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A NEW METHOD TO SYNTHESIZE FAMCICLOVIR

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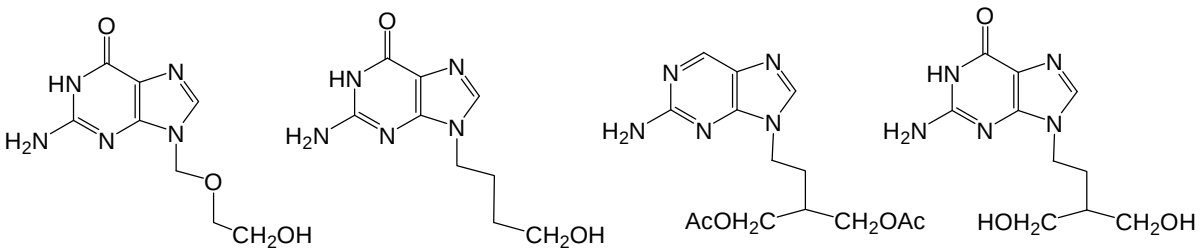
Abstract - A new and efficient method has been reported for the synthesis of 2-amino-9-[4-acetoxy-3-(acetoxymethyl)butyl-1-yl]purine (famciclovir) starting from guanine. The route involves chlorination of guanine, optimized Mitsunobu reaction, coupling with diethyl malonate, hydrogenation, reduction and esterification, and the overall yield is about 29%. This method does not require any form of chromatographic purification to give pure famciclovir, and it is an industrially viable manufacturing process for this drug.

INTRODUCTION

Acyclic analogues of nucleosides (acyclonucleosides) have remained major biomedical research targets since the discovery of the potent antiviral activity of 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir,**1**, Figure 1),[1] the standard drug for the treatment of herpes viral infections. Additional acylonucleosides, including 2-amino-9-(4-hydroxybutyl)purine(**2**),[2] famciclovir(**3**),[3] and 2-amino-9-[4-hydroxyl-3-(hydroxylmethyl)butyl]purine (penciclovir, **4**),[4] have been prepared and found to have such activities. Most of these nucleoside analogues have the structure of *N*-9-alkylation which is probably necessary for the antiviral activities.



