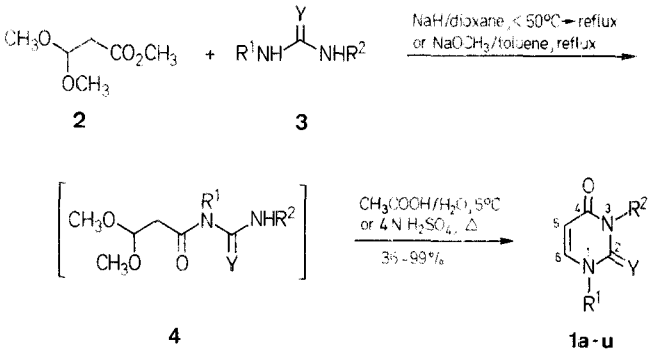

2 3 4 1a-u

Improved One-Step Procedure for the Preparation of 1-Substituted and 1,3-Disubstituted Uracils and 2-Thiouracils

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A convenient one-pot procedure for the synthesis of 1-substituted and 1,3-disubstituted uracils and 2-thiouracils consists of acylation of ureas or thioureas with methyl 3,3-dimethoxypropanoate in the presence of a strong base, and acidic work-up. The yields range from 36 to 99%. In all cases, only one regioisomer is isolated.

Uracils (**1**, Y = O) and 2-thiouracils (**1**, Y = S) can be prepared by a variety of methods[1]. However, most of these methods are either multistep procedures or afford low yields. Only uracils with small aliphatic substituents can be prepared effectively via direct alkylation[2] whereas uracils with aromatic or bulky aliphatic substituents as well as 2-thiouracils can only be prepared *via* multistep reactions either via rearrangements or ring synthesis.

During our work on 3,3-dialkoxypropanoic esters such as **2** we have found that methyl 3,3-dialkoxypropanoate (**2**) is an excellent formylacetic acid („malonic acid monoaldehyde") equivalent. Under strongly basic conditions it reacts smoothly with substituted or *N,N'*-disubstituted ureas (**3**, Y = O) and thioureas (**3**, Y = S) to give uracils (**1**, Y = O) or 2-thiouracils (**1**, Y = S), respectively, in moderate to high yields. Uracil syntheses from 3,3-dialkoxypropanoic esters have already been reported[3-8]; however all of these syntheses suffer from drawbacks such as low yields or multistep procedures. We present here an improved procedure which is easy to perform and affords satisfactory yields.

The reaction proceeds *via* a two-step mechanism. First, the anion of urea or thiourea **3** reacts with the carboxylic ester **2** to give the acylurea or acylthiourea **4**. This intermediate then undergoes ring-closure either spontaneously or when heated in sulfuric acid. In some cases, TLC (and GLC) shows the crude reaction product to be a mixture of **1** and **4**, but after acidic work-up only product **1** is isolated. When the substituents are R^1 = alkyl, R^2 = H, and Y = O, the intermediate **4** seems to be more stable than in the other cases examined. In one case (**4d**), the intermediate was actually isolated and characterized.

The positions of the groups R^1 and R^2 in products **1** depend on the nature of these groups. In the case of monosubstituted ureas or thioureas (**3**, R^2 = H), the resultant products **1** are always substituted at N-1. The other isomer has only been isolated in low yields when the ring closure was performed under acidic conditions[3]. When compounds **3** have two unbranched aliphatic groups at N and N', the products **1** show isomer ratios (larger: smaller substituent at N-3) better than 95:5 as determined by GLC and NMR. These results refer only to Method A; with Method C, mixtures of the two possible isomers are obtained.

If R^1 is an aromatic or a bulky aliphatic group and R^2 is not H, only dimerization products of esters **2** and no traces of products **1** are obtained[9].

The isolated products **1** were identified by comparison of their melting points with the reported data, by microanalyses, and by their ^{1}H- and ^{13}C-NMR spectra. The structures of products **1r** and **1t** were further confirmed by NOE- and ^{15}N-NMR experiments. [There is a significant Nuclear Overhauser effect between N–CH_3 and 6-H in both **1r** and **1t**. Further, the ^{15}N-NMR signals of N-1 in both compounds are double quartets. INEPT-^{15}N-NMR show the 6-H–H-1 coupling constant to be J = 4.5 Hz and that of the 1-methyl-H to be J = 1.4 Hz. The ^{15}N-chemical shifts and coupling constants are very much the same in **1r** and **1t**.] Product **1u** was prepared using the regiospecific four-step method of Lit.[10] and was shown to be different from product **1t** by means of TLC, GLC, and NMR.

