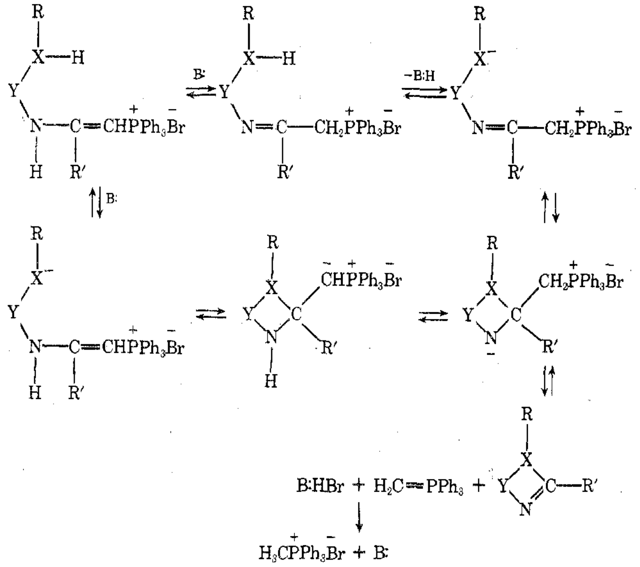
Reactions of Phosphorus Compounds. 36. Heterocyclic Synthesis *via* Methylenetriphenylphosphorane Extrusion

Summary: A synthetically useful ylide elimination reaction has been shown to be generally useful for the preparation of a variety of heterocyclic species.

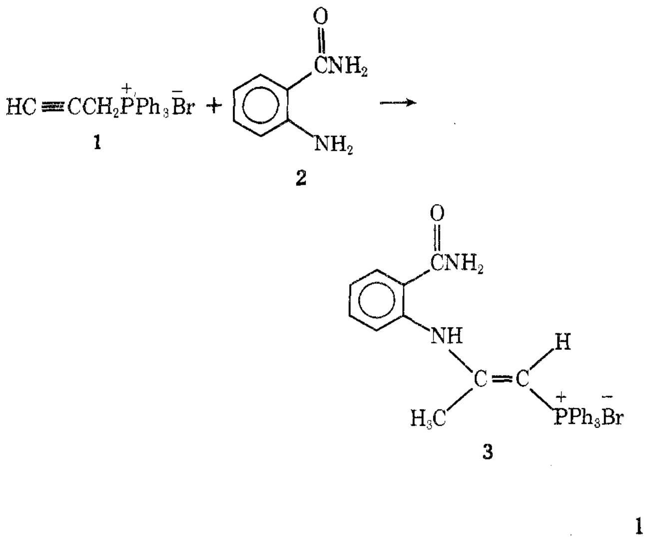
Sir: A number of reactions have been observed which involve the elimination of a phosphorane.[1–4] To date we know of no generally useful synthetic process where the loss of a phosphorane is envisaged.

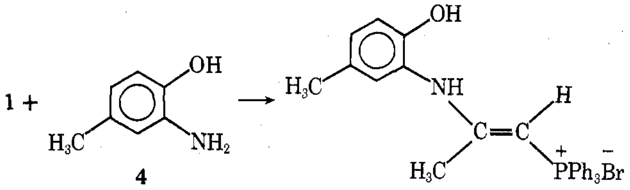
We wish to propose a general base catalyzed heterocyclic synthesis involving the extrusion of methylenetriphenylphosphorane. The overall reaction pathway may be depicted in the following manner.



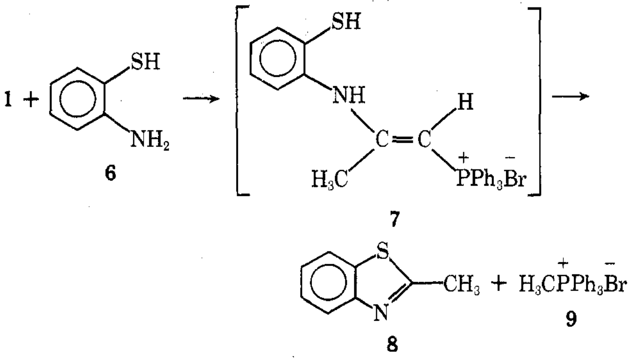
It has been shown that triphenyl(prop-2-ynyl)phosphonium bromide (1) undergoes nucleophillic addition with primary amines yielding β-aminopropenyltriphenylphosphonium bromides of synthetic utility for the preparation of substituted quinolines.[5] The β-phosphoniopropenylation reaction is used to prepare the intermediates employed to demonstrate the utility of the current reaction.

