

A Facile Synthesis of 5-Iodo-6-Substituted Pyrimidines from Uracil-6-Carboxylic acid (Orotic acid)

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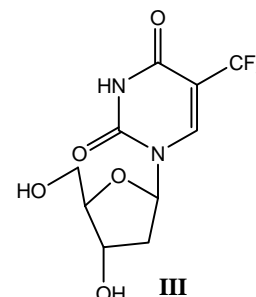
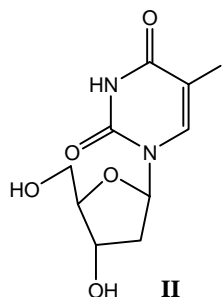
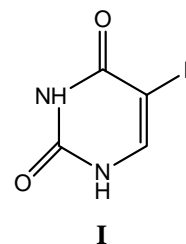
ABSTRACT: 2,4-Dichloro-pyrimidine-6-carbonylchloride (**2**) was synthesized by refluxing orotic acid (**1**) with phosphorus oxychloride and phosphorus pentachloride. Compound (**2**) underwent a smooth Friedel-Craft's reaction with a number of substituted benzene to yield 2,4-Dichloro-6-arylpyrimidines **6** and **7** which were converted to the corresponding dimethoxy pyrimidines (**8**, **9**) on treatment with sodium methoxide in methanol. The iodination reaction on 2,4-dimethoxy-6-arylpyrimidines (**8**, **9**) was attempted by several methods but only NIS-TFA-TFAA method gave the desired products, 2,4-dimethoxy-5-iodo-6-arylpyrimidine (**10**, **11**) in good yields.

Key words: Synthesis, 5-Iodo-6-Substituted pyrimidines, Orotic acid.

INTRODUCTION

Idoxuridine (IDU) **I** and Trifluorothymidine (TFT) **II** were the first pyrimidine nucleoside¹ analogues ever shown to be effective against herpesviruses in particular HSV-1. They were also the first to be approved for clinical use, and are, as of today, still used as eye drops in the topical treatment of HSV-1 keratitis. However, neither IDU nor TFT can be used systematically because they are too toxic, especially to the bone marrow. The importance of 5-substituted derivatives of uracil as anticancer and antiviral (including anti-AIDS) agents is well-established. For example, 5-fluorouracil (5-FU) **III** and the corresponding 2-deoxyribonucleoside (FUdR)² have been of importance in cancer chemotherapy for decades.

Dihydroalkoxybenzoyloxypyrimidines (DABOs) are a new class of specific inhibitors of human immunodeficiency virus type 1 (HIV-1) which possess a benzyl moiety and an alkyl (cycloalkyl) chain linked through an oxygen bridge to the uracil or



thymine base.³⁻⁵ Various thio analogues⁶ of dihydroalkoxybenzoyloxypyrimidines (DABOs), a new class of non-nucleoside reverse transcriptase inhibitors, were found to be selectively inhibit the HIV-1 multiplication *in vitro*. 5-Isopropyl-2-[(methylthiomethyl)thio]-6-(benzyl)-pyrimidin-4-(1*H*)-one⁷ was found to be potent anti-HIV activity with an IC₅₀ value of less than 1nM for inhibition of

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HIV replication-without any evidence of cytotoxicity. 6-Substituted-2-[(4-hydroxybutyl)amino]-4(3*H*)-pyrimidinones was found as HIV-1 RT active inhibitor.⁸ Several 6-benzyl 1-[(2-hydroxyethoxy)methyl]-6-phenylthio thymine (HEPT) have shown potent and selective *in vitro* activity against HIV-1.⁹ The antiviral activities of a series of 6-arylmethyl-1-allyloxymethyl-5-alkyluracil derivatives were found.¹⁰ Iodo derivatives of pyrimidines and uracils have been utilized for the synthesis of corresponding carbon substituted derivatives.¹¹ Thus, the availability of suitable iodo derivatives of pyrimidines and uracils become important. Recently, we have reported a synthesis of 4-acyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidines (6-acyluracils and 4-acyl-6-aryl-2-oxo-2,3-dihydropyrimidines).¹² In connection to our studies on orotic acid, we needed a large quantity of 5-iodo-2,4-dimethoxypyrimidine.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes on Gallenkamp (England) melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu FTIR spectrophotometer and UV spectra were recorded in dry EtOH with a Shimadzu visible spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DPX - 400 spectrometer (400-MHz) using TMS as internal reference. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F₂₅₄ (E. Merck), and the spots were visualized with UV light. Column chromatography was performed on silica gel (60-120 mesh). Elemental analyses (C, H, N) were carried out on a Perkin- Elmer 240 C analyser. Orotic acid, POCl₃, primary arylamine, NIS, TFA, TFAA and other reagents were purchased from E. Merck (Germany) and Fluka (Switzerland).

