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# HMDS/KI a simple, a cheap and efficient catalyst for the one-pot synthesis of *N*-functionalized pyrimidines

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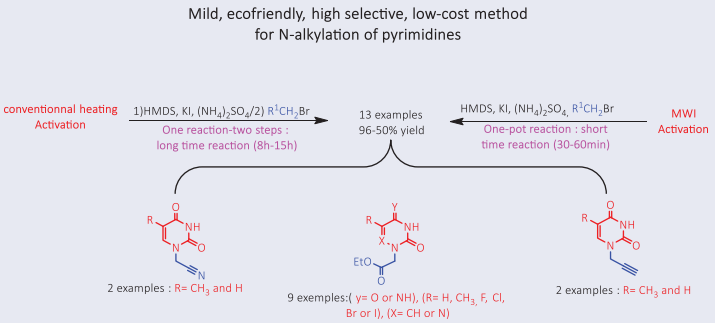
**ABSTRACT**

The syntheses of *N*-Alkylpyrimidine derivatives by reacting pyrimidin-2,4-diones with appropriate alkyl halide under microwave irradiation at 400 W were compared to the conventional synthesis route. These methodologies are regioselective and compatible with numerous substrates and furnish the corresponding *N*-alkylpyrimidines in good yields using a cheap catalyst HMDS/KI in MeCN. A comparison study between these two different modes of heating was investigated.

**GRAPHICAL ABSTRACT**

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**KEYWORDS**
Hilbert–Johnson reaction; microwave irradiation; N-alkylation; pyrimidin-2,4-diones

## Introduction

Numerous biologically important small molecules containing pyrimidines (e.g., Uracil, Thymine, Cytosine, etc.) possess the ability to inhibit vital enzymes responsible for DNA biosynthesis, such as thymidylate synthase, thymidine phosphorylase, and reverse transcriptase. Most of the antiviral compounds that are currently used in the treatment of the herpes simplex virus (HSV), human immunodeficiency virus (HIV), hepatitis B

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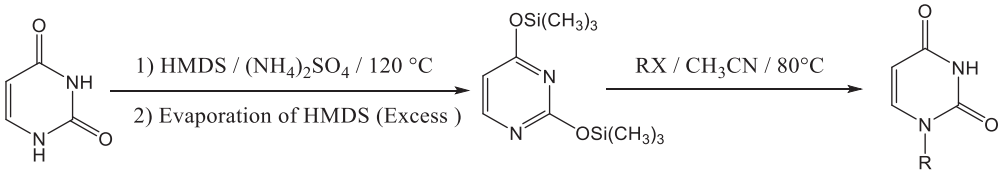



**Scheme 1.** Usual classical heating conditions of Hilbert–Johnson reaction.

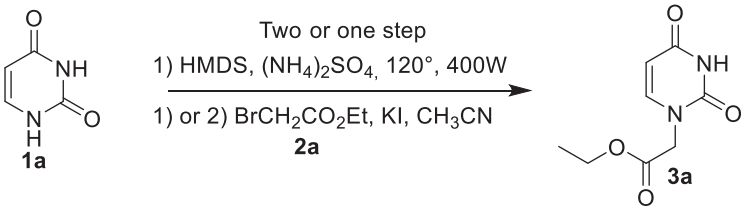
virus (HBV), varicella zoster virus (VZV), and cytomegalovirus (CMV) infections can be described as acyclic nucleoside or nucleotide analogs.[1]

