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HSAB Driven Chemoselectivity in Alkylation of Uracil Derivatives. A High Yielding Preparation of 3-Alkylated and Unsymmetrically 1,3-Dialkylated Uracils.

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Abstract: A qualitative hardness scale ($N^1<N^3<O^4$) has been found for the conjugated bases of 2-methoxy-4(3H)-pyrimidinones **1-3** and applied to high yielding chemoselective N^3 methylation, ethylation and benzylation reactions. Removal of the 2-methoxy group followed by a second alkylation affords unsymmetrically 1,3-disubstituted uracils. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: Pyrimidinones; Uracils; Regioselection; Alkylation.

N^1- and/or N^3-alkyl derivatives in the uracil family are of interest because of their inherent bioactivity[1] or their use as starting materials for the synthesis of oligonucleotides,[2] polymeric analogues of nucleic acids[3] and non-nucleoside reverse transcriptase inhibitors.[4] However, due to the tetradentate nucleophilic nature of uracils or their conjugated bases, chemoselective alkylations are a critical step and afford mixtures of N^1 and N^1+N^3 alkyl derivatives with some O^4-substitution.[5]

In view of the wide natural occurrence and high bioactivity of N^1-derivatives, much chemical effort has been devoted to control the N^1-regioselectivity by the use of 2,4-dialkoxypyrimidines[6] or their silyloxy analogues,[7] but little attention has been dedicated to study conditions for selective N^3-alkylation. This latter seems to be possible only for 2,6-disubstituted uracils where prevalent[8] or quantitative[9] N^3-attack has been reported and attributed to both steric[8] and electronic[1d] effects. Therefore, in view of the synthesis of N^3-alkylated uracils, further investigation to control the regioselectivity in the alkylation of uracil family is required.

Literature data showed that the N/O alkylation ratio decreases with increasing hardness of the alkylating agent. The use of methyl or primary halides results in a sharp prevalence of N^1 and N^1+N^3 attack,[5a,c,e] while the use of secondary halides[5h] or primary diazoalkanes[5f,g] affords relatively high amounts of O^2 and O^4 attack. Accordingly, benzoylation has been shown to occur at the two oxygens under kinetic conditions[1d], but is followed by a smooth intramolecular rearrangement leading to the thermodynamically more stable N^1,N^3-dibenzoylated derivative, previously reported as the only product.[10]

On these grounds, the hypothesis of a HSAB[11] control in the N/O chemoselection arose, as previously put forward for the benzylation of guanosine.[12] Therefore, we felt that the HSAB principle could be also used to

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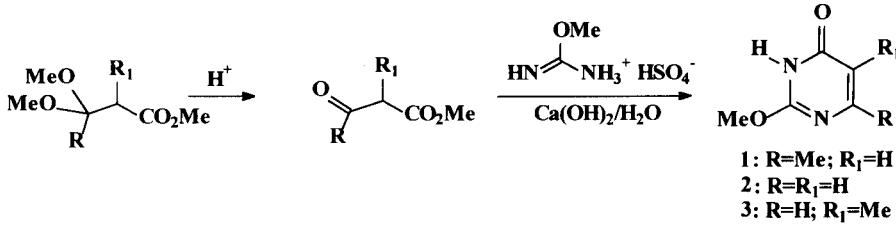
drive the N^1/N^3 chemoselectivity in uracils and that the presence of an easily removable methoxy group at C_2 should make the N^3 harder than the N^1. Therefore, in order to confirm our hypothesis and to take synthetic advantage, we investigated the effects of different solvents, counterions, bases and alkylating agents on the distribution of products of N^3-, O^4- and N^1-alkylation obtained by base-promoted alkylation of the 2-methoxy-4(3H)-pyrimidinones **1-3**.

Results

Substrate **1** was prepared, according to the literature,[9] by $Ca(OH)_2$ catalysed condensation between methyl acetoacetate and O-methylisourea bisulphate. Substrates **2**[13] and **3**[13] were obtained in high yields with the same procedure starting from methyl 2-formylacetate and methyl 2-formylpropionate, respectively, generated *in situ* by mild acid hydrolysis of the corresponding dimethylacetals (Scheme 1). Non-commercial methyl 2-methyl-3,3-dimethoxypropionate was prepared from methyl 2,3-dibromo-2-methylpropionate[14] by treatment with excess NaOMe in methanol.[15]

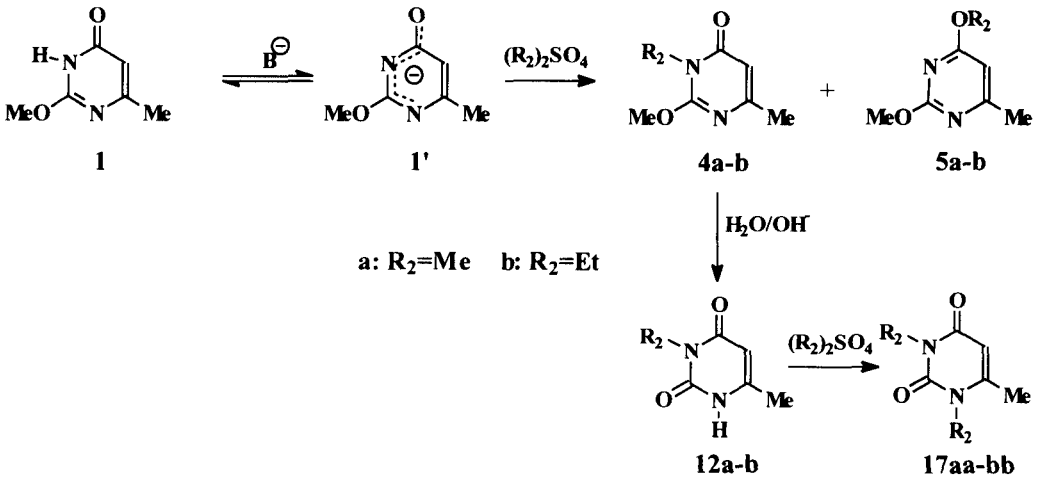


Scheme 1

With substrates **1-3** in hand, we first investigated the factors affecting the N^3/O^4 chemoselectivity by using substrate **1**, unreactive at the N^1 position,[9] as a model. Therefore, 6-methyl-2-methoxyuracil **1** was alkylated under different conditions and the relative amounts of the products **4a-b** and **5a-b** (Scheme 2), resulting respectively from N^3- and O^4-attack, were measured.

Reference samples of the reaction products were obtained by reacting **1** in 0.7N NaOH with dimethylsulphate (DMS) and diethylsulphate (DES) as alkylating agents of increasing hardness but unable to activate possible competing Hilbert-Johnson processes.[6] As expected, products of N^1-alkylation were always absent in the reaction mixtures, while, at variance with previous reports,[9] products **5a-b** arising from O^4-attack were always found in small amounts together with the main products **4a-b**.

