Nucleic acid related compounds. 38. Smooth and high-yield iodination and chlorination at C-5 of uracil bases and *p*-toluyl-protected nucleosides[1]

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Received July 13, 1981

MORRIS J. ROBINS, PHILIP J. BARR, and JERZY GIZIEWICZ. Can. J. Chem. **60**, 554 (1982).

Treatment of uracil bases and protected nucleosides with iodine monochloride (ICl) gave the corresponding 5-iodouracil products in over 95% purified yields. Analogously facile chlorination was effected with iodobenzene dichloride ($PhICl_2$). Protection of the nucleosides as *p*-toluyl esters provided reactants that were soluble in organic solvents and crystallized readily in high yields.

MORRIS J. ROBINS, PHILIP J. BARR et JERZY GIZIEWICZ. Can. J. Chem. **60**, 554 (1982).

Les bases du type uracile et les nucléosides protégés réagissent avec le monochlorure d'iode (ICl) en donnant les produits iodo-5 uraciles correspondants avec un rendement en produits purs supérieur à 95%. D'une façon analogue, on a pu faire facilement une chloration à l'aide du dichlorure d'iodobenzène ($PhICl_2$). La protection des nucléosides par un groupe ester *p*-tolyle fournit des réactifs solubles dans les solvants organiques et qui peuvent être cristallisés facilement avec d'excellents rendements.

[Traduit par le journal]

A number of 5-substituted uracil derivatives, especially 2′-deoxyuridines, have been investigated extensively in the experimental and clinical treatment of neoplastic and viral diseases (2–4). The 5-fluorouracil and 2′-deoxyuridine compounds are potent inhibitors of cell growth and 5-fluorouracil has been used widely in the clinical treatment of cancer (2). The related 5-iodo-2′-deoxyuridine has been in clinical use as a herpes antiviral drug for over a decade (3). Recently (*E*)-5-(2-bromovinyl)-2′-deoxyuridine has been reported to have extraordinary activity and selectivity against herpes type I viruses (4, 5). There is strong current interest in the study of 5-substituted-2′-deoxyuridine 5′-monophosphates as mechanism based inhibitors of the crucial anabolic enzyme thymidylate synthetase (see ref. 6 and references therein).

We recently have devised an efficient route to uracil nucleosides with a functionalizable carbon chain at C-5 via the palladium–copper catalyzed coupling of terminal alkynes with 5-iodouracil compounds (7). A second reported coupling of terminal alkynes (as their chlorozinc derivatives) with a protected 5-iodo-2′-deoxyuridine gave the 5-(1-alkynyl) derivatives in variable yields (8). Both of these syntheses utilize 5-iodouracil precursors. The availability of the iodo compound in high yield is especially important when beginning with the expensive 2′-deoxyuridine.

Prior reports on the direct iodination of uridine, 2′-deoxyuridine, and their nucleotides have frequently employed the classical iodine/nitric acid/organic solvent mixture of Prusoff *et al.* (9). More recently, iodination of 5-mercuriuridine derivatives in aqueous alcohol has been described (10). However, these procedures can give troublesome by-products with resulting moderate yields of the purified 5-iodo compounds. The use of *N*-iodosuccinimide with pyrimidine nucleosides has been reasonably successful (11) and iodine monochloride has given moderate yields of uracil nucleosides with "unnatural" sugars (12).

We have found that treatment of uracil compounds with iodine monochloride under appropriate conditions gives clean conversion to the 5-iodo derivatives. Yields of the purified products depend primarily on the ease of crystallization. Treatment of 1-methyluracil (**1***b*) (see Scheme 1) with 2 equivalents of ICl in methanol at 50°C gave 5-iodo-1-methyluracil (**2***b*) in 95% yield after purification. Analogous treatment of uridine (**1***c*) and 2′-deoxyuridine (**1***d*) gave the corresponding 5-iodo nucleosides **2***c* and **2***d* in 82% and 76% yields.

Protection of the sugar hydroxyl groups as *p*-toluyl esters gave the organic soluble and readily crystallized derivatives **1***f* and **1***g*. Treatment of 2′,3′,5′-tri-*O*-*p*-toluyluridine (**1***f*), 3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (**1***g*), and 1-(2,3,5-tri-*O*-*p*-toluyl-β-D-arabinofuranosyl)uracil (**1***h*) with 1.5 equivalents of ICl in dichloromethane at reflux gave 96%, 98%, and 95% crystallized yields of the 5-iodo products **2***f*, *g*, and *h*. Synthetic and characterization data are given in Table 1.

