An efficient synthesis of Ceritinib (LDK378) using a Sandmeyer reaction

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A convenient route for the synthesis of Novartis's second-generation anaplastic lymphoma kinase inhibitor Ceritinib (LDK378) involving starting materials that are commercially available has been achieved. The procedure employed mild reaction conditions and avoided the use of expensive reagents compared to the original synthetic route reported by Novartis. More importantly, gram scale synthesis was accomplished and this protocol could be valid in drug discovery synthesis.

Keywords: ceritinib, LDK378, Sandmeyer reaction, diazonium salts, 2,4-dichloro-5-nitropyrimidine

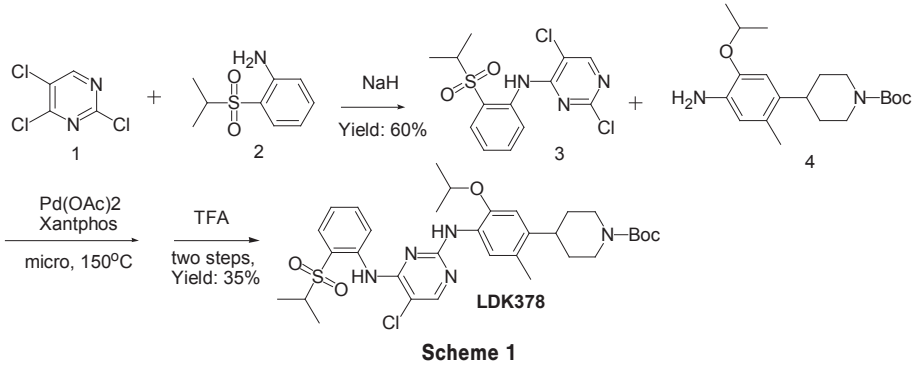
The treatment of non–small cell lung cancer (NSCLC) is being targeted by several different small molecules and inhibitors. Crizotinib is a first-generation tyrosine kinase inhibitor, becoming highly active in patients with ALK-rearranged NSCLC and is used as first-line therapy in the setting of advanced disease.[1-3] However, resistance to crizotinib occurs through a variety of ways. Ceritinib (LDK378) is a new ALK inhibitor that has shown greater antitumor potency than crizotinib in clinical studies.[4-9] Since ceritinib has demonstrated promising anticancer activity in (ALK)-positive non-small cell lung cancer (NSCLC) and can overcome resistance following crizotinib exposure, it provides a new option for the treatment of ALK-positive NSCLC. [10-15]

The method shown in Scheme 1 for the synthesis of LDK378 was reported by Marsilje *et al*.[9] The general route contains two transformations, C–N bond formation and Buchwald–Hartwig coupling. The latter was difficult under mild conditions due to the electronic characteristics of compound **3** and a steric effect in compound **4**; moreover, the yield was low in a sealed tube under microwave irradiation and pressure at high temperature. The Xantphos and $Pd(OAc)_2$ reagents used in this route are expensive, and so it is not suitable for large-scale production. On the other hand, the Sandmeyer-type transformation is a classical and valuable method used to synthesise halogeno, cyano, hydroxyl and sulfonate groups from the amino group.[16] In these transformations, aryl diazonium salts which have been recently explored in various new reactions,[17-23] are the crucial reaction intermediates.

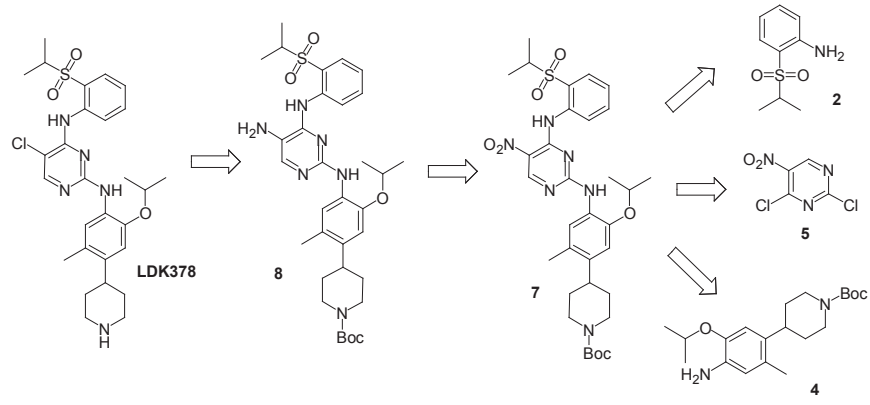
We now report a novel and efficient route for the preparation of LDK378 through a Sandmeyer reaction which proceeds in high yield under mild conditions.