In addition, due to a little hydrolysis of the 2-methoxy group in compounds **4a-b**, small amounts of the pyrimidinediones **12a-b** and their 1,3-dialkylated derivatives **17aa-bb** were found in the reaction mixtures. Alkylations were repeated in water, dry HMPT and dry dioxane as solvents with decreasing dielectric constant, and hydrides, hydroxides and carbonates of alkali metals with decreasing hardness[11] were used as bases to generate the anion **1'**.



Scheme 2

Product distributions under the different conditions are reported in Table 1 where **4/5** ratios are reported as N^3 *vs* O^4 ratios and products **12a-b** and **17aa-bb**, observed only in water, are counted as N^3-alkylation derivatives. Compounds **4a-b** and **5a-b** proved to be stable under all tested reaction conditions and this ruled out any possible equilibrium interconversion.

Table 1. N^3 *vs* O^4 ratios *via* GC in alkylation of **1** with DMS and DES.

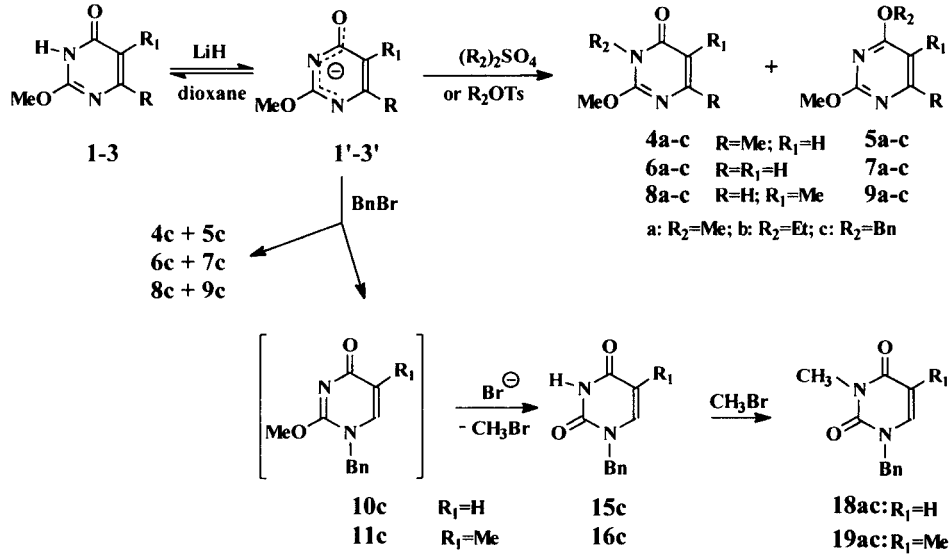
Counterion[a]	Base	Solvent and alkylating reagent					
		H_2O		HMPT		Dioxane	
		DMS	DES	DMS	DES	DMS	DES
Li^+	H^-	-	-	2.9	0.4	>200	60.5
	OH^-	17.6	1.0	3.0	0.4	>200	50.0
	CO_3^{2-}	-	-	2.8	0.3	6.1[b]	1.0[b]
Na^+	H^-	-	-	3.0	0.4	28.0	3.3
	OH^-	15.3	1.0	2.9	0.4	25.0	4.0
	CO_3^{2-}	-	-	3.0	0.4	13.0[b]	2.5[b]
K^+	H^-	-	-	3.1	0.5	20.0	3.3
	OH^-	16.5	1.1	3.0	0.4	20.0	3.5
		-	-	3.0	0.4	20.0[b]	5.5[b]

[a]RbOH and CsOH gave very fast reactions, but N^3/O^4 ratios close to those reported for KOH. [b]Reactions in heterogeneous phase.

The reported data are in agreement with the HSAB principle[11] if the N^3 nucleophilic centre in the tridentate anion **1'** is assumed softer than the O^4 anion. High dielectric constant solvents (H_2O, HMPT), where ionic couples are very loose, show nearly constant N^3/O^4 alkylation ratios, irrespective of the counterion hardness. On the contrary, the N^3/O^4 ratios observed in dry dioxane, where ionic couples are very tight, sharply increase as the hardness of the counterion increases as well. Thus, an increasing hard-hard matching between the metallic ion and the O^4-nucleophilic centre, strongly favours the soft-soft interaction between the alkylating agents and the N^3-nucleophilic centre. Moreover, under all tested conditions, methylations are always faster and more chemoselective at N^3 than the corresponding ethylations. This, besides possible steric effects, is in good agreement with the well known softer electrophilic character of the methyl group as compared with the ethyl one.[11a] Accordingly, a sharp increasing preference for the harder O^4 position is observed in ethylations going from dioxane to water to HMPT.[16]

Alkylations with carbonates in dioxane are at variance and show a quite reversed trend. This can be a consequence of both the heterogeneous phase reaction conditions and the increasing solubility of carbonates going from lithium to potassium.

With the highly N^3/O^4 chemoselective LiH/dry dioxane alkylation system in hand, we investigated the N^3/N^1 chemoselection by alkylating, under those conditions, the 2-methoxyuracils **1-3** and focussed our attention on substrates **2** and **3**, where the absence of the methyl group at C_6 could allow N^1-attack. DMS and DES were used again and, in addition, benzylbromide (BnBr) and benzyltosylate[17] (BnOTs) were tested as alkylating reagents with increasing hardness, but easily removable. Alkylations of **1-3** with the hard reagents DMS, DES and BnOTs (Scheme 3) showed to be highly chemoselective at N^3 and afforded the N^3-substitution products **4a-c**, **6a-c** and **8a-c**, respectively, in high yields with very small amounts of the alkoxypyrimidines **5a-c**, **7a-c** and **9a-c**.



Scheme 3

On the contrary, the use of the soft benzyl bromide resulted in formation of N^3-benzylation products **6c** and **8c** as well as prevalent N^1-benzylation products **15c** and **16c**. Due to the steric hindrance at C_6, N^1-benzylation products were absent in the reaction mixtures of **1** with BnBr. Formation of **15c** and **16c** can be explained in terms of bromide ion-promoted Hilbert-Johnson reactions[6] of the intermediate N^1-benzyl-2-methoxy derivatives **10c** and **11c**. Accordingly, some N^3-methylation products (**18ac** and **19ac**), arising from methylbromide attack on **15c** and **16c**, were found in the reaction mixtures. Product distributions in the various alkylations are reported in Table 2 as N^3 *vs* O^4 and N^3 *vs* N^1 ratios and products **18ac** and **19ac** (Scheme 4) are counted as N^1-alkylation derivatives.

Table 2. N^3/O^4 and N^3/N^1 GC ratios in alkylation of **1-3** with LiH in dry dioxane.