The starting materials were either purchased (Aldrich) or prepared by standard methods. Melting points were determined in a Büchi 510 apparatus and are uncorrected. GLC was done on a Hewlett Packard 5090 gas chromatograph equipped with a 10 m methylsilicone column (ID 0.53 mm). Preparative HPLC was done on a Waters Prep LC 500A (Silica – 2-propanol/hexane). ^{1}H-NMR spectra of **1a–p** were run on a JEOL-JMN-PMX 60 spectrometer ^{1}H- and ^{13}C-NMR spectra of **1q–u** and ^{15}N-NMR of **1r** and **1t** were run on a Bruker AC 250 spectrometer.

2,4-Dioxo- and 4-Oxo-2-thioxo-1,2,3,4-tetrahydropyrimidines (Uracils and 2-Thiouracils), 1; General Procedures:

Method A: The urea or thiourea **3** (0.01 mol) is added in small portions to a stirred slurry of sodium hydride (0.015 mol, 0.72 g of a 50% suspension in oil) in dry dioxane (20 ml). The mixture is briefly heated at 50°C, and then allowed to cool to room temperature. When hydrogen evolution has ceased, methyl 3,3-dimethoxypropanoate (**2**; 2.22 g, 0.015 mol) is added at a rate that keeps the temperature below 50°C. When all **2** has been added, the mixture is refluxed until TLC (Silica, ethyl acetate/hexane) or GLC shows that compound **3** has disappeared. The orange mixture is poured into 40% acetic acid (100 ml) and this mixture is cooled to 5°C. The