Results and discussion

Our retrosynthetic approach to LDK378 is outlined in Scheme 2, where the ceritinib was envisioned as arising from key



Scheme 1



Scheme 2

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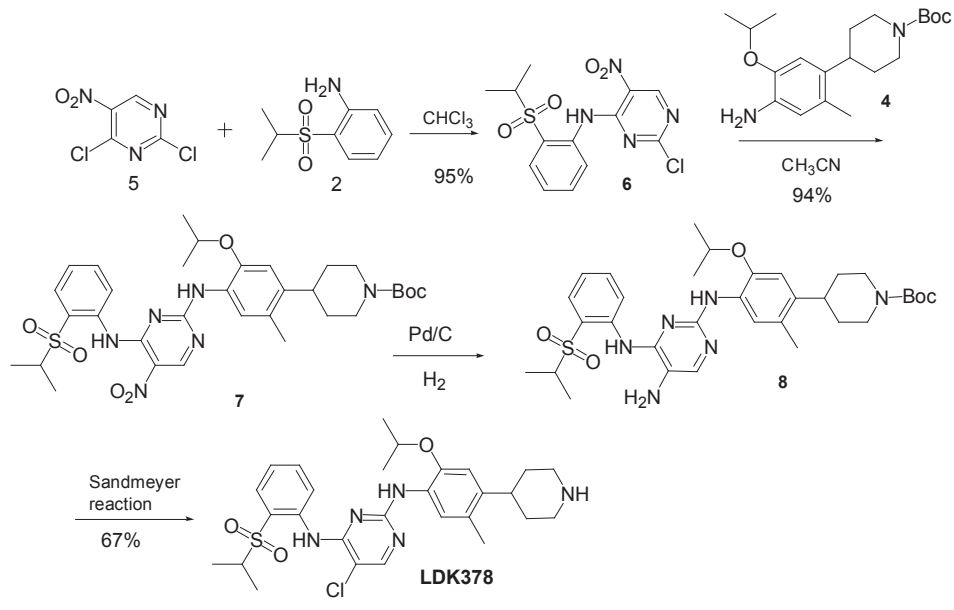

Scheme 3

intermediate **8**. The 5-amino group of **8** would derive from the 5-nitro group of **7** by reduction. Finally, the tetracyclic 5-nitro compound **7** can be broken into three fragments, 1,3-dichloro-4-nitropyridine **5**, 2-(propane-2-sulfonyl)-phenylamine **2** and the Boc-protected compound **4**, the latter two compounds are the starting materials for the Novartis synthesis.[9] We saw the nitro group as an activator providing an enhanced intrinsic reactivity difference between the two chlorine atoms in compound **5** to sequentially introduce the two variously substituted aniline **2** and **4** to the central pyrimidine ring via intermolecular SN_{Ar} reactions.[24] This procedure employed mild reaction conditions and avoided the use of expensive reagents (*e.g.* Xantphos ligand) compared to the original synthetic route reported by the Novartis group.[9]

The total synthesis of LDK378 commenced with commercially available 1,3-dichloro-4-nitropyridine **5** as outlined in Scheme 3. Initially displacement of the 3-chloro group of **5** by the amino group of compound **2** in chloroform provided **6** in 95% yield. Then, displacement of the 1-chloro group of **6** by the amino group of **4** in acetonitrile at a higher temperature yielded **7** in 94% yield. Catalytic reduction of **7** with hydrogen over Pd/C gave a quantitative yield of the corresponding amine **8**. Introduction of the 5-chloro group of LDK378 was achieved from 5-amino derivative **8** through a Sandmeyer reaction under optimal reactions in 67% yield. To further evaluate the synthetic potential of this procedure, gram-scale reactions were performed under the optimised reaction conditions. Gratifyingly, the reactions proceeded smoothly to give the desired product in 63% yield. Finally, comparison of the ^{1}H NMR spectra at 400 MHz of LDK378 in $CDCl_3$ proved to fully align with previously reported spectral data.[9]

Experimental

All reagents including analytical-grade solvents were purchased from Sigma-Aldrich (USA), Aladdin (China), or Sinopharm Chemical Reagent (China) and used without further purification. Melting points are uncorrected. NMR spectra were obtained on a Bruker 400 MHz spectrometer (^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) in $CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. Mass spectra (MS) were obtained from Finnigan (USA) MAT-95 Spectrometry Services. Silica gel (200–300 μm) for flash chromatography was purchased from Qingdao Haiyang Chemical (China).