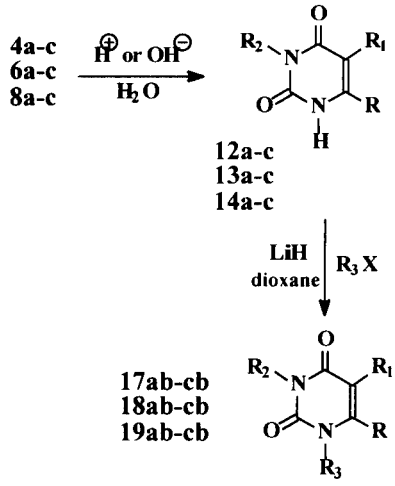
Substrate	Reagent	GC alkylation ratios	
		N^3/O^4	N^3/N^1
1	DMS	>200	-
1	DES	60.5	-
1	BnOTs	46.6	-
1	BnBr	49.0	-
2	DMS	>200	-
2	DES	61.0	-
2	BnOTs	42.0	-
2	BnBr	41.8	0.4
3	DMS	>200	-
3	DES	80.0	-
3	BnOTs	49.0	-
3	BnBr	50.0	0.4

Reactions with DMS at 25°C for 1h. Reactions with DES, BnOTs and BnBr at 60°C for 2h.

Once more, results can be explained in terms of HSAB principle[11] if the N^3 nucleophilic centre in the tridentate anions **2'** and **3'** is assumed harder than N^1, as hypothesised. Irrespective of the steric hindrance at C_6, harder electrophiles (alkylsulphates or tosylates) react almost quantitatively at N^3 with very little O^4 substitution, while the softer benzyl bromide undergoes preferential N^1-attack. Thus, the different reactivity of the two nitrogen atoms is not only influenced by the steric hindrance or electronic effect of the C_6-methyl, as previously supposed for substrate **1**,[8,1d] but also by the intrinsic difference in hardness between the two nitrogens. Therefore, the three nucleophilic centres in conjugated bases of 2-methoxy-4(3H)-pyrimidinones **1-3** can be ordered in a qualitative decreasing hardness scale as $O^4>N^3>N^1$.

The synthetic application of the above findings allowed a simple one-pot procedure to 3-alkyl-2,4(1H)-pyrimidinediones and a two-step protocol for unsymmetrically 1,3-dialkylated-uracils. N^3-alkylation of the lithium salts of substrates **1-3** in dry dioxane afforded 2-methoxyderivatives **4a-c**, **6a-c** and **8a-c** in high yield (88-98%; see Experimental). Restoration of the carbonyl at C_2 by acid or basic hydrolysis gave the 3-alkyl-2,4-(1H)-pyrimidinediones **12a-c**, **13a-c** and **14a-c** (Scheme 4), which, without further purification, were alkylated

at N^1 under the same conditions to afford the unsymmetrically 1,3-dialkylated pyrimidinediones **17**, **18** and **19** in high isolated yields. All new products were completely characterised by spectroscopic analysis.



4;12;17: R=Me; R_1=H 6;13;18: R=R_1=H 8;14;19: R=H; R_1=Me	R_2	R_3
a	Me	-
b	Et	-
c	Bn	-
ab	Me	Et
ac	Me	Bn
ba	Et	Me
bc	Et	Bn
ca	Bn	Me
cb	Bn	Et

Scheme 4

Due to the mobility of the benzyl cation, acid hydrolysis of the N^3-benzyl derivatives **6c** and **8c** resulted in migration of the benzyl group from N^3 to N^1 to give the thermodynamically more stable N^1-benzylated pyrimidinediones **15c** and **16c** respectively. However, basic hydrolysis of **6c** and **8c** afforded **13c** and **14c** as the only products.

In conclusion, the N^3 position in 2-methoxy-4(3H)-pyrimidinones is harder than the N^1 position and this allows a high yielding chemoselective N^3-alkylation when O^4 is tightly bonded to lithium cation and hard electrophiles are used in a low dielectric constant solvent. The above procedure complements previous well-established methodologies for selective N^1-alkylation.[6,7]

Experimental

General. GC analyses were obtained on a FISON GC 8000 gas-chromatograph with a capillary column (CP-Wax 52 CB Crompack, 15 m-long, ID 0.25 mm, film thickness 0.25 μm) and GC/MS analyses were done with the same gas-chromatograph equipped with a capillary column (CP-Sil 8 CB Crompack, 30 m-long, ID 0.25 mm, film thickness 0.25 μm) coupled with a FISON MD800 mass detector. FT-IR spectra were performed in $CHCl_3$on a Brucker Vector 22 spectrometer. ^1H NMR and ^{13}C NMR spectra were performed in $CDCl_3$ on a Gemini 200 and VARIAN XL300 spectrometers. HRMS were obtained on a Kratos MS-80 mass spectrometer. Solvents were dried before the use and DMS and DES were distilled to neutrality. Metal hydroxides were dried (110°C/0.1 mmHg) before use. Only spectroscopic data of new compounds are reported but spectra of all known compounds are available on request.

6-methyl-2-methoxy-4(3H)-pyrimidinone **1** was prepared according to literature.[9]

2-Methoxy-4(3H)-pyrimidinone **2.** Methyl 3,3-dimethoxypropionate (4.70 g, 31.8 mmol) was dissolved in a stirred solution of 2M HCl (30 ml). The mixture was left stirring until disappearance of the substrate and formation of *methyl 2-formylacetate* (GC/MS analysis) and then cooled to 0°C and slowly neutralised with 2N NaOH. This solution was added dropwise to a vigorously stirred solution of O-methylisourea bisulphate (5.6 g, 32 mmol) and calcium hydroxide (2.90 g) in H_2O (100 ml). After 24 hours stirring at room temperature, the reaction mixture was neutralised with NH_4Cl (std. sol.) and evaporated, the solid phase was triturated four times with hot $CHCl_3$ and the organic extracts, dried over Na_2SO_4, were evaporated *in vacuo* and crystallised ($CHCl_3$: n-hexane = 1:1) to afford **2** (3.61 g, yield 90%); mp 166-168 °C (lit. 167-168);[13] GC-MS *m/z*: 126 (M^+, 100), 125 (31),97 (36), 95 (14), 69 (30), 68 (24), 58 (36); ^1H NMR ($CDCl_3$) δ: 7.76 (d, 1H, *J* 6.6 Hz, C_6-H), 6.11 (d, 1H, *J* 6.6 Hz, C_5-H), 3.98 (s, 3H, OCH_3); ^{13}C NMR δ: 165.83 (C_4), 157.91 (C_2), 155.45 (C_6), 108.92 (C_5), 55.33 (OCH_3).