The reported synthesis methods of acyclic nucleoside analogs involve alkylation of purine or pyrimidine bases with various alkylating agents. The most frequently used alkylating agents are halogenated compounds.[2] Some alkylating agents are mesylate[3] or tosylate.[4] The coupling reaction at one of the nitrogen atoms in the pyrimidine is the most effective method for introducing certain substituent with desired functionalities into the heterocyclic base. Furthermore, Peptide Nucleic Acids (PNAs) are oligonucleotide analogs in which the sugar-phosphate backbone is replaced by a *N*-(2-amino-ethyl) glycine unit leading to polyamide oligomers, PNA has attracted wide attention in medicinal chemistry for the development of gene therapy drugs or molecular probes. $N_1$-alkylation of nucleobases affords the important building blocks for PNAs, which have been widely described in the literature.[5] For this purpose, several bases, such as potassium fluoride[5b] potassium carbonate, in DMF, $Et_3N$/DMF[6] or in DMSO[7] have been used. These methods using basic medium are often associated with one or more of the following drawbacks: (i) the use of DMF or DMSO as solvent with cumbersome workup of the reaction mixture (ii) low yields and (iii) harsh conditions of work up. The other promising method for the synthesis of N-alkyl pyrimidine under milder conditions is the use of Hilbert–Johnson-type reaction (Scheme 1).[8] Moreover, The improved silyl-Hilbert–Johnson reaction, the most widely used synthetic method, involves the coupling of per-silylated heterocyclic bases with per-acylated sugars or alkylating agents in the presence of Friedel-Crafts catalysts (e.g., $SnCl_4$, TMSOTf and $(CH_3)_3SiI$)[9] (Scheme 1).

Microwave Assisted Organic Synthesis (MAOS)[10] has been widely applied in heterocyclic chemistry especially in the synthesis of nucleosides and acyclonucleosides[11]. The combination of microwave irradiation with the use of catalysts provides chemical processes with special attributes, such as enhanced reaction rates, higher yields, better activity, and improved ease of manipulation.[12] This reaction has been the dominant method for the preparation of pyrimidine, purine and other heterocyclic nucleoside analogs. On the other hand, potassium iodide (KI) as abundant, green, and inexpensive alkali metal halide is a better choice due to the leaving ability of halide anion ($I^- > Br^- > Cl^-$) and alkali metal cation ($K^+ > Na^+ > Li^+$), which is dominant for the catalytic activity.[13] For these reasons potassium iodide has been used in the alkylation reaction such as *O*-alkylation[14] and *N*-alkylation.[15,16]

We present here a new application of the HMDS/KI for the catalysis of the synthesis of N-alkylpyrimidine derivatives by reacting pyrimidines with appropriate alkyl halide in MeCN under conventional heating (Method A) and/or under microwave irradiation

**Table 1.** Optimal conditions for N-alkylation of uracil by ethyl bromoacetate using conventional heating[a].




| Entry | Ethyl bromoacetate (eq) | KI (eq) | Time (h) | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 1 | – | 12 | $CH_3CN$ | 54 |
| 2 | 1 | 0.5 | 12 | $CH_3CN$ | 68 |
| 3 | 1.5 | 0.5 | 12 | $CH_3CN$ | 82 |
| 4 | 2 | 0.5 | 5 | $CH_3CN$ | 94 |
| 5 | 2 | 0.25 | 5 | $CH_3CN$ | 83 |
| 6 | 2 | – | 5 | $CH_3CN$ | 62 |
| 7 | 2 | 0.5 | 5 | $ClCH_2CH_2Cl$ | 89 |

[a]Reaction Conditions: (1) **1a** (1 mmol), $(NH_4)_2SO_4$ (0.1 mmol), HMDS (1.5 ml), 120 °C, 3 h. (2) **2a** (2 mmol), KI (0.5 mmol), Acetonitrile (2.5 ml), Temp: 80 °C.
[b]Isolated yield.

