HETEROCYCLES, Vol. 89, No. 4, 2014, pp. 1035 - 1040. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 8th January, 2014, Accepted, 21st February, 2014, Published online, 6th March, 2014
DOI: 10.3987/COM-14-12933

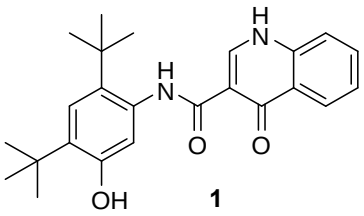
EXPEDITIOUS SYNTHESIS OF IVACAFTOR

Yang He,[a,1] Qien Xu,[b,1] Wenpeng Ma,[b] Jian Zhang,[a] Hongbing Sun,[b] and Jingshan Shen[*a]

[1]The authors contributed equally to this work. [a]Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Pudong, Shanghai 201203, China. [b]College of Pharmacy, China Pharmaceutical University, 639 Longmian Road, Jiangning, Nanjing 211100, China. E-mail: shenjingshan@simm.ac.cn

Abstract – An expeditious synthesis for Ivacaftor featuring modified Leimgruber-Batcho procedure was described. The overall yield is 39% over six steps from commercially available 2-nitrobenzoyl chloride.

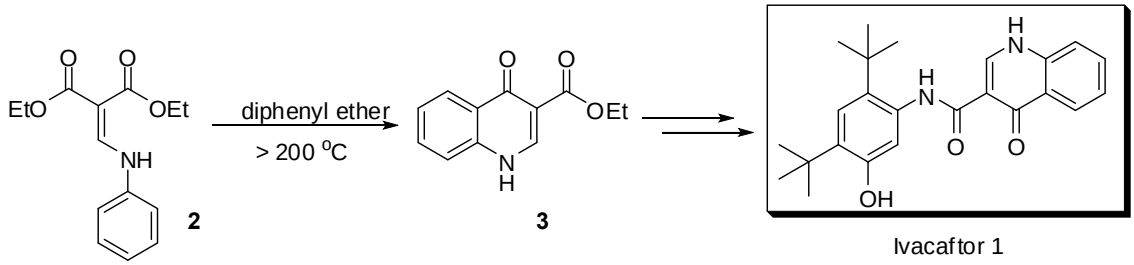
Ivacaftor (also known as VX-770) **1** (Figure 1), a potentiator of the cystic fibrosis transmembrane conductance regulator (CFTR), was a drug approved by FDA in 2012. As novel mutation-specific therapy to treat CF, Ivacaftor **1** represents a landmark in the treatment of this disease.[1,2]



