Tetrahedron Letters,Vol.30,No.50,pp 7017-7020,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF POLYCYCLIC LACTAMS VIA INTRAMOLECULAR DIPOLAR CYCLOADDITIONS OF STABILIZED AZOMETHINE YLIDES

Stephen F. Martin* and Tom H. Cheavens
Department of Chemistry, The University of Texas, Austin, TX 78712

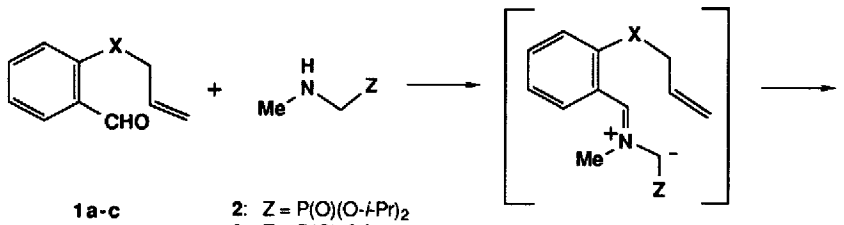
Abstract. A stereoselective two step sequence for the construction of fused pyrrolidone ring systems has been developed which features the intramolecular [3+2] dipolar cycloaddition of unsaturated azomethine ylides. The ylides are produced upon reaction of aminomethylphosphonates with α,ω-olefinic aldehydes, followed by oxidative removal of the phosphonate ester group using a newly developed method.

The intermolecular [3+2] cycloaddition reactions of azomethine ylides[1] have been widely exploited for the construction of substituted pyrrolidine ring systems, and more recently the related intramolecular variant of this process has been introduced as a key step in the total synthesis of fused pyrrolidine ring subunits that are common to a variety of alkaloids.[2] It was felt that certain variations in these ylides might permit easier refunctionalization of the resultant cycloadducts. Accordingly, we initiated a study (Scheme 1) of the intramolecular [3+2] cycloaddition of phosphonate-stabilized[4] azomethine ylides (*e.g.* **5** → **8**), which through oxidative dephosphonation might afford lactams of type **18**. An alternative sequence of interest was the analogous process involving nitrile stabilized azomethine ylides (*e.g.* **7** → **10** → **18**).[5] We now report some of our initial results directed toward these goals.

Not only do electron withdrawing groups stabilize azomethine ylides, but such groups also play an important role in facilitating proton transfer during the formation of azomethine ylides from aldehydes and secondary amines. We therefore reasoned that the aminomethylphosphonates **2** and **3** as well as the related aminoacetonitrile **4** would react by addition-elimination with aldehydes **1a-c** to give intermediate azomethine ylides **5a-c**, **6a-c**, and **7a-c**. These would in turn undergo facile intramolecular [3+2] cycloadditions to give mixtures of the corresponding C-2 epimeric *cis*- and *trans*-cycloadducts **8a-c** to **11a-c**, **16**, **17** and **12a-c** to **15a-c**, respectively. Although the ratio of the *cis*- and *trans*-cycloadducts would play a significant role in the eventual application of such reactions to synthetic targets, the stereochemistry at the carbon bearing the activating function (C-2) would be of little consequence, since oxidative removal of the pendant group would reveal a lactam carbonyl.

The [3+2] dipolar cycloadditions were conveniently executed in a single operation by dissolving aldehydes **1a-c** and the secondary amines **2**, **3**, or **4** in ethylene glycol diethylether which was then refluxed over molecular sieves in a Soxhlet extractor thimble to remove water. Reactions proceeded in moderate to good overall yields, as summarized in Table 1.[6] The aldehydes **1a** and **1c** were prepared from salicylaldehyde and anthranilic acid by conventional methods.[7,8] Preparation of **1b**, which had been previously made by a multi-step procedure,[9] was readily accomplished in one pot by sequential treatment of *o*-tolualdehyde with lithio *N*, *N*, *N'*-trimethylethylenediamine, *sec*-butyllithium, and allyl bromide.[10] The amines **2**, **3**, and **4** were formed according to literature methods.[11] The overall yields of the cycloadducts were found to be better when ethylene glycol diethyl

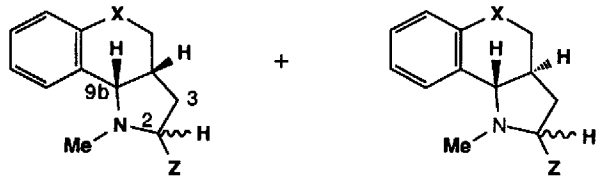
Scheme 1



1a-c

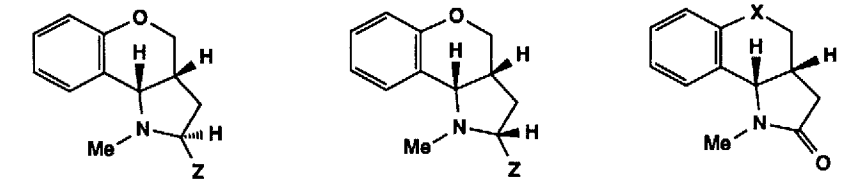
2: Z = P(O)(O-*i*-Pr)$_2$
3: Z = P(O)(OCH$_2$-*t*-Bu)$_2$
4: Z = CN

5a-c: Z = P(O)(O-*i*-Pr)$_2$
6a: Z = P(O)(OCH$_2$-*t*-Bu)$_2$
7a-c: Z = CN



8a-c: Z = P(O)(O-*i*-Pr)$_2$, H-2 = α
9a-c: Z = P(O)(O-*i*-Pr)$_2$, H-2 = β
10a-c: Z = CN, H-2 = α
11a-c: Z = CN, H-2 = β

12a-c: Z = P(O)(O-*i*-Pr)$_2$, H-2 = α
13a-c: Z = P(O)(O-*i*-Pr)$_2$, H-2 = β
14a-c: Z = CN, H-2 = α
15a-c: Z = CN, H-2 = β



16: Z = P(O)(OCH$_2$-*t*-Bu)$_2$

17: Z = P(O)(OCH$_2$-*t*-Bu)$_2$

18a,b

Series a: X = O
Series b: X = CH$_2$
Series c: X = NSO$_2$Me

ether (EGDEE) was used as a solvent instead of toluene.[12] Since the boiling points of these two solvents differ by only 10 °C and [3+2] cycloadditions are known to be little influenced by solvent effects,[1] the origin of this improvement remains obscure.

