Synthesis of the CDK-Inhibitor Paullone by Cyclization of a Deprotonated α-Aminonitrile

Till Opatz,*a Dorota Ferencb

a Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, 20146 Hamburg, Germany
b Institut für Organische Chemie, Universität Mainz, Duesbergweg 10-14, 55128 Mainz, Germany
E-mail: opatz@chemie.uni-hamburg.de
Received 15 July 2008

Abstract: Cyclization of a deprotonated N-monosubstituted α-amino nitrile obtained by Strecker reaction of a protected 2-amino benzaldehyde with ethyl 2-aminocinnamate serves as the key step in a short synthesis of the tetracyclic ε-lactam paullone.

Key words: Michael addition, α-aminonitriles, indoles, deprotonation

Strecker products derived from ammonia or primary amines and aromatic, heteroaromatic, or non-enolizable α,β-unsaturated aldehydes can serve as readily accessible starting materials for the generation of stabilized α-amino carbanions. Their quantitative deprotonation with potassium bis(trimethylsilyl)amide in tetrahydrofuran at low temperatures will furnish the corresponding potassium keteniminate anions without inducing the competing retro-Strecker reaction.1–6 If, on the other hand, weaker bases such as potassium tert-butoxide are employed, reprotonation of the carbanion obtained can not be prevented. This ultimately leads to the elimination of HCN from the aminonitrile to furnish the corresponding imine. Only if the keteniminate anion is consumed in a fast consecutive reaction, clean α-substitution of an aminonitrile can be achieved under ‘thermodynamic’ deprotonation conditions. An example of such a process is the one-pot synthesis of substituted indoles from α-aminonitriles derived from 2-aminocinnamic acid esters and amides.7 In this case, the 5-exo-trig-cyclization of the carbanion 3 is fast enough to furnish the indole 5 via the 2-cyanoindoline 4 in up to quantitative yield (Scheme 1).

If the reaction is performed in an aprotic solvent, the intermediates 4 can be isolated and characterized, whereas in protic solvents, the elimination of HCN is fast and indoles 5 are obtained directly. Here, we report on the application of this method to the synthesis of the CDK inhibitor paullone (11),8 which represents the prototype of a class of potent inhibitors of cyclin-dependent kinases (CDKs) that have attracted much attention in recent years.9–12 The CDKs are a family of protein kinases that are involved in the regulation of the cell cycle. As a large fraction of human tumors exhibit aberrant CDK activity, the design of inhibitors of CDKs that induce arrest of the cell cycle has become an important task with respect to antiproliferative chemotherapy.13 While paullone (11) itself is active in the low micromolar range, some close derivatives inhibit cyclin-dependent kinases at nanomolar or even subnanomolar concentrations.14

For the synthesis of 11, 2-aminobenzyl alcohol was Boc-protected and converted into aldehyde 6 by Swern oxidation. Presumably due to the bulky ortho-substituent, the Strecker reaction of 6 with ethyl 2-aminocinnamate (7) proceeded sluggishly and required repeated addition of potassium cyanide and acetic acid. Surprisingly, the prolonged reaction times and elevated reaction temperatures already led to the formation of substantial amounts (13%) of indole 9; aminonitrile 8 was obtained in 47% yield along with imine 10 (5%). Cyclization of aminonitrile 8 with potassium tert-butoxide in ethanol gave indole 9 in 74% yield. Again, imine 10 (17%) was obtained as a side product. Thus, the combined yield for the conversion of aminocinnamate 7 into indole 9 amounted to 48%. Acidolytic removal of the Boc group and subsequent formation of the seven-membered lactam ring by heating the

SYNTHESIS 2008, No. 24, pp 3941–3944
Advanced online publication: 01.12.2008
DOI: 10.1055/s-0028-1083250; Art ID: T11408SS
© Georg Thieme Verlag Stuttgart · New York
indole synthesis,8 the presented route avoids the use of azepine-2,5-dione and phenylhydrazine in a Fischer preparation of the 7,12-dihydroindolo[3,2-TLC was performed on aluminum sheets coated with silica gel (60 purification. Petroleum ether (PE) had a boiling range of 40–70 °C.

