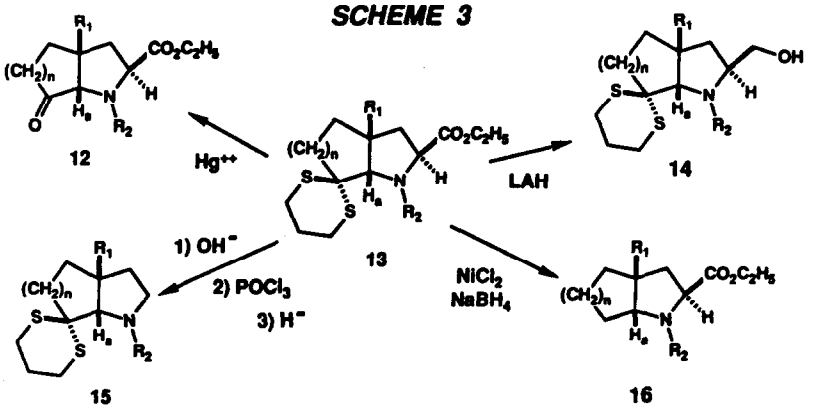
SCHEME 2



(a) O_3, MeOH / CH_2Cl_2 (95%) (b) $HS(CH_2)_3SH$ $BF_3{\cdot}OEt_2$ (54%) (c) $Ph_3P{=}CH_2$ (84%) (d) n-BuLi / DMF (32%)

The major product of these dipolarcycloadditions is the one in which the newly formed bicyclic system is cis fused and the pendant ester group is oriented cis to the hydrogen(s) at the ring junction.[1,2,7] These assignments are supported by the chemical shift and coupling constant exhibited by Ha: **7a**, δ3.38 (d, J=9); **7b**, δ3.11 (d, J=7); **7c**, δ3.29 (d, J=8); **7d**, δ3.83 (s). The successful cyclization of these functionalized olefin aldehydes overcomes some limitations observed in the "parent" cases. For example, the cycloaddition reaction fails totally for 6-heptenal and 6-phenyl-6-heptenal, presumably a consequence of the competing aldol polymerization pathway often found in enolizable aldehydes. Attempted modifications such as the use of the silyl esters[2a,b] of alpha amino acids or the free amino acids themselves , successful in some other recalcitrant cases, did not yield any dipolarcycloaddition products in these examples.

SCHEME 3

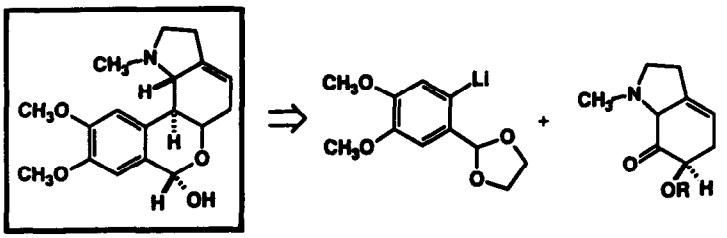


Some useful transformations of the functionalized cycloadducts are presented in Scheme 3. Mercuric ion-catalyzed hydrolysis of the dithiane moiety in cycloadducts such as **13** yields the ketone **12** while maintaining the cis ring fusion (Ha: 3.51 (d,J=9). The ester group can be reduced to the alcohol **14**, a potential intermediate for ring expansion chemistry,[8a,8b] or totally removed by the methodology of Rapoport[8c] to provide the pyrrolidine derivative **15**. Finally, the dithiane group itself may be reductively removed with nickel boride[9] to afford the unsubstituted case **16**. Such a transformation "remedies" the failure of some enolizable aldehydes to undergo the cycloaddition and afford products such as **16** directly.

A large number of naturally occurring alkaloids contain a cis-fused perhydroindole ring system as a key structural element, most notably members of the Amaryllidaceae family such as crinine, tazettine, lycorenine, and mesembrine.[10] A model study for the synthesis of the antihypertensive alkaloid lycorenine is presented in Scheme 4. An important consideration for such an approach to lycorenine based on azomethine ylide cycloaddition chemistry is the regiochemistry of the intramolecular reaction in which the C-C multiple bond is an allene. Thus, the allenic aldehyde **20** is prepared from ethyl 1,3-dithiane-2-carboxylate (**17**) and 5-bromo-1,2-pentadiene (**18**)[11] to yield **19** via the method of Eliel,[12] followed by reduction with lithium aluminum hydride and oxidation by DMSO/oxalyl chloride.[13] Condensation of **20** with sarcosine ethyl ester provides the two cycloadducts **21** [δ3.62 (d,1, J=9), 4.91 (d,1, J=2), 5.14 (d,1, J=2) 19%] and the **22** [δ3.61 (s,1), 5.47 (s,1) 28%]. Fortunately, the observed regiochemistry favors the desired isomer **22** in this unoptimized reaction and is opposite to that reported by Le Bel[14] in an analogous study involving intramolecular nitrone-allene [3+2] cycloadditions. Therefore, this chemistry provides a ready access to the lycorenine system and represents a novel approach to the natural product and its cogeners.

