ramethylsilane. Analytical gas chromatography was performed with a Dohrmann Series 15 gas chromatograph. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Combustion analyses were performed by Industrial Testing Laboratories of St. Louis. 4,4-Dimethyl-3,5-diphenyl-4*H*-pyrazole[10] and 2,2-dimethyl-1,3-diphenyl-1,3-propanedione[11] were prepared as previously described.

Reaction of 4,4-Dimethyl-3,5-diphenyl-4*H*-pyrazole with H_2O_2 and 1,3-Dibromo-5,5-dimethyl-1,3-hydantoin. Ninety percent hydrogen peroxide (6 g, 159 mmol) was added to an ice-cold slurry of 4,4-dimethyl-3,5-diphenyl-4*H*-pyrazole (1.98 g, 8.0 mmol) in anhydrous ether. The solution was warmed to room temperature, and 1,3-dibromo-5,5-dimethyl-1,3-hydantoin (1.17 g, 4.1 mmol) was added portionwise over a 20-min interval. The resulting solution was kept at −20 °C for 48 h. The solution was then washed with cold 10% aqueous sodium bicarbonate and dried over magnesium sulfate. Solvent was removed at reduced pressure at 0 °C, affording a yellow oil. Recrystallization from CH_2Cl_2–hexane (1:5) at −20 °C yielded 2.18 g (6.04 mmol, 75%) of **3** as a white solid: mp 77–80 °C dec; IR (KBr pellet) 3250 (OOH), 1540 (N=N) cm^{-1}; ^1H NMR ($CDCl_3$), δ −0.05 (s, 3 H), 1.68 (s, 3 H), 7.2–7.8 (m, 11 H); ^{13}C NMR ($CDCl_3$) aromatics δ 138.9, 135.4, 132.1, 129.1, 128.3, 128.2, 125.7, 119.7; ^{13}C NMR ($CDCl_3$) aliphatics δ 102.4, 48.6, 25.8, 23.0, 19.9. Anal. Calcd for $C_{17}H_{17}BrN_2O_2$: C, 56.52; H, 4.74; N, 7.75. Found: C, 56.47; H, 4.78; N, 7.70.

Reaction of 3 with Ethanolic $AgNO_3$. **3** (7.6 mg, 0.021 mmol) was dissolved in 1 mL of 95% ethanol and added to 5 mL of 5% $AgNO_3$ (w/v) in ethanol. This solution was allowed to staand for 1 h in the dark. The precipitated AgBr (yellow solid) was filtered with a sintered-glass filter and dried, yielding 3.8 mg (0.02 mmol) of AgBr, 96% of the theoretical yield.

Thermolysis of 3. A solution of 0.727 g (2.02 mmol) of **3** in 25 mL of methylene chloride was heated with a water bath at 40 °C for 90 min. A ^1H NMR spectrum of the solution indicated the complete conversion of **3** into products, the hydrobromide salt **5** of pyrazole **4** and 2,2-dimethyl-1,3-diphenyl-1,3-propanedione (**6**) in the ratio of 76:24. Solvent was removed at reduced pressure, and the resulting yellow semisolid was dissolved in hot methylene chloride. Hexane was added until the hot solution became cloudy. The solution was allowed to stand at room temperature for 24 h while yellow crystals of **5** (0.4 g, 62%) precipitated. The hydrobromide salt **5** was identified by comparison of its IR and ^1H NMR spectra with those of an authentic sample prepared by the addition of HBr to **4**: IR (KBr pellet) 2350 ($^+$NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (br s, 6 H), 7.1 (variable s, 1 H), 7.6–7.9 (m, 6 H), 8.1–8.4 (m, 4 H). Removal of solvent from the recrystallization filtrant affords 0.11 g (23%) of diketone **6**, identified by comparison of its IR and ^1H NMR spectra with those of an authentic sample.[11]

Analysis of Gaseous Products from the Thermolysis of 3. **3** (0.1 g, 0.28 mmol) was dissolved in 40 mL of methylene chloride and placed in a 100-mL Erlenmeyer flask tightly stoppered with a rubber septum. The solution was cooled to −78 °C in an acetone/dry ice bath and degassed with argon for 30 min. The solution was heated with a water bath at 40 °C, and 0.5-mL samples of the gas phase were withdrawn periodically over a 45-min interval. VPC analysis for N_2 and O_2 (retention times of 5 and 2 min, respectively) content was performed on a $^1/_4$ in. × 10 ft 4A molecular sieves (20–50 mesh) column at 25 °C with argon as the carrier gas. The thermal conductivity response ratio of N_2 to O_2, as determined by analysis of air, was determined to be 1, thereby eliminating the necessity for a response correction. The ratio of O_2 to N_2 (70:30) remained constant throughout the thermal decomposition.

