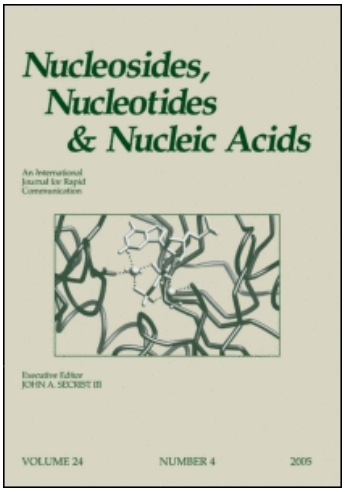

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Facile Synthesis of N-(1-Alkenyl) Derivatives of 2,4-Pyrimidinediones

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(7), 1093–1100 (2000)

FACILE SYNTHESIS OF *N*-(1-ALKENYL) DERIVATIVES OF 2,4-PYRIMIDINEDIONES

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ABSTRACT: *N*-(1-alkenyl) derivatives of 2,4-pyrimidinediones (**6** - **9**) were prepared in a one pot synthesis from aldehydes and the nucleobases using trimethylsilyl trifluoromethanesulfonate (TfOTMS) as coupling reagent. Presilylation of the above nucleobases, and N^6-benzoyladenine, with excess *N,O*-bis(trimethylsilyl)acetamide (BSA) followed by addition of one mol eq. TfOTMS yielded the *N*-(1-trimethylsilyloxyalkyl) derivatives **1** - **5**.

In search for new nucleoside analogues with biological activity[1], we are interested in methods to prepare *N*-(1-alkenyl) derivatives (enamines) of nucleobases[2]. A few compounds of this type have been prepared by the following methods: i) Michael additions of nucleobases to activated alkynes[3]; ii) alkylations of nucleobases followed by eliminations[4]; iii) rearrangements of 2-alkenyl nucleobases[5]; iv) double $S_{RN}1$ substitutions followed by Grob-type eliminations[6]. A general method to prepare enamines is the reaction between an aldehyde (or a ketone) and a secondary amine[7], but no *N*-(1-alkenyl) derivatives of nucleobases has so far been prepared by this method. We have investigated the reaction between nucleobases and aldehydes and prepared *N*-(1-alkenyl) derivatives of 2,4-pyrimidinediones in an efficient "one pot" synthesis.

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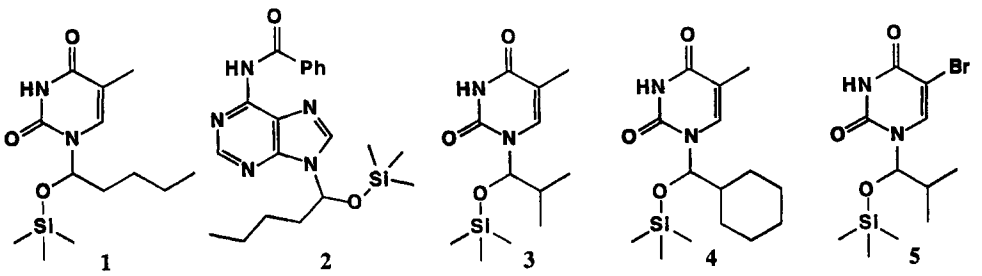
RESULTS AND DISCUSSION

A series of conditions for the reaction between nucleobases and aldehydes has been investigated, using thymine and N^6-benzoyladenine as model nucleobases and pentanal as the aldehyde component. $N(1)$ alkylation of the pyrimidine nucleobases and $N(9)$ alkylation of the purine nucleobases are usually performed under basic conditions (K_2CO_3, NaH), but all attempts to prepare enamines of the nucleobases under these conditions were unsuccessful. Alternatively, aldehydes can be activated by acid catalysis and nucleobases by silylation, and the reaction between persilylated thymine or N^6-benzoyladenine and pentanal in toluene containing a small amount of *p*-toluenesulfonic acid (TsOH) led to product formation upon heating to 80°C, but the products were the *O*-silylated derivatives **1** and **2**, respectively (**SCHEME 1**).