2-Methoxy-5-methyl-4(3H)-pyrimidinone **3.** Methyl 2,3-dibromo-2-methylpropionate[14] (14.0 g, 57.0 mmol) was added to a solution of NaOMe (6.15 g, 114 mmol) in dry methanol (100 ml) and the solution was refluxed for 1 hour with stirring.[15] The resulting suspension was filtered to remove NaBr and the methanol was removed by distillation. The residue was dissolved in NH_4Cl (std. sol.), extracted with Et_2O, dried, evaporated and distilled to afford *methyl 3,3-dimethoxy-2-methylpropionate*[18] (8.5 g; yield 92%); Bp 101-102 °C/42 mmHg; GC-MS *m/z*: 162 (M^+, 0), 161(0.2), 147(1), 131(13), 75(100). The latter compound was dissolved in ice-cold 2N HCl (100 ml) and stirred at room temperature for 1 hour to afford *methyl 2-formylpropionate* (GC-MS *m/z*: 116 (M^+, 48), 88 (12), 85 (61), 84 (72), 83 (32), 56 (100)). The solution was cooled to 0 °C, slowly neutralised with 2N NaOH and added dropwise to a stirred solution of O-methylisourea bisulphate (9.02 g, 52.4 mmol) and calcium hydroxide (4.5 g) in H_2O (100 ml). After 24 hours stirring at room temperature, the reaction mixture was worked up as described for **2** to afford **3** (6.19 g, yield 85%); mp 197-198 °C (lit. 198-199).[13] GC-MS *m/z*: 140 (M^+, 100), 138 (28), 125 (11), 111 (17), 110 822), 97 (10), 83 (16), 82 (43), 70 (10), 58 (21), 55 (24), 54 (15); ^1H NMR ($CDCl_3$) δ: 7.60 (q, 1H, *J* 1.1 Hz, C_6-H), 3.93 (s, 3H, OCH_3), 1.98 (d, 3H, *J* 1.1 Hz, CH_3); ^{13}C NMR δ: 165.85 (C_4), 155.41 (C_2), 150.55 (C_6), 117.00 (C_5), 55.10 (OCH_3), 12.02 (C_5-CH_3).

Synthesis of reference compounds **4a-b** *and* **5a-b**.

Freshly distilled DMS (0.85 ml, 9 mmol) was added to a solution of **1** (0.420 g, 3 mmol) in 0.7M NaOH (40 ml) and the mixture was stirred at room temperature for 1 hour (GC monitoring) and then neutralised with NH_4Cl (std. sol.). The aqueous phase was extracted four times with ethyl acetate and the organic extracts, dried over Na_2SO_4, were evaporated in a Vigreaux distillation apparatus. The crude residue was purified by chromatography on silica gel (petroleum ether 40°-70°: ethyl acetate, 8:2) to give, in elution order:

2,4-Dimethoxy-6-methylpyrimidine **5a**: (23 mg, 5%); IR: ν_{max} 1590, 1575, 1468, 1284 cm^{-1}; GC-MS *m/z*: 154 (M^+, 100), 153 (91), 124 (80), 109 (57), 83 (39), 67 (32); ^1H NMR ($CDCl_3$) δ: 6.17 (s, 1H, C_5-H), 3.93 (s, 3H, OCH_2), 3.90 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3); HRMS: found 154.0741, $C_7H_{10}N_2O_2$ requires 154.0742.

3,6-Dimethyl-2-methoxy-4-pyrimidinone **4a**: (0.415 g, 90%); mp 80-81 °C(lit. 79-81).[9]

1,3,6-Trimethyl-2,4-pyrimidinedione **17aa**: (15 mg, 3%); mp 112-113 °C (lit. 114).[1a] GC/MS analysis showed traces of **12a** (*vide infra*).

Ethylation with DES was carried out in the same way, but 15 ml of dioxane were also added and the reaction ended after 12 hours. After the usual work up, chromatography afforded, in elution order:

4-Ethoxy-2-methoxy-6-methylpyrimidine **5b**: (0.232 g, 46%); oil; IR: ν_{max} 1570, 1559, 1470, 1455, 1256 cm^{-1}; GC-MS *m/z*: 168 (M^+, 23), 153 (100), 140 (57), 139 (29), 124 (36), 110 (55), 109 (74), 83 (28); ^1H NMR ($CDCl_3$) δ: 6.16 (s, 1H, C_5-H), 4.36 (q, 2H, *J* 7.0 Hz, OCH_2), 3.93 (s, 3H, OCH_3), 2.32 (s, 3H, C_6-CH_3), 1.34 (t, 3H, J 7.0 Hz, CH_3); HRMS: found 168.0898, $C_8H_{12}N_2O_2$ requires 168.0899.

3-Ethyl-2-methoxy-6-methyl-4-pyrimidinone **4b**: (0.242 g, 48%); oil; IR: ν_{max} 1711, 1676, 1672, 1546, 1537, 1420 cm^{-1}; GC-MS *m/z*: 168 (M^+, 70), 140 (31), 139 (59), 111 (27), 110 (100), 58 (12); ^1H NMR ($CDCl_3$) δ: 5.84 (q, 1H, *J* 0.9 Hz, C_5-H), 3.90 (q, 2H, *J* 7.1 Hz, N^3CH_2), 3.89 (s, 3H, OCH_3), 2.06 (d, 3H, *J* 0.9 Hz, CH_3), 1.11 (t, 3H, *J* 7.1 Hz, CH_3); ^{13}C NMR δ: 163.01 (C_4), 162.44 (C_2), 156.07 (C_6), 105.99 (C_5), 55.22 (OCH_3), 35.76 (N^3CH_2), 23.28 (CH_3), 12.08 (CH_3). HRMS: found 168.0900, $C_8H_{12}N_2O_2$ requires 168.0899.

GC/MS traces of **12b** (*vide infra*) and **17bb** (GC-MS *m/z*: 182 (M^+, 95), 167 (30), 154 (50), 139 (100)) were also detected.

Effect of bases, solvents and counterions in methylation and ethylation of **1** (Table 1).

All reaction were performed in duplicate by adding excess DMS or DES to stirred 0.07M solutions of **1** (4 ml) in the appropriate solvent and the reaction progresses were monitored by GC. Three samples of the final mixtures were analysed *via* GC/MS by comparison with pure samples of **4a-b** and **5a-b** and the resulting N^3/O^4 average ratios are reported in Table 1. Reactions in H_2O were carried out at 25° in 0.1N LiOH, NaOH and KOH, respectively, and, at the end, the reactions were quenched by NH_4Cl and extracted with EtOAc. Alkylations in dry HMPT or in dry dioxane were performed under argon atmosphere at 25°C (60°C for ethylations) by first adding 1 equivalent of the appropriate washed metal hydride or 3 equivalents of the appropriate dried metal hydroxide. After 0.5h stirring, 1.3 equivalents of alkylating agent were added and stirring was continued for 1h. Reaction mixtures from HMPT were analysed without any work-up, while mixtures from dioxane were worked up as described for the aqueous medium.

Preparative N^3-alkylation of **1**, **2** *and* **3** *with LiH/dioxane system.*

a) With alkylsulphates or tosylates. Washed LiH (1.5 mmol) and the appropriate substrate (**1**, **2** or **3**: 1.5 mmol) were dissolved in 20 ml of dry dioxane and stirred at room temp. for 0.5h under an argon atmosphere. Then 1.3 equivalents of the alkylating reagent (DMS, DES or benzyl tosylate[17]) were added and solutions were stirred at the reported temp. for the reported time. At the end, the reaction mixtures were neutralised with NH_4Cl (std. soln.), the aqueous phase extracted four times with ethyl acetate, the organic extracts dried over Na_2SO_4 and evaporated. GC/MS analyses gave results reported in Table 2. The crude mixtures were purified by chromatography on silica gel (petroleum ether 40°-70° : ethyl acetate, 8:2) and products were isolated in each case, with the reported yields. Spectroscopic data are reported only for new isolated products.

