Efficient Synthesis of Chiral Amides of 2-(2’-Carboxyphenyl)-4-hydroxyquinoline

Zdenko Hamersak, Mladen Litić, Dragan Šepac, Andreja Lesac, Zlata Raza, Vitomir Šunjić*
Ruder Bošković Institute, Bjenčka c. 54, P.O.B. 180, 10002 Zagreb, Croatia
Fax +385(1)4680195; E-mail: sunjic@rudjer.irb.hr
Received 5 April 2002; revised 19 July 2002

Abstract: On deprotonation by lithium bistrimethylsilylamide (LBTSA), 2-phthalimidoacetophenone (1) is quantitatively converted to 6H,12H-isooindolo[2,1-a]-6,7a-dihydroxyquinolin-12-one (2); weaker bases proved much less effective. Thermal dehydration of 2 to vinillogous imide 3, then the AlCl₃-catalyzed aminolysis by (1S)-arylethylamines afforded (1S)-amides of 2-(2’-carboxyphenyl)-4-hydroxyquinolines (5–7). This sequence represents an efficient assembling of novel chiral heterocycles, potentially useful in enantioselection as ligands or chiral selectors. In situ prepared Pd(II) complexes of 5–7 exhibited catalytic activity in allylic alkylation of 1,3-diphenyl-1-acetoxyprop-2-ene (8) by dimethylmalonate anion; the complex of 7 afforded the highest (64%) enantioemic excess of 1,3-diphenyl-1-dimethylmalonylprop-2-ene (9).

Key words: quinolines, amides, stereoselective synthesis, alkylations, heterocycles

The need for improved methods in heterocyclic syntheses stimulates development of novel chemistry, whose ultimate utility extends to unexpected applications that were not initially envisioned. Related to our studies of chiral selectors in the Pirkle-type chiral stationary phases (CSPs),¹⁻³ we discovered a short and efficient route to the compounds 5–7, Scheme 1.

These chiral derivatives of 4-hydroxy-2-aryquinoline contain π-donor/acceptor units, a 1,6-arrangement of nitrogen atoms, and a 4-hydroxy group amenable to binding via a spacer, e.g. via 4-O-allyl group, to silica as a solid support.

Reinvestigating the reaction between acetophenone and phthalic anhydride,⁴⁻⁵ we have found that some formerly reported conditions either do not afford the desired product or can be significantly improved. Two papers reported the synthesis of pyrrolo-quinoline derivative 3, starting either from 2-phthalimidoacetophenone⁴ or phthalimidothranilic acid.⁵ While cyclization of the latter was claimed to require a specific reagent, N-phenyl(triphenylphosphoranylidene)ethylenimine, in the former paper was reported a tedious approach to 3 via α-bromination of the acetophenone derivative 1 and formation of the Wittig reagent. This paper also mentioned triethylamine in pyridine to afford 3 ‘in good yields’; only 15% yield was claimed with the much stronger base BuLi in DMSO, however.⁴ When we attempted cyclization to 3 with trieth-

Scheme 1 Synthesis of 2’-carboxamidophenyl-4-hydroxyquinolines 5–7; reagents and conditions: a) LBTSA, THF, –78 °C, 1 h; b) A, 220 °C, 1 h; c) 2 M KOH in MeOH, 80 °C, 0.5 h, HCl in MeOH; d) AlCl₃, CH₂Cl₂,CH₂Cl₂, 80 °C, 15 h.

Art Id.1437-210X,E:2002.0,15,2174,2176,ftx,en,Z06202SS.pdf.
© Georg Thieme Verlag Stuttgart · New York
ISSN 0039-7881
ynamine in pyridine, no reaction was observed over 24 h at room temperature. On heating at 90 °C slow cyclization took place and only after 40 h did starting material disappear. On crystallization 3 was isolated in ca. 60% yield.

Critical for the whole sequence in the Scheme 1 is the formation of carbanion of 1 and cyclization to 2 by intramolecular nucleophilic attack on the phthalimido carbonyl group. On screening of a number of weak and strong bases we have found lithium bis(trimethylsilylamide) (LBTSAs) to be the most effective base which substantially shortened the reaction time and improved the overall yield of 2 up to 90%.

