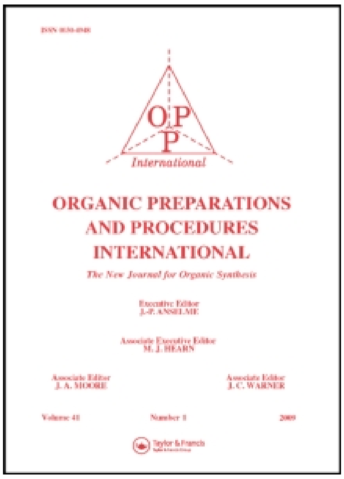
This article was downloaded by:
On: *27 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

# PHOSPHORINO [4, 3-*d*] PYRIMIDINES. II. SYNTHESIS UTILIZING METHYL 4-OXO-1-PHENYL-3-PHOSPHORINANECARBOXYLATE 1-SULFIDE

Theodore E. Snider[a]; K. D. Berlin[a]
[a] Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma

**To cite this Article** Snider, Theodore E. and Berlin, K. D.(1972) 'PHOSPHORINO [4, 3-*d*] PYRIMIDINES. II. SYNTHESIS UTILIZING METHYL 4-OXO-1-PHENYL-3-PHOSPHORINANECARBOXYLATE 1-SULFIDE', Organic Preparations and Procedures International, 4: 5, 237 — 245

**To link to this Article: DOI:** 10.1080/00304947209355552

**URL:** http://dx.doi.org/10.1080/00304947209355552

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

ORGANIC PREPARATION AND PPROCEDURES INT. 4(5), 237-245 (1972)

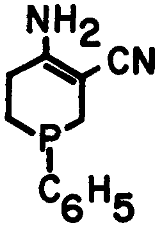
# PHOSPHORINO[4,3-d]PYRIMIDINES. II. SYNTHESIS UTILIZING METHYL 4-OXO-1-PHENYL-3-PHOSPHORINANECARBOXYLATE 1-SULFIDE[1,2]

Theodore E. Snider[3] and K. D. Berlin*
Department of Chemistry, Oklahoma State University,
Stillwater, Oklahoma 74074

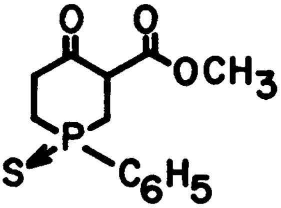
Downloaded At: 13:29 27 January 2011

Carbon-phosphorus heterocycles possessing functionality are extremely rare in the literature.[2,4-13] An almost singular example is the classic Thorpe condensation of bis(2-cyanoethyl)phenylphosphine to form the 2-enamino nitrile 1.[6]

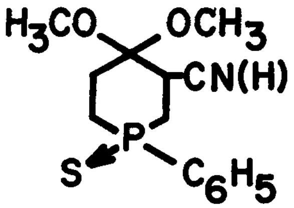
Our interest in phosphorino[4,3-d]pyrimidines led us to consider the condensation of amidines with β-keto esters.[14,15] The attempted hydrolysis of 1 by known procedures for the formation of β-keto esters[16] gave only the cyano ketal 3 isolated as the sulfide. A well-known alternate route to cyclic β-keto esters is the Dieckmann condensation of diesters.[17]



