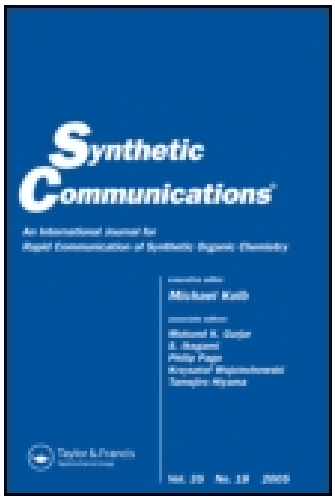


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

THE HIGH STEREOSELECTIVE SYNTHESIS OF β-ALKYNYL-ENOL PHOSPHATES

Yixiang Ding [a] & Xiaogen Huang [a]
[a] Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences , 354 Fenglin Road, Shanghai, 200032, People's Republic of China
Published online: 09 Nov 2006.

To cite this article: Yixiang Ding & Xiaogen Huang (2001) THE HIGH STEREOSELECTIVE SYNTHESIS OF β-ALKYNYL-ENOL PHOSPHATES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:3, 449-454, DOI: 10.1081/SCC-100000538

To link to this article: http://dx.doi.org/10.1081/SCC-100000538

SYNTHETIC COMMUNICATIONS, 31(3), 449–454 (2001)

THE HIGH STEREOSELECTIVE SYNTHESIS OF β-ALKYNYL-ENOL PHOSPHATES

Yixiang Ding* and Xiaogen Huang

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, People's Republic of China

ABSTRACT

A high stereoselective synthesis for β-alkynyl-enol phosphates from β-alkynyl ketone and dialkyl phosphite, via Atherton–Todd reaction, was reported. NaH as base gave a nearly pure Z-isomer.

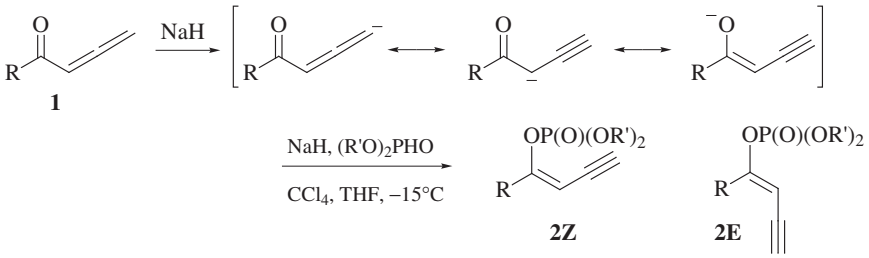
Enol phosphates are a class of important organic compounds. For example, phosphenol pyruvate (PEP) is a well-known high-energy species that plays a vital role in a number of biological processes. Further efforts have been made in the preparation of bioactive enol phosphates. As a pesticide, they are very potent, with a wide field of application. Recently, Raushel (1) described the bioactivity of alkynyl phosphate as a mechanism-based inactivation of bacterial phosphotriesterase. Widlauski (2) reported the synthesis of enol phosphates with leaving groups at the 1-position that should have substantial utility in the design of

*Corresponding author.

phosphatase or phosphodiesterase inhibitors. Enol phosphates are also key intermediates in certain organic synthesis (3–8).

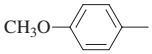
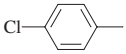
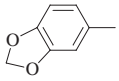
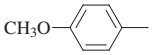
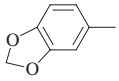
Now we report a high stereoselective synthesis for β-alkynyl-enol phosphates via Atherton–Todd reaction, which are a kind of new compound. β-alkynyl-enol phosphates would undergo hydrolytic reaction to give a reactive allenyl ketones. Such a molecular structure would be valuable for the design of mechanism-based inactivators of phosphatase. At the same time, they are useful intermediates for the preparation of enynes.

Because of the base-catalyzed "propargylic rearrangements," the enolate anion of β-alkynyl ketone can be obtained from allenyl ketone or β-alkynyl ketone. This anion then reacted with dialkyl phosphorochloride, intermediate of Atherton–Todd reaction, to give the β-alkynyl-enol phosphates. We prepared a number of different compounds as shown in Table 1. All of the products formed Z-isomer in a high stereoselective manner using NaH as bases.



