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

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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.

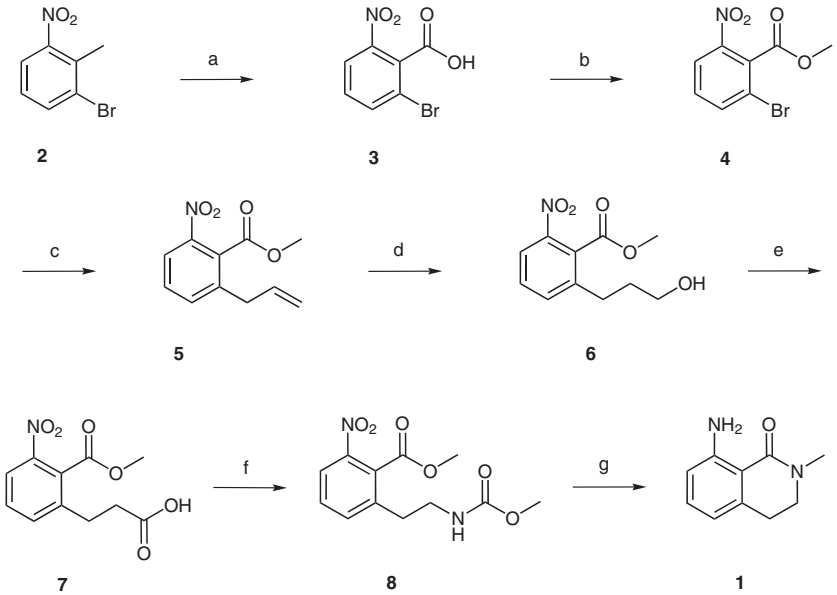
Key words: lactam, microwaves, cyclization, Bredereck's reagent, isoquinolinone

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[1,2] 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, CrO_3/H_2SO_4 and $(PhO)_2P(O)N_3$, along with the particularly low-yielding permanganate oxidation step[3] (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**).[4,5] 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) $KMnO_4$, Na_2CO_3, H_2O, 100 °C, 18 h, 40%; (b) Cs_2CO_3, MeOH, r.t., then MeI, DMF, 0 °C to r.t., 14 h, ca. 100%; (c) allyltributyltin, $Pd(Ph_3P)_4$, toluene, 110 °C, 20 h then CsF, H_2O, ca. 100%; (d) $BH_3{\cdot}SMe_2$, THF, 0 °C, 4 h, then H_2O_2, NaOH, r.t., 1 h, 90%; (e) CrO_3, H_2SO_4, 0 °C to r.t., 4 h, 80%; (f) $(PhO)_2P(O)N_3$, Et_3N, toluene, 80 °C, 2 h then $CuCl_2$, MeOH, 80 °C, 2 h, 68%; (g) NaH, THF, MeI, 0 °C to r.t., then Fe (powder), 1 N HCl, EtOH, 59%.

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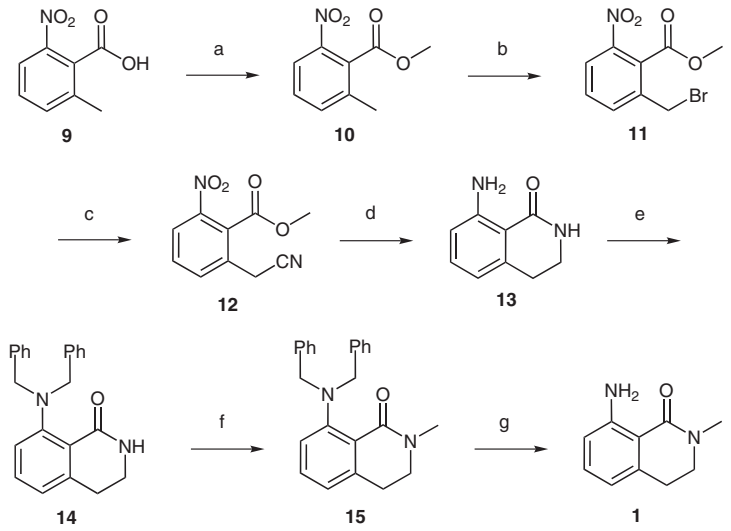
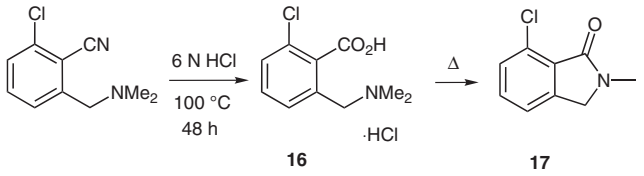
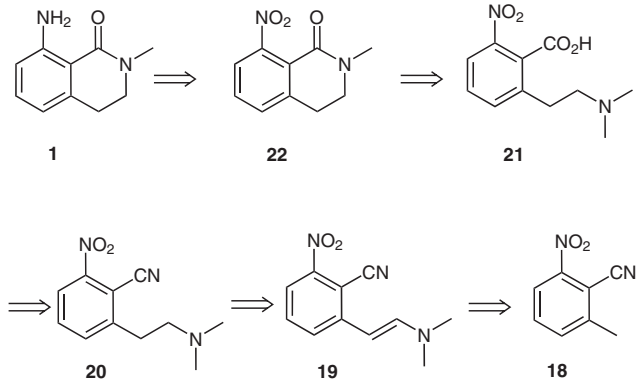


Scheme 2 WO 2006/021544 – *Reagents and conditions*: (a) $(MeO)_2SO_2$, DIPEA, acetone; (b) NBS, CCl_4, $(PhCO)_2O_2$, *hν*; (c) NaCN, solvent; (d) Raney-Nickel, H_2, MeOH, r.t., 16 h; (e) BnBr (3.5 equiv), K_2CO_3, DMF, 50 °C, 16 h; (f) NaH, DMF, MeI, 30 h; (g) $Pd(OH)_2$, H_2, MeOH, 48 h.