Chlorination of uracil compounds has been effected previously using elemental chlorine (13) or

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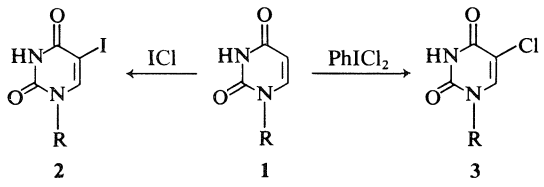
0008-4042/82/050554-04$01.00/0

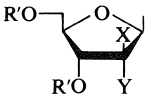
TABLE 1. Synthetic and characterization data

Starting material			Product					Calculated			Found		
				Yield		Melting point							
Compound	Weight (g)	Method[a]	Compound	(g)	%	°C	Solvent[a]	C	H	N	C	H	N
1*c*	4.88	A	**1***f*	11.2	94	198–201	A	66.22	5.05	4.68	66.38	4.89	4.64
d	11.4	A	*g*	21.8	94	215–217[b]	A	64.65	5.21	6.03	64.52	5.26	5.78
e	10.98	A	*h*	25.6	95	245–246	A	66.22	5.05	4.68	66.05	5.01	4.68
1*b*	2.52	B	**2***b*	4.77	95	260–264	B	23.83	2.00	11.12	23.93	2.03	11.29
c	2.44	B	*c*	3.04	82	208–210[c,d]	B	29.21	3.00	7.57	29.03	2.95	7.56
f	2.99	C	*f*	3.47	96	230–232	A	54.71	4.03	3.87	54.64	4.14	3.66
g	16.3	C	*g*	20.3	98	195–196[e]	A	50.87	3.93	4.75	50.88	3.98	4.67
h	25.1	C	*h*	28.74	95	214–216	A	54.71	4.03	3.87	54.80	4.06	3.71
1*a*	0.224	D[f]	**3***a*	0.268	92	>325[g]	C	32.79	2.06	19.12	32.77	1.95	18.83
b	0.252	D	*b*	0.301	94	>270[h]	D	37.41	3.14	17.45	37.31	3.03	17.22
f	8.38	D	*f*	7.45	84	224–226	A	62.62	4.62	4.43	62.46	4.70	4.22
g	1.16	D	*g*	1.17	94	214–215[i]	A	60.19	4.65	5.62	59.99	4.71	5.30

[a]See the Experimental for Methods A–D and crystallization solvents A–D.
[b]Literature (20) mp 216–217°C.
[c]With decomposition.
[d]Literature (9) mp 205–208°C dec.
[e]Literature (21) mp 196–197°C.
[f]Reaction solvent was 50% AcOH/H_2O.
[g]Sublimed at >240°C and the resulting condensed prisms melted with decomposition at >325°C; lit. (14) mp 324–325°C dec.
[h]Sublimed without melting; lit. (15) mp 285°C dec.
[i]Literature (22) mp 213.5–214.5°C.



Series: *a*, R = H
b, R = CH_3
c–h, R =



c, R′ = X = H, Y = OH
d, R′ = X = Y = H
e, R′ = Y = H, X = OH
f, R′ = $COC_6H_4CH_3$-*p*, X = H, Y = $OCOC_6H_4CH_3$-*p*
g, R′ = $COC_6H_4CH_3$-*p*, X = Y = H
h, R′ = $COC_6H_4CH_3$-*p*, X = $OCOC_6H_4CH_3$-*p*, Y = H

SCHEME 1

N-chlorosuccinimide in acetic acid (14, 15) to provide the 5-chlorouracils in moderate yields. A new procedure that utilizes hydrogen chloride and *m*-chloroperoxybenzoic acid has been described very recently by Ryu and MacCoss (16).

We have found that treatment of uracil compounds with 1.2 equivalents of iodobenzene dichloride in warm acetic acid solutions gives rapid and clean conversion to the 5-chloro products. Treatment of 1-methyluracil (**1***b*) with $PhICl_2$ in acetic acid at 80°C for 15 min gave 94% of purified 5-chloro-1-methyluracil (**3***b*). Analogous treatment of 3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine (**1***g*) gave 94% of the purified 5-chloro nucleoside (**3***g*). Other examples and data are given in the table.

This investigation has determined convenient access to the readily crystallized *p*-toluyl esters of uridine, 2′-deoxyuridine, and their 5-chloro and 5-iodo analogues. High-yield iodination and chlorination of uracil bases and protected nucleosides have been achieved using iodine monochloride and iodobenzene dichloride, respectively. These procedures complement known methods for efficient access to the corresponding 5-fluoro (17) and 5-bromo (18) series. The precursor 5-iodouracils (**2**) now are readily available for coupling with terminal alkynes (7).

