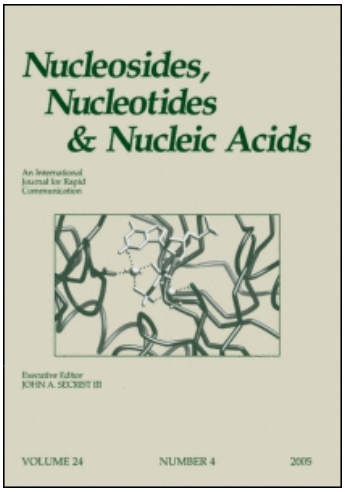

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Microwave-assisted Ribosylation of modified heterocyclic bases by Vorbrüggen method

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MICROWAVE-ASSISTED RIBOSYLATION OF MODIFIED HETEROCYCLIC BASES BY VORBRÜGGEN METHOD

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□ *During the last decades the nucleoside synthesis has proven to be important. The modified silyl-Hilbert-Johnson nucleoside synthesis modified by Vorbrüggen is one of the most often used methods. We have studied N-glycosilation of modifieded heterocyclic bases by Vorbrüggen method with microwave irradiation and we were able to shorten the reaction time and obtain higher yields. The method was demonstrated by fluoroquinolone and purine.*

Keywords Ribosylation; modified heterocyclic bases

INTRODUCTION

Nucleosides and nucleotides have provided a productive area of chemical and biological research. The monomeric units of DNA and RNA are involved in the regulation of a myriad of cellular metabolic pathways and have been the subject of intense areas of research seeking to identify therapeutic agents for a varaiety of diseases including viral infection, cancer, cardiovascular diseases, central nervous system diseases, etc. Among the various synthetic methods the reaction of silylated heterocyclic bases with peracylated sugars in the presence of Lewis acid catalysts has become the standard procedure which affords nucleosides routinely in high yields.[1] In short, nucleoside synthesis includes the silylation of a heterocyclic base, the generative sugar cation from peracylated ribose and the nucleophilic attack of a heterocyclic base on C1.[2]

Here we present some examples of ribosylation of modified heterocyclic bases (1–4) by the conventional Vorbrüggen method and with the use of

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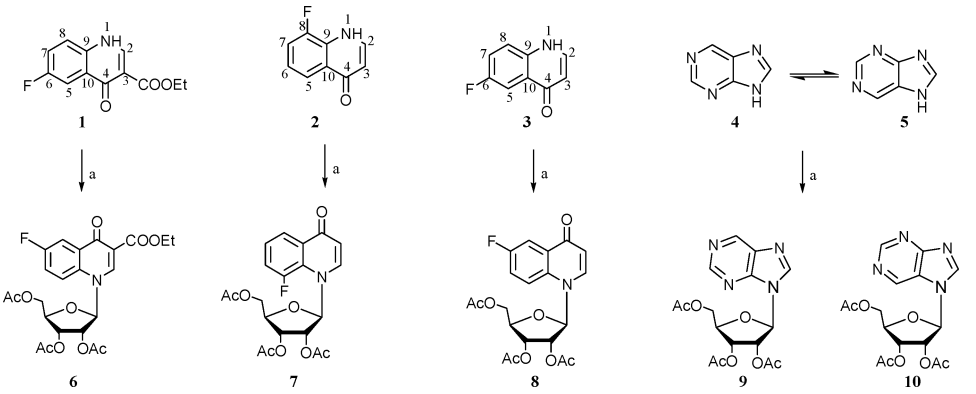

SCHEME 1 Reagents and conditions: a) 1,2,3,5-*O*-tetraacetyl-D-ribofuranose, MeCN, bis(trimethylsilyl)acetamide, trimethylsilyl triflate, Δ, 3 hours, 82–92% or 1,2,3,5-*O*-tetraacetyl-D-ribofuranose, MeCN, bis(trimethylsilyl)acetamide, trimethylsilyl triflate, MW, 50 minutes, 80–96%.

microwave irridiation (MWI). The last approach permits us to get higher yields of target nucleosides in a shorter time compared to the standard method (Scheme 1 and Table 1).

RESULTS AND DISCUSSION

In the synthesis of the heterocycles high temperatures are needed, and we decided to use microwave applicator. Therefore, we modified the procedure of Kidwai et al.[3] on the first step. 2-, 3-, and 4-Fluoroanilines were *N*-substituted with diethyl (ethoxymethylidene)malonate to give diethyl[(fluoroanilino)methylidene]malonates. The electrophilic ring closure was performed in diphenyl ether according to Koga's procedure.[4] The synthesis of fluoroquinolones was reduced from a two-step synthesis by hydrolysis and decarboxylation to a single-step, one-pot reaction.[5] Using this method we were able to shorten the synthesis by one step and to obtain very good yields (87–96%).

Several attempts to synthesize the nucleosides failed due to the lack of solubility of the fluoroquinolones during Vorbrüggen reaction. A slightly modified Vorbrüggen method of Moore et al.[6] gave better results then general procedure, but we improved efficiency of the method by using microwave irradiation on steps of the silylation of heterocyclic bases and ribosylation of them. We do explain these results by a combination of optimal solubility and heat distribution due to the microwave irradiation.

The microwave-assisted glycosylation is the best method for the preparation of fluoroquinolone nucleosides **7** and **8** because the yields are higher and the reaction time is much shorter compared to the conventional method. But in the case of ethyl-6- fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate, the yield of nucleoside **6** microwave irradiated synthesis is

TABLE 1

Compound		Compound		Compound		Compound	
6		**7**		**8**		**9** and **10**	
Conventional	Microwave-assisted	Conventional	Microwave-assisted	Conventional	Microwave-assisted	Conventional	Microwave-assisted
Silylation		Silylation		Silylation		Silylation	
80 °C reflux	80°C	80 °C reflux	80°C	80 °C reflux	80°C	80°C reflux	80°C
30 min	15 min	30 min	15 min	30 min	15 min	15 min	15 min
—	150 W	—	150 W	—	150 W	—	150 W
Nucleoside synthesis		Nucleoside synthesis		Nucleoside synthesis		Nucleoside synthesis	
80°C reflux	80°C	80°C reflux	80°C	80°C reflux	80°C	80°C reflux	80 °C
3 h	50 min	3 h	50 min	3 h	50 min	2,5 h	50 min
—	150 W	—	150 W	—	150 W	—	150 W
Yield		Yield		Yield		Yield	
92%	63%	39%	80%	64%	96%	66% 9 11.6% 10	64.2% 9 17.1% 10

lower than the one of the conventional method. It is still a good method to prepare a nucleoside due to the shorter reaction time and so we can save time in the synthesis. The synthesis of compound **10** with making use of MWI also is preferential, because it seems to favor a kinetic controlled reaction and the ratio of desired nucleoside **10** in the total yield of isomeric N-7 and N-9 nucleosides is changed from 1:5.7 to 1:3.7 (compound **10** to compound **9**).

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