On melting under Kofler microscope amorphous 2 turned above 200 °C into yellow plate-like crystals that sharply melted at 260 °C and sublimate above 300 °C. The second heating run of the solidified melt gave the same melting point, revealing formation of polycyclic lactam 3 and thermal water elimination from 2 as the method of choice for its preparation. When this reaction was tested on a gram scale of 2, heating at 220 °C for 2 hours quantitatively afforded compound 3. Heating 3 under basic conditions in aqueous methanol at slightly elevated temperature led to clean lactam ring opening to 4. No harsh conditions for hydrolysis of 3 to 4 reported in an early paper (heating at 140 °C in 15% sodium hydroxide; autoclave) are needed.

To obtain enantiopure carboxamides 5–7, aminolysis of vinillogous imide 3 was required. Bon et al. recently reported aminolysis of cyclic imides under mild conditions using aluminum trichloride as a promoter of the ring-opening reaction, while Rao et al. used indium trichloride as the catalyst for amonolitic ring opening of epoxides. Under reaction conditions reported by Bon et al., aminolysis of 3 with (S)-1-arylthylamines afforded 5–7 in ca. 70% yield. Determination of enantiomeric purity of (−)-5 by chiral HPLC revealed no racemization during this final step.

To prove the utility of 5–7 as potential ligands in catalytic organometallic complexes, we selected allylic alkylation of 1,3-diphenyl-1-acetoxyprop-2-ene (8) by dimethylamironate anion to enantiomerically enriched 9, according to the Scheme 2 by their Pd(II) complexes prepared in situ using acetoniitrile, which we recently have found as the solvent of choice.

In conclusion, we have demonstrated that (1S)-(1-arylthylamido)-2-carboxyquinolines 5–7 can be conveniently obtained in three steps from 2-phenolphosimidoacetophenone, and for the first time was shown successful application of a 1,6-dinitrogen ligand in Pd(II) catalyzed allylic alkylation. A variety of commercial anhydrides, acenophenone derivatives, and in particular of chiral amines available in both enantiomeric forms, allow design of a number of their structural congeners.

1 H and 13C NMR spectra were obtained on Varian Gemini XL 300 spectrometer, δ in ppm are reported downfield from TMS as internal reference. IR spectra were recorded on a Perkin–Elmer 297 spectrometer. Mps were determined on an electrothermal mp apparatus and were not corrected. Optical rotations were determined on an AA-10 polarimeter. HPLC determination of the enantiomeric purity of 5 was performed on a Hewlett–Packard instrument Series 1050 with UV detector (λ (254 nm) and HP integrator 3396A, on Chiralcel OD column using hexane–isopropanol (80:20) as eluent.

To obtain a sample of racemic 5 was prepared by amonolysis of 3 on ca. 10 mg with racemic 1-phenylethylamine. The enantiomeric purity of 9 was determined on a Chiralcel OD-H column, using an HPLC instrument with a Knauer WellChrom Max-Star K-1000 pump, and detection was performed at 254 nm with a Knauer WellChrom K-2500 detector.

Elemental analyses were performed at laboratories for microanalysis at ‘Ru Bošković’ Institute and Karl Franzens University, Graz (Austria).

1H,12H-Isiodindole[2,1-a]-6,7a-dihydroxyquinolin-12-one (2)

To the solution of 2-phthalimidoacetophenone (1) (3.5 g, 20 mmol) prepared according to ref. in absolute THF (100 mL) cooled to –78 °C under argon atmosphere, lithium bis(trimethylsilylamide) (LBTSAs, 40 mmol; as 40 mL of a 1 M solution in THF, Aldrich) was added dropwise under vigorous stirring. The reaction was continued for 1 h at the same temperature. H2O was added, the pH adjusted to 3 by dilute aq HCl and the THF was evaporated. The precipitate (5.0 g) was collected by filtration and triturated with CH2Cl2 to afford pure 2.

Yield: 4.8 g (89.6%); mp 200 °C (decomp.);

IR (KBr): 3500, 3300, 3180, 3000, 1720, 1640, 1600, 1575, 1540, 1470, 1440, 1410, 1360, 1300, 1250, 1140, 850, 800, 715 cm–1.

1H NMR (DMSO-d6): δ = 6.04 (s, 1 H), 7.35–7.77 (m, 5 H), 8.03 (d, J = 7.3 Hz, 1 H), 8.15 (d, J = 7.8 Hz, 1 H), 12.10 (br s, 2 H).