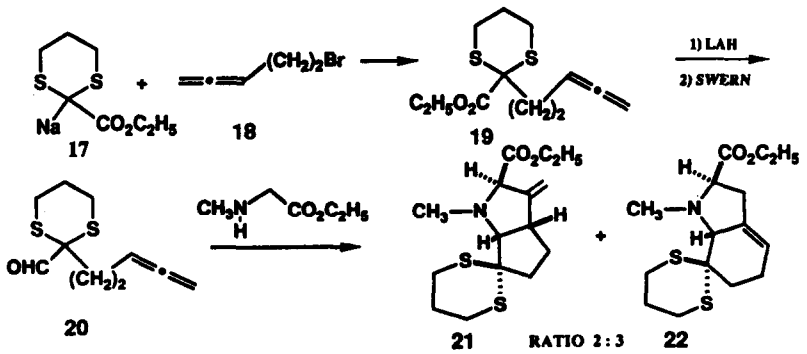
SCHEME 4

RETROSYNTHETIC PLAN



LYCORENINE

MODEL STUDY



In summary, the use of alpha dithiane-substituted olefin aldehydes as precursors to functionalized azomethine ylides has been shown to offer several advantages: 1) the preparation of the olefin-aldehydes is greatly facilitated by the use of dithiane anion chemistry; 2) the 1,3-dithiane moiety is thermally stable, allowing sluggish cycloaddition reactions to be carried out; 3) the "protection" of the labile enolizable hydrogens of the aldehyde group now permits cycloaddition reactions which fail in the parent case to be performed successfully; and 4) the versatile dithiane group is an effective agent for the introduction of other functionality in the resulting cycloadducts.

REFERENCES

1. P. N. Confalone and E. M. Huie, J. Am Chem. Soc., **1984**, 106, 7175.

2. (a) C.-L. J. Wang, W. C. Ripka, and P. N. Confalone, Tetrahedron Lett., **1984**, 25, 4613; (b) P. N. Confalone and E. M. Huie, J. Org. Chem., **1983**, 48, 2994; (c) R. Grigg, M. F. Aly, U. Sridharan, and S. Thianpatanagul, J. Chem. Soc., Chem. Commun., **1984**, 182; (d) R. Grigg, S. Thianpatanagul, J. Chem. Soc., Chem. Commun., **1984**, 180.

3. For related chemistry see: P. DeShong, D. A. Kell, and D. R. Sidler, J. Org. Chem., **1985**, 50, 2309 and leading references therein.

4. A typical cyclization procedure is as follows: A solution of aldehyde **4** (5 mmol), aminoacid ester **5** (10 mmol) and about 10 mg camphorsulfonic acid in 15 mL xylene is heated under reflux using a Dean-Stark trap containing molecular sieves until the aldehyde is consumed (TLC analysis, 1-3 days). The solvent is removed under vacuum, and the product **7** is purified via column chromatography on silica gel.

5. K. F. Burri, R. A. Cardone, W. Y. Chen, and P. Rosen, J. Am. Chem. Soc., **1978**. 100, 7069.

6. S. L. Schreiber, R. E. Claus, and J. Reagan, Tetrahedron Lett., **1982**, 23, 3867.

7. (a) A. Padwa and H. Ku, J. Org. Chem., **1979**, 44, 255. For ^{1}H NMR spectra of related ring systems see: (b) N. A. LeBel and E. G. Banucci, J. Org. Chem., **1971**, 36, 2440; (c) P. B. Woller, and N. H. Cromwell, J. Org. Chem., **1970**, 35, 888.

8. (a) K. E. Harding and S. R. Burks, J. Org. Chem., **1984**, 49, 40; (b) D. St. C. Black and J. E. Doyle, Adv. Heterocyclic Chem., **1980**, 27, 1; (c) T. Dean, M. C. Padgett, and H. Rapoport, J. Am. Chem. Soc., **1976**, 98, 7448.

9. L. A. Flippin and M. A. Dombroski, Tetrahedron Lett., **1985**, 26, 2977; R. B. Boar, D. W. Hawkins, J. F. McGhie, and D. H. R. Barton, J. Chem. Soc. Perkin I, **1973**, 654.

10. For general reviews of this field see: (a) M. Sanisbury, In "Rodds Chemistry of Carbon Compounds, IVB"; S. Coffey, Ed.; Elsevier Scientific, Amsterdam, 1977. pp. 16-200; (b) "The Alkaloids"; Specialist Reports; The Royal Society of Chemistry: London, 1969-1982; Vol. 1-12; (c) "The Alkaloids"; Academic Press: New York, 1950-1983; Vol. 1-21.

11. R. M. Coates, P. D. Senter, and W. R. Baker, J. Org. Chem., **1982**, 47, 3597.

12. E. L. Eliel and A. A. Hartmann, J. Org. Chem., **1972**, 37, 505.

13. A. J. Mancuso, S.-L. Huang, and D. Swern, J. Org. Chem., **1978**, 43, 2480.

14. N. A. LeBel and E. Banucci, J. Am. Chem. Soc., **1970**, 92, 5278.

(Received in USA 14 February 1986)