X-ray structure analysis: $C_{17}H_{17}O_2N_2Br$, M_r = 316.2, monoclinic, space group $P2_1/a$, a = 23.179 (6) Å, b = 6.388 (2) Å, c = 10.947 (3) Å, β = 104.00 (4)°, V = 1508.2(7) Å^3, Z = 4, d_{calcd} = 1.591 g cm^{-3}.

A crystalline sample of 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole was packed in dry ice and shipped by air freight to Texas Christian University. A single crystal was mounted on a Syntex $P2_1$ diffractometer and unit cell and intensity data were collected as rapidly as possible. Room-temperature unit cell dimensions were refined by a least-squares procedure utilizing 15 reflections whose angles were measured by a centering routine associated with the diffractometer. Intensity data were collected by the θ–2θ scanning technique using Cu Kα radiation (λ = 1.541 78 Å) and a graphite monochromator. Total data collection was completed within 14 h; however, the intensity of a standard reflection decreased by 40% during this period. A total of 2306 independent reflections were measured and 1608 had intensities greater than $2\sigma(I)$.

The decrease in intensity of the standard reflection was used to correct the remaining intensity data. Lorentz and polarization corrections were applied, but no absorption corrections were made. The structure was solved by the direct methods program MULTAN.[12] The nonhydrogen atoms were refined anisotropically by least-squares techniques to an R factor of 11%. The hydrogen atoms could not be located and no further refinement was made. Atomic scattering factors were taken from ref 13 and the scattering factors for bromine were corrected for the real part of the anomalous dispersion. A list of observed and calculated structure factors is available from M.E.L.

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Registry No. **3**, 72229-10-8; **4**, 30169-45-0; **5**, 72229-11-9; **6**, 41169-42-0; hydrogen peroxide, 7722-84-1; 1,3-dibromo-5,5-dimethyl-1,3-hydantoin, 77-48-5.

Supplementary Material Available: Positional parameters for 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole (1 page). Ordering information is given on any current masthead page.

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Aromatic Chlorination of *p*-Aminobenzoic Acid Derivatives. Improved Syntheses of Mono- and Dichloromethotrexate

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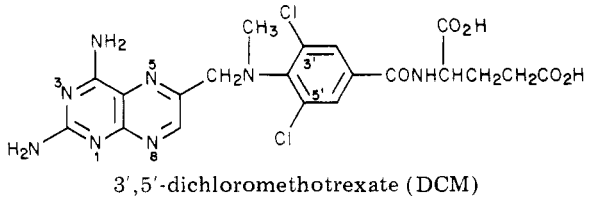
The reported syntheses of the clinically interesting[1] antitumor agent 3′,5′-dichloromethotrexate (DCM)[2] involve



3′,5′-dichloromethotrexate (DCM)

chlorination of methotrexate (MTX) with Cl_2 in formamide, dimethylformamide, or aqueous HCl with yields

(1) I. Takahashi, T. Ohnuma, and J. F. Holland, *Cancer Res.*, **39**, 1264 (1979), and references therein.

(2) *N*-[3,5-Dichloro-4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid; CAS Registry No. 528-74-5; NCI No. 29630.

