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Synthesis of Some Novel Non-Nucleoside Reverse Transcriptase Inhibitor

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New approaches towards synthesis of new anti-HIV agents have lead to development of non-nucleoside reverse transcriptase inhibitors (NNRTI's). New NNRTI's have been synthesized by substitution of 2-amino diaryl pyridine. In the present study a series of substituted 2-amino pyrimidine derivatives were synthesized using Schotten-Bauman and Baker-Venkatraman rearrangement principle. The formed derivatives were characterized by spectral analysis and the purity was checked by TLC.

Key Words: 2-Amino diaryl pyridine, Non-nucleoside transcriptase inhibitor.

INTRODUCTION

Discovery of HIV as a causative agent of AIDS[1,2] has stimulated an extensive research towards both prevention and treatment of AIDS, which is caused by HIV-1 (majority) and HIV-2 retrovirus. Development of AIDS is characterized by susceptibility to various infections and malignancies. The development of the highly effective antiretroviral[3,4] agents made it possible to probe viral pathogenesis. Administering such agents disrupts the steady state equilibrium between virion production and clearance.

Due to increasing resistance of HIV many new anti HIV agents have been developed that are effective against the new strain of viruses. One such development is synthesis of non-nucleoside reverse transcriptase inhibitors (NNRTI's)[5-7]. The procedure used for the synthesis involved four synthetic steps. The first step is the synthesis of ester using Schotten-Baumann reaction. It involves reaction of acid chloride with an alcohol or phenol in the presence of a base like sodium hydroxide or pyridine to obtain an acid derivative. The acid chloride was generated *in situ* by reaction of substituted benzoic acid and phosphorous oxychloride in the presence of pyridine and subsequent esterification of acid chloride with *o*-hydroxy acetophenone to obtain 2-acetyl-1-(substituted benzoyloxy)benzene. In case of unsubstituted compound, the compound was obtained directly from reaction of benzoyl chloride and *o*-hydroxy-acteophenone. The second step uses the principle of Baker-Venkatraman rearrangement.

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Rearrangement is carried out in the presence of a base to obtain a β-diketo derivative, which was converted to flavone by acidification with sulphuric acid and acetic acid. The flavone obtained was finally converted to 2-amino pyrimidine derivatives[7,8] using guanidine hydrochloride.

EXPERIMENTAL

The melting points were determined in open capillaries, using the heating block type apparatus and are uncorrected. Analytical TLC was carried out on glass plates coated with silica gel G, activated at 110 °C for 0.5 h. The plates were developed by exposure to iodine vapours and anhydrous sodium sulphate was used as drying agent. The IR spectra were recorded on Shimadzu-8300 FTIR instrument using KBr pallets. Solvents and reagents were obtained from S.D. Fine, Spectrochem and Loba Chemicals. All moisture free operation was performed in oven dried glassware under a positive pressure of nitrogen unless otherwise stated.

Method: The synthetic **Scheme** has been divided into following steps: **Scheme (A)**

(i) Synthesis of 2-acetyl-1-(substituted benzoyloxy)benzene[9]. (ii) Synthesis of β-diketo derivatives. (iii) Syntheses of flavones. (iv) Conversion of flavones to 2-amino diaryl/heteroaryl pyrimidine derivatives (**Chart-4**).

