Synthesis and Synthetic Application of α-Formylvinylphosphonates. Facile Synthesis of Phosphono-Substituted Heterocyclic Compounds

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Received February 2, 2000

The β-ethoxy-α-phosphonovinyl anion, generated from β-(ethoxy)vinylphosphonate **1** and LDA, reacted with aldehydes and ketones or phenyl isocyanate to give the corresponding allylic alcohols **2a**−**m** or 1,3-diphenyl-5-phosphonouracil **4** in good or moderate yields. Treatment of the alcohols **2a**−**d**,**g**,**h**,**j** with trifluoroacetic acid led to α-formylvinylphosphonates **5a**−**d**,**g**,**h**,**j** in excellent yields. Synthetic application of the α-formylvinylphosphonates **5a**−**d**,**g**,**h** to phosphono-substituted heterocyclic compounds was studied.

Generation of various types of vinyl anions and their synthetic utilization have been extensively studied so far.[1] α-Heteroatom-substituted vinyl anions have often more potential utility than the parent vinyl anions because of their useful reactivities modified by the presence of a heteroatom functional group in addition to those of the vinyl anions.[2] Since vinylphosphonates containing various functional groups have been shown to have valuable synthetic versatility[3] and biological activities,[4] a wide variety of synthetic methods of functionalized vinylphosphonates has been developed to date.[3] Despite the attractive possibility of their synthesis via the reaction of α-phosphonovinyl anions, which are a family of α-heteroatom-substituted vinyl anions, with various electrophiles, successful utilization of the carbanions have been limited[5] due to the difficulty of generating the carbanions via deprotonation of vinylphosphonates with lithium reagents,[6] the ease of isomerization of the α-phosphonovinyl anions,[7] etc. We have recently reported preparation of a new type of α-phosphonovinyl anion bearing β,β-bis(alkylthio), β-alkylthio, or β-alkyloxy substituents, and their some synthetic utilization.[8,9] As a continuation of the studies on α-phosphonovinyl anions, we became interested in further application of β-ethoxy-α-phosphonovinyl anion to the synthesis of α-formylvinylphosphonates. Their general synthesis has not, to our knowledge, been developed although the vinylphosphonates containing the α-formyl group can be anticipated to serve as building blocks for synthesis of phosphono-substituted heterocyclic compounds,[10] which are expected to show biologically active or useful properties.[11] We report here a convenient synthesis of α-formylvinylphosphonates and synthetic application to phosphono-containing heterocyclic compounds. We also describe the use of the α-phosphonovinyl anion to a new type of uracil derivatives bearing the phosphono group.

Results and Discussion

Reaction of an α-Phosphonovinyl Anion with Carbonyl Compounds. We have recently reported that the β-ethoxy-α-phosphonovinyl anion was easily prepared and trapped with various heteroatom electrophiles to produce α-heteroatom-substituted vinylphosphonates.[9] To extend the synthetic utility of this method, the reaction of β-ethoxy-α-phosphonovinyl anion, generated in situ from the vinylphosphonate **1** and lithium diisopropylamide (LDA), with various aldehydes or ketones

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(1) See, for examples, (a) Knight, D. W. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 1.6. (b) Chamberlin, A. R.; Bloom, S. H. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1990; Vol. 39, Chapter 1.

(2) For a review of α-heteroatom-substituted vinyl anions, see: (a) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 430. For the preparation of α-hetero (B, Si, O, Se, Te)-substituted vinyl anions and their synthetic application, see, ref 9 and references therein.

(3) For a review on synthetic uses of vinylphosphonates, see: Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.

(4) Breaker, R. R.; Gough, G. R.; Gilham, P. T. *Biochemistry* **1993**, *32*, 9125. Harnden, M. R.; Parkin, A.; Parratt, M. J.; Perkins, R. M. *J. Med. Chem.* **1993**, *36*, 1343.

(5) For the preparation of α-phosphonovinyl anion, via conjugate addition of nucleophiles to 1-alkynylphosphonates, see: (a) Gil, J. M.; Oh, D. Y. *J. Org. Chem.* **1999**, *64*, 2950. via transmetalation, see: (b) Mimouni, N.; About-Jaudet, E.; Collignon, N.; Savignac, Ph. *Phosphorus, Sulfur, and Silicon* **1993**, *75*, 99. via deprotonation of vinylphosphonates, see: (c) Atta, F. M.; Betz, R.; Schmid, B.; Schmidt, R. R. *Chem. Ber.* **1986**, *119*, 472.

(6) For conjugate addition of lithium reagents to vinylphosphonates, for example, Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 6428 and references therein.

(7)) For isomerization of β-alkyl-α-phosphonio- or phosphonovinyl anion into the corresponding allyl anion, see, for examples: (a) Minami, T.; Shikita, S.; So, S.; Nakayama, M.; Yamamoto, I. *J. Org. Chem.* **1988**, *53*, 2937. (b) Kiddle, J. J.; Babler, J. H. *Ibid.* **1993**, *58*, 3572.

(8) For the synthesis and synthetic application of phosphonoketene dithioacetals, see: Minami, T.; Okauchi, T.; Matsuki, H.; Nakamura, M.; Ichikawa, J.; Ishida, M. *J. Org. Chem.* **1996**, *61*, 8132.

(9) For the synthetic application of β-oxy- or β-thio-substituted vinylphosphonates, see: (a) Kouno, R.; Okauchi, T.; Nakamura, M.; Ichikawa, J.; Minami, T. *J. Org. Chem.* **1998**, *63*, 6239. (b) Minami, T.; Kouno, R.; Okauchi, T.; Nakamura, M.; Ichikawa, J. *Phosphorus, Sulfur, and Silicon* **1999**, *146*, 689.

(10) For the synthesis of phosphono-substituted heterocyclic compounds, see, for examples: (a) Yuan, C.; Huang, W.; Onnis, V. *Synthesis* **1993**, 473. (b) Attanasi, O. A.; Filippone, P.; Giovagnoli, D.; Mei, A. *Ibid.* **1994**, 181. (c) Leost, F.; Chantegrel, B.; Deshayes, C. *Tetrahedron* **1998**, *54*, 6457. (d) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J. *Ibid.* **1999**, 55, 5947. (e) Schrader, T.; Steglich, W. *Synthesis* **1990**, 1153. (f) Loussouarn, A.; Servant, G.; Guervenou, J.; Sturtz, G. *Phosphorus, Sulfur, and Silicon* **1996**, *113*, 275.

(11) For biologically active phosphono-substituted heterocyclic compounds, see, for example: Seto, K.; Tanaka, S.; Sakoda, R.; Sakai, T.; Masuda, Y. EP 230944, 1987; *Chem. Abstr.* **1987**, *107*, 237009a.

10.1021/jo000149t CCC: $19.00
Published on Web 06/17/2000

Table 1. Reaction of α-Phosphonovinyl Anion with Aldehydes or Ketones[a]

entry	R	R'	reaction time / h	product[b] (yield , %)
1	Ph	H	1.0	**2a** (95)
2		H	1.0	**2b** (96)
3		H	2.0	**2c** (quant)
4	*t*-Bu	H	4.0	**2d** (88)
5	*n*-C_5H_{11}	H	3.5	**2e** (72)
6	$(CH_3)_2C{=}CH(CH_2)_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2$-	H	3.1	**2f** (79)
7	Me	Me	2.0	**2g** (67)
8	Ph	Ph	3.0	**2h** (87)
9	-$(CH_2)_5$-		0.5	**2i** (77)
10	(*E*)-PhCH=CH-	H	1.0	**2j** (93)
11	(*E*)-CH_3CH=CH-	H	1.0	**2k** (87)
12	$(CH_3)_2$C=CH-	H	2.0	**2l** (96)
13	-$(CH_2)_3$-CH=CH-		2.0	**2m** (50)[c]

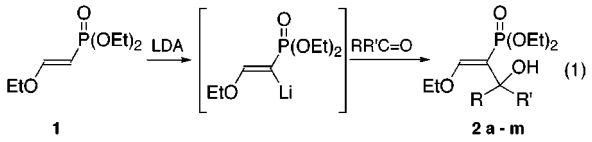
[a] All reactions were carried out in THF at -78°C. [b] Isolated yield. [c] Unreacted **1** (43%) was recovered.

