Organic Process Research & Development

Technical Note

pubs.acs.org/OPRD

A Practical Synthesis of a *cis*-4,5-Bis(4-chlorophenyl)imidazoline Intermediate for Nutlin Analogues

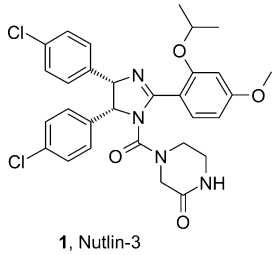
Lianhe Shu,* Ping Wang, Wen Liu, and Chen Gu

Process Research and Synthesis, Pharma Research and Early Development (pRED), Hoffmann-La Roche, Inc., 340 Kingsland Street, Nutley, New Jersey 07110, United States

ABSTRACT: A practical synthesis of *cis*-4,5-bis(4-chlorophenyl)imidazoline, a key intermediate for Nutlin analogues, is reported. The title compound was prepared in 81−88% yield by boric acid catalyzed direct condensation of *meso*-bis(4-chlorophenyl)ethane-1,2-diamine with a benzoic acid. The process was successfully scaled up in a pilot plant, resulting in >15 kg of the product.

INTRODUCTION

Since their discovery in 2004, Nutlins (e.g., Nutlin-3, **1**) have received extensive attention due to their cancer treatment potential.[1,2] A variety of Nutlin analogues have been prepared and evaluated in preclinical studies.[3] A common component of these compounds is a *cis*-4,5-diaryl-4,5-dihydro-1*H*-imidazole core, such as **4**. In the original synthesis (Scheme 1), this imidazoline moiety was constructed *via* condensation of *meso*-diamine **2** with benzoate **3** in the presence of a stoichiometric amount of trimethylaluminum.[3] Due to safety concerns regarding the handling of pyrophoric alkylaluminum compounds and the tedious workup caused by the alumina gel, this direct condensation method is not suitable for large scale production. A number of approaches for the synthesis of imidazolines from 1,2-diamines have been reported in the literature,[4] but none appeared promising for scale-up. After the completion of this investigation, two interesting papers appeared: a novel asymmetric synthesis of Nutlin-3 using the aza-Henry reaction[5] and a catalytic desymmetrization of *meso*-diamines.[6] While the reactions gave encouraging enantioselectivities and yields, both syntheses are not considered ready for large scale preparation before those catalysts used become readily available. Herein, we describe a convenient one-step synthesis of 2-(4-*tert*-butyl-2-ethoxyphenyl)-*cis*-4,5-bis(4-chlorophenyl)-4,5-dihydro-1*H*-imidazole (**4**), a key intermediate for a number of Nutlin analogues.[3] This process has been successfully scaled up in a pilot plant.



1, Nutlin-3

RESULTS AND DISCUSSION

Because initial attempts to replace $AlMe_3$ with catalytic amounts of relatively less pyrophoric aluminum reagents, such as $EtAlCl_2$ and $MeAlCl_2$, were unsuccessful, a two-step process *via* the cyclization of monoamide **6** was pursued. As shown in Scheme 2, treatment of acid **5** with 1,1′-carbonyldiimidazole (CDI) in THF, followed by the addition of diamine **2**, produced a mixture of the desired monoamide **6** and bis-amide **7**. The monoacylation of a diamine is challenging since the resulting monoamide is usually more reactive than the diamine.[7] In order to improve the selectivity of **6**, solvent and concentration effects were investigated. Among the solvents screened,[8] THF gave the best selectivity. When the reaction was run under high concentrations, compound **6** precipitated from the reaction mixture, thus effectively minimizing the formation of bis-amide **7**. It has been reported that carbon dioxide could catalyze the coupling of amines with imidazolides,[9] but the coupling of diamine **2** with the imidazolide of **5** proceeded faster under CO_2-free conditions and gave better mono selectivity. The acylation was complete within 16 h and gave **6** and **7** in a ratio of *ca.* 15−20:1. Crude **6** containing 5−9% of **7** was obtained in *ca.* 84% yield by precipitation. The purity could not be upgraded by crystallization as **7** is significantly less soluble than **6**.

