A New Route to 5,6-Dihydropyrimidin-4(3*H*)-ones

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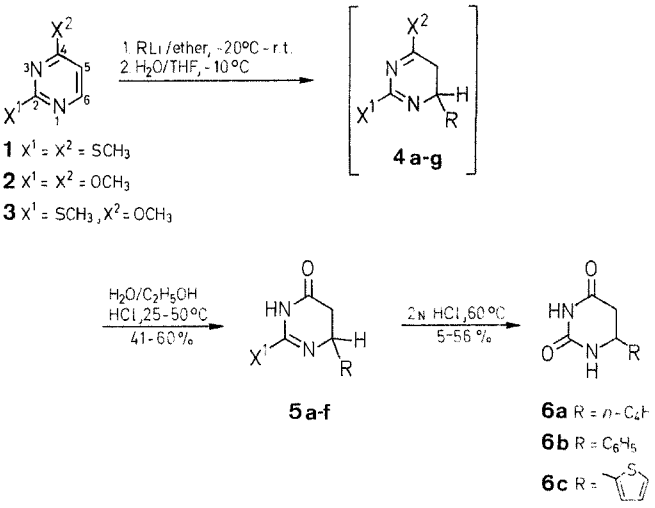
The addition reaction of 2,4-bis(methylthio)pyrimidine or 2,4-dimethoxypyrimidine with organolithium reagents produces unstable 6-substituted 2,4-bis(methylthio)-5,6-dihydropyrimidines and 2,4-dimethoxy-5,6-dihydropyrimidines, respectively. The regioselective hydrolysis of these addition products gives the respective 6-substituted 2-methylthio-5,6-dihydropyrimidin-4(3*H*)ones and 6-substituted 2-methoxy-5,6-dihydropyrimidin-4(3*H*)ones. The methoxy products can be hydrolyzed further to 6-substituted dihydrouracils.

5,6-Dihydropyrimidin-4-ones have been obtained through condensations of 3-aminopropanoic acids with 1-(*N*-alkyliminomethyl)imidazoles[1] or ethyl benzimidate,[2] cycloaddition of amidines to diphenylcyclopropenone,[3] condensation of a non-enolizable dimethyl derivative of ethyl acetoacetate with 2-alkylisothioureas or 2-methylisourea,[4] and in several related preparations.[5]

We have found that 5,6-dihydropyrimidin-4-(3*H*)ones **5a–d** are easily prepared through the addition reaction of organolithium reagents with readily available 2,4-bis(methylthio)pyrimidine **(1)**, followed by regioselective hydrolysis of the resultant dihydropyrimidines **4a–d** (Table 1). In the same way, the addition reaction with 2,4-dimethoxypyrimidine **(2)** is followed by hydrolysis of the intermediate dihydropyrimidines **4e, f** to furnish the respective 5,6-dihydropyrimidin-4(3*H*)ones **5e, f**. In agreement with the regioselective, hydrolytical removal of the 4-SCH_3 or 4-OCH_3 group in **4**, both intermediate dihydropyrimidines **4c** and **4g** are hydrolyzed to the same dihydropyrimidinone **5c**. The two-step transformations are conveniently conducted in one reaction vessel without isolation of dihydropyrimidines **4**. Modest yields of **5** are obtained but this inconvenience is offset by simplicity of the experimental procedure.

Dihydropyrimidinones **5** can be hydrolyzed further to dihydrouracils **6** which are convenient precursors in the preparation of β-amino acids.[6] Thus, compounds **5b** and **5f** were hydrolyzed to the known dihydrouracils[7,8] **6b** and **6c**, respectively. In a similar way, hydrolysis of **5a** and **5e** gave dihydrouracil **6a**. However, good yields of **6** were obtained from methoxy compounds only.

