τ 9.07–8.88 (m, 12 H, 5′-C**H**$_3$), 8.58–8.35 (m, 8 H, 4′-C**H**$_2$), 8.40 (t, 3 H, OCH$_2$C**H**$_3$), 8.33–8.10 (m, 8 H, 3′-C**H**$_2$), 8.00–7.60 (m, 8 H, 2′-C**H**$_2$), 6.45, 6.43, 6.41, 6.40 (each s, 3 H, 1,3,5,7-C**H**$_3$), 6.12–5.87 (m, 8 H, 1′-C**H**$_2$), 5.86 (q, 2 H, OC**H**$_2$CH$_3$), 3.78 (s, 2 H, C**H**$_2$O), 0.11 (s, 1 H, γ-*meso*-**H**), −0.06 (s, 2 H, β,δ-*meso*-**H**); MS, *m/e* (rel intensity) 704 (M^+, 69), 660 (100), 646 (31), 589 (14), 532 (7), 475 (3), 417 (1), 352 (1); vis λ_{max} (CH_2Cl_2) 404 (ϵ 155 000), 505 (11 700), 540 (8000), 575 (5900), 628 (4000), and 659 nm (700). Anal. Calcd for $C_{47}H_{68}N_4O$: C, 80.06; H, 9.72; N, 7.95. Found: C, 79.86; H, 9.88; N, 7.72.

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Direct Metalation of Pyrimidine. Synthesis of Some 4-Substituted Pyrimidines

Thomas J. Kress

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

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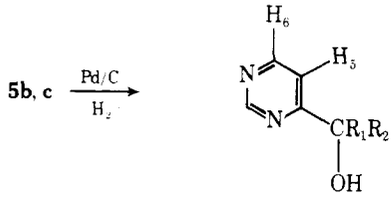
Direct metalation of 5-bromopyrimidine with lithium diisopropylamide afforded 4-lithio-5-bromopyrimidine. The intermediate lithiopyrimidine could be trapped by a variety of carbonyl compounds, giving 5-bromo-4-pyrimidine carbinols which were easily dehalogenated. The structure of each product was determined by ^{1}H NMR, mass spectra, and elemental analyses. The stability of the lithiopyrimidine was also examined. This simple two-step method represents a new method of entry into the 4-position of pyrimidine.

Considerable interest has been centered on the reaction of halogen-substituted heterocycles with strong base. Several comprehensive reviews have appeared on the subject, and evidence has been presented that these reactions do not always occur by a single pathway but instead proceed via competing mechanisms.[1,2] One of these pathways is the elimination–addition (EA) mechanism, where the position ortho to the halogen atom is first deprotonated or metalated prior to elimination of halide or metal halide. The resulting aryne can then add a nucleophile, affording the product. In the case of pyrimidine, the existence of the proposed aryne intermediate has recently been demonstrated by Promel and co-workers by the trapping of 2-*tert*-butyl-4,5-pyrimidyne with furan.[3] We now wish to report conclusive evidence for the existence of 4-lithio-5-bromopyrimidine (**2**), another intermediate in this scheme, and present some data on its stability.

Results and Discussion

The lithiopyrimidine **2**, generated by reaction of 5-bromopyrimidine (**1**) with lithium diisopropylamide (LDA), could be intercepted by a variety of carbonyl compounds to give the 4,5-disubstituted pyrimidines **5a–c** listed in Table I.

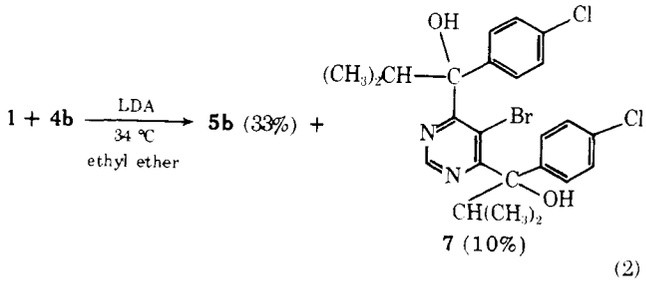
The structure of each carbinol **5a–c** was readily determined by physical data (elemental analysis, ^{1}H NMR, mass spectrum) and finally by removal of bromine from **5b** and **5c** by catalytic reduction giving the 4-substituted pyrimidines **6a** and **6b** (eq 1). The appearance of a new AB system in the ^{1}H NMR spectra of **6a** and **6b** (due to H_5–H_6 coupling) confirmed the position of substitution in **5a–c** and **6a,b.**



