Synthesis of 2,4-Dimethoxy-5-(3-oxo-1-alkynyl)pyrimidines, 2,4-Dimethoxy-5-(3-oxoalkyl)pyrimidines, and 5-(3-Oxoalkyl)uracils by a Highly Convenient Procedure[1]

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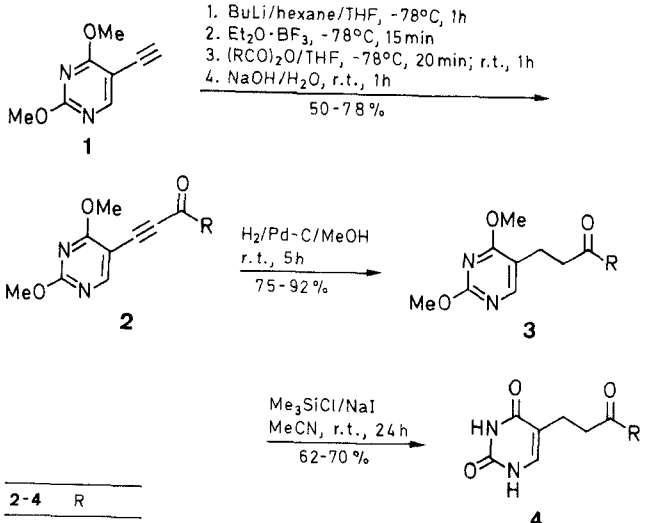
A simple synthesis of 2,4-dimethoxy-5-(3-oxoalkynyl)pyrimidines from the readily available 5-ethynyl-2,4-dimethoxypyrimidine is described. The sequence proceeds via an ethynylboron intermediate which is acylated with carboxylic anhydrides. The 5-(3-oxo-1-alkynyl) products are hydrogenated to the saturated analogs and these are *O*-dealkylated with chlorotrimethylsilane/sodium iodide to give 5-(3-oxoalkyl)uracils, e.g., 5-(3-oxobutyl)-, 5-(3-oxopentyl)-, and 5-(3-oxohexyl)uracil. These compounds and the nucleosides derived therefrom are of interest as anticancer and antiviral agents.

Our interest in the development of inhibitors of thymidylate synthetase and dihydroorotate dehydrogenase which are essential enzymes required for the cellular multiplication processes, made us synthesize various 5- and 6-substituted derivatives of uracil[2,3] and dihydrouracil.[4] Thus, we also became interested in uracil derivatives with highly activated 5-substituents, e.g., substituents like $-C\equiv C-COR$ or $C=C-COR$. These compounds could be converted into the corresponding nucleotides which might act as inhibitors of thymidylate synthetase. With this objective, we looked for general methods for the synthesis of 5-substituted uracils.

A search of the literature showed that most of the methods for the synthesis of 5-substituted uracil derivatives have primarily been developed for the synthesis of specific 5-substituted uracils[5-9] and only a few general syntheses of 5-substituted uracils and the corresponding nucleosides have been reported.[10-16] We recently described[17,18] novel methods for the synthesis of 5-substituted 2,4-dimethoxypyrimidines and 5-(3-oxo-1-alkynyl)uracils; we have found some of these compounds to be active against CCRF-CEM and L1210 cell lines *in vitro* and also against EAC cells *in vivo*.[19] In view of the promising biological results obtained with the 5-(3-oxo-1-alkynyl)uracils, we also investigated the synthesis of other new 5-substituted derivatives of uracil. We now report convenient procedures for the synthesis of some 2,4-dimethoxy-5-(3-oxo-1-alkynyl)pyrimidines, 2,4-dimethoxy-5-(3-oxoalkyl)pyrimidines, and 5-(3-oxoalkyl)-uracils.



2-4	R
a	CH_3
b	C_2H_5
c	n-C_3H_7

Scheme A

5-Ethynyl-2,4-dimethoxypyrimidine **(1)** has been obtained[3] in high yield by treatment of 2,4-dichloro-5-(1-chlorovinyl)pyrimidine with sodium methoxide in methanol and a *C*-silylated derivative of **1**, 2,4-dimethoxy-5-[2-(trimethylsilyl)ethynyl]pyrimidine has been converted to 2,4-dimethoxy-5-(3-oxo-1-alkynyl)pyrimidines.[17] Acetylenic compounds may be conveniently converted into 1-alkynyl ketones via a 1-alkynyltrifluoroborate ($R-C\equiv C-BF_3Li^+$) as intermediate.[20] The application of this procedure to 5-ethynyl-2,4-dimethoxypyrimidine **(1)** led to the formation of 2,4-dimethoxy-5-(3-oxo-1-alkynyl)pyrimidines **(2)** (Scheme **A**).