Due to hydrolytical instability and ease of polymerization, even at −20°C, the oily intermediate dihydropyrimidines **4a, b, c** and **4e, f, g** could not be fully characterized. However, the more stable and crystalline thiazolyl derivative **4d** was obtained in an analytically pure form. As shown by ^{1}H-NMR spectroscopy, compound **4d** is a 5,6-dihydro tautomer. Thus, it did not exchange deuterons for protons upon treatment of a $CDCl_3$ solution with D_2O, and gave an ABX pattern for 5,5-H_2 (AB) and 6-H (X) (Table 2). Since similar spectra were obtained for other crude adducts **4**, all these compounds are probably 5,6-dihydro tautomers. This is an interesting observation because all known examples of similar addition reactions with other pyrimidines do not produce a 5,6-dihydropyrimidine, a 1,6(or 3,4)-dihydro derivative being the isomer most frequently observed.[5]



4	X^1	X^2	R
a	SCH_3	SCH_3	n-C_4H_9
b	SCH_3	SCH_3	C_6H_5
c	SCH_3	SCH_3	2-thienyl
d	SCH_3	SCH_3	2-thiazolyl
e	OCH_3	OCH_3	n-C_4H_9
f	OCH_3	OCH_3	2-thienyl
g	SCH_3	OCH_3	2-thienyl

5	X^1	R
a	SCH_3	n-C_4H_9
b	SCH_3	C_6H_5
c	SCH_3	2-thienyl
d	SCH_3	2-thiazolyl
e	OCH_3	n-C_4H_9
f	OCH_3	2-thienyl

Table 1. Syntheses of Dihydropyrimidinones **5a–f**

Reaction of Compounds **1**, **2**, **3** with R–Li				Hydrolysis of **4**		
Pyrimidine	Organolithium Reagent	Conditions Temperature, Time	Product	Conditions pH, Temperature, Time	Product	Yield[a,b] (%)
1	Butyllithium	0°C, 1 h	**4a**	4.0, 50°C, 1 h	**5a**	45
1	Phenyllithium	23°C, 1 h	**4b**	6.0, 50°C, 1 h	**5b**	48
1	2-Thienyllithium	23°C, 1 h	**4c**	6.0, 50°C, 1 h	**5c**	49
1	2-Thiazolyllithium	−10°C, 1 h	**4d**[a]	1.0, 50°C, 2 h	**5d**	60
2	Butyllithium	−20°C, 0.5 h	**4e**	7.0, 25°C, 24 h	**5e**	41
2	2-Thienyllithium	23°C, 0.5 h	**4f**	6.0, 25°C, 1 h	**5f**	51
3	2-Thienyllithium	0°C, 1 h	**4g**	4.0, 30°C, 1 h	**5c**	46

[a] Satisfactory microanalyses were obtained: C ±0.2, H ±0.1, N ±0.2.
[b] Yield of products isolated by flash chromatography[14] and based on pyrimidines **1**, **2**, **3**.

The 5,6-saturation site is retained in the hydrolysis products **5**. The ^{1}H-NMR spectra of **5** taken in an anhydrous $CDCl_3$ or DMSO-d_6 solution (Table 2) gave the ABX patterns for 5,5-H_2 and 6-H, similar to those of **4**, and a slightly broadened singlet for N—H. Sharp two doublets for H-6 in **5b, c, d, f** were observed, which strongly suggested the location of the imino proton 3-H in **5**. Accordingly, dihydrouracils **6b** and **6c** (Table 2) gave two broad doublets for 6-H due to additional coupling with the adjacent imino proton. The location of the imino proton 3-H in **5** was confirmed with the help of proton nuclear Overhauser difference spectroscopy. Thus, irradiation of 6-H in **5b** gave strong NOE signals to 5,5-H_2 of the pyrimidine ring and *ortho*-protons of the phenyl ring, but not to N—H of the pyrimidine. In the same way, irradiation of the imino proton 3-H resulted in an NOE signal at the methylthio group but not at 6-H. It should be noted that under similar conditions we have observed NOE interactions between N—H and 6-H for 1,6-dihydropyrimidines.[9]

