Commun. Fac. Sci. Univ. Ank. Series B
V. 38. pp. 57–61 (1992)

SYNTHESIS OF URIDINE DERIVATIVES

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(Received Dec. 25, 1991; Accepted Nov. 27, 1992)

ABSTRACT

2′, 3′–0 isopropylidene–5–aminomethyl uridine was condensed with some aldehydes. In the same time, reduction "in situ" of the reaction products was achieved Nevertheless, the resulting compounds showed to be unstable during chromatographic processes. It was necessary, to increase their stability by suitable protection of their exo amino groups. On the other side, reactions concerning both of 5–formyl uridine derivative with some halides, and 5–chloromethyl derivative of uridine with the previous aldehydes were also performed via Grignard reactions.

INTRODUCTION

It should be noted that little is yet known about pathways of modified uridines biosynthesis, but evenmore controversial is the molecular mechanism of their activity in the decoding of a genetic message[1,2]. If so, a modified unite introduced into the anticodon loop architecture.

As a rational base for such operation conformational dynamic of tRNA anticodon loop should be considered. The present work was mainly devoted for the synthesis of some modified nucleosides that expected to be valuable and exhibit interesting biological activity as well as suitably amino blocked uridine derivatives which could be utilized for oligoribonucleatides synthesis[3,4]. The synthetic routes that applied for such synthesis seemed to be practical and suitable ways for the synthesis of these nucleosides. Trifluoro–acetyl group[5] is used as suitable protecting group for the oxo–amino function because it is stable at both the acidic and alkaline conditions and can be readily

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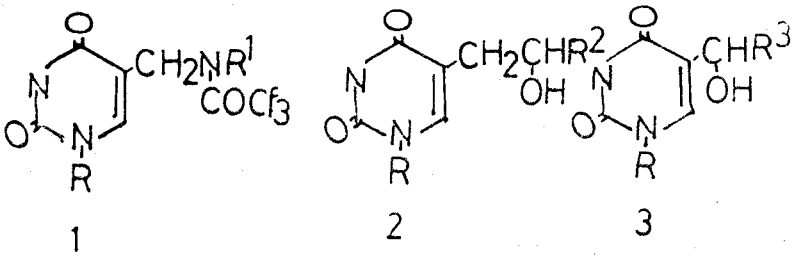
removed. Consequently, the required reactants are either accessible or easily prepared. In this context, 5–hydroxymethyl uridine[6] could be considered as a potential substrate in the preparation of all compounds.

DISCUSSION

As a practical route for the synthesis of such N–blocked–5–substituted derivative of uridine is the condensation of 2′,3′–O– isopropylidene–5–aminomethyl uridine with each of isobutyraldehyde, isovaleraldehyde, pivaldehyde, 3–phenyl propionaldehyde respectively under slightly acidic conditions then reduction "in situ" the formed compounds with sodium cyanoborohydride to form secondary amines. However, separation of such products from the reaction mixture either on silica gel column or TLC plates was unsuccessful. In order to increase their stability, it was necessary to prepare the N–trifluoroacetylated derivatives. Consequently, the products were reacted with trifluoroacetic anhydride in pyridine to give 5′, O, N ditrifluoroacetylated derivatives in good yield. These resulting residues were subjected for hydrolysis by 5 % sodium bicarbonate. The nucleosides 1a, 1b, 1c and 1d were individually chromatographed on silica gel column. As an alternative, the conventional Grignard reactions[7] of their 2′, 3′–O–isopropylidene–5–chloromethyl uridine with each isobutyraldehyde, isovaleraldehyde, pivaldehyde, 3–phenyl propionaldehyde gave compounds 2a, 2b, 2c and 2d or 2, 3–isopropylidene–5–formyl uridine with each of methyl iodide, ethyl bromide, 2–propenyl chloride, 2–methyl–2–propenyl chloride and 3–methyl–2–butenyl bromide were also accomplished to afford compounds 3a, 3b, 3c, 3d, 3e respectively. Both of 5–formyl derivative of uridine and 5–chloro analogue were synthesized from 2′, 3′,–O–isopropylidene–5–hydroxy methyl uridine. Deprotection of the isopropylidene group can be performed as in literature[8]. The structure of the compounds were confirmed by spectral analysis.