(1)

6a, R_1 = *p*-ClPh; R_2 = $CH(CH_3)_2$
b, R_1 = Ph; R_2 = H

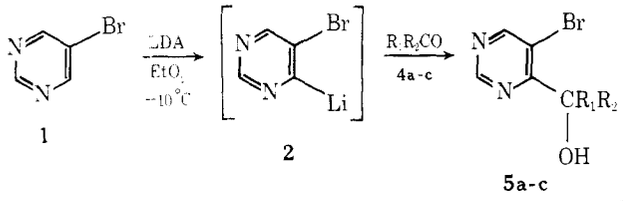
The stability of **2** was of interest with respect to temperature and mode of reagent addition. When the metalation reaction (eq 2) was performed in refluxing ethyl ether with the ketone **4b**, in addition to the major product **5b** a disubstituted carbinol was also formed. The symmetrical ^{1}H NMR pattern for the isopropyl and phenyl moieties established **7** as the structure of this product. At lower temperature (−65 vs. −10 °C), reaction of **2** with benzaldehyde (**4c**) afforded only a 5% yield improvement.



(2)

0022-3263/79/1944-2081$01.00/0

Table I. Synthesis of Some 4,5-Disubstituted Pyrimidines

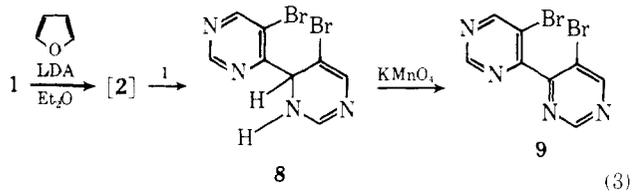


1 2 5a-c

compd	R_1	R_2	% yield
a	*p*-FPh	*o*-ClPh	25
b	*p*-ClPh	$CH(CH_3)_2$	40
c	Ph	H	36 (41)[a]

[a] This yield was obtained at a reaction temperature of −65 °C.

Although the stepwise addition of LDA to **1** followed by benzaldehyde (**4c**) at either −10 or −65 °C gave no isolable pyrimidine product, slightly different conditions and workup gave positive results. The generation of **2** in the presence of 2 mol of furan (an electrophile trap for any 4,5-pyrimidyne which might be formed) afforded the dihydropyrimidylpyrimidine **8** in 32% yield (eq 3).[4] Due to the facile oxidation of **8** by air, its structure was determined spectroscopically (^1H NMR, high-resolution mass spectrum) and finally by complete oxidation to the symmetrical 4,4′-pyrimidylpyrimidine **9**.



8 **9** (3)

These results indicate that the relative rate of lithium bromide loss from **2** to form a hetaryne must be considerably slower than the rate of addition of **2** to a carbonyl group or to a carbon–nitrogen bond such as in **1**.

Experimental Section[5]

^1H NMR spectra were determined on a Varian T-60 spectrometer. The high-resolution spectrum was determined on a Model 21-110 Consolidated Electrodynamics Corp. spectrometer. Other mass spectra were determined on a Hitachi RMU-6E spectrometer. Melting points were run on a Thomas Hoover apparatus and were corrected. Elemental analyses were performed by Mr. G. Maciak and associates of Eli Lilly and Co.

General Procedure. (Synthesis of 4-Substituted 5-Bromopyrimidines). To a mixture of 5-bromopyrimidine (**1**) (7.95 g; 0.05 mol) and the appropriate carbonyl compound (0.05 mol) in 200 mL of ethyl ether at −10 °C (ice–methanol bath) was added dropwise over 0.5-h a freshly prepared solution of LDA [made from 31.5 mL (0.05 mol) of 15% butyllithium in hexane and 7.0 mL (0.05 mol) of diisopropylamine] in 100 mL of ethyl ether. After being stirred for 2 h at 0 °C to −10 °C, 100 mL of 7% aqueous hydrochloric acid was added. The organic layer was separated, washed with water (4 × 100 mL), dried over magnesium sulfate, filtered, and evaporated in vacuo affording the crude product.