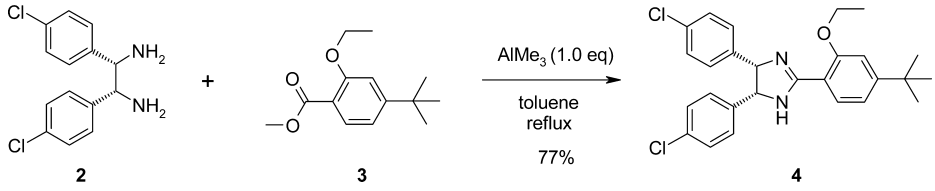
With compound **6** in hand, the cyclization (Scheme 3) was examined in xylenes at reflux in the presence of a strong acid, *e.g.*, *p*-toluenesulfonic acid (*p*-TSA) or sulfuric acid. Water generated from the reaction was removed *via* a Dean−Stark trap. While reactions catalyzed by a catalytic or stoichiometric amount of *p*-TSA did not go to completion, presumably due to the formation of *p*-TSA anhydride, reactions with 1 equiv of sulfuric acid in xylenes proceeded quite smoothly. After the reaction mixture was stirred at reflux overnight, the sulfate of **4** was collected in 90−95% yield by filtration. The impurity **7** carried through from the previous step was removed as it remained in the solution phase.

The scale-up of this process, however, was not as smooth. As shown in Table 1, whereas a 1 g scale reaction (entry 1) was complete within 6 h using only 0.05 equiv of sulfuric acid, a 100 g scale reaction required 1 equiv of sulfuric acid and heating for 40 h (entry 3), though **4**-H_2SO_4 was still obtained in good yield

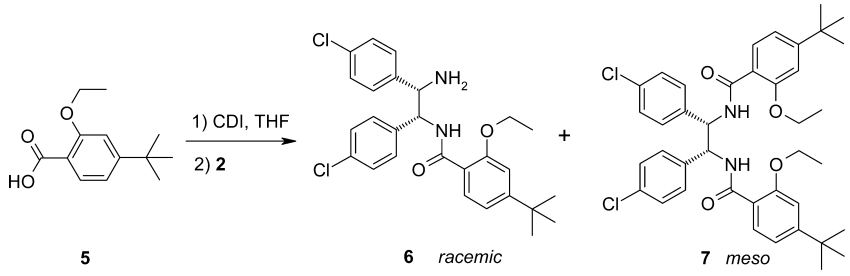
Received: September 13, 2012
Published: October 19, 2012

dx.doi.org/10.1021/op300254q | *Org. Process Res. Dev.* 2012, 16, 1866−1869

Scheme 1. Original Synthesis of 4



Scheme 2. Preparation of Monoamide 6



Scheme 3. Cyclization of 6 to 4

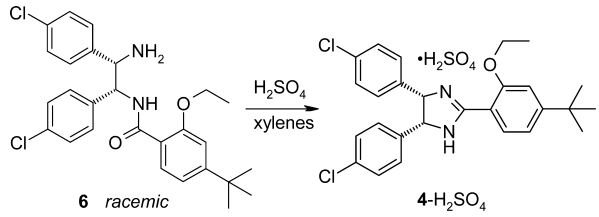


Table 1. Condensation of 6 at Different Scale

entry	scale (g)	H_2SO_4 (equiv)	time (h)	yield (%)
1	1.0	0.05	6	89
2	10	1.0	16	95
3	100	1.0	40	92
4	1300	1.0	100	78

and purity. At the 1.3 kg scale (entry 4), the reaction became even slower and the prolonged heating caused significant degradation, impacting the yield and quality of the product. The reaction was stopped prematurely at 100 h, and the product was obtained in only 78% yield.

The reason for the diminished reaction rate on scale-up is not evident, but if it is assumed that the reaction occurs only at the hot surface of the reaction vessel, which is at a higher temperature than xylenes at reflux, the scale-up effect could then be explained by a decrease in the surface area per reaction volume.

As the strong acid catalyzed process was deemed unsuitable for further scale-up, the direct condensation of **2** and **5** was investigated. Treatment of a mixture of **2** and **5** with strong acids, such as sulfuric acid or *p*-toluenesulfonic acid, or dehydration agent (i.e., thionyl chloride) gave either very low conversion or significant decomposition. Fortunately, boric acid, a cheap, nontoxic, and environmentally benign weak acid, was found to be an effective catalyst. Boric acid was previously reported to be a good catalyst for the formation of amides from carboxylic acids and amines.[10]

When a mixture of **2**, **5**, and a catalytic amount of boric acid in xylenes was heated to reflux, the reaction directly gave the cyclized product **4** (Scheme 4), with only a trace amount of **6** detected in the reaction mixture. With 5−10 mol % of boric acid, the reaction was complete after stirring at reflux overnight. After dilution with dichloromethane[11] and aqueous work-up, the resulting solution of **4** was treated with conc HCl. Upon azeotropic removal of water, the product, **4**-HCl, crystallized and was collected by filtration in 81−88% yield and >98% purity. Unlike the two-step synthesis that did not scale up, this direct condensation process performed consistently from milligram to multikilogram at pilot plant scale. Besides **4**, this method has also been successfully utilized for the preparation of the imidazoline core of Nutlin-3 (**1**) at the kilogram scale.