Preparation of 2,4-Dichloropyrimidine-6-carbonyl chloride (2). A mixture of 2,4-dioxo-1,3,5-trihydropyrimidine-6-carboxylic acid (orotic acid) 5.0 g (0.032 mol) and phosphorus oxychloride (POCl₃, 40 ml) was refluxed for 24 hours at 105-108 °C, then phosphorus pentachloride (15 g, 0.072 mol) was added into the reaction mixture.¹³ The mixture was

then refluxed for 24 hours. Phosphorus oxychloride was recovered under reduced pressure. The residue was distilled under reduced pressure and 2, 4-dichloropyrimidine-6-carbonyl chloride (**2**), (4.0 g) was obtained as dense colorless liquid.

Synthesis of 2,4-dichloro-6-arylpyrimidines (6,7). To the substituted benzenes **4**, **5** (60 ml) anhydrous aluminium chloride (6 g) was added at 0 °C. To the cold solution 2, 4-dichloropyrimidine-6-carbonyl chloride (**2**) (6 g) was added slowly. The mixture was allowed to warm up to room temperature and stirred for 5-6 hours and poured into cold hydrochloric acid solution (2 ml, 12 M HCl in 60 ml water). The mixture was extracted with chloroform (3 x 25 ml). The combined organic layer was washed with sodium bicarbonate, distilled water and dried over anhydrous sodium sulfate. After removal of solvent, the product was purified by column chromatography over silica gel and then it was crystallized to afford the desired products **6** and **7** in good yield.

2,4-Dichloro-6-*p*-bromobenzoylpyrimidine (6).

Colourless needles (CCl₄), mp 122-124 °C; IR: ν_{\max} (KBr) 3112.9, 3070.5, 1664.5, 1587.3, 1548.7, 1519.8, 1401.2, 1325.0, 1303.8, 1325.0, 1246.9, 1217.0, 1181.3, 1071.4, 1011.6, 975.9, 847.7, 833.2, 790.8, 773.4, 742.5, 691.4, 606.6, 484.1 cm⁻¹; UV: λ_{\max} 284.80 nm; ¹H NMR (400 MHz CDCl₃) δ 7.67(2H, d, *J* = 8.5 Hz, Ar-H), 7.88 (1H, s, C-5H), 8.01(2H, d, *J* = 8.5 Hz, Ar-H); ¹³C NMR (100 MHz CDCl₃) δ 119.7 (Py-CH), 130.2, 132.0 (Ar-H), 132.4, 132.6 (Ar-C), 160.2, 164.2, 164.6 (Py-C), 188.1 (C=O).

Anal. Calcd for C₁₁H₅N₂OBrCl₂ : C, 39.80; H 1.52; N, 8.44. Found: C, 39.73, H, 1.58; N, 8.34.

2,4-Dichloro-6-*p*-methoxyl benzoyl pyrimidine (7).

Yellow crystals (CCl₄); mp 110 -112 °C; IR: ν_{\max} (KBr) 1652.9, 1596.9, 1552.6, 1519.8, 1508.2, 1323.1, 1278.7, 1257.5, 1168.8, 1118.6, 1033.8, 846.7, 781.1, 756.0, 746.4 and 607 cm⁻¹; UV (EtOH): λ_{\max} 278.80, 224.60 nm; ¹H NMR (400 MHz, CDCl₃) δ 3.90 (3H, s, ArOCH₃), 6.98 (2H, d, *J* = 9 Hz, ArH), 7.80 (1H, s, C-5H), 8.12 (2H, d, *J* = 9 Hz, ArH).

