Synthesis of 9-substituted 9-deazaguanine derivatives

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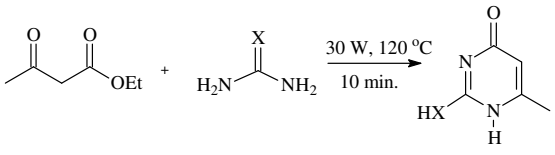
INTRODUCTION

Various derivatives of 9-substituted 9-deazaguanine and 9-deazahypoxanthine have been described as potent competitive inhibitors of purine nucleoside phosphorylase (PNP).[1,2] In this work, we describe a greener method for the synthesis of 9-deazaguanines employing microwaves (MW).

RESULTS AND DISCUSSION

Our synthetic strategy was based on the work described by Shih et al.[3] (Scheme 1). Several procedures are described for the preparation of the starting material, 6-methyl-4-pyrimidinone derivatives **1**, using guanidine or thiourea, ethyl acetoacetate, with or without base, under reflux of ethanol or methanol for several hours.[4,5] Schmink et al.[6] described recently a MW assisted synthesis of 6-methylthiouracil (**1b**) using KOH in ethanol.

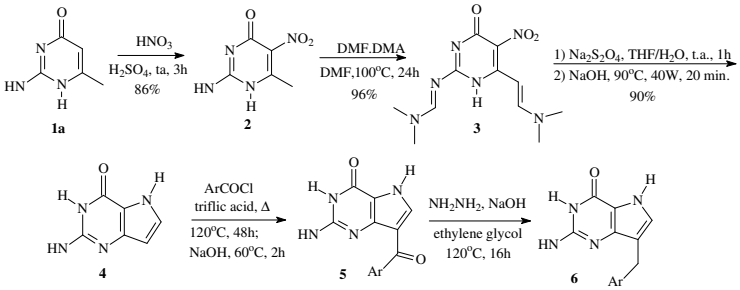
We tested the reaction for the preparation of **1a-c** with and without base, solvent, under conventional heating and also under MW. The best results were obtained without base and solvent under MW irradiation in 65 and 56% yield, for **1a** and **1b**, respectively (Scheme 1). 6-Methyluracil (**1c**) has not been obtained in any experimental condition we have tested.



1a, X=NH **1b**, X=S **1c**, X=O

Scheme 1. Synthesis of 6-methyl-4-pyrimidinones.

The synthesis of 9-deazaguanines was then performed, by nitration of **1a**, followed by alkylation using *N,N*-dimethylformamide dimethyl acetal furnishing **3**. Reductive cyclization followed by microwave irradiation furnished 9-deazaguanine **4** in 90% yield. Under reflux for 2 h, **4** was obtained in only 61% yield. Friedel–Crafts aroylation using trifluoromethane sulfonic acid as catalyst, followed by the Wolff–Kishner reaction leads to the 9-substituted 9-deazaguanines **6** in low to moderate overall yield (Scheme 2, Table 1).[3]



Scheme 1. Synthesis of 9-deazaguanines.

Table 1: Yields obtained in the synthesis of **6**

Benzoyl Chloride	5, Yield (%)	6, Yield (%)
4-chloro	68	58
4-bromo	65	55
3-fluor	71	14
3-chloro	73	-
3,4-dichloro	75	-
3-nitro	68	-
3,5-dichloro	62	-
-	53	-
4-fluor	64	16
2,4,6-trichloro	52	-
2-chloro	61	11
4-iodo	56	15

CONCLUSION

New 9-substituted 9-deazaguanines were obtained employing MW in two steps of the synthetic route. These compounds are being evaluated against human and *S. mansoni* PNP enzymes.

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