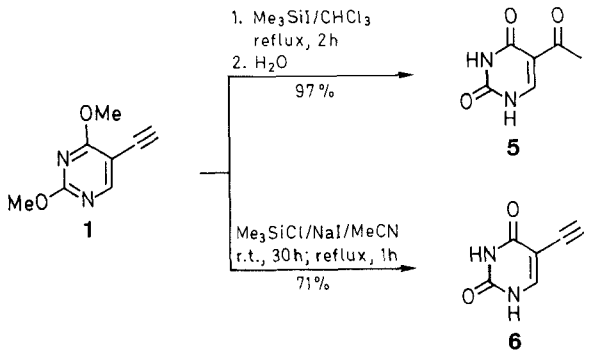
5-Ethynyl-2,4-dimethoxy pyrimidine **(1)** was converted into the lithium acetylenide with butyllithium in tetrahydrofuran at $-78\,^{\circ}C$ and then treated with diethyl etherboron trifluoride complex to give lithium 2,4-dimethoxypyrimidin-5-ylethynyltrifluoroborate which was not isolated but treated *in situ* with acid anhydrides to afford the corresponding 5-(3-oxo-1-alkynyl)pyrimidines **2** in fairly good yields. Acetic, propanoic, and butanoic anhydrides underwent the reaction smoothly whereas the attempted analogous reaction of the corresponding acid chlorides failed.

The acetylenic ketones **2** were characterized by microanalyses and spectrometric data. In the IR spectra, all acetylenic ketones **2** showed strong bands at ν = 2200 cm^{-1} ($-C\equiv C-$) and 1670 cm^{-1} (conjugated ketone). The ^{1}H-NMR spectra showed the absence of the signal of $C\equiv C\underline{H}$ at $\delta = 3.32$ (which was found for the starting material **1**) and the appearance of signals attributable to the acyl groups (Table).

The acetylenic ketones **2a–c** were hydrogenated catalytically to the corresponding saturated ketones, the 2,4-dimethoxy-5-(3-oxoalkyl)pyrimidines **3a–c**, which were characterized by the absence of the IR band at ν = 2200 cm^{-1} and the presence of a band at ν = 1710 cm^{-1} (saturated carbonyl). The UV absorption at λ = 297 nm was also lacking. In the ^{1}H-NMR spectra, the signals of the two methylene groups of the side chain of compounds **3a,b,c** had nearly identical values (see Table), presumably due to magnetic equivalence of the methylene protons.

Iodotrimethylsilane has been found to be a mild and versatile reagent for the cleavage of ethers.[21,22] However, its use in the *O*-dealkylation of alkoxypyrimidines is of limited applicability; it has only been used in the case of simply substituted 2,4-dialkoxypyrimidines.[23] We have

found that 5-ethynyl-2,4-dimethoxypyrimidine **(1)** on treatment with iodotrimethylsilane in chloroform followed by hydrolysis is converted into 5-acetyluracil[3] **(5)**. In contrast, chlorotrimethylsilane/sodium iodide[24] in acetonitrile smoothly converted compound **1** to 5-ethynyluracil **(6)** in good yield.



Scheme **B**

Thus, chlorotrimethylsilane/sodium iodide in acetonitrile has been found to be the reagent of choice for the *O*-dealkylation of dialkoxypyrimidines of the types **1** and **3** to give the corresponding uracils (e.g., **6** and **4**, respectively) in good yields (Table). No aldol type reaction[25] of **3** was observed under the conditions employed.

The new simple synthesis of 5-(3-oxoalkyl)uracils is of interest since we have recently found that 5-(3-oxo-1-alkynyl)uracils exhibit antitumour activity and that inspite of their bulky 5-substituents they are inhibitors of thymidylate synthetase in L1210/0 cell culture systems[19] like other uracil nucleosides with bulky 5-substituents.[26,27] Thus, the saturated analogues, e.g., 5-(3-oxoalkyl)uracils and nucleosides derived therefrom, become of interest as anticancer and antiviral agents, their thymidylate synthetase inhibition properties still requiring investigation.

