Condensation of Phosphonate Anions with 4-Amino-5-nitrosopyrimidines: a New Pteridine Synthesis[1]

By EDWARD C. TAYLOR* and BEN E. EVANS
(*Department of Chemistry, Princeton University, Princeton, New Jersey* 08540)

Summary The condensation of diethyl phosphonate carbanions, prepared from α-bromo-esters, -nitriles, or -ketones, with 4,6-diamino-5-nitrosopyrimidines constitutes a versatile and unequivocal route to pteridin-7(8*H*)-ones, 7-aminopteridines, and 7-alkyl- or aryl-pteridines.

A RECENT report[2] describing a novel method for the synthesis of pteridin-7(8*H*)-ones by the condensation of triethyl phosphonoacetate with several 2-substituted 4,6-diamino-5-nitrosopyrimidines prompts us to report our independent observation that the reaction has greater scope than previously indicated, and constitutes a versatile, unequivocal synthetic route to pteridin-7(8*H*)-ones, 7-aminopteridines, and 7-alkyl- or aryl-pteridines.

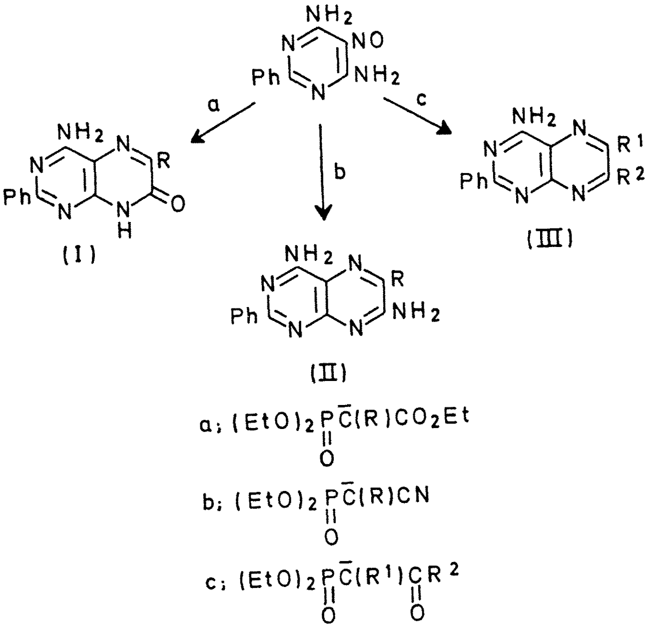
Addition of phosphonate carbanions to carbonyl groups to afford olefins is a widely employed modification of the Wittig reaction.[3] The analogous addition of such anions to the nitroso-group has also been successful,[4] and these latter reports prompted our interest in the possible condensation of phosphonate anions with 4-amino-5-nitrosopyrimidines as a general synthetic approach to pteridines.†

TABLE

Pteridine	m.p. (° C)	Yield (%)
(I) R=H	331—332 (decomp)[a]	90
(I) R=Me	289—291 (decomp)[b]	74
(I) R=Me (H for Ph at C-2)	>350[c]	78
(II) R=H	295—298 (decomp)[d]	28
(II) R=Ph	368 (decomp)[e]	27
(III) R^1=H, R^2=Ph	253·5—254 (decomp)	75
(III) R^1=R^2= $-CH_2{\cdot}CH(Me){\cdot}[CH_2]_2-$	317 (decomp)	32

[a] Lit. m.p. >340° (ref. 2).
[b] Lit. m.p. 282—284°: J. Weinstock, R. Y. Dunoff, J. E. Carevic, J. G. Williams, and A. J. Villani, *J. Medicin. Chem.*, 1968, **11**, 618.
[c] Lit. m.p. >350°: D. Söll and W. Pfleiderer, *Chem. Ber.*, 1963, **96**, 2977.
[d] Lit. m.p. 299—302°: J. Weinstock, R. Y. Dunoff, and J. G. Williams, *J. Medicin. Chem.*, 1968, **11**, 542.
[e] Lit. m.p. >320°: I. J. Pachter and P. E. Nemeth, *J. Org. Chem.*, 1963, **28**, 1187.

Condensation of 4,6-diamino-5-nitroso-2-phenylpyrimidine with the anion of triethyl phosphonoacetate in tetrahydrofuran proceeded rapidly at room temperature to give 4-amino-2-phenylpteridin-7(8*H*)-one in 90% yield, in good agreement with results already reported.[2] A variety of other phosphonate anions, readily prepared by reaction of α-bromo-esters, -nitriles or -ketones with triethyl phosphite followed by addition of base, reacted analogously to give pteridin-7(8*H*)-ones, 7-amino-, and 7-alkyl- or aryl-pteridines, respectively, carrying alkyl or aryl groups (or hydrogen) at C-6. Some representative 4-amino-2-phenyl-pteridines prepared from 4,6-diamino-5-nitroso-2-phenyl-pyrimidine by these procedures are listed in the Table.



The condensation of phosphonate anions with 4-amino-5-nitrosopyrimidines may be considered as a special case of the Timmis reaction[5] involving active methylene components. In the present instance, however, the phosphonate intermediate constitutes a doubly activated methylene compound which loses one of its activating groups (*i.e.*, the phosphonate) during the course of the condensation. The reaction proceeds with a variety of 2-substituents[2] and should prove a useful addition to the select number of pteridine syntheses which are unequivocal in their placement of substituents in the pyrazine ring.[6]

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† All attempts to condense 4-amino-5-nitrosopyrimidines with Wittig reagents were unsuccessful.

[1] For the previous paper in this series, see E. C. Taylor and K. Lenard, *Annalen*, 1969, **726**, 100.
[2] R. D. Youssefyeh and A. Kalmus, *Chem. Comm.*, 1970, 1371.
[3] W. S. Wadsworth, Jun. and W. D. Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.
[4] J. A. Maassen, Th. A. J. W. Wajer, and Th. J. de Boer, *Rec. Trav. chim.*, 1969, **88**, 5; H. Zimmer, P. J. Berecz, and G. E. Heuer, *Tetrahedron Letters*, 1968, 171.
[5] For a review of the Timmis reaction, see T. S. Osdene, in "Pteridine Chemistry", eds. W. Pfleiderer and E. C. Taylor, Pergamon Press Ltd., London, 1964, pp. 65—73.
[6] E. C. Taylor and K. Lenard, *J. Amer. Chem. Soc.*, 1968, **90**, 2424.