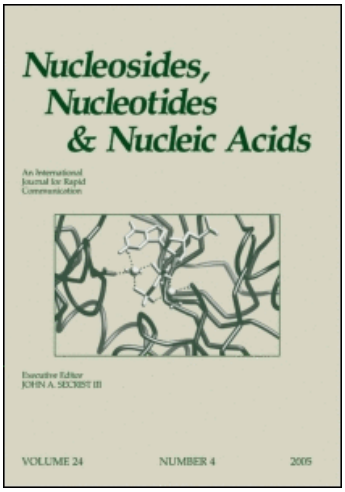

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A NEW METHOD OF SYNTHESIS OF 4-N-ALKYL SUBSTITUTED CYTOSINE DERIVATIVES via 4-N-ARYLSULFONYL OR ALKYLSULFONYL INTERMEDIATES

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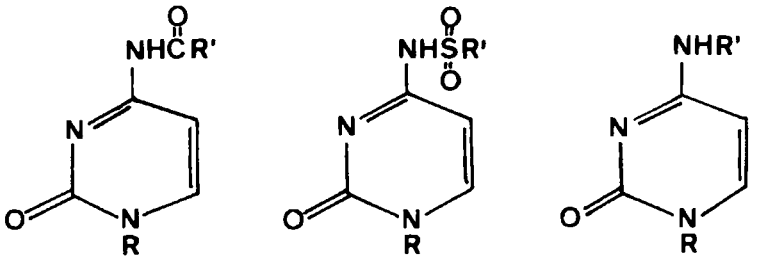
ABSTRACT: 4-N-p-Toluenesulfonyl and 4-N-methanesulfonyl cytosine derivatives are easily prepared from O-protected cytosine nucleosides and corresponding sulfonyl chlorides and then converted in high yields into 4-N-alkyl derivatives by treatment with 1^{o} amines under moderate conditions.

Several methods of preparative importance have been reported for the synthesis of 4-N-alkyl derivatives of cytosine nucleosides [1-7]. Most of these procedures [1,3-7] is based on uracil and thymine derivatives as substates for the preparation of reactive intermediates. 4-N-Alkyl cytosine nucleosides are among important minor constituents of nucleic acids[8] and as such make an interesting object of structure-function relationship studies. Their synthesis is valuable also for the development of synthetic oligonucleotide hybridization probes in which cytosine unit bears a marker "handle"[9].

Ring substitution reaction at C-4 of amide protected cytosine derivatives[10], e.g. 1b /R'=Ph, X=H/ during treatment with 1^{o} amines leads to 4-N-alkyl derivatives, however in poor yields /Table 1, entry 1/.



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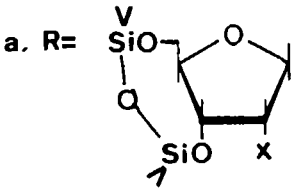

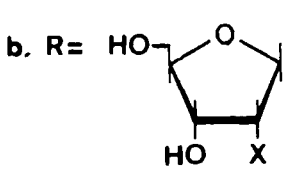

>Si= iPr_2Si

In the case of derivatives 1a /X=H, R'=$pO_2NC_6H_4$/ in which benzoyl group bears electron withdrawing NO_2 substituent the yield of C-4 substitution product could be increased to ca 40% /Table 1, entry 2/. The yield of desired N-alkyl cytosine derivatives 3 /R'=nBu/ is lowered in the case of carboxylic amides 1 due to the nucleophilic attack at amide carbonyl. Sulfonyl sulfur hardly undergoes nucleophilic attack and thus sulfonamides 2 should be better substrates for the studied reaction. The compound 2a /X=H, R'=$pH_3CC_6H_4$/ is obtained quantitatively /TLC, 80% isolated yield/ after treatment of 3',5'-O-/tetraisopropyldisiloxane-1,3-diyl/-2'-deoxycytidine with p-toluenesulfonyl chloride /2 eqval, in pyridine, 60° C, 16 h/. Tetraisopropyldisiloxane-1,3-diyl group[11] was found to be a convenient protection of nucleoside for the reaction of amides 1 and 2 with amines. The reaction of 2a /R'=$H_3CC_6H_4$, X=H, Table 1, entry 3/ with n-butylamine /1 M in pyridine, 5 eqval, 60°C, 24 h / gave desired 4-N-alkyl derivative 3a /R'=nBu/ as the sole product. The reaction with 2° amines was very slow. Methanesulfonyl derivative 2a

Table 1. Reaction of cytosine amides with n-butylamine in pyridine.

Entry	Substrate	Product 3a R'=nBu, %
1	1a /X=H, R'=Ph/	20
2	1a /X=H, R'=$pH_3CC_6H_4$/	40
3	2a /X=H, R'=$pH_3CC_6H_4$/	100
4	2a /X=H, R'=CH_3/	100
5	2a /X=Othp$^+$, R'=$pH_3CC_6H_4$/	100

$^+$thp = tetrahydropyranyl

/R'=CH_3, X=H/ as well as ribo analogue 2a /R'=$pH_3CC_6H_4$, X=Othp/ were synthetized and found to react with amines analogously /Table 1, entries 4,5/. The p-toluenesulfonyl derivatives were ca 1.5 times more reactive than methanesulfonyl ones at room temperature whereas at 60°C their reactivity towards n-$BuNH_2$ was practically the same.

Unfortunately cytosine sulfonamides 2 did not react with other nucleophilic reagents /NaN_3, thiophenol, methanol/ neither under "neutral" /DMF, pyridine, dioxan/ nor "acidic" conditions /pyridinium p-toluenesulfonate-DMF, dioxan/. These data as well as the clean reaction with amines indicate that N-/pyrimidine-4-yl/pyridinium salts are not the intermediates of the reaction of cytosine derived sulfonamides. Compounds 3a could be desilylated [9,11] to 3b derivatives. The structure of all compounds was confirmed by ^1H, ^{13}C NMR and UV spectra. The sulfonamides 2 have characteristic UV spectra: λ_{max} 290 nm, λ_{min} 245 nm.

The above results show that cytosine sulfonamides 2 can be useful intermediates in the synthesis of N-alkyl derivatives of cytosine nucleosides.

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