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An Improved Synthesis of Etravirine

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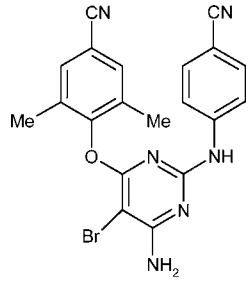
Abstract:

Etravirine (1) is a novel diarylpyrimidine non-nucleoside reverse transcriptase inhibitor and has recently been approved by the U.S. Federal Drug Administsration for the treatment of AIDS. Its reported synthesis is fraught with many difficulties, the foremost being the poor yield and long reaction time required at the aminolysis stage. We attributed this problem to the presence of a bromide group adjacent to the reaction site of the advance intermediate (6). In order to circumvent this issue, we proposed to defer the installation of the bromide group at a later stage, preferably after aminolysis. Indeed, this protocol has worked well. However, in the process of installation of diarylether and diarylamine functionalities at appropriate positions, we had to reverse the sequence of displacement reactions of the dichloride intermediate (9) with 3,5-dimethyl-4-hydroxybenzonitrile (5) and 4-aminobenzonitrile (3). The classical bromination led to the completion of etravirine synthesis.

Introduction

The non-nucleoside reverse transcriptase inhibitors (NNRTI) play a pivotal role as key components of highly active antiretroviral therapy.[1−4] NNRTIs have an ability to target an allosteric binding pocket on the reverse transcriptase (RT) enzyme. This property allows them to be useful as broad-spectrum agents against human immunodeficiency virus (HIV) RT mutations. The diarylpyrimidine-based NNRTIs constitute the second-generation drugs and are useful for treatment of HIV-infected patients with NNRTI-resistant viruses. Etravirine (TMC 125),[2] 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile, was approved in 2008 by the U.S. Federal Drug Administration for use in combination therapy along with other antiretroviral agents in adult patients with multidrug-resistant HIV infections.



Etravirine (1)

The procedure to prepare etravirine (**1**) is disclosed in Scheme 1[5,6] in which 5-bromo-2,4,6-trichloropyrimidine (**2**) was initially reacted with 4-aminobenzonitrile (**3**) in the presence of diisopropylethylamine in refluxing dioxane to give the diarylamine derivative (**4**) whose reaction with 4-hydroxy-3,5-dimethylbenzonitrile (**5**) in the presence of NaH in *N*-methylpyrrolidone solvent provided the intermediate (**2**) (Scheme 1).

In another synthesis of etravirine (**1**),[1,6,7] 4-guanidinobenzonitrile (**7**) was cyclized with diethylmalonate in the presence of sodium ethoxide in ethanol to give 4-(4,6-dihydroxypyrimidine-2-yl-amino)benzonitrile (**8**) which was subsequently treated with $POCl_3$ to form the corresponding dichloro derivative **9** (86%). The bromination of **9** with bromine and sodium bicarbonate in aqueous methanol afforded 4-(5-bromo-4,6-dichloropyrimidin-2-yl-amine)benzonitrile (**10**) which, when condensed with a sodium salt of cyano-2,6-dimethylphenolate (**11**) in the presence of *N*-methylpyrrolidone and dioxane, gave the intermediate (**6**). Aminolysis of **6** with ammonia in isopropanol solvent gave etravirine (**1**) with ∼10% overall yield (Scheme 2).

The critical step of aminolysis of **6** under ammonia at high pressure was not satisfactory because of low yield (41%) and long reaction time of approximately 4 days. The low yield and long reaction period could be attributed to the presence of the bromine atom situated adjacent to the amination site. We argued that this issue could be resolved if we avoided the placement of bromine in **6** prior to the aminolysis reaction. Once the amino group is in place, then bromine could be installed by many conventional methods which are at our disposal.