1 **2Z** **2E**

Table 1. The Preparation of β-Alkynyl-enol Phosphates

Entry	R	R′	Z/E	Yield %
2a		Et	>95/5	62
2b		Et	>95/5	65
2c		Et	>95/5	69
2d		Et	>95/5	61
2e		Me	>95/5	74
2f		Me	>95/5	75
2g		Me	>95/5	62

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 2. Effect of Bases to the Ratio of *Z* and *E* of **2a**

Entry	Reaction Condition	Yield %	*Z*/*E*
1	NaH/−15°C	62	>95/5
2	BuLi/−78°C	52	66/34
3	LDA/−78°C	54	67/33
4	LDA/HMPA/−78°C	71	34/66

The effect of bases on the stereochemistry of the reaction was studied. The results are shown in Table 2. We found that the ratio of geometrical isomers **2aZ** and **2aE** is closely related to the used bases. The smaller base NaH gave nearly pure *Z*-isomer. The *Z*/*E* were determined by NMR analysis of the reaction mixture. The E and Z configurations of enol phosphates were determined using the Tobey–Pascual substituent shielding constants method (9). The calculated values are close to the observed values.

EXPERIMENTS

All melting points were uncorrected. IR spectra were measured with a Shimadzu IR-440 spectrometer. ^{1}H NMR spectra were Recorded at FX-90Q using TMS as internal standard and CCl_4 as solvent. ^{31}P NMR were recorded on 300 MHz at 161.97 MHz using $CDCl_3$ as solvent and 85% of H_3PO_4 as external standard. Mass spectra were taken on a Finnigan GC-MS-4021 spectrometer. Elemental analyses were performed on a Rapid CHN−O−S analyzer.

All allenyl aryl ketones were prepared according to the literature procedures (10,11) by the Jones oxidation of corresponding arylbutynol that were obtained by treatment of arylaldehyde with 3-bromo-propyne in the presence of Zn. All known precursor compounds (GC purity >95%) were characterized by ^{1}H NMR and physical constants in agreement with the literature (10–12), **1b** is a new compound. Diethyl phosphite (purity >99%) was purchased from FLUKA company and was distilled prior to use. CCl_4 was distilled prior to use. THF was treated with sodium and benzophenone. **1b**: Jonse oxidation yield 80%, m.p. 55–56°C. ^{1}H NMR: δ 7.93 (m, 2H), 6.93 (m, 2H), 6.46 (t, J = 6.5 Hz, 1H), 5.25 (d, J = 6.5 Hz, 2H), 3.86 (s, 3H). MS (m/z, %): 174 (M, 5.33), 107 (3.86), 92 (10.63), 77 (9.26), 63 (8.03). IR (KBr, cm^{-1}): 1957, 1923, 1644, 1592, 1233. Anal. calcd. for $C_{11}H_{10}OH_2$: C, 75.83; H, 5.79. Found: C, 76.00; H, 5.68.

General Procedure

A multinecked round-bottom flask was charged with NaH (1.0 mmol) and anhydrous THF (5 mL). The mixture was stirred under a nitrogen atmosphere

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

and cooled to −10°C. A solution of allenyl ketone (1.0 mmol) in THF was added slowly. After the mixture had been stirred for 0.5 h, diethyl phosphite (1.2 mmol) in CCl_4 was added dropwise. After stirring for about 1.5 h, the reaction mixture was neutralized with acetic acid and diluted with ether. The solution was washed with water, dried, and concentrated in vacuum to give an oil. The ratios of isomers were determined by NMR spectroscopy. The pure product was obtained after chromatography on silica gel using petroleum ether and ethyl acetate as eluent.

1-Phenyl-1-buten-3-ynyl Diethyl Phosphate (2aZ). Deep red oil. ^{1}H NMR: δ 7.25–7.68 (m, 5H, Ph), 5.60 (t, $J_{HH} = J_{PH} = 2.4$ Hz, 1H, HC═C), 4.12 (m, 4H, $2CH_2$), 3.17 (m, 1H, C≡CH), 1.25 (t, $J = 7$Hz, 6H, $2CH_3$). ^{31}P NMR: δ-6.596. MS (m/z, %): 280 (M, 34.23), 253 (2.80), 225 (3.92), 154 (2.56), 126 (100), 105 (18.70), 77 (16.43). IR (neat film, cm^{-1}): 1623, 1448, 1274, 1166, 1034. Anal. calcd. for $C_{14}H_{17}O_4P$: C, 59.99; H, 6.13. Found: C, 60.18, H, 6.02.