1

Figure 1. Chemical structure of Ivacaftor

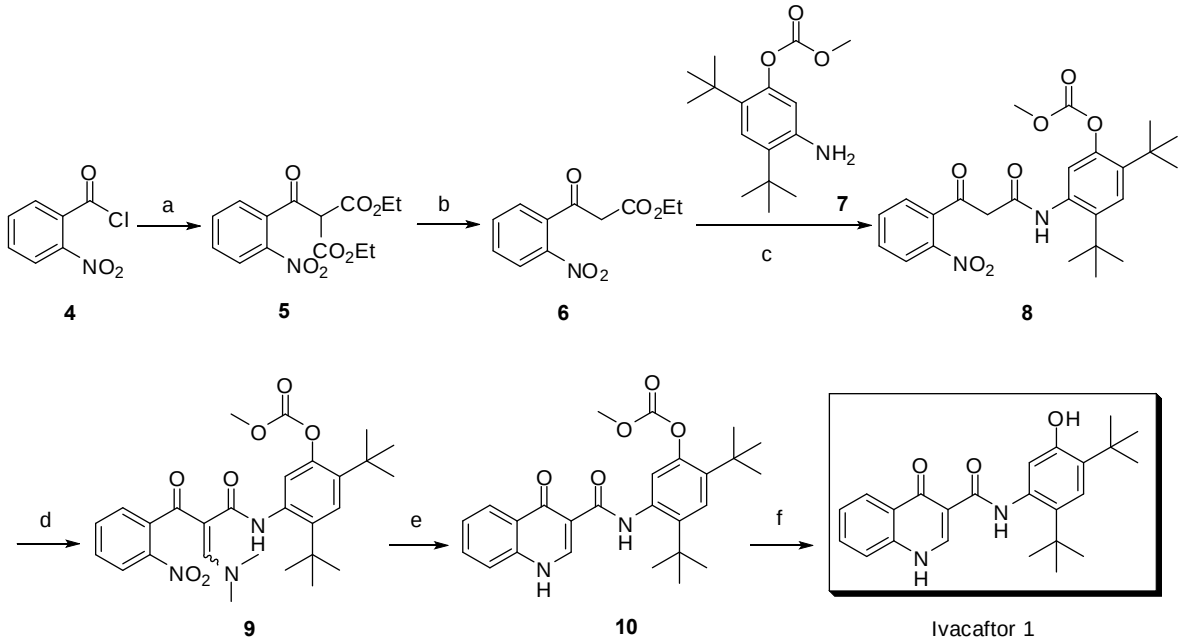
The reported approach[3] to the synthesis of Ivacaftor **1** (Scheme 1**)** suffered from several drawbacks associated with the Gould-Jacobs procedure[4-6] to build quinolone skeleton. The harsh conditions required for the cyclization step led to a messy and tedious operation. Furthermore, diphenyl ether involved in the process is high-boiling point solvent which is difficult to recover, harmful to the environment; and also causes allergic reactions in the operation people. Thus, development of a simple and efficient synthetic route is in urgent need.



Scheme 1. Reported synthesis of Ivacaftor

The Leimgruber-Batcho procedure is a widely used method for the preparation of indole containing structures.[7-9] Previously, Zhang in our group reported the synthesis of *N*-(3-cyano-7-ethoxy-1,4-dihydro-4-oxoquinolin-6-yl)acetamide[10] in 31% yield for 10 steps utilizing a modified Leimgruber-Batcho procedure. We had also applied this strategy in the synthesis of Ivacaftor **1**. Compared with the reported routes, our approach featuring reductive cyclization of enaminone is efficient and atom-economic. The use of several expensive condensation reagents such as T_3P or HATU was also avoided.

As shown in **Scheme 2**, keto-ester **6** could be readily synthesized from 2-nitrobenzoyl chloride **4** according to the well-established chemistry. Firstly, diethyl malonate was coupled with 0.95 equivalents of **4** using triethylamine in the presence of anhydrous magnesium chloride. Then, crude diethyl 2-(2-nitrobenzoyl)malonate **5** was decarboxylated in water to afford **6** as a yellow oil.

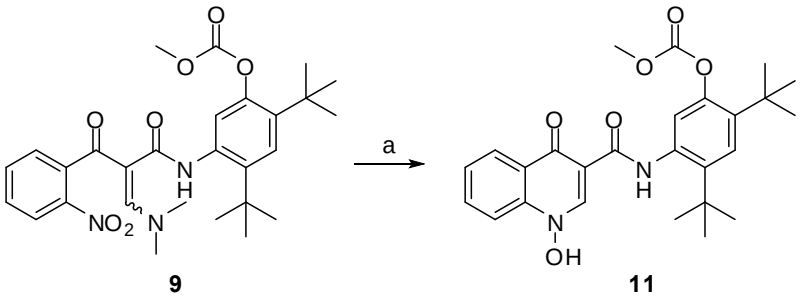


Reagents and conditions: (a) $MgCl_2$, Et_3N, $CH_2(CO_2Et)_2$, MeCN, 0-5 °C then rt, 100%; (b) H_2O, reflux, 95%; (c) toluene, reflux, 65%; (d) DMF-DMA, toluene, rt, 98%; (e) Fe, AcOH, 90 °C; (f) NaOH, MeOH-H_2O, rt, 65% over two steps.

