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SYNTHESIS OF 5-BROMO-2-METHYLTHIO-2`,-3` DIDEHYDRO-2`,3`-DIDEOXYURIDINE AND 5- BROMOISOCYTIDINE DERIVATIVES

Magdy A.Zahran

*Department of Chemistry, Faculty of Science, Menoufiea University, Shebin El-Koam, Egypt.

ABSTRACT

5-Bromo-2- methylthiouracil 1 was silylated and condensed with 1, 2, 3, 5-tetra-O-acetyl- B-D-ribofuranose 2 to give the 5-bromo-2-methylthiouridine 3, the reaction with saturated ammonia in methanol afforded two products 4a and 4b depending on the reaction conditions employed. When the uridine 4a was allowed to react with dimethoxytrityl chloride 6 was obtained which was submitted to the reaction with 1, 1- thiocarbonylimidazole where by the cyclic thiocarbonate 7 was obtained. The 2`, 3- didehydro 2,3-dideoxyuridine 9 was obtained throught the reaction of 7 with triethyl phosphite followed by deprotection of the DMT- group from nucleoside 8 by refluxing it in 80% CH3 COOH. Also the 5-bromo -isocytidine 10a -c were synthesized from the reaction of 3 with the appropriate amine

INTRODUCTION

The synthesis of nucleoside derivatives has recently received a considerable attebtion since the discovery that 3'- azido-3' deoxythymidine (AZT) and a number of related 2`,3`-dideoxynucleoside derivatives possess high anti-HIV activity[1,2]. The 2', 3',- didehydro-2`, 3`- dideoxynucleosides (d4 nucleosides) constitute one such class of uncleoside analogues that has been synthesized in this context, and indeed 2',3'-didehydro- 3'-deoxythymidine (d4T) and 2',3'- didehydro-2`,3`-dideoxycytidine

(d4C) have both been found to be powerful anti-HIV-agents [1].

Methods have been developed for the transformation of both 2',-deoxyribonucleosides [3-13] and ribonucleosides [14-18] into the corresponding d4 uncleosides. In general, these transformations involve the modification only of the sugar moiety of the nucleoside with the aglycone remaining unchanged.

Recently, much more attention have been given to the sulfur modified nucleoside derivatives [14, 15] as well as, the sulfur modified oligonucleotides owing to the stability of the double helical structures with their complementary strand [16]. On the other hand, the 2-alkylthiouracil nucleoside derivatives are also considered as a verstile starting materials for synthesizing the corresponding isocytidine derivative, since, the alkythio-group is considered as a good leaving group and could be easily substituted with nucleophiles Kanai and Maruyama [18] reported that, the isocytidine derivatives can be synthesized by treating 6,2'- anhydro derivatives with liquid ammonia for about two weeks. Delia and Beranek [19] snthesized the isocytidine derivatives by the reaction of 2,2'-anhydro pyrimidine nucleosides with amine nucleophiles. Also, Hirota *et.al.*[20] investigated the reactivities of 2',5'- dichlorouridines toward various nucleophiles and obtained some isocytosine derivatives by the use of amines as nucleophiles. In this investigation, an easy and convienient route to synthesize the isocytidine dervatives *via* the reactions of amines with 5-bromo 2-methylthiouracil nucleosides 10a-c as well as the 5-bromo 2- methylthio-2',3' didehydro-2',3' dideoxyuridine 9 is reported.

RESULTS AND DISCUSSION

In this investigation, a modified method for the synthesis of 5-Bromo -2- methylthiouracil 1 Silylation of 1 with 1,1,1,3,3,3 hexamethyl- disilazane (HMDS) was carried out acording to the procedure described by Vorbruggen *et.al.*[22]. Condensation of 1,2,3,5-tetra-*O* - acetyl-B-D- ribofuranose 2 with the silylated base was carried out according to the Vorbruggen conditions [23] in dry acetonitrile, using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as a catalyst to yield 3. The deprotection of nucleoside 3 using ammonia in methanol at room temperature to gives 4b, whose ^{1}H and ^{13}C NMR spectra showed singlet at 3.9 ppm and 59.74 ppm respectively charcteristic of a methoxy group. On the other hand, if the deprotection is carried out using ammonia in methanol at O° C for 10 minutes the methylthio- group survived, also the nucleophilic attack of the methoxy group could be hindered and the 2-methythio-nucleoside 4a was obtained. ^{1}H and ^{13}CNMR spectra of this product showed singlet at 2.51 ppm and 14.36 ppm respectively charcteristic of the methylthio- group.

