

Reductive Cyclisation of 2-Cyanomethyl-3-Nitrobenzoates

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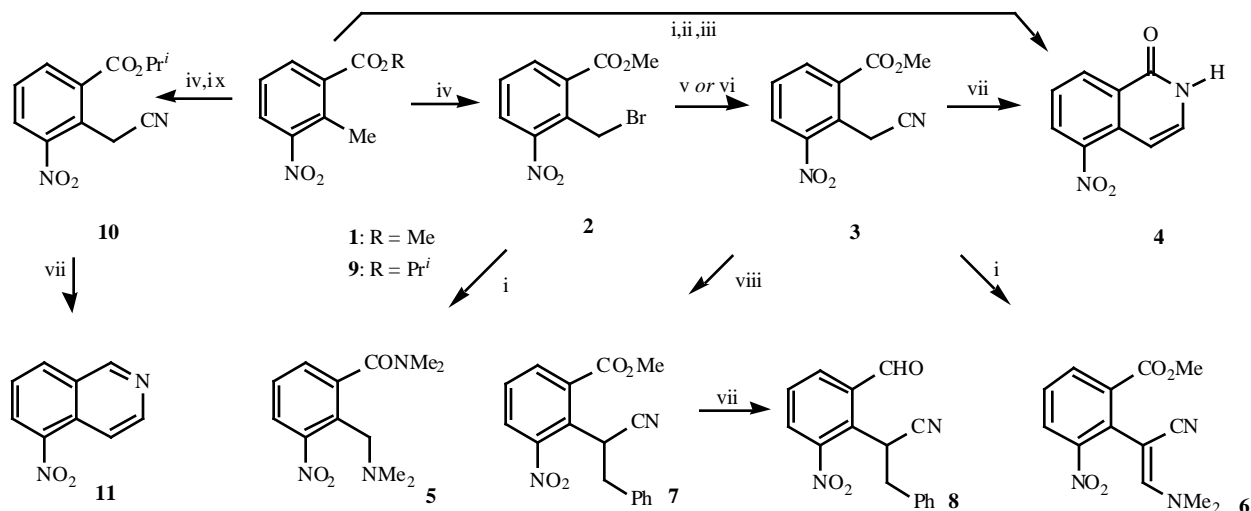
Abstract: Selective reduction of the nitrile in methyl 2-cyanomethyl-3-nitrobenzoate with DiBAL-H at low temperature, followed by cyclisation *in situ* gave 5-nitroisoquinolin-1-one, leading towards the lead PARP-1 inhibitor 5-AIQ. However, increasing steric bulk at the methylene switched reduction to the ester only, giving the corresponding benzaldehyde. Surprisingly, increasing steric bulk in the ester also allowed reduction of the ester prior to cyclisation, giving 5-nitroisoquinoline.

Keywords: Reductive cyclisation, isoquinolinone, isoquinoline, DiBAL-H.

5-Aminoisoquinolin-1-one (5-AIQ) [1] is an exciting lead inhibitor of PARP-1 [2], which is highly water-soluble and shows exceptional organ-protective activity in models of haemorrhagic shock, myocardial infarction, acute lung inflammation, ischaemic liver and kidney disease and spinal cord trauma [2,3]. In our programme on PARP-1 inhibitors, we are investigating new approaches to 5-aminoisoquinolin-1-ones. Few of the known routes to isoquinolin-1-ones are applicable to the 5-substituted analogues. Curtius rearrangement and cyclisation of cinnamoyl azides gives isoquinolin-1-ones but this is limited to compounds lacking electron-withdrawing groups [1]. The first route to 5-AIQ involved

quinolin-1-one **4** [1]. Reduction gave 5-AIQ [1]. Condensation of **1** with DMFDMA and treatment with silica gives 5-nitroisocoumarin, which can be elaborated to 5-AIQ by replacement of heterocyclic O with N and reduction [3]. However, this method cannot be used for the 3-alkyl analogues [4].

In the present work, we postulated that the isoquinolin-1-one 2-N and 3-C could be introduced at a higher oxidation level, as cyanide. Radical bromination at the Ar-methyl of **1** was achieved in high yield (Scheme 1) [5]. Displacement of the bromine with cyanide was carried out by two methods.