Melting points were determined on a Reichert 285980 (Austria) melting point apparatus and are uncorrected. Microanalyses were performed using a Perkin Elmer Element Analyzer 240C. IR spectra were recorded on a Perkin Elmer 298 spectrophotometer,

Table. Synthesis of 5-Substituted 2,4-Dimethoxypyrimidines **2**, **3** and 5-(3-Oxoalkyl)uracils **4**

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR (KBr)[b] ν (cm^{-1})	UV (EtOH) λ_{max} (nm) (log ε)	^{1}H-NMR (200 MHz, $CDCl_3$/TMS)[c] δ, J(Hz)
2a	64	94–96 (petroleum ether)	$C_{10}H_{10}N_2O_3$ (206.2)	2200, 1670, 1605	297 (4.21)	2.44 (s, 3H, $COCH_3$), 4.04 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 8.46 (s, 1H, H-6)
2b	78	78–80 (MeOH)	$C_{11}H_{12}N_2O_3$ (220.2)	2200, 1675, 1596	297 (4.22) 271 (4.06)	1.24 (t, 3H, J = 7, $COCH_2CH_3$), 2.72 (q, 2H, J = 7, $COCH_2CH_3$), 4.06 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 8.50 (s, 1H, H-6)
2c	50	gum	$C_{12}H_{14}N_2O_3$ (224.25)	2200, 1665, 1590	297 (4.20) 271 (4.05)	1.0 (t, 3H, J = 7, $COCH_2CH_2CH_3$), 1.8 (m, 2H, $COCH_2CH_2CH_3$), 2.67 (t, 2H, $COCH_2CH_2CH_3$), 4.06 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 8.41 (s, 1H, H-6)
3a	85	gum	$C_{10}H_{14}N_2O_3$ (210.2)	1710, 1600	267 (3.79)	2.18 (s, 3H, $COCH_3$), 2.60–2.76 (m, 4H, CH_2CH_2), 3.96 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 8.08 (s, 1H, H-6)
3b	92	gum	$C_{11}H_{16}N_2O_3$ (224.25)	1710, 1600	267 (3.78)	1.06 (t, 3H, J = 7, CH_2CH_3), 2.46 (q, 2H, J = 7, CH_2CH_3), 2.74 (m, 4H, CH_2CH_2CO), 3.98 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 8.08 (s, 1H, H-6)
3c	75	gum	$C_{12}H_{18}N_2O_3$ (238.3)	1710, 1600	267 (3.74)	0.92 (t, 3H, J = 8, CH_3), 1.62 (m, 2H, J = 8, $CH_2CH_2CH_3$), 2.40 (t, 2H, J = 8, $CH_2CH_2CH_3$), 2.72 (m, 4H, CH_2CH_2CO), 3.98 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 8.08 (s, 1H, H-6)
4a	62	255–257 (MeOH)	$C_8H_{10}N_2O_3$ (182.2)	1705, 1665	266 (3.89)	2.0 (s, 3H, $COCH_3$), 2.32 (t, 2H, J = 8, CH_2CH_2CO), 2.56 (t, 2H, J = 8, CH_2CH_2CO), 7.16 (d, 1H, J = 4, H-6), 10.64 (bs, 1H, NH), 10.96 (s, 1H, NH)
4b	70	264–265 (MeOH)	$C_9H_{12}N_2O_3$ (196.2)	1705, 1665	266 (3.86)	0.96 (t, 3H, J = 7, CH_3), 2.39 (t, 2H, J = 7, CH_2CH_2CO), 2.46 (q, 2H, J = 7, CH_2CH_3), 2.64 (t, 2H, J = 7, CH_2CH_2CO), 7.25 (d, 1H, J = 6, H-6), 10.70 (m, 2H, NH)
4c	69	265–267 (MeOH)	$C_{10}H_{14}N_2O_3$ (224.25)	1700, 1665	266 (3.92)	0.92 (t, 3H, J = 7.4, CH_3), 1.56 (q, 2H, J = 7.4, CH_2CH_3), 2.43 (t, 2H, J = 7.5, CH_2CH_2CO), 2.47 (t, 2H, J = 7.5, $COCH_2CH_2CH_3$), 2.67 (t, 2H, J = 7, CH_2COPr-*n*), 7.30 (d, 1H, J = 5.7, H-6), 10.74 (m, 2H, NH)

[a] Satisfactory microanalyses: C ±0.33, H ±0.40, N ±0.38.