Treatment of 4a with potassium cyanide afforded 5- cyano- 2-methylthiouridine 5, whose ^{1}H,^{13}C- NMR and the mass spectrum are in accordance with the reportd nucleoside [24]. It was of interest to explore the procedure of simultanous deoxygenation of ribonucleosides *via* cyclic thiocarbonate which was previously applied [25] to uridine. Therefore, the nucleoside 4a was allowed to react with 4,4' dimethoxy trityl chloride in dry pyridine and in presence of catalytic amount of 4- dimethylaminopyridine to give the corresponding 5'-0 protected nucleoside 6. The reaction of nucloside

6 with 1,1'- thiocarbonylimidazole in DMF afforded the cyclic thionocarbonate7, which upon treatment with triethyl phosphite yielded the 2',3'- unsaturated nucleoside 8. The deprotection of 8 was carried out in 80% acetic acid to furnish the correspnod 2',3'- unsaturated nucleoside 9.

When the nucleoside 3 was allowed to react with primary amines *viz* methylamine, propylamine and butylamine, nucleophilic attack at the methylthio group occured with the formation of the corresponding isocytidine derivatives 10a -c.

EXPERIMENTAL

The NMR sepectra were recordeed on a Bruker AC 250FT NMR Spectrometer. Chemical shifts are reported in ppm. FAB mass spectra were recorded on a varian MAT 311A spectrometer. Silica gel TLC were performed on 60F- 254 precoated plates (merck silica gel(0.040-0.063). All solvents were distilled.

5-Bromo-2-Methylthio-1- (2, 3, 5 tri-O-acetyl- D- ribo-furansoyl) Pyrimidin -4 (IH) one 3

5-Bromo-2-methylthio pyrimidin-4-one (5.30g,24 mmol) was treated with 1, 1, 1, 3, 3, 3-hexamethyldisilazane (120 ml) and $(NH_4)_2SO_4$ (180mg) at reflux temperature for 1h. The solvent was removed in *vacuo* and the residue was dissolved in dry MeCN (60ml). 1,2,3,5 Tetra-o-acetyl-B- ribofuranose 2 (5.13g 16.2mmol) was added and the reaction mixture was cooled to -30°C, TMS triflate (3.9ml,19.5mmol) in dry MeCN (15ml) was added dropwise with stirring. The mixture was stirred for 30min. at-25°C and then at

room tempearture for 1h., diluted with CH_2CL_2 and extracted with ice-cold sat. aq. $NaHCO_3$ (900ml). The organic phase was separated, washed with cold H_2O (3x300ml), dried over $Na_2 SO_4$ and evaporated to give the crude product which was chromatographed on a silica gel column with CHCL3 7.81 g (68%) as a white foam. FABMs ($CDCL_3$+ 3.nitrobenzylalcohol) : *m/z* 480 ($M+H^+$) ^{1}H-NMR ($CDCL_3$) δ 2.07 (3H,s,Ac), 2.15 (3H,s ,Ac) 2.19 (3H,s,Ac), 2.51 (3H,s,SCH3) 4.34 (3H,m,4'-H,5'-H), 5.43 (2H,m,2'-H,3'-H), 5.72 (IH,d,J= 6.5Hz,1`-H), 8.35 (IH,s,6-H). ^{13}C-NMR ($CDCL_3$) : 418.36 (SCH3), 20.08. 20.33,2.55 (3xAc), 63.03 (C-5'), 69.97 (C-3'), 72.38 (C-2'), 80.01 (C-4'), 90.10 (C-1'), 113.60 (C-5), 144.69 (C-6), 163.48 (C-2), 169.73 (C-4).

5-Bromo-2- Methylthio-1- (D-ribofuranosyl) Pyrimidin-4 (IH) one 4a.

