Methyl Orthocarboxylates as Methylating Agents of Heterocycles

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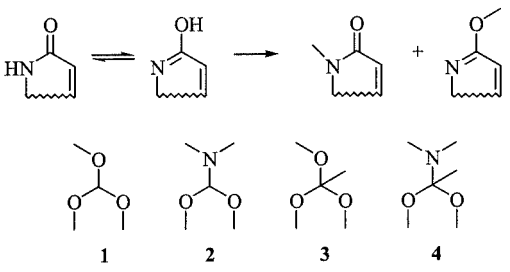
Methylation reactions occurring between trimethyl orthocarboxylates or *N,N*-dimethylcarboxamide dimethyl acetals and various hydroxylated heterocycles, involving a lactam-lactim tautomeric equilibrium, were investigated as an alternative to classic methylation methods. The corresponding *O*-methylated or *N*-methylated compounds were isolated in a number of instances and the reaction's regioselectivity was shown to sometimes follow and sometimes differ from the corresponding outcome using standard methylation methods. In the course of this work, previously unreported effects were noticed. In one case the use of toluene as a reaction solvent led to much more *N*-methylated material. In other instances, the influence of the reagent's steric bulk and/or stability (orthoformate vs. orthoacetate or *N,N*-dimethylformamide dimethyl acetal vs. its acetamide homologue) was also noticed. An unwanted formylation reaction could sometimes be avoided and, less often, an increase of *O*-methylated material was observed. The previously unreported 1-dimethoxymethylpyridin-2(1*H*)-one was characterized and its acid-catalyzed rearrangement into, mostly, 1-methylpyridin-2(1*H*)-one was studied. The new techniques described here (methanol trapping with 4 Å molecular sieves and Lewis acid-catalyzed reaction) greatly increase the potential of trimethyl orthocarboxylates. These reagents can be considered as possible alternatives to the dimethyl formamide-producing *N,N*-dimethylformamide dimethyl acetal and may sometimes be attractive options compared to the usual carcinogenic and salt-producing methylating agents.

Introduction

Dimethyl carbonate, dimethyl sulfate and trimethyl phosphate are classical reagents usually requiring a base to achieve methylation reactions. In the case of hydroxylated heterocycles featuring a tautomeric equilibrium between a lactam and a lactim function (Scheme 1) the use of these reagents often leads to a mixture of *N*- and *O*-methyl derivatives in a ratio dependent on the heterocycle under consideration and, to a lesser extent, on the combination of solvent and base employed.



Scheme 1

A regioselective alkylation of these ambident compounds is a recurrent goal in heterocyclic chemistry. An *O*-methylation of such a heterocycle leads to a methoxy group which can be an easily hydrolysed protecting group,[1] whereas the corresponding *N*-methyl isomer usually requires far harsher reaction conditions for an *N*-demethylation. We recently extended the use of trimethyl orthoformate (**1**) to the *O*-methylation of 3-cyano-5-ethyl-2,6-dihydroxy-4-methylpyridine,[2] and thus elaborated new compounds from the corresponding bismethoxylated heterocycle.[3] Unexpected results obtained with the bulkier trimethyl orthoacetate (**3**) led us to investigate its reaction with various hydroxylated heterocycles. Moreover, the fact that *N,N*-dimethylformamide dimethyl acetal (**2**) has often been used as a methylating agent,[4–7] drove us to also test the corresponding acetamide homologue **4**. In an attempt to illustrate the potential and limits of reagents **3** and **4**, we report herein, in a condensed fashion, some of the results obtained.

Results and Discussion

Equation A

Reaction of 3-cyano-2,6-dihydroxy-4-methylpyridine (**5**) with 1.1 equiv. of trimethyl orthoacetate (**3**) in toluene leads to the 2-methoxy derivative **6** and its 6-methoxy isomer **8** in 48 and 24% yield, respectively. A smaller amount of the 2,6-dimethoxy compound **7** is also isolated. A necessary ex-