Results and Discussion

In accordance with our proposed strategy, the reaction of the trichloride **12** with 4-aminobenzonitrile (**3**) in the presence of diisopropylethylamine (DIEA) was performed. The expected product **13** was carefully analyzed with respect to the position of aniline placement. The NOE studies of the derived product

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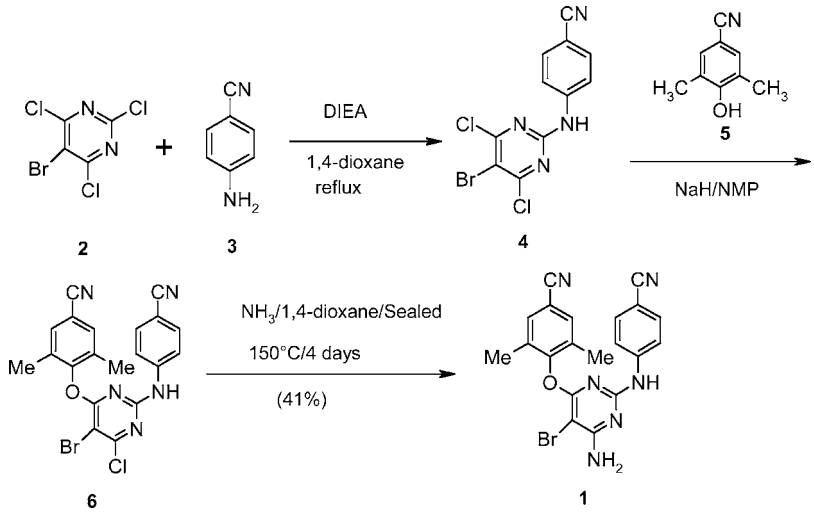
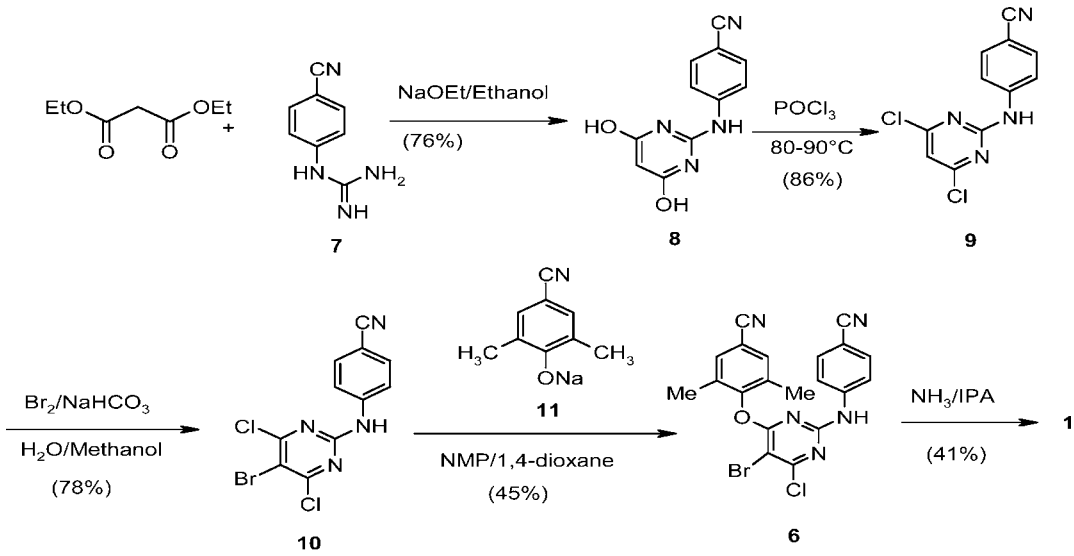
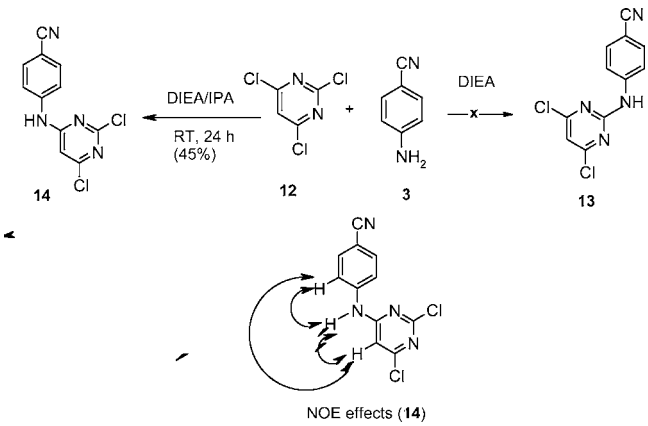
Scheme 1