Preparation of 2,4-dimethoxy-6-arylpurimidine (8, 9). 2, 4-Dichloro-6-*p*-arylpurimidine **6**, **7** (1.6506 mmol) was added dropwise to an ice-cold solution of sodium (0.1138g) in dry methanol (30 mL). The whole solution was refluxed at 80 °C for 4 hours. A solid mass was obtained after removal of solvent. To this solid mass 100 mL water was added and neutralized by dilute hydrochloric acid. Then it was extracted with chloroform (50 mL × 3). The organic layer was then washed with 10% NaHCO₃ water and dried over Na₂SO₄ (anhyd.). After removal of the solvent solid was obtained and crystallized from methanol. A needle shaped crystal was obtained in good yield.

2,4-Dimethoxy-6-*p*-bromobenzoyl pyrimidine (8). Colourless needle (methanol); yield 450 mg. mp 121-122 °C; IR: ν_{\max} (KBr) 1674.1, 1582.5, 1559.3, 1484.1, 1463.9, 1395.4, 1386.4, 1349.1, 1259.4, 1205.4, 1105.1, 974.9, 835.3, 763.8 cm⁻¹; UV(EtOH) : λ_{\max} 277.20 nm; ¹H NMR (400 MHz, CDCl₃) δ 4.01(3H, s, OCH₃), 4.04 (3H, s, OCH₃), 6.93 (1H, s, C-5H), 7.63 (2H, d, *J* = 8.6 Hz, ArH), 8.00 (2H, d, *J* = 8.6 Hz, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 54.3 (OCH₃), 55.1 (OCH₃), 102.0 (C-5H), 128.8 (Ar-C), 132.2 (Ar-CH), 133.9 (Ar-C), 163.1, 165.0, 172.7 (Py-C), 190.8 (C=O).

Anal. Calcd for C₁₃H₁₁N₂BrO₃: C, 48.32; H, 3.43; N, 8.60. Found: C, 48.97; H, 3.42; N, 8.50.

2,4-Dimethoxy-6-*p*-methoxybenzoyl pyrimidine (9). Light yellow needle (methanol); mp 139-141°C; IR: ν_{\max} (KBr) 3190, 1658.7, 1598.9, 1558.4, 1427.2, 1388.7, 1350.1, 1182, 1182.3, and 1095.5 cm⁻¹; UV(EtOH): λ_{\max} 296.60, 214.20 nm; ¹H NMR δ (400 MHz, CDCl₃) 3.88 (3H, s, Ar-OCH₃) 4.02 (3H, d, OCH₃), 4.03 (3H, s, OCH₃), 6.85(H, s, C₅-H), 6.96 (2H, d, *J* = 8 Hz, Ar-H) 8.13 (2H, d, *J* = 8 Hz, Ar-H)

Preparation of 2,4-dimethoxy-6-methyl orotate (3). 2,4-Dichloro pyrimidine-6-carboxyl chloride **2** (1m mol) in dry methanol (50 ml) was added drop wise to an ice-cold solution of sodium (1.95g, 0.084 mol) in dry methanol (50 ml). The whole solution was stirred at room temperature for 4 hours. After removal of solvent a solid mass was obtained. To this

solid mass 100 mL water was added and neutralized by dilute hydrochloric acid. Then it was extracted with chloroform (50 mL × 3). The organic layer was then washed with water, 10% NaHCO₃ and dried over anhyd. Na₂SO₄. After removal of chloroform the solid mass was obtained and crystallized from methanol. A needle shaped crystal was obtained. mp 106-107°C; IR: ν_{\max} (KBr) 1724.2, 1600.8, 1569.0, 1439.0, 1435.9, 1393.5, 1271.0, 1286.4, 1353.9, 1119.6, 1125.1, 1102.2, 780.2, and 772.4 cm⁻¹; UV: λ_{\max} 280.40, 225.40 nm; ¹H NMR (400 MHz, CDCl₃) δ 3.97 (3H, s, OCH₃), 4.03 (3H, s, OCH₃), 4.07 (3H, s, COOCH₃), 7.07 (1H, s, C-5H); ¹³C NMR (100 MHz, CDCl₃) δ 52.9 (OCH₃), 54.3 (OCH₃), 55.0 (COOCH₃), 103.1 (Py-H), 156.7 (Py-C), 164.4 (Py-C), 165.7 (Py-C), 172.7(C=O).