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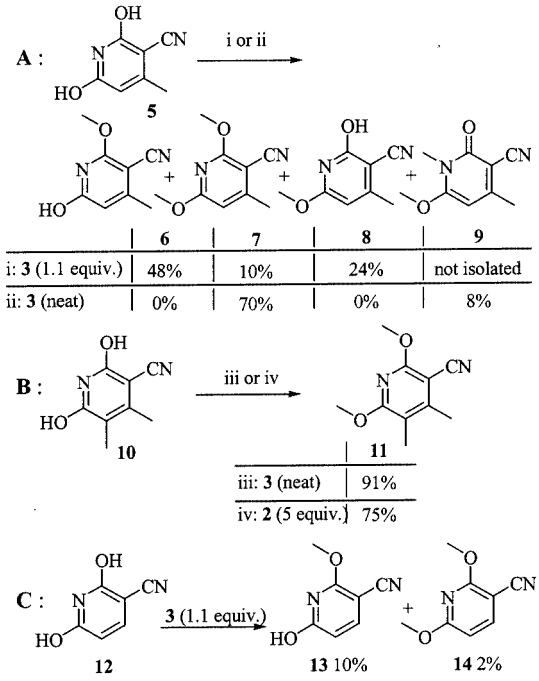
perimental condition is to distil the methanol and methyl acetate from the reaction mixture continuously, otherwise the reaction is completely stalled. Previous work[2] has demonstrated that a free alcohol is a hindering factor to such reactions, contrary to an ester function. The use of an excess of reagent **3** leads to the bis-methoxy derivatives **7** in 70% yield along with a small amount of its *N*-methyl isomer **9**. Determination of the methyl position for all these isomeric compounds was achieved by homo- and heteronuclear NMR long distance correlation experiments. It is noteworthy that a highly colored inseparable mixture of substances is the only result[2] of the reaction between compound **5** and trimethyl orthoformate (**1**).



Equation B

In the case of the 4,5-dimethyl derivative **10**, the use of the reagent **3** leads to the bis-methoxy derivative **11** in 91% yield. The exclusive *O*-methylation observed here is one more illustration of the steric hindrance governing the chemistry of this type of compounds. On a small scale, use of the reagent **2** leads to 75% of compound **11** along with unidentified material. This regioselectivity is drastically different from the mostly *N*-methylation reaction observed with these compounds when using methyl iodide and a base.[2]

Equation C

Surprisingly, the reaction between pyridine derivative **12** and reagent **3** in toluene leads to an almost complete transformation into a deep-purple mixture of compounds from which only 10% of the 2-methoxy compound **13** can be isolated along with 2% of the 2,6-dimethoxy derivative **14**. In refluxing trimethyl orthoacetate (**3**), the formation of an unidentified highly polar and highly colored material is the only result. One explanation for the low yield of methylation observed would be competing side reactions, starting with a plausible[8] acylation (as seen for compound **25** below) at C-5. Contrary to pyridine derivatives **5** and **10**, this reaction would be prominent in the case of the unhindered pyridine **12**.

Equation D

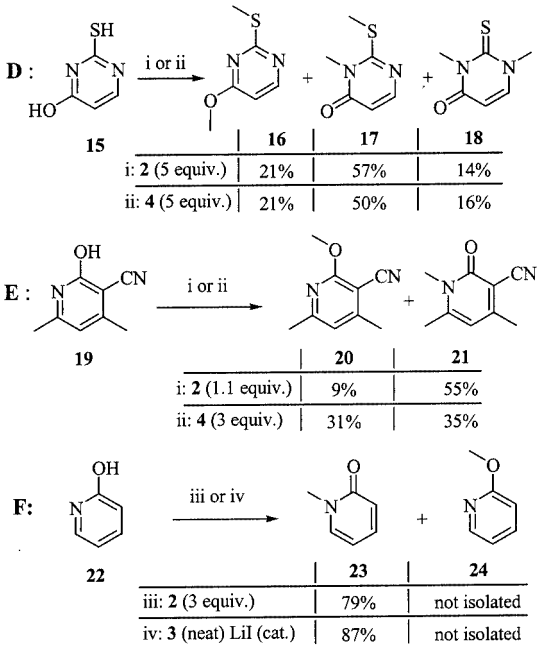
The reaction of 2-thiouracil (**15**) with **2** gives a mixture of compounds from which the *S*- and *O*-dimethyl derivative **16**, its *S*- and *N*3-dimethyl isomer **17**, and the *N*1-, *N*3-dimethyl isomer **18** are easily isolated in 21, 57 and 14% yields, respectively. Little change in this distribution is noticed (21, 50 and 16%) if reagent **4** is used instead. The ^{1}H NMR monitoring of the reaction between compound **15** and reagent **3** shows that compounds **16**, **17** and **18** are formed very slowly (in proportions similar to the above one) only if methyl acetate and methanol are removed from the reaction mixture in the course of the reaction. Apart from compound **18**, these results are actually related to the previously published[9] reaction of 2-thiomethyluracil and reagent **2**. On the other hand, methylation of **15** with a classical agent yields mainly[10] compound **17** and the corresponding *N*1-substituted isomer.

Equation E

Reaction between the less functionalized pyridine **19** and an excess of the reagent **2** leads to a previously reported[11] dimethylaminomethylation reaction, which occurs indiscriminately at the two methyl groups of compound **21**. This side reaction can be mostly avoided by using 1.1 equivalent of **2** in toluene; this reaction leads to *O*- and *N*-methyl derivatives **20** and **21** in 9% and 55% yield, respectively. Moreover, little methyl "acylation" is observed when using an excess of *N,N*-dimethylacetamide dimethyl acetal (**4**), and an increase in *O*-methylation is also seen (from 9% to 31% yield of compound **20**).

