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

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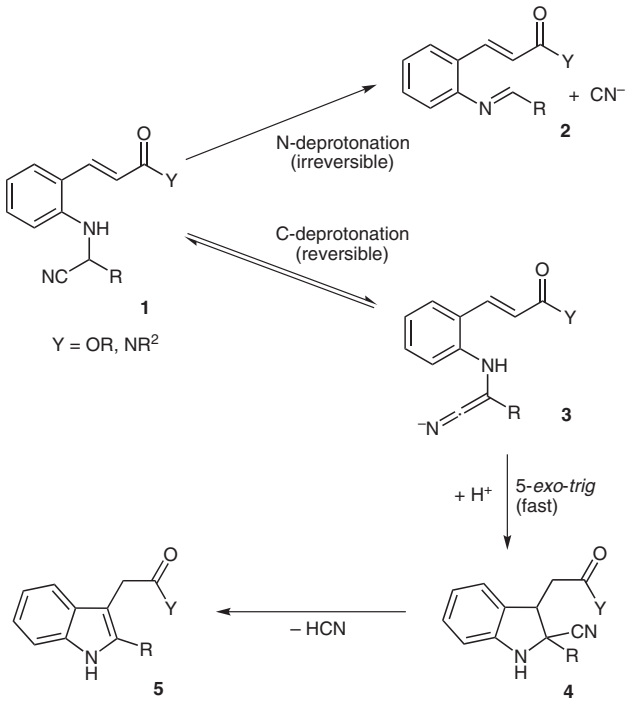
Abstract: Cyclization of a deprotonated N-monosubstituted α-aminonitrile obtained by Strecker reaction of a protected 2-aminobenzaldehyde with ethyl 2-aminocinnamate serves as the key step in a short synthesis of the tetracyclic ε-lactam paullone.

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 keteneiminates 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 keteneiminate 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]



Scheme 1 One-pot synthesis of indoles from α-aminonitriles

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

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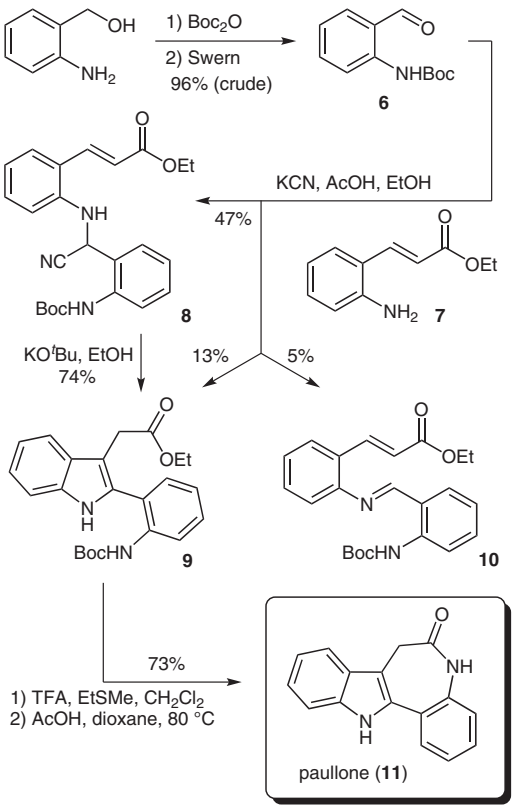

Scheme 2 Synthesis of paullone (**11**) from aminocinnamate **7**

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

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(5*H*)-one core from 3,4-dihydro-1*H*-1-benzazepine-2,5-dione and phenylhydrazine in a Fischer indole synthesis,[8] the presented route avoids the use of harsh reaction conditions. As the preparation of indoles by the cyclization of deprotonated α-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 reactions[15,16] or radical cyclizations.[17,18]

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 or Avance-II 400 spectrometer, chemical shifts were referenced to the residual solvent signal ($CDCl_3$: $\delta_H = 7.26$, $\delta_C = 77.0$). 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. CH_2Cl_2 and Et_3N were freshly distilled from CaH_2 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. Petroleum ether (PE) had a boiling range of 40–70 °C. TLC was performed on aluminum sheets coated with silica gel (60 F_{254}, E. Merck). Flash column chromatography was carried out on silica gel (32–63 μm, 60 Å, MP Biomedicals GmbH).

