A Microwave-Assisted Alternative Synthesis of 8-Amino-2-methyl-3,4-dihydroisoquinolin-1-one

Steve C. Glossop*
AstraZeneca Plc., Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK
Fax +44(1625)586707; E-mail: steve.glossop@astrazeneca.com
Received 29 November 2006; revised 20 January 2007

Abstract: A shorter, alternative synthesis of 8-amino-2-methyl-3,4-dihydroisoquinolin-1-one is described in 32% overall yield, over three steps starting from commercially available 2-methyl-6-nitrobenzonitrile. The synthesis includes two ‘one-pot’ procedures in which the key process involves the microwave-assisted hydrolysis of a nitrile group followed by lactamization under elevated temperatures.

Key words: lactam, microwaves, cyclization, Bredereck’s reagent, isoquinolinone

In the course of our research, access to 8-amino-2-methyl-3,4-dihydroisoquinolin-1-one (1) was required. Although the structure of 1 is quite simple, the known syntheses are quite lengthy. Two recent reports describe syntheses of compound 1; however, both procedures involve seven synthetic steps from commercially available starting materials and utilize a number of toxic reagents. Herein is reported a shorter, alternative synthesis of the title compound from commercially available 2-methyl-6-nitrobenzonitrile. The two literature routes based on patents are briefly summarized in Schemes 1 and 2.

The use of toxic reagents such as allyltributyltin, CrO₃/H₂SO₄ and (PhO)₂P(O)N₃, along with the particularly low-yielding permanganate oxidation step (a) and an overall yield of 12% made the first route (Scheme 1) unattractive.

In the second sequence (Scheme 2), synthesis of compound 1 begins with the Raney-Nickel reduction of methyl 2-(cyanomethyl)-6-nitrobenzoate (12). This intermediate is not commercially available but can be prepared in three steps from 2-methyl-6-nitrobenzoic acid (9). Unfortunately, the yields for the individual reactions are not quoted and due to the number of synthetic steps, as well as the use of cyanide, this is also an unattractive route.

We observed that subjecting compound 16 (Scheme 3) to elevated temperatures led to an unexpected side reaction.

Scheme 1  WO 2006/021454 – Reagents and conditions: (a) KMnO₄, Na₂CO₃, H₂O, 100 °C, 18 h, 40%; (b) Cs₂CO₃, MeOH, r.t., then MeI, DMF, 0 °C to r.t., 14 h, ca. 100%; (c) allyltributyltin, Pd(Ph₃P)₄, toluene, 110 °C, 20 h then CsF, H₂O, ca. 100%; (d) BH₃·SMe₂, THF, 0 °C, 4 h, then H₂O₂, NaOH, r.t., 1 h, 90%; (e) CrO₃, H₂SO₄, 0 °C to r.t., 4 h, 80%; (f) (PhO)₂P(O)N₃, Et₃N, toluene, 80 °C, 2 h then CuCl₂, MeOH, 80 °C, 2 h, 68%; (g) NaH, THF, MeI, 0 °C to r.t., then Fe (powder), 1 N HCl, EtOH, 59%.

SYNTHESIS 2007, No. 7, pp 0981–0983
Advanced online publication: 12.03.2007
© Georg Thieme Verlag Stuttgart · New York
During the purification process for compound 16, it was noted that when the crude hydrochloride salt was heated to >120 °C a ‘clean’ decomposition reaction occurred, leading to the lactam compound 17. Due to the similarities between the title compound 1 and the thermal degradation product 17, it seemed feasible that this route might be applicable to the synthesis of compound 1 following the retrosynthetic strategy outlined in Scheme 4.

Scheme 4 Alternative retrosynthesis towards 8-amino-2-methyl-3,4-dihydroisoquinolin-1-one

The alternative synthesis (Scheme 5) begins with the reaction between commercially available 2-methyl-6-nitrobenzonitrile (18) and neat Bredereck’s reagent,6 at 100 °C for one hour. The methyl group of 18 is sufficiently activated by the presence of both the nitrile and nitro groups that the reaction proceeds quickly, generating the enamine intermediate 19. Attempts to synthesize 19 using dimethylformamide dimethylacetal7 (DMFDMA), with or without the presence of a Lewis acid, were unsuccessful. The crude enamine compound was reduced under mild conditions with NaBH(OAc)₃ in the presence of acetic acid to give 2-(2-dimethylaminoethyl)-6-nitrobenzonitrile 20 in 81% yield, over two stages.

Scheme 5 Alternative synthesis of compound 1. Reagents and conditions: (a) i. t-BuOCH(NMe₂)₂ (Bredereck’s reagent), neat, 100 °C, 1 h, ii. NaBH(OAc)₃, DME, AcOH, r.t., 18 h, 81%; (b) i. 6 N HCl, microwave, 160 °C, 15 h, ii. sulfolane, 200 °C, 2 h, 48%; (c) 10% Pd/C, H₂, EtOAc, EtOH, 24 h, 83%.