5-Bromo-α-(2-chlorophenyl)-α-(4-fluorophenyl)-4-pyrimidinemethanol (5a). The crude product was chromatogrammed on silica gel and eluted with methylene chloride affording 5.0 g of white crystals (25.5%). Recrystallization from hexane gave cubes: mp 145–147 °C; mass spectrum *m/e* M^+ 392, 394, 396 (BrCl isotopes), 357, 359 (base peak, $M^+ - Cl$); ^1H NMR ($CDCl_3$) δ 5.97 (s, 1, OH), 7.20 (multiplet, 8, phenyl rings), 9.05 (s, 1 H-2 pyrimidine), 8.78 (s, 1, H-6 pyrimidine).

5-Bromo-α-(4-chlorophenyl)-α-(1-methylethyl)-4-pyrimidinemethanol (5b). The product mixture was chromatogrammed as in the case of **5a** giving 5.6 g (33%) of white crystalline **5b**. Recrystallization from methylcyclopentane gave cubes: mp 83–85 °C; mass spectrum *m/e* M^+ 340, 342, 344 (BrCl isotopes), 297, 299, 301 (base peak, $M^+ -$ isopropyl); ^1H NMR ($CDCl_3$) δ 6.00 (s, 1, OH), 7.30 (9, 4, phenyl ring), 3.50 (heptuplet, 1, –CH– isopropyl, J = 6.0 Hz), 1.06 and 0.71 (6, $-(CH_3)_2$ nonequivalent, J = 6.0 Hz), 9.10 (s, 1, H-2 pyrimidine), 8.70 (s, 1, H-6 pyrimidine).

5-Bromo-α-phenyl-4-pyrimidinemethanol (5c). To the crude product was added 50 mL of water, and the unreacted benzaldehyde was removed by steam distillation. The resulting oil was extracted into ethyl ether, dried over magnesium sulfate, filtered, and evaporated affording 4.8 g (36%) of **5c** as a clear amber oil which crystallized on standing. Recrystallization from ethanol gave white cubes: mp 88–89 °C; ^1H NMR ($CDCl_3$) δ 4.90 (d, 1, OH, J = 8.0 Hz), 5.96 (d, 1, benzylic CH, J = 8.0 Hz), 7.33 (s, 5, phenyl), 1.15 (s, 1, H-2 pyrimidine), 8.73 (s, 1, H-6 pyrimidine).

α-(4-Chlorophenyl)-α-(1-methylethyl)-4-pyrimidinemethanol (6a). **5b** (700 mg, 2.05 mmol), triethylamine (207 mg, 2.05 mmol), 10% Pd/C (100 mg), in 140 mL of ethanol was treated in a Parr shaker under 50 psi of hydrogen for 15 min. The mixture was filtered and evaporated to dryness, and to the residue was added 50 mL of water. The mixture was extracted with chloroform (3 × 50 mL), dried over magnesium sulfate, filtered, and evaporated giving 530 mg (ca. 100%) of **6a** as white crystals. Recrystallization from methylcyclopentane gave needles: mp 114–117 °C; ^1H NMR ($CDCl_3$) δ 4.00 (s, 1, OH), 6.50 (heptuplet, 1, isopropyl CH, J = 6.0 Hz), 0.90 and 0.70 (d, 6, nonequivalent, $(CH_3)_2$, J = 6.0 Hz), 7.50 (m, 5, phenyl), 9.10 (d, 1, H-2 pyrimidine, J = 5.0 Hz), 7.50 (m, 1, H-6 pyrimidine proton buried under phenyl multiplet).

α-Phenyl-4-pyrimidinemethanol (6b). Compound **5c** (500 mg, 1.88 mmol) was reduced by the same procedure as **6a.** Crystallization of the crude product from methylcyclopentane afforded white cubes: 210 mg (60%); mp 95–96 °C; ^1H NMR ($CDCl_3$) δ 4.76 (s, 1, OH), 5.73 (s, 1, methine), 7.33 (s, 5, phenyl), 7.30 (d, 1, H-6 pyrimidine, J = 5.0 Hz), 8.63 (d, 1, H-4 pyrimidine, J = 5 Hz), 9.16 (s, 1, H-2 pyrimidine).