Table 2. Reaction of α-Phosphonovinyl Anion with Phenyl Isocyanate[a]

entry	Additive (equiv)	PhNCO (equiv)	product / yield (%)[b]	
			3	**4**
1	none	1.5	17	35
2	$MgCl_2$ (1.1)	1.5	trace	52
3	$MgCl_2$ (1.1)	5.0	—	65

[a] All reactions were carried out in THF at -78°C. [b] Isolated yield.

was carried out to give the desired allylic alcohols **2a**−**i** in good to quantitative yields (eq 1, entries 1−9 in Table 1).[5c]



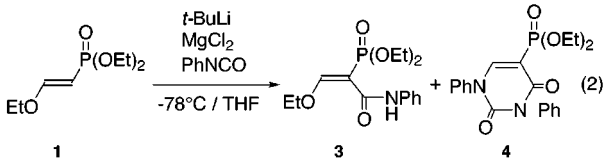
α,β-Unsaturated aldehydes or ketone such as crotonaldehyde or 2-cyclohexen-1-one were also reacted with the α-phosphonovinyl anion to produce exclusively the 1,2-addition products **2j**−**m** in good to moderate yields (entries 10−13), and no conjugate addition product was observed.[12]

We further attempted to trap the α-phosphonovinyl anion with phenyl isocyanate instead of aldehydes and ketones. The reaction of the α-phosphonovinyl anion with phenyl isocyanate (1.5 equiv) under similar conditions interestingly afforded 1,3-diphenyl-5-phosphonouracil **4** in 35% yield in addition to an expected β-ethoxy-α-(*N*-phenylaminocarbonyl)vinylphosphonate **3** (17%) (eq 2, entry 1 in Table 2). Use of excess amount of phenyl isocyanate (1.5−5.0 equiv) in the presence of $MgCl_2$ increased the yield up to 52−65% with high selectivity as expected (eq 2, entries 2 and 3).

Table 3. Synthesis of α-Formylvinylphosphonates[a,b]

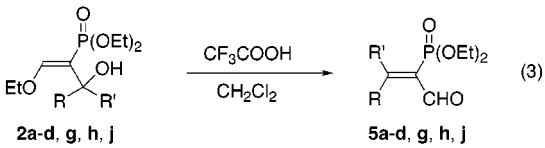
entry	starting material	R	R'	product[c] (Yield , %)
1	**2a**	Ph	H	**5a** (99)
2	**2b**		H	**5b** (98)
3	**2c**		H	**5c** (97)
4	**2d**	*t*-Bu	H	**5d** (99)
5	**2g**	Me	Me	**5g** (98)
6	**2h**	Ph	Ph	**5h** (96)
7	**2j**	(*E*)-PhCH=CH	H	**5j** (95)

[a] All reactions were carried out in CH_2Cl_2 at 0°C. [b] 5 equiv of trifluoroacetic acid was used. [c] Isolated yield.



The formation of the uracil **4** can be explained by a sequence of stepwise addition of the α-phosphonovinyl anion to two molecules of phenyl isocyanate, intramolecular conjugate addition of the resulting amide anion to the β-carbon of the vinylphosphonate, and elimination of an ethoxide anion. This reaction suggests a possible method for the synthesis of various 1,3-disubstituted-5-phosphono uracils.

Synthesis of α-Formylvinylphosphonates. In analogy to acid-catalyzed conversion of α-(hydroxymethyl)-phosphonoketene dithioacetals into phosphonodithioacrylates,[8] the related β-ethoxy-α-(hydroxymethyl)vinylphosphonates **2** were treated under acidic conditions. Treatment of allylic alcohol **2a** with trifluoroacetic acid in CH_2Cl_2 at 0 °C gave α-formyl-β-phenylvinylphosphonate **5a** in quantitative yield (eq 3, entry 1 in Table 3).[13]



Similar treatment of the other allylic alcohols **2b**−**d**,**g**,**h**,**j** readily led to α-formylvinyl or α-formyldienylphosphonates, **5b**−**d**,**g**,**h**,**j**, either as *E*-isomer or as a mixture of *E*- and *Z*-isomers,[14] in high yields (entries 2−7 in Table 3). These results indicate that β-ethoxy-α-phosphonovinyl anion can be considered as a convenient synthon of a phosphonoacetaldehyde anion. This procedure has proven to be a useful method for the synthesis of a wide range of α-formylvinylphosphonates.[15]

In contrast to **2j**, the closely related allylic alcohol **2k** was similarly exposed to trifluoroacetic acid (5.0 equiv) at 0 °C to afford a 1:1 mixture of 1-formyl-1,3-pentadienylphosphonate **5k** and 2-methyl-5-phosphonopyran **6k**

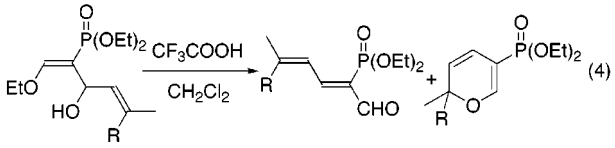
(12) Only 1,2-adduct products were produced even in the presence of the Cu(I) salt.

(13) For acid-catalyzed conversion of (hydroxymethyl)vinyl ethers into unsaturated aldehydes, see: (a) Vlattas, I.; Vecchia, L. D.; Lee, A. O. *J. Am. Chem. Soc.* **1976**, *98*, 2008. (b) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595.

(14) The stereochemistry was determined on the basis of the phosphorus−vinyl proton coupling constant, see: Xu, Y.; Flavin, M. T.; Xu, Z.-Q. *J. Org. Chem.* **1996**, *61*, 7697 and references therein.

(15) For the synthesis of limited α-formylvinylphosphonates such as 1-formyl-1-propenylphosphonate and 2-amino-1-(formyl)vinylphosphonate, see (a) Al-Badri, H.; About-Jaudet, E.; Combret, J.-C.; Collignon, N. *Synthesis* **1995**, 1401. (b) Aboujaoude, E. E.; Collignon, N. *Tetrahedron* **1985**, *41*, 433.

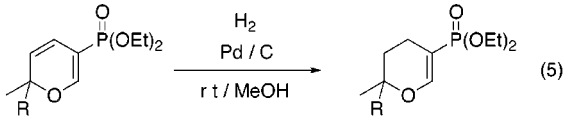
in 92% yield.[16] Furthermore, the homologous allylic alcohol **2l** on similar treatment with the acid gave a 1:4 mixture of the corresponding aldehyde **5l** and phosphonopyran **6l** in 93% yield (eq 4).[17]



(4)

2 k : R = H **5 k**: R = H **6 k**: R = H (92% ; **5 k**:**6 k**=1:1)
2 l : R = Me **5 l** : R = Me **6 l** : R = Me (93% ; **5 l**:**6 l**=1:4)

The aldehydes **5** and pyrans **6** were inseparable. Hydrogenation of each mixture of **5** and **6** over Pd/C was carried out resulting in partially reduced 3,4-dihydro-5-phosphono-2*H*-pyrans **7k**[18] and **7l** in 43% and 67% overall yields from **2k** and **2l**, respectively, which were successfully isolated in pure form (eq 5).



(5)

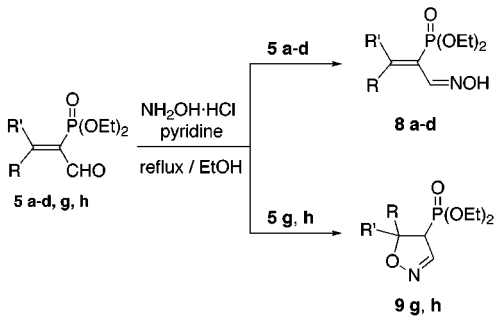
6 k : R = H
6 l : R = Me

7 k : R = H
7 l : R = Me

These results suggest that such an electrocyclic reaction of **2** to give phosphonopyran derivatives requires the alkyl substituent on the *δ*-carbon of the α-formyldienylphosphonates.