0022-3263/80/1945-0527$01.00/0

Table I. Chlorination Products with *t*-BuOCl-Glacial HOAc at 10-25 °C

compd	corr mp, °C	isolated yield, %	^{1}H NMR (in TFA-d_1)	TLC R_f	UV (in EtOH) λ_{max} (ϵ)	UV (in EtOH) λ_{min} (ϵ)
dichloromethotrexate		80[a]	8.05 (s, 2 H)[b]	0.50[c]		
monochloromethotrexate		98[a]	7.3-8.4 (m, 3 H)[b]	0.62[c]		
methotrexate				0.71[c]		
dichlorofolic acid		90[a]	8.05 (s, 2 H)[b]	0.47[d]		
folic acid				0.37[d]		
dimethyl *N*-(3,5-dichloro-4-aminobenzoyl)-L-glutamate	116-117 (117-118)[e]	64[f,g]	7.8 (s, 2 H), 7.1 (br d, $J \sim 7$ Hz), 4.6-5.0 (m, 3 H), 3.75 (s, 3 H), 3.63 (s, 3 H), 2.0-2.6 (m, 4 H)[h]	0.73[i]	278 (19 850)	244 (3030)
dimethyl *N*-(4-aminobenzoyl)-L-glutamate				0.20[i]		
3,5-dichloro-4-(methylamino)-benzoic acid	195-196	80	8.3 (s, 2 H), 3.45 (s, 3 H)	0.81[k]	292 (18 700)	252 (3440)[j]
3-chloro-4-(methylamino)-benzoic acid	208-210	94.5	8.3-8.5 (m, 2 H), 7.8-8.0 (m, 1 H), 3.5 (s, 3 H)	0.85[k]	293 (18 610)	246 (2480)
4-(methylamino)benzoic acid				0.77[k]		
3,5-dichloro-4-(dimethylamino)-benzoic acid	162-163 (144-147)[l]	69[f]	8.4 (s, 2 H), 3.8 (s, 6 H)	0.38[m]	316 (7730)	269 (1840)
3-chloro-4-(dimethylamino)-benzoic acid	176-177.5 (178-179)[n]	67[f]	8.3-8.5 (m, 2 H), 7.8-8.1 (m, 1 H), 3.6 (s, 6 H)	0.31[m]	299 (15 420)	253 (2660)
4-(dimethylamino)benzoic acid				0.53[m]		

[a] Calculated as the dihydrate. [b] Only aromatic region reported. [c] Cellulose, 0.1 M phosphate buffer, pH 7.5. [d] Cellulose, 0.5 M NaCl, 0.2 M 2-mercaptoethanol, 0.005 M phosphate buffer, pH 6.78. [e] E. L. Whittle, B. L. O'Dell, J. M. Vanderbelt, and J. J. Pfiffner, *J. Am. Chem. Soc.*, **69**, 1786 (1947). [f] Chlorination in 15% HOAc-CH_2Cl_2. [g] $[\alpha]^{25}_D$ +9.6° (*c* 4.043, CH_2Cl_2), lit.[e] $[\alpha]^{27}_D$ −3° (unspecified). [h] $CDCl_3$. [i] Silica, $CHCl_3$. [j] λ_{max} (0.1 N NaOH) 269 nm (ϵ 11 000); λ_{max} (8 N HCl) 288 nm (ϵ 13 000), 295 (12 500). [k] Silica, *n*-PrOH-NH_4OH (7:3). [l] B. W. Horrom, German Patent 1 126 398 (1962); *Chem. Abstr.*, **57**, 11116*f* (1962). [m] Silica, 10% EtOH-EtOAc. [n] F. Reverdin, *Chem. Ber.*, **40**, 3686 (1907), *Beilstein, 4th ed.*, **14**, 438 (1952).

of 50[3a,b]–70%[3c] after a difficult purification. Side reactions can include hydrolysis of the 4-amino group,[3d,4a] oxidative cleavage of the C^9–N^{10} bond,[4b] and chlorination–decarboxylation of the *p*-aminobenzoyl group to afford a 2,4,6-trichloroaniline derivative either prior to or subsequent to cleavage of the C^9–N^{10} bond.[4c,d]

We now report the facile mono- or dichlorination of MTX and other *p*-aminobenzoic acids or amides in 80–100% yield and high purity by using *tert*-butyl hypochlorite in glacial acetic acid and/or other organic solvent. The generality of the method and the excellent control of mono- vs. dichlorination are supported by the examples summarized in Table I. Derivatives are clearly distinguished by TLC (Table I). Unsubstituted, monoalkyl-substituted, and dialkyl-substituted aniline derivatives all show excellent results.

The solubility problem of pteridine analogues is circumvented by using glacial HOAc (1 g/20 mL) at 25 °C or at slightly elevated temperature. Although folic acid is rather insoluble in HOAc at this concentration, treatment of the slurry with *t*-BuOCl gradually gave a homogeneous solution. Other compounds were more conveniently chlorinated in CH_2Cl_2–HOAc solutions. The dichlorination of *p*-(dimethylamino)benzoic acid was accompanied by 5–10% demethylation to 3,5-dichloro-4-(methylamino)benzoic acid. Demethylation was not observed in other instances. For the simple anilines, lower yields were the result of high product solubility in the recrystallization solvents.