Quite harsh conditions, involving microwave irradiation at 160 °C for 15 hours, were required to hydrolyze the cyano compound 20 to the acid 21. The 15 hours heating time was necessary as shorter reaction times led to complex mixtures of starting material 20, required product 21 and the amide 23. The crude hydrochloride salt of compound 21 was then heated in an open vessel to effect the cyclization, via the effective loss of methanol, to give 2-
methyl-8-nitro-3,4-dihydroisoquinolin-1-one (22) in 48% yield. Compound 22 was hydrogenated in the presence of Pt/C catalyst to afford the title compound 1 in 83% yield.

In summary, this chemistry represents a shorter alternative synthesis of 8-amino-2-methyl-3,4-dihydroisoquinolin-1-one (1) which can be carried out quickly and easily, yielding excellent quality material in 32% total yield from 2-methyl-6-nitrobenzonitrile (18), over three stages.

All chemicals used were of reagent grade and used as supplied. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (2–400 mbar) with a bath temperature of up to 60 °C. Microwave chemistry was carried out on the Emrys-Optimiser microwave synthesizer apparatus. Chromatography was carried out on silica gel; TLC carried out on silica plates (Merck, Art. 5554). In general, the course of reactions was followed by TLC and/or LC-MS. NMR spectra were obtained on a Bruker DPX-300 spectrometer at 300 MHz using CDCl3, or DMSO-d6 as solvent. Chemi-Shifts are expressed in ppm downfield from TMS, which was used as an internal standard. Melting points of small samples were obtained after recrystallization; solvents given in parentheses. LC-MS data was recorded utilizing the electrospray (ES+) technique. Values for m/z are given; the mass ion quoted is [MH]+ which refers to the protonated mass ion.

2-(2-Dimethylaminoethyl)-6-nitrobenzonitrile (20)

2-Methyl-6-nitrobenzonitrile (18; 3.24 g, 20 mmol) was taken up in DME (60 mL), AcOH (5.2 mL) was added and then the mixture was heated in an open vessel at 200 °C for 15 h. The reaction was allowed to cool and the excess Bredereck's reagent was removed in vacuo. The crude residue was then allowed to cool and aq 2 N HCl (20 mL) was added with vigorous stirring and sonication to form a light brown precipitate. The solid was filtered and dried in a desiccator to give 22 as a buff-colored product (0.68 g, 48%); mp 177–179 °C (MeCN); Rf = 0.58 (EtOAc).

IR (KBr): 3043, 2922, 1658, 1536 cm–1.

1H NMR (300 MHz, CDCl3): δ = 3.05 (t, J = 6.4 Hz, 2 H, ArCH2), 3.15 (s, 3 H, CH3), 3.62 (t, J = 6.4 Hz, 2 H, NCH2), 7.32–7.38 (m, 2 H, H-5,7), 7.49 (t, J = 7.7 Hz, 1 H, H-6).

13C NMR (300 MHz, DMSO-d6): δ = 27.4, 34.3, 46.8, 120.9, 132.0, 132.2, 141.6, 150.0, 159.3.

MS (ES+); m/z = 207.58.

8-Amino-2-methyl-3,4-dihydroisoquinolin-1-one (1)

2-Methyl-8-nitro-3,4-dihydroisoquinolin-1-one (22; 2.01 g, 9.73 mmol) was dissolved in warm EtOAc (100 mL) and EtOH (10 mL) and to this was added 10% Pt/C (300 mg). The mixture was stirred under an atmosphere of H2 for 24 h. The catalyst was removed by filtration and washed with cold EtOAc (50 mL). The filtrate was evaporated and the crude residue was chromatographed on silica gel, eluting with 0–10% MeOH in EtOAc to give 1 as a light brown solid (1.41 g, 82%); mp 124–126 °C (MeCN); Rf = 0.79 (EtOAc).

IR (KBr): 3428, 3309, 2948, 2869, 1615, 1554 cm–1.

1H NMR (300 MHz, CDCl3): δ = 2.89 (t, J = 6.6 Hz, 2 H, ArCH2), 3.10 (s, 3 H, CH3), 3.48 (t, J = 6.6 Hz, 2 H, NCH2), 6.19 (br s, 2 H, NH2), 6.38 (d, J = 7.2 Hz, 1 H, H-5), 6.51 (d, J = 8.2 Hz, 1 H, H-7), 7.08 (t, J = 7.7 Hz, 1 H, H-6).

13C NMR (300 MHz, DMSO-d6): δ = 28.3, 34.3, 47.3, 109.4, 113.5, 114.6, 131.8, 139.8, 150.5, 166.7.

MS (ES+); m/z = 177.50.

References