1-Phenyl-1-buten-3-ynyl Diethyl Phosphate (2aE). Deep red oil. ^{1}H NMR: δ 7.24–7.90 (m, 5H, Ph), 5.82 (t, $J_{HH} = J_{PH} = 2.6$Hz, 1H, HC═C), 4.10 (m, 4H, $2CH_2$), 3.10 (m, 1H, C≡CH), 1.25 (m, 6H, $2CH_3$). ^{31}P NMR: δ −6.207. MS (m/z, %): 280 (M, 34.77), 253 (1.89), 225 (2.34), 155 (9.47), 126 (100.00), 105 (20.08), 77 (20.07). IR (neat film, cm^{-1}): 1614, 1496, 1276, 1166, 1031. Anal. calcd. for $C_{14}H_{17}O_4P$: C, 59.99, H, 6.13. Found: C, 59.81, H, 6.27.

1-(4-Methoxyl-phenyl)-1-buten-3-ynyl Diethyl Phosphate (2bZ). Deep red oil. ^{1}H NMR: δ 6.72–7.45(m, 4H, Ph), 5.48 (t, $J_{HH} = J_{PH} = 2.4$Hz, 1H, HC═C), 4.11 (m, 4H, $2CH_2$), 3.75 (s, 3H, CH_3O), 3.15 (m, 1H, C≡CH), 1.24 (t, $J = 6$Hz, 6H, $2CH_3$). ^{31}P NMR: δ −6.562. MS (m/z, %): 310 (M, 16.48), 184 (2.69), 156 (100.00), 145 (5.00), 135 (12.46), 113 (3.52), 77 (4.18). IR (neat film, cm^{-1}): 2100, 1606, 1531, 1256, 1031. Anal. calcd. for $C_{15}H_{19}O_5P$: C, 58.05; H, 6.18. Found: C, 58.34; H, 6.40.

1-(4-Chlorophenyl)-1-buten-3-ynyl Diethyl Phosphate (2cZ). Deep red oil. ^{1}H NMR: δ 7.50–7.95 (m, 4H, Ph), 5.92 (dd, $J = 2.5$Hz, $J = 2.3$Hz, 1H, HC═C), 4.43 (m, 4H, $2CH_2$), 3.53 (m, 1H, C≡CH), 1.55 (m, 6H, $2CH_3$). ^{31}P NMR: δ −6.525. MS (m/z, %): 314 (M, 9.13), 286 (2.26), 258 (2.90), 160 (100.00), 139 (16.67), 126 (5.55), 99 (3.99). IR (neat film, cm^{-1}): 1619, 1492, 1272, 1052, 1001. Anal. calcd. for $C_{14}H_{16}ClO_4P$: C, 53.24; H, 5.13. Found: C, 53.51; H, 5.20.

1-(3,4-Methylenedioxyphenyl)-1-buten-3-ynyl Diethyl Phosphate (2dZ). Deep red oil. ^{1}H NMR: δ 6.77–7.30 (m, 3H, Ph), 6.00 (s, 2H, OCH_2O), 5.58 (t, $J = J = 2.4$Hz, 1H, HC═C), 4.24 (m, 4H, $2CH_2$), 3.28 (m, 1H, C≡CH), 1.35 (t, $J = 6$Hz, 6H, $2CH_3$). ^{31}P NMR: δ −6.544. MS (m/z, %): 324 (M, 36.4), 268 (3.22), 188 (5.56), 170 (100.00), 149 (14.57), 121 (7.96), 91 (6.06). IR (neat film,

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

cm^{-1}): 1606, 1492, 1446, 1257, 1037, 949. Anal. calcd. for $C_{15}H_{17}O_6P$: C, 55.55; H, 5.29, C. 55.33; H, 5.27.

1-Phenyl-1-buten-3-ynyl Dimethyl Phosphate (2eZ). Deep red oil. ^1H NMR: δ 7.20–7.65 (m, 5H, Ph), 5.63 (dd, $J = 1.8$Hz, $J = 3.2$Hz, 1H, HC=C), 3.25 (m, 1H, C≡CH), 3.75 (d, $J = 12$Hz, 6H, $2CH_3$). ^{31}P NMR: δ −4.1834. MS (m/z, %): 252 (M, 31.99), 235 (1.90), 203 (1.88), 126 (100.00), 109 (15.47), 105 (10.83), 77 (20.30). IR (neat film, cm^{-1}): 1625, 1448, 1284, 1187, 1049, 909. Anal. calcd. for $C_{12}H_{13}O_4P$: C, 57.14; H, 5.21. Found: C, 56.88; H, 5.40.