Scheme 2. Synthesis of Ivacaftor

Aminolysis of **6** with **7**[3] was carried out in toluene to give **8** at reflux temperature for 24 hours. The crude *β*-keto amide **8** was purified by recrystallization in *t*-BuOMe/EtOAc solvent in 65% overall yield and 99% purity (HPLC). When xylene was used instead of toluene, the isolated yield of **8** decreased obviously. Condensation of **8** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) at room temperature gave enaminone **9** smoothly.

Treatment of enaminone **9** with 10% Pd/C in methanol under hydrogen atmosphere yielded exclusively *N*-hydroxyquinolone **11**, presumably due to nitro group was partially reduced to hydroxylamine, followed by an intramolecular cyclization immediately.



9 **11**

Reagents and conditions: (a) H_2, 10% Pd/C, MeOH, 88%.

Scheme 3. Synthesis of *N*-hydroxyquinolone **11**

We also examined whether it could be possible to get **10** under catalytic transfer hydrogenation[11-13] condition utilizing cyclohexene as hydrogen source and 10% Pd/C as catalyst. However, enaminone **9** remained intact under this condition. Upon treatment of **9** with iron powder in glacial acetic acid, **10** was obtained without purification. Finally, synthesis of Ivacaftor **1** was achieved through hydrolysis. All spectral data for the synthesized Ivacaftor **1** were identical with the published results.

In summary, we have developed a simple and efficient approach to the synthesis of Ivacaftor **1** in 6 steps with 39% overall yield. Scale-up and related studies is now ongoing in our laboratories. And we are confident that the present route should be valuable in the synthesis of Ivacaftor.

EXPERIMENTAL

All commercially available materials and solvents were used directly without further purification. ^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer and ^{13}C NMR spectra were obtained from a Bruker AMX 400/600 spectrometer at 100 MHz using TMS as an internal standard. The mass spectra (LRMS and HRMS) were recorded on a finnigan MAT-95/711 spectrometer.

Diethyl 2-(2-nitrobenzoyl)malonate (5)

The procedure of Bunce and Nammalwar was modified:[14,15] Anhydrous magnesium chloride (11.3 g, 118

mmol) was added to a solution of diethyl malonate (17.2 mL, 113 mmol) in MeCN (50 mL) at 5 °C for 10 min. Subsequently, triethylamine (32.8 mL, 237 mmol) was added at 0-5 °C and the mixture was stirred at room temperature for 1 h. After cooling to 0 °C, a solution of 2-nitrobenzoyl chloride **4** (19.8 g, 107 mmol) in CH_2Cl_2 (25 mL) was added dropwise to the resulting mixture at 0-5 °C, and the mixture was stirred at room temperature for 2 h. The resulting solution was poured into chilled water (200 mL), acidified to pH 2-3 with conc. HCl. MeCN was evaporated and the reaction mixture was diluted with EtOAc. The organic layer was washed with brine, dried and concentrated under reduced pressure to give **5** (33 g, 100%) as pale yellow oil. MS (*m/z*): 309 (M^+), 150.

Ethyl 3-(2-nitrophenyl)-3-oxopropanoate (6)

A mixture of **5** (33 g, 107 mmol) and water (50 mL) was heated at 100-110 °C for 5 h. Then the solution was cooled to room temperature and extracted with EtOAc. The organic layer was dried and evaporated under reduced pressure to provide **6** (26 g, 95%) as pale yellow oil, which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.14 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.89 (td, *J* = 7.5, 1.5 Hz, 1H), 7.75-7.83 (m, 2H), 4.11 (s, 2H), 4.08 (q, *J* = 6.9 Hz, 2H), 1.14 (t, *J* = 6.9 Hz, 3H); MS (*m/z*): 238 (M^+), 191, 163, 150.