1



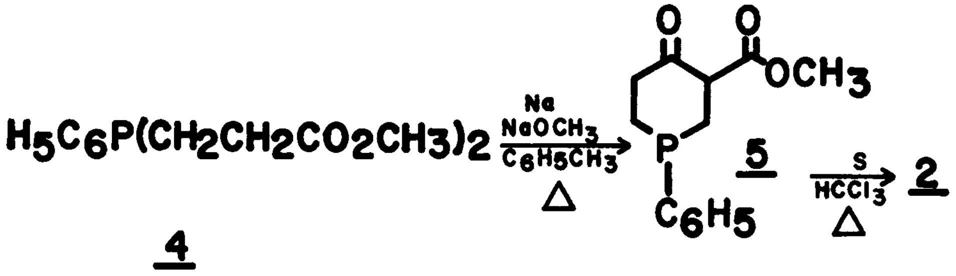
2



3

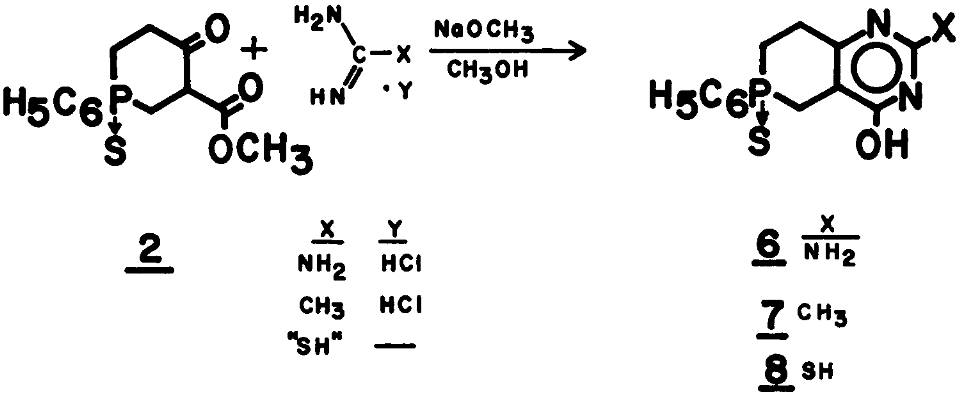
© 1972 by Organic Preparations and Procedures, Inc.

The appropriate diester, bis(2-carbomethoxyethyl)phenylphosphine 4[18] was successfully cyclized with sodium/sodium methylate in boiling toluene to form 5. The β-keto ester 5 decomposed on distillation and was thus converted to the corresponding



phosphine sulfide 2 in a boiling mixture of chloroform and sulfur. The overall yield of 2, 4→5→2, was 45-60% for three preparations.

Condensation[19] of 2 with guanidine hydrochloride, acetamidine hydrochloride, and thiourea under anhydrous basic conditions gave, after neutralization, the corresponding 6-phenylphosphorino[4,3-*d*]-pyrimidine-4-ol. The pyrimidinols are easily isolated and purified by solution in



Downloaded At: 13:29 27 January 2011

dilute base, decolorization of the solution with Nuchar, and subsequent acidification with dilute acetic acid to regenerate free pyrimidine. Of particular note in the proton nmr spectrum of these phosphorino[4,3-d] pyrimidine 6-sulfides is the phenyl region. One may easily discern the ortho protons of the phenyl group down field from the remaining phenyl signals.

## Experimental[20]

4-Oxo-1-phenyl-3-phosphorinanecarbonitrile dimethyl acetal 1-sulfide (3).--A mixture of the 2-enamino nitrile 1[6] (10.8 g., 0.05 mole), hydrochloric acid (20 ml., 12 M), water (20 ml.) and methanol (120 ml.) was boiled for 1 hr. The mixture was then evaporated to dryness and the residue was dissolved in methanol (120 ml.). Saturation of the solution with HCl gas followed; this solution stood for 24 hr. at room temperature. Pouring the mixture into 300 ml. of ice water quenched the reaction. The aqueous solution was made basic with 10% NaOH and then extracted twice with $HCCl_3$ and twice with ethyl acetate. The organic extracts were combined, washed (with saturated NaCl, followed by $H_2O$), dried ($MgSO_4$) and evaporated to dryness. Attempts to vacuum distill the residual oil resulted in decomposition. Therefore, the residual oil was dissolved in $HCCl_3$ (100 ml.) containing sulfur (1.6 g., 0.05 mole) and boiled for 1 hr. Concentration of the solution to ca. 25 ml. and dilution with hexane precipitated unreacted sulfur and some product. The precipitate was washed ($CS_2$) to remove excess sulfur. The hexane-chloroform solution was evaporated to dryness, and the residue was combined with the residue from the $CS_2$ washings. Recrystallization of the combined residues, a mixture of the diastereomers of 3, from ethyl acetate/2-propanol gave 4.25 g. of 3 (m.p. 145-168°, 29%). Subsequent recrystallization of the diastereomeric

Downloaded At: 13:29 27 January 2011

mixture from $CH_3OH$ gave a pure diastereomeric ketal <u>3</u> (m.p. 170-172°); pmr ($DCCl_3$) δ 1.8-2.9 (m, 7, phosphorinane ring), 3.25 (5, 3, $OC\underline{H}_3$), 3.33 (5, 3, $OC\underline{H}_3$), 7.3-8.0 (m, 5, $C_6\underline{H}_5$).

<u>Anal</u>. Calcd. for $C_{14}H_{18}NO_2PS$: C, 56.95; H, 6.10; P, 10.51.

Found: C, 57.03; H, 6.26; P, 10.36.