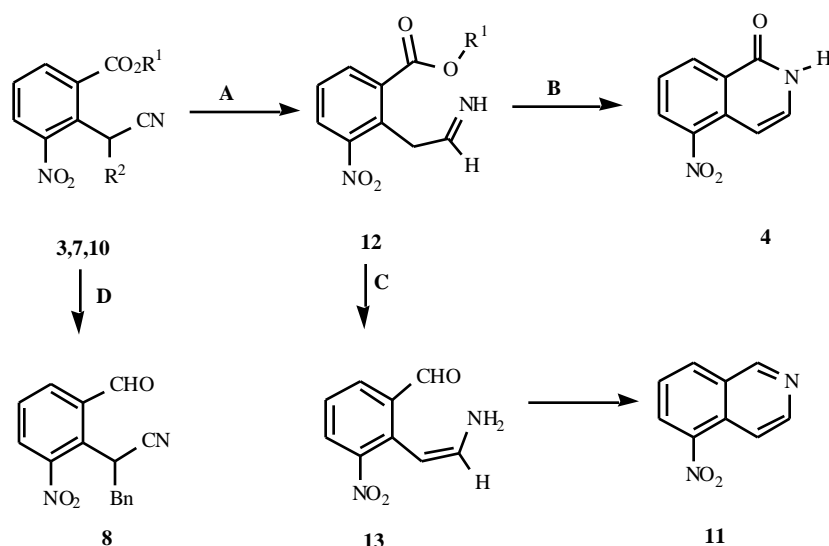


Scheme 1. Synthesis of 2-cyanomethyl-3-nitrobenzoate esters **3,7,10** and reaction with DiBAL-H. *Reagents & conditions:* i, (MeO)₂CHNMe₂, DMF, reflux, 16 h; [3] ii, SiO₂, EtOAc, hexane; [3] iii, NH₃, MeO-(CH₂)₂-OH, reflux, 4 h, 39% from **1**; [3] iv, Br₂, (PhCO₂)₂, CCl₄, h, reflux, 49 h, 98% (**2**), 93% (**10**); v, Et₄NCN, MeCN, 4 h, 68%; vi, KCN, Bu₄NBr, MeOH, 2 h, 22% (**3**), 7% (**4**); vii, Bu^t₂AlH, CH₂Cl₂, -78°C, 1 h, 23% (**4**), 44% (**8**), 14% (**11**); viii, LiN(SiMe₃)₂, BnBr, THF, -78°C → 20°C, 67%; ix, KCN, Bu₄NBr, Pr^tOH, 45%.

N-oxidation of 5-nitroisoquinoline **11**, followed by an unreliable Polonovski rearrangement, to give 5-nitroiso-

Reaction of **2** with Et₄NCN in acetonitrile afforded **3** [6] in good yield. Treatment of **2** with KCN and Bu₄NBr in methanol gave a satisfactory yield of **3**, along with a trace of material provisionally characterised as 3-methoxy-5-nitroisoquinolin-1-one, presumably formed by Pinner reaction of the nitrile of **3** with solvent, followed by attack

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Scheme 2. Steps in formation of **4**, **8**, **11** from **3**, **7**, **10**, respectively.

of the imidate N on the adjacent ester. In the main sequence, the nitrile of **3** was reduced [7] selectively with DiBAL-H at -78°C , generating the intermediate imine which cyclised to give **4** in moderate yield.

The DiBAL reductions of two analogues of **3** with bulky substituents at either the ester or methylene position were studied to explore the generality of this route. A benzyl group was introduced to the methylene group of **3** by deprotonation with lithium hexamethyldisilazide and quench with benzyl bromide, affording **7** [8]. Reduction with DiBAL-H at -78°C , however, gave only the aldehyde **8** [9], arising from reduction of the ester while leaving the nitrile unscathed. The isopropyl ester **9** [4] was brominated and converted to the nitrile **10**, as for the synthesis of **3**. Reduction with DiBAL-H, however, gave the isoquinoline **11** as the sole identifiable product, formed from reduction of both the ester and the nitrile. This indicates, surprisingly, that increasing the steric bulk of the ester makes it more prone to reduction. Scheme 2 shows a rationalisation of these observations. The nitrile of **3** is reduced rapidly (step A) to give intermediate **12** ($\text{R}^1 = \text{Me}$); intramolecular attack of the imine (or the tautomeric enamine) (step B) is also fast, allowing cyclisation to **4** before reduction of the ester can occur. For the isopropyl ester **10**, step A is also fast, giving **12** ($\text{R}^1 = \text{Pr}^i$) but approach of the nucleophile in step B is slowed by the steric bulk of the Pr^i , allowing time for reduction of the ester (step C), leading to aldehyde **13** and on to product **11**. In substrate **7**, approach of the DiBAL-H to the nitrile is obstructed by the adjacent benzyl group, leading to reduction at the ester only, giving **8** via step D.

