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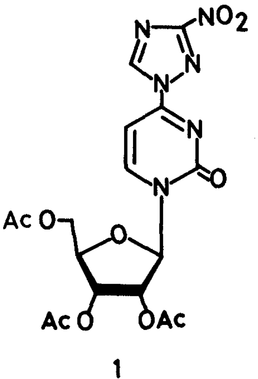
# REACTION OF URACIL NUCLEOSIDES WITH 1-METHYLIMIDAZOLE IN THE PRESENCE OF PHOSPHORYL CHLORIDE: A CONVENIENT METHOD FOR THE SYNTHESIS OF 4-SUBSTITUTED PYRIMIDIN-2(1H)-ONE NUCLEOSIDES

Akira Matsuda,*[1] Kikoh Obi, and Tadashi Miyasaka
School of Pharmaceutical Sciences, Showa University,
Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan

Reaction of 2',3',5'-tri-*O*-benzoyluridine (3) with 1-methylimidazole in the presence of phosphoryl chloride in acetonitrile afforded 3-methyl-1-imidazolium intermediate (4), from which a variety of 4-substituted pyrimidin-2(1H)-one ribosides (5-12) were obtained in a one-pot manner by nucleophilic substitutions under mild conditions. Application of this method to 2'-deoxyriboside of several pyrimidines (13a,b,c) is also described.

KEYWORDS ——— 1-methylimidazole; 4-substituted pyrimidin-2(1H)-one nucleoside; uridine; thymidine; 2'-deoxyuridine; 2'-deoxy-5-iodouridine; nucleophilic substitution; oligonucleotide synthesis

During the course of the phosphotriester approach in oligonucleotide synthesis using a large excess of 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT) as the condensing agent, Reese and Ubasawa[2] observed that the reaction proceeded slowly and gave a mixture of the products due to side reactions. Model studies with protected nucleosides and MSNT in the presence of diphenyl phosphate have been carried out and one of the products was identified as 4-(3-nitro-1,2,4-triazol-1-yl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrimidin-2(1H)-one (1). Sung[3] has also found that thymidine derivatives reacted with 1,2,4-triazole in the presence of p-chlorophenyl phosphodichloridate to afford 2. While 1 and 2 as well as oligonucleotides containing 2[4] have been shown to be of considerable synthetic value to the 4-substituted 2-pyrimidinone derivatives[5,6] by nucleophilic substitution under mild conditions, it would not be suitable for large scale works since these reagents are rather expensive. We have now devised an economical and efficient procedure for the preparation of 4-substituted 2-pyrimidinone nucleosides using 1-methylimidazole (MI).