3,6-Dimethyl-2-methoxy-4-pyrimidinone **4a** (r. t., 1h, yield 98%) (*vide infra*).

3-Ethyl-2-methoxy-6-methyl-4-pyrimidinone **4b** (60°C, 2h, yield 94%) (*vide infra*).

4-Ethoxy-2-methoxy-6-methylpyrimidine **5b** (2% *via* GC-MS) (*vide infra*).

3-Benzyl-2-methoxy-6-methyl-4-pyrimidinone **4c** (60°C, 2h, yield 95%); oil; IR: ν_{max} 1731, 1675, 1543, 1249 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.35-7.20 (m, 5H, Ph), 5.98 (q, 1H, *J* 0.9 Hz, C_5-H), 5.12 (s, 2H, N^3CH_2), 3.99 (s, 3H, OCH_3), 2.15 (d, 3H, *J* 0.9 Hz, CH_3); ^{13}C NMR δ: 163.14 (C_4), 162.05 (C_2), 156.12 (C_6), 138.35 (Ph), 128.64 (Ph), 128.50 (Ph), 127.84 (Ph), 105.45 (C_5), 55.30 (OCH_3), 44.10 (N^3CH_2), 23.04 (CH_3); GC-MS *m/z*: 230 (M^+, 100), 153 (6), 124 (34), 110 (25), 109 (19), 104 (34), 91 (94). HRMS: found 230.1056, $C_{13}H_{14}N_2O_2$ requires 230.1055.

4-Benzyloxy-2-methoxy-6-methylpyrimidine **5c** (yield 2%); oil; ^1H NMR ($CDCl_3$) δ: 7.45-7.20 (m, 5H, Ph), 6.25 (s, 1H, C_5-H), 5.38 (s, 2H, CH_2Ph), 3.95 (s, 3H, OCH_3), 2.34 (s, 3H, C_6-CH_3). GC-MS *m/z*: 230 (M^+, 46), 153 (12), 125 (15), 124 (69), 109 (32), 91 (100).

2-Methoxy-3-methyl-4-pyrimidinone **6a** (r.t., 1h, yield 96%); mp 92-95 °C (lit. 93-95).[19]

3-Ethyl-2-methoxy-4-pyrimidinone **6b** (60°C, 2h, yield 93%); oil; IR: ν_{max} 1709, 1672, 1359 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.58 (d, *J* 6.5 Hz, 1H, C_6-H), 6.03 (d, 1H, *J* 6.5 Hz, C_5-H), 4.00 (q, 2H, *J* 7.1 Hz, N^3CH_2), 3.97 (s, 3H, OCH_3), 1.20 (t, 3H, *J* 7.1 Hz, CH_3); ^{13}C NMR δ: 163.24 (C_4), 157.83 (C_2), 152.23 (C_6), 109.31 (C_5), 55.99 (OCH_3), 36.68 (N^3CH_2), 13.31 (CH_3); GC-MS *m/z*: 154 (M^+, 54), 126 (32), 125 (37), 97 (24), 96 (100), 72 (10), 68 (11), 58 (21); HRMS: found 154.0743, $C_7H_{10}N_2O_2$ requires 154.0742.

4-Ethoxy-2-methoxypyrimidine **7b** (yield 1%); ^1H NMR ($CDCl_3$) δ: 8.17 (d, *J* 5.6 Hz, 1H, C_6-H), 6.32 (d, *J* 5.6Hz, 1H, C_5-H), 4.39 (q, *J* 7.0 Hz, 2H, OCH_2-), 3.95 (s, 3H, OCH_3), 1.36 (t, *J* 7.0, 3H, CH_3); GC-MS *m/z*: 154 (M^+, 24), 139 (100), 126(88), 125 (28), 110 (57), 97 (27), 96 (88), 95 (83), 69 (35), 68 (31).

3-Benzyl-2-methoxy-4-pyrimidinone **6c** (60°C, 2h, yield 97%); oil; IR: ν_{max} 1711, 1670, 1638, 1362 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.60 (d, 1H, *J* 6.5 Hz, C_6-H), 7.40-7.20 (m, 5H, Ph), 6.14 (d, 1H, *J* 6.5 Hz, C_5-H), 5.15 (s, 2H, N^3CH_2), 3.95 (s, 3H, OCH_3); ^{13}C NMR δ: 163.15 (C_4), 157.60 (C_2), 152.07 (C_6), 136.28 (Ph), 128.66 (Ph), 128.48 (Ph), 127.86 (Ph), 109.05 (C_5), 55.60 (OCH_3), 44.16 (N^3CH_2); GC-MS *m/z*: 216 (M^+, 88), 111 (10), 110 (34), 106 (10), 104 (28), 96 (25), 91 (100), 65 (13); HRMS: found 216.0900, $C_{12}H_{12}N_2O_2$ requires 216.0899.

4-Benzyloxy-2-methoxy-pyrimidine **7c** (yield 2%); ^1H NMR ($CDCl_3$) δ: 8.19 (d, *J* 5.7Hz, 1H, C_6-H), 7.45-7.10 (m, 5H, Ph), 6.41 (d, *J* 5.7 Hz, 1H, C_5-H), 5.39 (s, 2H, OCH_2Ph), 3.98 (s, 3H, OCH_3); GC-MS *m/z*: 216 (M^+, 28), 139 (5), 110 (30), 96 (18), 91 (100), 65 (20).

3,5-Dimethyl-2-methoxy-4-pyrimidinone **8a** (r.t., 1h, yield 96%); mp 97-98 °C; IR: ν_{max} 1735, 1674, 1555, 1371, 1224 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.47 (q, 1H, *J* 1.2 Hz, C_6-H), 3.96 (s, 3H, OCH_3), 3.37 (s, 3H, N^3CH_3), 1.94 (d, 3H, *J* 1.2 Hz, C_5-CH_3); ^{13}C NMR δ: 163.80 (C_4), 155.97 (C_2), 148.24 (C_6), 116.78 (C_5), 55.29 (OCH_3), 27.61 (N^3CH_3), 12.19 (CH_3); GC-MS *m/z*: 154 (M^+, 100), 139 (41), 124 (16), 111 (13), 110 (27), 96 (13), 72 (30), 56 (14), 55 (18); HRMS: found 154.0743, $C_7H_{10}N_2O_2$ requires 154.0742.

3-Ethyl-2-methoxy-5-methyl-4-pyrimidinone **8b** (60°C, 2h, yield 95%); mp 41-43 °C; IR: ν_{max} 1741, 1664, 1554, 1407, 1312 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.43 (q, 1H, *J* 1.1 Hz, C_6-H), 4.00 (q, 2H, *J* 7.1 Hz, N^3CH_2), 3.93 (s, 3H, OCH_3), 1.93 (d, 3H, *J* 1.1 Hz, C_5-CH_3), 1.18 (s, 3H, CH_3); ^{13}C NMR δ: 163.36 (C_4), 155.93 (C_2), 148.24 (C_6), 117.14 (C_5), 55.19 (OCH_3), 36.47 (N^3CH_2), 12.94 (CH_3), 12.88 (CH_3); GC-MS *m/z*: 168 (M^+, 100), 140 (35), 125 (15), 111 (13), 82 (18), 70 (11), 58 (22), 55 (20), 54 (16); HRMS: found 168.0898, $C_8H_{12}N_2O_2$ requires 168.0899.