<u>Bis(2-carbomethoxyethyl)phenylphosphine</u> (<u>4</u>).--Methyl acrylate (15.5 g., 0.18 mole) was added dropwise to a stirred mixture of phenylphosphine (10 g., 0.09 mole), potassium hydroxide (1 ml., 10 <u>N</u>), and acetonitrile (10 ml.). The reaction temperature was maintained between 20-35°C by controlled addition of phenylphosphine and/or by cooling in an ice bath. After addition was complete, the reaction mixture was stirred for 3 hrs. at room temperature. The organic layer was separated, washed with two 15-ml. portions of saturated sodium chloride solution, dried (anhydrous $Na_2SO_4$), and distilled to yield bis(2-carbomethoxyethyl)phenylphosphine (<u>4</u>) (b.p. 156-60°/0.51.0 mm., lit.[17] 149-150°/1mm., 13 g., 51%); ir (NaCl film) µ 5.77 (C=O); pmr ($DCCl_3$) δ 1.8-2.6 (m, 8, $C\underline{H}_2C\underline{H}_2$), 3.5 (s,6,$OC\underline{H}_3$), 7.1-7.5 (m, 5, $C_6\underline{H}_5$). The 40.5 MHz nmr spectrum of <u>4</u> shows $^{31}P$ absorption at δ+ 20.62 (50% in $CH_3OH$) relative to 85% $H_3PO_4$.

<u>Methyl 4-oxo-1-phenyl-3-phosphorinanecarboxylate 1-Sulfide</u> (<u>2</u>).--A solution of bis(2-carbomethoxyethyl)phenylphosphine (<u>4</u>) (9.4 g., 0.033 mole) in 50 ml. of toluene was added dropwise to a boiling solution of sodium methoxide (1.8 g., 0.033 mole) in 150 ml. of toluene. After the reaction mixture had boiled for 2 hrs., metallic sodium (0.7 g., 0.033 g-at) was added and the mixture was stirred and boiled overnight. After cooling, the mixture was treated with 100 ml. of $H_2O$. The aqueous layer was separated and extracted three times with 50-ml. portions of $HCCl_3$, the extracts being combined with the organic layer. The combined organic layers were dried ($Na_2SO_4$) and evaporated to an oily residue. Again

Downloaded At: 13:29 27 January 2011

attempts to distill this residue resulted in extensive decomposition; therefore the residue was dissolved in 75 ml. of $HCCl_3$ and the solution was boiled for 1 hr. in the presence of sulfur (2.1 g., 0.066 mole). The $HCCl_3$ was removed via rotary evaporation, and the residue was recrystallized from $CH_3OH/H_2O$ to yield **2** (4.2 g., m.p. 142-48°, 45%); ir (KBr) μ 5.73 (C=O), 5.81 (C=O); pmr ($DCCl_3$) δ 2.0-3.3 (m, 6, phosphorinane ring), 3.7 (s, 3, $OC\underline{H}_3$), 7.3-8.0 (m, 5, $C_6\underline{H}_5$), 12.5 (s,1,O$\underline{H}$); mass spectrum m/e (rel intensity) 282 (100), 283 (14), 251 (11), 250 (30), 223 (11), 222 (44), 166 (11), 141 (16), 109 (54), 63 (23), 55 (38), 32 (22). The $^{31}P$ magnetic resonance absorption occurred as two broad multiplets at δ-19.0 and δ-19.3 (20% in $CH_3OH$) relative to 85% $H_3PO_4$.

The 40.5 MHz nmr of **2** in methanol is not wholly unexpected,[21] but the doublet $^{31}P$ absorption is novel. This double absorption would be expected in molecules such as **2** which have two asymmetric centers and thereby exist as a pair of diastereomers. However, the pmr spectrum and integration of **2** indicated that the enol and not the keto form of **2** was predominate in chloroform solution. This enolization of **2** would equilibrate the diastereomers. The observation of both diastereomers in the $^{31}P$ nmr spectrum may be caused by the difference in solvent [22] or may be an illustration of the extreme sensitivity of $^{31}P$ nuclei to structural modifications.

Anal. Calcd. for $C_{13}H_{15}O_3PS$: C, 55.32; H, 5.32; P, 10.99; S, 11.34.
Found: C, 55.43; H, 5.42; P, 10.82; S, 11.15.

2-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-d]pyrimidine-4-ol 6-Sulfide (**6**).--The β-keto ester **2** (5.44 g., 0.02 mole), guanidine hydrochloride (1.91 g., 0.02 mole), and sodium methoxide (2.16 g., 0.04 mole) in 150 ml. of methanol were boiled for 3 hr. under an $N_2$ atmosphere. The reaction mixture was subsequently cooled and stirred at room temperature

