Pergamon

Tetrahedron Letters, Vol. 35, No 21, pp. 3473-3476, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0654-G

Cycloaddition of Enamines With Alkynylphosphonates. A Route to Functionalized Medium Sized Rings.[1]

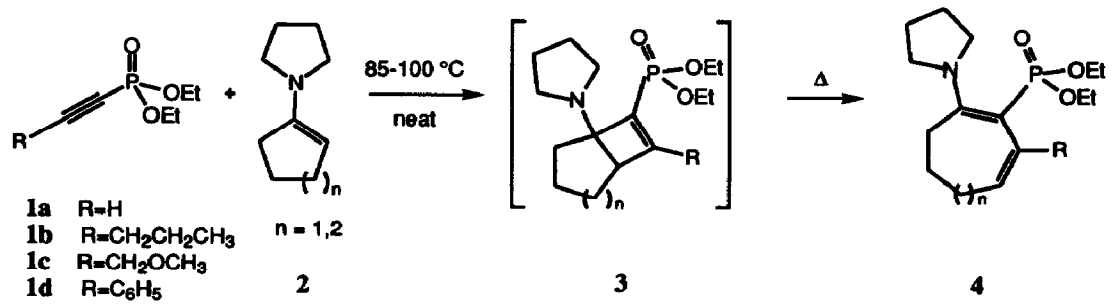
Suzanne M. Ruder* and Bradley K. Norwood

Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia, 23284-2006

Abstract: Substituted seven and eight membered rings were formed from cyclopentanone and cyclohexanone via cycloadditions of pyrrolidine enamines with alkynyl phosphonates. This procedure provides straightforward access to functionalized medium sized rings that could be further manipulated in the synthesis of a number of natural products.

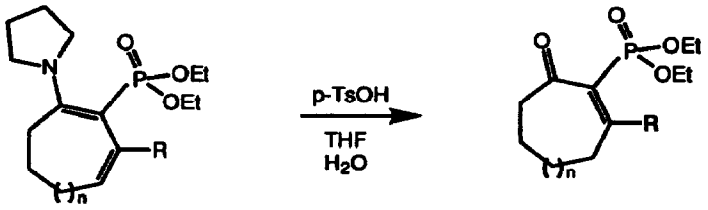
Many natural products of biological interest contain highly functionalized medium sized rings. As part of continuing studies in our labs, we have been exploring the use of phosphonates in ring expansion reactions to construct functionalized medium sized rings. While cycloadditions of enamines[2-5] or silyl enol ethers[6] with activated alkynes are known to give ring expanded products *via* cyclobutene intermediates, to our knowledge the use of alkynyl phosphonates in ring expansion reactions has not been accomplished to date. Vinyl phosphonates, however, undergo cycloaddition with enamines to give cyclobutane rings which do not undergo ring enlargement.[7] Phosphonates are useful auxiliary groups for such ring expansion reactions as they can be utilized further in the formation of an alkene via the Horner-Wadsworth-Emmons (HWE) reaction.[8] We herein report that seven and eight membered rings bearing a phosphonate group can be prepared from readily available five and six-membered cyclic ketones *via* cycloaddition of the enamine with alkynyl phosphonates.

The alkynyl phosphonates **1a-d** were obtained in good yields *via* a procedure adapted from a method reported by Chatta and Aguiar.[9] Ethynyl phosphonate **1a** was most easily obtained by reaction of trimethylsilyl ethyne with n-butyl lithium at -78 °C, followed by addition to a solution of diethyl chlorophosphate at 0 °C. The resulting trimethylsilylethynyl phosphonate was then deprotected by washing with 10% Na_2CO_3 to generate diethyl ethynylphosphonate (**1a**) in good yield. Earlier attempts to form **1a** by reaction of ethynyl magnesium bromide with diethyl chlorophosphate gave very low product yields, presumably arising from side reactions involving the relatively acidic alkynyl proton. Phosphonates **1b - d** were readily prepared from the appropriate terminal alkynes by similar treatment as described above. This gave good yields (70-80%) of the desired alkynyl phosphonates. The pyrrolidine enamines of cyclic ketones were easily prepared using standard methods.[3]