The above observation prompted us to develop a new synthesis of phosphono-containing fused pyrans via the intramolecular hetero Diels−Alder reaction of an α-formylvinylphosphonate moiety with a dialkyl-substituted ene component.[19,20] The allylic alcohol **2f**, derived from citoronellal and the α-phosphonovinyl anion, was similarly treated with the acid to afford a trans-fused pyran **6f** in 58% yield (eq 6). Accordingly, the formation of **6f** can be rationalized by considering that in situ generated α-formylvinylphosphonate moiety acted as a heterodiene.

Scheme 1



5 a-d, g, h

8 a-d

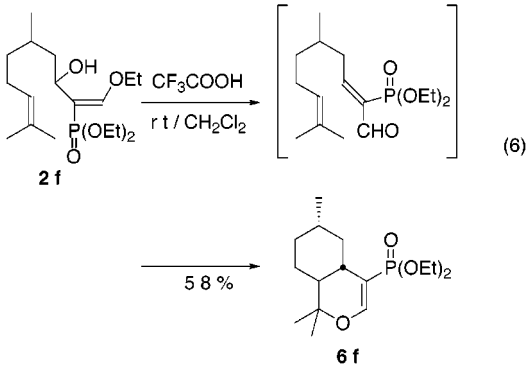
9 g, h

Table 4. Reaction of α-Formylvinylphosphonates with Hydroxylamine[a,b]

entry	starting material	R	R′	reaction time / h	product[c,d] (yield / %)
1	**5 a**	Ph	H	23	**8 a** (53)
2	**5 b**		H	9.0	**8 b** (60)
3	**5 c**		H	5.0	**8 c** (69)
4	**5 d**	*t*-Bu	H	9.0	**8 d** (61)
5	**5 g**	Me	Me	9.0	**9 g** (76)
6	**5 h**	Ph	Ph	9.0	**9 h** (74)

[a] All reactions were carried out in ethanol under reflux. [b] 1.2 equiv of hydroxylamine hydrochloride and 1.3 equiv of pyridine were used. [c] Isolated yield. [d] Overall yield from corresponding allylic alcohol **2**.

The stereochemical assignment of **6f** was made on the lack of an NOE between the protons at the ring fusion.



2 f

6 f

Thus, an α-formylvinylphosphonate moiety was recognized to function as a novel type of phosphono-modified heterodiene in hetero Diels−Alder reaction.

Synthesis of Phosphorus-Functionalized Heterocycles. We have recently reported a convenient synthesis of phosphono-substituted heterocyclic compounds via the reaction of α-acyl-*β*-heteroatom-substituted vinylphosphonates with bifunctional heteronucleophiles.[9] Having accomplished the convenient synthesis of more reactive α-formylvinylphosphonates as shown above, we next focused on their synthetic application to various types of heterocyclic compounds via condensation-intramolecular 1,4-addition sequence. *β*,*β*-Disubstituted-α-formylvinylphosphonates **5g** and **5h** were treated with hydroxylamine hydrochloride (1.2 equiv) and pyridine (1.3 equiv) in ethanol under reflux to afford 4,5-dihydro-4-phosphono-5,5-disubstituted isoxazoles **9g** (76%) and **9h** (74%), respectively, while similar reaction using *β*-monosubstituted-α-formylvinylphosphonates **5a**−**d** failed to give the

(16) Isolation of each of the products **5k** and **6k** in pure form was unsuccessful, but the **5**/**6** ratios were determined by ^{1}H NMR analysis (see Experimental Section).

(17) Although contamination of a small amount of unidentified aldehyde other than **5l** was observed by ^{1}H NMR, its isolation was not attempted.

(18) Diethyl 1-formylpentylphosphonate, which is hydrogenation product of **5k**, was isolated in 37% yield along with **7k**. The structure was identified by comparison of spectral data with those of an authentic sample.

(19) For intramolecular cycloadditions of 1,7-dienes with the carbonyl group on the C-1 carbon, see (a) Tietze, L. F.; Kiedrowski, G. v. *Tetrahedron Lett.* **1981**, *22*, 219. (b) Minami, T.; Utsunomiya, T.; Nakamura, S.; Okubo, M.; Kitamura, N.; Okada, Y.; Ichikawa, J. *J. Org. Chem.* **1994**, *59*, 6717 and references therein.

(20) For hetero Diels−Alder reaction of α,*β*-unsaturated acylphosphonates with enol ethers, see, for example, Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1988**, *110*, 4895.

(21) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734 (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L. I. Silberman, L.; Thomas, R. C. *Ibid* **1976**, 736. (c) Baldwin, J. E.; Thomas, R. C.; Cutting, J.; Dupont, W.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846.

(22) Although the compound **10** is composed of a single isomer, its stereochemical assignment was not made.

(23) For the synthesis of fluorinated pyrazoles from the reaction of 2,2-difluorovinyl ketones with hydrazines, see: Ichikawa, J.; Kobayashi, M.; Noda, Y.; Yokota, N.; Amano, K.; Minami, T. *J. Org. Chem.* **1996**, *61*, 2763.

(24) For the synthesis of pyrazole from the reaction of α-oxo ketene dithioacetals with hydrazine, see, a review: Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029. See also ref 15b.

Scheme 2

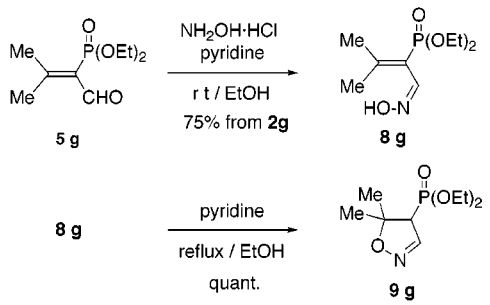


Table 5. Synthesis of Phosphono-Substituted Dihydropyrazoles 11[a,b]

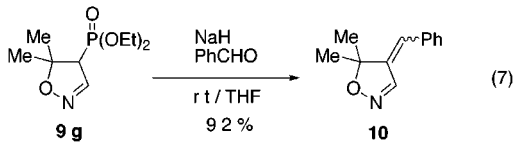
entry	starting material	R	R'	reaction time / h	product[c,d] (yield , %)
1	**5a**	Ph	H	11	**11a** (84)
2	**5b**		H	18	**11b** (75)
3	**5c**		H	17	**11c** (80)
4	**5d**	*t*-Bu	H	16	**11d** (88)
5	**5g**	Me	Me	20	**11g** (81)
6	**5h**	Ph	Ph	26	**11h** (71)

[a] All reactions were carried out in ethanol at room temperature. [b] Excess amounts of hydrazine monohydrate (15 equiv) was used. [c] Isolated yield. [d] Overall yield from corresponding allylic alcohol **2**.

corresponding isoxazoles and only oximes **8a**−**d** were formed in 53−69% yields (Scheme 1, Table 4).

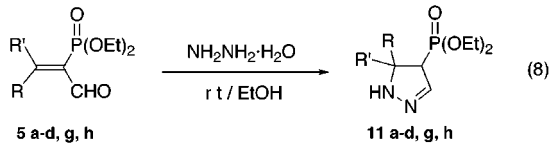
Treatment of the independently prepared oxime **8g** with 1.3 equiv of pyridine in ethanol under reflux for 9 h afforded the isoxazole **9g** in quantitative yield (Scheme 2). This result demonstrates that the oxime **8g** clearly underwent the 5-endo-trigonal cyclization to give the isoxazole **9g**, although the 5-endo-trigonal cyclizations have been generally thought to be disfavored in Baldwin's rules.[21] Accordingly, this cyclization is of interest from view of both synthetic and mechanistic points.