Equation F

Methylation of 2-hydroxypyridine (**22**) with reagent **2** in toluene gives the *N*-methyl compound **23** in 79% yield. This *N- versus O-* methylation ratio does not follows the trend of the methylation of **22** with diazomethane[12] (ratio of 60:40) but follows that obtained with methyl iodide[13] (ratio of 95:5). The reaction of **22** in boiling trimethyl orthoacetate (**3**) also leads to the *N*-methyl derivative **23** in 87% yield, but only if methanol is removed by trapping it with 4 Å molecular sieves and if *a catalytic amount of lithium iodide is present*. Under the same reaction conditions, the *N*-methylation of **22** also proceeds in neat trimethyl orthoformate (**1**), but at a much slower rate. More about this particular case is described below.



Equations G and H

Contrary to the case of unfunctionalized pyrazole,[14] no methylation of pyrazolone **25** took place. The reaction with reagent **3** gives a good yield of the known C4-acylated compound **26**,[15,16] whereas the reaction with reagent **2** results in an exclusive dimethylaminomethylation at the same position (as seen in the ^{1}H and ^{13}C NMR spectra of the crude reaction product). Subsequent acid hydrolysis of enamine **27** allowed a proper characterization of the previously unknown aldehyde **28** in 65% overall yield.

Equation I

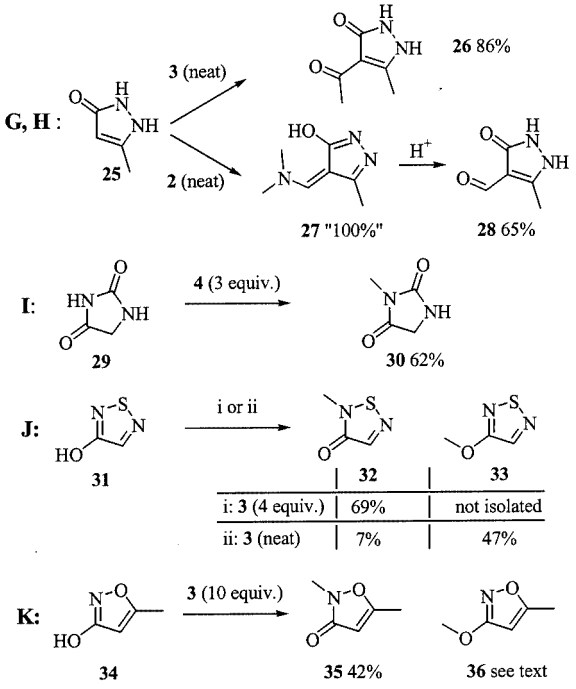
No methylation takes place between hydantoin (**29**) and reagent **3**. The use of reagent **2** leads to a complex mixture of C5-formylated and *N*-methylated derivatives. Finally, reagent **4** gives rise to *N*3-methylhydantoin (**30**) in 62% yield. The reaction between **2** and 5-substituted hydantoins has actually been reported[17] and gives the corresponding *N*3-methylated derivatives as well.

Equation J

From 3-hydroxy-1,2,5-thiadiazole (**31**), the corresponding *N*1-methyl derivative **32** can be obtained in 69% yield if compound **31**[18] is reacted with reagent **3** in toluene. On the other hand, ^{1}H and ^{13}C NMR monitoring of the reaction of **31** in neat trimethyl orthoacetate (**3**) shows that the conversion into the *N*- and *O*- methyl derivatives **32** and **33** occurs in a 20:80 ratio. The lack of high-boiling solvents in this last protocol allows the isolation of the water-soluble and volatile compound **33** in a nonoptimized 47% yield after the hydrolysis of **3** into methyl acetate and methanol. From the aqueous phase resulting from the workup, 7% of compound **32** is also isolated.

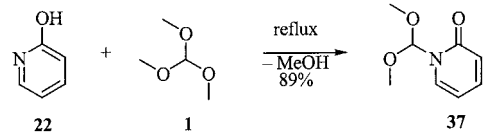
Equation K

Methylation of 3-hydroxy-5-methylisoxazole (**34**) with reagent **3** can also be conducted in toluene but turns out to be quite slow. Following evaporation of toluene — and thus loss of the *O*-methyl derivative **36** — the *N*-methyl isomer **35** is obtained in 42% yield. On a small scale the ^{1}H and ^{13}C NMR monitoring of a reaction of **34** in neat trimethyl orthoacetate (**3**) shows the quick conversion of **34** in both *N*- and *O*-methyl derivatives **35** and **36** in a 55:45 ratio. It is noteworthy that the reaction of diazomethane with **34** gives an identical result.[19]



