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Microwaves – a Powerful Tool for the Base Protection of Cytidine[1]

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Abstract: Use of microwaves for the base protection of cytidine is described. The procedure gives N-acylcytidine in nearly quantitative yield in 40-60 seconds.

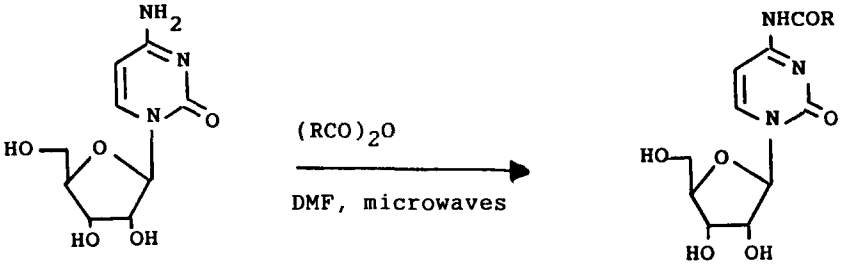
Exocyclic amino protection of cytidine is required for making building blocks for oligonucleotide synthesis or making different cytidine derivatives of biological importance e.g. 2',3'-dideoxycytidine - a potential antiviral agent, particularly against human immunodeficiency virus (HIV)[2]. Usually, benzoyl or acetyl group is introduced to protect the exocyclic amino function of cytidine by peracylation,[3] transient protection[4] or selective acylation method.[2,5-7] All the procedures are quite tedious and require special reagents except the one where an acid anhydride was used directly in presence of a solvent. Although this method is simple, it requires longer reaction time (3-8 h) and the results are variable.[6-8]

Herein, we report the use of microwaves[9] as a powerful tool for the base protection of cytidine within a minute in nearly quantitative yield.

Thus, cytidine (5 mmol) and acetic anhydride (10 mmol),dissolved in DMF (40 ml) was irradiated by microwaves for 40 seconds at 650 watts, after which the solvent was removed under reduced pressure to give white solid. After washing the solid by methanol N^4-acetylcytidine (2a) was obtained in 96% yield. The same procedure gave N^4-benzoylcytidine (2b) in 98% yield when acetic anhydride was replaced by benzoic anhydride (7.5 mmol) and the reaction time was increased to 60 seconds. When methanol was choosen as a solvent the yield of N^4-acetylcy-tidine was decreased to 59% suggesting that , DMF was a better reaction medium. The products obtained were characterized by ^{1}H- NMR and comparison with the authentic samples.[4,10]

No work has been done for the N-acylation of cytidine by the use of microwaves, may be anticipating the fact that primary and secondary hydroxyl groups of the cytidine moiety will also compete in

the acylation reaction at high temparature generated by microwaves. In fact, when the identical reaction was carried out in boiling DMF by conventional heating instead of microwaves, for 10 min., N^4-acetylcytidine was obtained in 30% yield only, 50% cytidine remained unchanged and about 20% gave di- and polyacylated products.Further



1 2 (a-b)

R : a) CH_3, b) C_6H_5

increase in reaction time gave more side products. In contrast to this microwave mediated reaction gave no side products or starting material although reaction temperature was as high as in conventional heating.

This clearly indicates the advantage of doing the above reactions by microwave irradiation. This is the fastest method for the preparation of N^4-acetyl and N^4-benzoylcytidine, which also gives excellent yields and has clear advantages over existing methods.

References and notes :

1. Nahar, P. Indian Patent Pending. No. 1798- Del.96
2. Marcuccio,S.M.; Elmes,B.C.; Holan,G. and Middleton, E.J.*Nucleosides & Nucleotides* **1992**, *11*,1695-1701.
3. Rammler, D.H. and Khorana H.G.*J.Am.Chem.Soc.***1962**,*84*,3112-3122.
4. Chaix,C.; Duplaa, A.M.; Molko,D. and Teoule,R.*Nucleic Acids Res.* **1989**, *17*, 7381-7393.
5. Steinfeld,A.S.;Naider,F.and Becker,J.M.*J.Chem.Research (S)***1979**,129.
6. Watanabe,K.A. and Fox,J.J.*Angew Chem.Int.Edn.Engl.***1966**, *5*,579-580.
7. Bleaney,R.C.; Jones, A.S. and Walker,R.T.*Tetrahedron***1975**, *31*, 2423.
8. Takuma Sasaki and Yoshihisa Mizuno,*Chem.Pharm.Bull.***1967**,*15*,894-896
9. Reactions were carried out in a domestic microwave oven with the frequency of 2450 MHz and purchased from BPL,India,Model- BMO-700 T.
10. Ogilvie, K.K.; Schifman, A.L. and Penney, C.L.*Can.J.Chem.***1979**, *57*, 2230.

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