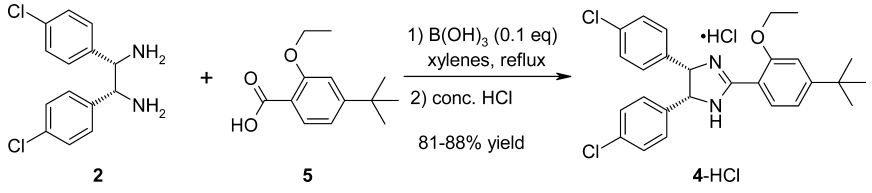
■ CONCLUSION

In summary, we have developed a simple and convenient one-step synthesis of 2-(4-*tert*-butyl-2-ethoxyphenyl)-*cis*-4,5-bis(4-chlorophenyl)-4,5-dihydro-1*H*-imidazole using boric acid as the catalyst. The robustness of this process was subsequently demonstrated in a pilot plant.

■ EXPERIMENTAL SECTION

General. HPLC analysis was performed on Agilent Zorbax XDB-C8 (100 mm × 3 mm, 3.5 μm) column with 5−100% CH_3CN/water (+0.1% TFA) over 10 min as mobile phase at a

Scheme 4. Boric Acid Catalyzed Condensation of 2 and 5 to Give 4



dx.doi.org/10.1021/op300254q | *Org. Process Res. Dev.* 2012, 16, 1866−1869

flow rate of 0.5 mL/min. Compound **2** was prepared in 51% yield from *p*-chlorobenzaldehyde using an optimized process based on a published route.[12] Bulk quantity of compound **5** was prepared by contract suppliers following the procedure described below.

2-Bromo-5-*tert*-butylphenol. A 500 mL 3-necked round bottomed flask equipped with a magnetic stirrer, addition funnel, thermometer, and nitrogen inlet/bubbler was charged with 3-*tert*-butylphenol (48.0 g, 319 mmol) and dichloromethane (100 mL), and then a solution of bromine (16.5 mL, 320 mmol) in dichloromethane (50 mL) was added over 15 min, while maintaining the temperature of the reaction mixture below 35 °C. After the addition was complete, NMR analysis indicated a complete reaction. The reaction was then quenched with a solution of $NaHSO_3$ (1.0 g) in water (150 mL). After 5 min of stirring, the organic layer was separated, washed with water (200 mL), and concentrated at 30 °C/20 mmHg to give 2-bromo-5-*tert*-butylphenol[13,14] (72.5 g, 99% yield) as a colorless oil, which was used directly in the next step.

1-Bromo-2-ethoxy-4-*tert*-butylbenzene. A 500 mL three-neck round bottomed flask equipped with a magnetic stirrer, additional funnel, condenser, and nitrogen inlet/bubbler was charged with 2-bromo-5-*tert*-butylphenol (20.0 g, 87.3 mmol) and THF (200 mL). Then, potassium *tert*-butoxide (10.3 g, 91.7 mmol) was added with stirring. To the resulting yellow solution was added iodoethane (7.4 mL, 92.6 mmol). The mixture was heated to reflux for 3 h, additional iodoethane (1.0 mL, 12.6 mmol) was added, and heating was continued for an additional 5 h. TLC analysis indicated complete reaction. After cooling to room temperature, the reaction mixture was diluted with *n*-heptane (50 mL), washed with water (2 × 50 mL) and saturated sodium chloride solution (50 mL), and concentrated at 30 °C/20 mmHg to give 1-bromo-2-ethoxy-4-*tert*-butylbenzene[15] (21.8 g, 97% yield) as a colorless oil, which was directly used in the next step.