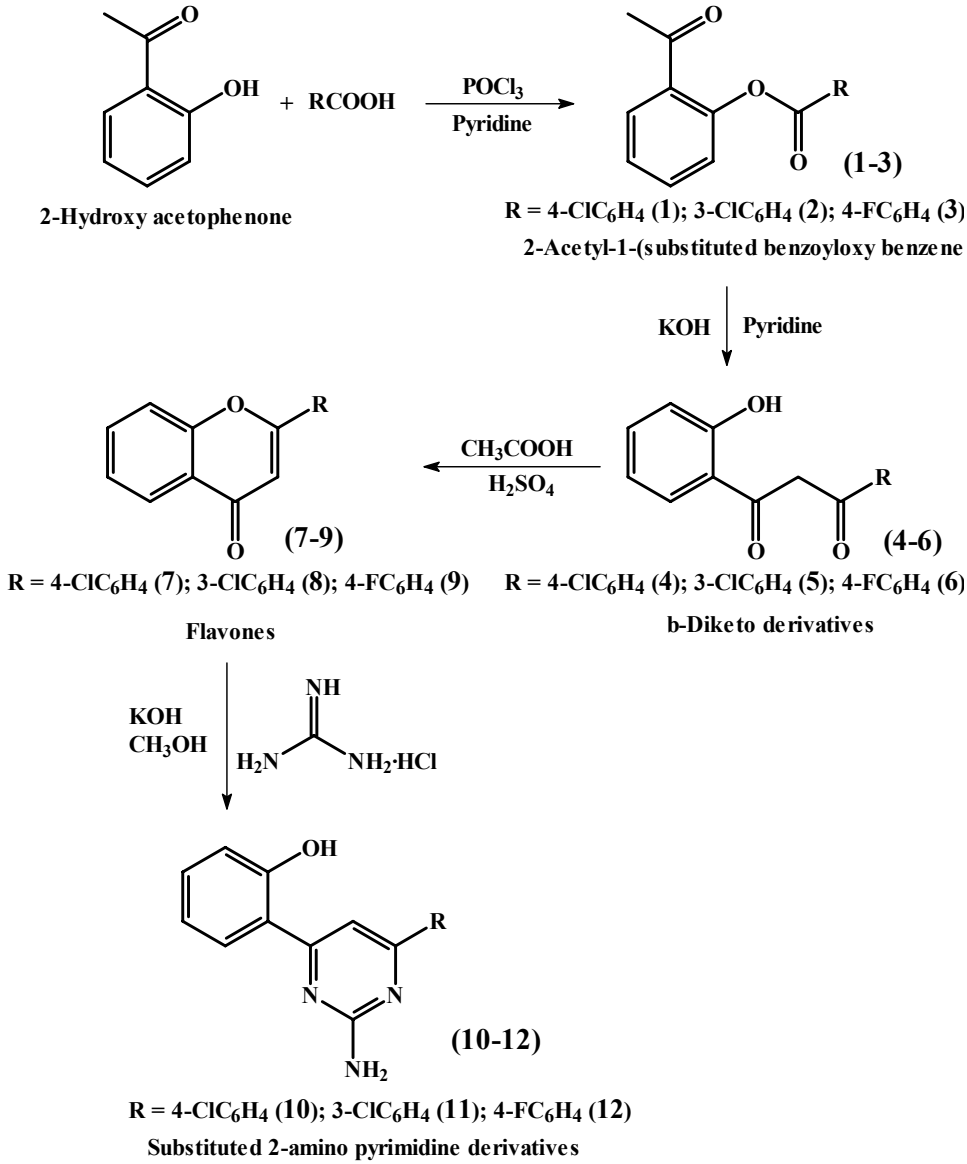
Synthesis of 2-acetyl-1-(substituted benzoyloxy)benzene derivatives: A cold solution of *o*-hydroxyacetophenone, 4.36 g (0.032 mol), 4.34 g (0.031 mol), 5.15 mL (0.042 mol) for compounds (**1-3**), respectively and 4-chloro benzoic acid 5 g (0.032 mol) for (**1**), 3-chloro benzoic acid 5 g (0.032 mol) for (**2**) and 4-fluorobenzoic acid 6 g (0.042 mol) for (**3**) was taken in pyridine (25 mL) and to it phosphorous oxychloride (4 mL) was added slowly. The reaction mixture was stirred at room temperature for 3 h and poured into the mixture of crushed ice and HCl. The solid so obtained was filtered, dried and recrystallized from methanol to obtain pure compound.

2-Acetyl-1-(4-chlorobenzoyloxy)benzene (1): Yield: 6.5 g (74.7 %); m.p. 60-62 °C; R_f 0.9 (3 % methanol in benzene); IR (KBr, ν_{max}, cm^{-1}): 1739 (C=O *str.*) benzoate ester, 1681 (C=O *str.*).

2-Acetyl-1-(3-chlorobenzoyloxy)benzene (2): Yield: 7 g (80 %); m.p. 86-88 °C; R_f 0.5 (benzene); IR (KBr, ν_{max}, cm^{-1}): 1739 (C=O *str.*) benzoate ester, 1685 (C=O *str.*).

2-Acetyl-1-(4-flourobenzoyloxy)benzene (3): Yield 8.2 g (89 %); m.p. 70-72 °C; R_f 0.8 (benzene); IR (KBr, ν_{max}, cm^{-1}): 1741 (C=O *str.*) benzoate ester, 1685 (C=O *str.*).

Synthesis of β-diketo derivatives: The above-formed compound 4 g, 6 g, 8.1 g of (**1-3**), respectively were stirred individually with potassium hydroxide (pulverized and fused) 4 g, in pyridine (20 mL) at room temperature till a paste was obtained. This paste was poured into a mixture of crushed ice and HCl. The solid so obtained was filtered, dried and recrystallized from methanol to obtain compound **4**, **5** and **6**.



