# A versatile synthesis of diverse 3,4-fused cinnolines *via* the base-catalysed condensation of 2-amino-2′-nitrobiaryls†

**Åsa Slevin, Tobias Koolmeister and Martin Scobie***

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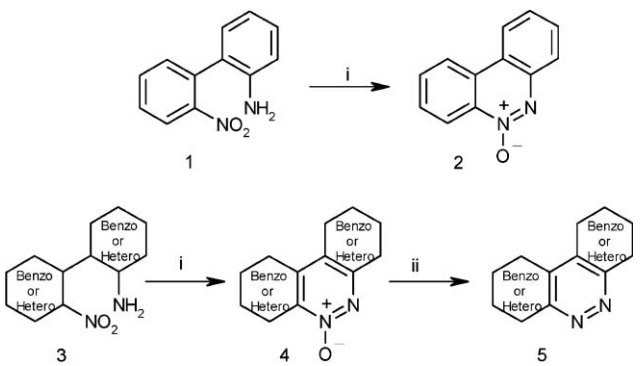
**Benzo[*c*]cinnolines, thieno[3,2-*c*]cinnolines, pyrido[3,2-*c*]cinnolines and the previously undescribed quinoxalino[6,7-*c*]cinnoline ring system are conveniently prepared by a short synthetic route comprised of Suzuki coupling, base-catalysed cyclisation and deoxygenation. The use of tandem borylation–Suzuki coupling further extends the scope of this process to include highly substituted benzo[*c*]cinnolines.**

The high yielding base-catalysed cyclisation (Scheme 1) of 2-amino-2′-nitrobiphenyl (**l**) to afford benzo[*c*]cinnoline 6-*N*-oxide (**2**) was first reported by Muth and colleagues in 1960.[1] This unusual process has remained largely unexploited, and little is known regarding its scope or mechanism.[2,3] Since the deoxygenation of heteroaromatic *N*-oxides is a well-studied and generally straightforward process, Muth's cyclisation provides an unexplored, potentially versatile route into functionalised benzo[*c*]cinnolines and other, much rarer, fused pyridazine-based systems in general. We anticipated that the cyclisation of appropriate aminonitrobiaryls **3** would provide a general synthetic approach to diverse tricyclic *N*-oxides, exemplified by structure **4**. Biaryl and heterobiaryl substrates **3** are readily prepared by Suzuki-coupling methodology, thus providing a concise and flexible route into some interesting tricyclic systems bearing a central pyridazine motif **5**.

Since little was known about the scope of Muth's cyclisation, particularly regarding the effect of substitution in the nitrophenyl




**Scheme 1** *Reagents and conditions*: i, methanolic NaOH (1 M), 70 °C, 2 h; ii, deoxygenation.

*Biovitrum AB, Discovery Research, Retzius Väg 8, SE-112 76, Stockholm, Sweden. E-mail: martin.scobie@biovitrum.com; Fax: +46 869 72533; Tel: +46 869 73863*

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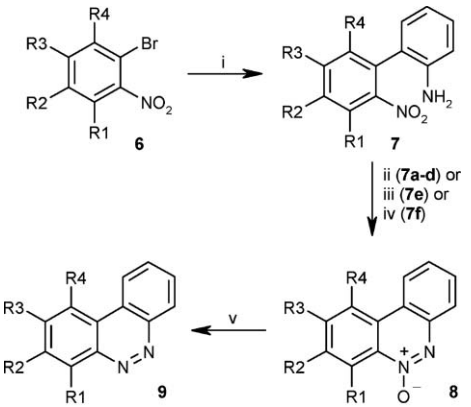



**Scheme 2** *Reagents and conditions*: i, 2-aminophenylboronic acid hydrochloride, $Pd(PPh_3)_4$ (5 mol%), $Na_2CO_3$, toluene, EtOH, reflux, 12 h; ii, methanolic NaOH (1 M), 70 °C, 2 h; iii, $^t$BuOK, THF, r.t., 5 min; iv, methanolic NaOH (1 M), 150 °C, 1 min.; v, In, $NH_4Cl$ (aq.), EtOH, 80 °C, 1 h.

ring, we constructed (Scheme 2) a set of biaryl substrates **7** *via* the Suzuki-coupling of *ortho*-bromonitroarenes **6** with commercially available 2-aminobenzeneboronic acid. The use of *tetrakis*(triphenylphosphine)palladium(0) as the catalyst (Table 1) generally gave satisfactory yields of the corresponding 2-amino-2′-nitrobiaryls **7**. However, the sterically-hindered biaryl **7e** was formed in only 29% yield, presumably due to unfavourable steric crowding around the biaryl axis.