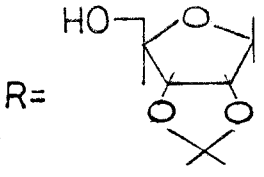
EXPERIMENTAL

Melting points are uncorrected. Mass spectra are recorded on Varian Mat 112. ^{1}HNMR spectra: Varian GEM–200 MH_2. TMS as internal reference (chemical shift in δ scale), DMSO as a solvent. 2′, 3′–O–isopropylidene–5–amino methyl uridine[9] and both of the corresponding 5–chlorlmetyl[10] and 5–formyl analogues[11] and 3–methyl–2–butenyl bromide[12,13] were prepared as reported in literature.



1 2 3

a, R^1=$(CH_3)_3CHCH_2$ a, R^2=$(CH_3)_2CH$ a, R^3=CH_3
b, R^1=$(CH_3)_3CHCH_2CH_2$ b, R^2=$(CH_3)_3CHCH_2$ b, R^3=CH_2CH_3
c, R^1=$(CH_3)_3CCH_2$ c, R^3=$(CH_3)_3C$ c, R^3=CH_2=$CHCH_2$
d, R^1=$Ph(CH_2)_3$ d, R^2=$Ph(CH_2)_2$ d, R^3=CH_2=CCH_2
e, R^3=CH_3, CH_3, CH_3–C=$CHCH_2$



Synthesis of compounds 1a–d:

A mixture of 2′, 3′,–O–isopropylidene–5–amino methyl uridine (1 mmol) and an aldehyde (isobutyraldehyde, iso valeraldehyde, pivaldehyde, and 3–phenyl propionaldehyde) (1 mmol) from each separately, sodium cyanoborohydride (0.5 mmol) and formic acid (9 ml) in dry methanol (10 ml) were stirred for 3 h at room temperature. The solvent was evaparated after addition few drops of triethyl amine to make it alkaline.

The dry residue was dissolved in pyridine (20 ml) and treated with trifluoro acetic anhydride (2.5 ml) for 16 h at 4°C. The solution was concentrated to 5 ml and stirred for 10 minutes with ice–cold 5 % solution of sodium bicarbonate (50 ml) and the mixture was extracted with chloroform (3 x 40 ml). The extract was dried, the solvent evaporated and the residue was chromatographed on a silica gel column. Table 1. Compounds 1a: Mass spectra: $^m/_e$ 463 (M^+). ^{1}HNMR spectra: 8.02 (br. s., 1H, H_6), 5.84 (br. s., 1H, H_1), 4.45 (s, 2H,–CH_2N), 4.2

(s, 2H,–NCH_2), 1.5, 1.35 (ds, 6H,–C $(CH_3)_3$), 1.25 (s, 1H, –CH), 1.15, 1.05 (s, 6H,–C $(CH_3)_2$).

Compound 1d:

^{1}HNMR spectrum: 8.35, 8.3 (ds, 1H, H_6), 7.25 (s, 5H, Ph^1, 6.2 (d.J = $2H_z$, 1H, H_1), 4.75 (s, 2H,–CH_2N–), 4.65 (m, 4H,–N CH_2CH_2), 1.55, 1.35 (s, 6H,–C $(CH_3)_2$).

