A Facile Synthesis of 1-Monosubstituted and Unsymmetrically 1,3-Disubstituted Uracils

Harjit Singh,* Pawan Aggarwal, Subodh Kumar
Department of Chemistry, Guru Nanak Dev University, Amritsar - 143005, India

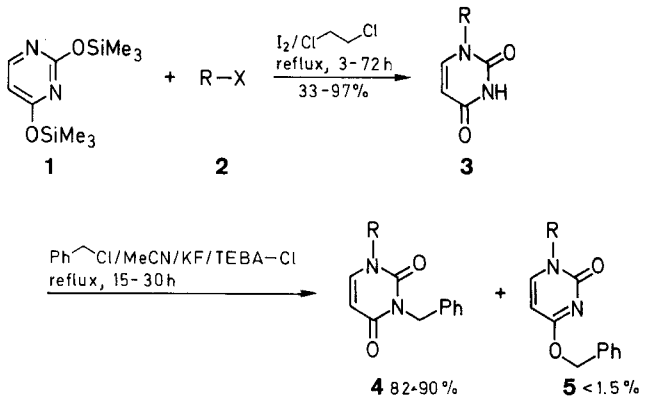
Heating of 2,4-bis(trimethylsiloxy)pyrimidine with functionalised alkyl halides in 1,2-dichloroethane in the presence of iodine affords exclusively 1-substituted uracils, which can be benzylated at N-3 with benzyl chloride under phase-transfer catalysis.

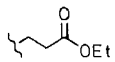
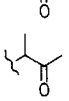
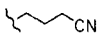
For investigating intramolecular C-C bond formation at C-6 of uracil derivatives through nucleophilic carbanion addition, in analogy with carbon-hetero bond formation in dihydropyrimidines,[1] we had to attach appropriately functionalized chains at N-1 of uracil. Nucleophilic substitution of alkylating reagents with uracil even under phase-transfer catalytic conditions provide 1- or 3-monosubstituted and 1,3-disubstituted products.[2,3] Selective syntheses of these products involve multistep procedures.[4,5] However, the reaction of 2,3-bis-(trimethylsiloxy)pyrimidine (**1**) with sugar halides,[6] 1,3-dioxolanes,[7] and acetates[10] in the presence of Lewis acids or with methyl iodide[8] provides the corresponding 1-substituted uracil derivatives. In our hands, reactions of **1** with functionalised organic halides under these conditions were not successful.

We have now found that 2,4-bis(trimethylsiloxy)-pyrimidine (**1**) reacts with functionalised (–CN, –CO, $-CO_2R$ groups) alkyl halides **2** in the presence of iodine to afford exclusively 1-substituted uracils **3a–h** (Table 1).

The reaction of 2,4-bis(trimethylsiloxy)pyrimidine (**1**) with ethyl chloroacetate (**2a**), ethyl 3-bromopropanoate (**2b**), ethyl 2-bromopropanoate (**2c**), chloroacetone (**2d**), phenacyl bromide (**2e**), 3-bromobutanone (**2f**), chloroacetonitrile (**2g**), and 4-chlorobutanenitrile (**2h**) in 1,2-dichloroethane containing iodine as catalyst affords the corresponding monosubstituted uracil derivatives **3a–h** (Table 1). In the mass spectra of compounds **3**, the presence of a peak at $M^+ - NH-CO$ and the absence of a peak at $M^+ - RN-CO$ corroborate the structures of **3** as 1-substituted uracils.[9] In the absence of iodine, the reactions require the five- to sixfold time for completion except for the reactions of chloroacetonitrile (**2g**) and 4-chlorobutanenitrile (**2h**). Titanium(IV) chloride, tin(IV) chloride, and sodium iodide do not catalyse the reactions. The reaction of **1** with 4-chlorobutanenitrile proceeds smoothly even in the absence of solvent. However, heating of **1** with chloroacetone (**2d**) or phenacyl bromide (**2e**) without solvent gives products showing positive spot tests for silicon and halide. On treatment with acidified ethanol, these products furnish uracil along with the corresponding products **3**. However, the reactions of **1** with the other alkyl halides **2** do not proceed in the absence of solvent.