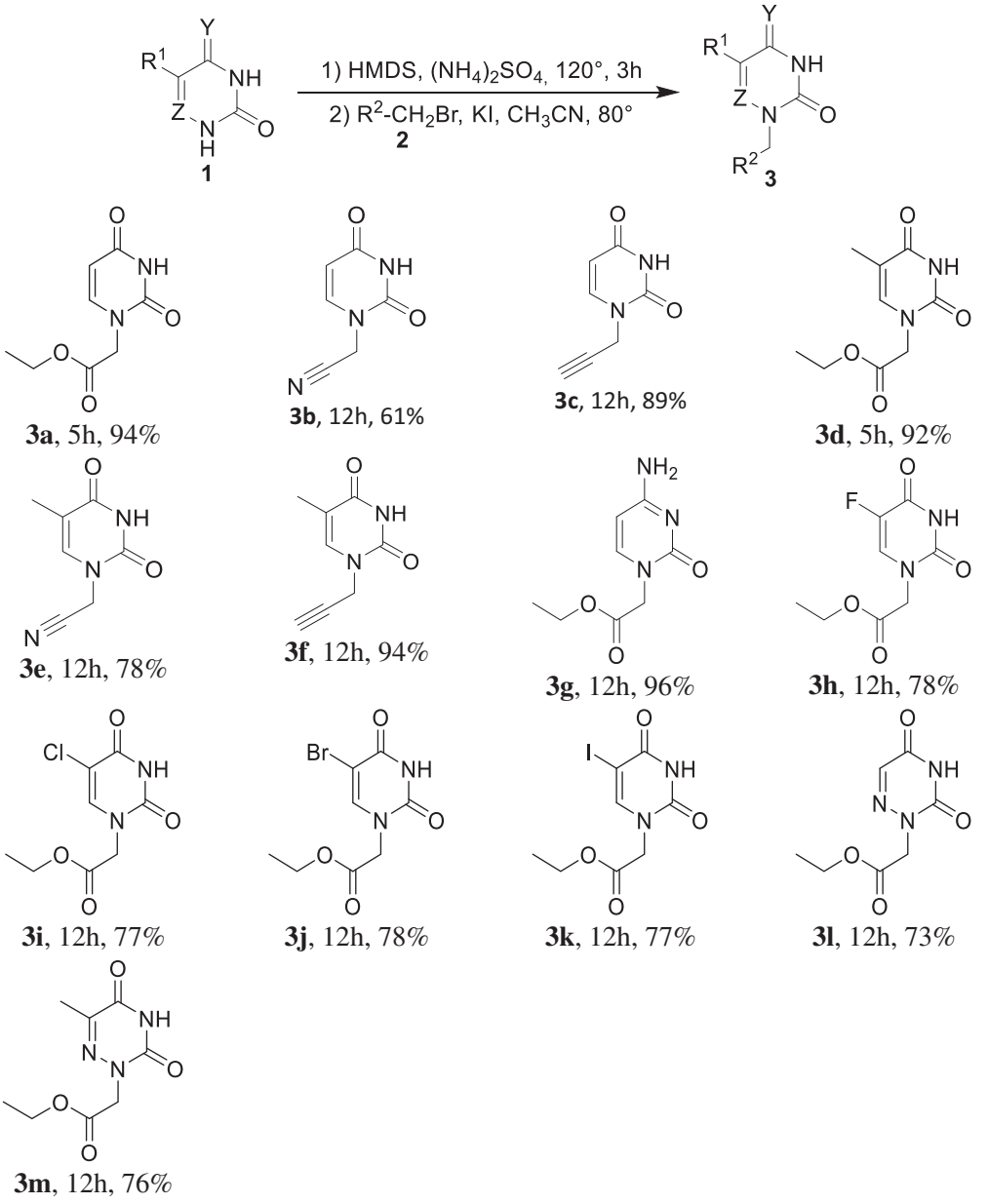
(Method B). Thus, we have conducted several experiments to identify and optimize the effect of the process parameters involved in the development of a slightly modified procedure of Hilbert–Johnson reaction using a catalytic amount of HMDS/KI[17] in acetonitrile.

