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

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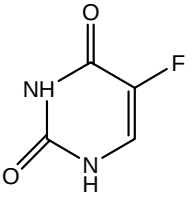
ABSTRACT: 2,4-Dichloro-pyrimidine-6-carbonylchloride (**2**) was synthesized by refluxing orotic acid (**1**) with phosphorus oxychloride and phosphorus pentachloride. Compound (**2**) underwent a smooth Friedel-Craft's reaction with a number of substituted benzene to yield 2,4-Dichloro-6-aroylpyrimidines **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-aroylpyrimidines (**8**, **9**) was attempted by several methods but only NIS-TFA-TFAA method gave the desired products, 2,4-dimethoxy-5-iodo-6-aroylpyrimidine (**10**, **11**) in good yields.

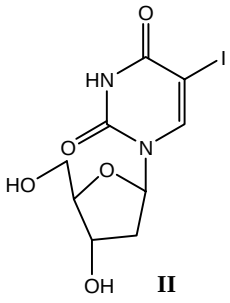
Key words: Synthesis, 5-Iodo-6-Substituted pyrimidines, Orotic acid.

INTRODUCTION

Idoxuridine (IDU) **I** and Trifluorothymidine (TFT) **II** were the first pyrimidine nucleoside[1] 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.



I



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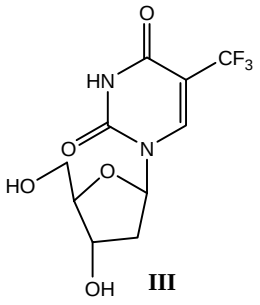

III

Dihydroalkoxybenzyloxopyrimidines (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 analogues[6] of dihydroalkoxybenzyloxopyrimidines (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*)-one[7] was found to be potent anti-HIV activity with an IC_{50} 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-tetrahydro-pyrimidines (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. ^{1}H NMR and ^{13}C 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 F_{254} (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, $POCl_3$, 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 ($POCl_3$, 40 ml) was refluxed for 24 hours at 105-108 ^{o}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-aroylpyrimidines (6,7). To the substituted benzenes **4**, **5** (60 ml) anhydrous aluminium chloride (6 g) was added at 0 ^{o}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 (CCl_4), mp 122-124 ^{o}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; ^{1}H NMR (400 MHz $CDCl_3$) 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); ^{13}C NMR (100 MHz $CDCl_3$) 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 $C_{11}H_5N_2OBrCl_2$: 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 (CCl_4); 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (3H, s, $ArOCH_3$), 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-aroylpyrimidines (8, 9). 2, 4-Dichloro-6-*p*-aroylpyri-midine **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 ^{o}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% $NaHCO_3$, water and dried over Na_2SO_4 (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 ^{o}C; IR: ν_{max} (KBr) 1674.1, 1582.5, 1559.3, 1484.1, 1463.9, 1395.4, 1386.4, 1349.1, 1259.4, 12054, 1105.1, 974.9, 835.3, 763.8 cm^{-1}; UV(EtOH) : λ_{max} 277.20 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01(3H, s, OCH_3), 4.04 (3H, s, OCH_3), 6.93 (1H, s, C-5H), 7.63 (2H, d, *J* = 8.6 Hz, ArH), 8.00 (2H, d, *J* = 8.6 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.3 (OCH_3), 55.1 (OCH_3), 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 $C_{13}H_{11}N_2BrO_3$: 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; ^{1}H NMR δ (400 MHz, $CDCl_3$) 3.88 (3H, s, Ar-OCH_3) 4.02 (3H, d, OCH_3), 4.03 (3H, s, OCH_3), 6.85(H, s, C_5 - 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% $NaHCO_3$ and dried over anhyd. Na_2SO_4. After removal of chloroform the solid mass was obtained and crystallized from methanol. A needle shaped crystal was obtained. mp 106-107^{o}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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.07 (3H, s, $COOCH_3$), 7.07 (1H, s, C-$_5$H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.9 (OCH_3), 54.3 (OCH_3), 55.0 ($COOCH_3$), 103.1 (Py-H), 156.7 (Py-C), 164.4 (Py-C), 165.7 (Py-C), 172.7(C=O).

Anal. Calcd for $C_8H_{10}N_2O_4$: 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-aroyl pyrimidines (10, 11). A mixture of 2, 4-dimethoxy-6-*p*-aroylpyrimidine (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 ^{o}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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 7.62 (2H, d, *J* = 7.2 Hz, Ar-H), 7.73 (2H, d, *J* = 7.2 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6

(OCH_3), 55.7(OCH_3), 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 ^oC; 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, $CDCl_3$) δ 3.96 (3H, s, Ar-OCH_3), 4.03 (6H, s, C-$_2$, OCH_3 and C-$_4$ OCH_3), 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.47 (OCH_3) 55.34 (OCH_3), 56.78 (OCH_3), 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).