2-(*tert*-Butoxycarbonylamino)benzaldehyde (6)[19,20]

To a soln of 2-aminobenzyl alcohol (2.50 g, 20.3 mmol) in THF (10 mL) was added Boc_2O (4.60 g, 21.1 mmol). The soln was stirred overnight at r.t. and then heated to 50 °C for 5 h. After removal of the solvent in vacuo, the residue was filtered over silica gel (cyclohexane–EtOAc, 6:1). Concentration in vacuo furnished crude 2-(*tert*-butoxycarbonylamino)benzyl alcohol (4.54 g) as a yellow oil which was subjected to oxidation without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (br d, *J* = 8.0 Hz, 1 H, H3), 7.65 (br s, 1 H, NH), 7.30 (d pseudo t, J_t = 7.5 Hz, J_d = 1.7 Hz, 1 H, H4), 7.15 (dd, *J* = 7.5, 1.7 Hz, 1 H, H6), 7.01 (dt, J_t = 7.5 Hz, J_d = 1.1 Hz, 1 H, H5), 4.65 (s, 2 H, CH_2), 2.30 (br s, 1 H, OH), 1.52 (s, 9 H, *t*-Bu).

A soln of oxalyl chloride (732 μL, 8.39 mmol) in anhyd CH_2Cl_2 (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) in anhyd CH_2Cl_2 (8.3 mL) was added and the mixture was stirred at –78 °C for 30 min. Anhyd Et_3N (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] H_2O (20 mL) was added and the mixture was partitioned between H_2O and Et_2O. The aqueous phase was extracted with Et_2O, the combined organic layers were washed with 1 M $KHSO_4$ soln and brine, dried (Na_2SO_4), and the solvent was removed in vacuo to furnish **6** (1.89 g, 96% over 2 steps) as a yellowish oil that solidified upon standing and was used without further purification; mp 50–51 °C (crude)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.39 (br s, 1 H, NH), 9.88 (s, 1 H, CHO), 8.44 (d, *J* = 8.5 Hz, 1 H), 7.61 (dd, *J* = 7.7, 1.7 Hz, 1 H), 7.55 (ddd, *J* = 8.5, 7.3, 1.7 Hz, 1 H), 7.12 (pseudo t, *J* = 7.5 Hz, 1 H), 1.51 (s, 9 H, *t*-Bu).

Ethyl (*E*)-2-({[2-(*tert*-Butoxycarbonylamino)phenyl]cyanomethyl}amino)cinnamate (8) and Ethyl (*E,E*)-2-{[2-(*tert*-Butoxycarbonylamino)benzylidene]amino}cinnamate (10)

To a soln of **6** (1.13 g, 5.11 mmol) and ethyl (*E*)-2-aminocinnamate[22,23] (**7**, 813 mg, 4.25 mmol) in EtOH (5 mL) was added AcOH (100 μL, 1.75 mmol) and the mixture was stirred at 50 °C for 3 h. After the addition of KCN (747 mg, 11.5 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 at 60 °C for 5 h. The mixture was partitioned between H_2O and CH_2Cl_2, the organic layer was washed with sat. aq $NaHCO_3$ soln, dried (Na_2SO_4), and concentrated in vacuo. As the ^{1}H 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 H_2O and CH_2Cl_2, the organic layer was washed with sat. aq $NaHCO_3$ soln, dried (Na_2SO_4), 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, 642 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}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.78 (m, 3 H) [contained in this multiplet: 7.76 (d, *J* = 15.6 Hz, 1 H, Hβ)], 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, Hα), 5.58 (d, *J* = 9.0 Hz, 1 H, CHN), 4.50 (d, *J* = 9.0 Hz, 1

H, NH), 4.20 (q, J = 7.2 Hz, 2 H, OCH_2), 1.44 (s, 9 H, *t*-Bu), 1.29 (t, J = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.7 (CO_2Et), 153.3 (OCONH), 142.6 (C2), 138.8 (Cβ), 136.4 (C2′), 131.5, 130.6, 128.4, 128.3, 125.3, 124.7 (2C), 123.4, 121.5, 120.6, 117.1 (CN), 114.6 (C3), 81.1 [$C(CH_3)_3$], 60.6 (OCH_2), 48.2 (CHN), 28.1 [$C(CH_3)_3$], 14.2 (CH_3).

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

Anal. Calcd for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.12; H, 6.43; N, 9.66.

(Benzylideneamino)cinnamate 10

Yellowish crystals; mp 137–138 °C.

IR (KBr): 3424 (br), 2982, 1722, 1708, 1632, 1619, 1583, 1531, 1481, 1540, 1366, 1317, 1272, 1245, 1197, 1179, 1159, 1161, 1030 (sh), 771, 760 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 11.85 (br s, 1 H, NH), 8.52 (d, J = 8.3 Hz, 1 H), 8.46 (s, 1 H, CH=N), 8.14 (d, J = 16.0 Hz, 1 H, Hβ), 7.65 (dd, J = 7.7, 1.5 Hz, 1 H), 7.41–7.50 (m, 3 H), 7.29 (pseudo t, J = 7.6 Hz, 1 H), 7.00–7.10 (m, 2 H), 6.46 (d, J = 16.0 Hz, 1 H, Hα), 4.25 (q, J = 7.1 Hz, 2 H, OCH_2), 1.51 (s, 9 H, *t*-Bu), 1.31 (t, J = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.6 (CO_2Et), 163.9 (CH=N), 153.3 (OCONH), 149.8 (C2), 141.4 (C2′), 140.7 (Cβ), 134.6, 132.9, 131.2, 128.7 (C1), 127.5, 126.5, 121.2, 120.1, 120.0 (C1′), 119.2, 118.0, 80.2 [$C(CH_3)_3$], 60.4 (OCH_2), 28.1 [$C(CH_3)_3$], 14.3 (CH_3).

