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DESULFURIZATIVE STANNYLATION OF URACIL DERIVATIVES

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Summary Phenylthio group in the C-6 or C-5 position of uracil moiety can be removed by radical mediated stannylation with tributyltin hydride followed by protonolysis, providing a new route to 5-substituted uridines.

In continuation of our studies on the lithiation of nucleosides,[1)] we found that, when LTMP (lithium 2,2,6,6-tetramethylpiperidide) was employed as a lithiating agent,[2)] the C-5 position of 2',3'-O-isopropylidene-5'-O-methoxymethyl-6-phenylthiouridine (1) was metallated in an essentially quantitative yield and that the action of a wide variety of electrophiles on the lithiated species of 1 gave 2-7 as shown in Table 1. These findings prompted us to investigate an effective method for desulfurization of the 6-phenylthio group, since overall reaction sequence would provide a new route for the transformation of uridine to 5-substituted uridines.[3)]

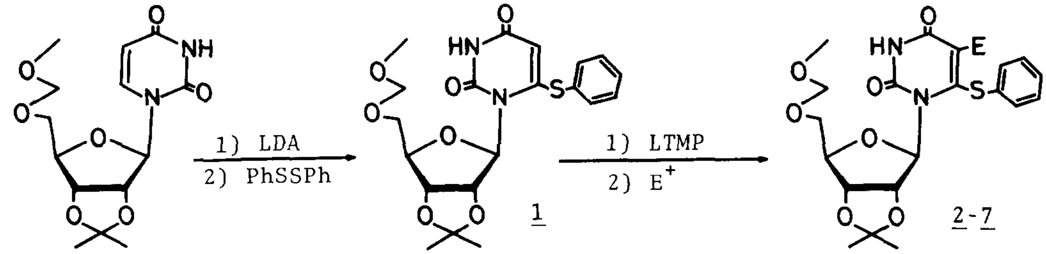


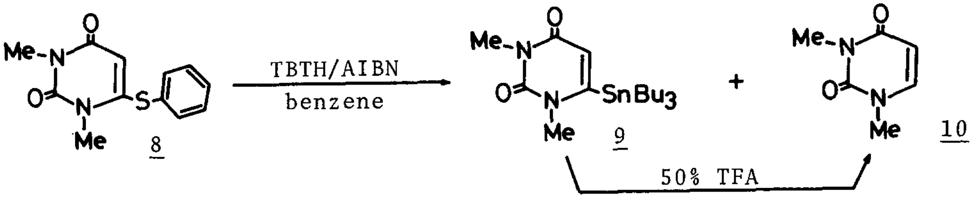
Table 1*

Electrophile	E	Product	Yield (%)
MeI	Me	2	81
EtI	Et	3	30
BuI	Bu	4	13
ClCOOEt	COOEt	5	86
$ClSiMe_3$	$SiMe_3$	6	91
PhSSPh	SPh	7	94

* Reactions were carried out in THF at below -70 °C using 2.5 equiv of LTMP.

After several unsuccessful experiments in which aluminum amalgam[4] or Raney nickel was used as a desulfurizating agent, tributyltin hydride (TBTH) was found to be suitable for our purpose.

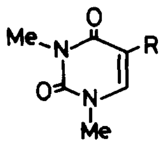
When a benzene solution of 1,3-dimethyl-6-phenylthiouracil (8),[5] a model compound, was treated with 5 equiv of TBTH in the presence of AIBN, the reaction went to completion after 8 h. The main product isolated by preparative TLC[6] in 97% yield as colorless oil was identified as 1,3-dimethyl-6-tributylstannyluracil (9). PMR spectrum of 9 in $CDCl_3$ (δ 0.90, 9H, t, $CH_2CH_2CH_2\underline{Me}$; δ 1.08-1.56, 18H, m, $\underline{CH_2CH_2CH_2}Me$; δ 3.34, 3H, s, N^1-Me; δ 3.42, 3H, s, N^3-Me; δ 5.77, 1H, s, H-5) was in good agreement with its structure and MS spectrum (M-1 m/z: 429, 427 and 425, M-Bu m/z: 373, 371 and 369)[7] was characteristic of an organotin compound. A 2% yield of 1,3-dimethyluracil (10) was also isolated in this reaction.



Although Ueno and Okawara[8] have reported the reaction of 2-(allylthio)-1,3-benzothiazole with TBTH to yield the allyltin product, the formation of stannylated product can be observed only in the TBTH reaction which proceeds through the S_{H}' process.[9] We are not aware of any example for the direct substitution of an arylthio substituent with tributylstannyl group in organotin hydride-mediated desulfurization.

The 6-stannylated product (9) is susceptible to protonolysis.[10] When 9 was treated with 50% aqueous trifluoroacetic acid (TFA) at room temperature for 7 h, 10 was obtained in 89% yield.