4-*tert*-Butyl-2-ethoxy-benzoic Acid (5). A 500 mL three-necked round bottomed flask equipped with a mechanic stirrer, condenser, thermometer, and nitrogen inlet/outlet was charged with magnesium (2.16 g, 88.8 mmol) and THF (160 mL), and 1-bromo-2-ethoxy-4-*tert*-butylbenzene (2.0 g, 7.8 mmol) was added, followed by a few crystals of iodine. Upon heating to 40 °C, the reaction initiated, and then additional 1-bromo-2-ethoxy-4-*tert*-butylbenzene (18.0 g, 70.0 mmol) was added dropwise at a rate to maintain a gentle reflux. The resulting mixture was heated to reflux with stirring for 2.5 h. NMR analysis indicated complete reaction. The reaction mixture was cooled to −20 °C with a dry ice−acetone bath, then carbon dioxide was bubbled into the reaction mixture until the absorption of gas was complete. TLC analysis indicated complete reaction. The mixture was allowed to warm to room temperature and was stirred overnight. Then 1 M HCl (160 mL, 160 mmol) was added, and the mixture was extracted with ethyl acetate (160 mL). The organic layer was washed with saturated sodium chloride solution (160 mL), dried over magnesium sulfate, and concentrated under reduced pressure to give 17.0 g of crude **5** as an orange solid. This material was redissolved in *n*-heptane (120 mL) at reflux. After cooling to 0 °C and stirring at this temperature for 20 min, the resulting solid was collected by filtration, washed with cold *n*-heptane (20 mL), and dried by suction to give **5** (14.80 g, 85.6% yield) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.90 (brs, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.15 (dd, J = 8.3, 1.5 Hz, 1H), 7.03 (d, J = 1.5 Hz, 1H), 4.35 (q, J = 7.0 Hz, 2H), 1.57 (t, J = 7.0 Hz, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.44, 159.44, 157.26, 133.31, 119.48, 114.94, 109.63, 65.77, 35.41, 30.96, 14.66.

***rac*-*N*-[(1*R*,2*S*)-2-Amino-1,2-bis(4-chlorophenyl)ethyl]-4-*tert*-butyl-2-ethoxybenzamide (6).** A 500 mL three-necked round bottomed flask equipped with a mechanic stirrer, thermometer, and nitrogen inlet/outlet was charged with **5** (20.0 g, 90.0 mmol) and THF (40 mL). Then CDI (15.0 g, 92.3 mmol) was added portionwise over 10 min. After 30 min of stirring, NMR analysis indicated the complete conversion to imidazolide. The flask was evacuated under vacuum to remove CO_2, and then **2** (27.8 g, 99.0 mmol) was added. The solution was stirred at room temperature overnight, and NMR analysis indicated a complete reaction. The resulting thick suspension was dissolved in THF (40 mL) and isopropyl acetate (120 mL). After being washed with water (2 × 80 mL), the organic phase was concentrated under atmospheric pressure. Additional isopropyl acetate (80 mL) was added to ensure that water was removed azeotropically. After a total of *ca.* 200 mL of solvent was removed, *n*-heptane (240 mL) was added slowly. The resulting suspension was filtered. The filter cake was washed with *n*-heptane (2 × 100 mL) and dried to give **6** (40.2 g, containing 9 wt % of **7** as determined by NMR, 84% yield) as off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 1.5 Hz, 1H), 7.02 (dd, J = 8.2, 1.5 Hz, 1H), 5.21 (dd, J = 8.3, 5.8 Hz, 1H), 4.26 (d, J = 5.8 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.92 (s, 2H), 1.39 (t, J = 7.1 Hz, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.64, 156.26, 155.86, 142.33, 138.86, 131.42, 131.26, 130.51, 129.45, 128.97, 127.68, 127.66, 119.45, 117.48, 109.97, 64.31, 58.41, 58.23, 34.84, 30.84, 14.58; HRMS calcd for $C_{27}H_{31}Cl_2N_2O_2$ [M + 1] 485.1763, found 485.1757.

2-(4-*tert*-Butyl-2-ethoxyphenyl)-*cis*-4,5-bis(4-chlorophenyl)-4,5-dihydro-1*H*-imidazole hydrochloride (4-HCl). A mixture of **2** (10.40 kg, 36.98 mol), **5** (8.70 kg, 39.13 mol), and boric acid (228.3 g, 3.69 mol) in xylenes (71.6 kg) was agitated at 145−148 °C for 24 h while a total of 41 L of solvent was removed by distillation *via* a Dean−Stark trap. The reaction mixture was cooled to room temperature, diluted with dichloromethane (150 kg), washed with 7.5 wt % aqueous sodium bicarbonate (53.9 kg), and water (2 × 52 L), and then concentrated at atmospheric pressure. The residue was diluted with toluene (112 kg), and an additional 10 L of solvent was removed. Concentrated hydrochloric acid (4.1 kg, 49.87 mol) was added, and a further 63 L of solvent was then removed by distillation at atmospheric pressure. The batch was cooled to room temperature and dropped to a filter dryer with the aid of toluene (8.7 kg). The collected solids were washed with toluene (26.0 kg) and dried to give **4**-HCl (15.1 kg, 81% yield, HPLC purity 98.64%) as a white solid. Mp 227−228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 2H), 7.98 (d, J = 8.1 Hz, 1H), 7.27 (dd, J = 7.4, 1.6 Hz, 1H), 7.26−7.22 (m, 5H), 7.12 (m, 4H), 5.98 (s, 2H), 4.35 (q, J = 7.0 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.58, 160.17, 157.65, 134.12, 132.47, 130.69, 129.32, 127.94, 117.89, 110.28, 108.98, 64.57, 63.42, 35.47, 30.62, 14.24; HRMS calcd for $C_{27}H_{29}Cl_2N_2O$ [M + 1] 467.1657, found 467.1652.