1-(4-Methoxyl-phenyl)-1-buten-3-ynyl Dimethyl Phosphate (2fZ). Deep red oil. ^1H NMR: δ 6.85–7.58 (d, 2H, Ph), 5.64 (dd, $J = 2.4$Hz, $J = 2.2$Hz, 1H, HC=C), 3.90 (d, $J = 6$Hz, 6H, $2CH_3$), 3.80 (s, 3H, CH_3O), 3.3 (m, 1H, C≡CH). ^{31}P NMR: δ −4.1439. MS (m/z, %): 282 (M, 99.59), 203 (0.50), 156 (100.00), 141 (21.78), 127 (5.82), 109 (17.85), 92 (6.86). IR (neat film, cm^{-1}): 1606, 1513, 1284, 1182, 1048, 911. Anal. calcd. for $C_{13}H_{15}O_5P$: C, 55.32; H, 5.37. Found: C, 55.31; H, 5.40.

1-(3,4-Methylenedioxyphenyl)-1-buten-3-ynyl Dimethyl Phosphate (2gZ). Deep red solid. m.p. 81–82°C. ^1H NMR: δ 6.48–7.03 (m, 3H, Ph), 5.74 (s, 2H, OCH_2O), 5.34 (dd, $J = 1.8$Hz, $J = 3.2$Hz, 1H, HC=C), 3.70 (d, $J = 4$Hz, 6H, $2CH_3$), 3.27 (m, 1H, C≡CH). ^{31}P NMR: δ − 4.1270. MS (m/z, %): 296 (M, 32.24), 184 (3.32), 170 (100.00), 149 (6.56), 109 (14.39), 101 (3.57), 79 (8.79), IR (KBr, cm^{-1}): 1604, 1491, 1446, 1286, 1256, 1256, 1010. Anal. calcd. for $C_{13}H_{13}O_6P$: C, 52.71; H, 4.43. Found: C, 52.97; H, 4.52.

ACKNOWLEDGMENT

The project was supported by the National Science Foundation of China.

REFERENCES

1. Blankenship, J.N.; Abu-Soud, H.; Francisco, W.A.; Raushel, F.M. Mechanism-Based Inactivation of a Bacterial Phosphotriesterase by an Alkynyl Phosphate Ester. J. Am. Chem. Soc. **1991**, *113*, 8560.
2. Stowell, J.K.; Widlauski, T.S. Halo Enol Phosphates: Regioselective Synthesis of Phosphatase Inactivators via a Complex-Induced Proximity Effect. J. Am. Chem. Soc. **1994**, *116*, 789.

3. Calogeropoulou, T.; Hammoad, G.B.; Weimer, D.F. Synthesis of β-Keto Phosphonates from Vinyl Phosphates via a 1,3-Phosphorus Migration. J. Org. Chem. **1987**, *52*, 4185.
4. Borowitz, I.J.; Casper, E.W.R.; Crouch, R.K.; Yee, K.C. Fomation and Alkylation of Lithium Enolates from Enol Phosphorylated Species. J. Org. Chem. **1972**, *37*, 3873.
5. Ireland, R.E.; Pfister, G. A New Method for the Synthesis of Structurally Specific Olefins from Enolate Anions. Tetrahedron Lett. **1969**, 2145.
6. Blaszczak, L.; Winkler, J.; O'kuha, S. A New Synthesis of Olefins from Ketones via Coupling of Lithium Dialkylcuprates with Enol Diphenylphosphate Esters. Tetrahedron Lett. **1976**, 4405.
7. Kienzle, F.; Rosen, P. The Synthesis and Reaction of Dialkyl 1-Vinylvinyl-Phosphates. Helv. Chim. Acta **1979**, *62*, 442.
8. Yoo, H.Y.; Honk, K.N. Claisen Rearrangements of Enol Phosphates. Chemtracts: Org. Chem. **1994**, *7*, 49.
9. Gaydou, E.M. Can. J. Chem. **1973**, *51*, 3412; Tobey, S.W. Phosphates d'enols-X. Determination des Isomers Giometigues Diversement Substitues par Resonance Magnetique Nucleaire. J. Org. Chem. **1969**, *34*, 1281.
10. Henbest, H.B.; Jones, E.R.H.; Walls, I.M.S. Researches on Acetylenic Compounds Part XXI. Reformatsky Reaction with Propargyl Bromides. J. Chem. Soc. **1949**, 2696.
11. Henbest, H.B. Phenyl Propargyl Ketone. J. Chem. Soc. **1952**, 4536.
12. Nagao, Y.; Lee, W.-S.; Kim, K. New Intramolecular Five-Endo-Mode Cyclization of Allenyl Aryl Ketones. Chem. Lett. **1994**, 389.

Received in Japan March 21, 2000