HETEROCYCLES, Vol. 31, No. 10, 1990

NOVEL THYMIDINE ANALOGUES VIA REACTION OF UNPROTECTED 5'-DEOXY-5'-IODOTHYMIDINE WITH DIANIONS

Partha S. Ray*[#] and Albert A. Jaxa-Chamiec[##]

Department of Chemistry, Searle Research and Development,
High Wycombe, Buckinghamshire HP12 4HL, UK.

Abstract -Reaction of 5'-deoxy-5'-iodothymidine with a variety of dianions gave novel thymidine analogues in moderate to good yields.

There is currently much synthetic effort being expended in nucleoside chemistry due to the potential of modified nucleosides as antimetabolites. We were therefore surprised to find no examples of carbon-carbon bond forming reactions with anions or dianions using unprotected nucleoside derivatives. Carbon-carbon bond formation from the 5'-carbon of a nucleoside is generaly conducted in six or more steps: selective protection of the 5'-primary alcohol, protection of the secondary hydroxy group(s), selective deprotection of the primary alcohol, oxidation of the alcohol to the corresponding aldehyde, Wittig reaction followed by hydrogenation if required, and finally deprotection of the secondary hydroxy group(s).[1] Such unattractive protection-deprotection sequences are common in nucleoside chemistry. Despite its wide synthetic importance, the displacement reaction of primary halides or tosylates by carbanions has rarely been used in nucleoside chemistry.[2]

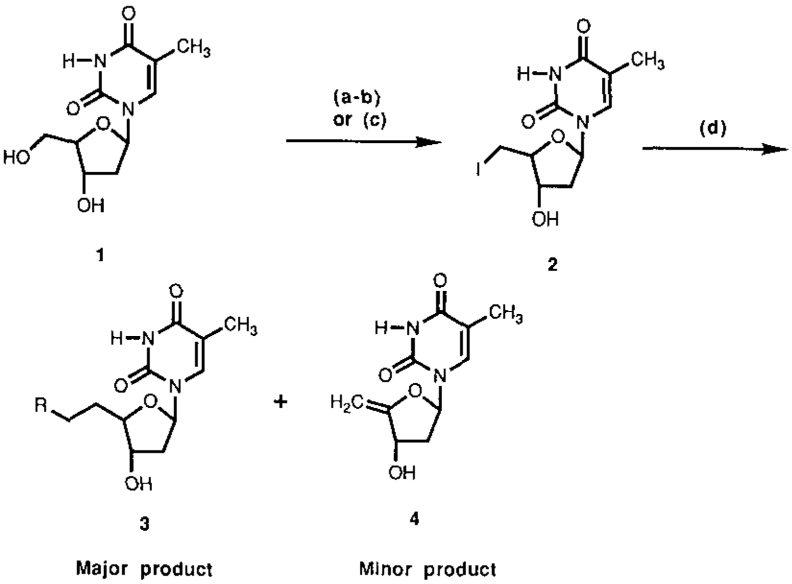
As part of our program to develop inhibitors of enzymes involved in the metabolism of thymidine nucleosides, we wish to report an efficient method for forming a carbon-carbon bond at the 5'-carbon of 5'-deoxy-5'-iodothymidine (**2**) by displacement of the halide with the anion of thioanisole and a variety of dianions (see Scheme and Table). This one-step procedure, from **2** to the 5'-deoxy-5'-carbon derivatives (**3**), is to be compared to the three-step process which would be required via the classical protection-deprotection sequence. 5'-Deoxy-5'-iodothymidine (**2**) was prepared from the reaction of thymidine with tosyl chloride to give the 5'-tosyl derivative[3] followed by reaction with sodium iodide in refluxing butanone. It can also be prepared from the reaction of thymidine with methyltriphenoxyphosphonium iodide as reported by Verheyden and Moffatt.[4]

[#] Present address: Department of Chemistry, Agricultural Chemical Group, FMC Corporation, P.O. Box 8, Princeton, New Jersey 08543, U.S.A.

[##] Present address: Department of Chemistry, Smith-Kline and Beecham Research Limited, The Frythe, Welwyn, Herts., AL6 9AR, UK.