The salt 1 was allowed to react with *o*-aminobenzamide (2) and 2-hydroxy-5-methylaniline (4) in acetonitrile to give the corresponding salts in 96 and 87% yields, respectively.[6]

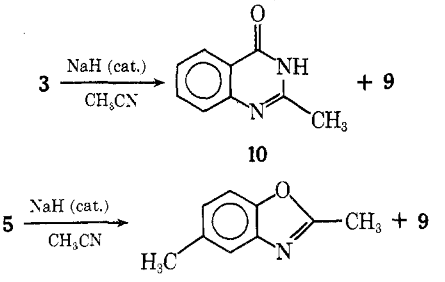

1 2 3


4 5

Treatment of *o*-mercaptoaniline (6) in acetonitrile with 1 gave the 2-methylbenzothiazole (8)[7] in 62% yield and methyltriphenylphosphonium bromide (9) directly, presumably *via* the intermediacy of 7.


6 7 8 9

The heating of salts 3 and 5 in acetonitrile under reflux with a catalytic amount of sodium hydride gave the corresponding heterocycles, 2-methylquinazol-4-one (10)[8] and 2,5-dimethylbenzoxazole (11)[9] and the salt 9.



10 11

The salt 9[10] was isolated in essentially quantitative yield by adding ethyl acetate to the solutions of all three of the final reaction mixtures and filtering; the desired heterocycles[11] 10 and 11 were isolated from the filtrate in 75 and 80% yields, respectively.[12]

A careful evaluation of the full scope and utility of this procedure for the preparation of heterocyclic species is underway and will be reported at a later data.

Supplementary Material Available. Procedures for the preparation of compounds 3, 5, 8, 10, and 11 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-144.

References and Notes

(1) E. E. Schweizer and C. M. Kopay, *Chem. Commun.*, 677 (1970).
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(5) E. E. Schweizer, C. S. Kim, C. S. Labaw, and W. P. Murray, *Chem. Commun.*, 7 (1973); S. V. DeVoe unpublished results.
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(7) A. W. Hofmann, *Chem. Ber.*, **13**, 21 (1880).
(8) R. Anschutz, O. Schmidt, and A. Grieftenberg, *Chem. Ber.*, **35**, 3480 (1902).
(9) K. Noelting, *Chem. Ber.*, **17**, 361 (1884).
(10) L. Horner and A. Mentrup, *Justus Liebigs Ann. Chem.*, **646**, 65 (1961).
(11) No attempts were made to maximize the yields of the heterocyclic species formed.
(12) See paragraph regarding supplementary material.

Department of Chemistry **Edward E. Schweizer***
University of Delaware **Susan V. DeVoe**
Newark, Delaware 19711

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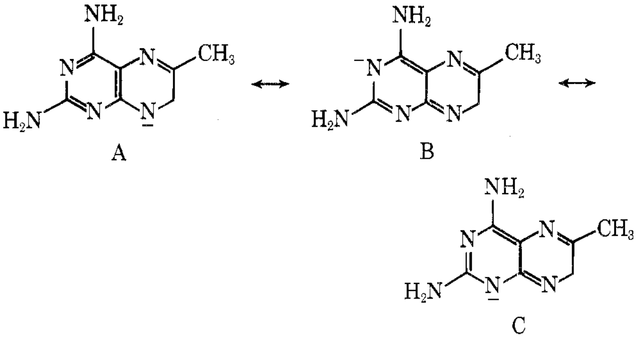
Direct N^8-Alkylation of 2,4-Diamino-7,8-dihydropteridines. Preparation of 7,8-Dihydro-8-methylmethotrexate[1]

Summary: A method is described for the N^8-alkylation of 2,4-diamino-7,8-dihydropteridines by reaction of these compounds with *n*-butyllithium in DMSO followed by treatment with an alkyl halide.

Sir: Dihydro and tetrahydropteridines in which the pyrazine ring is the reduced site are intermediates in many biological reactions in diverse living organisms.[2] The study of the chemical and biological properties of reduced pteridines is complicated by the fact that they are readily oxidized to the parent aromatic compounds, even upon standing in air. Substitution of methyl groups for hydrogen at N^8 in 7,8-dihydropteridines[3] and at N^5 and/or N^8 in 5,6,7,8-tetrahydropteridines[4] results in derivatives which resist facile oxidative degradation at the 5,6 and/or 7,8 positions. Although direct substitution at N^5 in 5,6,7,8-tetrahydropteridines can be accomplished rather easily under mild conditions,[4-7] N^8 is resistant to alkylation[6] and can be acylated only under drastic conditions.[5] In this communication we describe a method by which 2,4-diamino-7,8-dihydropteridines can be directly monoalkylated at N^8 without substitution either in the pyrimidine ring or on the 2- or 4-amino groups. The resulting products can then be hydrogenated catalytically to tetrahydropteridines.