This work extends an already known method to previously unsuitable substrates. We recently reviewed the use of trialkyl orthoformates,[2] and it appears that sometimes trimethyl phosphite,[20,21] but more often *N,N*-dimethylformamide dialkyl acetal,[4−7,9,17,22,23] have been used for the alkylation of heterocycles. Regioselectivity is very good in some cases, either leading exclusively to an *N*-alkyl derivative[4,6,17,22] or an *O*-alkyl derivative.[2] However, more often, a mixture of regioisomers is obtained.[9,11,24] The results presented here indicate that a change from trimethyl orthoformate (**1**) to the more hindered/stable trimethyl orthoacetate (**3**), as well as a change from *N,N*-dimethylformamide dimethyl acetal (**2**) to its acetamide homologue **4** sometimes enables the avoidance of "formylation" reactions (equations A, E, I) that tend to lower the efficiency of reagents **1** and **2**. We have also shown here that the use of reagent **3** mostly leads to *O*-methyl derivatives (equations A, B, J). Concerning equation F, the most notable result is the fact that the reaction between pyridone **22** and trimethyl orthoformate (**1**) does not give any methylation reaction without a catalytic amount of lithium iodide and methanol removal from the reaction mixture using 4 Å molecular sieves. However, in the absence of the added Lewis acid, the previously

unreported *N*-acetal **37** can be isolated in 89% yield. A similar reaction takes place between compound **22** and reagent **3**, although the corresponding acetal could not be purified satisfactorily. Other thermally stable *N*-acetals of heterocycles have been reported previously.[25,26]

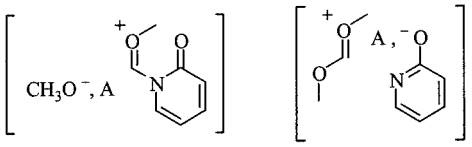


22 **1** **37**

Heating compound **37** at 180 °C for some hours did not lead to any methylated material, heating it in the presence of various acids led to the hydrolysed compound **22**, the *N*-methyl pyridone **23** and, to a lesser extent, to methoxypyridine **24**. For instance, ^{1}H NMR monitoring of the reaction of **37** and a catalytic amount of sulfuric acid at 100 °C showed the formation of compounds **23** and **24** in an 8:1 ratio in one hour. Under the same conditions, using one equivalent of dry lithium iodide, the reaction led to the hydrolysed material **22** and *N*-methyl derivative **23** in a 2:1 ratio. The use of one equivalent of boron trifluoride diethyl etherate gave the same result. A trial with formic acid only led to the hydrolysis of **37**. The reaction with one equivalent of titanium tetrachloride led to an equal proportion of the hydrolysed material **22** and the *N*-methyl derivative **23**. A control experiment indicated that titanium tetrachloride (but not lithium iodide) can cause a Chapman-type[27] rearrangement of the *O*-methyl derivative **24** into the *N*-methyl isomer **23** at 100 °C.

Conclusion

The difference of reactivity between orthocarboxylates **1** or **3** and dimethyl acetals **2** or **4** can be explained by reaction intermediates such as **37**. Under neutral reaction conditions, acetal **37** does not undergo further transformation, whereas an equivalent amino acetal intermediate, arising from the reaction with compound **2** or **4**, is less stable because of the much easier formation of an iminium intermediate. The variation of oxygen vs. nitrogen methylation (equation E and equation J) we sometimes observe may also be explained with species such as **37** which would react differently according to the acidity of the heterocycle under consideration and the solvent used. Concerning compound **37**, the different path that the acid-catalyzed reaction takes may be based on two transition states such as **38** and **39** arising from two kinds of oxygen complexation with the vacant orbital of the Lewis acid "A". Complex **38** would lead to an *O*-methylation, via a rearrangement, whereas complex **39** would give *O*- and *N*-methylated material according to the inherent, and ambident, nucleophilic properties of the pyridone "anion". Although we sometimes observed an acid-catalyzed rearrangement of *O*-methylated **23** into the *N*-methyl compound **24**, further investigations may lead to an exclusive reaction via intermediate **38** and thus to an *O*-methylation.



38 **39**

The results presented here demonstrate that reagents **3** or **4** are original, noncarcinogenic, options to be considered for the everlasting problem of regioselective methylation of "ambident heterocycles". Moreover the use of 4 Å molecular sieves as a methanol trap and, if needed, lithium iodide makes trimethoxy orthocarboxylates better reagents when thinking of the high boiling dimethylamides produced by reagents **2** and **4**, especially in very large scale reactions.

Experimental Section

General Remarks: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300 spectrometer at 300 MHz and 75 MHz, respectively. Unless otherwise noted, $CDCl_3$ was the solvent used. Chemical shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (*J*) are given in Hertz. Signal attribution and structure assignment (especially for compounds **6**, **8**, **9** and **13**) were often confirmed by two dimensional NMR experiments (COSY, NOESY, HMQC, HMBCR). Column chromatography was performed on Merck silica gel 60 (0.035−0.070 mm).