Scheme 2

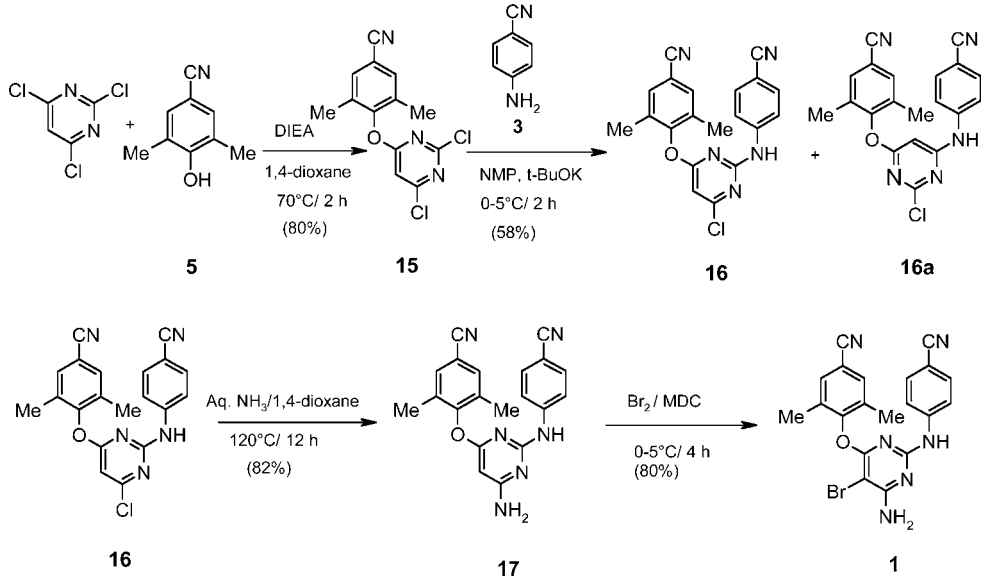


Scheme 3



clearly indicated that **13** was not formed. However, NOE studies revealed the structure **14** to be the product (Scheme 3). Other spectroscopic studies substantiated the structure of **14**. This observation was contrary to the reported synthesis of etravirine (Scheme 1). The difference between the two precursors **2** and **12** was the presence of a bromide group in structure **2**. It became obvious for us to reverse the sequence of nucleophilic substitution reactions (Scheme 4). Compound **12** was first reacted with phenol derivative **5** under similar conditions to give the biaryl ether derivative (**15**). The structure was scrupulously analyzed by spectroscopic methods. Conversion of **12** to **15** was optimized in the laboratory w.r.t. solvent ratio, reaction temperature, molar ratio of compound **5**, and isolation temperature. The second substitution reaction with aniline derivative (**3**) using potassium *tert*-butoxide as a base and *N*-methylpyrrolidone as a solvent gave **16** with a yield of 58%. The major byproduct formed in this step was the isomer **16a** as shown in Scheme 4. Experiments were carried out in the laboratory to avoid the formation of **16a** by lowering the reaction temperature to −10 to −15 °C, using different solvents such as DMSO, DMF, bases such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium methoxide, diisopropyl ethyl amine, pyridine, and triethylamine. The aminolysis of **16** went smoothly at 120−125 °C in 8−12 h to give the amine (**17**) in good yield (82%). Compound **16** contained about 2−3% of **16a** prior to aminolysis which was also converted to the corresponding amino compound during aminolysis. Aminolysis compound of **16a** was removed during isolation of **17** by crystallization from

Scheme 4



1,4-dioxane. Since the aminolysis product of **16a** is absent in **17**, the formation of the bromo isomer during bromination is ruled out. Aminolysis reaction condition was optimized by using different solvents such as methanol, water, and 1,4-dioxane. Reactions were also carried out at 100 and 140 °C. Finally, bromination of **17** was conducted in the presence of liquid bromine in CH_2Cl_2 at 0−5 °C to give etravirine (**1**) in 85% yield. For bromination of **17**, we also tried solvents such as acetic acid or propionic acid, but better results were obtained in methyl dichloride. The spectral and analytical data of **1** were in agreement with reported data. The results were reproduced by scaling up the process from 50-g to 1.2-kg scale.