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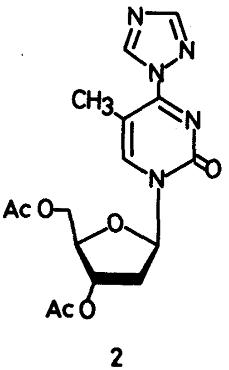
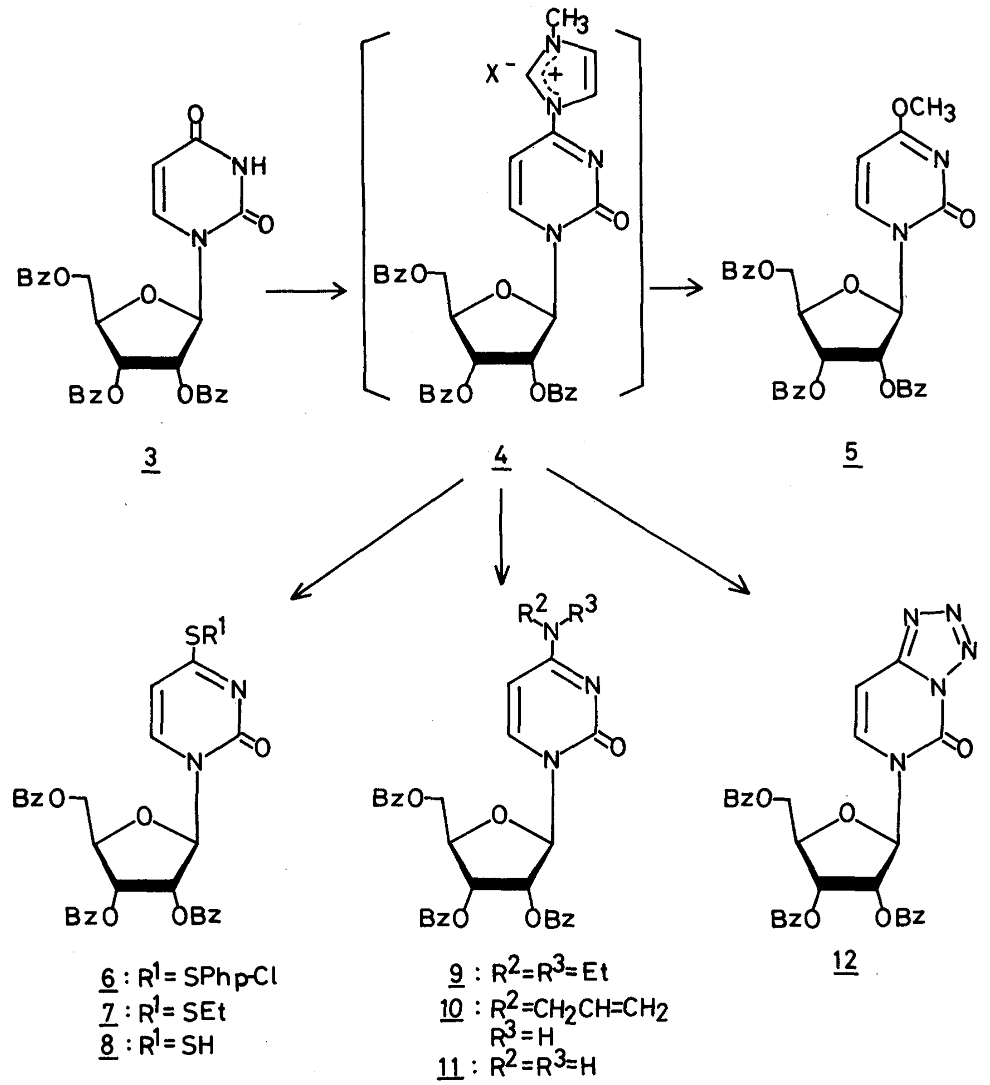


2

When MI and phosphoryl chloride ($POCl_3$)