Downloaded At: 13:29 27 January 2011

overnight. The mixture was then evaporated to dryness on the rotary evaporator, and the residue was dissolved in 150 ml. of $H_2O$. The pH of the solution was adjusted to pH 5-6 with glacial $CH_3CO_2H$, whereupon a small amount of $H_2S$ was liberated. The precipitate which formed was filtered out and washed twice with $H_2O$ while on the filter. The pink solid was recrystallized from DMSO and then dissolved in 10% NaOH and treated with Nuchar, the solution filtered, and the solid precipitated with 50% $CH_3CO_2H$. The solution and precipitation procedure was repeated two more times to give 6 (4 g., m.p. 243-246° s.t., 67%); ir (KBr) μ 2.89 (O-H), 3.0 (N-H), 5.88 (pyrimidine ring); pmr (DMSO-$d_6$) δ 2.0-3.5 (m, 6, phosphorin ring), 6.47 (s, 2, $NH_2$), 7.5 (m, 3, meta and para $C_6H_5$), 7.75-8.0 (m, 2, o-$C_6H_5$); mass spectrum m/e (rel intensity) 291 (100), 292 (16), 259 (14), 258 (47), 150 (75), 151 (11), 108 (33), 43 (11). The $^{31}P$ magnetic resonance of 6 occurred at δ-31.41 (5% in DMSO) relative to 85% $H_3PO_4$.

Anal. Calcd. for $C_{13}H_{14}N_3OPS$: N, 14.43; P, 10.66; S, 10.99.
Found: N, 14.54; P, 10.49; S, 11.06.

5,6,7,8-Tetrahydro-2-methyl-6-phenylphosphorino[4,3-d]pyrimidine-4-ol 6-Sulfide (7).--Acetamidine hydrochloride (0.95 g., 0.01 mole) and sodium methoxide (1.1 g., 0.02 mole) were mixed and stirred in 30 ml. of anhydrous ethanol for 10 min. at room temperature. The mixture was then filtered and added to a solution of the β-keto ester 2 (2.2 g., 0.008 mole) in 50 ml. of ethanol. (The mixture turned orange in color.) The reaction mixture was boiled for 10 min. and then allowed to stir overnight at room temperature. (The color darkened to black.) The mixture was subsequently boiled for 1 hr., cooled, and evaporated to dryness on the rotary evaporator. The brown oily residue was dissolved in 10% NaOH, treated with Nuchar, filtered, acidified (50% $CH_3CO_2H$), and filtered to yield 7 (1.2 g., m.p.

Downloaded At: 13:29 27 January 2011

269-271° s.t., 52%). An analytical sample was prepared by thrice dissolving a sample of 7 in 6% NaOH, treating with Nuchar, and precipitating with 50% $CH_3CO_2H$): ir (KBr) μ 2.89 (OH), 6.05 (pyrimidine ring); pmr (DMSO-$d_6$) δ 2.26 (s, 3, $CH_3$), 2.6-3.2 (m, 6, phosphorin ring), 7.6 (m, 3, meta and para $C_6H_5$), 7.8-8.2 (m, 2, o-$C_6H_5$); mass spectrum m/e (rel intensity) 290 (92), 291 (15), 258 (24), 257 (100), 149 (25), 109 (8), 42 (16). The $^{31}P$ magnetic resonance absorption of 7 occurred at δ-39.02 (2% in DMSO) relative to 85% $H_3PO_4$.

Anal. Calcd. for $C_{14}H_{15}N_2OPS$: N, 9.66; P, 10.69; S, 11.03.
Found: N, 9.57; P, 10.56; S, 11.08.

5,6,7,8-Tetrahydro-2-mercapto-6-phenylphosphorino[4,3-d]pyrimidine-4-ol 6-Sulfide (8).--Thiourea (2.2 g., 0.03 mole), sodium methoxide (1.5 g., 0.03 mole) and the β-keto ester 2 (5.6 g., 0.02 mole) were dissolved in 100 ml. of $CH_3OH$. The solution was then boiled for 4 hr., cooled, and allowed to stir overnight. Precipitation occurred. The heterogeneous reaction mixture was evaporated to dryness on the rotary evaporator, and the residue was dissolved in 10% NaOH. The solution was treated with Nuchar and filtered, and the filtrate was acidified (50% $CH_3CO_2H$) to precipitate crude 8. Purification was effected by solution in 10% NaOH, treatment with Nuchar, and precipitation with 20% $CH_3CO_2H$. This procedure was performed twice to give 4.8 g. (80%) of pure 8 (m.p. 344-346°); ir (KBr) μ 2.91 (O-H), 6.05 (pyrimidine ring); (DMSO-$d_6$) δ 2.0-3.5 (m, 6, phosphorin ring), 7.6 (m, 3, meta and para $C_6H_5$), 7.8-8.1 (m, 2, o-$C_6H_5$); mass spectrum m/e (rel intensity) 308 (100), 309 (17), 310 (11), 167 (12), 108 (27), 63 (11). The $^{31}P$ magnetic resonance absorption of 8 occurred at δ-39.0 (5% in DMSO) relative to 85% $H_3PO_4$.