Compound 3 (1.05g,2.2mmol) was treated with saturated solution of ammonia in MeOH (20ml) at O°C. After stirring at room temparature for 1/2h, the solvent was removed in *vacuo* and the residue was chromatographed on a silica column with 8-10% MeOH/$CHCL_3$ to give 4a. 0.44g (57%) as white foam. FAB Ms (DMSO + 3nitrobenzylalcohol) : m/z 354 ($M+H^+$). ^{1}H-NMR (DMSO) δ 2.51 (3H,s,SCH3), 3.56 (2H,m,5'-H) 3,88 (1H,m,4'-H), 4.01 (1H,m,3'-H), 4.21 (1H,m,2'-H) 5.55 (IH,d,J=6.2Hz,I'-H), 7.80 (IH,s,6-H). ^{13}C-NMR (DMSO) : δ 14.36 (SCH3), 61.28 (C-5') 70.41 (C-3') 73.77 (C-2') 85.10 (C-4`), 91.91 (C-1`), 118.22 (C-5), 145.08 (C-6`). 163.92 (C-2`), 169.82 (C-4`).

5- Bromo-2-mcthoxy-1 (D-ribofuranosyl) pyrimidin-4 (1 H) one 4b.

Compound 3 (1,05g, 2.2 mmol) was treated with saurated

solution of ammonia in MeOH (20 ml) at O°C with strring at room temperature for 3h., the solvent was removed in *vacuo* and the residue was chromatographed on a silica gel column with 8-10% MeOH in CHCl3 to give 4b. 0.51g (71%) as a white foam. FAB Ms (DMSO + 3. nitrobenzylalcohol) : m/z 338 (M+ H^+). 1H-NMR (DMSO) : δ 3.57 (2H,m, 5`-H), 3.81 (1H, m, 4`-H), 3.90 (3H,s, OCH3), 4.00 (1H, m, 3`-H), 4.16 (1H, m, 2`-H), 5.61(1H, d, J= 6.2 Hz, 1`-H), 7.97 (1H,s,6-H). $^{13}$C-NMR (DMSO) : δ 59.74 (OCH3), 61.27 (C-5`), 70.39 (C-3`), 73.75 (C-2`), 85.19 (C-4`), 91.21 (C-1`), 118.18 (C-5), 144.91 (C-6), 163.88 (C-2), 169.32 (C-4).

5-Bromo-1-[5`-0-(4,4`-dimethoxytrity1)-D-ribo-furanosy1)-2-methylthiopyrimidin-4 (1H) one 6.

To a solution of 4a (3.17g, 9mmol) in 45ml dry pyridine, 4.4` - dimethoxytrityl chloride (3.15g, 9.3 mmol) and 4 - dimethylamino-pyridine (0.61g, 5mmol) were added, the mixture was stirred overnight at room temperature. The reaction mixture was poured into ice- water and extracted with chloroform. The combined organic extracts were dried over (MgSO4) and chromatographed through a silica gel column with2-4% MeOH in $CHCl_3$ to give 3.47g (59%) of a white product. FAB Ms (CDCl3 + 3-nitrobenzylalcohol) : *m/z* 656 (M+ H^+). ^{1} H-NMR (CDCl3) : δ 2.57 (3H, s, SCH_3), 3.39-3.52 (3H, m, 4` - and 5`-H), 3.75(6H, s, 2xOCH_3) 4.26 (1H, m, 3`-H), 4.44 (1H, m, 2`-H), 4.71 (1H, br. m, OH), 5.86 (1H,d, J=5.28 Hz, 1`-H), 6.88-7.44 (arom., 14H). $^{13}$C- NMR ($CDCl_3$) 15.50 ($SCH_3$), 55.12 (2x $OCH_3$), 71.52 (C-5`), 74.88 (C-3`), 84.99 (C-2`), 87.08 (C-4`), 91.56 (C-1`), 107.24 (C-5), 113.35, 123.79, 126.90, 127.86, 128.10, 129.89, 135.11, 135.27, 139.30, 144.05, 149.35, (arom.& C-6), 158.51 (C-2),

164.33 (C-4).

5-Bromo-1-[5`-0-(4,4` - dimethoxytrityl) -2`, 3`-O -(cyclicthio-carbonate) - D- ribofuranosyl] 2-methy- thio-pyrimidin-4 (1H)one 7.