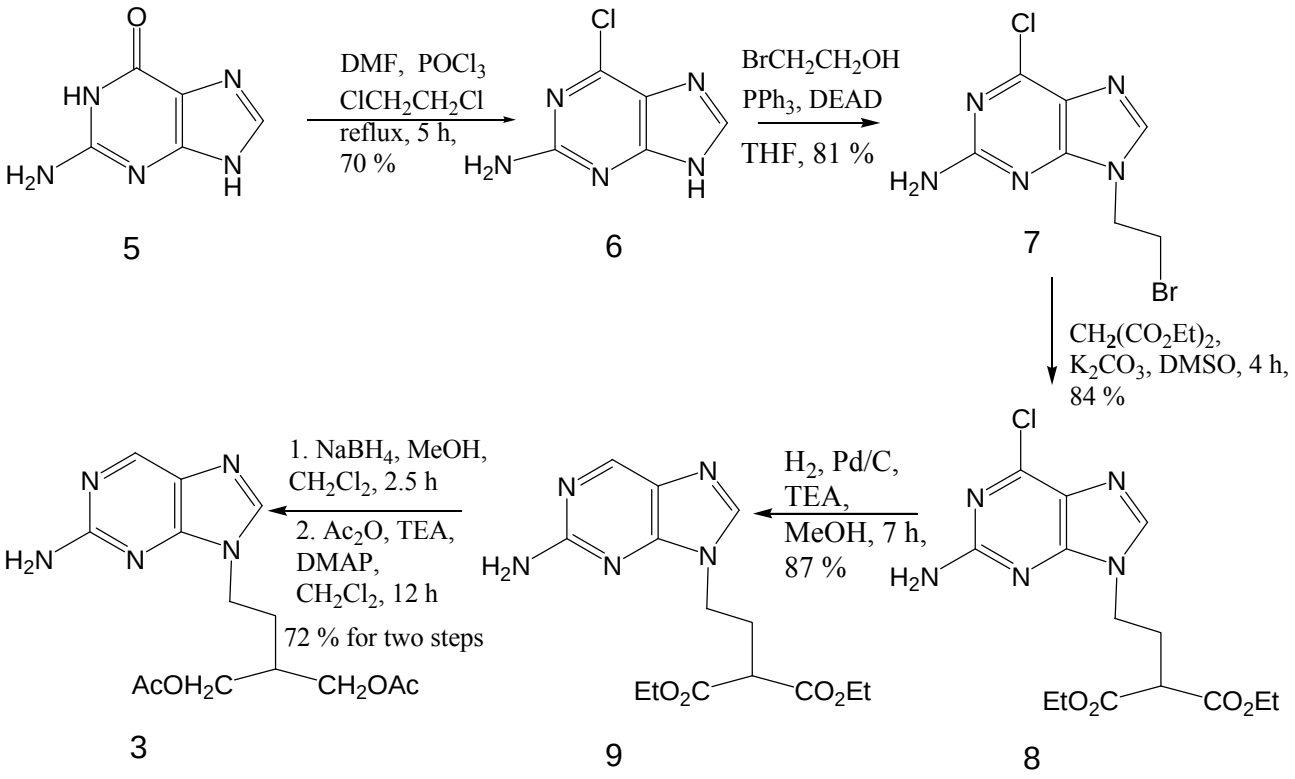
1 2 3 4

Figure 1

Famciclovir is a prodrug of penciclovir (**4**, Figure 1), and it has been approved by FDA for treatment of herpes zoster (shingles) and acute recurrent genital herpes. Four methods have been reported for preparation of purine derivatives such as famciclovir: (a) construction of purines and pyrimidines from respective aminoalkanes,[5] but this route usually involves more steps and gives low overall yield; (b) palladium- catalyzed displacement of an allylic ester or carbonate,[6] however, it is limited to use for the application of heavy metals; (c) direct nucleophilic displacement of halides or activated alcohols,[7] while the ratios of the regionisomers are not usually ideal when using this method; (d) Mitsunobu coupling.[8] Although the Mitsunobu reaction can afford good regioselectivities at *N*-9, the protected-deportected process is needed and the route is long generally. Considering the above methods, we wish to report a new and efficient method for the preparation of famciclovir using the optimized Mitsunobu coupling reaction.[8c]

RESULTS AND DISCUSSION

Guanine (**5**, Scheme 1) was converted into 2-amino-6-chloropurine (**6**) according to the reported procedures,[9] and the yield was 70%. As the starting material, guanine is quite cheap and commercially available. The key intermediate product **7** was obtained from compound **6** via the optimized Mitsunobu coupling reaction in 81% yield. Although it has been noted that the yield of the *N*-9 alkylation was influenced significantly by the size of the substituent at *C*-6 on purine rings,[7b] the protected- deportected process was omitted in this progress, and the route was shorter. Coupling of compound **7** with diethylmalonate afford **8** in 84%. Catalytic hydrogenation of **8** affected the *C*-*Cl* bond to provide **9** in a yield of 87%. Diester reduction and *O*-acetylation were achieved without isolation of the intermediate diol to give 72% of famciclovir **3**. The overall yield was about 29%, and this method did not require any form of chromatographic purification to give pure famciclovir, and it was an industrially viable manufacturing process for this drug.



Scheme 1

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and were uncorrected. Mass spectra were measured on a Finnigan MAT-95 mass spectrometer operating at an ionization potential of 70eV. ^{1}H and ^{13}C NMR spectra were run on a Bruker AM-400 spectrometer using tetramethylsilane as the internal standard (chemical shifts in parts per million). Splitting patterns were designated as 's, d, t, q, and m', these symbols indicated 'singlet, doublet, triplet, quartet, and multiplet', respectively. All reactions were monitored by TLC (Yantai Marine Chemical Co. Ltd, China).

2-Amino-6-chloropurine (6)

To a solution of **5** (10 g, 66.2 mmol) in dry DMF (20 mL) and CH_2Cl_2 (100 mL) was added phosphorus oxychloride (12.3 mL, 132.4 mmol) at the temperature of 0 ℃. The mixture was stirred for 1 h at the same temperature, and then refluxed for 5 h. After the completion of the reaction, the mixture was poured into cold water (150 mL) and the organic layer was recovered. The pH value of the aqueous phase was adjusted to 7-8 by 10% NaOH aq and the precipitate was filtered off. The compound was dissolved in 12% AcOH aq (50 mL), and stirred for 1 h at 70 ℃. Cooled to rt, the precipitate was filtered off and

again dissolved in 10% NaOH aq (75 mL). After stirred for 3 h at rt, the pH of the solution was adjusted to 7.5 by 6M HCl aq. The precipitate was filtered off and washed with cold water (45 mL). After the residue was dried, compound 6 (8 g, 70%) was obtained as light yellow powder: mp 300 ℃(lit.,[9] 300 ℃); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.795 (2H, s), 7.181 (1H, s), 8.516 (1H, s). The other spectral data for this compound were identical to those reported previously.[9]

2-Amino-6-chloro-9-(2-bromoethyl)purine (7)

Compound **6** (3.392 g, 20 mmol) was added to a solution of 2-bromoethanol (1.5 mL, 21 mmol) and PPh_3 (5.508 g, 21 mmol) in anhydrous THF under an N_2 atmosphere. The resulting suspension was treated with diethyl azodicarboxylate (DEAD, 3.3 mL, 21 mmol) and the reaction mixture was then stirred at 70 ℃ for 6 h. Then the second portions of 2-bromoethanol (1.5 mL, 21 mmol), PPh_3 (5.508 g, 21 mmol), and DEAD (3.3 mL, 21 mmol) were added to the reaction mixture sequentially. The mixture was stirred for another 6 h at the same temperature. The mixture was cooled, treated with saturated brine, and extracted with CH_2Cl_2. The combined organic layer was then washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The resulting syrup was recrystallized from mixture of $CHCl_3$ and MeOH (5:2), and the key intermediate product **7** was obtained as a colorless crystals in 81% yield: mp 181-182 ℃ (lit.,[10] 182-183 ℃); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.909 (2H, t, J = 6.3 Hz), 4.472 (2H, t, J = 6.2 Hz), 6.984 (2H, s), 8.171 (1H, s); ^{13}C NMR (DMSO-d_6) δ: 159.793, 154.030, 149.402, 143.103, 123.206, 44.567, 30.883; MS (70eV) *m/z* (%): 277 (M^+, 42)，275(32), 171(36), 169(100), 134(39), 133(7). The other spectral data for this compound were identical to those reported previously.[10]