Table 1. Uracils and 2-Thiouracils 1 Prepared

1	R^1	R^2	Y	Method	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a] or m.p. [°C] from Lit.	^{1}H-NMR[b] δ [ppm]
a	C_6H_5	H	O	A	64	m.p. 244–245	246[13]	11.55 (s, N–H); 7.49 (m, H_{arom}); 7.42 (d, J = 8 Hz, 6-H); 5.68 (d, J = 8 Hz, 5-H)
b	3-ClC_6H_4	H	O	A	92	m.p. 273–274	$C_{10}H_7ClN_2O_2$ (222.6)	11.72 (s, N-H); 7.77 (d, J = 8 Hz, 6-H); 7.6–7.5 (m, H_{arom}); 5.63 (d, J = 8 Hz, 5-H)
c	4-ClC_6H_4	H	O	A	95	m.p. 263–264	258[14]	11.59 (s, N–H); 7.72 (d, J = 8 Hz, 6-H); 7.56 (s, H_{arom}); 5.71 (d, 8 Hz, 5-H)
d	C_2H_5	H	O	B	61	m.p. 144–146	146–147[2]	11.20 (s, N–H); 7.49 (d, J = 8 Hz, 6-H); 5.57 (d, J = 8 Hz, 5-H); 3.77 (q, J = 7 Hz, CH_2); 1.25 (t, J = 7 Hz, CH_3)
e	i-C_3H_7	H	O	B	65	m.p. 131–132	132–134[2]	11.25 (s, N–H); 7.75 (d, J = 8 Hz, 6-H); 5.60 (d, J = 8 Hz, 5-H); 4.69 (sept, J = 7 Hz, CH); 1.25 (d, J = 7 Hz, CH_3)
f	n-C_4H_9	H	O	B	66	m.p. 103–104	101–103[15]	10.43 (s, N–H); 7.31 (d, J = 8 Hz, 6-H); 5.77 (d, J = 8 Hz, 5-H); 3.80 (t, J = 7 Hz, N–CH_2); 1.9–0.9 (m, $CH_2CH_2CH_3$)
g	t-C_4H_9	H	O	B	80	m.p. 173–175	$C_8H_{12}N_2O_2$ (163.2)	10.10 (s, N–H); 7.59 (d, J = 8 Hz, 6-H); 5.69 (d, J = 8 Hz, 5-H); 1.57 (s, CH_3)
h	C_6H_5–CH=N	H	O	A	73	m.p. 224–225	224–225[16]	11.67 (s, N–H); 9.23 (s, CH=N); 8.10 (d, J = 8 Hz, 6-H); 8.0–7.5 (m, H_{arom}); 5.77 (d, J = 8 Hz, 5-H)
i	H	H	S	C	80	m.p. 302–304	304[8]	11.00 (s, 1-H + 3-H); 7.49 (d, J = 8 Hz, 6-H); 5.82 (d, J = 8 Hz, 5-H)
j	C_6H_5	H	S	C	53	m.p. 242–243	236[8]	12.85 (s, NH); 7.68 (d, J = 8 Hz, 6-H); 7.47 (m, H_{arom}); 6.01 (d, J = 8 Hz, 5-H)
k	3-ClC_6H_4	H	S	A	61	m.p. 249–251	$C_{10}H_7ClN_2OS$ (238.6)	12.93 (s, NH); 7.82 (d, J = 8 Hz, 6-H); 7.7–7.5 (m, H_{arom}); 6.04 (d, J = 8 Hz, 5-H)
l	C_2H_5	H	S	A	82	m.p. 242–243	239–240[10]	12.81 (s, NH); 7.88 (d, J = 8 Hz, 6-H); 5.98 (d, J = 8 Hz, 5-H); 4.22 (q, J = 7 Hz, CH_2); 1.25 (t, J = 7 Hz, CH_3)
m	n-C_4H_9	H	S	A	49	m.p. 131–132	132–133[11]	12.55 (s, NH); 7.87 (d, J = 8 Hz, 6-H); 5.94 (d, J = 8 Hz, 5-H); 4.17 (t, J = 7 Hz, N–CH_2); 1.9–0.8 (m, $CH_2CH_2CH_3$)
n	H_2C=CH–CH_2	H	S	A	99	m.p. 195–196	197–198[12]	12.60 (s, NH); 7.83 (d, J = 8 Hz, 6-H); 6.17 (d, J = 8 Hz, 5-H); 6.1–5.9 (m, CH); 5.7–4.8 (m, CH_2 + CH_2)
o	C_6H_5–CH_2	H	S	A	92	m.p. 230–231	230–232[13]	12.50 (s, NH); 7.75 (d, J = 8 Hz, 6-H); 7.38 (s, H_{arom}); 5.91 (d, J = 8 Hz, 5-H); 5.48 (s, CH_2)
p	C_6H_5–CH=N	H	S	A	77	m.p. 219–220	$C_{11}H_9N_3OS$ (231.2)	11.95 (s, NH); 8.43 (s, CH=N); 7.9–7.3 (m, H_{arom}); 7.77 (d, J = 8 Hz, 6-H); 6.32 (d, J = 8 Hz, 5-H)
q	CH_3	CH_3	S	A	92	m.p. 110–111	109[10]	8.01 (d, J = 8 Hz, 6-H); 6.10 (d, J = 8 Hz, 5-H); 3.76 (s, 1-CH_3); 3.73 (s, 3-CH_3)
r	CH_3	C_2H_5	S	A	70	m.p. 72–73	73[10]	7.46 (d, J = 8 Hz, 6-H); 5.97 (d, J = 8 Hz, 5-H); 4.53 (q, J = 7 Hz, N–CH_2); 3.75 (s, N–CH_3); 1.28 (t, J = 7 Hz, C–CH_3)

Table 1. (continued)

1	R^1	R^2	Y	Method	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a] or m.p. [°C] from Lit.	^{1}H-NMR[b] δ[ppm]
s	C_2H_5	CH_3	S	C	36[c]	m.p. 52–53	56[10]	7.61 (d, J = 8 Hz, 6-H); 6.04 (d, J = 8 Hz, 5-H); 4.38 (q, J = 7 Hz, N–CH_2); 3.68 (s, N–CH_3); 1.41 (t, J = 7 Hz, C–CH_3)
t	CH_3	n-C_4H_9	S	A	80	b.p. 190/0.04	$C_9H_{14}N_2OS$ (198.3)	7.47 (d, J = 8 Hz, 6-H); 5.98 (d, J = 8 Hz, 5-H); 4.46 (q, J = 7 Hz, N–CH_2); 3.74 (s, N–CH_3); 1.69 (m, CH_2); 1.39 (m, CH_2); 0.95 (t, J = 7 Hz, C–CH_3)
u	n-C_4H_9	CH_3	S	[d]	73	b.p. 200/0.1	$C_9H_{14}N_2OS$ (198.3)	7.45 (d, J = 8 Hz, 6-H); 5.97 (d, J = 8 Hz, 5-H); 4.30 (t, J = 7 Hz, N–CH_2); 3.72 (s, N–CH_3); 1.80 (m, CH_2); 1.40 (m, CH_2); 0.98 (t, J = 7 Hz, C–CH_3)

[a] Satisfactory microanalyses obtained: C ±0.2, H ±0.2, N ±0.3.
[b] Compounds **1a–p** in DMSO-d_6, compounds **1q–u** in $CDCl_3$.
[c] Isolated as a 60/40 mixture of **1s/1r** (total yield 60%) and separated by liquid chromatography (2-propanol in heptane on silica).
[d] Prepared from propynoic acid, *N*-methyldithiocarbamic acid, and 1-aminobutane according to Lit.[10].