Scheme 1

When freshly distilled enamine **2** was combined with the alkynyl phosphonate **1** and heated to 85 - 100 °C, the corresponding cycloaddition product **4** was obtained. The cycloaddition of enamines with more highly activated alkynes, such as dimethylacetylene dicarboxylate,[3] was reported to occur at room temperature to form the bicyclic intermediate corresponding to **3**. The alkynyl phosphonates are less reactive in the cycloaddition reaction with enamines, however, and a reaction temperature of at least 85 °C was required in order to accomplish cycloaddition. Under these conditions, spontaneous ring opening of the thermally unstable cyclobutene **3** afforded ring enlarged product **4** in one step. The presence of **4a** in the crude reaction mixture was confirmed by a strong IR absorption at 1570 cm^{-1}. However, the product enamine proved to be unstable to distillation or chromatography, and was therefore not isolated. Hydrolysis of the crude reaction mixture with either dilute ethanolic acetic acid or p-TsOH/THF/H_2O at room temperature gave **5**. In some cases, the partially hydrolyzed phosphonate **6** was detected when hydrolysis was conducted in aqueous acetic acid, therefore, 95% ethanol/acetic acid was chosen in an attempt to minimize formation of **6**. The monophosphonic ester **6** was also formed when the hydrolysis reaction was heated. The hydrolysis of **4** to **5** with pTsOH proved to be superior to the prior method as none of the monoester **6** was obtained. The unsaturated β-ketophosphonate **5** thus obtained was purified using radial or column chromatography on alumina, eluted with 20% ethyl acetate/heptane.[10]

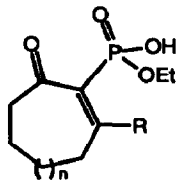


Scheme 2

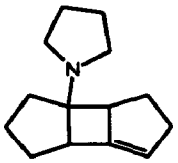
The cycloaddition reaction must be carefully controlled in order to obtain the best yields. One byproduct encountered in this process resulted from self-condensation of the enamine **2** (n=1). Significant self condensation products were detected in reactions that had been heated to 100 °C or more. In a control reaction, where the neat enamine was stirred under argon in a sealed ampule at 110 °C, the same product, with

a mass of 203, was detected after 48 h. One possible structure for this compound is **7** shown below. When reaction temperatures were kept below 100 °C, then formation of **7** was minimized. Neither the morpholine enamine of cyclopentanone nor the pyrrolidine enamine of cyclohexanone exhibited the formation of analogous products, perhaps owing to their lower reactivity.

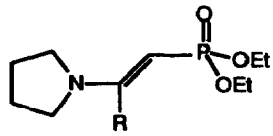
Careful exclusion of any moisture from the reaction mixture was also required to give the best results of cycloaddition products. Formation of the β-amino vinylphosphonate **8** resulted from the Michael addition of pyrrolidine, liberated from the enamine by contact with water, to the alkynyl phosphonate **1**. Control experiments showed the reaction between pyrrolidine and alkynylphosphonate **1a** to be rapid and exothermic, generating **8** as the sole product. The byproduct **8** was easily identified by the presence of the vinylic protons adjacent to phosphorous at 3.7 ppm (J= 14.2 Hz). To minimize the formation of adduct **8**, the enamines were distilled immediately prior to use. The alkynyl phosphonates were also distilled prior to use, since they were found to absorb water readily.



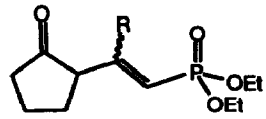
6



7



8



9

The best results for the cycloaddition reaction were thus found when all moisture was excluded from the reaction flask and temperatures were held below 100 °C. These conditions were met by carrying out the cycloaddition reactions in glass ampules which had been flame-dried and purged with argon. Reaction times varied from 24 h for **1a** to 8 days for **1c**. Shorter reaction times or temperatures lower than 85 °C normally resulted in isolation of considerable amounts of the Michael adduct **9**. This suggests that the reaction is a two step process involving rapid Michael addition of the enamine to the phosphonate, followed by the slow ring closure to give bicyclic intermediate **3**. This is in agreement with earlier reports involving vinylphosphonates[7] and activated acetylenes.[4] Control reactions in our lab have shown that initial Michael addition can occur at room temperature, but in order to force cyclobutene ring closure, elevated temperatures were required. The vinyl phosphonate **9** was formed when the reaction was quenched before ring closure could occur to form the bicyclic intermediate **3**.