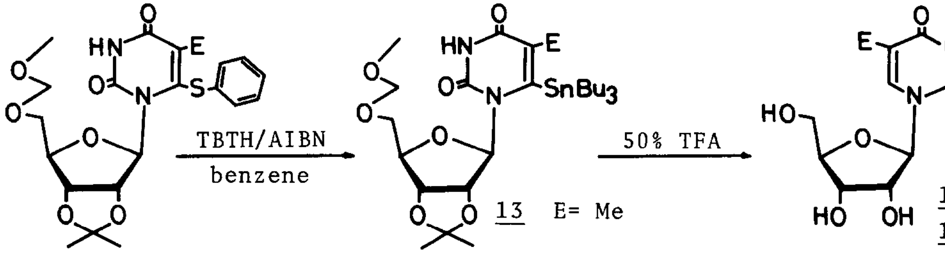
We have also examined the desulfurizative stannylation in the case of 5-phenylthio derivative (11).[5] Compound 11 was treated in a similar manner with 2 equiv of TBTH for 1 h to afford the corresponding 5-tributylstannylated product 12 in 96% yield. Its PMR spectrum in $CDCl_3$ (δ 0.89, 9H, t, $CH_2CH_2CH_2\underline{Me}$; δ 1.03-1.47, 18H, m, $\underline{CH_2CH_2CH_2}$-Me; δ 3.33, 3H, s, N^1-Me; δ 3.37, 3H, s, N^3-Me; δ 6.88, 1H, s, H-6) and MS spectrum (M+1 m/z: 431, 429 and 427, M-Bu m/z: 373, 371 and 369) were again well indicative of 12's structure. It should be noted that 12 possesses a higher propensity to undergo protonolysis. Thus, upon treatment with 50% TFA at room temperature, 12 was converted to 10 in 92% yield within 10 min.



11 R= SPh
12 R= $SnBu_3$

The above mentioned results in hand, we then carried out the preparation of 5-substituted uridines from the 6-phenylthiouridine derivatives (2-7).

When 2 was subjected to the desulfurizative stannylation (3 equiv of TBTH, 3 h), the corresponding stannylated product 13[11] was obtained in 81% yield. Subsequent treatment of 13 with 50% TFA effected concurrent deprotection of 2',3'-O-isopropylidene and 5'-O-methoxymethyl groups and protonolysis of 6-tributylstannyl group at the same time to furnish 5-methyluridine (14). The overall yield of 14 from 2 was 79%. Similarly, 5-ethyluridine (15) was prepared in 82% yield from 3.

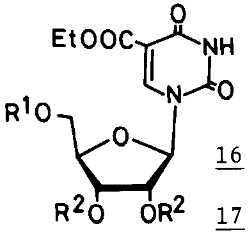


13 E= Me

14 E= Me

15 E= Et

The special case of 5-ethoxycarbonyl derivative (5) deserves a short comment since the TBTH reaction (2 equiv of TBTH, 10 min) gave 16 in 91% yield instead of the expected 6-stannylated product. 5-Ethoxycarbonyluridine (17) was obtained in 84% overall yield from 5 after 50% TFA treatment of 16.

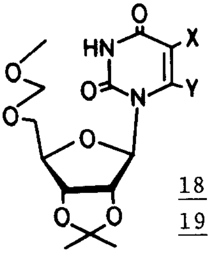


16 R^1= methoxymethyl
R^2= isopropylidene

17 R^1= R^2= H

The TBTH reaction process did not work, however, with 5-trimethylsilyl derivative (6) resulting in complete recovery of the starting material.

Finally, the TBTH reaction of 5,6-diphenylthiouridine derivative (7) was investigated to examine a competitive stannylation between 5- and 6-phenylthio groups. The reaction was carried out with 2 equiv of TBTH for 40 min whereupon two products were formed. Based on their PMR and MS spectra, it revealed that one was 6-phenylthio-5-tributylstannyluridine derivative (18; 40%) and the other was 6-tributylstannylated product (19; 22%).[12] This result is consistent with those of 1,3-dimethyluracil derivatives (8 and 11) and it seems likely phenylthio group in the C-5 position of uracil moiety is more susceptible to TBTH-mediated desulfurizative stannylation than that in the C-6 position.



18 X= $SnBu_3$, Y= SPh

19 X= SPh, Y= $SnBu_3$

REFERENCES AND NOTES

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2) The use of butyllithium gave, after deuteration, a complex mixture of products from which a small amount of 6-butyluridine derivative was isolated. LDA was not effective to generate the C-5 anion of 1.

3) Methods so far available for the transformation of uridine to 5-substituted uridines: H. Hayakawa, H. Tanaka, and T. Miyasaka, Tetrahedron, 41, 1675 (1985) and references cited therein.

4) Aluminum amalgam did work to remove the 6-phenylthio group but the concomitant formation of 5,6-dihydrogenated product could not be avoided.

5) S. Senda, K. Hirota, and M. Takahashi, J. Chem. Soc. Perkin I, 1975, 503.

6) The use of basic alumina is crucial to prevent decomposition of 9 to 10.

7) Isotope peaks corresponding to ^{120}Sn, ^{118}Sn, and ^{116}Sn are shown.

8) Y. Ueno and M. Okawara, J. Am. Chem. Soc., 101, 1893 (1979).

9) C. G. Gutierrez and L. R. Summerhays, J. Org. Chem., 49, 5206 (1984).

10) It has been reported that tributylstannyl group alpha to carbonyl can be removed by acidic treatment: A. Rahm and M. Pereyre, J. Organomet. Chem., 88, 79 (1975).

11) All the compounds in the present study, including the stannylated nucleosides, gave satisfactory physical data.

12) The structures of 18 and 19 were confirmed by 50% TFA treatment which gave 6-phenylthio- and 5-phenylthiouridines, respectively.

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