Methylation of 5 with Trimethyl Orthoacetate (3) in Toluene: In a distillation apparatus, powdered compound **5** (2 g; 13.3 mmol) was heated to reflux in toluene (80 mL) for some minutes in order to remove all traces of water. The moisture-protected (calcium chloride guard) suspension was then allowed to cool and trimethyl orthoacetate (1.9 mL, 14.6 mmol) was added. The suspension was then gently heated (up to 110 °C) until no more methanol and methyl acetate formed (from one to two hours). The resulting dark red suspension was concentrated to dryness and the residue was purified by chromatography over silica gel, starting the elution with a mixture of cyclohexane and ethyl acetate (3:1) and ending with pure ethyl acetate, to yield, in order of elution, compounds **7** (0.24 g; 10%), **6** (1.08 g; 48%) and **8** (0.58 g; 24%) as described below:

3-Cyano-2,6-dimethoxy-4-methylpyridine (7): M.p. 114 °C (heptane). ^{1}H NMR: δ = 2.39 (s, 3 H, CH_3), 3.92 and 3.99 (2s, 6 H, 2 OCH_3), 6.20 (s, 1 H, CH-5) ppm. ^{13}C NMR: δ = 20.0 (CH_3), 53.8 and 54.1 (OCH_3), 87.8 (C-3), 103.2 (C-5), 115.3 (CN), 155.6 (C-4), 165.1 (C-6 and C-2) ppm. $C_9H_{10}N_2O_2$ (178.2): calcd. C 60.67, H 5.66, N 15.72; found C 60.57, H 5.66, N 15.64.

3-Cyano-6-hydroxy-2-methoxy-4-methylpyridine (6): M.p. 173 °C (toluene). ^{1}H NMR: δ = 2.38 (s, 3 H, CH_3), 3.90 (s, 3 H, OCH_3), 6.19 (s, 1 H, CH-5) ppm. ^{13}C NMR: δ = 20.0 (CH_3), 54.8 (OCH_3), 90.0 (C-3), 102.4 (C-5), 112.9 (CN), 157.4 (C-4), 163.4 (C-6), 164.8 (C-2) ppm. $C_8H_8N_2O_2$ (164.2): calcd. C 58.53, H 4.91, N 17.07; found C 58.45, H 4.89, N 16.92.

3-Cyano-2-hydroxy-6-methoxy-4-methylpyridine (8): M.p. 215 °C (toluene). ^{1}H NMR ([D_6]DMSO**):** δ = 2.31 (s, 3 H, CH_3), 3.85 (s,

3 H, OCH_3), 6.15 (s, 1 H, CH-5), 12.4 [s(br.), 1 H, OH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 20.2 (CH_3), 50.1 (OCH_3), 88.9 (C-3), 97.3 (C-5 (broad signal)], 116.1 (CN), 158.0 (C-4), 163.3 and 163.6 (C-6 and C-2) ppm. $C_8H_8N_2O_2$ (164.2): calcd. C 58.53, H 4.91, N 17.07; found C 58.33, H 4.91, N 16.96.

Application of the above procedure to compound **12**[28] led to **14** and **13** as described below:

3-Cyano-2,6-dimethoxypyridine (14): M.p. 91−92 °C (heptane) (ref.[29] 92−93 °C). ^1H NMR: δ = 3.96 and 4.02 (2s, 6 H, OCH_3), 6.34 (d, *J* = 8.4 Hz, 1 H, CH-5), 7.68 (d, *J* = 8.4 Hz, 1 H, CH-4) ppm. ^{13}C NMR: δ = 54.2 (OCH_3), 54.4 (OCH_3), 86.8 (C-3), 102.8 (C-5), 116.2 (CN), 144.3 (C-4), 164.8 and 165.7 (C6 and C-2) ppm.

3-Cyano-6-hydroxy-2-methoxypyridine (13): M.p. 132−133 °C (heptane) (ref.[29] 135−137 °C). ^1H NMR: δ = 3.97 (s, 3 H, OCH_3), 6.36 (d, *J* = 8.4 Hz, 1 H, CH-5), 7.75 (d, *J* = 8.4 Hz, 1 H, CH-4) ppm. ^{13}C NMR: δ = 59.9 (OCH_3), 87.2 (C-3), 101.9 (C-5), 115.8 (CN), 145.6 (C-4), 164.3 and 164.6 (C-6 and C-2) ppm.