Table 2. ^{13}C-NMR Spectra of Compounds **1q–u**

1	^{13}C-NMR ($CDCl_3$/TMS_{int}) δ[ppm]
q	177.67 (C=S); 160.41 (C=O); 143.27 (C-6); 104.99 (C-5); 45.17 (1-CH_3); 34.84 (3-CH_3)
r	177.16 (C=S); 159.82 (C=O); 143.55 (C-6); 105.22 (C-5); 45.09 (N–CH_3); 42.73 (N–CH_2); 11.28 (C–CH_3)
s	176.74 (C=S); 160.01 (C=O); 142.77 (C-6); 104.99 (C-5); 51.63 (N–CH_2); 34.61 (N–CH_3); 13.35 (C–CH_3)
t	177.32 (C=S); 160.32 (C=O); 143.55 (C-6); 105.20 (C-5); 47.40 (N–CH_2); 45.23 (N–CH_3); 27.90 (C–CH_2); 20.16 (C–CH_2); 13.76 (C–CH_3)
u	177.31 (C=S); 160.40 (C=O); 142.69 (C-6); 105.01 (C-5); 56.64 (N–CH_2); 34.96 (N–CH_3); 30.00 (C–CH_2); 19.76 (C–CH_2); 13.73 (C–CH_3)

Table 3. ^{15}N-NMR Spectra of Compounds **1r** and **1t**

1	^{15}N-NMR ($CDCl_3$/CH_3NO_{2int}) δ[ppm]
r	−184.4 (t, J = 1.4 Hz, N-3); −229.4 (dq, J = 4.3 Hz, 1.4 Hz, N-1)
t	−186.3 (t, J = 1.4 Hz, N-3); −228.9 (dq, J = 4.3 Hz, 1.4 Hz, N-1)

precipitate is isolated and the filtrate extracted with dichloromethane (2 × 50 ml). The extract is dried with sodium sulfate and concentrated *in vacuo*. The two portions of solid material **1** are combined and either recrystallized or chromatographed and bulb-to-bulb distilled.

Method B: The reaction is carried out as in Method A, but the reaction mixture is poured into 4 normal sulfuric acid (100 ml). The resultant turbid solution is gently refluxed for 10 min, cooled to room temperature, and extracted with dichloromethane (3 × 50 ml). The organic phase is dried with sodium sulfate and concentrated *in vacuo* and the remaining solid is recrystallized.

Method C:[17] Sodium (0.34 g, 0.015 g-atom) is dissolved in methanol (30 ml) and the thiourea **3** (0.01 mol) and methyl 3,3-dimethoxypropanoate (**2**; 2.22 g, 0.015 mol) are added. The mixture is refluxed for 30 min, then concentrated in vacuo, and dry toluene (50 ml) is added. The mixture is refluxed for 2–5 h (the reaction being monitored by TLC/GLC) with vigorous stirring. The resultant two-phase system is concentrated *in vacuo* and the residue acidified with 40% acetic acid (100 ml). The solid product **1** is isolated, dried, and recrystallized.

***N*-(3,3-Dimethoxypropanoyl)-N-Ethyl-urea (4d):**
Method A is followed till disappearance of compound **3d** (TLC/GLC). The reaction mixture is poured into 10% acetic acid (100 ml) and extracted with dichloromethane (2 × 50 ml). The extract is dried with sodium sulfate and concentrated *in vacuo*. The remaining oil crystallizes on standing; yield: 1.34 g (66%); m.p. 74–75 °C (isooctane).

^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 10.15 (br. s, 1 H); 8.30 (br. s, 1 H); 4.80 (t, 1 H, J = 6 Hz); 3.37 (s, 6 H); 3.30 (q, 2 H, J = 7 Hz); 2.68 (d, 2 H, J = 6 Hz); 1.17 ppm (t, 3 H, J = 7 Hz).

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[17] Method C is an improved version of the method of Lit.[5]; the change in solvent from alcohol to toluene results in significantly higher yields.