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# An Unexpected Result in the Alkylation of Thymine

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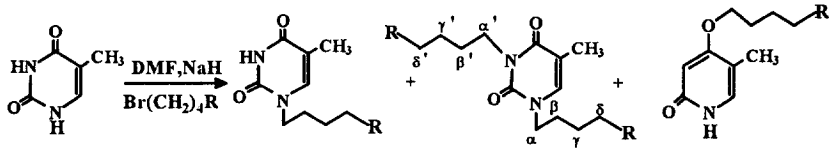
**Abstract:** A moderate yield (55%) preparation of N-1 substituted thymine has been achieved by reacting an excess of 4-bromobutylacetate at 100 °C for 48 hrs. N-1, N-3 bisalkylated and O-alkylated compounds were also obtained as by-products. © 1997 Published by Elsevier Science Ltd.

Since the discovery of modified nucleosides as antiviral agents, increasing efforts have been devoted to the synthesis and biological evaluation of such compounds. As part of our continuing program dealing with the study of novel nucleoside analogues[1], we noted a surprising result while studying the N-1 alkylation of thymine. With the normal procedure this substitution is not regioselective. In addition to N-1 alkylation, N-1, N-3 bisalkylation is also observed. To optimize the yield of the N-1 alkylated product we had to minimize the yield of the N-1, N-3 bisubstituted product. Several authors have tried to reduce the ratio of bisalkylated product by using an excess of thymine[2,3] or at least by working in stoechiometric conditions[4].

Initial attempts, using phase transfer conditions[5], were unsuccessful as they required the separation of numerous by-products. Using a modified methodology of Pedersen *et al.*[4], thymine was stirred with sodium hydride (1.5 eq.) in DMF at 100 °C for 4 hrs and then cooled to room temperature. 4-Bromobutylacetate (1.1 eq.) was then added and the reaction mixture was stirred for 2 hrs at room temperature and then at 100 °C for 7 hrs (Table 1, Entry 1).




R= OAc **1a** **2a** **3a**

R= H **1b** **2b** **3b**

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After treatment and purification by chromatography, the three compounds **1a**, **2a** and **3a** were isolated (Scheme). NMR[6] and mass spectral studies indicate that the major products were the N-1 monoalkylated compound **1a** and N-1, N-3 bisalkylated compound **2a**. The O-alkylated product **3a** was a minor product.(Scheme). Structural data were determinated by mass (IC-$NH_3$) and $^1H$ and $^{13}C$ NMR.The results of $^1H$ NMR are presented in table 2. The three compounds can be distinguished using NMR. H-1, a doublet (4.9 Hz), is upfield from H-3, a singlet.

| Entry [a] | Heating time (hours) | $Br(CH_2)_4OAc$ (eq.) | NaH (eq.) | 1a (%) | 2a (%) | 3a (%) | Overall yield (%) | Ratio of 1a:2a |
|---|---|---|---|---|---|---|---|---|
| 1 | 7 | 1.1 | 1. 5 | 15 | 24 | 3 | 42 | 0.6 |
| 2 | 24 | // | 1. 5 | 17 | 24 | 3 | 44 | 0.7 |
| 3 | 48 | // | 1. 5 | 25 | 16 | 6 | 47 | 1.6 |
| 4 | 24 | 1.3 | 1. 5 | 23 | 30 | 5 | 58 | 0.76 |
| 5 | // | 2.0 | 2 | 28 | 38 | 2 | 67 | 0.74 |
| 6 | // | 2.3 | 2 | 48 | 23 | 9 | 80 | 2.1 |
| 7 | 48 | // | 2 | 55 | 25 | 9 | 89 | 2.2 |

a: Experimental conditions: thymine (6 mmol), DMF (10 ml).

**Table 1**

The use of 1.1 eq. of 4-bromobutylacetate during 24 hrs at 100 °C did not result in an overall yield higher than 50% with the N-1, N-3 bisalkylated product systematically predominating (Table 1, Entry 2). An increase in the heating time (up to 48 hrs) led to an overall yield equivalent to that observed previously (50%) as well as an increase in the yield of **1a** and a decrease in the yield of **2a** (Table 1, Entry 3). However, when an excess of alkylating agent was used (2-2.3 eq.) the overall yield increased and more interestingly, the **1a:2a** ratio increased 3 folds, bringing the yield of N-1 alkylated product up to 55%. In all cases, the percentage of compound **3a** observed did not exceed 9%.

In order to test the different hypotheses concerning the mechanism we made the following experiments:

In a first attempt, we stirred the N-1, N-3 bisalkylated product with NaH (1.5 eq.), in a second one, we added one equivalent of halide. After three days at 100 °C, no evolution was observed. The experiment realized on the O-alkylated product with one equivalent of halide and NaH (1.5 eq.) did not lead to any new product.

In a second experiment, thymine was added to the bisalkylated derivative and stirred at 100 °C in DMF with 1.5 eq. of NaH. No alkyl transfer product from the bisalkylated product to thymine was observed. Thus, the observed regioselectivity is not due to the transformation of the bisalkylated product into the $N_1$ alkylated one. On the other hand, no transfer of the alkyl chain of the N-1, N-3 dialkylated product to the thymine was observed. To evaluate the degree of generalisation of our system, we used the optimal conditions (Entry 7, Table 1) with bromobutane as alkylating agent. In these conditions the overall yield is nearly quantitative (90%), and the percentage of N-1 alkylated product (compound **1b**) is the same than that obtained with the 4-bromobutylacetate (55%).

| | **1a** | **2a** | **3a** |
|---|---|---|---|
| H-1 | - | - | 10.10 d (4.9) |
| H-3 | 8.85 s | - | - |
| H-6 | 6.98 q (1.3) | 6.95 q (1.2) | 6.98 dd (4.5, 1.0) |
| $CH_3$-C | 1.91 d (1.1) | 1.91 d (1.6) | 1.90 d (1.1) |
| H-α | 3.72 t (6.8) | 3.73 t (6.9) | 3.95 t (6.8) |
| H-β-H-γ | 1.70 m | 1.68 m | 1.71 m |
| H-δ | 4.09 t (6.1) | 4.07[a] t (6.0) | 4.10 t (5.8) |
| $CH_3$-CO | 2.04 s | 2.04 s | 2.00 s |
| H-α' | - | 3.96 t (6.0) | - |
| H-β'-H-γ' | - | 1.68 m | - |
| H-δ' | - | 4.09[a] t (6.2) | - |
| $CH_3$-CO | - | 2.01 s | - |

a: Assignments with the same superscript in one column may be interchanged

**Table 2: $^1$H NMR of 1a-3a** (200 MHz, $CDCl_3$, δ ppm,.J Hz.)

In summary, these results indicate for the first time that an excess of alkylating reagent leads to an optimum yield of N-1 monoalkylated thymine (55%) with an overall yield of 89%. This observation is contrary to already published results indicating that an optimum yield of monoalkylated product is achieved by using a stoechiometric amount of alkylating reagent or using an excess of base.

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6 Satisfactory elemental analyses, and mass data were obtained for all compounds.

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