In summary, 7 was converted into paullone (11) in four steps in 35% overall yield. In contrast to the classical preparation of the 7,12-dihydroindolo[3,2-d][1]benzazepin-6(5H)-one core from 3,4-dihydro-1H-1-benzazepine-2,5-dione and phenylhydrazine in a Fischer indole synthesis,3 the presented route avoids the use of harsh reaction conditions. As the preparation of indoles by the cyclization of deprotonated a-aminonitriles allows the introduction of substituents to both benzene rings, a wide variety of paullone derivatives should be accessible. In terms of simplicity and efficiency, the method compares favorably with other alternative approaches to the paullones, e.g. by palladium-catalyzed reactions15,16 or radical cyclizations.17,18

1H and 13C NMR spectra were recorded on a Bruker AC-300 or Avance-II 400 spectrometer, chemical shifts were referenced to the residual solvent signal (CDCl3; δC = 77.0). FD-MS spectra were measured on a Finnigan MAT-95 spectrometer. ESI-HRMS spectra were measured on a Waters Q-TOF-Ultima 3 equipped with a LockSpray interface (trihexylamine as external reference). IR spectra were recorded on a Perkin-Elmer 1760X FTIR spectrophotometer. The melting points were measured on a Dr. Tottoli apparatus (Büchi) and are uncorrected. CH2Cl2 and Et3N were freshly distilled from CaH2 under argon. EtOH was distilled from Mg(OEt)2 under argon. All other solvents and reagents were purchased from commercial suppliers and were used without further purification.

Scheme 2  Synthesis of paullone (11) from aminocinnamate 7

aniline with acetic acid in dioxane furnished paullone (11) in 73% yield.

A soln of oxalyl chloride (732 μL, 8.39 mmol) in anhyd CH2Cl2 (5 mL) was cooled to –78 °C under an argon atmosphere. After the addition of DMSO (1.79 mL, 25.2 mmol), the soln was stirred for 45 min. A soln of the crude amino alcohol (2.00 g, 21.1 mmol) in anhyd CH2Cl2 (8.3 mL) was added and the mixture was stirred at –78 °C for 30 min. Anhyd Et3N (7.00 mL, 50.3 mmol) was added and the mixture was stirred at –78 °C for 45 min and at –20 °C for 30 min.21 H2O (20 mL) was added and the mixture was partitioned between H2O and Et2O. The aqueous phase was extracted with Et2O, the combined organic layers were washed with sat. aq NaHCO3 soln, dried (Na2SO4), and concentrated in vacuo. As the 1H NMR spectrum of the crude aldehyde revealed incomplete conversion, the material was dissolved in EtOH (5 mL) and AcOH (243 μL, 4.25 mmol) was added and the mixture was stirred at 60 °C for 5 h. The mixture was partitioned between H2O and CH2Cl2, the organic layer was washed with sat. aq NaHCO3 soln, dried (Na2SO4), and concentrated in vacuo. As the 1H NMR spectrum of the crude product revealed incomplete conversion, the material was dissolved in EtOH (5 mL), KCN (747 mg, 11.5 mmol), and AcOH (779 μL, 13.6 mmol) were added and the mixture was stirred at 60 °C for 18 h. Another portion of KCN (277 mg, 4.25 mmol) and AcOH (779 μL, 13.6 mmol) were added and the mixture was stirred at 50 °C for 3 h. After the addition of K2CO3 (747 mg, 5.11 mmol) and AcOH (779 μL, 13.6 mmol), stirring was continued at 60 °C for 18 h. Another portion of KCN (277 mg, 4.25 mmol) and AcOH (243 μL, 4.25 mmol) was added and the mixture was stirred for 60 °C for 5 h. The mixture was partitioned between H2O and CH2Cl2, the organic layer was washed with sat. aq NaHCO3 soln, dried (Na2SO4), and concentrated in vacuo. As the 1H NMR spectrum of the crude product revealed incomplete conversion, the material was dissolved in EtOH (5 mL), KCN (747 mg, 11.5 mmol), and AcOH (779 μL, 13.6 mmol) were added and the mixture was stirred at 60 °C for 3 h. After partitioning between H2O and CH2Cl2, the organic layer was washed with sat. aq NaHCO3 soln, dried (Na2SO4), and concentrated in vacuo to furnish the crude product (1.86 g). Flash chromatography (silica gel, PE–t-BuOMe, 6:1) furnished 8 (843 mg, 47%) along with imine 10 (87 mg, 5%), indole 9 (223 mg, 13%), and unreacted aldehyde 6 (142 mg, 64 μmol).

