

PHOSPHORYL-SUBSTITUTED 1-AZADIENES FOR USE IN INTRAMOLECULAR DIELS-ALDER CYCLIZATIONS

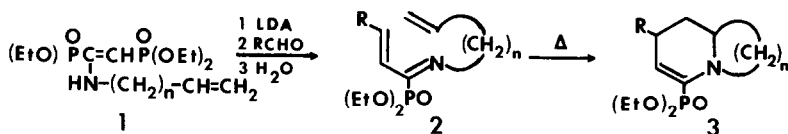
Marilyn A. Whitesell and Evan P. Kyba*

Department of Chemistry, The University of Texas, Austin, Texas 78712

Abstract: The preparation and isolation of 2-(diethoxyphosphoryl)-1-azadienes and their use in the formation of functionalized quinolizidine and indolizidine ring systems via an intramolecular Diels-Alder reaction is described.

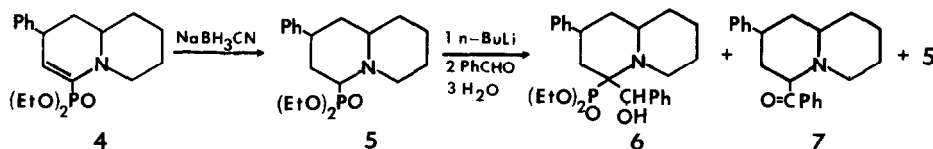
The intramolecular Diels-Alder reaction is a familiar approach to the synthesis of bicyclic compounds including azacyclic systems, which can be obtained when nitrogen is incorporated in the diene or dieneophile framework.¹ In those examples which employ azadienes² the instability of the functional group dictates that it be generated in situ for the subsequent ring-forming reaction. We have previously reported³ the synthesis of stabilized 1-azadienes which can be isolated and stored for up to one month. Here, we would like to demonstrate the synthetic utility of these compounds to make substituted indolizidine and quinolizidine compounds via an intramolecular Diels-Alder cyclization.

The enamines **1**, were synthesized from 4-pentenyl- and 5-hexenyl-amine as described previously,³ and subsequent reaction with the appropriate aldehydes in a Wittig-Horner-Emmons type of reaction⁴ gave the 1-azadienes **2**, where R is phenyl, p-nitrophenyl, methyl, or isopropyl.⁵ Upon heating in refluxing toluene overnight, the cyclized product **3** was obtained in all but the isopropyl case.⁶ Isolated yields after purification by HPLC were: n = 3, R = Ph (46%); n = 4, R = Ph (63%), R = 4-NO₂C₆H₄ (35%), R = Me (30%).⁷



Further investigation of these compounds was carried out on the phenyl derivative **4** (³¹P NMR, δ +16) shown below. The enamine was reduced by sodium cyanoborohydride⁸ to the phosphonate **5** (³¹P NMR, δ +27) in 50% yield. Treatment of this compound with n-BuLi at -78 °C in THF generated the anion (³¹P NMR, δ +40) and addition of benzaldehyde at -78 °C gave an addition product (³¹P NMR, δ +32, broad) which, upon warming to room temperature decomposed to several

compounds including starting material. After workup with water, two isomeric forms of 5 (presumably equatorial/axial isomers at C-5) were isolated in 22% yield by HPLC as the major components, along with compounds 6 (6%) and 7 (5%), and several unidentified compounds in very small amounts. Species 6 was unstable and decomposed slowly to 7, as well as other products which may explain why only about one third of the amount of 6 anticipated by ^{31}P NMR was actually isolated. The reluctance of the adduct 6 to eliminate in the Wittig-Horner-Emmons fashion has been observed in similar systems before,⁹ and further experiments to effect this elimination as well as the elimination to the ketone^{9b} are underway.



Acknowledgment. We are indebted to the Robert A. Welch Foundation (Grant No. F-573) and the National Science Foundation (Grant No. 81-13090) for their generous support of this work. Helpful discussions with Professor Craig Wilcox are gratefully acknowledged.

References and Notes.

- Weinreb, S.M.; Staib, R.R. *Tetrahedron* 1982, **38**, 3087.
- Cheng, Y.-S.; Lupo, A.T.; Fowler, R.W. *J. Am. Chem. Soc.* 1983, **105**, 7696, and references therein.
- Whitesell, M.A.; Kyba, E.P. *Tetrahedron Lett.* 1983, **24**, 1679.
- (a) Walker, B.J. in "Organophosphorus Reagents in Organic Reagents"; Cadogan, J.T.G., Ed.; Academic Press, New York, NY, 1979; Chapter 3. (b) Nagata, W.; Hayase, Y. *J. Chem. Soc., (C)* 1969, 460.
- All compounds described herein were identified on the basis of their spectroscopic (^{31}P , ^{13}C , ^1H NMR, IR, MS) and combustion analytic or HRMS properties. The ^{31}P NMR spectra reported were determined on ca. 0.1 M CDCl_3 solutions and are referenced to external 85% H_3PO_4 . Peaks downfield from the standard are defined as positive.
- Two unstable products (^{31}P NMR, δ +18 and +17 ppm) were obtained.
- In all cases, two ^{31}P NMR signals, very similar in chemical shift in ratios of ca. 5:1 were observed for the crude reaction mixture. Only the major component was isolated by HPLC in each case. We presume the major product is that derived from an exo transition state.²
- Borch, R.; Bernstein, M.; Durst, H.D. *J. Am. Chem. Soc.* 1971, **93**, 2897. Single stereoisomers from 3 ($n = 4$) and mixtures of two isomers from 3 ($n = 3$) were isolated.
- (a) Mikolajczyk, M.; Grzejszczak, S.; Lyzwa, P. *Tetrahedron Lett.* 1982, **23**, 2237. (b) Broekhof, N.; van der Gen, A. *Tetrahedron Lett.* 1981, **22**, 2799.

(Received in USA 6 February 1984)