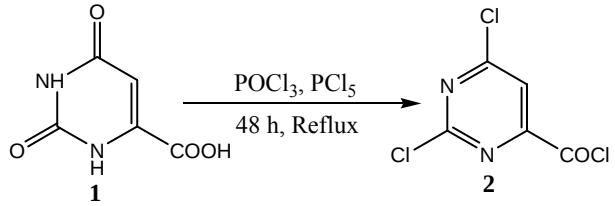
2,4-Dimethoxy-5-iodo-6-methylorotate (12). 2, 4-Dimethoxy-5-iodo-6-methyl orotate **12** was prepared from 2, 4-dimethoxy-6-methylorotate **3** (2.2 g 0.1138 mmol) by using the above iodination procedure. The crude mass was crystallized from methanol. Light yellow crystals, mp 167-168 °C; IR: ν_{max} (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, $CDCl_3$) δ 3.92 (3H, s, OCH_3), 3.95(3H, s, OCH_3), 4.00 (3H, s, $COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0 (OCH_3), 54.3 (OCH_3), 55.5 (OCH_3), 66.57, 103.6, 162.0, 165.38, 169.97(C=O).

Anal. Calcd for $C_8H_9N_2O_4I$: (C, 29.65, H, 2.80; N, 8.64. Found**:** C, 30.17, H, 2.80, N, 8.66.

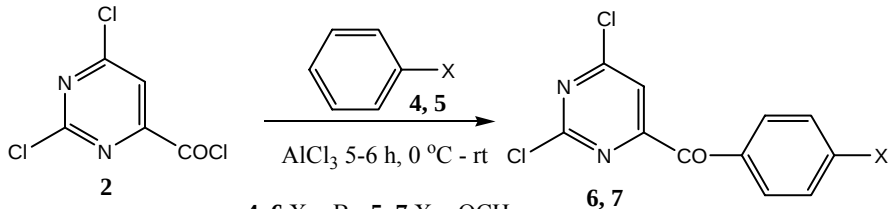
RESULTS AND DISCUSSION

2,4-Dichloropyrimidine-6-carbonyl chloride (**2**) was synthesized according to the procedure of Gershon[13] 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



4, 6 X = Br; **5, 7** X = OCH_3

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

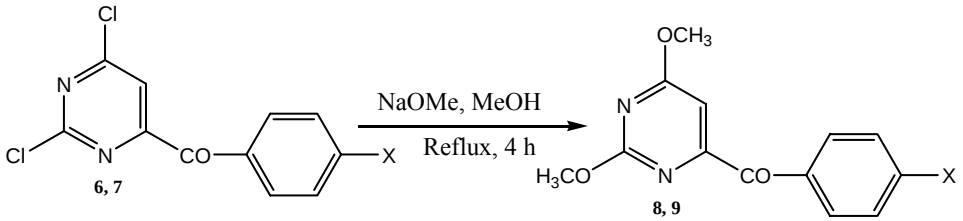
6-Aroyl-2,4-dichloropyrimidines (**6**,**7**) were converted to the corresponding 2, 4-dimethoxy pyrimidines (**8**,**9**) on treatment with sodium methoxide in methanol as shown in the **scheme 3**.

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, I_2 in alkali solution, ICl in methanol, I_2 in $CHCl_3$ 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-aroyl pyrimidine was carried out by using NIS-TFA-TFAA under refluxing condition but desired compound 5-iodo pyrimidine was not obtained.

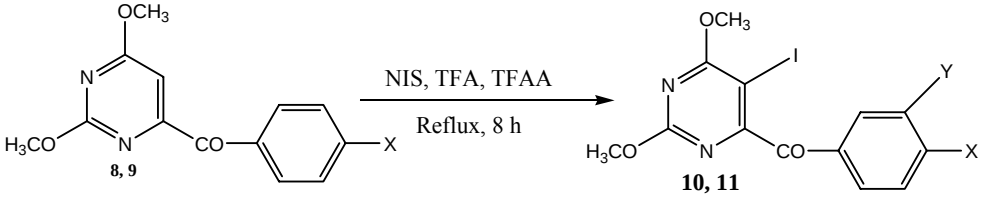
When 2, 4-dimethoxy-6-aroyl pyrimidines (**8**, **9)** were subjected to iodination reaction utilizing NIS-TFA-TFAA under refluxing condition as shown in the **scheme 4**, the desired product 2, 4-dimethoxy-5-iodo-6-aroylpyrimidines (**10**, **11**) were obtained in good yield.

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-dimethooxy-5-iodo 6-methyl orotate (**12**) as shown in the **scheme 5**.



