Facile Preparation of 6-Substituted Uracils

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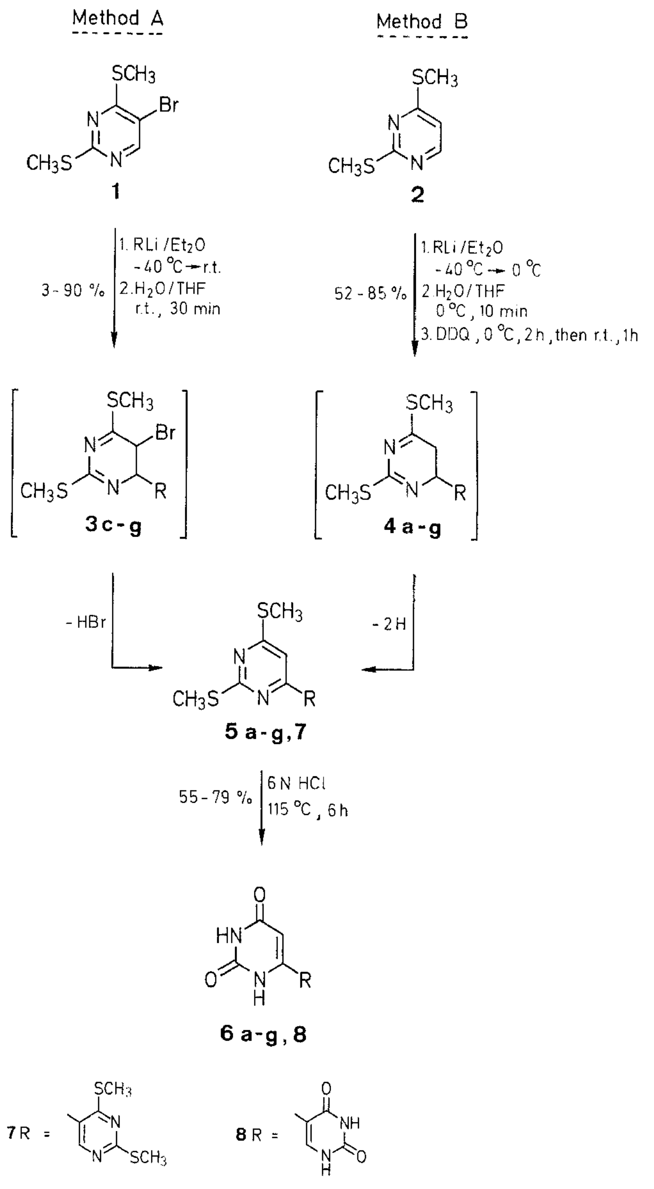
6-Substituted 2,4-bis(methylthio)pyrimidines **5** are obtained in the reaction of (i) 5-bromo-2,4-bis(methylthio)pyrimidine (**1**) with aryllithium and heteroaryllithium reagents, followed by spontaneous dehydrobromination of the intermediate bromo dihydropyrimidines **3** or (ii) 2,4-bis(methylthio)pyrimidine (**2**) with alkyllithium, aryllithium, and heteroaryllithium reagents, followed by aromatization of the intermediate dihydropyrimidines **4** with DDQ. Hydrolysis of these compounds produces 6-substituted uracils **6**.

To date the only general and practical approach to the synthesis of 6-substituted uracils has been the construction of the pyrimidine ring in the classical condensation reaction of β-oxo esters with thiourea or *S*-alkylisothiourea, followed by hydrolysis of the intermediate 2-thio- or 2-alkylthiopyrimidines.[1] In this communication we wish to report two new routes to 6-substituted uracils that are based on the addition reaction of organolithium reagents with readily available 5-bromo-2,4-bis(methylthio)pyrimidine (**1**) (Method A) and 2,4-bis(methylthio)pyrimidine (**2**) (Method B). The resultant dihydropyrimidines **3** and **4** are aromatized to pyrimidines **5**. Subsequent hydrolysis of **5** produces uracils **6**.