Experimental Section

The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Varian 400 MHz; the chemical shifts were reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state KBr dispersion using Perkins Elmer FT-IR spectrophotometer. The mass spectra were recorded on Applied Biosystems spectrometer. The melting points were determined by using Buchi apparatus .The solvents and reagents were used without purification. *N*-Methylpyrrolidone with moisture content less than 0.1% was used in the process.

4-[(2,6-Dichloro)-4-pyrimidinyloxy]-3,5-dimethylbenzonitrile (15). 2,4,6-Trichloropyrimidine (1200 g, 6.54 mol), 3,5,-dimethyl-4-hydroxybenzonitrile (961.0 g, 6.54 mol), *N*,*N*-diisopropylethylamine (1014 g, 7.85 mol), and 1,4-dioxane (3.6 L) were heated at 70 °C for 2 h. The reaction mixture was brought to 10−15 °C and filtered, and the residue was washed with 600 mL of chilled 1,4-dioxane. The wet cake was treated with 3.6 L of water at 25−30 °C, filtered, and dried at 55−60 °C under vacuum (600−700 mm of Hg) to give **15** (1539 g, 80% yield with >98% purity by HPLC); mp: 208−210 °C; IR (KBr): 2227, 1559, 1545, 1476, 1406, 1338, 1304, 1264, 1189, 1134, 1106, 980 cm^{-1}; MS (*m/z*): 394, 396, 398; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.11 (s, 6 H), 7.60 (s, 1 H), 7.73 (s, 2 H); ^{13}C NMR (DMSO-d_6, 100 MHz): 15.6, 106.8, 109.3, 116.8, 118.3, 132.3, 132.9, 152.0, 158.5, 162.1, 169.3. Anal. Calcd for $C_{13}H_9Cl_2ON_3$: C, 53.06; H, 3.06; N, 14.28. Found: C, 53.09; H, 3.07; N, 14.31%.

4-[[6-Chloro-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile (16). To a solution of compound **15** (1500 g, 5.1 mol) and 4-aminobenzonitrile (602.0 g, 5.1 mol) in *N*-methylpyrrolidone (7.5 L) at 0−5 °C was added potassium *tert*-butoxide (1144.0 g, 10.2 mol) over a period of 2 h. The reaction was allowed to attain RT followed by careful addition of cold water (30 L). The reaction mixture was filtered; the residue was suspended in water (15.0 lit.) and acidified to pH 6−7 using conc. HCl. The reaction mixture was filtered and washed with 1.5 L of water. Wet cake was dried at 60−65 °C until water content was <1.0%. Crude product containing about 20−25% **16a**, was purified by ethyl acetate treatments (2 × 4.5 L) at 65−70 °C followed by filtration at 10−15 °C and washing the cake with 1.5 L of chilled ethyl acetate. The wet cake was finally dried at 55−60 °C under vacuum (600−700 mm of Hg) to give **16** (1112 g, 58% yield, >95% purity and **16a** 2−3% by HPLC); mp 278.5−280.5 °C, IR (KBr): 3352, 2229, 1522, 1458, 1418, 1365, 1331, 1290, 1223, 1195, 1137, 1108 cm^{-1}; MS(*m/z*): 376, 378; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.12 (s, 6 H), 6.92 (s, 1 H), 7.44 −7.50 (br s, 4 H), 7.78 (s, 2 H), 10.55 (br s, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz): 15.9, 98.1, 103.8, 109.1, 118.8, 119.5, 132.9, 133.0, 143.7, 153.4, 158.4, 161.6, 169.2. Anal. Calcd for $C_{20}H_{14}ClON_5$: C, 63.91; H, 3.72; N, 18.64. Found: C, 63.99; H, 3.64; N, 18.56%.