Discussion

Previous mechanistic studies[5a,b] confirmed the earlier evidence[5c] of *N*-chloroanilines as intermediates in the aromatic chlorination of aniline derivatives.[5d] The Brønsted plot of the ionic rearrangement with acetate buffer of the *N*-chloro-*p*-substituted anilines revealed an excellent linear correlation and a ρ of −6.35.[5a] In the absence of acetate buffer, a greatly increased reaction rate and a change in product distribution only for anilines with the strongly electron-withdrawing para substituents carboxyethyl and cyano suggested a change in mechanism. Discussion of the control of chlorination has centered on steric and electronic effects. In the present case the presumed initial N-chlorination is analogous to the alkylation of alkyl-substituted anilines with benzyl and 2-methylbenzyl chloride where steric effects rather than electronic effects correlated with reaction rates.[6,7] If a substantial negative ρ obtains for the present examples, then control of mono- vs. dichlorination is the expected result of cooperative steric and electronic effects which retard the reactivity of the monochloro intermediate toward a second chlorination.

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(7) The dramatically different λ_{max} and ϵ of 3,5-dichloro-4-(dimethylamino)benzoic acid are consistent with steric inhibition of resonance.

Experimental Section

TLC was routinely performed on Eastman 13181 silica or 13254 cellulose as detailed in Table I. Melting points were determined on a Mel-Temp apparatus in sealed, Pyrex capillaries and are corrected. The spectrometers used were as follows: Cary 15 (UV), Perkin-Elmer 241MC (polarimetry) with a Lauda RC-3B refrigerated circulator, Varian T-60 (NMR).

3′,5′-Dichloromethotrexate (DCM). Methotrexate disodium salt (Lederle) (5.00 g, 11.0 mmol) was dissolved in 100 mL of glacial HOAc at 25 °C. Slow addition of 2.3 equiv of *t*-BuOCl (Frinton) in 10 mL of HOAc followed by 1 h of reaction gave complete formation of DCM uncontaminated by MTX or monochloromethotrexate (MCM) by TLC. The solution was evaporated to dryness and redissolved in aqueous NaOH. The pH was lowered to 4 with concentrated HCl. The solid was filtered to give DCM (4.63 g, 80%) identical with authentic DCM (Lederle) by TLC, NMR, and UV.

Similarly, 1.1 equiv of *t*-BuOCl afforded 98% (MCM).

3-Chloro-4-(dimethylamino)benzoic Acid. To 3.3 g (20 mmol) of 4-(dimethylamino)benzoic acid (Aldrich) in 100 mL of 10% HOAc–CH_2Cl_2 was added slowly 2.3 g (21 mmol) of *t*-BuOCl in 18 mL of 20% HOAc–CH_2Cl_2 at 25 °C. After 3 h, a second addition of 0.2 mL of *t*-BuOCl in 7 mL of CH_2Cl_2 completely converted the starting material into a single product by TLC (silica). The solution was extracted twice with H_2O (150 mL), dried ($MgSO_4$), and evaporated to dryness. Recrystallization from EtOAc–hexane in two crops afforded 3-chloro-4-(dimethylamino)benzoic acid (2.66 g, 67%).

Acknowledgment. This work was supported by Research Grant No. CA 17718, awarded to Michael Chaykovsky by the National Cancer Institute, Department of Health, Eduation, and Welfare.

Registry No. Dichloromethotrexate, 528-74-5; monochloromethotrexate, 5472-96-8; methotrexate, 59-05-2; dichlorofolic acid, 47748-46-9; folic acid, 59-30-3; dimethyl *N*-(3,5-dichloro-4-aminobenzoyl)-L-glutamate, 72244-64-5; dimethyl *N*-(4-aminobenzoyl-L-glutamate, 52407-60-0; 3,5-dichloro-4-(methylamino)benzoic acid, 51928-43-9; 3-chloro-4-(methylamino)benzoic acid, 72228-73-0; 4-(methylamino)benzoic acid, 10541-83-0; 3,5-dichloro-4-(dimethylamino)benzoic acid, 72228-74-1; 3-chloro-4-(dimethylamino)benzoic acid, 72228-75-2; 4-(dimethylamino)benzoic acid, 619-84-1.