For synthetic applications of the obtained phosphonoisoxazoles, the isoxazole **9g** was subjected to the Wittig−Horner reaction with benzaldehyde to give an expected 4-benzylidene-5,5-dimethylisoxazole **10** in good yield (92%) (eq 7).[22]



(7)

Next, the reaction of **5** with various nitrogen-containing nucleophiles carrying a group such as NH_2 and SH was similarly examined. Treatment of the α-formylvinylphosphonates **5a**−**d**,**g**,**h** with hydrazine led to the corresponding 4,5-dihydro-4-phosphonopyrazoles **11a**−**d**,**g**,**h** in good yields, regardless of *β*-substituents of the α-formylvinylphosphonates (eq 8 and Table 5).[23, 24]



(8)

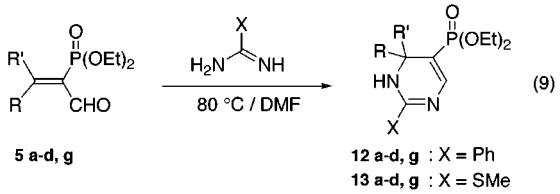
Similar to phosphonoisoxazoles, the formation of the pyrazoles may be explained by 5-endo-trigonal addition

Table 6. Synthesis of Phosphono-Substituted Dihydropyrimidines 12 and 13 from 5 and Bifunctional Nucleophiles[a]

entry	starting material	R	R'	bifunctional[b] nucleophile	reaction time / h	product[c,d] (yield , %)
1	**5a**	Ph	H	**A**	16	**12a** (62)
2	**5b**		H	**A**	15	**12b** (28)
3	**5c**		H	**A**	11	**12c** (49)
4	**5d**	*t*-Bu	H	**A**	17	**12d** (41)
5	**5g**	Me	Me	**A**	19	**12g** (52)
6	**5a**	Ph	H	**B**	11	**13a** (95)
7	**5b**		H	**B**	15	**13b** (63)
8	**5c**		H	**B**	27	**13c** (58)
9	**5d**	*t*-Bu	H	**B**	10	**13d** (70)
10	**5g**	Me	Me	**B**	13	**13g** (75)

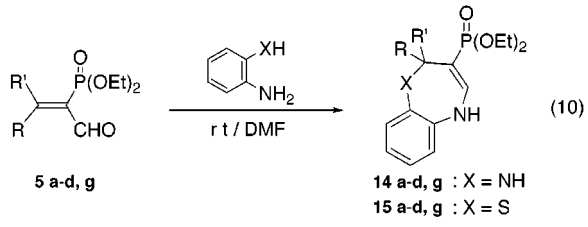
[a] All reactions were carried out in DMF at 80°C in the presence of pyridine (1.3 equiv). [b] **A**:1.2 equiv of $NH_2C(Ph)NH·HCl$ was used. **B**:0.6 equiv of $(NH_2C(SMe)NH)_2·H_2SO_4$ was used. [c] Isolated yield. [d] Overall yield from corresponding allylic alcohol **2**.

of an amino nucleophile of initially formed hydrazones to the *β*-carbon of vinylphosphonates. Treatment of **5a**−**d**,**g** with benzamidine or *S*-methylisothiourea led to the corresponding six-membered heterocyclic compounds, 2-phenyl- or 2-(methylthio)-5-phosphonopyrimidines **12a**−**d**,**g** or **13a**−**d**,**g** in moderate to good yields (eq 9 and Table 6).



(9)

Furthermore, use of 1,2-phenylenediamine or 2-sulfanylbenzenamine as a bifunctional nucleophile led to phosphono-functionalized dihydrodiazepines **14a**−**d**,**g**[15b] or dihydrothiazepines **15a**−**d**,**g** in comparable yields. These reactions may also involve a sequence of dehydration−conjugate addition of 1,2-phenylenediamine or 2-sulfanylbenzenamine with α-formylvinylphosphonates **5** (eq 10 and Table 7).



(10)

Thus, the α-formylvinylphosphonates **5** undergo cyclocondensation reaction with a wide variety of nitrogen nucleophiles bearing an NH_2, OH, or SH group to give phosphono-substituted heterocyclic compounds.

Conclusion. We note the following results from this investigation: (1) α-phosphonovinyl anion reacted with various types of aldehydes and ketones or an isocyanate to afford α-(hydroxymethyl)vinylphosphonates or uracils in good to moderate yield; (2) *β*-substituted α-formylvinylphosphonates were easily synthesized from corre-

Table 7. Synthesis of Phosphono-Substituted Dihydrodiazepines 14 and Dihydrothiazepines 15 from 5 and Bifunctional Nucleophiles [a]

entry	starting material	R	R'	bifunctional[b] nucleophile	reaction time / h	product [c,d] (yield , %)
1	**5a**	Ph	H	**A**	17	**14a** (56)
2	**5b**		H	**A**	11	**14b** (71)
3	**5c**		H	**A**	12	**14c** (72)
4	**5d**	*t*-Bu	H	**A**	15	**14d** (59)
5	**5g**	Me	Me	**A**	15	**14g** (65)
6	**5a**	Ph	H	**B**	15	**15a** (55)
7	**5b**		H	**B**	13	**15b** (76)
8	**5c**		H	**B**	37	**15c** (32)
9	**5d**	*t*-Bu	H	**B**	16	**15d** (79)
10	**5g**	Me	Me	**B**	17	**15g** (83)

[a] All reactions were carried out in DMF at room temperature. [b] **A**:1.1 equiv of 1,2-phenylenediamine was used. **B**:1.1 equiv of 2-sulfanylbenzenamine was used. [c] Isolated yield. [d] Overall yield from corresponding allylic alcohol **2**.

sponding α-(hydroxymethyl)vinylphosphonates under acidic conditions; (3) an α-formylvinylphosphonate moiety acted as a good 4π-component in electrocyclic reaction or hetero Diels−Alder reaction; (4) synthetic application of α-formylvinylphosphonate to phosphono-functionalized heterocyclic compounds was developed.

Experimental Section

Materials. Dichloromethane was distilled from P_2O_5. THF was distilled from sodium benzophenone ketyl in a recycling still. Diisopropylamine (DIA), dimethylformamide (DMF), and pyridine were refluxed with CaH_2 and then distilled. Commercial solution of BuLi (3.54 or 1.64 M in hexane) and *t*-BuLi (1.64 M in pentane) were used. The starting material **1** was prepared according to the established procedures.[9]

General. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$, operating ^{1}H NMR at 500.00 MHz, and ^{13}C NMR at 125.65 MHz, with Me_4Si as an internal standard unless otherwise noted. Infrared spectra were recorded of thin films on KBr plates. Mass spectra were recorded at 70 eV by GC inlet or by direct inlet for the thermally labile products. Melting points were measured in open capillary tubes and are uncorrected.

General Procedure for the Synthesis of α-(Hydroxymethyl)vinylphosphonates 2. To a solution of LDA, generated in situ from DIA (0.18 mL, 1.3 mmol) in THF (5.0 mL) and BuLi (1.64 M in hexane, 0.73 mL, 1.2 mmol) at −78 °C for 1.3 h under nitrogen atmosphere, was added dropwise a solution of **1** (208 mg, 1.0 mmol) in THF (2.0 mL), and the mixture was stirred at this temperature for 1.0 h. A carbonyl reagent (1.5 mmol) was added, and the reaction mixture was stirred for 0.5−4.0 h. The reaction was quenched by the addition of phosphate buffer (pH = 7), and the organic layer was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane = 2:1) to give **2**. The reaction conditions and yields of **2a**−**m** were summarized in Table 1. The compound **2a** had the following properties. The properties for compounds **2b**−**m** were provided in the Supporting Information.

Diethyl (*E*)-1-ethoxy-3-hydroxy-3-phenyl-1-propen-2-ylphosphonate (2a): colorless oil; IR 3401, 1625, 1025 cm^{-1}; ^{1}H NMR δ 1.13 (3 H, t, J = 7.0 Hz), 1.19 (3 H, t, J = 7.0 Hz), 1.33 (3 H, t, J = 7.3 Hz), 2.14 (1 H, brs), 3.71−4.14 (6 H, m), 5.77 (1 H, dd, $^3J_{P-H}$ = 23.2 Hz, J = 8.2 Hz), 7.00 (1 H, d, $^3J_{P-H}$ = 10.7 Hz), 7.19−7.23 (1 H, m), 7.29−7.32 (2 H, m), 7.43−7.45 (2 H, m); ^{13}C NMR δ 15.3, 16.1 (d, $^3J_{P-C}$ = 5.2 Hz), 61.8 (d, $^2J_{P-C}$ = 5.2 Hz), 68.6 (d, $^2J_{P-C}$= 5.2 Hz), 70.6, 107.9 (d, $^1J_{P-C}$= 188.1 Hz), 125.7, 126.9, 128.0, 143.4 (d, $^3J_{P-C}$= 2.0 Hz), 158.3 (d, $^2J_{P-C}$= 24.8 Hz); MS m/z 314 (M^+). Anal. Calcd for $C_{15}H_{23}O_5P_1$: C, 57.32; H, 7.38. Found: C, 56.92; H, 7.39.