3

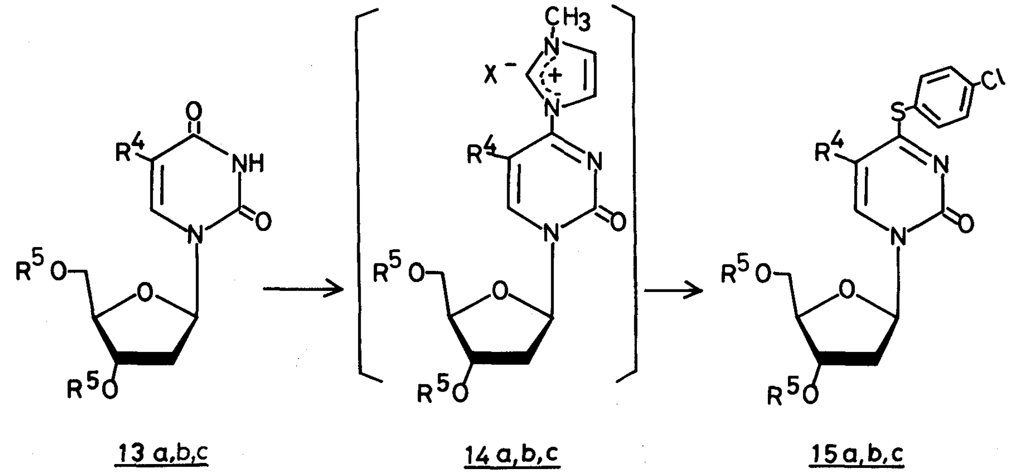
4

5

6 : $R^1$= SPh*p*-Cl
7 : $R^1$= SEt
8 : $R^1$= SH

9 : $R^2$=$R^3$= Et
10 : $R^2$=$CH_2CH=CH_2$
$R^3$= H
11 : $R^2$=$R^3$=H

12



13 a,b,c

14 a,b,c

15 a,b,c

a series : $R^4$=Me , $R^5$=Bz
b series : $R^4$= I , $R^5$=Ac
c series : $R^4$=H , $R^5$=1,1,3,3-tetraisopropyldisilox-1,3-diyl

were mixed in acetonitrile at 0°C, a yellow precipitate resulted and then 2',3',5'-tri-O-benzoyluridine (3) was added to the mixture. The suspension became a clear yellow solution within 2 h at room temperature. At that time, analysis by thin layer chromatography (TLC) showed a new fluorescent spot at the origin (benzene: ethyl acetate, 3:1 or chloroform:ethanol, 15:1). The UV spectrum of the reaction mixture indicated a maximum at 318 nm in methanol, a pattern akin to that of 4-(imidazol-1-yl)-2-pyrimidinone riboside, a product of the reaction between uridine-4-sulfonate and imidazole.$^{7)}$ The spectrum was stable under acidic conditions. However, the absorption at 318 nm immediately disappeared when triethylamine was added to the cuvette and a new absorbance at 271 nm was observed as a shoulder. From the reaction mixture treated with methanol (excess) and triethylamine (9.5 mol eq) in a one-pot manner for 3 h at room temperature, crystalline 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-methoxypyrimidin-2(1H)-one (5, 92%, δ 3.86:OMe, mp 198-199°C, lit.$^{8)}$ mp 199-200°C) was obtained without cleaving the ester groups in the sugar moiety. The MI (10 mol eq) and $POCl_3$ (3 mol eq) combination appears to produce the best result. This experiment clearly shows that MI is capable of coupling to the 4-position of 3 to produce the 3-methyl-1-imidazolium salt of pyrimidin-2(1H)-one riboside (4), tentatively assigned according to the above-mentioned UV and TLC characteristics, and subsequent substitution with methanol furnishes 5.

In order to obtain information about the reactivity we examined the behaviour of the salt (4) under conditions of nucleophilic substitutions. When intermediate 4 was treated with p-chlorothiophenol (3 mol eq) in the presence of triethylamine in a one-pot manner at room temperature, 6 was obtained (1 h, 94%, mp 198-199.5°C). Similarly ethanethiol and NaSH were allowed to react with 4 to give 7 (1.5 h, 85%, mp 187.5-189.5°C) and 8 (3 h, 97%),$^{9)}$ respectively. While the reaction of 1 with p-toluenethiol required elevated temperature,$^{5)}$ 4 was found to react readily with thiols due to the difference of leaving ability between the imidazolium salt in 4 and the triazole in 1. Amines such as diethylamine, allylamine, and ammonia also reacted with 4 in analogous fashion to afford 9 (1.5 h, 95%, mp 136-138°C), 10 ( 2 h, 88%, foam), and 11 (4 h, 63%, mp 185-187°C, lit.$^{10)}$ mp 174.5-175.5°C). Treatment of 4 with $NaN_3$ for 18 h at room temperature furnished the tetrazolo-pyrimidin-2(1H)-one riboside (12, 93%, mp 218-219°C dec.). Since the IR spectrum of 12 does not show the $\nu N_3$ band, the equilibrium of this compound lies strongly on the side of the tetrazole structure, as was found in the thymidine derivative.$^{11)}$ Thus, the intermediate 4 reacted smoothly with a variety of nucleophiles under mild conditions. This process demonstrated to be a general and useful route to the various 4-substituted 2-pyrimidinone ribosides, was applied to 2'-deoxyuridine derivatives.