4-Ethoxy-2-methoxy-5-methylpyrimidine **9b** (traces via GC-MS).

3-Benzyl-2-methoxy-5-methyl-4-pyrimidinone **8c** (60°C, 2h, yield 88%); mp 68-70 °C; IR: ν_{max} 1745, 1665, 1550, 1395 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.49 (d, 1H, *J* 1.1 Hz, C_6-H), 7.29 (m, 5H, Ph), 5.16 (s, 2H, N^3CH_2), 3.93 (s, 3H, OCH_3), 1.98 (d, 3H, *J* 1.1 Hz, CH_3); ^{13}C NMR δ: 162.96 (C_4), 156.02 (C_2), 148.48 (C_6), 138.42 (Ph), 128.62 (Ph), 127.80 (Ph), 116.75 (C_5), 55.35 (OCH_3), 44.48 (N^3CH_2), 13.01 (CH_3); GC-MS *m/z*: 230 (M^+, 47), 139 (32), 124 (20), 91 (100), 65 (10); HRMS: found 230.1057, $C_{13}H_{14}N_2O_2$ requires 230.1055.

4-Benzyloxy-2-methoxy-5-methyl-pyrimidine **9c** (yield 1%); ^1H NMR ($CDCl_3$) δ: 8.19 (s, 1H, C_6-H), 7.25-7.45 (m, 5H, Ph), 5.39 (s, 2H, OCH_2Ph), 3.96 (s, 3H, OCH_3), 2.35 (s, 3H, C_5-CH_3); GC-MS *m/z*: 230 (M^+, 18), 139 (31), 124 (17), 91 (100), 65 (15).

b) with benzylbromide.

Reactions were carried out as described in a) but 1.3 equivalents of benzylbromide were used as alkylating agent. After 24h stirring the reaction mixtures were worked up as described above and purified by chromatography on silica gel (petroleum ether 40°-70° : ethyl acetate, 8:2). Products were obtained with the reported yields.

4c (90%); **5c** (2%).

6c (26%); **7c** (0.6% via GC-MS); *1-Benzyl-2,4(3H)-pyrimidinedione* **15c** (72%); mp 174-176 °C (lit. 174-176).[20] GC-MS traces of **18ac** (*vide infra*) were also detected.

8c (27%); **9c** (0.5%); *1-benzyl-5-methyl-2,4-pyrimidinedione* **16c** (67%); mp 165-167 °C (lit. 164-166).[21] GC-MS traces of **19ac** (*vide infra*) were also detected.

2,4(1H)-Pyrimidinedione derivatives **12, 13** *and* **14.**

0.7 mmol of the appropriate substrate (**4a-c**, **6a-c**, or **8a-c**) were dissolved in 7 ml of 2M HCl / dioxane (1:1 mixture) and stirred for 2h at 60°C. The reaction mixture was then neutralised with 2M NaOH and extracted four times with ethyl acetate. The organic extracts, dried over Na_2SO_4, were concentrated *in vacuo*. Crude products from **4a-c**, **6a-b** and **8a-b** were directly recrystallised from a $CHCl_3$: n-hexane solution (1:1). Purified products were obtained with the reported yields.

3,6-Dimethyl-2,4(1H)-pyrimidinedione **12a**: (yield 98%); mp 262-263 °C (lit. 262-263).[9]

3-Ethyl-6-methyl-2,4(1H)-pyrimidinedione **12b**: (yield 98%); mp 190-191 °C (lit. 195).[22]

3-Benzyl-6-methyl-2,4(1H)-pyrimidinedione **12c**: (yield 98%); mp 185-186 °C(lit. 184-186).[23]

3-Methyl-2,4(1H)-pyrimidinedione **13a**: (yield 98%); mp 180-182 °C (lit. 180-182).[24]

3-Ethyl-2,4(1H)-pyrimidinedione **13b**: (yield 98%); mp 166-169 °C (lit. 168-170).[25]

3,5-Dimethyl-2,4(1H)-pyrimidinedione **14a**: (yield 96%); mp 206-208 °C(lit. 204-206).[24]

3-Ethyl-5-methyl-2,4(1H)-pyrimidinedione **14b**: (yield 95%); mp 203-205 °C (lit. 203)[26]

The crude mixture from **6c** was separated by chromatography on silica gel (petroleum ether 40°-70°: ethyl acetate, 8:2) to give **15c** (58%, *vide infra*) and *3-benzyl-2,4(1H)-pyrimidinedione* **13c** (42%): mp 169-172 °C (lit. 173-174).[27] Repetition of the hydrolysis by using 2M NaOH/ dioxane (1:1) followed by neutralisation with 2M HCl and extraction with ethyl acetate, afforded **13c** as the only product (98%).

The crude mixture from **8c** was separated by chromatography on silica gel (petroleum ether 40°-70°: ethyl acetate, 8:2) to give **16c** (60%, *vide infra*) and *3-benzyl-5-methyl-2,4(1H)-pyrimidinedione* **14c**: (yield 40%);

mp 202-204 °C (lit. 200-202).[23] Repetition of the hydrolysis by using 2M NaOH/ dioxane (1:1) followed by neutralisation with 2M HCl and extraction with ethyl acetate, afforded **14c** as the only product (yield 96%).

Synthesis of N^1,N^3-dialkyl-2,4-pyrimidinediones **17, 18** *and* **19**.

Washed LiH (1.5 mmol) was added at room temp. and under argon atmosphere to a stirred solution of the appropriate substrate (**12a-c, 13a-c**, or **14a-c**; 1.5 mmol) in 25 ml of anhydrous dioxane. After 0.5 h, the temperature was raised to 60°C and 3 equivalents of the alkylating reagent (DMS, DES, benzyltosylate) were added. After the appropriate time of stirring the reaction mixture was neutralised with a saturated solution of NH_4Cl and the aqueous phase extracted four times with ethyl acetate. The organic extracts, dried over Na_2SO_4, were concentrated *in vacuo*. The crude mixture was purified by chromatography on silica gel (petroleum ether 40°-70° : ethyl acetate, 8:2). Purified products were obtained with the reported yields.

3,6-Dimethyl-1-ethyl-2,4-pyrimidinedione **17ab**: (reaction time 24h, yield 92%); mp 102-103 °C; IR: ν_{max} 1701, 1666, 1659, 1621, 1474 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.55 (s, 1H, C_5-H), 3.86 (q, 2H, *J* 7.2, Hz, N^1CH_2), 3.27 (s, 3H, N^3CH_3), 2.21 (s, 3H, C_6-CH_3), 1.23 (t, 3H, *J* 7.2 Hz, CH_3); ^{13}C NMR δ 163.08 (C_2), 152.66 (C_4), 151.42 (C_6), 101.89 (C_5), 40.45 (N^1CH_2), 27.96 (N^3CH_3), 19.66 (C_6-CH_3), 14.18 (CH_3); GC-MS *m/z*: 168 (M^+, 79), 140 (43), 110 (11), 96 (100), 83 (29), 70 (13), 68 (21); HRMS: found 168.0897, $C_8H_{12}N_2O_2$ requires 168.0899.