Reaction of the α-Phosphonovinyl Anion with Phenyl Isocyanate. Procedure A. To a solution of **1** (101 mg, 0.49 mmol) in THF (5.0 mL) at −78 °C was added dropwise *t*-BuLi (0.30 mL, 0.49 mmol) under a nitrogen atmosphere. After the solution was stirred for 45 min, phenyl isocyanate (0.73 mmol) in THF (2.0 mL) was added, and the mixture was stirred at this temperature for 1.5 h. After similar workup as above, the residue was purified by preparative TLC silica gel (AcOEt:hexane = 2:1) to give **3** (27 mg, 17%) and **4** (68 mg, 35%).

Procedure B. To a solution of **1** (96.3 mg, 0.46 mmol) in THF (5.0 mL) at −78 °C was added dropwise *t*-BuLi (0.28 mL, 0.46 mmol) under a nitrogen atmosphere. After the solution was stirred for 45 min, magnesium chloride (48.4 mg, 0.51 mmol) was added. After magnesium chloride was completely dissolved, phenyl isocyanate (2.3 mmol) in THF (2.0 mL) was added, and the mixture was stirred at this temperature for 3.0 h. After similar workup as above, the residue was chromatographed on silica gel (AcOEt:hexane = 2:1) to give **4** (120 mg, 65%). The compounds **3** and **4** had the following properties.

Diethyl (*E*)-2-ethoxy-1-(*N*-phenylaminocarbonyl)vinylphosphonate (3): colorless oil; IR 1668, 1024 cm^{-1}; ^{1}H NMR δ 1.36 (6 H, t, J = 7.0 Hz), 1.48 (3 H, t, J = 7.0 Hz), 4.11−4.25 (4 H, m), 4.33 (2 H, q, J = 7.0 Hz), 7.07−7.10 (1 H, m), 7.28−7.33 (2 H, m), 7.55−7.56 (2 H, m), 7.59 (1 H, d, $^3J_{P-H}$ = 11.6 Hz), 8.78 (1 H, brs); ^{13}C NMR δ 15.3, 16.3 (d, $^3J_{P-C}$ = 6.2 Hz), 62.7 (d, $^2J_{P-C}$ = 5.2 Hz), 73.1, 103.2 (d, $^1J_{P-C}$ = 192.2 Hz), 119.8, 124.0, 128.9, 138.0, 160.7 (d, $^2J_{P-C}$ = 9.3 Hz), 165.3 (d, $^2J_{P-C}$ = 21.6 Hz); MS m/z 327 (M^+); HRMS calcd for $C_{15}H_{22}O_5P_1N_1$ 327.1234 (M^+); found 327.1203.

Diehyl *N*,*N*-diphenyl-2,4(1*H*,3*H*)pyrimidinediono-4-ylphosphonate (4): white solid; mp 48.0−50.0 °C; IR 1729, 1681, 1022 cm^{-1}; ^{1}H NMR δ 1.36 (6 H, t, J = 7.0 Hz), 4.21−4.31 (4 H, m), 7.27−7.29 (2 H, m), 7.38−7.51 (8 H, m), 8.20 (1 H, d, $^3J_{P-H}$ = 13.5 Hz); ^{13}C NMR δ 16.4 (d, $^3J_{P-C}$ = 6.3 Hz), 63.4 (d, $^2J_{P-C}$ = 6.3 Hz), 103.2 (d, $^1J_{P-C}$ = 208.7 Hz), 126.4, 128.2, 129.0, 129.4, 129.4, 129.6, 134.3, 138.4, 150.6, 151.9 (d, $^2J_{P-C}$ = 15.6 Hz), 160.6 (d, $^2J_{P-C}$ = 9.3 Hz); MS m/z 400 (M^+); HRMS calcd for $C_{20}H_{21}O_5P_1N_2$ 400.1187 (M^+); found 400.1185.

General Procedure for the Synthesis of α-Formylvinylphosphonates 5a−d,g,h,j. To a solution of **2a**−**d**,**g**,**h**,**j** (0.5 mmol) in CH_2Cl_2 (5.0 mL) was added trifluoroacetic acid (0.20 mL, 2.5 mmol) at 0 °C, and the mixture was stirred at this temperature for 0.5 h. The reaction was quenched by the addition of phosphate buffer (pH = 7), and the organic layer was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane = 2:1) to give **5a**−**d**,**g**,**h**,**j**. The reaction conditions and yields of **5a**−**d**,**g**,**h**,**j** were summarized in Table 3. The compound **5j** had the following properties. The properties for compounds **5a**−**d**,**g**,**h** were provided in the Supporting Information.

Diethyl (3*E*)-1-formyl-4-phenyl-1,3-butadienylphosphonate (5j): yellow oil; IR (*E*, *Z* mixture) 1683, 1608, 1577, 1556, 1024 cm^{-1}; ^{1}H NMR (*E*, *Z* mixture) δ 1.36 (6 H, t, J = 7.0 Hz), 4.10−4.25 (4 H, m), 7.21 (0.5 H, d, J = 15.5 Hz), 7.22 (0.5 H, d, J = 15.5 Hz), 7.38−7.43 (3 H, m), 7.56−7.60 (1 H, m), 7.60−7.64 (1 H, m), 7.79 (0.5 H, dd, $^3J_{P-H}$ = 20.2 Hz, J = 11.5 Hz), 7,79 (0.5 H, dd, $^3J_{P-H}$ = 42.0 Hz, J = 11.5 Hz), 8.02 (0.5 H, ddd, $^4J_{P-H}$ = 2.0 Hz, J = 11.5, 15.5 Hz), 8.19 (0.5 H, ddd, $^4J_{P-H}$ = 20.2 Hz, J = 11.5, 15.5 Hz), 9.66 (0.5 H, d, $^3J_{P-H}$ = 13.7 Hz), 10.01 (0.5 H, d, $^3J_{P-H}$ = 10.5 Hz); ^{13}C NMR δ 16.4 (d, $^3J_{P-C}$ = 6.2 Hz), 16.4 (d, $^3J_{P-C}$ = 6.2 Hz), 62.4 (d, $^2J_{P-C}$ = 6.2 Hz), 62.5 (d, $^2J_{P-C}$ = 5.2 Hz), 122.6 (d, $^3J_{P-C}$ = 19.7 Hz), 124.7 (d, $^3J_{P-C}$ = 5.2 Hz), 124.9 (d, $^1J_{P-C}$ = 180.0 Hz), 126.9 (d, $^1J_{P-C}$ = 177.9 Hz), 128.5, 128.6, 129.0, 129.1, 130.8, 135.1, 135.3, 149.4, 149.4, 149.8, 156.9 (d, $^2J_{P-C}$ = 8.3 Hz), 160.6 (d, $^2J_{P-C}$ = 9.3 Hz), 188.7 (d, $^2J_{P-C}$ = 12.4 Hz), 190.9 (d, $^2J_{P-C}$ = 12.4 Hz). Anal. Calcd for $C_{15}H_{19}O_4P_1$: C, 61.22; H, 6.51. Found (*E*, *Z* mixture): C, 61.15; H, 6.59.