Table 2. Properties of Compounds **4d**, **5a–f**, **6a, b, c**

Compound	m.p. (°C)	Molecular Formula or m.p. (°C) reported	MS *m/e* (%)	IR (Nujol) ν(cm^{-1})	^{1}H-NMR[a] δ(ppm)
4d	113–114	$C_9H_{11}N_3S_3$ (257.4)	257 (56), 137 (100)		2.43 (2d, 5-H, A); 2.46 (s, 3H); 3.04 (2d, 5-H, B); 4.84 (2d, 6-H, X); 7.29 (d, 1H, J = 3 Hz); 7.75 (d, 1H, J = 3 Hz); J_{AB} = 16 Hz, J_{AX} = 13.5 Hz, J_{BX} = 5.4 Hz
5a	74–76	$C_9H_{16}N_2OS$ (200.3)	200 (19), 143 (100)	1692, 1628	0.85–1.7 (m, 9H); 2.26 (2d, 5-H, A); 2.43 (s, 3H); 2.55 (2d, 5-H, B); 3.62 (m, 6-H, X); 8.93 (br. s, 1H); J_{AB} = 16 Hz, J_{AX} = 11 Hz, J_{BX} = 5.6 Hz
5b	164.5–165.5	$C_{11}H_{12}N_2OS$ (220.1)	220 (100), 131 (68)[b]	1697, 1629	2.49 (s, 3H); 2.51 (2d, 5-H, A); 2.82 (2d, 5-H, B); 4.83 (2d, 6-H, X); 7.24–7.42 (m, 5H); 8.30 (br. s, 1H); J_{AB} = 16 Hz, J_{AX} = 11 Hz, J_{BX} = 5.4 Hz
5c	163–164	$C_9H_{10}N_2OS_2$ (226.3)	226 (91), 211 (100), 137 (77)[b]	1693, 1628	2.38 (s, 3H); 2.52 (2d, 5-H, A); 2.82 (2d, 5-H, B); 5.07 (2d, 6-H, X); 7.00 (d, 2H, J = 4 Hz); 7.38 (t, 1H, J = 4 Hz); 10.85 (br. s, 1H); J_{AB} = 16 Hz, J_{AX} = 11 Hz, J_{BX} = 5.4 Hz
5d	143–144	$C_8H_9N_3OS_2$ (227.3)	227 (100), 138 (83)[b]	1699, 1629	2.42 (s, 3H); 2.61 (2d, 5-H, A); 2.86 (2d, 5-H, B); 5.14 (2d, 6-H, X); 7.64 (d, 1H, J = 3 Hz); 7.77 (d, 1H, J = 3 Hz); 10.95 (br. s, 1H); J_{AB} = 16 Hz, J_{AX} = 11 Hz, J_{BX} = 5.4 Hz
5e	oil	$C_9H_{16}N_2O_2$ (184.2)	184 (20), 127 (100)	1711, 1678	0.9–1.7 (m, 9H); 2.15 (2d, 5-H, A); 2.63 (2d, 5-H, B); 3.50 (m, 6-H, X); 3.77 (s, 3H); 8.90 (br. s, 1H); J_{AB} = 15 Hz, J_{AX} = 9 Hz, J_{BX} = 6 Hz
5f	141–143	$C_9H_{10}N_2O_2S$ (210.0)	210 (100), 137 (8)[b]	1716, 1671	2.50 (2d, 5-H, A); 2.80 (2d, 5-H, B); 3.77 (s, 3H); 4.92 (2d, 6-H, X); 6.73–7.20 (m, 3H); 8.30 (br. s, 1H); J_{AB} = 17 Hz, J_{AX} = 9 Hz, J_{BX} = 6 Hz
6a	170–171	$C_8H_{14}N_2O_2$[c] (170.2)			0.6–1.6 (m, 9H); 2.20 (2d, 5-H, A); 2.60 (2d, 5-H, B); 3.35 (m, 6-H); 7.50 (br. s, 1H); 9.90 (br. s, 1H); J_{AB} = 16 Hz, J_{AX} = 8 Hz, J_{BX} = 5 Hz
6b	216–218	217–217.5[7]			2.60 (2d, 5-H, A); 3.11 (2d, 5-H, B); 4.92 (2br. d, 6-H, X); 7.25–7.45 (m, 5H); 7.50 (br. s, 1H); 10.00 (br. s, 1H); J_{AB} = 16 Hz, J_{AX} = 5 Hz, J_{BX} = 6 Hz
6c	243–245	244–244.5[7,8]			2.59 (2d, 5-H, A); 3.03 (2d, 5-H, B); 4.80 (2br. d, 6-H, X); 6.97 (m, 2H); 7.42 (m, 1H); 8.15 (br. s, 1H); 10.13 (br. s, 1H); J_{AB} = 16 Hz, J_{AX} = 5 Hz, J_{BX} = 6 Hz