The sterically hindered methyl group at the 5-position in the thymidine derivative (13a) did not prevent the formation of the 3-methyl-1-imidazolium salt (14a) under standard conditions (3 h). Subsequent treatment of 14a with p-chlorothiophenol afforded 15a (3 h, 82%, foam). The 5-iodo derivative (13b) afforded the salt (14b) under the same conditions within 2.5 h. This was smoothly converted with the thiol into 15b (1 h, 90%, foam) without reduction of the iodo function and cleaving the acetyl groups in the sugar moiety. A cyclic silyl protecting group in 13c was also tolerated under the condition of the salt formation (14c) and the nucleophilic displacement of 14c with the thiol afforded 15c (1.5 h, 90%, foam).[12] From a preparative point of view, therefore, the convenient one-pot method described herein provides a uniquely facile route to a variety of 4-substituted 2-pyrimidinone nucleosides and is a potentially powerful alternative to the previously reported methods.

Although 1-methylimidazole has often been utilized to activate the phosphate group in oligonucleotide synthesis,[13] possibilities of a side reaction have never been examined. As shown in this paper, the 3-methyl-1-imidazolium salt (4, 14) formation reaction could be a significant side reaction if a large amount of MI is used for a long period of time in oligonucleotide synthesis.

## REFERENCES AND NOTES

1) Present address: Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan
2) C.B.Reese and A.Ubasawa, Nucleic Acids Res. Sympodium Series, 7, 5 (1980); idem, Tetrahedron Lett., 21, 2265 (1980).
3) W.L.Sung, J.Chem.Soc., Chem.Commun., 1981, 1089.
4) W.L.Sung, Nucleic Acids Res., 9, 6139 (1982); idem, J.Org.Chem., 47, 3623 (1982).
5) K.J.Divakar and C.B.Reese, J.Chem.Soc.Perkin Trans. 1, 1982, 1171.
6) S.S.Jones, C.B.Reese, S.Sibanda, and A.Ubasawa, Tetrahedron Lett., 22, 4755 (1981); C.B.Reese and P.A.Skone, J.Chem.Soc.Perkin Trans. 1, 1984, 1263.
7) M.Yano and H.Hayatsu, Biochim.Biophys.Acta, 199, 303 (1970).
8) M.Prystas and F.Sorm, Collect.Czech.Chem.Commun., 31, 1035 (1966).
9) After debenzoylation of 8 with NaOMe, 4-thiouridine was obtained in crystalline form, mp 137-138°C; see N.K.Kochetkov, E.I.Budowsky, V.N.Shibaev, G.I.Yeliseeva, M.A.Grachev, and V.P.Demushkin, Tetrahedron, 19, 1207 (1963).
10) T.Ueda and H.Ohtsuka, Chem.Pharm.Bull., 21, 1530 (1973).
11) J.J.Fox, D.van Praag, I.Wempen, I.L.Doerr, L.Cheong, J.E.Knoll, M.L.Eidinoff, A.Bendich, and G.B.Brown, J.Am.Chem.Soc., 81, 178 (1959).
12) All new compounds involved in this study exhibited satisfactory spectral and physical properties.
13) J.H.van Boom, J.F.M.deRooy, and C.B.Reese, J.Chem.Soc.Perkin Trans. 1, 1973, 2513; J.H.van Boom, P.M.J.Burgers, G.R.Owen, C.B.Reese, and R.Saffhill, J.Chem.Soc., Chem.Commun., 1971, 869; R.C.Pless and R.L.Letsinger, Nucleic Acids Res., 2, 773 (1975); V.A.Efimov, S.V.Reverdatto, and O.G.Chakhamakhcheva, Nucleic Acids Res., 10, 6675 (1982); B.C.Froehler and M.D.Matteucci, J.Am.Chem. Soc., 107, 278 (1985).

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