1,6-Dimethyl-3-ethyl-2,4-pyrimidinedione **17ba**: (reaction time 16h, yield 93%); mp 108-109 °C; IR: ν_{max} 1702, 1666, 1659, 1623, 1473 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.61 (q, 1H, *J* 1.0 Hz, C_5-H), 3.93 (q, 2H, *J* 7.0, Hz, N^3CH_2), 3.34 (s, 3H, N^1CH_3), 2.18 (d, 3H, *J* 1.0 Hz, C_6-CH_3), 1.14 (t, 3H, *J* 7.0 Hz, CH_3); ^{13}C NMR δ 162.54 (C_2), 152.27 (C_4), 152.07(C_6), 101.24 (C_5), 36.41 (N^3CH_2), 31.41 (N^1CH_3), 19.99 (C_6-CH_3), 12.55 (CH_3); GC-MS *m/z*: 168 (M^+, 85), 140 (100), 98 (64), 97 (19), 96 (17), 82 (62), 56 (70), 55 (12); HRMS: found 168.0898, $C_8H_{12}N_2O_2$ requires 168.0899.

3-Benzyl-1,6-dimethyl-2,4-pyrimidinedione **17ca**: (reaction time 16h, yield 85%); mp 164-165 °C (lit. 165).[1a]

1-Benzyl-3,6-dimethyl-2,4-pyrimidinedione **17ac:** (reaction time 10h, yield 82%); mp 84-85 °C (lit. 84-85).[29]

3-Benzyl-1-ethyl-6-methyl-2,4-pyrimidinedione **17cb**: (reaction time 24h, yield 84%); mp 120-121 °C; IR: ν_{max} 1698, 1661, 1659, 1623, 1471 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.45-7.15 (m, 5H, Ph), 5.57 (q, 1H, *J* 0.8 Hz, C_5-H), 5.07 (s, 2H, N^3CH_2), 3.63 (q, 2H, *J* 6.9, Hz, N^1CH_2), 2.19 (d, 3H, *J* 0.8 Hz, CH_3), 1.22 (t, 3H, *J* 6.9 Hz, CH_3); ^{13}C NMR δ: 162.43 (C_2), 152.07 (C_4), 151.34 (C_6), 137.26 (Ph), 129.11 (Ph), 128.42 (Ph), 127.60 (Ph), 101.62 (C_5), 44.22 (N^3CH_2), 40.17 (N^1CH_2), 19.36 (C_6-CH_3) 13.06 (CH_3); GC-MS *m/z*: 244 (M^+, 100), 140 (29), 112 (35), 110 (30), 96 (22), 91 (54), 65 (10); HRMS: found 244.1214, $C_{14}H_{16}N_2O_2$ requires 244.1212.

1-Benzyl-3-ethyl-6-methyl-2,4-pyrimidinedione **17bc**: (reaction time 10h, yield 84%); oil; IR: ν_{max} 1701, 1663, 1621, 1466, 1448 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.40-7.10 (m, 5H, Ph), 5.58 (s, 1H, C_5-H), 5.09 (s, 2H, N^1CH_2), 4.01 (q, 2H, *J* 7.1, Hz, N^3CH_2), 2.12 (s, 3H, C_6-CH_3), 1.21 (t, 3H, *J* 7.1 Hz, CH_3); ^{13}C NMR δ: 162.14 (C_2), 152.54 (C_4), 151.64 (C_6), 136.30 (Ph), 129.06 (Ph), 127.81 (Ph), 126.19 (Ph), 102.04 (C_5), 47.66 (N^1CH_2), 36.41 (N^3CH_2), 19.61 (C_6-CH_3) 12.57 (CH_3); GC-MS *m/z*: 244 (M^+, 30), 110 (12), 91 (100), 65 (9); HRMS: found 244.1211, $C_{14}H_{16}N_2O_2$ requires 244.1212.

1-Ethyl-3-methyl-2,4-pyrimidinedione **18ab**: (reaction time 24h, yield 90%); mp 72-75 °C (lit. 73-75).[30]

3-Ethyl-1-methyl-2,4-pyrimidinedione **18ba**: (reaction time 16h, yield 91%); mp 57-60 °C (lit. 60-61).[6a]

3-Benzyl-1-methyl-2,4-pyrimidinedione **18ca**: (reaction time 16h, yield 84%); mp 91-94°C (lit. 105-106 from ethanol).[31].

1-Benzyl-3-methyl-2,4-pyrimidinedione **18ac**: (reaction time 10h, yield 85%); mp 67-70 °C (lit. 71-72).[32]

3-Benzyl-1-ethyl-2,4-pyrimidinedione **18cb**: (reaction time 24h, yield 83%); mp 102-104 °C; IR: ν_{max} 1710, 1666, 1636, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.50-7.20 (m, 5H, Ph), 7.09 (d, 1H, *J* 7.8 Hz, C_6-H), 5.73 (d, 1H, *J* 7.8 Hz, C_5-H), 5.10 (s, 2H, N^3CH_2), 3.76 (q, 2H, *J* 6.0 Hz, N^1CH_2), 1.28 (t, 3H, *J* 6.0 Hz, CH_3); ^{13}C NMR δ: 163.07 (C_2), 150.01 (C_4), 141.77 (C_6), 136.85 (Ph), 129.03 (Ph), 128.36 (Ph), 127.55 (Ph), 101.87 (C_5), 44.90 (N^3CH_2), 44.26 (N^1CH_2), 14.33 (CH_3); GC-MS *m/z*: 230 (M^+, 100), 201 (17), 158 (56), 92 (11), 91 (100), 65 (12); HRMS: found 230.1056, $C_{13}H_{14}N_2O_2$ requires 230.1055.

1-Benzyl-3-ethyl-2,4-pyrimidinedione **18bc**: (reaction time 10h, yield 85%); oil; IR: ν_{max} 1705, 1661, 1632, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.40-7.20 (m, 5H, Ph), 7.10 (d, 1H, *J* 7.9 Hz, C_6-H), 5.66 (d, 1H, *J* 7.9 Hz, C_5-H), 4.88 (s, 2H, N^1CH_2), 3.97 (q, 2H, *J* 7.0 Hz, N^3CH_2), 1.19 (t, 3H, *J* 7.0 Hz, CH_3); ^{13}C NMR δ: 162.88 (C_2), 151.63 (C_4), 141.75 (C_6), 135.49 (Ph), 129.13 (Ph), 128.49 (Ph), 128.05 (Ph), 102.08 (C_5), 51.99 (N^1CH_2), 36.28 (N^3CH_2), 12.52 (CH_3); GC-MS *m/z*: 230 (M^+, 32), 213 (15), 132 (28), 98 (22), 96 (19), 91 (51), 82 (18), 77 (14), 65 (17); HRMS: found 230.1057, $C_{13}H_{14}N_2O_2$ requires 230.1055.