To a solution of compound 6 (2.62g, 4mmol) in anhydrous acetonitrile (100ml), was 1,1- thiocarbonylimidazole (4.05g, 9 mmol) was added, the mixture was stirred at room temperature under nitrogen overnight. The solvent was evaporated and the residue was chromatoraphed through a silica gel column with 0.0.5% MeOH/CHCl3 to give 1.86g (67%) of white foam. FAB Ms (DMSO= 3-nitrobenzyllcohol) : *m/z* 698 (M + H^+). ^{1} HNMR (DMSO) : δ 2.54 (3H, s, SCH3), 3.80 (6H,s,2xOCH3), 3.83 (2H,d,J=5.57 Hz, 5-H) 4.55-4.75 (1H,m, 4-H), 5.79 (1H, dd, J=2.35, 7.32 Hz, 3`-H), 6.28 (1H, dd, J= 1.76, 7.32 Hz, 2-H) 6.59 (1H, d, J= 1.76 Hz, I`-H), 7.31 (arom., 14H).

5-Bromo-1-[2`,3`,-didehydro-2`,3`-dideoxy-5`-O(dimethoxytrityl)-D-ribfuranosyl [2-methyl-thio- pyrimidin 4 (1H) one 8.

A solution of 7 (1.67g, 2.4 mmol) in triethyl-phosphite (30 ml) was heated to gentle reflux in nitrogen atmosphere for 1h. Excess reagent was evaporated under reduced pressure , and the residue was purified by flash chromatography on a silica gel column using $CHCl_3$ / MeOH (15/1) to give 0.58 g 39% FAB Ms ($CDCl_3$ + 3 nitrobenzylalcohol) : *m/z* 622 (M + H+). 1H-NMR ($CDCl_3$). δ 2.55 (3H, s, SCH_3), 3.79 (2H, d,J= 3.8 Hz, 5`-H), 3.84 (6H,s, 2x$OCH_3$), 4.96 (1H,m, 4`-H), 6.22 (1H,dt, J=1.5,5. 86hz, 2`-H), 6.52 (1H, dt, J= 1.5,5.86 Hz, 3`-H), 6.95 (1H,m, 1`-H), 7.33 (arom, 14H).

5-Bromo-1-[2`,3`-didehydro-2`-3`-dideoxy-D-ribfuranosly]-2-methyl-thio- pyrimidine 4 (1H) one 9.

Compound 8 (0.49, 0.8 mmol) was deprotected in 80% acetic acid (10ml) by heating at 80°C for 10min . The solvent was removed under reduced pressure, and the residue was purified by chromatography using $CHCl_3$-MeOH (20 : 1) to obtain 145 mg (57%) of 9 FAB MS ($CDCl_3$ + nitrobenzylacohol) m/z 320 ($M + H^+$) ^1H NMR ($CDCl_3$) : δ 2.45 (3H,s, SCH3), 3.69 (2H, dd, J=3.52, 4.98Hz, 5`-H), 4.75 (1H, m, 4` - H), 4.95 (1H, t, J=4.98 Hz, 5`-OH), 5.85 (1`H, br d, J=6.2 Hz, 2`-H) 6.40 (1H, br, d, J= 6.2 Hz, 3`-H), 6.80 (1H, m, 1`-H) 7.72 (1H, s, 6-H).

Preparation of 5- Bromoisocytidines 10a-c.

A solution of 3 (0.57g, 1.2 mmol) in an excess of the appropriate amine (10ml) was stirred overnight. The solvent was removed in *vacuo* and the residue was chromatographed on a silica gel column using 6-8% MeOH in $CHCl_3$ to remove the impurities and then the product obtained was crysallised from MeOH to give 10a- c in 42-66% yield .

5- Bromo-N^2- methylisocytidine 10a

209 mg (52%). FAB Ms (DMSO + 3nitro-benzyl-alcohol) : m/z, 337 ($M+H^+$). ^1H-NMR (DMSO) : δ 2.73 (3H, d, J= 4.1 Hz, $NHCH_3$), 3.63 (2H,br s, 5`-H), 3.96 (1H, m, 4`-H), 3.98 (1H, m, 3`-H) 4.17 (1H, t, J=5.8Hz, 2`-H), 5.25 (1H,br s, OH), 5,43 (1H, d, J= 6.6Hz, 1`-H), 5.49 (2H, br, s, 2 xOH) 7.26 (1H, q, J=4.1 Hz, NH), 8.16 (1H, s, 6-H). $^{13}C$-NMR (DMSO) : δ 28.24 ($NH-CH_3$), 60.55 (C-5`). 69.88

(C-3`), 72.41 (C-2`), 86.06 (C-4`), 91.98 (C-1`) 102.07 (C-5), 139.29 (C-6), 152.64 (C-2), 163.92 (C-4).