3-Cyano-2,6-dimethoxy-4,5-dimethylpyridine (11): In a distillation apparatus, compound **10**[30] (11.8 g, 71.9 mmol) and trimethyl orthoacetate (70 mL, 550 mmol) were heated at reflux until methanol and methyl acetate evolution was complete (2−3 hours). The residue was concentrated to dryness and purified by chromatography over silica gel eluting with heptane/ethyl acetate (3:1) to give partially hydrated compound **11** (12.7 g, 91%). M.p. 135 °C (heptane/ethyl acetate). ^1H NMR: δ = 2.00 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 3.93 and 3.94 (2s, 6 H, OCH_3) ppm. ^{13}C NMR: δ = 10.7 (CH_3-5), 17.8 (CH_3-4), 53.9 and 54.0 (OCH_3), 87.9 (C-3), 100.8 (C-5), 116.2 (CN), 152.5 (C-4), 162.8 (C-6 and C-2) ppm. $C_9H_{10}N_2O_2 \cdot 1/6H_2O$ (179.2 + 3): calcd. C 61.53, H 6.37, N 14.35; found C 61.72, H 6.22, N 14.38.

3-Cyano-6-methoxy-1,4-dimethylpyridin-2(1*H*)-one (9): Using the procedure for preparation of **11**, compound **7** was obtained from compound **5** along with a much more polar fraction identified as compound **9**. M.p. 229 °C (ethanol). ^1H NMR: δ = 2.35 (s, 3 H, CH_3), 3.38 (s, 3 H, NCH_3), 3.93 (s, 3 H, OCH_3), 5.49 (s, 1 H, CH-5) ppm. ^{13}C NMR: δ = 21.9 (CH_3), 28.6 (NCH_3), 57.8 (OCH_3), 88.3 (C-5), 95.3 (C-3), 116.4 (CN), 159.6 (C-4), 160.2 (C-6), 160.8 (C-2) ppm. $C_9H_{10}N_2O_2$ (178.2): calcd. C 60.66, H 5.66, N 15.72; found C 60.69, H 5.68, N 15.85.

4-Acetyl-3-hydroxy-5-methylpyrazole (26): Compound **25** (2 g, 20.4 mmol) was refluxed in trimethyl orthoacetate (15 mL, 116 mmol) and, after concentration to dryness, the residue was dispersed in hot water and then filtered at room temperature to yield **26** (2.48 g, 86%). M.p. 260 °C (dec.) [ref.[16] 260 °C (dec.)]. ^1H NMR ([D_6]DMSO): δ = 2.29 (s, 3 H, $COCH_3$), 2.32 (s, 3 H, CH_3-5) ppm. ^{13}C NMR ([D_6]DMSO): δ = 12.5 (CH_3-5), 29.2 ($COCH_3$), 104.5 (C-4), 143.9 (C-5), 161.6 (C-3), 192.9 (CO) ppm.

Methylation of 3-Hydroxy-1,2,5-thiadiazole (31). Method with Toluene: Compound **31** (0.33 g, 2.75 mmol; obtained using the reported procedure[18] and recrystallized from heptane) and compound **3** (1.05 mL, 8.2 mmol) were refluxed in toluene (40 mL) for 4 hours. After evaporation, the residue was recrystallized from heptane to yield **32** (0.22 g, 69%) .

Method without Solvent: In a distillation apparatus, compound **31** (4.82 g, 47.2 mmol) was refluxed in trimethyl orthoacetate (**3**; 25 mL, 189 mmol) for 90 minutes allowing for the continuous distillation of methanol and methyl acetate. Water (100 mL) was then added and the solution was stirred for 1 hour at room temperature. The reaction mixture was extracted with diethyl ether, the organic phase was washed with water, dried over magnesium sulfate and concentrated to dryness at atmospheric pressure. A distillation led to **33** (2.6 g, 47%). Extraction of the aqueous phase with dichloromethane led, after concentration at atmospheric pressure, to a mixture of methanol, and compounds **32** and **33**. Concentration to dryness under reduced pressure followed by recrystallization of the residue from heptane only allowed the isolation of the water soluble compound **32** (0.4 g, 7%).

2-Methyl-1,2,5-thiadiazol-3(2*H*)one (32): M.p. 117 °C (ref.[31] 116−117 °C). ^1H NMR: δ = 3.39 (s, 3 H, CH_3), 7.71 (s, 1 H, CH-4) ppm. ^{13}C NMR: δ = 29.2 (CH_3), 145.1 (CH-4), 163.6 (C-3) ppm.

3-Methoxy-1,2,5-thiadiazole (33): B.p. 124−126 °C. ^1H NMR: δ = 4.07 (s, 3 H, CH_3), 7.95 (s, 1 H, CH-4) ppm. ^{13}C NMR: δ = 57.2 (CH_3), 138.7 (CH-4), 166.2 (C-3) ppm. Microanalysis was not possible on this very volatile compound. *m/z* (GC/MS) = 116.