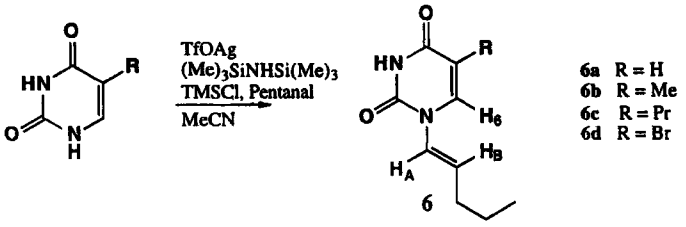
Vorbrüggen and Bennua[8] introduced a simplified nucleoside synthesis using trimethylsilyl trifluoromethanesulfonate (TfOTMS) as catalyst[9]. We found that a convenient way to prepare TfOTMS *in situ* is from silver trifluoromethanesulfonate (TfOAg) and chlorotrimethylsilane (TMSCl) and decided to investigate the potential of TfOTMS as catalyst in the reaction between nucleobases and aldehydes. Presilylation of thymine with excess *N,O*-bis(trimethylsilyl)acetamide (BSA) in MeCN followed by addition of TfOAg (1 eq.) and TMSCl (1 eq.) and pentanal (2 eq.) at room temperature led to the *O*-trimethylsilyl derivative **1** in much higher yield than the TsOH catalysed reaction mentioned above. Similar treatment of the purine nucleobase gave **2** (**SCHEME 1**). This reaction is general and performs well, both with less reactive nucleobases and with more hindered aldehydes (*e. g.* **3 - 5** in **SCHEME 1**).

The desired enamine (**6b**) was obtained in high yield in less than one h when thymine (1 mol eq.) was treated with TfOAg (2.4 mol eq.), hexamethyldisilazane (HMDS, 0.7 mol eq.), TMSCl (3 mol eq.), and pentanal (2 mol eq.) in MeCN at room temperature (**SCHEME 2**). TfOAg catalyses the silylation of thymine by HMDS and a clear solution is formed when mixing thymine, pentanal, TfOAg, and HMDS in MeCN, but no reaction takes place until TMSCl is added.

The enamine **6b** was also obtained in high yield when commercial TfOTMS was used instead of TfOAg + TMSCl or when thymine was presilylated with HMDS and reacted with TfOTMS (1 mol eq.) and pentanal (2 mol eq.) after evaporation of excess HMDS; *i. e.* neither the silver ion nor excess TfOTMS are essential for the reaction.

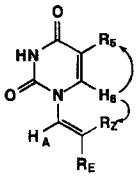


SCHEME 1



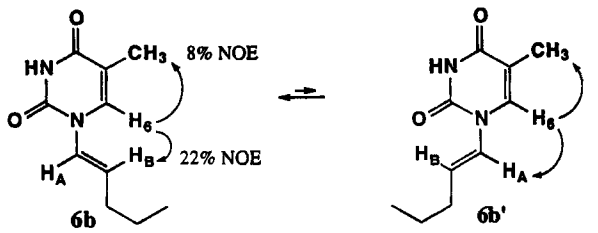
SCHEME 2

TABLE 1. NOE data (% in DMSO-d_6) for **6 - 9** irradiated at H_6



	6a	6b	6c	6d	7	8	9
R_Z	18	22	22	15	14	5	3
R_5	17	8	5		9	6.5	7.5
H_A	1	2	1.5	1.5	< 1	3	2.5

The structure of the enamine **6b** was investigated by NMR spectroscopy. Only the E isomer is formed ($J_{H(A),H(B)}$= 14.4 Hz). Nuclear Overhauser Effect (NOE) experiments showed that the compound, as expected, is the *N*(1) derivative since a strong NOE (22%, **TABLE 1**) is observed for H_B when H_6 is irradiated. NOE (8%) was also observed for the 5-Me protons, but only a weak NOE (1.8%) was observed for H_A. The strong NOE for H_B in combination with the weak NOE for H_A indicates that the compound has the prefered conformation **6b** (**SCHEME 3**) corresponding to the *anti*-conformation for pyrimidine nucleosides.