[a] Compounds **4d**, **5a, b, e, f**: $CDCl_3$/TMS; Compounds **5c, d** and **6a, b, c**: DMSO-d_6/TMS.

[b] A possible structure is R—CH=CH—C=O resulting from the expulsion of X^1—CHN_2 and 5-H from the molecular ion. The exact mass of this ion for **5b** was measured using a peak matching technique: C_9H_7O, calc. 131.0497, found 131.0495.

[c] calc. C 56.45 H 8.29 N 16.46
found 56.58 8.24 16.30.

Melting points are uncorrected. Mass, IR, and ^{1}H-NMR spectra were recorded on Varian MAT 112S (70 eV), Perkin-Elmer 283, and JEOL GX-270 (270 MHz) spectrometers, respectively.

Butyllithium (2.6 molar in hexanes) and phenyllithium (1.8 molar in cyclohexane/ether) were obtained from Aldrich. 2,4-Bis(methylthio)pyrimidine,[10] 2,4-dimethoxypyrimidine,[11] and 4-methoxy-2-methylthiopyrimidine[12] were prepared, and 2-thienyllithium and 2-thiazolyllithium[13] in ether were generated as described. Ether was distilled from sodium benzophenone ketyl immediately before use.

5,6-Dihydropyrimidin-4(3*H*)ones (5a–f); General Procedure:
To a stirred solution of an organolithium reagent R–Li (10 mmol) in ether (50 ml) under nitrogen atmosphere at –40 °C is added dropwise a solution of pyrimidine **1**, **2**, or **3** (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 (2 ml) in tetrahydrofuran (5 ml) at –10 °C and concentrated to a volume of 20 ml on a rotary evaporator at 23 °C. Crude dihydropyrimidines **4a–g** are hydrolyzed in 50:50 ethanol/water (50 ml) in the presence of hydrochloric acid under the conditions given in Table 1. The solution is neutralized with diluted ammonium hydroxide, concentrated to a volume of 25 ml, and extracted with dichloromethane (3 × 25 ml). Products **5a–f** are isolated by flash chromatography,[14] eluting typically with 97:3 dichloromethane/ethanol, and crystallized from ethanol.

2,4-Bis(methylthio)-6-(2-thiazolyl)-5,6-dihydropyrimidine (4d):
2,4-Bis(methylthio)pyrimidine (**1**) is reacted with 2-thiazolyllithium and the reaction mixture is quenched with water as described above. The ether layer is separated, the aqueous residue is extracted with dichloromethane (2 × 10 ml), and the organic solutions containing **4d** are combined. Product **4d** is isolated by flash chromatography eluting with 98:2 dichloromethane/ethanol, and crystallized from ethanol; yield 82%; m.p. 113–114 °C.

Dihydrouracils 6; General Procedure:
A solution of a compound **5** (3 mmol) in 2 normal hydrochloric acid (3 ml) is heated at 60 °C for 1.5 h. After cooling, the precipitated dihydrouracil **6** is isolated by filtration and washed with cold water; yields: 5% (**6a** from **5a**), 56% (**6a** from **5e**), 5% (**6b** from **5b**), 52% (**6c** from **5f**).

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