Method A is an extension of our earlier work on the synthesis of bipyrimidines from 5-bromopyrimidines and more recent mechanistic studies on this reaction.[2] We have shown previously that a mixture of **1** and its 5-lithio derivative (obtained upon treatment of **1** with 0.5 molar equivalent of butyllithium) produces unstable dihydropyrimidine **3** [R = 2,4-bis(methylthio)pyrimidin-5-yl], which undergoes spontaneous dehydrobromination at 0 °C to yield 2,2′,4′,6-tetrakis(methylthio)-4,5′-bipyrimidine (**7**). Hydrolysis of **7** produced 5,6′-biuracil (**8**).



3–6	R
a	CH_3
b	n-C_4H_9
c	C_6H_5
d	2-$CH_3OC_6H_4$
e	2-thienyl
f	3-thienyl
g	2-thiazolyl

In this work we have examined the reaction of other lithium reagents with **1**. Good yields of pyrimidines **5c, e, f, g** are obtained from the respective, sterically unhindered phenyl-, 2-thienyl-, 3-thienyl-, and 2-thiazolyllithium reagents (Table 1). However, the reaction of 2-methoxyphenyllithium with **1** gave the desired pyrimidine **5d** in a very low yield, pyrimidine **2** and 2-bromo-anisole being the major products. This result indicates an extensive bromine-lithium exchange reaction between **1** and the lithium reagent. For the same reason, Method A failed to produce 6-methyl- and 6-butylpyrimidines, **5a** and **5b**, in the reaction of **1** with methyllithium and butyllithium, respectively, under a variety of experimental conditions.

The undesired bromine-lithium exchange reaction is avoided in Method B. An organolithium reagent, RLi, is reacted with pyrimidine **2** to give a 5,6-dihydropyrimidine **4**, which is then dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). We have shown recently that products **4**, in general, are unstable and cannot be isolated.[3] They hydrolyze to 5,6-dihydropyrimidin-4(3*H*)-ones and polymerize easily. However, this difficulty is avoided if the mixture is quenched at 0 °C with only one equivalent of water and then treated with DDQ at 0 °C. This route gives excellent yields of pyrimidines **5**, including compounds that cannot be obtained in Method A.

The examples cited in Table 1 are representative of the many successful aromatizations of unstable 5,6-dihydropyrimidines conducted at low temperatures by the DDQ method. Recently, we have also reported a similar facile dehydrogenation of 1,6-dihydropyrimidines.[2]

Table 1. Syntheses of Compounds **5c–g** from Pyrimidine **1** (Method A) and Compounds **5a–g** from Pyrimidine **2** (Method B), and Hydrolysis of **5a–g** to Uracils **6a–g**

Reaction of Pyrimidines **1**, **2** with R-Li				Hydrolysis of **5**	
Method	Conditions: Temp./Time	Product	Yield (%)	Product	Yield (%)
B	0 °C/1 h	**5a**	85	**6a**	73
B	0 °C/1 h	**5b**	77	**6b**	76
A	−30 °C/0.3 h	**5c**	82	**6c**	79
B	23 °C/1 h	**5c**	83		
A	−20 °C/1 h	**5d**	3	**6d**	60
B	−20 °C/1 h	**5d**	70		
A	−20 °C/0.3 h	**5e**	90	**6e**	66
B	23 °C/1 h	**5e**	76		
A	−35 °C/1 h	**5f**	33	**6f**	75
B	−10 °C/1 h	**5f**	76		
A	−20 °C/1 h	**5g**	77	**6g**	55
B	−10 °C/1 h	**5g**	52		

For both Methods A and B it is essential that ethyl ether is used as the medium for the addition reaction. Tetrahydrofuran promotes bromine-lithium exchange and lithiation reactions that result in much lower yields of **5**. Hydrocarbon solvents cannot be used, because of the low solubility of **1** and **2** in these solvents.