5-Bromo-α,α′-bis(4-chlorophenyl)-α,α′-bis(1-methylethyl)-4,6-pyrimidinedimethanol (7). The general procedure was followed except that the reaction mixture was refluxed for 2 h. The crude product was chromatogrammed as in the case of **5a** affording 1.4 g (10%) of a white solid. Recrystallization from methylcyclopentane gave white cubes: mp 155–159 °C; mass spectrum *m/e* M^+ 522, 524, 526, 528 ($BrCl_2$ isotopes); ^1H NMR ($CDCl_3$) δ 6.02 (s, 2, OH), 7.26 (s, 8, phenyl rings), 3.38 (heptuplet, 2, –CH–isopropyl, J = 6.0 Hz), 1.05 and 0.47 (12, $-(CH_3)_2$ nonequivalent, J = 6.0 Hz), 9.01 (s, 1, H-2 pyrimidine).

4-(5-Bromo-4-pyrimidyl)-1,2-dihydro-5-bromopyrimidine (8). The general procedure was followed except that 6.8 g (0.1 mol) of furan was added to the 5-bromopyrimidine. The organic layer contained a trace of **1**. The acidic aqueous layer was adjusted to pH 10, giving a thick black gum. The gum was continuously extracted with chloroform. The chloroform layer was dried, filtered, and concentrated in vacuo, affording 2.6 g (32%) of a tan solid. Attempted crystallization or salt formation resulted in formation of a new spot by TLC (silica gel, 1:1 ethyl acetate–toluene) corresponding to **9**: ^1H NMR was taken on the crude tan solid, ($CDCl_3$) δ (s, 1, H-2 pyrimidine), 8.85 (s, 1, H-4 pyrimidine), 7.50 (br s, 1, exchangeable NH dihydropyrimidine), 7.10 (s, 1, H-2 dihydropyrimidine), 6.55 (s, 1, H-6 dihydropyrimidine), 6.00 (s, 1, H-4 dihydropyrimidine), 6.00 (s, 1, H-4 dihydropyrimidine); mass spectrum *m/e* M^+ 316, 318, 320 (two Br isotopes), 236, 238 ($M^+ -$ HBr), 182, 184 ($M^+ -$ 2HCN), 159–161 (base peak, $M^+ - C_4H_2BrN_2$, 5-bromo-4-pyrimidyl); exact mass, M^+, calcd for $C_8H_6{}^{79}Br^{81}BrN_4$, 317.8940 and found, 317.8925.

4-(5-Bromo-4-pyrimidyl)-5-bromopyrimidine (9). A mixture of 800 mg (25.2 mmol) of **8**, 790 mg (50 mmol) of potassium permanganate, and 100 mL of acetone was stirred at 25 °C for 6 h and filtered through celite; the filtrate was evaporated to dryness giving a clear yellow oil (400 mg, 50%) which crystallized on scratching. The solid was sublimed at 80 °C (15 mm) affording white crystals: mp 87–89 °C; mass spectrum *m/e* M^+ 314, 316, 318 (base peak, two Br isotopes), 287, 289, 291 ($M^+ -$ HCN), 260, 262, 264 ($M^+ -$ 2HCN), 235, 237 ($M^+ -$ Br); ^1H NMR ($CDCl_3$) δ 9.23 (s, 2, H-2 and 2′), 9.02 (s, 2, H-4 and 4′).

Registry No.—**1**, 4595-59-9; **2**, 69927-51-1; **4a**, 1806-23-1; **4b**, 18713-58-1; **4c**, 100-52-7; **5a**, 69927-43-1; **5b**, 69927-44-2; **5c**, 69927-45-3; **6a**, 69927-46-4; **6b**, 69927-47-5; **7**, 69927-48-6; **8**, 69927-49-7; **9**, 69927-50-0.

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(4) The structure of **8** could, of course, be represented as the 1,4-addition product.
(5) The editor has been supplied with acceptable C, H, N analyses for compounds **5a–c**, **6a,b**, **7**, and **9**.