Anal. Calcd for C₈H₁₀N₂O₄: C, 48.48, H, 5.09, N, 14.14. Found: C, 48.90; H, 5.02, N, 13.76.

Synthesis of 2, 4-dimethoxy-5-iodo-6-arylpurimidines (10, 11). A mixture of 2, 4-dimethoxy-6-*p*-arylpurimidine (500 mg, 1.6954 mmol) trifluoroacetic acid (50 ml and trifluoroacetic anhydride (1 ml was refluxed for 20 minutes. *N*-Iodosuccinimide (1.2 equiv, 457.74 mg) was added and the reaction mixture was further refluxed for 8 hours. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (300 ml, and successively washed with water (50 ml), saturated sodium bicarbonate (2×40 ml, saturated sodium thiosulfates (2 × 40 ml and water (2 × 40 ml. The chloroform layer was dried over anhyd. Sodium sulfate and concentrated to dryness to give 1.15g crude mass. The crude mass was crystallized from methanol.

2,4-Dimethoxy-5-iodo-6-*p*-bromobenzoyl pyrimidine (10). Light yellow crystals, mp 185-186 °C; IR: ν_{\max} (KBr) 2958.0, 1681.8, 1576.7, 1588.3, 1555.5, 1479.3, 1449.4, 1403.1, 1379.0, 1364.5, 1248.8, 1227.6, 1069.5, 1017.4, 1010.6, 979.8, 931.6, 849.6, 784.0 and 768.6 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.97 (3H, s, OCH₃), 4.10 (3H, s, OCH₃), 7.62 (2H, d, *J* = 7.2 Hz, Ar-H), 7.73 (2H, d, *J* = 7.2 Hz, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 55.6

(OCH₃), 55.7(OCH₃), 65.68 (Py-C), 129.90 (Ar-C), 131.6, 132.27(Ar-CH), 133.33 (Ar-C), 165.8, 168.6, 169.7 (Py-C), 191.8 (C=O).

2,4-Dimethoxy-5-iodo-6-*p*-methoxy-*m*-iodo-benzoyl pyrimidine (11). Light yellow crystals, mp 1181-119 °C; IR: ν_{\max} (KBr) 1651.0, 1577.7, 1562.25, 1477.4, 1380.9, 1352.0, 1269.1, 1201.6, 1049.2 and 767.6 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.96 (3H, s, Ar-OCH₃), 4.03 (6H, s, C-2, OCH₃ and C-4 OCH₃), 6.86 (1H, d, *J* = 8.6 Hz, Ar-H), 8.18 (1H, d, *J* = 8.6 Hz, Ar-H), 8.69 (1H, s, Ar-H); ¹³C NMR (100 MHz, CDCl₃) δ 54.47 (OCH₃) 55.34 (OCH₃), 56.78 (OCH₃), 85.53 (Py-C), 102.17 (Ar-CH), 110.02, 129.86 (Ar-C), 133.23, 142.87(Ar-CH), 142.98 (Ar-C), 162.27, 163.75, 172(Py-C) and 189.03 (C=O).