4-[[6-Amino-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile (17). A mixture of **16** (1100 g, 2.93 mol), 25% aq ammonia (6.6 L), and 1,4-dioxane (11.0 L) was heated in an autoclave at 120 °C for 12 h. To the reaction mixture, was added 1.65 L of water slowly at 50−60 °C, cooled to 5−10 °C, and filtered. The residue was washed with 275 mL of chilled 1,4-dioxane and dried at 55−60 °C to give **17** (860 g, 82% yield, >98% purity by HPLC); mp 284.5−287 °C, IR (KBr): 3505, 3366, 2225, 1611, 1532, 1507, 1456, 1408, 1375, 1244, 1206, 1176 cm^{-1}; MS (*m/z*): 357; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.12 (s, 6 H), 5.45 (s, 1 H), 6.78 (br

s, 2 H), 7.46 (d, 2 H), 7.64 (d, 2 H), 7.72 (s, 2 H), 9.56 (s, 1H): ^{13}C NMR (DMSO-d_6, 100 MHz): 15.8, 78.6, 101.6, 108.0, 117.9, 118.7, 119.6, 132.4, 132.5, 132.9, 145.3, 153.9, 158.9, 166.4, 168.1. Anal. Calcd for $C_{20}H_{16}ON_6$: C, 67.41; H, 4.49; N, 23.59. Found: C, 67.39; H, 4.43; N, 23.51%.

Etravirine (1). To a cooled solution of **17** (850 g, 2.387 mol) in DCM (6.8 L) at 0−5 °C was added bromine solution (401 g, 2.5 mol in 1.7 L of DCM). The reaction was stirred at this temperature for 4 h, diluted with water (6.8 L), and basified with 4 M NaOH solution at pH 9−10. At this point, sodium metabisulphite solution (42.5 g in 170 mL water) was added. The pH of the reaction was maintained between 7.5−8.5 over a period of 1 h by adding 4 M NaOH solution. The solid was filtered, washed with water (12 L), and dried at 55−60 °C temperature to get crude etravirine.

The crude product was dissolved in 15.9 L of acetone at 50−55 °C and treated with 11 g of activated charcoal. After charcoal clarification, 12.5 L of acetone was distilled out, and the residue was cooled to 5−10 °C and filtered. Wet cake was washed with 1.0 L of chilled acetone and finally dried at 55−60 °C under vacuum (600−700 mm of Hg) to give **1** (836 g, 80% yield with 99.80% purity by HPLC); mp 255−257 °C (lit.[5] mp 255−256 °C); IR (KBr): 3484, 3380, 3349, 2223, 1523, 1505, 1454, 1403, 1313, 1243, 1200, 1174, 1139, 1059, 1005 cm^{-1}; MS (*m/z)*: 435, 437; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.12 (s, 6 H),7.11 (br s, 2 H),7.42 (d, 2 H), 7.54 (d, 2 H), 7.74 (s, 2 H), 9.57 (br s, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz): 15.9, 74.6, 102.4, 108.6, 118.4, 119.0, 119.8, 132.7, 133.1, 144.9, 154.4, 156.8, 162.7, 163.75.

2,6-Dichloro,4-[*N*-(4′-cyanophenyl)amino]pyrimidine (14). 2,4,6-Trichloropyrimidine (5.0 g, 27.25 mmol), 4-aminobenzonitrile (2.66 g, 22.5 mmol), *N*,*N*-diisopropylethylamine (5.26 g), and isopropanol (25 mL) were stirred at RT for 24 h, filtered, and washed with water and cold IPA to give **14**, (3.2 g, 45.0%); mp 293−295 °C; IR (KBr): 3316, 3212, 3112, 2230, 1633, 1558, 1510, 1449, 1274, 1240, 1180, 1120 cm^{-1}; MS (*m/z)*: 263, 265, 267; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.89 (s, 1 H), 7.78 (d, 2 H), 7.84 (d, 2 H), 10.66 (b s, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz): 105.1, 105.3, 118.9, 119.9, 133.3, 142.5, 158.5, 161.6. Anal. Calcd for $C_{11}H_6Cl_2N_4$: C, 49.81; H, 2.26; N, 21.13. Found: C, 49.82; H, 2.28; N, 20.92%.

Conclusion

In conclusion, we have successfully developed a simple, cost-effective, and industrially scalable process for the synthesis of etravirine.

Acknowledgment

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Supporting Information Available

Mass, IR, ^{1}H and ^{13}C NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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