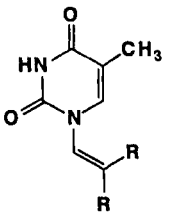
SCHEME 3

All attempts to prepare enamines of purine nucleobases were unsuccessful (only *O*-trimethyl derivatives analogous to **2** could be isolated), but enamine formation is general for 2,4-pyrimidinediones. The reaction is very sensitive to the reactivity of the reagents. The less reactive 2,4-pyrimidinediones, uracil and 5-bromouracil gave the enamines **6a** and **6d**, respectively, in lower yield than thymine, whereas 5-propyluracil gave the enamine **6c** in a yield similar to thymine (**SCHEME 2**). The NOE data (**TABLE 1**) of the enamines **6a,c,d** show the same pattern as found for **6b**.

Aldehydes undergo self-condensations under the reaction conditions. This competitive reaction is responsible for the lower yields of compounds **6a,d**. The self-reaction was predominant with the very reactive acetaldehyde, and the yield of the enamine **7** (**SCHEME 4**) was low.

In reactions with more hindered aldehydes, *e. g.* between 2-methylpropanal or *cyclo*hexanecarboxaldehyde and thymine, enamine formation takes place, but in lower yields than with pentanal. The products **8** and **9** are depicted in **SCHEME 4**. The structures of compounds **7 - 9** were investigated by NOE experiments and the data are shown in TABLE 1.

As mentioned above one mol eq. of TfOTMS is essential for the enamine formation. Aldehydes react with TfOTMS forming silyl enol ethers[9], but these are unlikely as intermediates in enamine formation (they react with electrophiles[10]). The mechanism of the reaction is not known in detail, but it is improbable that *O*-silylated compounds (*e. g.* **1**) are intermediates in the enamine formation for the following reasons. All attempts to prepare enamines from compounds **1 - 5** by desilylation and elimination failed; only starting material and/or the nucleobase and the aldehyde could be isolated. Treatment of **1** with TfOTMS gave thymine and pentanal immediately, followed by formation of a little enamine **6b**. Presilylation with excess BSA



7 R = H
8 R = CH_3
9 R, R = -$(CH_2)_5$-

SCHEME 4

followed by addition of TfOTMS and pentanal yielded the *O*-silylated compound **1**, whereas presilylation with HMDS (no excess) gave enamine **6b**. The most likely explanation for this observation is that the intermediate aminol is silylated by excess BSA in the former case, whereas elimination is mediated by TfOTMS in the latter case.

EXPERIMENTAL

NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Varian Mercury 300 MHz or a Varian Unity 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Mass spectra were recorded on a JEOL HX 110/110 mass spectrometer. TLC (CH_2Cl_2:MeOH, 9:1, v/v) was performed on Merck 5554 silica 60 aluminum sheets and column chromatography was performed using Meck 9385 silica 60 (0,040-0,063 mm). All solvents were HPLC grade from LABSCAN and dryed over molecular sieves. All other chemicals were used as received (Aldrich or Sigma). All chemical reactions were performed under nitrogen.