Treatment of Allylic Alcohol 2l with Trifluoroacetic Acid. To a solution of **2l** (150 mg, 0.51 mmol) in CH_2Cl_2 (4.0

mL) was added trifluoroacetic acid (0.20 mL, 2.6 mmol) at 0 °C, and the mixture was stirred for 6.0 h at this temperature. After similar workup as above, the residue was purified by preparative TLC silica gel (AcOEt:hexane = 1:1) to give diethyl (1*Z*)-1-formyl-4-methyl-1,3-pentadienylphosphonate (**5l**) and diethyl 2,2-dimethyl-2*H*-pyran-5-ylphosphonate (**6l**) as a 1:4 mixture (118 mg, 0.48 mmol, 93%): ^{1}H NMR δ 1.31−1.35 (7.5 H, m), 1.40 (6 H, s), 2.04−2.06 (1.5 H, m), 4.01−4.15 (5 H, m), 5.24 (1 H, dd, J = 8.5 Hz, $^4J_{P-H}$ = 3.5 Hz), 5.85 (1 H, dd, J = 8.5 Hz, $^3J_{P-H}$ = 8.5 Hz), 7.09 (1 H, d, $^3J_{P-H}$ = 8.5 Hz), 7.13 (0.12 H, d, J = 12.5 Hz), 7.24 (0.12 H, d, J = 12.5 Hz), 7.97 (0.12 H, dd, J = 12.5 Hz, $^3J_{P-H}$ = 43.0 Hz), 8.03 (0.12 H, dd, J = 12.5 Hz, $^3J_{P-H}$ = 15.0 Hz), 9.64 (0.12 H, d, $^3J_{P-H}$ = 12.0 Hz), 10.09 (0.12 H, d, $^3J_{P-H}$ = 15.0 Hz); ^{13}C NMR δ 16.3 (d, $^3J_{P-C}$ = 6.2 Hz), 19.3, 19.4, 27.7, 27.9, 28.0, 61.6 (d, $^2J_{P-C}$ = 6.3 Hz), 62.2 (d, $^2J_{P-C}$ = 6.2 Hz), 62.3 (d, $^2J_{P-C}$ = 4.1 Hz), 77.9, 99.8 (d, $^1J_{P-C}$ = 206.7 Hz), 117.4 (d, $^3J_{P-C}$ = 8.2 Hz), 120.5 (d, $^3J_{P-C}$ = 18.6 Hz), 123.1, 124.1 (d, $^2J_{P-C}$ = 12.4 Hz), 124.4 (d, $^1J_{P-C}$ = 179.4 Hz), 153.0 (d, $^2J_{P-C}$ = 8.3 Hz), 155.6 (d, $^2J_{P-C}$ = 22.7 Hz), 155.7 (d, $^2J_{P-C}$ = 9.3 Hz), 158.2, 158.6, 188.9 (d, $^2J_{P-C}$ = 10.4 Hz), 191.3 (d, $^2J_{P-C}$ = 12.4 Hz). Isolation of each compound as pure sample was unsuccessful.

Hydrogenation of this mixture was accomplished under a hydrogen atmosphere (balloon) at room temperature for 12 h in EtOH (4.0 mL) containing palladium on activated carbon (10%, 12 mg). After removal of the catalyst by filtration and concentration of the filtrate in vacuo, the residue was chromatographed on silica gel (AcOEt:hexane = 1:1) to give diethyl 3,4-dihydro-2,2-dimethyl-2*H*-pyran-5-ylphosphonate **7l** (85.6 mg, 0.34 mmol, 67%) as a colorless oil.: IR 1623, 1025 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.98 (6 H, s), 1.10 (6 H, t, J = 7.0 Hz), 1.22 (2 H, t, J = 6.4 Hz), 2.10 (2 H, dt, $^3J_{P-H}$ = 6.4 Hz, J = 6.4 Hz), 3.91−4.04 (4 H, m), 7.49 (1 H, d, $^3J_{P-H}$ = 11.0 Hz); ^{13}C NMR δ 16.5 (d, $^3J_{P-C}$ = 6.2 Hz), 18.1 (d, $^2J_{P-C}$ = 11.1 Hz), 26.3, 32.1 (d, $^3J_{P-C}$ = 10.3 Hz), 61.1 (d, $^2J_{P-C}$ = 5.3 Hz), 75.1, 98.5 (d, $^1J_{P-C}$ = 198.4 Hz), 154.7 (d, $^2J_{P-C}$ = 24.9 Hz). Anal. Calcd for $C_{11}H_{21}O_4P_1$: C, 53.22; H, 8.52. Found: C, 53.19; H, 8.49.

Synthesis of Diethyl (4a*S,6*S**,8a*S**)-1,1,6-Trimethyl-4a,5,6,7,8,8a-hexahydro-1*H*-2-benzopyran-4-ylphosphonate (6f).** To a solution of **2f** (102 mg, 0.28 mmol) in CH_2Cl_2 (5.0 mL) was added trifluoroacetic acid (0.11 mL, 1.4 mmol) at 0 °C, and the mixture was warmed to room temperature and stirred for 6.0 h. After similar workup as above, the residue was purified by preparative TLC silica gel (AcOEt:$CHCl_3$ = 1:1) to give diastereomerically pure phosphonopyran **6f** (51 mg, 58%) as a colorless oil: IR 1727, 1027 cm^{-1}; ^{1}H NMR δ 0.74−0.82 (1 H, m), 0.93 (3 H, d, J = 6.7 Hz), 0.98−1.05 (2 H, m), 1.11 (3 H, s), 1.21−1.26 (1 H, m), 1.31 (3 H, s), 1.33 (6 H, t, J = 7.1 Hz), 1.43−1.47 (1 H, m), 1.73−1.81 (2 H, m), 1.96−2.00 (1 H, m), 2.26−2.28 (1 H, m), 3.97−4.12 (4 H, m), 7.08 (1 H, d, $^3J_{P-H}$ = 11.0 Hz); ^{13}C NMR δ 16.2 (d, $^3J_{P-C}$ = 10.3 Hz), 19.9, 22.3, 27.1, 27.1, 32.2, 33.8 (d, $^2J_{P-C}$ = 6.3 Hz), 34.9, 39.1, 47.1 (d, $^3J_{P-C}$ = 10.4 Hz), 61.1 (d, $^2J_{P-C}$ = 16.5 Hz), 79.3, 101.6 (d, $^1J_{P-C}$ = 192.2 Hz), 154.7 (d, $^2J_{P-C}$ = 24.8 Hz). Anal. Calcd for $C_{16}H_{29}O_4P_1$: C, 60.74; H, 9.24. Found: C, 60.49; H, 9.20.

General Procedure for the Preparation of Oximes 8a−d and Isoxazoles 9g,h. To a solution of hydroxylamine hydrochloride (1.2 equiv) and pyridine (1.3 equiv) in EtOH was added a solution of **5a**−**d**,**g**,**h** in EtOH at room temperature. After the reaction mixture was stirred at reflux for 5.0−23 h, the reaction was quenched by the addition of phosphate buffer (pH = 7), and the organic layer was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt:hexane = 1:1) to give oximes **8a**−**d** or isoxazoles **9g**,**h**. The reaction conditions and yields of **8a**−**d**, **9g**,**h** were summarized in Table 4. The compounds **8a** and **9g** had the following properties. The properties for compounds **8b**−**d**, **9h** were provided in the Supporting Information.

Diethyl (*E*)-1-(hydroxyimino)-3-phenyl-2-propen-2-ylphosphonate (8a): white solid; mp 69.0−71.0 °C; IR 3174, 1483 cm^{-1}; ^{1}H NMR δ 1.36 (6 H, t, J = 7.0 Hz), 4.17−4.23 (4 H, m), 7.36−7.41 (5 H, m), 7.84 (1 H, d, $^3J_{P-H}$ = 7.0 Hz), 8.84 (1 H, d, $^3J_{P-H}$ = 7.0 Hz), 9.76 (1 H, brs); ^{13}C NMR δ 16.3 (d, $^3J_{P-C}$ = 6.2 Hz), 62.6 (d, $^2J_{P-C}$ = 5.2 Hz), 123.8 (d, $^1J_{P-C}$ = 181.9 Hz), 128.7, 129.6, 129.9, 134.3 (d, $^3J_{P-C}$ = 19.6 Hz), 145.7 (d, $^2J_{P-C}$ = 6.2 Hz), 148.5 (d, $^2J_{P-C}$ = 7.2 Hz); MS *m*/*z* 282 (M^+-H). Anal. Calcd for $C_{13}H_{18}O_4P_1N_1$: C, 55.12; H, 6.40; N, 4.93. Found: C, 54.94; H, 6.30; N, 4.82.