5-Bromo-N^2- propylisocytidine 10 b

183 mg (42%); FAB Ms (DMSO_ 3 nitrobenzylalcohol) : m/z 365 ($M+H^+$). ^{1}H.NMR (DMSO) : δ 0.85 (3H, t,J=7.3Hz, CH_3), 1.55 (2H,m,CH_2), 2.49 (2H, q, J=1.7 Hz, NHCH2). 3.62 (2H, br s, 5`-H), 3.97 (1H, m, 4`-H), 4.01 (1H, m, 3`-H), 5.28 (1H, br s, OH) 5.46 (1H, d, J= 6.8 Hz, 1`-H), 5.51 (2H, br s 2xOH) 7.26 (1H, br NH), 8.14 (1H,s, 6-H) ^{13}C-NMR (DMSO) : δ 11.20 (CH_3) 21.48 (CH_2), 42.71 (NCH_2), 60.60 (C-5`), 69.92 (C-3`), 72.35 (C-2`), 86.20 (C-4`), 92.34 (C-1`), 102.05 (C-5), 139.57 (C-6), 152.12 (C-2), 163.89 (C-4).

5- Bromo- N^2- butylisocytidine 10c

299 mg (66%) FAB Ms (DMSO + 3- nitrobenzylalcohol) : *m/z* 379 (M+ H+). 1HNMR (DMSO) δ 0.88 (3H, t, J=7. 1Hz, CH3), 1.28 (2H, m, CH2), 1.47 (2H, m, CH2), 2.50 (2H, q, j=1.5 Hz, NCH2), 3.24 (2H, m, 5`-H), 3.96 (1H, m, 4`-H), 3.99 (1H, m, 3`-H) 4.19 (1H, t, j= 6.9 Hz, 2`-H), 5.28 (1H, br, s, OH), 5.45 (1H, d, J= 6.7 Hz, 1`-H), 5.51 (2H, br, s, 2xOH), 7.22 (1H, br, s, NH), 8.14 (1H, s, 6-H). $^{13}$C-NMR δ 13.69 ($CH_3$), 19.48 ($CH_2$), 30.42 ($CH_2$), 40.74 ($NCH_2$), 60.61 (C-5`), 69.94 (C-3`), 72.40 (C-2`) 86.23 (C-4`), 92.36 (C-1`), 102.03 (C-5), 139.59 (C-6), 152.13 (C-2), 163.95 (C-4).