Anal. Calcd. for $C_{13}H_{13}N_2OPS_2$: N, 9.09; P, 10.07; S, 20.78.
Found: N, 9.27; P, 9.95; S, 20.75.

Downloaded At: 13:29 27 January 2011

## References

1. We gratefully acknowledge partial support of this work by the Public Health Service Cancer Institute, Grant C A 11967-08. We are indebted to Dr. George R. Waller and Keith Kinnberg of the Biochemistry Department, Oklahoma State University for the mass spectral data (National Science Foundation, Washington, D.C., Research Grant No. GB-20, 296). We also express our thanks to the National Science Foundation (Grant No. GP 17641) for supplemental support for the purchase of the XL-100 NMR spectrometer.

2. See T. E. Snider and K. D. Berlin, Phosphorus, 2, in press (1972) for Part I of this series.

3. National Science Foundation Faculty Fellow, 1971-1972; NSF Trainee, 1970-1971; predoctoral candidate 1970-1972; present address, Cameron State College, Lawton, Oklahoma 73501.

4. K. D. Berlin and D. M. Hellwege in "Topics in Phosphorus Chemistry," Vol. 6, Chapter 1. M. Grayson and E. J. Griffith (Eds.), Inter-Science Publishers, New York, N. Y., 1969. See also T. E. Snider, C. H. Chen, and K. D. Berlin, Phosphorus, 1, 81 (1971).

5. F. G. Mann. "Heterocyclic Derivatives of Phosphorus," in THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS, A. Weissberger and E. C. Taylor (Eds.), Wiley-Interscience, New York, New York, 1970.

6. R. P. Welcher, G. A. Johnson, and R. P. Wystrach, J. Amer. Chem. Soc. 82, 4437 (1960).

7. M. J. Gallagher and F. G. Mann, J. Chem. Soc., 5110 (1962).

8. M. D. Martz and L. D. Quin, J. Org. Chem., 34, 3195 (1969).

9. F. Mathey and G. Muller, C. R. Acad. Sci. Paris, Ser. C, 273, 305 (1971).

10. H. E. Shook and L. D. Quin, J. Amer. Chem. Soc., 89, 1841 (1967).

11. R. P. Welcher and N. E. Day, J. Org. Chem., 27, 1824 (1962).

12. L. D. Quin and H. E. Shook, Tetrahedron Lett., 2193 (1965).

13. M. J. Gallagher and F. G. Mann, J. Chem. Soc., 4855 (1962).

14. J. P. Jonak, S. F. Zakrzewski, and L. H. Mead, J. Med. Chem., 15, 662 (1972).

15. R. Mayer, Angew. Chem., 68, 169 (1956).

16. E. C. Horning and A. F. Finelli, J. Amer. Chem. Soc., 72, 2731 (1950); E. C. Horning and A. F. Finelli, J. Amer. Chem. Soc., 73, 3741 (1951).

Downloaded At: 13:29 27 January 2011

17. J. P. Schaefer and J. J. Bloomfield, "The Dieckmann Condensation," in ORGANIC REACTION, Vol. 15, Chapter 1. A. C. Cope (Ed.), John Wiley and Sons, New York, N. Y., 1967.

18. B. A. Arbuzov, G. M. Vinokurova, and I. A. Perfil'eva, Dokl. Acad. Nauk USSR, 127, 657 (1970).

19. W.L.F. Armarego, "Fused Pyrimidines, Part I Quinazolines, D. J. Brown, Ed., in THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS, A Weissberger (Ed.), Interscience Publishers, New York, N. Y., 1967.

20. Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus using evacuated sealed tubes. Infrared spectra were obtained on a Beckman IR-5A spectrometer as potassium bromide pellets or as films on sodium chloride plates. Nuclear magnetic resonance spectra were determined on a Varian A-60 high resolution spectrometer and a Varian XL-100 spectrometer. Mass spectra were determined on an LKB-9000 prototype, single-focusing magnetic sector instrument. Elemental microanalyses were determined by Galbraith Laboratories, Knoxville, Tennessee.

21. M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wayer in "Topics in Phosphorus Chemistry," Vol. 5, M. Grayson and E. J. Griffith (Eds.), Interscience Publishers, New York, N. Y., 1967.

22. R.A.Y. Jones and A. R. Katritzky, Angew. Chem., 74, 60 (1962).

(Received August 9, 1972; in revised form November 2, 1972)

Downloaded At: 13:29 27 January 2011