Hydrolysis of **5** to uracils **6** is best conducted using 6 normal hydrochloric acid. The conditions employed permit isolation of thienyluracils **6e** and **6f** in good yields. The methoxy group in **6d** is also stable to hydrolysis under these conditions. In agreement with the given, general structures for products **5** and **6**, pyrimidines **5a** and **5c** are hydrolyzed to known 6-methyluracil[4] (**6a**) and 6-phenyluracil[5] (**6c**), respectively. Properties of new pyrimidines **5** and uracils **6** are given in Table 2.

n-Butyllithium (2.6 M in hexanes), methyllithium (1.4 M in ether), and phenyllithium (1.8 M in cyclohexane/ether) were obtained from Aldrich. 5-Bromo-2,4-bis(methylthio)pyrimidine[6] and 2,4-bis(methylthio)pyrimidine[7] were prepared, and 2-thienyllithium and 2-thiazolyllithium[8] in ether were generated as described. Solutions of 2-methoxyphenyllithium and 3-thienyllithium in ether were generated in the reaction of butyllithium with one mole equivalent of 2-bromoanisole and 3-bromothiophene, respectively. The solution of butyllithium was added dropwise to the ether solution of the respective bromo compound at −40 °C, and the mixture was stirred at −40 °C for 20 min before use. Ether was distilled from sodium benzophenone ketyl immediately before use.

6-Substituted 2,4-Bis(methylthio)pyrimidines 5a–g; General Procedures:

Method A: To a solution of an organolithium reagent R-Li (10 mmol) in ether (50 mL) under nitrogen atmosphere at −40 °C is added

Table 2. Properties[a] of Pyrimidines **5** and Uracils **6**

Compound	mp[b] (°C)	Molecular Formula[c]	^{1}H-NMR[d] δ, J(Hz)	MS[e] *m/z* (%)
5b	oil	$C_{10}H_{16}N_2S_2$ (228.4)	0.7–2.0 (m, 7H); 2.57 (s + t, 8H); 6.64 (s, 1H, H-5)	228 (16), 199 (11), 186 (100)
5c	74.5–76	$C_{12}H_{12}N_2S_2$ (248.4)	2.59 (s, 3H); 2.62 (s, 3H); 7.19 (s, 1H, H-5); 7.43 (m, 3H); 8.0 (m, 2H, H-2′, H-6′)	248 (100), 233 (27), 215 (44), 202 (24), 187 (21), 128 (44), 77 (34)
5d	78–79	$C_{13}H_{14}N_2OS_2$ (278.4)	2.59 (s, 3H); 2.62 (s, 3H); 3.85 (s, 3H); 6.90–7.45 (m, 3H); 7.54 (s, 1H, H-5); 7.95–8.15 (m, 1H, H-6′)	278 (100), 263 (23), 245 (27)
5f	94–95	$C_{10}H_{10}N_2S_3$ (254.4)	2.56 (s, 3H); 2.59 (s, 3H); 7.00 (s, 1H, H-5); 7.30 (2d, 1H, $J_{2'-5'}$ = 3.0, $J_{4'-5'}$ = 5.1, H-5′); 7.52 (2d, 1H, $J_{2'-4'}$ = 1.3, $J_{4'-5'}$ = 5.1, H-4′); 8.02 (2d, 1H, $J_{2'-4'}$ = 1.3, $J_{2'-5'}$ = 3.0, H-2′)	254 (100), 239 (25), 221 (27)
5g	143–144	$C_9H_9N_3S_3$ (255.4)	2.56 (s, 3H); 2.60 (s, 3H); 7.43 (d, 1H, $J_{4'-5'}$ = 3); 7.57 (s, 1H, H-5); 7.88 (d, 1H, $J_{4'-5'}$ = 3)	255 (100), 240 (36), 222 (18), 194 (16), 162 (24), 135 (18)
6b	180.5–181	$C_8H_{12}N_2O_2$ (168.2)	0.7–1.9 (m, 7H); 2.30 (t, 2H); 5.30 (s, 1H, H-5); 10.7 (br s, 2H, NH)	168 (16), 126 (100), 83 (52), 68 (16)
6d	239–240.5	$C_{11}H_{10}N_2O_3$ (218.2)	3.80 (s, 3H); 5.49 (s, 1H, H-5); 6.85–7.65 (m, 4H); 10.78 (br s, 1H, NH); 10.95 (br s, 1H, NH)	218 (100), 160 (96), 104 (42)
6e	> 320	$C_8H_6N_2O_2S$ (194.2)	5.75 (s, 1H, H-5); 7.20 (m, 1H, H-4′); 7.88 (m, 2H, H-3′, H-5′); 11.10 (br s, 2H, NH)	194 (100), 151 (32), 110 (85)
6f	291–293	$C_8H_6N_2O_2S$ (194.2)	5.97 (s, 1H, H-5); 7.62 (m, 2H, H-4′, H-5′); 8.32 (m, 1H, H-2′); 11.98 (br s, 2H, NH)	194 (100), 151 (28), 110 (49)
6g	282–285	$C_7H_5N_3O_2S$ (195.2)	6.10 (s, 1H, H-5); 8.04 (s, 2H, H-4′, H-5′); 11.1 (br s, 2H, NH)	195 (100), 124 (37), 111 (19), 85 (19), 68 (27), 58 (27)