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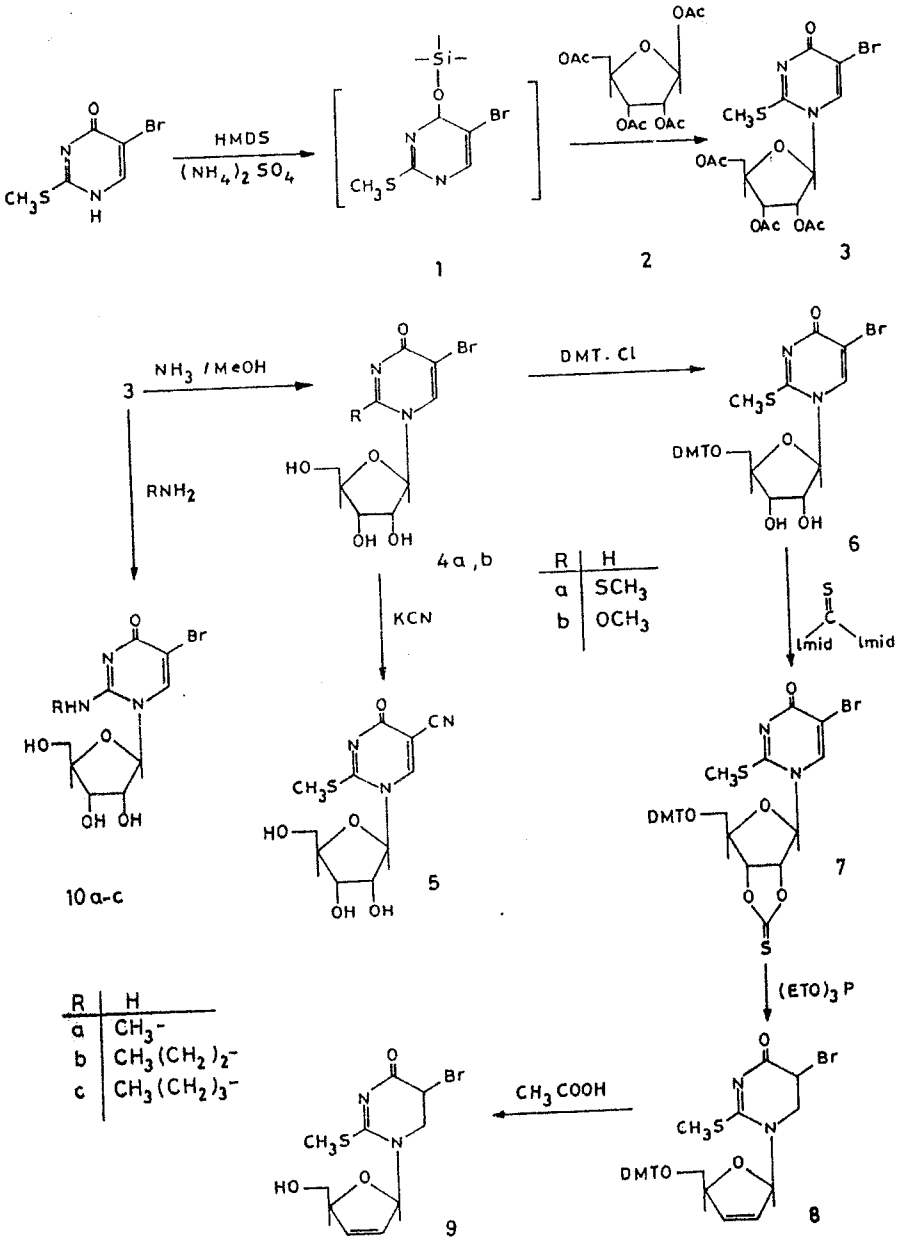
HMDS
$(NH_4)_2SO_4$
1
2
3
NH_3 / MeOH
RNH_2
4a, b
DMT. Cl
6
KCN
5
10a-c
7
$(ETO)_3P$
8
CH_3COOH
9
R | H
a | SCH_3
b | OCH_3
R | H
a | CH_3^-
b | $CH_3(CH_2)_2^-$
c | $CH_3(CH_2)_3^-$

ملخص عربى

تخليق ٥ – برومو – ٣ ميثيل ثيو `٢ ، `٣ داى ديهيدرو- `٢، `٣ داى ديوكسى يوريدين وكذلك مشتقات ٥ – بروم ايزوسيتدين

أجرى لمركب ٥ – برومو – ٢ ميثيل ثيويوراسيل (١) سيلله ثم وتكاثف مع الريبو فيورانوز (٢) ليعطى ٥–برومو – ٢ ميثيل ثيويوريدين (٣). وقد درست فاعلية مجموعة الميثيل ثيو للاستبدل عن طريق تفاعل (٣) مع محلول الأمونيا فى الميثانول ليعطى نيكلوزيد (٤ب) تحت ظروف تفاعل تختلف عن ظروف التفاعل للحصول على (٤أ) والذى بقيت مجموعة الميثيل ثيو به. وعند تفاعل نيكلوزيد (٤أ) مع ثنائى الميثوكسى ترتيل كلوريد يعطى النيكلوزيد (٦) والذى يتفاعل مع ١ ، ١ ثيوكربونيل الاميدازول مكونا الثيوكربونات الحلقى (٧). كما أمكن الحصول على المركب ˜٢، ˜ ٣ داى ديهيدرو ˜٢، ˜ ٣ داى ديوكسى يوريدين (٩) ثم يتفاعل (٧) ثم مع ثلاثى إيثيل الفوسفيت متبوعا بالتفاعل مع حمض الخليك ٨٠٪ مع التسخين . كما أجرى ايضا تفاعل للمركب (٣) مع بعض الأمنيات الأولية حيث حدث استبدال نيكلونيلى لمجموعة الثيوميثيل مع تكوين مشتقات ٥ – برومو ايزوسيتدين المناظرة (١٠أ–ج).