Tetrahedron Letters,Vol.25,No.31,pp 3325-3326,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SYNTHESIS AND REACTION OF 6-TRIALKYLSILYL SUBSTITUTED URACILS AND URIDINES

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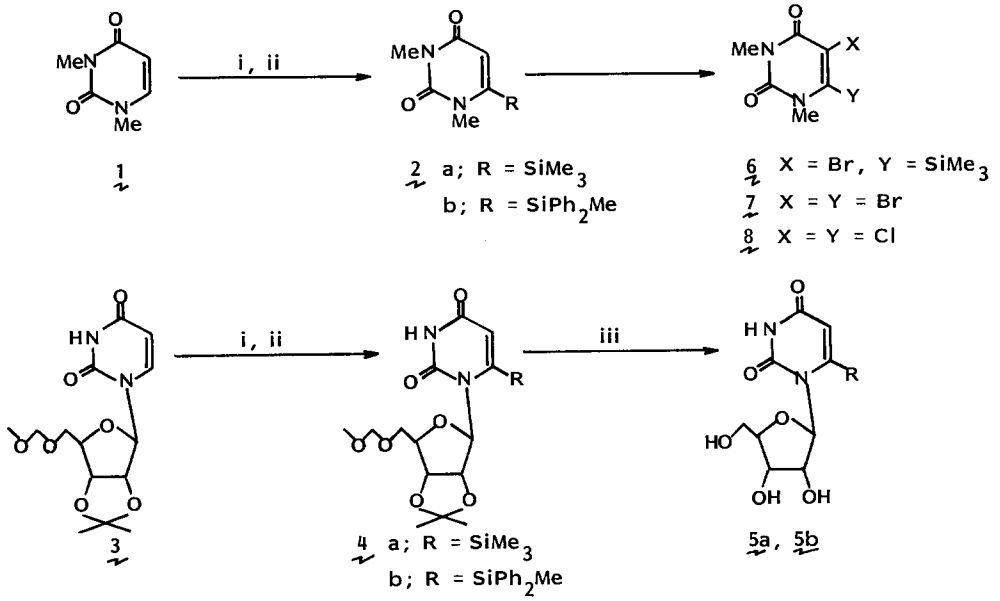
Summary: 6-Trimethylsilyl substituted 1,3-dimethyluracil and uridine were prepared via lithiation and successive trapping with trimethylsilylchloride in the presence of 4-dimethylaminopyridine and converted to 5,6-dihalogenated derivatives by treatment with NBS or NCS.

While a number of C-5 and C-6 substituted pyrimidine nucleosides have been prepared in view of their various biological activities,[1] pyrimidine nucleosides bearing a silicon functionality have received only little attention. To our knowledge, 5-trimethylsilyluracil and uridine are the only examples so far reported.[2] 6-Trimethylsilyl or 6-diphenylmethylsilyluracil derivatives seem to be an important class of compounds in view of their potential high synthetic utilities, since they possess a synthetically versatile alkenylsilane moiety which is readily removable under mild conditions. We report herein the first synthesis of 6-trimethylsilyluridine and 1,3-dimethyl-6-trimethylsilyluracil and demonstrate that the 6-trimethylsilyluracil is readily converted to synthetically useful 5,6-dihalouracils.

Among several methods available for the preparation of 6-substituted uracils and uridines,[3] lithiation at C-6 and successive trapping with electrophiles recently developed by Miyasaka *et al.*,[4] seems to be the most convenient and promising one for the synthesis of 6-trimethylsilyluracil derivatives. Lithiation of 1,3-dimethyluracil (1) with LDA in THF-HMPA at -78 °C followed by quenching with trimethylsilylchloride resulted in a complicated mixture of products including only minor amount of 1,3-dimethyl-6-trimethylsilyluracil[5] (2a). However, when 6-lithiated 1 was treated with trimethylsilylchloride or diphenylmethylsilylchloride in the presence of a catalytic amount of 4-dimethylaminopyridine, the yields of 2a and 2b were improved up to 38% and 60%, respectively. By a similar procedure 2',3'-O-isopropylidene-5'-O-methoxymethyluridine (3) was converted to the corresponding 6-trimethylsilyl derivative 4a (70%). Treatment of 4a with 50% aqueous trifluoroacetic acid gave 5a (80%). 6-Diphenylmethylsilyluridine (5b) was synthesized in a similar manner in 17% overall yield from 3.

A few examples of the synthetic application of these 6-trimethylsilyluracils are shown below. Reaction of 2a with excess bromine in dichloromethane at room temperature provided 6 as a sole product (51%). Treatment of 2a with NBS and NCS in DMF at 50 °C provided the corresponding 5,6-dihalogenated uracils 7 (21%) and 8 (23%), respectively. Such 5,6-dihalogenated uracils, hardly accessible by other routes,[6] are useful intermediates for further transformations including photoannelation of the pyrimidine ring which are currently investigating in our laboratory.



Reagents: i, LDA, DMAP, THF/HMPA, -78 °C; ii, $ClSiMe_3$ or $ClSiPh_2Me$, iii, 50% aq. CF_3COOH.

REFERENCES AND NOTES

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(5) All compounds gave satisfactory elemental analyses and spectroscopic data; Selected ^{1}H-NMR ($CDCl_3$) data follows: 2a, δ 0.40 (s, 9 H), 3.30 (s, 3 H), 3.41 (s, 3 H), 5.80 (s, 1 H); 4a, δ 0.41 (s, 9 H), 1.35 (s, 3 H), 1.54 (s, 3 H), 3.35 (s, 3 H), 3.79 (m, 2 H), 4.20 (m, 1 H), 4.61 (s, 2 H), 4.83 (m, 1 H), 5.20 (m, 1 H), 5.60 (m, 1 H, anomeric H), 5.80 (s, 1 H), 9.62-9.92 (br, 1 H); 5a, with D_2O, δ 0.45 (s, 9 H), 3.50-4.01 (m, 3 H), 4.23-4.83 (m, 2 H), 5.20-5.39 (m, 1 H, anomeric H), 5.73 (s, 1 H).
(6) Synthesis of 5-halogenated 6-iodouridines has recently been reported.[7] However, the same methodology cannot be applied for the preparation of 7 and 8.
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(Received in Japan 29 March 1984)