Dipolar Cycloadditions of an Acetylenic Phosphinate

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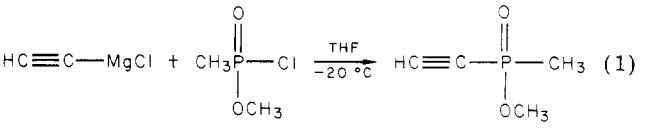
The literature abounds with methods of forming carbon–phosphorus bonds to prepare organophosphinates.[1] Although these transformations allow entry into a variety of chemical architecture, severe limitations are also encountered. For example, the Arbuzov reaction is restricted to a rather narrow range of halide types (primary, benzyl), and often stressing conditions are necessary. These problems are most acute when the carbon–phosphorus bond is formed late in a synthesis (substrates are usually multifunctional). An alternative to late incorporation of a phosphinate group is use of a small organophosphinate, with a reactive organic moiety, as an intermediate. The carbon–phosphorus bond, once formed, is quite stable and surprisingly inert to an array of conditions for carbon transformations.[1] This note describes the synthesis of such a reactive organophosphinate, acetylene **1**, and its use in the preparation of heterocyclic phosphinates.

Results

Equation 1 outlines a successful synthesis of **1**. Addition of the acetylenic Grignard at −20 °C to acid chloride **2** and workup give a 50% isolated yield of **1**. Use of lithium



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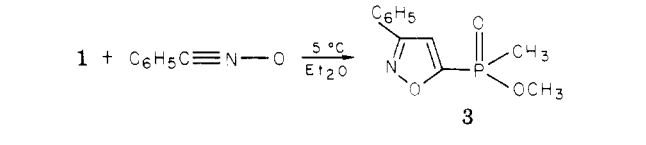
acetylide significantly decreases the yield of **1**. Acetylene **1** is a water-clear, distillable liquid, stable to storage at 0 °C. The ^1H NMR spectrum of **1** is characterized by doublets at δ 1.70 and 3.88 for the methyl groups and a doublet (J_{PH} = 10 Hz) at δ 3.14 for the acetylenic proton. This material is completely miscible with water, and the water used in the workup must be continuously extracted with CH_2Cl_2 to obtain the product in good yield.

Acetylene **1** has been found to be an excellent 1,3-dipolarophile. Reaction of **1** with benzonitrile oxide and 4-chlorobenzonitrile oxide proceeds to give good yields of 5-phosphinylisoxazoles (**3**, 81%; **4**, 53%). The isoxazole



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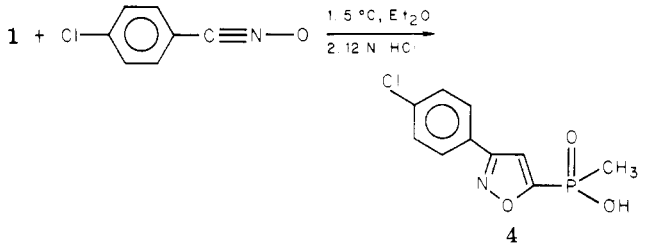

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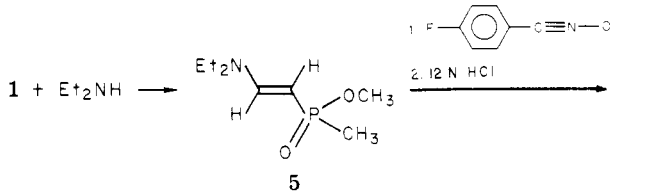

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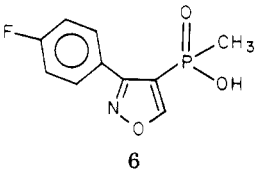

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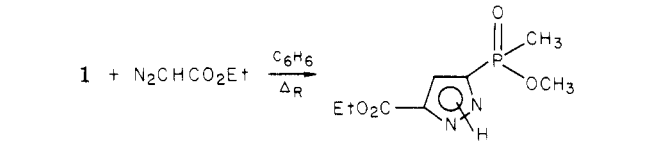

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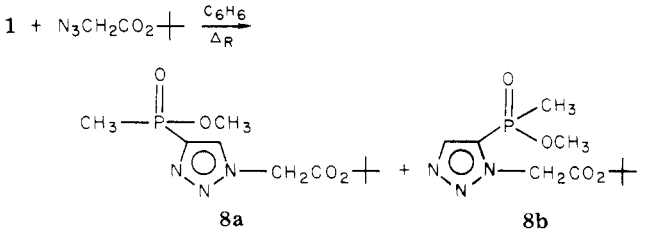

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