The cycloaddition of the substituted alkynyl phosphonates proceeded with lower yields than with the unsubstituted phosphonate **1a**, though these conditions are not fully optimized. This may be a result of a combination of steric and electronic effects, especially in the case of the pendant phenyl group of **1d**. Note that this is arguably the least suitable Michael acceptor, and the yields are poor. Table 1 summarizes the results obtained from the cycloaddition followed by hydrolysis to give **5**.

We have shown that a wide variety of alkynyl phosphonates will undergo cycloadditions with cyclic enamines to generate (n+2) ring enlarged β-keto vinylphosphonates. Especially in the case of diethyl ethynyl phosphonate, (**1a**), good yields were obtained given the proper precautions to exclude moisture. Care must be exercised in order to balance the temperature required to effect cycloaddition and those conditions which lead

to self-condensation of the enamine. We are continuing to explore the cycloaddition of substituted enamines with alkynyl phosphonates, as well as the use of β-keto vinylphosphonate systems **5** as Michael acceptors.

Table 1. Summary of Results

	R	n	t (h)	T,°C	%Yield[11]
5a	H	1	24	100	77
5b	$CH_2CH_2CH_3$	1	60	95	71
5c	CH_2OCH_3	1	180	60	56
5d	C_6H_5	1	48	105	17
5e	H	2	60	105	76

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of this research by the National Science Foundation (CHE-9113059).

REFERENCES

(1) Presented in part at the 205th National ACS meeting, Denver, CO, March 28-April 2, 1993.

(2) Berchtold, G. A.; Uhlig, G. F. *J. Org. Chem.* **1963**, *28*, 1459-1462.

(3) Huebner, C. F.; Dorfman, L.; Robison, M. M.; Donoghue, E.; Pierson, W. G.; Strachan, P. *J. Org. Chem.* **1963**, *28*, 3134-3140.

(4) Brannock, K. C.; Burpitt, R. D.; Goodlett, V. W.; Thweatt, J. G. *J. Org. Chem.* **1963**, *28*, 1464-1468.

(5) Brannock, K. C.; Burpitt, R. D.; Goodlett, V. W.; Thweatt, J. G. *J. Org. Chem.* **1964**, *29*, 818-823.

(6) Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 248-253.

(7) Darling, S. D.; Subramanian, N. *Tetrahedron Lett* **1975**, 3279-3282.

(8) Wadsworth Jr., W. S. In *Organic Reactions*; W. E. Dauben, Ed.; Wiley: New York, 1977; Vol. 25; Ch.2.

(9) Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1971**, *36*, 2719.

(10) General procedure for cycloaddition: A glass ampule was flame dried and cooled under flowing argon. While maintaining the flow of argon, freshly distilled phosphonate **1a** (R=H) was added, followed by a crushed 4Å sieve. Freshly distilled enamine **2a** (n=1) was added and the ampule sealed. The reaction was then heated to 85-100 °C for 24 h. The product **4a** was hydrolyzed directly by adding THF, p-TsOH, and H_2O and stirring overnight, giving **5a**. I.R. 1665, 1613, 1256, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.04(dd, J=8.2 Hz, 10.9 Hz, 1H), 4.2(m, 4H), 2.99 (t, J=7.5 Hz, 2H), 2.13 (m, 2H), 2.0 (m, 2H), 1.36 (m, 8H). MS: $^m/_e$ 246 ($M^{+\bullet}$), 218 (M-C_2H_4), 190 (M-2(C_2H_4)), 172 (M-C_2H_9OH, base peak). Anal. Calcd for $C_{11}H_{19}O_4P$ (246.24): C, 53.65, H, 7.78. Found: C, 53.95, H, 8.00.

(11) GC yields.

(Received in USA 14 *February* 1994; *revised* 17 *March* 1994; *accepted* 25 *March* 1994)