[b] The IR spectra of compounds **2c**, **3a**, **3b**, and **3c** were recorded neat.

[c] Exceptions: **2a** and **4a** at 100 MHz; **4b** and **4c** at 400 MHz in DMSO-d_6.

UV spectra on a Hitachi 200-20 spectrometer, and ^{1}H-NMR spectra on Varian XL200, FX100, and Bruker 400 MHz spectrometers.

2,4-Dimethoxy-5-(3-oxo-1-butynyl)pyrimidine (2a); Typical Procedure:

To a stirred, cooled solution of 5-ethynyl-2,4-dimethoxypyrimidine[3] (**1**; 2 g, 12.20 mmol) in dry THF (60 mL) at −78 °C under N_2, a 1.6 M solution of BuLi in hexane (9.2 mL, 14.72 mmol) is slowly added. The mixture is stirred for 1 h at −78 °C. Then, distilled $BF_3 \cdot Et_2O$ (2.13 g, 15 mmol) is added dropwise and stirring is continued for 15 min, whereupon a precooled (−78 °C) solution of distilled Ac_2O (1.8 g, 17.63 mmol) in THF (5 mL) is added. Stirring is continued at −78 °C for 20 min and the temperature then gradually raised to 20 °C (about 1 h). A 2 M aq solution of NaOH (16 mL) is added, the mixture is stirred for 1 h, then poured into ice water (50 mL). This mixture is extracted with $CHCl_3$ (3 × 50 mL). The combined chloroform extracts are washed with brine (2 × 30 mL), dried (Na_2SO_4), and evaporated using a water aspirator. The residue is crystallized from petroleum ether (bp 60–80 °C) to give **2a** as colorless needle-shaped crystals; yield: 1.6 g (7.77 mmol, 64%); mp 94–96 °C.

$C_{10}H_{10}N_2O_3$	calc.	C 58.25	H 4.85	N 13.59
(206.2)	found	58.51	4.84	13.15

2,4-Dimethoxy-5-(3-oxobutyl)pyrimidine (3a); Typical Procedure:

A solution of 2,4-dimethoxy-5-(3-oxo-1-butynyl)pyrimidine (**2a**; 150 mg, 0.73 mmol) in MeOH (12 mL) is hydrogenated in the presence of 10% Pd-C (90 mg) at ambient pressure for 5 h. The catalyst is filtered off and washed with MeOH (6 mL). The combined filtrates are evaporated to dryness using a water aspirator to give **3a** as a gum; yield: 130 mg (0.62 mmol, 85%).

2,4-Dioxo-5-(3-oxoalkyl)-1,2,3,4-tetrahydropyrimidines [5-(3-Oxoalkyl)uracils] 4; General Procedure:

To a stirred solution of the 5-substituted 2,4-dimethoxypyrimidine **3** (0.5 mmol) in dry MeCN (15.0 mL) under N_2, anhydrous NaI (250 mg, 1.67 mmol) and freshly distilled Me_3SiCl (0.2 mL, 1.58 mmol) are added, and stirring is continued at r.t. for 24 h. The solvent is removed using a water aspirator and the residue is heated with H_2O (2 mL) and sat. $NaHSO_3$ solution (3 mL). The solid is isolated by suction, washed with H_2O, and dried.

5-Ethynyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (5-Ethynyluracil, 6):

A mixture of 5-ethynyl-2,4-dimethoxypyrimidine[3] (**5**; 0.1 g, 0.61 mmol), anhydrous NaI (0.19 g, 1.27 mmol) and freshly distilled Me_3SiCl (0.18 mL, 1.42 mmol) in MeCN (4.0 mL) is stirred under N_2 at r.t. for 30 h, then refluxed for 1 h. The solvent is removed under reduced pressure and the residue is digested with MeOH and H_2O, cooled, isolated by suction, and crystallized from MeOH to give **6** as a colorless solid; yield: 60 mg (0.44 mmol, 72%); mp > 300 °C; identical with an authentic sample of 5-ethynyluracil according to IR and ^{1}H-NMR comparison.

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