Diethyl 4,5-dihydro-5,5-dimethylisoxazol-4-ylphosphonate (9g): colorless oil; IR 1255, 1022 cm^{-1}; ^{1}H NMR δ 1.35 (3 H, t, J = 7.0 Hz), 1.36 (3 H, t, J = 7.0 Hz), 1.48 (3 H, s), 1.57 (3 H, s), 3.34 (1 H, dd, J = 7.0 Hz, $^2J_{P-H}$ = 23.8 Hz), 4.14−4.21 (4 H, m), 7.10 (1 H, dd, J = 7.0 Hz, $^3J_{P-H}$ = 2.0 Hz); ^{13}C NMR δ 16.3 (d, $^3J_{P-C}$ = 6.2 Hz), 16.4 (d, $^3J_{P-C}$ = 6.2 Hz), 22.8 (d, $^3J_{P-C}$ = 5.2 Hz), 28.7 (d, $^3J_{P-C}$ = 11.4 Hz), 54.3 (d, $^1J_{P-C}$ = 147.9 Hz), 62.5 (d, $^2J_{P-C}$ = 7.2 Hz), 62.7 (d, $^2J_{P-C}$ = 7.2 Hz), 85.1, 143.3 (d, $^2J_{P-C}$ = 6.2 Hz). Anal. Calcd for $C_9H_{18}O_4P_1N_1$: C, 45.96; H, 7.71; N, 5.95. Found: C, 45.89; H, 7.74; N, 5.80.

Synthesis of Diethyl 1-(Hydroxyimino)-3-methyl-2-buten-2-ylphosphonate (8g). To a solution of hydroxylamine hydrochloride (1.2 equiv) and pyridine (1.3 equiv) in EtOH was added a solution of **5g** in EtOH at room temperature, and the mixture was stirred at this temperature for 2.5 h. After similar workup as above, the residue was chromatographed on silica gel (AcOEt:hexane = 1:1) to give the oxime **8g** (75% from **2g**) as a colorless oil.: IR 3263, 1616, 1022 cm^{-1}; ^{1}H NMR δ 1.32 (6 H, t, J = 7.1 Hz), 2.03 (3 H, d, $^4J_{P-H}$ = 4.5 Hz), 2.28 (3 H, d, $^4J_{P-H}$ = 2.8 Hz), 4.04−4.15 (4 H, m), 7.96 (1 H, d, $^3J_{P-H}$ = 12.5 Hz), 9.31 (1 H, brs); ^{13}C NMR δ 16.2 (d, $^3J_{P-C}$ = 6.2 Hz), 24.4 (d, $^3J_{P-C}$ = 9.3 Hz), 24.5 (d, $^3J_{P-C}$ = 15.6 Hz), 61.8 (d, $^2J_{P-C}$ = 5.2 Hz), 117.9 (d, $^1J_{P-C}$ = 186.2 Hz), 147.6 (d, $^2J_{P-C}$ = 11.4 Hz), 160.1 (d, $^2J_{P-C}$ = 8.3 Hz); MS *m*/*z* 235 (M^+); HRMS calcd for $C_9H_{18}O_4P_1N_1$ 235.0972 (M^+); found 235.0953.

Cyclization of Oxime 8g. To a solution of **8g** (30.1 mg, 0.13 mmol) in EtOH (3 mL) was added pyridine (0.013 mL, 0.17 mmol) at room temperature, and the mixture was refluxed for 9 h. After similar workup as above, the residue was chromatographed on silica gel (AcOEt:hexane = 1:1) to give **9g** (29.8 mg, 0.13 mmol, quant), whose physical properties were completely consistent with those of **9g** obtained in the above experiment.

Wittig−Horner Reaction of 9g with Benzaldehyde. To a mixture of NaH (11.6 mg, 0.29 mmol) and benzaldehyde (0.037 mL, 0.36 mmol) in THF (3 mL) was added a solution of **9g** (56.8 mg, 0.24 mmol) in THF (1.5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 h. After similar workup, the residue was chromatographed on silica gel (AcOEt:hexane = 1:4) to give 4-benzylidene-4,5-dihydro-5,5-dimethylisoxazole **10** (41.7 mg, 0.22 mmol, 92%) as a colorless oil: IR 2211, 1207 cm^{-1}; ^{1}H NMR δ 1.59 (6 H, s), 7.36−7.45 (5 H, m), 7.74 (1 H, d, J = 1.2 Hz), 7.76 (1 H, d, J = 1.2 Hz); ^{13}C NMR δ 29.5, 72.4, 118.0, 119.6, 128.8, 128.9, 130.2, 133.3, 140.6; MS *m*/*z* 172 ($M^+ - CH_3$); HRMS calcd for $C_{12}H_{13}O_1N_1$ 187.0996 (M^+); found 187.0999.

General Procedure for the Synthesis of Phosphonopyrazoles 11. To a solution of **5a**−**d**,**g**,**h** in EtOH was added hydrazine monohydrate (15 equiv) at room temperature, and the mixture was stirred for 11−26 h. After similar workup, the residue was chromatographed on silica gel (AcOEt:MeOH = 15:1) to give phosphonopyrazoles **11a**−**d**,**g**,**h**. The reaction conditions and yields of **11a**−**d**,**g**,**h** were summarized in Table 5. The compound **11a** had the following properties. The properties for compounds **11b**−**d**,**g**,**h** were provided in the Supporting Information.

Diethyl 4,5-dihydro-5-phenyl-1*H*-pyrazol-4-ylphosphonate (11a): yellow oil; IR 1241, 1022 cm^{-1}; ^{1}H NMR δ 1.28 (3 H, t, J = 7.0 Hz), 1.29 (3 H, t, J = 7.0 Hz), 3.39 (1 H, ddd, J = 1.8, 9.0 Hz, $^2J_{P-H}$ = 21.7 Hz), 4.02−4.19 (4 H, m), 4.98 (1 H, dd, J = 9.0 Hz, $^3J_{P-H}$ = 22.9 Hz), 6.03 (1 H, brs), 6.72 (1 H, dd, J = 1.8 Hz, $^3J_{P-H}$ = 1.8 Hz), 7.26−7.38 (5 H, m); ^{13}C NMR δ 16.3 (d, $^3J_{P-C}$ = 5.2 Hz), 16.4 (d, $^3J_{P-C}$ = 5.2 Hz), 54.3 (d, $^1J_{P-C}$ = 147.9 Hz), 62.6 (d, $^2J_{P-C}$ = 7.3 Hz), 62.7 (d, $^2J_{P-C}$ = 7.3 Hz), 64.1, 126.5, 128.2, 128.9, 136.9 (d, $^2J_{P-C}$ = 6.2 Hz), 141.6 (d, $^3J_{P-C}$ = 10.3 Hz); MS *m*/*z* 282 (M^+). Anal. Calcd for $C_{13}H_{19}O_3P_1N_2$: C, 55.32; H, 6.79; N, 9.92. Found: C, 55.02; H, 6.79; N, 9.61.

General Procedure for the Synthesis of Phosphonopyrimidines 12. To a solution of benzamidine hydrochloride (1.2 equiv) and pyridine (1.2 equiv) in DMF was added a

solution of **5a**−**d**,**g** in DMF at room temperature, and the mixture was stirred at 80 °C for 11−19 h. After similar workup, the residue was chromatographed on silica gel ($CHCl_3$:MeOH = 10:1) to give phosphonopyrimidines **12a**−**d**,**g**. The reaction conditions and yields of **12a**−**d**,**g** are summarized in Table 6. The compound **12a** had the following properties. The properties for compounds **12b**−**d**,**g** were provided in the Supporting Information.