Experimental

General

General procedures and instrumentation used are given in ref. 1. Melting points were determined on a Gallenkamp block apparatus in open capillary tubes and are uncorrected. Iodine monochloride (ICl) was purchased from Aldrich Chemical Co. and used directly without purification. Iodobenzene dichloride (phenyliodine(III) chloride, $PhICl_2$) was prepared as described by Lucas and Kennedy (19). Crystallization solvents used are: A, product dissolved in a minimum volume of hot $CHCl_3$ and ~5 volumes of MeOH added, followed by chilling at −18°C (further crops obtained by concentration and chilling of the mother liquor); B, MeOH (with addition of Et_2O for additional crops); C, MeOH–H_2O; D, MeOH.

Method A

3′,5′-Di-O-p-*toluyl-2′-deoxyuridine* (**1**g)

A magnetically stirred solution of 11.4 g (0.05 mol) of 2′-deoxyuridine (**1***d*) in 250 mL of dry pyridine was cooled to 0°C and 17 g (0.11 mol) of freshly distilled *p*-toluyl chloride was added slowly. The solution was allowed to warm to room temperature, heated at 50°C for 2 h, and evaporated *in vacuo* to give a white solid mass. Chloroform (400 mL) was added and the organic phase was washed with 2 × 300 mL of 1 *M* H_2SO_4/H_2O, 2 × 300 mL of H_2O, dried over Na_2SO_4, filtered, and evaporated to ~150 mL. Methanol (~750 mL) was added and the resulting colorless crystalline mass was filtered. The filtrate was reduced to a small volume and chilled at −18°C to give further crystalline product. The combined crystals were dried to give 21.8 g (94%) of **1***g*, mp 215–217°C; ^1H nmr (Me_2SO-d_6) δ: 2.40 (br, 6, two CH_3's), 4.50 (m, 3, H-4′,5′,5″), 5.58 (m, 2, H-3′ and H-5), 6.28 (t, 1, H-1′), 7.3–7.9 (m, 9, H-6 and aromatic), 11.39 (br, 1, NH).

Method B

5-Iodo-1-methyluracil (**2**b)

Iodine monochloride (6.5 g, 0.04 mol) was added to a stirred suspension of 2.52 g (0.02 mol) of 1-methyluracil (**1***b*) in 40 mL of MeOH and the resulting solution was heated at 50°C for 1.5 h. Separation of a crystalline mass occurred and tlc indicated complete conversion of **1***b* → **2***b*. The mixture was filtered and the crystals were washed with Et_2O. The combined filtrate and washings was chilled at 0°C for several hours and a second crop of crystals was collected to give 4.77 g (95%) of **2***b* after drying. This product had mp 220–224°C; ^1H nmr (Me_2SO-d_6) δ: 3.25 (s, 3, CH_3), 8.17 (s, 1, H-6), 11.74 (br, 1, NH).

Method C

5-Iodo-3′,5′-di-O-p-*toluyl-2′-deoxyuridine* (**2**g)

A stirred solution of 16.3 g (0.035 mol) of **1***g* and 8.53 g (0.0525 mol) of ICl in 300 mL of CH_2Cl_2 was heated at reflux for 2 h. Thin-layer chromatography indicated complete conversion of **1***g* → **2***g*. The solution was cooled, diluted with 200 mL of CH_2Cl_2, and decolorized (ICl) by careful washing with the *minimum* required volume of 2% $NaHSO_3/H_2O$ solution. The organic phase was washed with H_2O, dried over Na_2SO_4, filtered, and evaporated. The residue was dissolved in a minimum volume of hot $CHCl_3$, MeOH (~5 volumes) was added, and the mixture was chilled at −18°C to give (in three crops) 20.3 g (98%) of crystalline **2***g*, mp 195–196°C.

Method D

5-Chloro-3′,5′-di-O-p-*toluyl-2′-deoxyuridine* (**3**g)

Iodobenzene dichloride (825 mg, 3 mmol) was added to a stirred solution of 1.16 g (2.5 mmol) of **1***g* in 15 mL of acetic acid at 80°C. Stirring was continued at 80°C for 15 min and tlc indicated complete conversion of **1***g* → **3***g*. The mixture was evaporated *in vacuo*. Repeated addition and evaporation of MeOH/H_2O and then MeOH gave 1.21 g (97%) of **3***g* as a white powder. This product was dissolved in a minimum volume of hot $CHCl_3$, MeOH (~5 volumes) was added, and the mixture was chilled at −18°C to give (in two crops) 1.17 g (94%) of crystalline **3***g*, mp 214–215°C.

Acknowledgements

We thank the National Cancer Institute of Canada, the Natural Sciences and Engineering Research

Council of Canada (A5890), and The University of Alberta for generous financial support.

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