2,4-Di-*tert*-butyl-5-(3-(2-nitrophenyl)-3-oxopropanamido)phenyl methyl carbonate (8)

A mixture of **6** (3.25 g, 13.7 mmol), **7** (2.95 g, 10.5 mmol) and toluene (10 mL) was heated at 110 °C for 24 h. Then the solution was cooled to room temperature and concentrated. A solution of hexane/ *t*-BuOMe (v:v = 10 mL:10 mL) was added and the mixture was stirred for 1 h. The resulting solid was filtered and recrystallized from *t*-BuOMe/EtOAc (v:v = 15 mL:3 mL) to give **8** (3.2 g, 65%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (brs, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 8.4 Hz, 1H), 7.51 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.40 (s, 1H), 3.94 (s, 2H), 3.90 (s, 3H), 1.46 (s, 9H), 1.35(s, 9H); ^{13}C NMR (100 Hz, $CDCl_3$): δ 196.7, 160.9, 152.2, 145.4, 143.2, 137.7, 136.0, 134.7, 132.8, 130.9, 129.2, 125.4, 123.3, 122.5, 119.7, 53.4, 47.8, 32.7, 28.5, 28.1; ESI-MS (*m/z*): 471.4 $[M+H]^+$, 493.4 $[M+Na]^+$, 469.3 $[M-H]^-$; ESI-HRMS: Calcd for $C_{25}H_{30}N_2O_7Na$ $[M+Na]^+$: 493.1951. Found 493.1940.

2,4-Di-*tert*-butyl-5-(3-(dimethylamino)-2-(2-nitrobenzoyl)acrylamido)phenyl methyl carbonate (9)

To a stirred solution of **8** (0.972 g, 2.1 mmol) in toluene (5 mL) was added dropwise DMF-DMA (0.56 mL, 4.2 mmol) at room temperature. The mixture was stirred at room temperature for 3 h. Evaporation of the solvent afforded enamine **9** (1.1 g, 98%) as a bright yellow solid (mixtures of *E*- and *Z*-isomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.23 (brs, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 8.01 (s, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.38 (s, 1H), 7.25 (s, 1H), 3.89 (s, 3H), 3.11 (s, 6H), 1.45 (s, 9H), 1.33 (s, 9H); ESI-MS (*m/z*): 526.0 $[M+H]^+$, 548.2 $[M+Na]^+$; ESI-HRMS: Calcd for $C_{28}H_{35}N_3O_7Na$ $[M+Na]^+$: 548.2373. Found 548.2371.

2,4-Di-*tert*-butyl-5-(4-oxo-1,4-dihydroquinoline-3-carboxamido)phenyl methyl carbonate (10)

A suspension of **9** (900 mg, 1.7 mmol) and iron powder (287 mg, 5.1 mmol) in AcOH (3 mL) was heated at 90 °C for 3 h. The resulting mixture was cooled to room temperature and concentrated. The residue was neutralized by aqueous $NaHCO_3$ and filtered. The filtrate was extracted with EtOAc. The organic layer was dried and evaporated to afford crude **10** (830 mg) as a brown solid, which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.94 (d, J = 6.6 Hz, 1H), 12.07 (s, 1H), 8.87 (d, J = 6.6 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.72-7.85 (m, 2H), 7.58 (s, 1H), 7.52 (td, J = 7.5, 1.2 Hz, 1H), 7.38 (s, 1H), 3.84 (s, 3H), 1.45 (s, 9H), 1.31(s, 9H); ^{13}C NMR (100 Hz, $CDCl_3$): δ 177.6, 165.5, 154.2, 147.5, 144.4, 142.3, 139.1, 138.5, 133.7, 132.3, 126.5, 125.9, 125.3, 124.9, 124.0, 119.0, 110.3, 55.4, 35.1, 34.7, 30.5, 30.2; ESI-MS (*m/z*): 451.3 $[M+H]^+$, 449.3 $[M-H]^-$; ESI-HRMS: Calcd for $C_{26}H_{30}N_2O_5Na$ $[M+Na]^+$: 473.2052. Found 473.2028.