2-Chloro-4-[2-(propane-2-sulfonyl)-phenylamino]-5-nitropyrimidine (**6**): 2-(Propane-2-sulfonyl)-phenylamine **2**[9] (0.95 equiv.) was added to a solution of 2,4-dichloro-5-nitro-pyrimidine (5.0 g) in $CHCl_3$ (100 mL) at room temperature. The resulting reaction solution was heated to 60°C and stirred for 6 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and cooled to 0°C. Then methyl *t*-butyl ether (MTBE) was added. The mixture was filtered and the solid cake was washed with MTBE. The crude product was purified by recrystallisation to give **6** as a brown solid, m.p. 186–188°C ($CHCl_3$/MTBE); ^{1}H NMR δ 11.56 (s, 1H), 9.26 (s, 1H), 8.26 (d, *J*=8.4, 1H), 8.03 (d, *J*=8.0 Hz, 1H), 7.77(t, *J*=8.0, 16.0 Hz, 1H), 7.48(t, *J*=7.6, 15.2 Hz, 1H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C NMR δ 163.9, 157.9, 153.3, 135.2, 134.6, 131.6, 128.0 127.6, 126.4, 125.6, 55.8, 15.3; HRMS (*m/z*) $[M + Na]^+$ calcd for $C_{13}H_{13}ClN_4O_4S$ Na 379.0244, found 379.0237.

(**7**): Intermediate **6** (1.0 equiv.) was added to a solution of trisubstituted aniline **4**[9] (5.0 g) in 100 mL CH_3CN at room temperature. The resulting reaction mixture was heated to 80°C and stirred for 8 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The mixture was stirred at 0°C for 2 h and filtered. The crude product **7** was used in the next step without further purification. A small sample of **7** was recrystallised to give a brown solid, m.p. 220–221°C(CH_3CN/MTBE); ^{1}H NMR δ 11.3 (s, 1H), 9.21 (s, 1H), 8.01 (m, 3H), 7.87 (m, 1H), 7.65 (m, 1H), 7.45 (m, 1H), 6.73 (s, 1H), 4,59 (m, 1H), 4.28 (m, 2H), 3.27 (m, 1H), 2,79 (m, 3H), 2.07 (s, 1H), 1.93 (m, 2H). 1.41–1.75(m, 25H); ^{13}C NMR δ 154.9, 136.5, 134.2, 131.4, 125.8, 79.6, 71.7, 55.0, 38.4, 32.5, 28.5, 22.2, 18.8, 15.4; HRMS (*m/z*) $[M+Na]^+$ calcd for $C_{33}H_{44}N_6O_7SNa$ 691.2890, found 691.2885.

(**8**): Pd/C (0.5%) was added to a solution of intermediate **7** (5.0 g) in methanol (100 mL) under 1 atm hydrogen at room temperature. The resulting mixture was stirred for 8 h. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was filtered through celite and the solid cake was washed with methanol. The combined organics were concentrated under reduced pressure. The crude product **8** was used in the next step without further purification. A small sample of **8** was recrystallised to give a brown solid; m.p. 105–106°C (methanol/MTBE). ^{1}H NMR δ 9.50 (s, 1H), 8.71 (d, 1H), 8.13 (s, 1H), 7.91 (m, 2H), 7.64 (m, 1H), 7.41 (s, 1H), 7.29 (s, 1H), 7.19 (m, 1H), 6.72 (s, 1H), 4.56 (m, 1H), 4.28 (m, 2H), 3.28 (m, 1H), 2,83 (m, 5H), 1.33–1.52(m, 27H); ^{13}C NMR (100 MHz) δ 155.2, 154.9, 153.9, 147.5, 144.3, 139.6, 136.0, 134.8, 131.2, 128.8, 126.9, 123.4, 122.6, 122.0, 120.0, 118.0,

110.8, 79.5, 71.5, 55.5, 38.2, 32.7, 28.5, 22.3, 19.0, 15.4; HRMS (*m/z*) [M + H]+ calcd for $C_{33}H_{47}N_6O_5S$ 639.3329, found 639.3321.

5-Chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (LDK378): A mixture of intermediate **8** (8.0 mmol), a cuprous compound (1.0 equiv.) and isobutyl nitrite (1.2 equiv.) in acetone (80 mL) was cooled to 10°C. The resulting reaction mixture was stirred for 2 h. The solvent was removed under reduced pressure, 6N HCl aqueous (80 mL) was added to the residue and heated to 80°C and stirred for 1 h. After completion of the reaction, the reaction mixture was cooled to room temperature, neutralised with aqueous NaOH and extracted with EtOAc several times. The combined organic layers were washed with saturated brine, dried over anhydrous Mg_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (DCM-methanol=20:1) to give the corresponding LDK378 as a colourless solid; m.p. 107–109°C; MS (*m/z*) $[M + H]^+$ calcd for $C_{28}H_{37}ClN_5O_3S$, 558.2, found 558.1.

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