## Results and discussion

In order to optimize the reaction conditions of silyl-Hilbert–Johnson reaction (Table 1), the reaction of uracil **1a** with bromo-ethyl acetate **2a** was studied as a model reaction. To achieve this, we started by investigating the optimum conditions in detail by varying several parameters such as the used catalyst (KI), the choice of solvent and the amount of alkylating agent. The findings are described in Table 1. Initially, we developed a control reaction without KI as catalyst; in the first step we prepared the silylated uracil in-situ by heating the mixture of uracil, HMDS and ammonium sulfate at 120 °C for 3 h. Then, one equivalent of ethyl bromoacetate in acetonitrile was added in the second step (Table 1, entry 1). The product **3a** was obtained in 54% yield. Thereafter, when potassium iodide (0.5 equiv) was added in the second step the yield increased to 68% (entry 2). Then, the effect of the amount (weight) of the alkylating agent (1, 1.5, 2 equiv) on reaction yield was investigated. The best yield was obtained using 2 equivalents of alkylating agents, and the pure desired **3a** was obtained in 94% yield.

Finally, we studied the effect of potassium iodide (KI), when the amount of KI increases from 0, 0.25, and 0.5 equivalents the yield increased from 62% to reach 83% and 94% respectively (Table 1, entries 6, 5, 4). On the other hand, many attempts have been conducted with an aim to compare the catalytic activity of KI with others iodides. The reaction was carried out using different catalyst such as $Bu_4NI$, CuI and NaI. The obtained yields are 73, 78 and 84% respectively. It has been found that KI was the most suitable catalyst for the modified Hilbert–Johnson reaction for N-Alkylation of pyrimidine.[18]

**Table 2.** Results of N-alkylation of pyrimidines (**1a–c**) by different alkylating agents (**2a–c**).

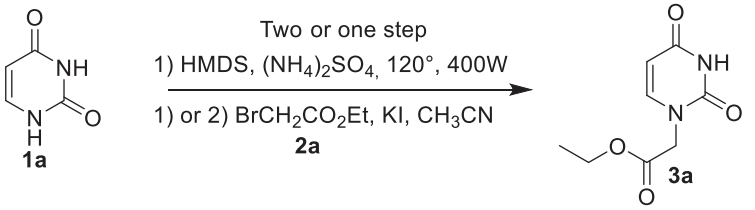



The optimal conditions (Table 1, entry 4) were generalized by changing the alkylating agents and the nucleobases to obtain the N1-alkylated pyrimidines in a moderate to a good yield. When Ethyl Bromoacetate was used as a reagent, the N1-alkylated uracil, thymine and cytosine (**3a**, **3d**, **3g**) were obtained with excellent yields within only 5 h (Table 2, entries 1, 4, and 7). When the bromoacetonitrile and the propargyl bromide were used, we noticed that the reaction time increased from 5 to 12 h and the yield

**Table 3.** Comparison of N-alkylation conditions with literature.

| | | Time (h) | | Yield (%) | |
|---|---|---|---|---|---|
| Entry | Product | In this work | Literature | In this work | Literature |
| 1 | 3a | 5 | 13 | 94 | 60 [19] |
| 2 | 3a | 5 | 20 [1] | 94 | 92 [1] |
| 3 | 3b | 12 | 73 [19] | 61 | 66 [19] |

**Table 4.** Conditions survey for N-alkylation of uracil by ethyl bromoacetate using MW[a].




| Entry | **2a** (equi) | Catalyst KI (equi) | First step time (min) | Second step time (min) | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | 2 | 0.5 | 10 | 5 | 87 |
| 2 | 2 | 0 | 10 | 5 | 60 |
| 3 | 1.2 | 0.5 | 10 | 20 | 75 |
| 4 | 1.2 | 0.5 | 20[b] | | 59 |
| 5 | 1.2 | 0.5 | 30[b] | | 88 |
| 6 | 1.2 | 0.5 | 40[b] | | 88 |

[a]Reaction conditions one-pot: Uracil (1 mmol), alkylating agent (1.2 mmol), HMDS (1 ml), KI (0.5 mmol), $CH_3CN$ (4 ml), time (30 min).
[b]All the reagents have been mixed in the beginning of the reaction (one-step reaction).
[c]Isolated yield.

decreased especially for Bromoacetonitrile (Table 2, compounds: **3b**, **3e**). Moreover, the introduction of halogen in $C_5$ or nitrogen in the position $C_6$ of the nucleobase had a negative effect on the reaction time and yields (Table 2). It should be noted that no reaction occurred when alkyl halides were used, for instance Br–$CH_2$–$CH_2$–$CO_2$Et, or Br–$CH_2$–$CH_2$–CN.