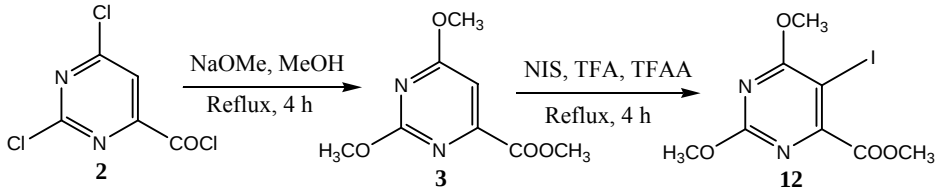
6, 8 X = Br; **7, 9** X = OCH_3

Scheme 3



8, 10 X = Br; **9, 11** X = OCH_3; **10** Y = H; **11** Y = I

Scheme 4



Scheme 5

N-Iodosuccinimide in trifluoroacetic acid and trifluoroacetic anhydride was found to be an excellent reagent for the iodonation 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-dicholoro-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-aroyl 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-aroyl 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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REFERENCES

1. De Clerck, E. 1995. Trends in the development of new antiviral agents for the chemotherapy of infections caused by herpes viruses and retroviruses. *Medical Virology.* **5**, 149-164.
2. Heidelberger, C. 1984. Pyrimidine and pyrimidine antimetabolities in cancer medicine (Holland JF, Frei E, eds) Lea and Febiger, Philadelphia, PA, pp. 801-824.
3. Artico, M., Massa, S., Mai, A., Marongiu, M. E., Piras, G., Tramontano, E. and La colla, P. 1993. 3, 4-Dihydro-2-alkoxy-6-benzyl-4-oxopyrimidinees (DABOs): A New Class of Specific Inhibitors of Human Immunodeficiency Virus Type 1. *Antiviral Chem. Chemther*. **4**, 361-368.
4. Tramontano, E., Marongiu, M. E., De Montis, A., Loi, A. G., Artico, M., Massa, S., Mai, A. and La Colla, P. 1994. Characterization of the anti-HIV-1 activity of 3, 4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs), new non-nucleoside reverse transcriptase inhibitors. *Microbiologica* **17**, 269-279.
5. Massa, S., Mai, A., Artico, M., Shardella, G., Tramontano, E., Loi, A. G., Scano, P. and La Colla, P. 1995. Synthesis and antiviral activity of new 3,4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs), specific inhibitors of human immunodeficiency virus type 1. *Antiviral Chem. Chemother*., **6**, 1-8.
6. Mai, A., Artico, M., Shardella, G., Massa, S., Loi, A.G., Tramontano, E., Scano, P. and Colla, P.L. 1995. Synthesis and anti-HIV-1 activity of thio analogues of dihydroalkoxy benyloxopyrimidines. *J. Med. Chem*. **39**, 3258-3263.
7. Vig, R., Mao, C., Venkatachalam, T.K., Lisa, T.-A., Sudbeck, E.A. and Uckun, F.M. 1998. 5-Alkyl-2-[(methyl thiomethyl)thio]-6-(benzyl)-pyrimidin-4-(1*H*)-ones as potent non-nucleoside teverse transcriptase inhibitors of S-DABO series. *Bioorg. Med. Chem. Lett*. **8**, 1461-1466.
8. Nizi, E., Botta, M., Corelli, F., Manetti, F., Messina, F. and Maga, G. 1998. Solid phase synthesis of 2, 6-disubstituted-4(3H)-pyrimidinones targeting HIV-1 reverse transcriptase. *Tetrahedron Lett*. **39**, 3307-3310.
9. Miyasaka, T., Tanaka, H., Baba, M., Haykawa, H., Walkr, R. T., Balzarini, J. and De Clercq, E. 1989. A novel lead for specific anti-HIV-1 agents: 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine. *J. Med. Chem*. **32**, 2507-2509.
10. Brollosy, El., Jorgensen, P.T., Dahan, B., Boel, A.M., Pedersen, E.B. and Nielsen, C. 2002. Synthesis of novel N-1 (allyloxymethyl) analogues of 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442, emivirine) with improved activity against HIV-1 and its mutants. *J. Med. Chem.* **45**, 5721-5726.
11. Bhatt, R.S., Kundu, N.G., Chwang, T.L. and Heidelberger, C. 1981. Synthesis of 5-ethynylorotic acid. *J. Heterocyclic Chem*. **18**, 771-774.
12. Khan, M.W. and Kundu, N.G. 1999. An expeditious synthesis of 4-acyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidines (6-acyl uracils) and 4-Acyl-6-aryl-2-oxo-2,3-dihydro-pyrimidines. *J. Chem. Res.* **20-21**, 0301-0318.
13. Gershon, H. 1962. Chlorinated pyrimidines derived from orotic acid. *J. Org. Chem*. **27**, 3507-3510.