[a] Compounds **5a**, **5e**, **6a**, **6c** [mp/Lit. mp (°C): 42–43/43–45,[10] 101–101.5/101–101.5,[2] 313–316/> 310,[4] 273–275/272–274,[5] respectively] gave virtually identical ^{1}H-NMR spectra with those of the samples obtained from other sources.

[b] Uncorrected.

[c] Satisfactory microanalyses obtained: C ± 0.2, H ± 0.1, N ± 0.2.

[d] Spectra of pyrimidines **5** and uracils **6** were taken in $CDCl_3$ and DMSO-d_6, respectively, with TMS as internal reference; Varian EM-360 (60 MHz) spectrometer.

[e] Varian MAT 112S spectrometer, at 70 eV.

dropwise a solution of 5-bromo-2,4-bis(methylthio)pyrimidine (**1**; 2.4 g, 9.6 mmol) in ether (5 mL). The mixture is allowed to react under the conditions given in Table 1. The mixture is then quenched with water (3 mL) in THF (7 mL), and stirred at 23 °C for 0.5 h. The ether layer is separated, the aqueous residue is extracted with CH_2Cl_2 (2 × 10 mL), and the organic solutions containing **5** are combined. Products **5c–g** are isolated by flash chromatography[9] on silica gel eluting with CH_2Cl_2/hexanes (1 : 3), and recrystallized from hexanes.

Method B: 2,4-Bis(methylthio)pyrimidine (**2**; 1.65 g, 9.6 mmol) is reacted with an organolithium reagent R-Li (10 mmol) under the conditions given in Table 1. The mixture is then quenched with water (0.2 mL, 11 mmol) in tetrahydrofuran (5 mL) at 0 °C, stirred at 0 °C for 10 min, and treated with a solution of DDQ (2.7 g, 11.9 mmol) in THF (20 mL). After stirring at 0 °C for 2 h and then at 23 °C for 1 h, the mixture is diluted with ether (50 mL) and extracted with 10% NaOH solution (3 × 25 mL). The organic phase is dried (Na_2SO_4) and concentrated. Products **5a–g** are isolated by chromatography as described in Method A, and recrystallized from hexanes (**5a** and **5c–g**) or distilled on a Kugelrohr apparatus (**5b**, 80 °C/5 Torr).

Uracils 6a–g; General Procedure:

A solution of the appropriate bis(methylthio)pyrimidine **5a–g** (3 mmol) in 6 N HCl (15 mL) is heated at 115 °C for 6 h in a pressure vessel. The acid is then evaporated on a rotary evaporator, and the residue is recrystallized from EtOH. Analytical samples are obtained by drying at 140 °C/0.1 Torr. Compounds **5a–g** are also hydrolyzed within 7 h under reflux conditions. This latter procedure requires frequent removal of crystals of compounds **5a–g** from the reflux condenser.

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