2,4-Dimethoxy-5-iodo-6-methylorotate (12). 2, 4-Dimethoxy-5-iodo-6-methyl orotate **12** was prepared from 2, 4-dimethoxy-6-methylorotate **3** (2.2 g 0.1138 mmol) by using the above iodination procedure. The crude mass was crystallized from methanol. Light yellow crystals, mp 167-168 °C; IR: ν_{\max} (KBr) 1728.1, 1553.6, 1486.1, 1454.2, 1437.8,

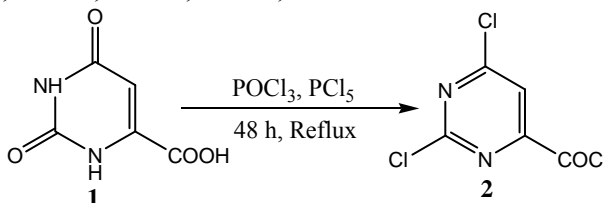
1383.8, 1354.9, 1234.4, 1198.7, 1169.7, 1108.0, 1039.6, 1016.4, 965.3 and 786.9 cm⁻¹; UV(EtOH): λ_{\max} 286.80, 234.80 nm; ¹H NMR (400 MHz, CDCl₃) δ 3.92 (3H, s, OCH₃), 3.95(3H, s, OCH₃), 4.00 (3H, s, COOCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 53.0 (OCH₃), 54.3 (OCH₃), 55.5 (OCH₃), 66.57, 103.6, 162.0, 165.38, 169.97(C=O).

Anal. Calcd for C₈H₉N₂O₄I: (C, 29.65, H, 2.80; N, 8.64. Found: C, 30.17, H, 2.80, N, 8.66.

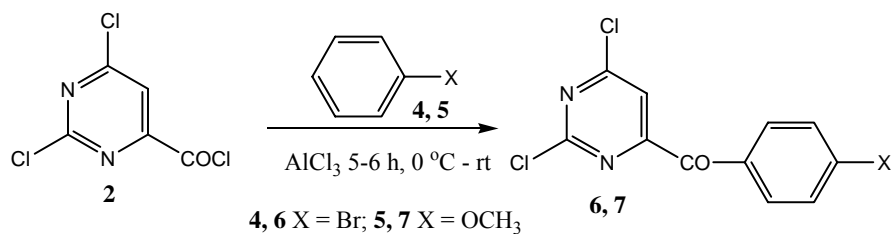
RESULTS AND DISCUSSION

2,4-Dichloropyrimidine-6-carbonyl chloride (**2**) was synthesized according to the procedure of Gershon¹³ by heating orotic acid (**1**) with phosphorus oxychloride and phosphorus pentachloride as shown in the **scheme 1**.

Compound **2** underwent a smooth Friedel-Crafts reaction with a number of substituted benzene derivatives in the presence of anhydrous aluminium chloride in which the acid chloride moiety was found to react predominantly as shown in the **scheme 2**.



Scheme 1



Scheme 2

The yields of the Friedel-Craft's products were good (70-87%). The Friedel-Crafts reaction took place at the *p*-position of the substituent on the benzene ring. The Friedel-Crafts reaction of 2,4-dichloropyrimidine-6-carbonylchloride (**2**) and

benzene derivatives with electron withdrawing substituents on the benzene ring, e.g. benzophenone, *p*-nitrotoluene and 2-methyl benzaldehyde, however failed. Similarly, phenyl acetylene and styrene failed to give desired products.

6-Aroyl-2,4-dichloropyrimidines (**6,7**) were converted to the corresponding 2, 4-dimethoxy pyrimidines (**8,9**) on treatment with sodium methoxide in methanol as shown in the **scheme 3**.

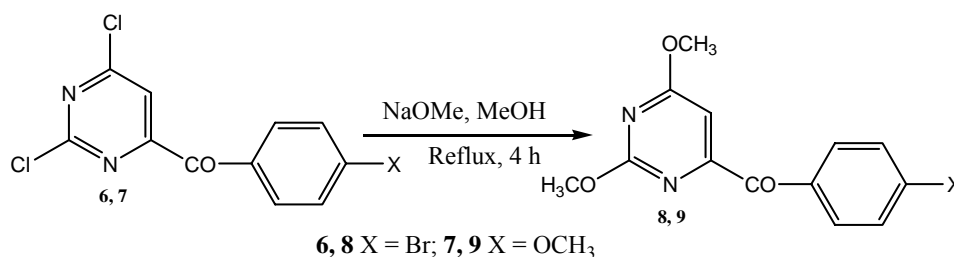
2,4- Dichloropyrimidine-6-carbonyl chloride was also converted to 2,4-dimethoxypyrimidine-6-methylorotate (**3**) by refluxing with sodium methoxide in methanol for 4 hrs.