Initially, reaction of **2** with an excess of phenylthiomethyllithium[5] in tetrahydrofuran (THF) gave a very low yield of the desired sulphide (**5**) apparently due to the poor solubility of the mono/dianion of **2**. We found that the addition of a small amount of hexamethylphosphoramide (HMPA) to the reaction mixture gave a much improved yield of the sulphide **5**. Reactions of **2** with various dianions[6] (5 equivalents) were also carried out in a mixture of THF and HMPA. The yields of the isolated, crystalline, pure products are shown in the Table.[7] It is well known that 5'-deoxy-5'-iodothymidine (**2**) and the corresponding 5'-tosylate and 5'-mesylate undergo cyclization to give 2,5'-anhydrothymidine in the presence of base.[8] Thus, it is likely that the above displacement reactions occur via the intermediacy of 2,5'-anhydrothymidine. Typically, 5-15% of 1-(2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)thymine (**4**) resulting, most probably, from the eliminative ring opening of 2,5'-anhydrothymidine was isolated from these reactions.[9] This minor side product (**4**) was easily separated by column chromatography on silica gel as the less polar material.

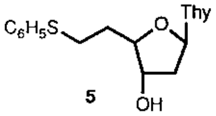
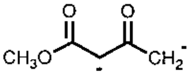
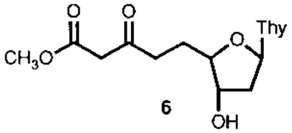
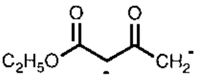
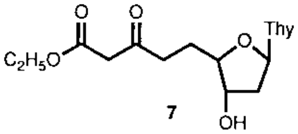
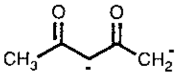
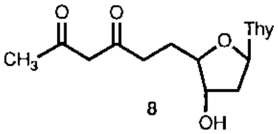
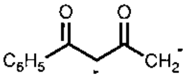
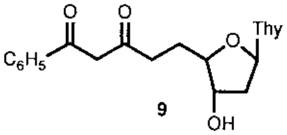
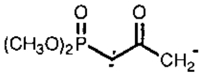
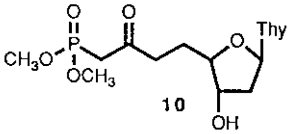
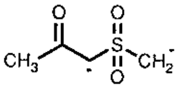
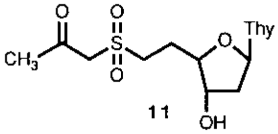
Scheme

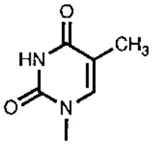


(a) Tosyl chloride, pyridine; (b) NaI, butanone; (c) $(PhO)_3P^+CH_3I^-$, DMF;
(d) $RCH_2^-Li^+$, THF, HMPA; followed by H_3O^+

Table

Reaction of anion/dianion with 5'-deoxy-5'-iodothymidine (2)

Anion/Dianion	Thymidine analogue	Isolated yield (%)	mp (°C)
$C_6H_5SCH_2^-$	 5	78	179-180
	 6	68	133-134
	 7	72	136-137
	 8	54	145-147
	 9	65	174-175
	 10	25	oil
	 11	58	195-197

Thy = 

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6. The dianion of dimethyl-2-oxopropylphosphonate and those of the β-keto esters were prepared by the treatment with one equivalent of sodium hydride followed by an equivalent of n-butyllithium as described in the literature.[10,11] The dianions of the β-diketones and that of methanesulphonyl acetone were prepared using two equivalents of LDA. The following experimental procedures illustrate the method:

   Reaction of **2** with dianions generated with NaH/n-BuLi: **2** (5 mmol) in HMPA (5 ml) was added dropwise to the dianion (25 mmol) in THF (50 ml) at 0°C. After addition, the mixture was allowed to warm to room temperature and stirring was continued for a further 3-4 h. The mixture was acidified with 2 N hydrochloric acid to pH 6 and extracted three times with ethyl acetate. The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed in vacuo. The residue was chromatographed on silica gel using 2-5% methanol in methylene chloride as eluent.

   Reaction of **2** with dianions generated with LDA: LDA (50 mmol) in THF (50 ml) was added dropwise to the β-diketone or methanesulphonylacetone (25 mmol) in THF (30 ml) cooled to -78 °C. The mixture was stirred and allowed to warm to 0 °C. **2** (5 mmol) in HMPA (5 ml) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature and then stirred for a further 3-4 h. The reaction mixture was worked up as described above.
7. All new compounds (**5-11**) described in this communication were characterised by ^{1}H nmr, ir, and lrms. Satisfactory elemental analyses were obtained for all of the compounds except **10**.
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Received, 20th August, 1990