Ethylation of Hydroxypyrimidines using Triethyloxonium Tetrafluoroborate (Meerwein's Reagent)

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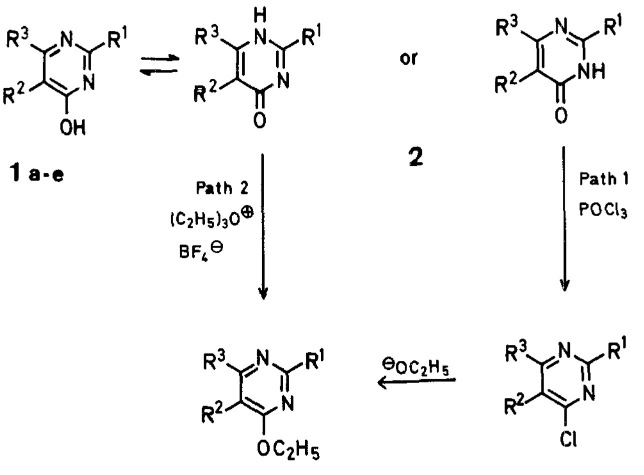
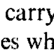
Transformation of hydroxypyrimidines ($1 \rightleftharpoons 2$) into the corresponding *O*-alkylated compounds **3** is normally accomplished[2] by conversion first to the chloro derivative followed by treatment with alkoxide (Path 1). Studies by Tieckelmann, et al.[3] on 2- and 4-hydroxypyrimidines have indicated that *O*-alkylation is always accompanied by significant *N*-alkylation when an alkyl halide is reacted with the salt of the hydroxypyrimidine. This is in contrast to their results[4] on 2-oxo-1,2-dihydropyridinium salts where proper selection of conditions led to selective alkylation of either N or O.

Since the tautomeric equilibrium of hydroxypyrimidines favors the oxo form (**2**), we thought that *O*-alkylation might be achieved by using Meerwein's reagent[5] (triethyloxonium tetrafluoroborate) in a manner analogous to the formation of imino ethers from alicyclic amides[6] (see Path 2).



	R^1	R^2	R^3
a	CH_3	$COOC_2H_5$	H
b	CH_3	H	CH_3
c	NH_2	H	CH_3
1d	OH	H	H
3d	OC_2H_5	H	H
e	CH_3	H	

We have succeeded in carrying out the desired conversion by two methods. In cases where the starting hydroxypyrimidine has sufficient solubility in a solvent such as dichloromethane or liquid sulfur dioxide, a simple homogeneous reaction gave the desired alkylated product in acceptable yield after a few hours reaction at room temperature or the temperature of refluxing sulfur dioxide. When the starting hydroxypyrimidine was too insoluble, some success could be attained by using excess Meerwein's reagent as solvent[7]; i.e., the solid oxopyrimidine and the Meerwein's reagent were added, under nitrogen, to a flask which was heated in an oil bath until the mixture melted (Meerwein's reagent melts at 92°). The hydroxypyrimidine would then dissolve and reaction would take place in this melt. In both cases the reaction was worked up by addition of sodium carbonate (10%) and extraction of the products into dichloromethane which could be washed with dilute base, dried, and evaporated to give the desired products.

It is interesting to note that 2-amino-4-hydroxy-6-methylpyrimidine (**1c**) when reacted with excess Meerwein's reagent gave **3c**, albeit in low yield. Apparently the amine function at the 2-position does not interfere with the desired *O*-alkylation, and is not alkylated itself.

Analytical reagent dichloromethane was dried over Linde 4A molecular sieves. Glassware was dried at 110° and cooled in a stream of dry nitrogen prior to use. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Infra-red spectra were determined on a Perkin-Elmer 237; ^1H-N.M.R. spectra on a Jeolco-C 60-A. Microanalyses were performed by Clark Microanalytical Laboratory, Urbana Illinois. Triethyloxonium tetrafluoroborate (Meerwein's reagent) was prepared according to the published method[5] and stored at 0° under diethyl ether until ready to be used, at which time a portion of the salt was pressed between filter paper to remove the bulk of the ether and then transferred to a previously weighed dry flask. Residual ether was removed on the pump, and the weight of the dry tetrafluoroborate salt determined by difference.

Preparation of Ethyl 4-Ethoxy-2-methylpyrimidine-5-carboxylate (3a):

Ethyl 4-hydroxy-2-methylpyrimidine-5-carboxylate[11] (3.24 g, 17.8 mmol) was dissolved in dry dichloromethane (100 ml) and triethyloxonium tetrafluoroborate (3.38 g, 17.8 mmol) in dry dichloromethane (50 ml) added. The solution was kept under dry nitrogen overnight, then added to 10% sodium carbonate and immediately separated. The basic aqueous solution was extracted with dichloromethane (3 × 20 ml), the combined organic layers dried ($MgSO_4$), and evaporated to give a red oil. Crystallization from hexane gave the product as long white needles; yield: 2.35 g (63%); m.p. 54–55° (Lit.[8]: 53–54.5°). Alternatively, the red oil could be sublimed at 70°/3 torr.