2-Amino-6-chloro-9-(ethyl 2-carboethoxybutanoate-4-yl)purine (8)

Intermediate compound **7** (2.105 g, 7.6 mmol) was completely dissolved in DMSO (14 mL). To the solution, diethyl malonate (3.5 mL, 22.8 mmol) and potassium carbonate (3.151 g, 22.8 mmol) were added, followed by stirring for 4 h at a temperature of 40-50 ℃. After completion of the reaction, the product was cooled to rt, and water (30 mL) was added. The resulting solution was extracted three times with portions of CH_2Cl_2 (60 mL). The organic layer was collected, and dried with anhydrous Na_2SO_4, followed by filtration and washing. The resulting filtrate was concentrated under reduced pressure and crystallized from butanol, thereby giving compound **8** as light yellow-colored solid in 84% yield: mp 121-123 ℃ (lit.,[11] 123-124 ℃); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.148 (6H, t, J = 7.2 Hz), 2.325 (2H, q, J = 6.9 Hz), 3.481 (1H, t, J = 7.0 Hz), 3.996- 4.100 (4H, m), 4.135 (2H, t, J = 3.4 Hz), 6.911 (2H, s), 8.075 (1H, s). The other spectral data for this compound were identical to those reported previously.[11]

2-Amino-9-(ethyl 2-carboethoxybutanoate-4-yl)purine (9)

A mixture of compound **8** (2.342 g, 6.6 mmol), triethylamine (TEA, 9.5 mL, 66 mmol), and palladium charcoal (10% Pd/C, 0.150g) in MeOH (300 mL) was stirred under hydrogen for 7 h at 55 ℃. The mixture was filtered through Celite after cooling down, evaporated in vacuo. The filtrate was dissolved by addition of CH_2Cl_2 and water. The separated aqueous layer was extracted with CH_2Cl_2 (120 mL). The combined organic solution was dried (Na_2SO_4), distilled to remove solvent and crystallized from butanol, giving compound **9** as a light yellow powder with the yield of 87%: mp 99-101 ℃ (lit.,[11] 102-103 ℃); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.245 (6H, t, J = 7.2 Hz), 2.450 (2H, q, J = 6.9 Hz), 3.332 (1H, t, J = 7.3 Hz), 4.129- 4.223 (6H, m), 6.500 (2H, s), 8.020 (1H, s), 8.553(1H, s). The other spectral data for this compound were identical to those reported previously.[11]

2-Amino-9-[4-acetoxy-3-(acetoxymethyl)butyl-1-yl]purine (3, famciclovir)

Compound **9** (1.650 g, 5.1 mmol) was dissolved in CH_2Cl_2 (30 mL), and $NaBH_4$ (1.158 g, 30.6 mmol) and MeOH (1.5 mL) were added. The reaction mixture was stirred at rt for 2.5 h, then diluted with water (20 mL) and settled. The separated organic layer was removed. The aqueous (along with the precipitated solid) was cooled down with an ice/water bath, and HCl acid (25-30%) was added slowly till the solution became neutral. The precipitate was collected by filtration, and then washed with cold brine and water. The collected diol was dried under vacuum and directly used in the next step without purification.

The intermediate diol, TEA (1.5 mL, 10.5 mmol) and catalytic 4-*N*,*N*-dimethylaminopyridine (DMAP, 0.106 g, 0.87 mmol) were dissolved in CH_2Cl_2 (30 mL). The acetic anhydride (2.0 mL, 21.0 mmol) was then added dropwise, keeping the solution at rt. The mixture was stirred for 12 h at the same temperature. Water (45 mL) was added to dilute the reaction mixture, and 5% NaOH aq was added till the solution turned neutral. The organic layer was washed with water, saturated brine and dried. The CH_2Cl_2 was removed under reduced pressure, and the residue was dissolved with boiling MeOH (15 mL). Famciclovir **3** was crystallized out by keeping the methanol solution at 0-4 ℃ for 4 h as white powder: 72%, mp 136-137 ℃ (lit.,[12] 137-139 ℃); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.798- 2.012 (9H, m), 4.035 (4H, d, J = 5.4 Hz), 4.151 (2H, t, J = 6.9 Hz), 6.542 (2H, s), 8.126 (1H, s), 8.588 (1H, s). The other spectral data for this compound were identical to those reported previously.[12]

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