As shown in Table 3, the obtained yields at variable reaction times in this study were compared with those published in the literature. For instance, the reaction time was reduced for N-alkylation of uracil using Ethyl bromoacetate from 13 h to 5 h[19] and from 20 h to 5 h,[1] while improving the yield of the reaction.

The influence of the use of microwave activation on the parameters of the silyl-Hilbert–Johnson reaction was investigated. In the first three experiments, the reaction was carried out in two steps. First, the silylated thymine in-situ was prepared by irradiating the mixture of thymine, HMDS, and ammonium sulfate in acetonitrile. Then, in the second step two equivalents of ethyl bromoacetate and 0.5 equivalent of potassium iodide was added, and the mixture was irradiated for 5 minutes to give product **3d** with a yield of 87% (Table 4, entry 1). In addition, the same reaction was carried out without using potassium iodide, in this case, the yield decreased from 87% to 66% (Table 4, entries 1 and 2). Moreover, the effect of the quantity of ethyl bromoacetate was studied by decreasing it from 2 to1.2 equivalents (Table 4, entries 1 and 3). Thereafter, ethyl bromacetate and potassium iodide were added from the beginning to obtain the acyclo-nucleoside **3d** in 59%. Next, the same reaction (one-pot) was carried out in 30 min

**Table 5.** Results of N-alkylation of pyrimidines by ethyl bromoacetate using MW.

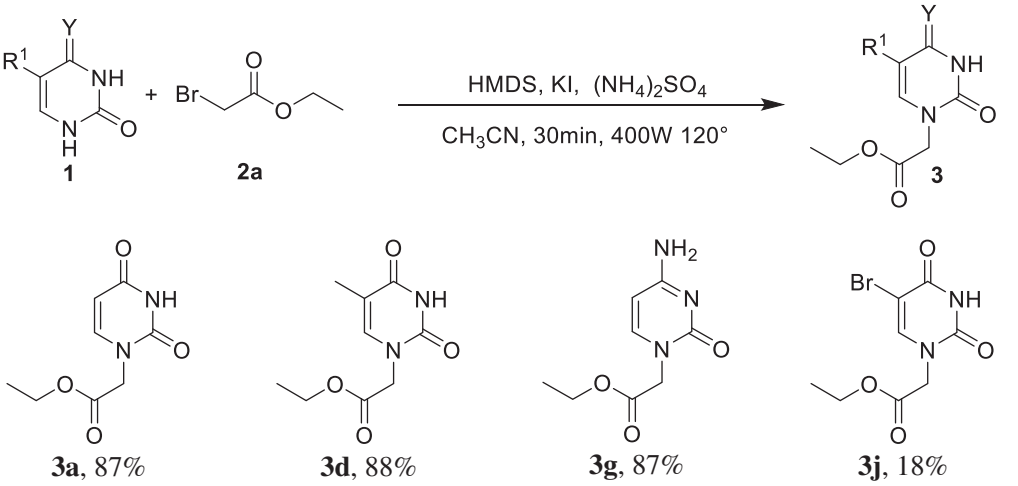
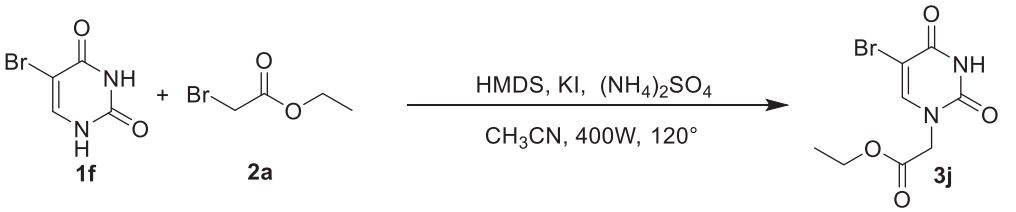