dx.doi.org/10.1021/op300254q | *Org. Process Res. Dev.* 2012, 16, 1866−1869

AUTHOR INFORMATION

Corresponding Author
lshu@verizon.net

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Hanspeter Michel of Formulation Research Department for HRMS analysis.

REFERENCES

(1) Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammlott, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. *Science* **2004**, *303*, 844.
(2) For a review on recent advances of a Nutlin, see: Seccinero, P.; Bosco, R.; Celeghini, C.; Zauli, G. *Curr. Pharm. Des.* **2011**, *17*, 569.
(3) Fotouhi, N.; Haley, G. J.; Simonsen, K. B.; Vu, B. T. Webber, S. E. Novel *cis*-Imidazolines. PCT Int. Appl. WO 2005110996, November 24, 2005.
(4) (a) Eissenstat, M. A.; Weaver, J. D., III *J. Org. Chem.* **1993**, *58*, 3387. (b) Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431. (c) You, S.-L.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 1681. (d) Arai, T.; Mizukami, T.; Yokoyama, N.; Nakazato, D.; Yanagisawa, A. *Synlett* **2005**, 2670. (e) Merriman, G. H.; Ma, L.; Shum, P.; McGarry, D.; Volz, F.; Sabol, J. S.; Gross, A.; Zhao, Z.; Rampe, D.; Wang, L.; Wirtz-Brugger, F.; Harris, B. A.; Macdonald, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 435. (f) Fujioka, H.; Murai, K.; Ohba, Y.; Hiramatsu, A.; Kita, Y. *Tetrahedron Lett.* **2005**, *46*, 2197. (g) Lin, S.-Y.; Isome, Y.; Stewart, E.; Liu, J.-F.; Yohannes, D.; Yu, L. *Tetrahedron Lett.* **2006**, *47*, 2883. (h) Ishihara, M.; Togo, H. *Synlett* **2006**, 227. (i) Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Tetrahedron* **2007**, *63*, 638. (j) Schneekloth, A. R.; Pucheault, M.; Tae, H. S.; Crews, C. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5904. (k) Sharma, S.; Gangal, S.; Rauf, A. *Eur. J. Med. Chem.* **2009**, *44*, 1751. (l) Wang, J.; He, Z.; Chen, X.; Song, W.; Lu, P.; Wang, Y. *Tetrahedron* **2010**, *66*, 1208. (m) Zhu, Q.; Lu, Y. *Org. Lett.* **2010**, *12*, 4156.
(5) Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076.
(6) De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 14538.
(7) Bender, J. A.; Meanwell, N. A.; Wang, T. *Tetrahedron* **2002**, *58*, 3111.
(8) The monoacylation of **2** was tested in the following solvents: THF, MTBE, toluene, xylenes, acetonitrile, and MeTHF.
(9) Vaidyanathan, R.; Kalthod, V. G.; Ngo, D. P.; Manley, J. M.; Lapekas, S. P. *J. Org. Chem.* **2004**, *69*, 2565.
(10) Tang, P. *Org. Synth.* **2005**, *81*, 262.
(11) Replacing dichloromethane with toluene resulted in somehow slower phase separation during the aqueous workup.
(12) Proskurnina, M. V.; Lozinskaya, N. A.; Tkachenko, S. E.; Zefirov, N. S. *Russ. J. Org. Chem* **2002**, *38*, 1149.
(13) A 98:2 mixture of the desired product vs. its regio-isomer was obtained under this condition. Bromination with NBS or 1,3-dibromo-5,5-dimethylhydantoin gave a lower selectivity (≤93:7).
(14) Hermann, G. J.; Annis, M. C.; Edwards, P. D.; Corrales, M.; Díaz, L.; Goodnow, R. A. *Synthesis* **2008**, 221.
(15) ^{1}H NMR spectrum of the crude product is in agreement with the structure.