General Procedure for the Preparation of the Trimethylsilyloxy Derivatives (SCHEME 1). To the nucleobase (1 mmol) in MeCN (10 ml) was added BSA (0.5 ml) followed by the aldehyde (2 mmol), TfOAg (1 mmol) and TMSCl (1 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, diluted with CH_2Cl_2 (50 ml), and filtered. The filtrate was washed with water (20 ml), sat. aq. $NaHCO_3$ (2 × 20 ml), brine (20 ml), dryed ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2:MeOH, 97:3, v/v). Analytically pure samples were obtained for some of the compounds by crystallisation from CH_2Cl_2/hexane. **1** From thymine and pentanal. Yield 86 %. ^1H NMR: 8.64

(1H, s); 7.23 (1H, q, J = 1.2); 5.95 (1H, dd, J = 7.0, 5.9); 1.95 (3H, d, J = 1.2); 1.67 (2H, m); 1.35 (4H, m); 0.89 (3H, t, J = 6.9); 0.13 (9H, s). FAB+ m/z 285.2 $(M+1)^+$. **2** From N^6-benzoyladenine and pentanal. Yield 60 %. ^{1}H NMR: 9.10 (1H, s); 8.79 (1H, s); 8.21 (1H, s); 8.02 (2H, d, J = 7.9); 7.55 (3H, m); 6.16 (1H, t, J = 6.2); 2.0 (2H, m); 1.3 (4H, m); 0.88 (3H, t, J = 6.9); 0.05 (9H, s). FAB+ m/z 398.2 $(M+1)^+$. **3** From thymine and 2-methylpropanal. Yield 85 %. Mp 149-150°C. Anal. Calcd. for $C_{12}H_{22}N_2O_3Si$: C, 53.30; H, 8.20; N, 10.36. Found: C, 53.22; H, 8.10; N, 10.32. ^{1}H NMR: 9.16 (1H, s); 7.19 (1H, q, J = 1.2); 5.61 (1H, d, J = 7.9); 1.94 (3H, d, J = 1.2); 1.91 (1H, m); 0.99 (3H, d, J = 6.7); 0.82 (3H, d, J = 6.7); 0.11 (9H, s). FAB+ m/z 271.1 $(M+1)^+$. **4** From thymine and *cyclo*hexanecarboxaldehyde. Yield 87 %. ^{1}H NMR: 8.96 (1H, s); 7.18 (1H, q, J = 1.2); 5.63 (1H, d, J = 8.2); 1.95 (3H, d, J = 1.2); 2 - 1 (11H, m), 0.10 (9H, s). FAB+ m/z 311.2 $(M+1)^+$. **5** From 5-bromouracil and 2-methylpropanal. Yield 69 %. Mp 145-146°C. Anal. Calcd. for $C_{11}H_{19}BrN_2O_3Si$: C, 61.86; H, 7.27; N, 14.42. Found: C, 61.57; H, 7.38; N, 14.27. ^{1}H NMR: 9.16 (1H, s); 7.64 (1H, s); 5.56 (1H, d, J = 7.3); 1.85 (1H, oct, J = 7); 0.92 (3H, d, J = 6.5); 0.79 (3H, d, J = 7.0); 0.08 (9H, s). FAB+ m/z 335.0 $(M+1)^+$.

General Procedure for the Preparation of *N*-(1-Alkenyl)-2,4-pyrimidinediones. 1-(1-Pentenyl)-5-methyl-2,4-pyrimidinedione (6b). To thymine (**1**, 1 mmol, 126 mg) in MeCN (10 ml) were added TfOAg (2.4 mmol, 617 mg), HMDA (0.7 mmol, 148 µl), TMSCl (3 mmol, 378 µl), and pentanal (2 mmol, 210 µl) at room temperature. The reaction mixture was stirred for 1 h at room temperature, diluted with CH_2Cl_2 (50 ml), and filtered. The filtrate was washed with water (20 ml), sat. aq. $NaHCO_3$ (2 × 20 ml), brine (20 ml), dryed ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2:MeOH, 97:3, v/v). The fractions containing the product (one spot on TLC, R_f 0.56) were evaporated *in vacuo*, yielding **6b** (160 mg, 88 %). An analytically pure sample was obtained by crystallisation from CH_2Cl_2/hexane. Mp 135-136°C. Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.86; H, 7.27; N, 14.42. Found: C, 61.57; H, 7.38; N, 14.27. ^{1}H NMR: 9.08 (1H, s); 7.27 (1H, q, J = 1.3); 6.88 (1H, dt, J = 14.4, 1.5); 5.59 (1H, dt, J = 14.4, 7.3); 2.13 (2H, qd, J = 7, 1.5); 1.96 (3H, d, J = 1.3); 1.46 (2H, sx, J = 7); 0.94 (3H, t, J = 7). ^{13}C NMR: 163.75; 149.41; 136.29; 124.03; 120.01; 111.29; 31.70; 22.41; 13.43; 12.35. FAB+ m/z 195.1 $(M+1)^+$.