Some of the compounds **3** are alkylated almost exclusively at N-3 upon treatment with benzyl chloride under solid-liquid phase-transfer conditions. However, benzylation of **3h** with benzyl chloride under these conditions gives two isolable isomeric compounds with $m/z = 269$ (M^+): 3-benzyl-1-(4-cyanobutyl)uracil (**4h**) and O^4-benzyl-1-(4-cyanobutyl)-2-oxo-1,2-dihydropyrimidine



2-5	X in 2	R	2-5	X in 2	R
a	Cl		e	Br	
b	Br		f	Br	
c	Br		g	Cl	
d	Cl		h	Cl	

(**5h**) in 90% and 1% yields, respectively (Table 2). The structure **5h** is corroborated by absence of the absorption band of $C^4=O$ in the IR spectrum, elimination of the $C_6H_5CH_2O$ moiety from the parent ion in the mass spectrum, and the appearance of the CH_2 signal downfield from the CH_2 signal of **4h**. Benzylation of 1-phenacyluracil (**3e**) and 1-acetonyluracil (**3d**) gives **4e** and **4d**, respectively, and the minor product O^4-benzyl-1-phenacyl-2-oxo-1,2-dihydropyrimidine (**5e**) in 1.5% yield, in the first case, whereas the corresponding product **5d** is not detected in the second case.

Thus, iodine catalyses the condensations of **1** with functionalised organic halides (primary as well as secondary) to give exclusively 1-substituted uracils which can be benzylated at N-3 to give various unsymmetrically 1,3-disubstituted uracils. The catalytic role of iodine is being investigated.

1-Substituted Uracils 3; General Procedure:
A solution of 2,4-bis(trimethylsiloxy)pyrimidine[8] (**1**; 1.12 g, 0.01 mol), the functionally substituted alkyl halide **2a–h** (0.012 mol), and I_2 (20 mg) in 1,2-dichloroethane (20 mL) is heated to reflux and the progress of the reaction is monitored by TLC. After completion of the reaction (Table 1), the mixture is cooled to r.t. and EtOH (35 mL) is added with stirring, whereupon the product separates within few minutes. It is isolated by suction and recrystallized from $CHCl_3$ or AcOH in case of products **2a,d–h**. Compounds **2b** and **2c** are isolated by column chromatography on silica gel (40 × 4 cm, 60–120 mesh) using benzene/EtOAc (1:1) as eluent, and recrystallized from $CHCl_3$.

Table 1. 1-Substituted Uracils **3** Prepared

Product	Reaction Time (h)[a]	Yield (%)	mp (°C) (Solvent)	Molecular Formula[b]	MS *m/z*	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)
3a	13[c] (72)	60	118–120 ($CHCl_3$)	$C_8H_{10}N_2O_4$ (198.2)	198 (M^+), 155 (M^+-NHCO)	1.30 (t, 3H, *J* = 8, $CH_2C\underline{H}_3$), 4.30 (q, 2H, *J* = 8, $C\underline{H}_2CH_3$), 4.60 (8, 2H, NCH_2), 6.02 (d, 1H, *J* = 8, H-5), 7.50 (d, 1H, *J* = 8, H-6)
3b	11 (60)	51	68–70 ($CHCl_3$)	$C_9H_{12}N_2O_4$ (212.2)	212 (M^+), 169 (M^+-NHCO)	1.25 (t, *J* = 7.5, 3H, $OCH_2C\underline{H}_3$), 2.70 (t, 2H, *J* = 7, $NCH_2C\underline{H}_2$), 3.80–4.30 (m, 4H, NCH_2, OCH_2), 5.60 (d, 1H, *J* = 8, H-5), 7.30 (d, 1H, *J* = 8, H-6)
3c	15 (65)	41	76–78 ($CHCl_3$)	$C_9H_{12}N_2O_4$ (212.2)	212 (M^+), 169 (M^+-NHCO)	1.30 (t, 3H, *J* = 7, $OCH_2C\underline{H}_3$), 1.70 (d, 3H, *J* = 7, $CHC\underline{H}_3$), 4.30 (q, 2H, *J* = 7, $OC\underline{H}_2CH_3$), 5.20 (q, 1H, *J* = 8, $C\underline{H}CH_3$), 5.90 (d, 1H, *J* = 8, H-5), 7.45 (d, 1H, *J* = 8, H-6)
3d	3.5 (20)	97	202–204 (AcOH)	$C_7H_8N_2O_3$ (168.15)	168 (M^+) 125 (M^+-NHCO)	2.05 (s, 3H, $COCH_3$), 4.65 (s, 2H, NCH_2), 5.45 (d, 1H, *J* = 8, H-5), 7.35 (d, 1H, *J* = 8, H-6)
3e	6 (28)	76	239–241 (AcOH)	$C_{12}H_{10}N_2O_3$ (230.2)	230 (M^+) 187 (M^+-NHCO)	5.15 (s, 2H, NCH_2), 5.45 (d, 1H, *J* = 8, H-5), 7.10–7.90 (m, 6H, $5H_{arom}$, H-6)
3f	3 (8)	33	140–142 (AcOH)	$C_8H_{10}N_2O_3$ (182.2)	182 (M^+) 139 (M^+-NHCO)	1.75 (d, 3H, *J* = 8, CH_3), 2.40 (s, 3H, $COCH_3$), 5.35 (q, 1H, *J* = 8, NCH), 6.10 (d, 1H, *J* = 8, H-5), 7.50 (d, 1H, *J* = 8, H-6)
3g	72 (72)	66	175–180 (AcOH)	$C_6H_5N_3O_2$ (151.1)	151 (M^+) 108 (M^+-NHCO)	5.0 (s, 2H, NCH_2), 6.20 (d, 1H, *J* = 8, H-5), 7.80 (d, 1H, *J* = 8, H-6)
3h	15 (15)	91	133 (AcOH)	$C_8H_9N_3O_2$ (179.2)	179 (M^+) 136 (M^+-NHCO)	1.90–2.65 (m, 4H, CH_2CH_2), 3.95 (t, 2H, *J* = 7, NCH_2), 6.05 (d, 1H, *J* = 8, H-5), 7.45 (d, 1H, *J* = 8, H-6)