**Table 6.** Optimal conditions for N-alkylation of 5-bromouracil **1f** by ethyl bromoacetate using MW[a].




| Entry | Alkylating Agent | Time (min) | Yield (%)[b] |
|---|---|---|---|
| 1 | 1.2 | 30 | 18 |
| 2 | 1.2 | 40 | 34 |
| 3 | 1.2 | 60 | 41 |
| 4 | 1.5 | 60 | 50 |
| 5 | 2 | 60 | 62 |

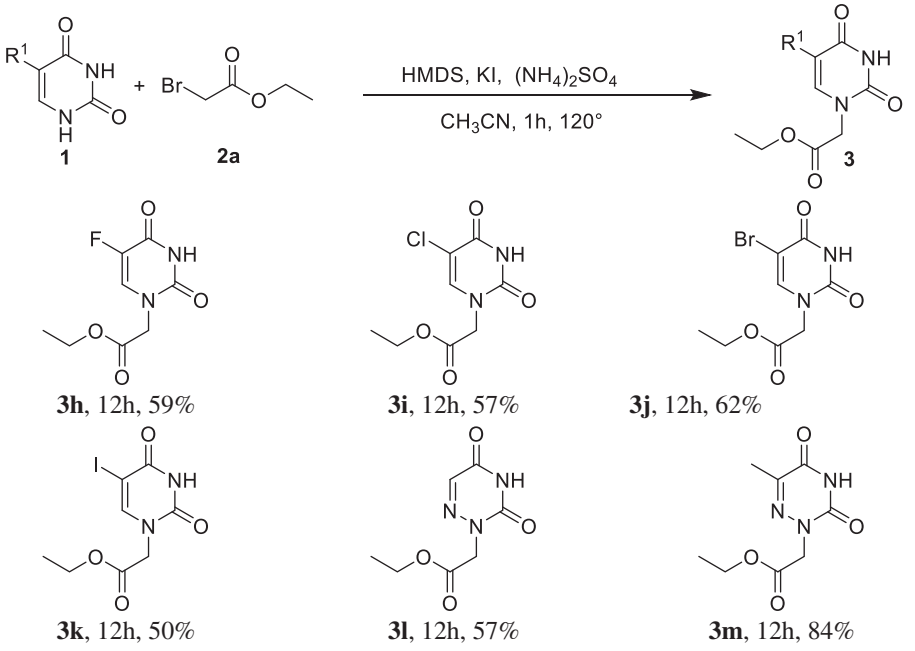
[a]Reaction conditions: **1f** (1 mmol), **2a** (2 mmol), HMDS (1 ml), KI (0.5 mmol), $CH_3CN$ (4 ml), time (60 min).
[b]Isolated yield.

instead of 20 min to lead to **3d** in 88% yield. Finally, the reaction time was increased to 40 min without any significant change in the reaction yield.

The conditions (Table 4, entry 5) were generalized by changing the nucleobases. The N-alkylation of uracil, thymine and cytosine by ethyl bromoacetate provided the corresponding products **3a**, **3d** and **3 g** with excellent yields (Table 5, entries 1, 2, 3). When the 5-bromouracil was used as a nucleobase the product **3j** was prepared only with 18%.

In order to optimize the N-alkylation of 5-bromouracil using ethyl bromoacetate, the effect of reaction time and the number of equivalents of alkylating agent were studied. The results are shown in Table 6. Initially, the reaction time was optimized to 60 min (Table 6, entry 3). Then, two equivalents of ethyl bromoacetate was used to give the

**Table 7.** Results of N-alkylation of 5-halogenouracils and 6-azapyrimidines by **2a** using MW.




corresponding product **3j** in 62%. With these optimized conditions in hand (Table 6, entry 4), the outcome of N-alkylation of 5-halogenouracils and 6-azapyrimidines was investigated. As can be seen in Table 7, the N-alkylation of 5-halogenouracils and 1,2,4-triazines (6-aza-pyrimidines) was studied with ethyl-bromoacetate using MW activation (one–pot reaction) the products (**3h–l**) were obtained in moderate to good yields.