2-Methylisoxazol-3(2*H*)-one (35): A mixture of compounds **34** (0.25 g, 2.5 mmol) and **3** (1.6 mL, 12.6 mmol) was refluxed in toluene (40 mL) for 2 hours. TLC monitoring of the reaction showed the reaction to be incomplete and thus five more equivalents of trimethyl orthoacetate were added and the reflux was resumed for another nine hours. Concentration of the solvents followed by chromatography of the residue over silica gel eluting with ethyl acetate gave compound **35** (0.12 g, 42%) M.p. < 30 °C (ref.[19] 25−30 °C). ^1H NMR: δ = 2.19 (s, 3 H, CH_3), 3.43 (s, 3 H, NCH_3), 5.45 (s, 1 H, CH-4) ppm. ^{13}C NMR: δ = 13.1 (CH_3), 32.4 (NCH_3), 98.1 (CH-4), 168.4, 169.1 (C3 and C5) ppm.

General Procedure using 2 or 4 for the Methylation of 2-thiouracil (15): Compound **15** (1 g, 7.8 mmol) and *N,N*-dimethylformamide dimethyl acetal (**2**) (or compound **4**) (5.2 mL, 39.0 mmol) were refluxed for 3 hours in toluene (50 mL). The mixture was then concentrated to dryness and the residue purified by chromatography over silica gel eluting initially with cyclohexane/ethyl acetate (6:1) and then with cyclohexane/ethyl acetate (3:2). Compounds **16** (0.26 g, 21%), **17** (0.7 g, 57%) and **18** (0.17 g, 14%) were obtained in that order.

4-Methoxy-2-methylthiopyrimidine (16): M.p. < 30 °C (ref.[9] 35 °C). ^1H NMR: δ = 2.46 (s, 3 H, SCH_3), 3.86 (s, 3 H, OCH_3), 6.28 (d, *J* = 5.5 Hz, 1 H, CH-5), 8.12 (d, *J* = 5.5 Hz, 1 H, CH-6) (^1H shifts are dependant on compound **16** concentration[10]) ppm. ^{13}C NMR: δ = 13.8 (SCH_3), 53.5 (OCH_3), 103.3 (CH-5), 156.9 (CH-6), 168.7, 171.9 (C-2 and C-4) ppm.

2-Methylthio-3-methylpyrimidin-4(3*H*)one (17): M.p. 125 °C (ref.[32] 124 °C). ^1H NMR: δ = 2.59 (s, 3 H, SCH_3), 3.53 (s, 3 H, NCH_3), 6.22 (d, *J* = 5.6 Hz, 1 H, CH-5), 7.77 (d, *J* = 5.6 Hz, 1 H, CH-6) ppm. ^{13}C NMR: δ = 15.4 (SCH_3), 30.6 (NCH_3), 110.2 (CH-5), 152.1 (CH-6), 162.4, 164.1 (C-2 and C-4) ppm.

1,3-Dimethylthiouracil (18): M.p. 105−106 °C (ethanol) (ref.[33] 107−108 °C). ^1H NMR: δ = 3.77 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3), 6.02 (d, *J* = 7.9 Hz, 1 H, CH-5), 7.37 (d, *J* = 7.9 Hz, 1 H, CH-6) ppm. ^{13}C NMR: δ = 34.7 (CH_3), 45.0 (CH_3), 104.8 (CH-5), 143.2 (CH-6), 160.2 (C-4), 177.5 (C-2) ppm.

The same procedure was used for the reaction of heterocycles **19**, **22** or **29** with reagent **2** or **4**, as indicated in the text, and gave the corresponding methylated derivatives **20** and **21**, **23** or **30** as described below.

3-Cyano-2-methoxy-4,6-dimethylpyridine (20): M.p. 98 °C (crystallized from chloroform) (ref.[34] 94−95 °C). ^1H NMR: δ = 2.42 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 3.98 (s, 3 H, OCH_3), 6.61 (m, 1 H,

CH-5) ppm. ^{13}C NMR: δ = 19.9 (CH_3–4), 24.4 (CH_3–6), 54.1 (OCH_3), 93.2 (CH-5), 115.0 (CN), 117.4 (C-3), 154.2 (C-4), 160.6, 164.2 (C-2 and C-6) ppm.

3-Cyano-1,4,6-trimethylpyridin-2(1*H*)-one (21): M.p. 202 °C (ethanol) (ref.[35] 203−204 °C). ^1H NMR: δ = 2.38 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 3.54 (s, 3 H, NCH_3), 6.06 (s, 1 H, CH-5) ppm. ^{13}C NMR: δ = 20.7 (CH_3), 21.3 (CH_3), 31.5 (NCH_3), 100.9 (CH-5), 109.0 (C-3), 115.5 (CN), 150.7, 157.7 (C-4 and C-6), 161.1 (C-2) ppm.