Sythesis of Compounds 2a–d:

To a stirred solution contain 2′, 3′–O–isopropylidene–5–chloromethyl uridine (1 mmol) and Mg (1 mg) in ether (10 ml) was added dropwise to a solution of each of the following aldehydes (isobutyraldehyde, isovaleraldehyde, pivaldehyde, 3–phenyl propionaldehyde) (1 mmol) in ether (5 ml) at 0°C for 3h. Then aqueous NH_4Cl was added and the mixture was extracted with ether. The extract was dried with $MgSO_4$. Then filtered and the solvent evaporated. Table (1) compound 2a: Mass spectrum: $^m/_e$ 368 (M^+), ^{1}HNMR spectrum: 7.85, 7.80 (ds, 1H, H_6), 5.82 (br.s, 1H, $H_{,1}$), 3.48 (s, 1H, CHOH), 1.55, 1.40 (s, 6H,

Table 1. Physical Data of compounds 1–3

Comp.	mp°C	Yield %	Mol. Formula	Analysis Calculated / found		
				C	H	N
1a	201	30	$C_{19}H_{24}F_3N_3O_7$	49.24 49.15	5.18 5.12	9.07 8.94
1b	186	36	$C_{20}H_{26}F_3N_3O_7$	50.31 50.05	5.45 5.38	8.80 8.61
1c	194	42	$2_{20}H_{26}F_3N_3O_7$	50.31 50.05	5.45 5.38	8.80 8.61
1d	212	35	$C_{24}H_{26}F_3N_3O_7$	54.85 54.75	4.95 4.82	8.00 7.95
2a	172	51	$C_{17}H_{24}N_2O_7$	55.43 55.37	6.52 6.50	7.60 7.53
2b	188	42	$C_{18}H_{26}N_2O_7$	56.54 56.52	6.80 6.72	7.32 7.28
2c	182	36	$C_{18}H_{26}N_2O_7$	56.54 56.52	6.80 6.72	7.32 7.28
2d	176	48	$C_{22}H_{26}N_2O_7$	61.39 61.37	6.04 6.02	6.51 6.49
3a	195	45	$C_{14}H_{18}N_2O_7$	51.53 51.52	5.52 5.45	8.58 8.42
3b	189	38	$C_{15}N_{20}N_2O_7$	52.94 52.92	5.88 5.81	8.23 8.21
3c	177	35	$C_{18}H_{20}N_2O_7$	54.54 54.50	5.68 5.64	7.95 7.87
3d	192	32	$C_{17}N_{22}N_2O_7$	55.73 55.71	6.01 5.97	7.65 7.63
3e	204	40	$C_{18}H_{24}N_2O_7$	56.84 56.82	6.31 6.30	7.36 7.32

isopropylidene group), 1.25 (s, 1H,–CH), 1.04 (s, 6H,–$(CH_3)_2$). Compound 2c, Mass spectrum $^m/_e$ 382 (M^+), ^{1}HNMR spectrum: 8.2 (br.s, 1H, H_6), 5.95 (br. s, 1H, $H_{,1}$), 3.45 (s, 1H,–CHOH), 1.54, 1.3 (ds, 6H, C $(CH_3)_2$), 1.02 (s, 9H,–$C(CH_3)_2$).

Synthesis of compouds 3a–d:

Each of the halides (methyl iodide, ethyl bromide, 2–propenyl chloride, 2–methyl–2–propenyl chloride[14], 3–methyl–2–butenyl bromide) (1 mmol) and Mg (1 mg) in ether (10 ml) was stirred then during stirring dropwise addition of a solution of 2′, 3′–O–isopropylidene–5–formyl uridine was done then other steps as in the above mentioned procedure for the synthesis of compounds (2a–d) were followed. Table (1). Compound 3a: Mass spectrum: $^m/_e$ 362 (M^+). ^{1}HNMR spectrum: 8.05, 7.92 (ds, 1H, H_6), 5.92 (br.s, 1H, H_1), 4.08 (s, 1H,–CHOH), 1.45, 1.35 (s, 6H,–C $(CH_3)_2$), 1.27 (s, 3H,–CH_3). Furthermore, compound 3e Mass spectra: 380 (M^+). ^{1}HNMR spectra: 8.28, 8.12 (ds, 1H, H_6), 6.08 (s, 1H, C=CH), 5.85 (br.s, 1H, H_1), 3.95 (s, 1H,–CHOH), 3.14 (m, 2H, –CH_2), 1.75 (s, 6H, $(CH_3)_2$) 1.62–1.4 (s, 6H, isopropylidene group).

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