Since most of the biologically important pteridines are substituted at the 6 position, we chose to experiment with 2,4-diamino-7,8-dihydro-6-methylpteridine (**1a**)[8] as a model compound. The nmr spectrum of this compound in DMSO-d_6 (TMS internal standard) shows the C^6 CH$_3$ at δ 1.86 (s), the 7-CH$_2$ at 3.96 (s), the amino groups at 5.53 and 5.65 (overlapping singlets), and the N^8 H at 6.27 (s). This spectrum indicates that the N^8 H is deshielded with respect to the hydrogens on the amino groups. It was expected that if **1a** were treated with a powerful base, nucleophilic attack with proton abstraction would occur at N^8 H rather than at either of the amino groups. What is more important is that the resulting anion could be stabilized by resonance forms such as B and C in which the charge is accommodated on the nitrogens of the pyrimidine ring. Treatment of this anion with an alkylating agent should result in attack preferentially at the least hindered N^8 position.



A solution of **1a** in DMSO, under nitrogen at room temperature, was treated with 1.1 equiv of *n*-butyllithium in hexane,[9] followed after a few minutes by the addition of 1.2 equiv of methyl iodide. Addition of water after 15 min precipitated a white solid (71%, mp 260–280° dec) which appeared as a single new compound on tlc (silica gel, 8% MeOH–CHCl$_3$). The product was stable in air and was unchanged upon treatment with hydrogen peroxide in DMF for 30 min, conditions which rapidly oxidized **1a** to the fully aromatic pteridine. Elemental analysis gave the formula $C_8H_{12}N_6$ for this compound, in accordance with the introduction of a single CH$_3$ group into the starting material, and the uv spectrum [$\lambda_{max}^{0.1N\ HCl}$ 236 nm (ϵ 26,700), 263 (sh, 8130), 292 (13,600)] showed little change from that of **1a**.[8] The nmr spectrum in DMSO-d_6 was similar to that of **1a** except that the N^8 H peak was absent and a new singlet appeared at δ 2.78 (3 H). In CF$_3$CO$_2$H, the nmr spectrum consisted of singlets at δ 2.61 (C^6 CH$_3$), 3.24 (N^8 CH$_3$), and 4.86 (7-CH$_2$), almost identical with the reported spectrum of 2-amino-4-hydroxy-6,8-dimethyl-7,8-dihydropteridine, prepared by Wahlefeld, *et al.*,[3] by an unambiguous synthesis. These data are consistent with the assignment of structure **2a** for the new product. Hydrogenation of **2a** with PtO$_2$ in CF$_3$CO$_2$H gave the tetrahydropteridine **3**: nmr (CF$_3$CO$_2$H) δ 1.67 (d, J = 6 Hz, C^6 CH$_3$), 3.36 (s, N^8 CH$_3$), 3.67–4.20 (m, C^6 H and 7-CH$_2$). This product was isolated as a fairly stable white solid as its dihydrochloride monohydrate.

Compounds **2b**, **2c**, and **2d** were prepared in the same manner as **2a** in yields of 60, 24, and 80%, respectively, by the use of ethyl bromide, isopropyl bromide, and benzyl chloride as the alkylating agents. The relatively low yield for **2c** may be the result of extensive dehydrohalogenation of the sterically hindered isopropyl bromide during the reaction. Elemental and spectral analyses of these compounds substantiated the proposed structures.

We next attempted the alkylation of the more complicated folate derivative 7,8-dihydromethotrexate **1b**.[10,11] A solution of **1b** (as the diacid monohydrate), in DMSO at room temperature under nitrogen, was treated with 4.5 equiv of *n*-butyllithium in hexane followed by 3 equiv of methyl iodide. After 5 min the mixture was diluted with water and the pH adjusted to 3.5 with HCl. The precipitated solid was collected and then reprecipitated from dilute alkali in the same manner to give **2e** as a light tan solid, 50%, mp 185–195° dec. *Anal.* Calcd for $C_{21}H_{26}N_8O_5 \cdot H_2O$: C, 51.63; H, 5.78; N, 22.94. Found: C, 51.84; H, 5.35; N, 22.25. Thin layer chromatography (Eastman 13254 cellulose; 5% aqueous NaHCO$_3$) showed the presence of one major compound (R_f 0.68) with only a trace of unreacted **1b** (R_f 0.55): uv $\lambda_{max}^{0.1N\ HCl}$ 295 nm (ϵ 23,700); nmr (CF$_3$CO$_2$H) δ 2.3–2.9 (m, side chain CH$_2$CH$_2$), 3.24 (s, N^8 CH$_3$), 3.64 (s, N^{10} CH$_3$), 4.46 (s, 9-CH$_2$), 4.72 (s, 7-CH$_2$), 5.10 (m, side-chain CH), 8.0