3,5-Dimethyl-1-ethyl-2,4-pyrimidinedione **19ab**: (reaction time 24h, yield 91%); mp 114-116 °C; IR: ν_{max} 1698, 1668, 1640, 1474 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.95 (q, 1H, *J* 1.1 Hz, C_6-H), 3.72 (q, 2H, *J* 7.3, Hz, N^1CH_2), 3.29 (s, 3H, N^3CH_3), 1.88 (d, 3H, *J* 1.1 Hz, C_5-CH_3), 1.24 (t, 3H, *J* 7.3 Hz, CH_3); ^{13}C NMR δ: 164.22 (C_2), 151.52 (C_4), 137.96 (C_6), 109.73 (C_5), 44.37 (N^1CH_2), 27.65 (N^3CH_3), 14.09 (C_5-CH_3), 12.78 (CH_3); GC-MS *m/z*: 168 (M^+, 100), 140 (34), 110 (11), 96 (69), 83 (29), 82 (25), 68 (37), 56 (17), 55 (20), 54 (14); HRMS: found 168.0898, $C_8H_{12}N_2O_2$ requires 168.0899.

1,5-Dimethyl-3-ethyl-2,4-pyrimidinedione **19ba**: (reaction time 16h, yield 90%); mp 79-81 °C; IR: ν_{max} 1699, 1668, 1640, 1464 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.92 (q, 1H, *J* 1.2 Hz, C_6-H), 3.92 (q, 2H, *J* 7.1, Hz, N^3CH_2), 3.27 (s, 3H, N^1CH_3), 1.83 (d, 3H, *J* 1.2 Hz, C_5-CH_3), 1.12 (t, 3H, *J* 7.1 Hz, CH_3); ^{13}C NMR δ163.88 (C_2), 151.68 (C_4), 139.25 (C_6), 109.68 (C_5), 36.34 (N^3CH_2), 36.27 (N^1CH_3), 12.67 (C_5-CH_3), 12.55 (CH_3); GC-MS *m/z*: 168 (M^+, 100), 140 (99), 141 (10), 98 (23), 97 (17), 96 (24), 70 (16), 69 (63), 68 (74), 56 (12), 55 (10); HRMS: found 168.0898, $C_8H_{12}N_2O_2$ requires 168.0899.

3-Benzyl-1,5-dimethyl-2,4-pyrimidinedione **19ca**: (reaction time 16h, yield 85%); mp 128-130 °C; IR: ν_{max} 1699, 1669, 1640, 1451 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.50-7.15 (m, 5H, Ph), 6.93 (q, 1H, *J* 1.2 Hz, C_6-H), 5.11 (s, 2H, N^3CH_2), 3.32 (s, 3H, N^1CH_3), 1.90 (d, 3H, *J* 1.2 Hz, C_5-CH_3); ^{13}C NMR δ: 163.84 (C_2), 151.75 (C_4), 139.20 (C_6), 136.95 (Ph), 129.13 (Ph), 128.32 (Ph), 127.53 (Ph), 109.81 (C_5), 44.52 (N^3CH_2), 36.64 (N^1CH_3), 12.99 (C_5-CH_3); GC-MS *m/z*: 230 (M^+, 100), 213 (12), 139 (63), 132 (38), 104 (12), 98 (24), 96 (21), 91 (98), 69 (12), 68 (14), 65 (13); HRMS: found 230.1054, $C_{13}H_{14}N_2O_2$ requires 230.1055.

1-Benzyl-3,5-dimethyl-2,4-pyrimidinedione **19ac**: (reaction time 10h, yield 88%); mp 97-99 °C; IR: ν_{max} 1699, 1669, 1639, 1472 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.40-7.20 (m, 5H, Ph), 6.98 (q, 1H, *J* 1.2 Hz, C_6-H), 4.87 (s, 2H, N^1CH_2), 3.32 (s, 3H, N^3CH_3), 1.85 (d, 3H, *J* 1.2 Hz, C_5-CH_3); ^{13}C NMR δ: 164.07 (C_2), 152.01 (C_4), 137.90 (C_6), 135.83 (Ph), 129.08 (Ph), 128.39 (Ph), 127.97 (Ph), 110.12 (C_5), 51.83 (N^1CH_2), 27.89 (N^3CH_3), 12.84

(C_5-CH_3); GC-MS *m/z*: 230 (M^+, 24), 92 (8), 91 (100), 65 (8); HRMS: found 230.1057, $C_{13}H_{14}N_2O_2$ requires 230.1055.

3-Benzyl-1-ethyl-5-methyl-2,4-pyrimidinedione **19cb**: (reaction time 24h, yield 85%); mp 107-109 °C; IR: ν_{max} 1699, 1668, 1639, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.50-7.15 (m, 5H, Ph), 6.94 (q, 1H, *J* 1.1 Hz, C_6-H), 5.12 (s, 2H, N^3CH_2), 3.74 (q, 2H, *J* 7.2, Hz, N^1CH_2), 1.91 (d, 3H, *J* 1.1 Hz, C_5-CH_3), 1.26 (t, 3H, *J* 7.2, Hz, CH_3); ^{13}C NMR δ: 164.04 (C_2), 151.72 (C_4), 138.20 (C_6), 137.23 (Ph), 129.27 (Ph), 128.47 (Ph), 127.62 (Ph), 110.10 (C_5), 44.43 (N^3CH_2 + N^1CH_2), 14.14 (C_5-CH_3), 12.87 (CH_3); GC-MS *m/z*: 244 (M^+, 89), 153 (94), 132 (28), 112 (22), 110 (42), 96 (11), 91 (100), 83 (11), 68 (11), 65 (16); HRMS: found 244.1213, $C_{14}H_{16}N_2O_2$ requires 244.1212.

1-Benzyl-3-ethyl-5-methyl-2,4-pyrimidinedione **19bc**: (reaction time 10h, yield 89%). mp 98-100 °C; IR: ν_{max} 1699, 1669, 1640, 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.50-7.20 (m, 5H, Ph), 6.94 (q, 1H, *J* 1.1 Hz, C_6-H), 4.89 (s, 2H, N^1CH_2), 4.02 (q, 2H, *J* 7.0, Hz, N^3CH_2), 1.86 (d, 3H, *J* 1.1 Hz, C_5-CH_3), 1.21 (t, 3H, *J* 1.1 Hz, CH_3); ^{13}C NMR δ: 164.05 (C_2), 152.02 (C_4), 137.87 (C_6), 129.17 (Ph), 128.44 (Ph), 128.04 (Ph), 127.67 (Ph), 110.45 (C_5), 51.77 (N^1CH_2), 36.57 (N^3CH_2), 12.87 (C_5-CH_3) 12.66 (CH_3); GC-MS *m/z*: 244 (M^+, 20) 153 (7), 92 (8), 91 (100), 65 (8).;HRMS: found 244.1210, $C_{14}H_{16}N_2O_2$ requires 244.1212.

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