Gratifyingly, and in contrast to previously reported results[2a] with carboxylic ester stabilized azomethine ylides and the aldehyde **1a**, exclusively *cis*-, and no *trans*-isomers, **12a-c** or **13a-c**, of the phosphonate cycloadducts were detected in the reaction mixtures. Intramolecular [3+2] cycloadditions of the cyano-stabilized

Table 1

Aldehyde	Amine	Cycloadduct(s) (Yield,%)[a]			
1a	**2**	**8a** (67)	**9a** (8)	-	-
1a	**3**	**16** (65)	**17** (15)	-	-
1a	**4**	**10a** (26)[b]	**11a** (37)[b]	**14a** (1)[b]	**15a** (6)[b]
1b	**2**	**8b + 9b** (50)[c]		-	-
1c	**4**	**8c + 9c** (55)[c]		-	-

[a]Isolated by flash chromatography, [b]Isolated *cis*- and *trans*-isomers, H-2 ratios by ^{1}HNMR, [c]H-2 ratios indeterminate.

azomethine ylides gave 6-7% of the *trans*-isomers **14a**, **15a** and **14c**, **15c** and were less selective with respect to the stereogenic center at C-2 than those of the corresponding phosphonate-stabilized azomethine ylides. The structure of **16** was determined by single crystal X-ray diffraction analysis.[13] Structures of the other cycloadducts were then assigned based upon homo- and heteronuclear NMR correlations together with extensive analysis of proton coupling constants.[14,15]

To verify that the postulated oxidative dephosphonation of cycloadducts of general types **8** and **9** to give the corresponding lactams could be achieved, preliminary experiments were conducted using the cycloadducts **8a** and **8b**. Sequential reaction of **8a** and **8b** with *n*-butyllithium (THF, -78 °C) and oxygen delivered the lactams **18a** and **18b**, respectively, in good overall yields, although variable quantities of the unoxidized H-2 epimers **9a** and **9b** were also isolated.[16]

Thus, in these investigations we have established that azomethine ylides stabilized with phosphonate groups enter into highly stereoselective intramolecular [3+2] dipolar cycloadditions to give *cis*- fused pyrrolidine derivatives that may be subsequently converted into easily refuctionalized 2-pyrrolidones. Application of this methodology to the total synthesis of alkaloid natural products is the subject of ongoing investigations, the results of which will be reported in due course.

Acknowledgments. We thank the National Institutes of Health (GM-25439) and the Robert A. Welch Foundation for generous support of these studies. We also thank Mr. Keith L. Minor for preparing **1a** and **2.**

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6. The structure assigned to each compound was in full accord with its spectral (^{1}H and ^{13}C NMR, IR, MS) characteristics. Analytical samples of all new compounds were obtained by recrystallization, preparative HPLC, or flash chromatography and gave satisfactory data for elemental composition via combustion analysis (C, H, N) and/or high-resolution mass spectrometry. All yields are based on isolated material except where inseparable isomer ratios were determined by ^{1}H NMR spectroscopy.
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11. (a) Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528. (b) McElvain, S. M.; Laughton, P. M. *Ibid.* **1951**, *73*, 449. Yields were much improved by reversing the order of addition.
12. In toluene the yields of **8a**, **8b**, and **10a** were only 40, 32, and 15%, respectively.
13. Conducted by Dr. Vincent M. Lynch (The University of Texas at Austin). Detailed structural information is available on request.
14. ^{1}H NMR data for these assignments were obtained at 300 MHz (500 MHz for **10a** only). Chemical shifts (ppm) and coupling constants for H-9b, H-2, and H-3α respectively were as follows (nr = unresolved). **8a**: 4.06 dd (J = 1.5, 4.5 Hz), 3.26 ddd (J = 1.1, 5.5, 9.1 Hz), 2.00 dddd (J = 4.0, 9.2, 13.3, 16.9 Hz); **9a**: 3.11 dd (J = 1.5, 4.5 Hz), 2.76 dd (J = 7.3, 9.8 Hz), nr; **10a:** 3.46 d (J = 6.3 Hz), 3.99 dd (1.8, 8.4 Hz), 2.40 ddd (J = 1.8, 8.8, 13.6 Hz); **11a**: 3.13 d (J = 5.1 Hz), nr, nr; **14a:** 3.49 d (J = 10.7 Hz), 4.34 dd (5.8, 8.4 Hz), 1.91 ddd (J = 5.8, 10.9, 16.4 Hz); **15a:** 3.30 d (J = 10.6 Hz), 3.68 dd (J = 2.4, 10.3 Hz), 2.01 ddd (J = 10.7, 12.2 Hz); **16:** 4.03 dd (2.2, 6.0 Hz), 3.43 ddd (J = 1.7, 5.0, 9.3 Hz), 2.01 ddd (J = 3.2, 9.2, 13.4 Hz); and **17:** 3.13 d (J = 4.2 Hz), 2.89 ddd (J = 4.6, 7.9, 9.6 Hz), 1.86 ddd (J = 7.0, 9.7, 9.8 Hz).
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(Received in USA 22 May 1989)