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

Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.79; H, 6.49; N, 6.98.

Ethyl {2-[2-(*tert*-Butoxycarbonylamino)phenyl]-1*H*-indol-3-yl}acetate (9)

To a soln of **8** (300 mg, 712 μmol) in anhyd EtOH (6 mL) was added KO*t*-Bu (88 mg, 784 μmol) and the soln was stirred at r.t. for 30 min. The mixture was partitioned between sat. aq $NaHCO_3$ and CH_2Cl_2, the organic layer was dried (Na_2SO_4) and concentrated in vacuo to furnish an orange foam (279 mg). Flash chromatography (silica gel, PE–*t*-BuOMe, 20:1) furnished **9** (209 mg, 74%) as colorless crystals; mp 113–115 °C. Imine **10** (47 mg, 17%) was also obtained.

IR (KBr): 3405 (br), 2980, 2933, 1730 (sh), 1586, 1519, 1461, 1446, 1393, 1369, 1300, 1242, 1158 (sh), 1049, 1027, 766, 745 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.32 (br s, 1 H, indole-NH), 8.16 (d, J = 8.3 Hz, 1 H), 7.66 (d, J = 8.3 Hz, 1 H), 7.37–7.45 (m, 2 H), 7.34 (dd, J = 7.5, 1.7 Hz, 1 H), 7.17–7.31 (m, 2 H), 7.12 (pseudo t, J = 7.5 Hz, 1 H), 6.93 (br s, 1 H, NHBoc), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2), 3.63 (s, 2 H, CH_2CO), 1.46 (s, 9 H, *t*-Bu), 1.22 (t, J = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.8 (CO), 153.2 (C2′), 137.3, 136.1, 132.3 (C2, C2′, C7a), 131.3 (CH), 129.9 (CH), 128.1, 122.9 (CH), 122.6 (CH), 121.6, 120.2 (CH), 119.1 (CH), 111.2 (C7), 108.0 (C3), 80.7 [$C(CH_3)_3$], 60.8 (OCH_2), 30.7 ($ArCH_2$), 28.2 [$C(CH_3)_3$], 14.1 (CH_3).

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

Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.97; H, 6.66; N, 7.08.

Paullone [7,12-Dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one, 11][8]

To a soln of **9** (100 mg, 254 μmol) in anhyd CH_2Cl_2 (2 mL) was added EtSMe (229 μL, 2.54 mmol) and TFA (195 μL, 2.54 mmol) and the soln was stirred at r.t. until TLC indicated complete conversion (1 d). The mixture was poured into sat. aq $NaHCO_3$ and after addition of EtOAc, the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to furnish a colorless foam (61 mg). The crude aniline was dissolved in dioxane (2 mL) and after addition of AcOH (250 μL, 4.37 mmol), the mixture was stirred at 80 °C until TLC indicated complete conversion (2 d). The mixture was partitioned between sat. aq $NaHCO_3$ and EtOAc and the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. Trituration of the residue (EtOAc–PE) furnished **11** (46 mg, 73%) as pale yellow crystals; mp >260 °C (dec.)[16]

IR (KBr): 3436 (br), 3230 (br), 2925, 1646, 1576 (sh), 1491 (sh), 1464, 1423, 1399, 743 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.59 (br s, 1 H, indole-NH), 10.10 (br s, 1 H, amide-NH), 7.74 (dd, J = 7.7, 1.6 Hz, 1 H), 7.66 (br d, J = 7.7 Hz, 1 H), 7.44 (dt, J_d = 8.0 Hz, J_t = 0.9 Hz, 1 H), 7.37 (ddd, J = 8.0, 7.4, 1.6 Hz, 1 H), 7.24–7.30 (m, 2 H), 7.17 (ddd, J = 8.1, 7.0, 1.2 Hz, 1 H), 7.07 (ddd, J = 8.0, 7.0, 1.0 Hz, 1 H), 3.50 (br s, 2 H, CH_2).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 171.6 (C6), 137.4, 135.4, 132.5 (C4a, C11a, C12a), 128.0, 126.9 (C1, C3), 126.6 (C7b), 123.7 (C2), 122.9 (C12b), 122.3, 122.1, 119.1, 118.0 (C4, C8, C9, C10), 111.5 (C11), 107.6 (C7a), 31.6 (C7).

MS (FD): m/z (%) = 248.1 (100) $[M]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{12}NaN_2O$: 271.0847; found: 271.0858.

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