Aminocinnamate 8

Yellow foam; mp 63–65 °C.

IR (KBr): 3405 (br), 2980, 1703, 1630, 1604, 1519 (sh), 1454, 1368, 1317, 1248 (sh), 1161 (sh), 1049 (sh), 753 cm–1.

1H NMR (300 MHz, CDCl3): δ = 7.76–7.78 (m, 3 H) [contained in this multiplet: 7.76 (d, J = 15.6 Hz, 1 H, Hb)], 7.37–7.50 (m, 3 H), 7.24 (dd, J = 7.6, 1.4 Hz, 1 H), 6.97–7.06 (m, 3 H), 6.33 (d, J = 15.6 Hz, 1 H, Hb), 5.58 (d, J = 9.0 Hz, 1 H, CHN), 4.50 (d, J = 9.0 Hz, 1

Synthesis 2008, No. 24, 3941–3944 © Thieme Stuttgart · New York
H, NH), 4.20 (q, J = 7.2 Hz, 2 H, OCH2), 1.44 (s, 9 H, t-Bu), 1.29 (t, J = 7.2 Hz, 3 H, CH3).

13C NMR (75.5 MHz, CDCl3): δ = 166.7 (CO2Et), 153.0 (OCN), 142.6 (C2), 138.8 (C3), 136.4 (C4), 131.5, 130.6, 128.4, 128.3, 125.3, 124.7 (2C), 124.3, 121.5, 120.6, 117.1 (CN), 114.6 (C3), 81.1 [(CH3)3], 60.6 (OCH2), 48.2 (CHN), 28.1 [(CH3)3], 14.2 (CH3).

MS (FD): m/z (%) = 421.5 (100) [M]+.


Yellowish crystals; mp >260 °C (dec.).

IR (KBr): 3436 (br), 2920, 1645, 1576 (sh), 1401 (s), 1384, 1363, 1331, 1281, 1220, 1200, 1191, 1180, 1082 [(CH3)3], 60.4 (OCH2), 28.1 [(CH3)3], 14.3 (CH3).

MS (FD): m/z (%) = 394.5 (100) [M]+.

Anal. Calcd for C28H36N2O4: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.79; H, 6.49; N, 6.98.

Ethyl-[2,2-(tert-Butoxy carbonylamino) phenyl]-1-indol-3-ylacetate (9)

To a soln of 8 (300 mg, 712 μmol) in anhyd EtOH (6 mL) was added K2O-Bu (88 mg, 784 μmol) and the soln was stirred at r.t. for 30 min. The mixture was partitioned between sat. aq NaHCO3 and CH3Cl, the organic layer was dried (Na2SO4) and concentrated in vacuo to furnish an orange foam (279 mg). Flash chromatography (silica gel, PE–tBuOMe, 20:1) furnished 9 (209 mg, 74%) as colorless crystals; mp 113–115 °C. Imine (47 mg, 73%) was also obtained.


Acknowledgment

This work was supported by the Deutsche Forschungsgemeinschaft. We thank H. Kolshorn (Mainz) for the NMR spectroscopic analyses and Dr. N. Hanold (Mainz) for mass spectrometry.

References