Since the reactive Ar-methyl group in **1** condenses efficiently with DMFDMA, leading to 5-nitroisocoumarin [3], the reactions of **2** and **3** (with acidic methylenes) with this reagent were studied (Scheme 1). Neither 3-bromo- nor 3-cyano-5-nitroisocoumarin were formed but dimethylamine from thermolysis of the DMFDMA displaced both bromine and methoxy of **2**, giving **5**. Nitrile **3** did condense with DMFDMA to give enamine **6** but this resisted all attempts at silica- or acid-catalysed conversion to an isocoumarin; the electron-withdrawing nitrile deactivates the enamine.

In this Letter, we report new reductive cyclisations of methyl 2-cyanomethyl-3-nitrobenzoate to 5-nitroisoquinolin-1-one and of the isopropyl ester to 5-nitroisoquinoline; similar reduction of analogue bearing a substituent at the methylene gave only the corresponding benzaldehyde. Thus the severe effects of steric bulk mitigate against the general utility of this new cyclisation.

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- Synthesis of 3.** Compound **2** (5.0 g, 18 mmol) was stirred with Et_4NCN (3.4 g, 22 mmol) in MeCN (70 mL) for 4 h. Evaporation and chromatography (Et_2O /hexane 1:1) gave **3** (2.8 g, 69%) as off-white crystals: mp $94\text{--}95^{\circ}\text{C}$ (lit. [10] mp $95.5\text{--}96^{\circ}\text{C}$).
- Synthesis of 4.** DiBAL-H (7.5 mmol) was stirred with **3** (1.1 g, 5.0 mmol) in dry CH_2Cl_2 (50 mL) at -78°C for 1 h. Aq. HCl (2 M, 35 mL) was added. Extraction (CH_2Cl_2), evaporation and chromatography (hexane/ EtOAc 2:3) gave **4** (220 mg, 23%) [3].
- Synthesis of 9.** Compound **3** (1.0 g, 4.5 mmol) was stirred with $\text{LiN}(\text{SiMe}_3)_2$ (5.6 mmol) and BnBr (1.1 g, 6.5 mmol) in THF (20 mL) at -78°C for 20 min and at 20°C for 4 h. Extraction (CH_2Cl_2), washing (aq. HCl), and chromatography (PhMe) gave **9** (930 mg, 67%), pale buff oil: NMR ^1H 3.42 (1 H, dd, $J = 13.1, 5.4$ Hz) and 3.75 (1 H, dd, $J = 13.1, 10.1$ Hz) (CH_2), 4.00 (3 H, s, Me), 5.07 (1 H, dd, $J = 10.1, 5.4$ Hz, CH), 7.28 (5 H, m, Ph- H_5), 7.56 (1 H, t, $J = 8.1$ Hz, 5-H), 7.97 (1 H, dd, $J = 8.1, 1.5$ Hz, 4-H), 8.08 (1 H, dd, $J = 7.9, 1.5$ Hz, 6-H); MS (FAB $^+$) m/z 311.1046 (M + H) ($\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_4$ requires 311.1031).

[9] **Data for 10.** NMR ^1H 3.30 (1 H, dd, $J = 13.1, 5.5$ Hz) and 3.59 (1 H, dd, $J = 13.1, 9.9$ Hz) (CH_2), 5.25 (1 H, dd, $J = 9.9, 5.5$ Hz, CH), 7.35 (5 H, m, Ph- H_5), 7.76 (1 H, t, $J = 7.9$ Hz, 5-H), 8.00 (1 H, dd, $J = 8.1, 1.5$ Hz, 4-H), 8.15 (1 H, dd, $J = 7.9, 1.5$ Hz, 6-H);

MS (EI^+) m/z 280.0850 (M + H) ($\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_3$ requires 280.0847).
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