[a] Reaction times in the absence of I_2 are given in parentheses, for comparison.
[b] Satisfactory microanalyses: C ±0.35, H ±0.12, N ±0.30.
[c] The reaction with ethyl bromoacetate in place of **2a** required only 5.5 h for completion.

Table 2. Benzylation Products **4** and **5** Obtained from 1-Substituted Uracils **3**

Substrate	Reaction Time (h)	Products	Yield (%)	mp (°C)	Molecular Formula[a]	MS *m/z*	IR ($CHCl_3$) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)
3d	27	**4d**	87	65–67	$C_{14}H_{14}N_2O_3$ (258.3)	258 (M^+)	1730, 1705, 1665	2.15 (s, 3H, $COCH_3$), 4.35 (s, 2H, NCH_2CO), 5.0 (s, 2H, NCH_2Ph), 5.60 (d, 1H, *J* = 8, H-5), 6.65–7.40 (m, 6H, $5H_{arom}$, H-6)
3e	30	**4e**	82	98–101	$C_{19}H_{16}N_2O_3$ (320.3)	318 (M^+)	1730, 1710, 1665, 1660	5.10 (s, 4H, $2NCH_2$), 5.80 (d, 1H, *J* = 8, H-b), 6.90 (d, 1H, *J* = 8, H-6), 7.10–8.0 (m, $10H_{arom}$)
		5e	1.5	207–209		318 (M^+) 211 (M^+-$C_6H_5CH_2O$)	1710, 1670	5.20 (s, 2H, NCH_2), 5.30 (s, 2H, OCH_2), 5.85 (d, 1H, *J* = 8, H-5), 7.1–8.0 (m, 11H, $10H_{arom}$, H-6)
3h	15	**4h**	90	65–67	$C_{15}H_{15}N_3O_2$ (269.3)	269 (M^+)	2240 (CN); 1710, 1665	1.70–2.30 (m, 4H, CH_2CH_2CN), 3.70 (t, 2H, *J* = 8, $NC\underline{H}_2CH_2$), 5.0 (s, 2H, NCH_2), 5.70 (d, 1H, *J* = 8, H-5), 6.90–7.30 (m, 6H, $5H_{arom}$, H-6)
		5h	1	110–112	$C_{15}H_{15}N_3O_2$ (269.3)	269 (M^+) 162 (M^+ -C_6H_5 -CH_2O)	2240 (CN); 1660	1.90–2.30 (m, 4H, CH_2CH_2CN), 3.80 (t, 2H, *J* = 7, $NC\underline{H}_2CH_2$), 5.20 (s, 2H, OCH_2), 5.70 (d, 1H, *J* = 7, H-5), 7.0–7.20 (m, 6H, $5H_{arom}$, H-6)

[a] Satisfactory microanalyses: C ±0.30, H ±0.10, N ±0.30.

1-Substituted 3-Benzyluracils 4 (and 1-Substituted 4-Benzyloxy-2-oxo-1,2-dihydropyrimidines 5); General Procedure:

A suspension of the 1-substituted uracil **3** (0.01 mol) in MeCN (25 mL) containing benzyl chloride (1.27 g, 0.01 mol), KF (4.01 g, 0.07 mol), and TEBA-Cl (40–50 mg) is heated to reflux and the progress of the reaction is followed by TLC.

After completion of the reaction, KF is filtered off and is washed with EtOAc. The filtrate and washings are combined, the solvents are distilled off, and the residual product mixture is column-chromatographed on silica gel (40 × 4 cm, 60–120 mesh) using benzene/EtOAc (3:1) as eluent to give products **4** and **5**, which are further purified by recrystallization from $CHCl_3$.

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