Diethyl 3,4-dihydro-2,4-diphenylpyrimidin-5-ylphosphonate (12a): viscous oil; IR 1664, 1483 cm^{-1}; ^1H NMR ($CDCl_3$ + 5% CF_3COOD) δ 0.99 (3 H, t, J = 7.0 Hz), 1.24 (3 H, t, J = 7.0 Hz), 3.61−3.69 (1 H, m), 3.84−3.95 (1 H, m), 3.98−4.04 (2 H, m), 5.70 (1 H, d, $^3J_{P-H}$ = 6.1 Hz), 7.26−7.48 (6 H, m), 7.55−7.58 (2 H, m), 7.68−7.70 (2 H, m), 7.74−7.78 (1 H, m); ^{13}C NMR δ 15.3 (d, $^3J_{P-C}$ = 7.3 Hz), 15.6 (d, $^3J_{P-C}$ = 6.2 Hz), 55.4 (d, $^2J_{P-C}$ = 15.6 Hz), 64.2 (d, $^2J_{P-C}$ = 6.2 Hz), 64.4 (d, $^2J_{P-C}$ = 7.3 Hz), 107.7 (d, $^1J_{P-C}$ = 208.8 Hz), 124.5, 127.4, 127.5, 129.7, 130.2, 130.6, 132.6 (d, $^2J_{P-C}$ = 18.6 Hz), 136.3, 138.8, 157.8; HRMS (FAB) calcd for $C_{20}H_{24}O_3P_1N_2$ 371.1524 (M^+ + H); found 371.1543.

General Procedure for the Synthesis of Phosphonopyrimidines 13. To a solution of *S*-methylisothiourea sulfate (0.6 equiv) and pyridine (1.3 equiv) in DMF was added a solution of **5a**−**d**,**g** in DMF at room temperature, and the mixture was stirred at 80 °C for 11−27 h. After similar workup, the residue was chromatographed on silica gel (AcOEt:MeOH = 15:1) to give phosphonopyrimidines **13a**−**d**,**g**. The reaction conditions and yields of **13a**−**d**,**g** were summarized in Table 6. The compound **13a** had the following properties. The properties for compounds **13b**−**d**,**g** were provided in the Supporting Information.

Diethyl 3,4-dihydro-2-(methylthio)-4-phenylpyrimidin-5-ylphosphonate (13a): white solid; mp 148.5−150.0 °C; IR 1656, 1492 cm^{-1}; ^1H NMR ($CDCl_3$ + 5% CF_3COOD) δ 0.94 (3 H, t, J = 7.0 Hz), 1.23 (3 H, t, J = 7.0 Hz), 2.60 (3 H, s), 3.52−3.60 (1 H, m), 3.81−3.89 (1 H, m), 3.97 (2 H, dq, $^2J_{P-H}$ = 7.0 Hz, J = 7.0 Hz), 5.42 (1 H, d, $^3J_{P-H}$ = 6.7 Hz), 7.16 (1 H, d, $^3J_{P-H}$ = 14.3 Hz), 7.30−7.31 (2 H, m), 7.38−7.41 (3 H, m); ^{13}C NMR δ 13.0, 15.3 (d, $^3J_{P-C}$ = 7.3 Hz), 15.6 (d, $^3J_{P-C}$ = 6.2 Hz), 56.0 (d, $^2J_{P-C}$ = 14.4 Hz), 63.7 (d, $^2J_{P-C}$ = 5.2 Hz), 63.9 (d, $^2J_{P-C}$ = 6.2 Hz), 106.4 (d, $^1J_{P-C}$ = 208.8 Hz), 127.4, 129.4, 130.2, 132.5 (d, $^2J_{P-C}$ = 18.6 Hz), 138.7, 164.7. Anal. Calcd for $C_{15}H_{21}O_3P_1N_2S_1$: C, 52.93; H, 6.22; N, 8.23. Found: C, 52.57; H, 6.34; N, 7.94.

General Procedure for the Synthesis of Phosphonobenzodiazepines 14. To a solution of **5a**−**d**,**g** in DMF was added a solution of 1,2-phenylenediamine (1.1 equiv) at room temperature, and the mixture was stirred for 11−17 h. After similar workup, the residue was chromatographed on silica gel (AcOEt:MeOH = 15:1) to give phosphonobenzodiazepines **14a**−**d**,**g**. The reaction conditions and yields of **14a**−**d**,**g** were summarized in Table 7. The compound **14d** had the following properties. The properties for compounds **14a**−**c**,**g** were provided in the Supporting Information.

Diethyl 4-*tert*-butyl-4,5-dihydro-1*H*-1,5-benzodiazepin-3-ylphosphonate (14d): yellow solid; mp 131.0−133.0 °C dec; IR 1637, 1502 cm^{-1}; ^1H NMR δ 0.92 (9 H, s), 1.30 (3 H, t, J = 7.0 Hz), 1.31 (3 H, t, J = 7.0 Hz), 3.76 (1 H, d, $^3J_{P-H}$ = 15.3 Hz), 4.00−4.12 (4 H, m), 6.61−6.66 (2 H, m), 6.70−6.74 (1 H, m), 6.77−6.80 (1 H, m), 7.19 (1 H, dd, J = 7.6 Hz, $^3J_{P-H}$ = 17.1 Hz), 7.27 (1 H, brs); ^{13}C NMR δ 16.2 (d, $^3J_{P-C}$ = 5.2 Hz), 16.3 (d, $^3J_{P-C}$ = 5.2 Hz), 28.2, 40.9 (d, $^3J_{P-C}$ = 2.0 Hz), 61.3 (d, $^2J_{P-C}$ = 5.2 Hz), 61.3 (d, $^2J_{P-C}$ = 4.1 Hz), 66.6 (d, $^2J_{P-C}$ = 12.4 Hz), 97.5 (d, $^1J_{P-C}$ = 198.4 Hz), 118.7, 120.1, 120.4, 122.3, 131.1, 138.1, 142.8 (d, $^2J_{P-C}$ = 19.6 Hz). Anal. Calcd for $C_{17}H_{27}O_3P_1N_2$: C, 60.34; H, 8.04; N, 8.28. Found: C, 59.98; H, 7.99; N, 8.21.

General Procedure for the Synthesis of Phosphonobenzothiazepines 15. To a solution of **5a**−**d**,**g** in DMF was added a solution of 2-sulfanylbenzenamine (1.1 equiv) at room temperature, and the mixture was stirred for 13−37 h. After similar workup, the residue was chromatographed on silica gel (AcOEt:MeOH = 15:1) to give phosphonobenzothiazepines **15a**−**d**,**g**. The reaction conditions and yields of **15a**−**d**,**g** were summarized in Table 7. The compound **15g** had the following properties. The properties for compounds **15a**−**d** were provided in the Supporting Information.

Diethyl 4,5-dihydro-4,4-dimethyl-1*H*-1,5-benzothiazepin-3-ylphosphonate (15g): yellow solid; mp 154.5−156.0 °C dec; IR 1606, 1483 cm^{-1}; ^1H NMR δ 1.34 (6 H, t, J = 7.0 Hz), 1.52 (6 H, s), 4.00−4.14 (4 H, m), 6.92−6.98 (2 H, m), 7.18−7.22 (1 H, m), 7.31−7.37 (2 H, m), 8.54−8.55 (1 H, m); ^{13}C NMR δ 16.3 (d, $^3J_{P-C}$ = 7.2 Hz), 31.6, 49.1 (d, $^2J_{P-C}$ = 10.3 Hz), 61.3 (d, $^2J_{P-C}$ = 5.2 Hz), 105.2 (d, $^1J_{P-C}$ = 185.0 Hz), 119.9, 122.4, 124.2, 128.3, 134.9, 142.1 (d, $^2J_{P-C}$ = 24.9 Hz), 144.7. Anal. Calcd for $C_{15}H_{22}O_3P_1N_1S_1$: C, 55.03; H, 6.77; N, 4.28. Found: C, 55.04; H, 6.88; N, 4.01.

Acknowledgment. We are grateful for financial support of this work by a Grant-in-Aid for Scientific Research (No. 10450344) from the Ministry of Education, Science, Sports and Culture of Japan and by the C. O. E. Research Fund of KIT. We also thank the Center for Instrumental Analysis KIT for the use of their facilities.

Supporting Information Available: Spectral and analytical data for compounds **2b**−**m**, **5a**−**d**,**g**,**h**, **7k**, **8b**−**d**, **9h**, **11b**−**d**,**g**,**h**, **12b**−**d**,**g**, **13b**−**d**,**g**, **14a**−**c**,**g**, **15a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000149T