I.R.: no absorption in the region 1640–1680 cm^{-1}.

U.V. (95% C_2H_5OH): $\lambda_{max} = 262$ nm.

^1H-N.M.R. ($CDCl_3$): $\delta = 1.37$ (t, 3H, CH_3), 1.42 (t, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.44 (q, 2H, CH_2), 4.53 (q, 2H, CH_2), 9.00 ppm (s, 1H_{arom}).

Preparation of 2,6-Dimethyl-4-ethoxypyrimidine (3b):

2,6-Dimethyl-4-hydroxypyrimidine (23.0 g, 185 mmol) was added in small portions to dry dichloromethane (100 ml) containing triethyloxonium tetrafluoroborate (38.5 g, 203 mmol). The reaction was stirred under nitrogen overnight and then added to 10% sodium carbonate solution (500 ml). The organic layer was separated, washed with sodium carbonate solution (3 × 50 ml), dried ($MgSO_4$), and evaporated to give a yellow liquid which was distilled to give pure **3b**; yield: 21.4 g (76%); b.p. 68°/2.7 torr.

I.R.: no absorption in the region 1640–1680 cm^{-1}.

U.V. (95% C_2H_5OH): $\lambda_{max} = 250$ nm.

^1H-N.M.R. (CCl_4): $\delta = 1.40$ (t, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.38 (q, 2H, CH_2), 6.25 ppm (s, 1H_{arom}).

The picrate was prepared and purified by recrystallization from ethanol; m.p. 118–119° (Lit.[9]: 124–125°).

Preparation of 2-Amino-4-ethoxy-6-methylpyrimidine (3c):

2-Amino-4-hydroxy-6-methylpyrimidine (2.63 g, 21.0 mmol) was suspended in liquid sulfur dioxide (50 ml) and excess triethyloxonium tetrafluoroborate (12.0 g, 63.2 mmol) added. The solution was stirred under nitrogen for 2 h at −40°, then at −15° for 2 h. Dichloromethane (60 ml) was added, the reaction mixture warmed to room temperature, and the sulfur dioxide allowed to evaporate. The organic layer was filtered to remove unreacted starting material (1.93 g), was then added to an equal volume of 10% sodium carbonate solution, the organic layer separated, and washed with additional sodium carbonate solution. It was then dried and evaporated to give a light brown solid which was recrystallized from hexane to give soft crystals; yield: 0.48 g (15%, or 56% based on recovered starting material); m.p. 86–88°.

$C_7H_{13}N_3O$	calc.	C 54.17	H 8.44	N 27.08
(155.2)	found	55.38	7.52	27.27

I.R.: no absorption in the region 1640–1680 cm^{-1}.

U.V. (95% C_2H_5OH): λ_{max} = 275 nm (Lit.[10]: 276 nm).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.32 (t, 3H, CH_3), 2.18 (s, 3H, Ar-CH_3), 4.23 (q, 2H, CH_2), 5.55 (s, 2H, NH_2), 5.81 ppm (s, 1H$_{arom}$).

Preparation of 2,4-Diethoxypyrimidine (3d):

Triethyloxonium tetrafluoroborate (12.8 g, 67.2 mmol) was placed in a 50 ml, 2-necked, round-bottom flask provided with a magnetic stirring bar, calcium chloride drying tube, and a nitrogen inlet. Uracil (1.88 g, 16.8 mmol) was added and the flask heated in an oil bath. When the bath temperature reached 75° the mixture melted and reaction proceeded with evolution of ether. After 30 min the reaction mixture was added to cold 10% sodium carbonate solution (50 ml) and extracted into dichloromethane (3 × 40 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give a yellow liquid. This was identical on T.L.C. [silica gel, chloroform/methanol (9:1)] to a known sample of **3d**; yield: 1.2 g (43%).

Preparation of 4-Ethoxy-2-methyl-6-phenylpyrimidine (3e):

4-Hydroxy-2-methyl-6-phenylpyrimidine[12] (1.00 g, 5.38 mmol) and *triethyloxonium tetrafluoroborate* (1.02 g, 5.38 mmol) were added to dry dichloromethane (800 ml) and stirred under reflux for 5 h. The solution was cooled to room temperature, filtered, and added to *10% sodium chloride solution*. The organic layer was separated, washed with additional sodium carbonate solution, then water, and dried ($MgSO_4$). The solvent was removed (rotary evaporator) to give **3e** as a clear yellow liquid which was distilled; yield: 0.52 g (46%); b.p. 90–100°/0.2 torr.

I.R.: no absorption in the region 1640–1680 cm^{-1}.

U.V. (95% C_2H_5OH): λ_{max} = 272 nm.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.47 (t, 3H, CH_3), 2.85 (s, 3H, Ar-CH_3), 4.68 (q, 2H, CH_2), 7.13 (s, 1H$_{arom}$), 7.5–8.5 ppm (m, 5H$_{arom}$).

This liquid was converted to the picrate salt and recrystallized from ethanol; m.p. 151–152°.

$C_{19}H_{17}N_5O_8$	calc.	C 51.47	H 3.87	N 15.80
(443.4)	found	51.50	3.90	15.45

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