13C NMR (DMSO-d6): δ = 108.8, 118.8, 123.6, 124.8, 125.0, 130.2, 130.5, 130.8, 131.4, 132.1, 132.2, 135.8, 140.5, 153.1, 167.5, 176.0.

6H,12H-Isiodindole[2,1-a][quinoline-6,12-dione (3)

Stirring 2 (1.8 g, 6.8 mmol) under argon at ca. 220 °C for 1 h afforded a deep-yellow melt which was triturated with CH2Cl2. The organic layer was dried (MgSO4) and evaporated to afford crude 3. On trituration with MeOH pure product was obtained.

Yield: 1.7 g; mp 260–263 °C; sublimation above 300 °C.

IR (KBr): 3470, 1770, 1740, 1650, 1640, 1605, 1570, 1485, 1350, 1300, 1290, 1275,1240, 1190, 1115, 1095, 1065, 1030, 860, 775, 720, 665, cm–1.

1H NMR (CDCl3): δ = 6.75 (s, 1 H), 7.44 (t, J = 7.8 Hz, 1 H), 7.63–7.83 (m, 4 H), 7.97 (d, J = 7.4 Hz, 1 H), 8.30 (d, J = 7.9 Hz, 9.11 (d, J = 8.4 Hz, 1 H).

13C NMR: δ = 106.7, 117.6, 121.7, 124.8, 125.2, 125.6, 126.8, 128.9, 132.23, 134.2, 134.5, 135.1, 137.7, 145.9, 166.0, 179.9.

Synthesis 2002, No. 15, 2174–2176 ISSN 0039-7881 © Thieme Stuttgart · New York
2-[(2-Carboxyphenyl)-4-hydroxyquinoline Hydrochloride (4)] Compound 3 (1.1 g, 4.5 mmol) was heated in KOH (2 M; 40 mL) at 80 °C for 30 min. On completed hydrolysis, the solution was acidified by aq HCl–MeOH to pH 1, and crude product 4 was filtered off and crystallized from aq MeOH. On heating above 200 °C compound 4 slowly converted back into 3.

Yield: 1.35g (100%).

IR (KBr): 3410, 2970, 1635, 1590, 1508, 1250, 1140, 760, 700 cm⁻¹.

1H NMR (DMSO-6): δ = 7.19 (1 H, s), 7.72–8.14 (m, 6 H), 8.16 (d, J = 6.2 Hz, 1 H), 8.37 (d, J = 8.5 Hz, 1 H), 14.8 (br s, 3 H).

13C NMR (DMSO-6): δ = 21.0, 45.1, 109.2, 118.5, 123.2, 125.0, 125.1, 126.1, 126.7, 128.0, 128.4, 129.8, 131.9, 133.6, 137.5, 140.5, 144.3, 150.3, 167.3, 176.8.

Anal. Calcd for C32H24N2O2 (468.55): C, 82.03; H, 5.16; N, 5.98. Found: C, 81.76; H, 5.15; N, 5.74.

Allylic Alkylation by Pd(II) Complexes of S–7; General Procedure

All reactions were performed under an argon atmosphere, using standard Schlenk techniques. To [Pd(allyl)Cl₂] (2.60 mg, 7.0 µmol) dissolved in MeCN (1.0 mL), freshly distilled over CaH₂, was added ligand S–7 (25 µmol). The resulting solution was de-aerated under argon, then heated at 50 °C for 2 h in an ultrasound bath. On cooling to r.t., compound 8 (125 mg, 0.5 mmol) was added, the Schlenk tube was rinsed with MeCN (0.8 mL), then dimethyl malonate (DMM, 350 mg, 2.6 mmol), bistrimethylsilylacetamide (BSA, 530 mg, 2.6 mmol) and KOAc (2.0 mg) were added. The reaction went to completeness at 50 °C overnight. On cooling CH₂Cl₂ (5.0 mL) was added, and the reaction solution was washed with sat. aq NH₄Cl (5.0 mL). The organic phase was dried, the solvent was removed and crude product purified by flash chromatography (30 g silica gel; hexane–EtOAc–MeOH, 10:1:1).

The yield and ee's of 7 were as follows: from 57.7% yield, 14% ee; from 66% yield, 4% ee; from 76% yield, 64% ee.

Acknowledgement

This work was supported by the Ministry of Science and Technology of Rep. Croatia; Project No. 980701.

References