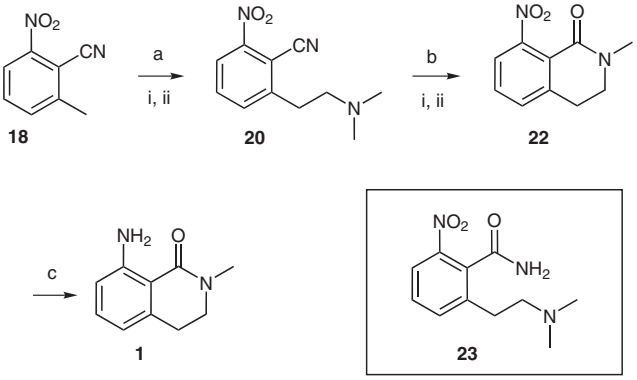
Scheme 3 Decomposition of 2-chloro-6-(dimethylaminomethyl)benzoic acid hydrochloride with heat

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 dimethylacetal[7] (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*-$BuOCH(NMe_2)_2$ (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% Pt/C, H_2, 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 (2–400mbar) with a bath temperature of up to 60 °C. Microwave chemistry was carried out on the Emrys-Optimizer 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 $CDCl_3$ or DMSO-d_6 as solvent. Chemical 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 Bredereck's reagent (10 mL) and heated to 100 °C for 1 h. The thick resulting mixture was allowed to cool and the excess Bredereck's reagent was removed in vacuo. The crude residue was taken up in DME (60 mL), AcOH (5.2 mL) was added and then the mixture was treated with $NaBH(OAc)_3$ (6.46 g, 30.4 mmol) with stirring at r.t. for 18 h under N_2. The mixture was concentrated in vacuo and then poured into EtOAc (300 mL) and washed with aq 2 N NaOH solution (200 mL). The mixture was extracted with EtOAc (2 × 300 mL), washed with aq 2 N NaOH solution (200 mL), H_2O (2 × 200 mL) and then brine (200 mL). The organic layer was dried ($MgSO_4$) and evaporated to afford a crude oily mixture. Chromatography on silica gel, eluting with a gradient of CH_2Cl_2 to CH_2Cl_2–MeOH–aq NH_3(7 N)–MeOH (90:9:1) gave **20** as a brown solid product (3.53 g, 81%); mp 71–73 °C (hexanes–EtOAc, 5:1); R_f = 0.39 (EtOAc–MeOH, 9:1).

IR (KBr): 2972, 2782, 2387, 2295, 2226, 1541, 1521, 1462, 1342 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.21 (s, 6 H, CH_3), 2.57 (t, *J* = 7.3 Hz, 2 H, ArCH_2), 3.07 (t, *J* = 7.3 Hz, 2 H, NCH_2), 7.89 (t, *J* = 8.0 Hz, 1 H, H-4), 7.97 (dd, *J* = 7.8, 1.2 Hz, 1 H, H-3), 8.22 (dd, *J* = 8.1, 1.3 Hz, 1 H, H-5).

^{13}C NMR (300 MHz, DMSO-d_6): δ = 31.7, 44.8, 59.0, 106.4, 114.0, 123.5, 133.5, 135.9, 147.9, 149.0.

MS (ES+): *m*/*z* = 220.54.

2-Methyl-8-nitro-3,4-dihydroisoquinolin-1-one (22)

2-(2-Dimethylaminoethyl)-6-nitrobenzonitrile (**20**; 1.5 g, 6.85 mmol) was taken up in aq 6 N HCl (15 mL), sealed in a closed microwave vessel and subjected to microwave irradiation at 160 °C for 15 h. The reaction was allowed to cool and the solvent was carefully removed in vacuo. Sulfolane (10 mL) was added to the crude residue and the mixture was heated in an open vessel at 200 °C for 2 h. The mixture was cooled to r.t. and then the residue was dissolved in CH_2Cl_2 (200 mL) with stirring for 10 min. The mixture was filtered and the resulting filtrate was evaporated to afford a viscous oily product, which was transferred to a Kugelrohr apparatus. The sulfolane solvent was distilled off (200 °C/8 mmHg) and the 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 dessicator to give **22** as a buff-colored product (0.68 g, 48%); mp 177–179 °C (MeCN); R_f = 0.58 (EtOAc).

IR (KBr): 3043, 2922, 1658, 1536 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.05 (t, *J* = 6.4 Hz, 2 H, ArCH_2), 3.15 (s, 3 H, CH_3), 3.62 (t, *J* = 6.4 Hz, 2 H, NCH_2), 7.32–7.38 (m, 2 H, H-5,7), 7.49 (t, *J* = 7.7 Hz, 1 H, H-6).

^{13}C NMR (300 MHz, DMSO-d_6): δ = 27.4, 34.3, 46.8, 120.9, 121.3, 130.2, 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 (500 mg). The mixture was stirred under an atmosphere of H_2 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); R_f = 0.79 (EtOAc).

IR (KBr): 3428, 3309, 2948, 2869, 1615, 1554 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.89 (t, *J* = 6.6 Hz, 2 H, ArCH_2), 3.10 (s, 3 H, CH_3), 3.48 (t, *J* = 6.6 Hz, 2 H, NCH_2), 6.19 (br s, 2 H, NH_2), 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).

^{13}C NMR (300 MHz, DMSO-d_6): 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.

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