Scheme

1-(4-Chlorophenyl)-3-(2-hydroxyphenyl)-1,3-propanedione (4): Yield 3.98 g (99.5 %); m.p.108-110 °C; R_f 0.9 (chloroform); IR (KBr, ν_{max}, cm^{-1}): 1625 (C=O *str.*).

1-(3-Chlorophenyl)-3-(2-hydroxyphenyl)-1,3-propanedione (5): Yield 5.1 g (85 %); m.p. 116-118 °C; R_f 0.9 (chloroform); IR (KBr, ν_{max}, cm^{-1}): 1618 (C=O *str.*).

1-(4-Flourophenyl)-3-(2-hydroxyphenyl)-1,3-propanedione (6): Yield 7.8 g (96.29 %); m.p. 133-135 °C; R_f 0.9 (chloroform); IR (KBr, ν_{max}, cm^{-1}): 1625 (C=O *str.*).

Synthesis of flavones: Sulphuric acid (2 mL) was added to a solution of β-diketo derivative 2 g, 5 g, 7.7 g of (**4-6**), respectively, in 15 mL of glacial acetic acid. The reaction mixture was refluxed on water bath for 2 h. The resulting solution was poured into crushed ice, filtered and dried to get solid compound. The compound was recrystallized with methanol to obtain the pure compound **7**, **8** and **9**.

4-Chloroflavone (7): Yield 1.5 g (80.6 %); m.p. 188-190 °C; R_f 0.5 (3 % methanol in benzene); IR (KBr, ν_{max}, cm^{-1}): 1662 (C=O *str.*).

3-Chloroflavone (8): Yield 4.3 g (93.4 %); m.p. 123-125 °C; R_f 0.82 (chloroform); IR (KBr, ν_{max}, cm^{-1}): 1641 (C=O *str.*).

4-Fluoroflavone (9): Yield 6 g (83 %); m.p. 145-148 ºC; R_f 0.5 (chloroform); IR (KBr, ν_{max}, cm^{-1}): 1634 (C=O *str.*).

Conversion of flavones to 2-amino diaryl pyrimidine derivatives: Each derivative of flavone 0.5 g of (**7-9**) was taken separately in round bottom flask and to it guanidine hydrochloride 1 g (0.01 mol) and potassium hydroxide 0.5 g and methanol (30 mL) was added and refluxed for 10 h. After the completion of reaction, the mixture was poured on crushed ice in acetic acid. The solid so obtained was filtered, washed with water, dried and recrystallized from methanol to obtain the final product **10**, **11** and **12**.

6-(4-Chlorophenyl)-4-(2-hydroxyphenyl)-2-amino pyrimidine (10): Yield 0.22 g (37.93 %); m.p. 239-241 °C; R_f 0.3 (chloroform).

6-(3-Chlorophenyl)-4-(2-hydroxyphenyl)-2-amino pyrimidine (11): Yield: 0.2 g (34.9 %); m.p. 183-185 °C; R_f 0.36 (3 % methanol in chloroform).

6-(4-Flourophenyl)-4-(2-hydroxyphenyl)-2-amino pyrimidine (12): Yield: 0.18 g (31.03 %); m.p. 221-223 °C; R_f 0.42 (benzene).

RESULTS AND DISCUSSION

The IR spectrum of the compound (**10**) showed a doublet for asymmetric and symmetric stretching for primary amine at 3502 and 3340 cm^{-1} (N-H *str.*), respectively. A characteristic peak at 3217 cm^{-1} has been assigned to ν(OH). A sharp singlet was observed for primary amino at δ 6.2 (s, 2H, NH_2) in the PMR spectra. H-5 proton of pyrimidine and eight aryl protons were appeared as multiplet at δ 6.9-8.0 (m, 9H, ArH) and 13.5 (br, 1H, OH). Compound (**11**) showed a characteristic peak at 3203 cm^{-1} ν(O-H) and 3502 cm^{-1}, 3346 cm^{-1} ν(N-H) in the IR spectrum. The PMR spectrum displayed δ 5.24 (s, 2H, NH_2), 6.9-8.0 (m, 9H, ArH) and 13.5 (br, 1H, OH). Compound (**12**) showed a characteristic peak at 3201 cm^{-1} ν(O-H) and 3400 cm^{-1}, 3321 cm^{-1} ν(N-H) in the IR spectrum. The PMR spectrum displayed at δ 5.5 (s, 2H, NH_2), 6.9-8.1 (m, 9H, ArH) and 14.1 (br, 1H, OH).

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