1-Methylpyridin-2(1*H*)-one (23): Identical to a commercially available sample.

1-Methylimidazol-2,5(1,3*H*)-dione (30): No purification by chromatography was necessary in this case as compound **30** crystallizes from toluene. M.p. 183 °C (ref.[36] 181−183 °C). ^1H NMR: δ = 3.05 (s, 3 H, CH_3), 4.0 (s, 2 H, CH_2), 6.12 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 24.9 (CH_3), 46.9 (CH_2–4), 159.1 (C-2), 171.8 (C-5) ppm.

4-Formyl-3-hydroxy-5-methylpyrazole (28): Compound **25** (0.5 g, 5.1 mmol) and *N,N*-dimethylformamide dimethyl acetal (**2**) (3.4 mL, 25.5 mmol) were refluxed for 90 minutes. The mixture was then concentrated to dryness to give the enamine **27** as a wax [^1H NMR: δ = 2.10 (s, 3 H, CH_3), 3.30 (s, 3 H, NCH_3), 3.86 (s, 3 H, NCH_3), 6.97 (s, 1 H, CH), 8.63 [s(br), 1 H, OH) ppm. ^{13}C NMR: δ = 13.8 (CH_3), 43.4 (NCH_3), 48.0 (NCH_3), 98.1 (C-4), 151.2 (CH), 152.3, 165.5 (C-3 and C-5) ppm]. This residue was treated with 6 N hydrochloric acid (10 mL) at room temperature for two days. After concentration to dryness, the solid was recrystallized from water to yield compound **28** (0.43 g, 65% from **25**) M.p. > 260 °C. ^1H NMR ([D_6]DMSO): δ = 2.33 (s, 3 H, CH_3), 9.68 (s, 1 H, CHO) ppm. ^{13}C NMR ([D_6]DMSO): δ = 11.5 (CH_3), 105.1 (C-4), 144.3, 162.5 (C-3 and C-5), 183.7 (CHO) ppm. $C_5H_6N_2O_2$ (126.1): calcd. C 47.62, H 4.8, N 22.21; found C 47.79, H 4.79, N 22.06.

Methylation of Pyridin-2(1*H*)-one (22) using Trimethyl Orthoformate, Lithium Iodide and 4 Å Molecular Sieves: In a round-bottomed flask fitted with a pressure-equalising dropping funnel fitted with a water condenser and a calcium chloride guard, compound **22** (1 g, 10.5 mmol) and lithium iodide (0.16 g, 1.2 mmol) in trimethyl orthoacetate (**3**) (20 mL) were heated to reflux for 2 hour. *Note*: the reflux was made to trickle back into the reaction flask through the dropping funnel that contained activated[2] 4 Å molecular sieves (40 g). The solvents were removed under reduced pressure and chromatography of the residue over silica gel eluting with dichloromethane/ethanol (96:4) gave compound **23** (1 g, 87%), which was found to be identical to a commercially available sample.

1-Dimethoxymethylpyridin-2(1*H*)-one (37): In a round-bottomed flask fitted with a pressure-equalising dropping funnel fitted with a water condenser and a calcium chloride guard, compound **22** (20.88 g, 0.22 mol) was heated to reflux in trimethyl orthoformate (**1**) (250 mL). The reflux was made to trickle back into the reaction flask through the dropping funnel that contained activated 4 Å molecular sieves (70 g). Every 24 hours, the reaction was monitored by measuring the ^1H NMR spectrum of a sample (in [D_6]DMSO since compound **37** is hydrolysed in unstabilized $CDCl_3$), and the 4 Å molecular sieves was replaced with a fresh batch. *Note*: as much as 3 wt.% of methanol could be trapped by the activated[2] molecular sieves. Upon disappearance of the starting material (6 days in the present case, the strength of the reflux is an important factor in this reaction) the solution was distilled under vacuum to yield compound **37** (33.1 g, 89%) as a hygroscopic liquid. B.p. (13 Torr) 140−143 °C. ^1H NMR ([D_6]DMSO): δ = 3.35 (s, 6 H, 2 OCH_3), 6.27 (m, 1 H, H5), 6.41 (d, *J* = 9.1 Hz, 1 H, H3), 6.46 (s, 1 H, CH), 7.43 (m, 1 H, H4), 7.51 (dd, *J* = 1.4, 6.9 Hz, 1 H, H6) ppm. ^{13}C NMR ([D_6]DMSO**):** δ = 54.3 (OCH_3), 101.6 (CH), 105.7 (C5), 120.1 (C3), 132.0 (C6), 140.6 (C4), 161.3 (C2) ppm. $C_8H_{10}NO_3 \cdot 1/4H_2O$ (168.1 + 4.5): calcd. C 55.32, H 6.67, N 8.06; found C 55.65, H 6.71, N 8.28.

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