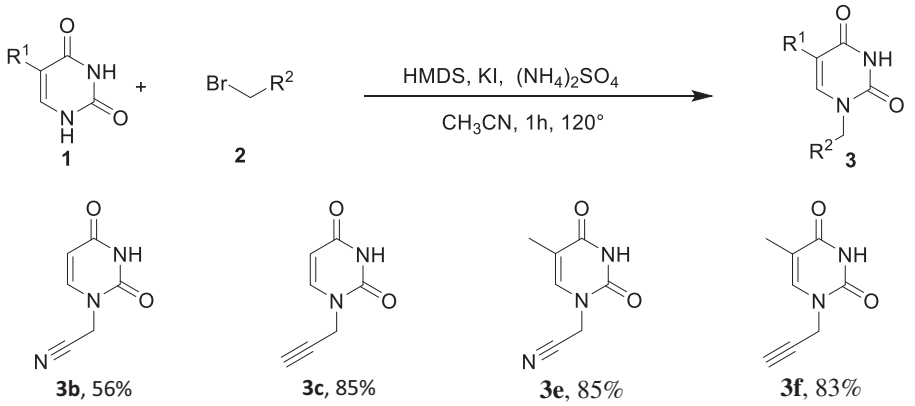
Moreover, taking into account the low reactivity of bromoacetonitrile and propargyl bromide we have chosen to use 1.5 equivalent of alkyl bromide. The results are summarized in the Table 8. The yield of the reactions was in general excellent for the N-alkylation of uracil. In addition, a wide range of nucleoside analogs could be prepared using N-alkylated pyrimidines **3**, for instance 1, 2, 3-triazolyl,[6c] 1, 3, 4 and 1, 2, 4-Oxadiazolyl nucleoside analogs.

## Experimental

### *Typical experimental procedure for the reaction of various pyrimidines and alkyl bromides using conventional heating*

A mixture of uracil (1 mmol, 112 mg) and ammonium sulfate (0.10mmol) in HMDS (1.5 ml) was refluxed until clear solution was obtained (3h). Then bromo-ethylacetate (2 mmol, 0.22ml), KI (0.5mmol, 83 mg) and acetonitrile (2.5ml) were added. Reaction mixture was heated at 90 °C for 5 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with dichloromethane and evaporated to dryness. The residue was purified by flash chromatography eluting with MeOH/dichloromethane (1:10).

**Table 8.** Results of N-alkylation of uracil and thymine by **2b** or **2c** using MW.




### *Typical experimental procedure for the reaction of various pyrimidines and alkyl bromides using Microwave irradiation*

Uracil (0.5 mmol), ammonium sulfate (5 mg), potassium iodide (0.25 mmol, 41 mg), acetonitrile (2 ml), hexamethyldisilazane (0.5ml) and Ethyl bromoacetate (1.2 mmol) were mixed into a pressure-resistant closed vessel and heated at 120 °C (400W) for 30–60 minutes in a professional microwave. Then the mixture cooled, treated with methanol and evaporated under reduced pressure. The residue was purified by flash chromatography using a mixture of methanol/dichloromethane as eluting to obtain the corresponding N-1 alkylated pyrimidines **3a, m**.

## Conclusions

In conclusion, the comparison of the results of *N*-alkylation of pyrimidine with appropriate alkyl halide (ethyl bromoacetate, propargyl bromide, bromo acetonitrile), using HMDS/KI as catalyst, under microwave irradiation (MWI) and conventional method shows that both methods gave higher yields in shorter time for MWI without the formation of by-products such as oxygen atom alkylation and bis $N_1$ and $N_3$ alkylation. All prepared *N*-alkylated pyrimidines are of potential practical interest in the PNA series and used as a starting material for the synthesis of 1,2,3-triazolyl, 1, 3, 4 and 1, 2, 4-oxadiazolyl nucleoside analogs.

Additional information associated with this article can be found in the Supplementary material.

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## Disclosure statement

The authors declare no competing financial interest.

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