In view of the extensive use of iodo derivatives of pyrimidine for the synthesis of the corresponding carbon-substituted derivatives, we attempted to synthesis 5-iodopyrimidines by using different methods. The iodination reaction was attempted by several methods, such as, I₂ in alkali solution, ICl in methanol, I₂ in CHCl₃ in presence of nitric acid, and NaI in DMF but only NIS-TFA-TFAA method gave

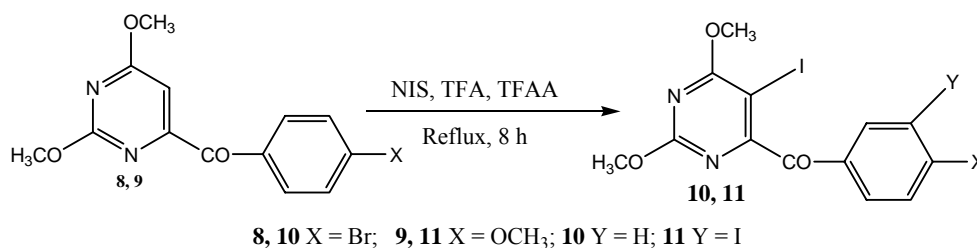
the desired products. The iodination reaction of 2, 4-dichloro-6-aryl pyrimidine was carried out by using NIS-TFA-TFAA under refluxing condition but desired compound 5-iodo pyrimidine was not obtained.

When 2, 4-dimethoxy-6-aryl pyrimidines (**8, 9**) were subjected to iodination reaction utilizing NIS-TFA-TFAA under refluxing condition as shown in the **scheme 4**, the desired product 2, 4-dimethoxy-5-iodo-6-arylpyrimidines (**10, 11**) were obtained in good yield.

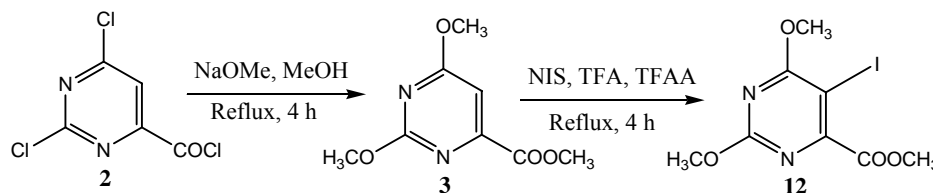
2,4-Dimethoxy-6-methyl orotate (**3**) was also subjected to iodination reaction using NIS-TFA-TFAA under the same condition to afford 2, 4-dimethoxy-5-iodo 6-methyl orotate (**12**) as shown in the **scheme 5**.



Scheme 3



Scheme 4



Scheme 5

N-Iodosuccinimide in trifluoroacetic acid and trifluoroacetic anhydride was found to be an excellent reagent for the iodination at C-5 position of 2, 4-dimethoxy-6-substituted pyrimidine.

CONCLUSION

Here, we have demonstrated a convenient and facile method for the synthesis of 2, 4-dichloro-6-*p*-aroyl-pyrimidine and 2, 4-dichloro-6-methyl orotate

and their corresponding 2, 4-dimethoxy pyrimidine. Iodination at C-5 position also described here. *N*-iodosuccinimide in trifluoroacetic acid and trifluoroacetic anhydride was found to be excellent reagents for the iodination at C-5 position of 2, 4-dimethoxy-6-aryl pyrimidine and 2, 4-dimethoxy-6-methyl orotate. The most important features of the synthesis are that readily available starting materials are used under relatively mild reaction conditions. Also, no toxic and hazardous compounds are produced by these syntheses. A variety of functional groups can be introduced at the C-5 and C-6 position of the pyrimidine ring by this procedure. Through this methodology biologically important uracil and pyrimidine derivatives can be easily synthesized. 2, 4-Dimethoxy-5-iodo-6-aryl pyrimidine might be used as an intermediate for the synthesis of biologically important compounds. This method will be attractive to both organic and medicinal chemists.

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