***N*-(2,4-Di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (1)**

To a stirred solution of **10** (830 mg, 1.8 mmol) in MeOH (2 mL) was added NaOH (142 mg, 3.5 mmol) dissolved in H_2O (2 mL). The reaction mixture was stirred at room temperature for 3 h and acidified with 2 M HCl to pH 5-6. The resulting precipitate was collected by suction filtration and recrystallized from EtOH to give **1** (436 mg, 65% for 2 steps) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.87 (brs, 1H), 11.81 (s, 1H), 9.19 (s, 1H), 8.86 (s, 1H), 8.32 (d, J = 8.1 Hz, 1H), 7.72-7.84 (m, 2H), 7.51 (td, J = 7.5, 1.5 Hz, 1H), 7.16 (s, 1H), 7.09 (s, 1H), 1.37 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (100 Hz, DMSO-d_6): δ 176.9, 163.3, 153.7, 144.6, 139.6, 134.0, 133.3, 132.7, 131.9, 126.4, 126.0, 125.5, 124.2, 119.5, 116.4, 111.2, 34.8, 34.4, 31.0, 29.8; ESI-MS (*m/z*): 393.1 $[M+H]^+$, 391.2 $[M-H]^-$; ESI-HRMS: Calcd for $C_{24}H_{28}N_2O_3Na$ $[M+Na]^+$: 415.1998. Found 415.1987.

2,4-Di-*tert*-butyl-5-(1-hydroxy-4-oxo-1,4-dihydroquinoline-3-carboxamido)phenyl methyl carbonate (11)

To a solution of **9** (200 mg, 0.38 mmol) in MeOH (1 mL) was added Pd/C (20 mg) under N_2. The reaction mixure was hydrogenated under H_2 for 3 h. Filtration followed by evaporation of the solvent afforded **11** (157 mg, 88%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.01 (s, 1H), 8.91 (s, 1H), 8.38 (d, J = 8.1 Hz, 1H), 7.89-8.02 (m, 2H), 7.56-7.65 (m, 2H), 7.38 (s, 1H), 3.85 (s, 3H), 1.45 (s, 9H), 1.31 (s, 9H); ESI-MS (*m/z*): 467.26 $[M+H]^+$, 465.25 $[M-H]^-$; ESI-HRMS: Calcd for $C_{26}H_{30}N_2O_6Na$ $[M+Na]^+$: 489.2002. Found 489.1989.

REFERENCES

1. S. V. Raju and S. M. Rowe, *Drugs Fut.*, 2012, **37**, 167.
2. E. D. Deeks, *Drugs*, 2013, **73**, 1595.
3. S. G. Arekar, S. C. Johnson, M. Krawiec, A. Medek, P. Mudunuri, and M. J. Sullivan, U.S. Pat. Appl.

Publ. 2011, US 2011/0230519.

4. E. Stern, G. G. Muccioli, R. Millet, B. Bosier, L. Hamtiaux, R. Millet, J. H. Poupaert, J. Henichart, P. Depreux, J. Goossens, and D. M. Lambert, *J. Med. Chem.*, 2006, **49**, 70.
5. P. Cernuchova, G. Vo-Thanh, V. Milata, and A. Loupy, *Heterocycles*, 2004, **64**, 177.
6. X. Cao, Z. Li, Y. Yang, and X. Wang, *Synth. Commun.*, 2009, **39**, 4375.
7. H. Maehr and J. M. Smallheer, *J. Org. Chem.*, 1981, **46**, 1752.
8. J. Siu, I. R. Baxendale, and S. V. Ley, *Org. Biomol. Chem.*, 2004, **2**, 160.
9. A. Shahrisa, Z. Ghasemi, and M. Saraei, *J. Heterocycl. Chem.*, 2009, **46**, 273.
10. Q. Zhang, Y. Mao, Z. Liu, K. Xie, Y. Zhu, Y. Wei, X. Jiang, and J. Shen, *Heterocycles*, 2011, **83**, 2851.
11. I. D. Entwistle, R. A. W. Johnstone, and T. J. Povall, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1300.
12. A. E. Jackson and R. A. W. Johnstone, *Synthesis*, 1976, 685.
13. J. Tois, M. Vahermo, and A. Koskinen, *Tetrahedron Lett.*, 2005, **46**, 735.
14. R. A. Bunce and B. Nammalwar, *Org. Prep. Proced. Int.*, 2010, **42**, 557.
15. M. Tamaru and Y. Saito, *Pestic. Sci.*, 1996, **47**, 125.