The following enamines were prepared in an analogous way. **6a** From uracil and pentanal. Yield 39 %. ^{1}H NMR: 9.29(1H, s); 7.43 (1H, d, J = 8.2); 6.87 (1H, dt, J = 14.2, 1.2); 5.78 (1H, d, J = 8.2); 5.63 (1H, dt, J = 14.2, 7.3); 2.14 (2H, qd, J = 7, 1.2); 1.47 (2H, sx, J = 7); 0.94 (3H, t, J = 7). FAB+ m/z 181.1 $(M+1)^+$. **6c** From 5-propyluracil and pentanal. Yield 68 %. Mp 150-151°C. Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.07; H, 8.08; N, 12.37. ^{1}H NMR: 9.80 (1H, s); 7.20 (1H, s); 6.88 (1H, dt, J = 14.2, 1.2); 5.57 (1H, dt, J = 14.2, 7.3); 2.30 (2H, t, J = 7); 2.11 (2H, qd, J = 7, 1.2); 1.53 (2H, sx, J = 7); 1.45 (2H, sx, J = 7); 0.92 (3H, t, J = 7); 0.91 (3H, t, J = 7). FAB+ m/z 223.1$(M+1)^+$. **6d** From 5-bromouracil and pentanal. Yield 35 %. ^{1}H NMR: 9.11 (1H, s); 7.76 (1H, s); 6.82 (1H, d, J = 14.2); 5.68 (1H, dt, J = 14.2, 7.0); 2.14 (2H, q, J = 7); 1.48 (2H, sx, J = 7); 0.94 (3H, t, J = 7). FAB+ m/z 259.1 $(M+1)^+$. **7** From thymine and acetaldehyde. Yield ca. 15 %. ^{1}H NMR (DMSO-d_6): 11.2 (1H, s); 7.90 (1H, s); 7.09 (1H, dd, J = 16.1, 9.4); 5.32 (1H, dd, J =16.1, 1.6); 4.83 (1H, dd, J = 9.4, 1.6); 1.83 (3H, s). FAB+ m/z 153.1 $(M+1)^+$. **8** From thymine and 2-methylpropanal. Yield 47 %. Mp 130-131°C. Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found C, 59.43; H, 6.80; N, 15.20. ^{1}H NMR: 8.90 (1H, s); 6.91 (1H, q, J = 1.2); 6.13 (1H, sep, J = 1.5); 1.92 (3H, d, J = 1.2); 1.83 (3H, d, J = 1.5); 1.68 (3H, d, J = 1.5). FAB+ m/z 181.1 $(M+1)^+$. **9** From thymine and *cyclo*hexanecarboxaldehyde. Yield ca. 15 %. Mp 159-160°C. Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H: 7.32; N: 12.72. Found C, 64.92; H, 7.35; N, 12.71. ^{1}H NMR: 8.91 (s, 1H, NH); 6.88 (q, 1H, J = 1.2); 6.12 (s, 1H); 2.21 (t, 2H, J = 5.5); 2.11 (t, 2H, J = 5.5), 1.92 (d, 3H, J = 1.2), 1.60 (m, 6H). FAB+ m/z 221.1 $(M+1)^+$.

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