Heating biphenyls **7a–d** with 1 M methanolic sodium hydroxide afforded the corresponding cinnoline *N*-oxides **8a–d** in high yields (>80%). Under these standard conditions, biphenyls **7e** and **7f** failed to react, even after prolonged heating at 70 °C for several days. We found that use of potassium *tert*-butoxide in THF induced the cyclisation of **7e** at room temperature within 5 min to give **8e** in high yield (96%). Surprisingly though, biaryl **7f** gave complex mixtures when treated with potassium *tert*-butoxide. In

**Table 1** Synthesis of benzo[*c*]cinnolines according to Scheme 2

| Entry | R1 | R2 | R3 | R4 | Yield **7** (%)[a] | Yield **8** (%)[a] | Yield **9** (%)[a] |
|---|---|---|---|---|---|---|---|
| **6a** | H | OMe | H | H | 47 | 91 | 96 |
| **6b** | H | $CF_3$ | H | H | 73 | 82 | 85 |
| **6c** | H | Me | H | H | 65 | 98 | 69 |
| **6d** | H | $CF_3$ | $CF_3$ | H | 74 | 86 | 83 |
| **6e** | H | H | H | Me | 29 | 96 | 76 |
| **6f** | Me | H | H | H | 61 | 65 | 78 |

[a] All yields refer to isolated products.

this case, efficient cyclisation was achieved by heating in methanolic sodium hydroxide at a high temperature (150 °C) using microwave irradiation.

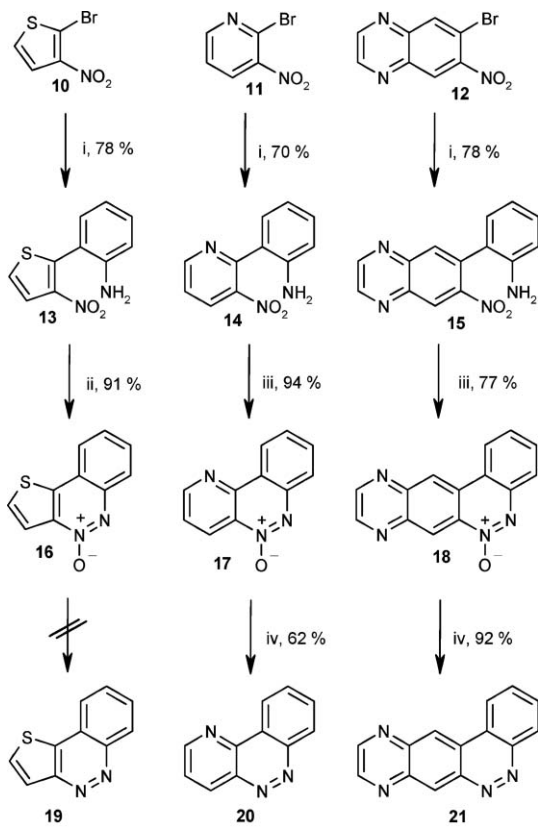
Having demonstrated that Suzuki coupling followed by base-catalysed cyclisation provides a general synthetic route into benzo[*c*]cinnoline *N*-oxides **8a–f** bearing electron withdrawing ($CF_3$) or electron donating substituents (OMe), we next investigated the deoxygenation of these compounds to give the parent benzo[*c*]cinnolines **9a–f**.

Indium dust in ethanolic ammonium chloride proved to be a reliable and high yielding method for the deoxygenation of *N*-oxides **8a–f**, although alternative methods, such as sodium dithionite, worked equally well.[4] The resulting benzo[*c*]cinnolines **9a–f** were isolated in high yields (69–96%)

The synthesis of rarer non-benzenoid, fused cinnolines was then investigated (Scheme 3); previous studies by one of our group having indicated that base-catalysed cyclisation should also be effective in heterobiaryl systems.[5] Three commercially available heterocyclic bromonitroarenes, **10–12**, were selected. The Suzuki coupling of these substrates with 2-aminobenzeneboronic acid was straightforward, affording biaryls **13–15** in 70–80% yields. Base-catalysed condensation using 1 M methanolic sodium hydroxide worked well for the pyridine and quinoxaline derivatives **14** and **15**; the expected *N*-oxides **17** and **18** were isolated in high yields (88 and 77%). Interestingly, the thiophene derivative **13** was not cyclised under these conditions, even after prolonged heating. In contrast, the use of potassium *tert*-butoxide in THF induced rapid cyclisation at room temperature, and the resulting *N*-oxide **16** was isolated in high yield. Attempted deoxygenation of the thiophene derivative **16** was unsuccessful using indium dust, and only intractable material was formed. We presume that the deoxygenation of **16** could be carried out by alternative means, although this was not followed up. Indium-mediated deoxygenation of the *N*-oxides **17** and **18** furnished the parent ring systems **20** and **21** very cleanly, and in high yields. The thieno[3,2-*c*]cinnoline **19** and pyrido[3,2-*c*]cinnoline **20** ring systems have both been described in the literature, though relatively few simple examples have been prepared, often by lengthy or inefficient synthetic routes.[6,7] The quinoxalino[6,7-*c*]cinnoline system **21** is hitherto undescribed.

Since relatively few 2-aminoarylboronic acids were commercially available at the outset of this work, we briefly investigated their *in situ* generation (Scheme 4) by using the tandem borylation–Suzuki coupling protocol reported by Baudoin *et al.*[8] Thus, in one pot, treatment of a 2-bromoaniline **22** with pinacolborane, palladium(II) acetate and 2-(dicyclohexylphosphino)biphenyl for 1 h, followed by the addition of 4-bromo-3-nitrobenzotrifluoride and barium hydroxide furnished the biaryl derivative **23** in 70% yield. Cyclisation and subsequent deoxygenation reactions were then carried out to afford the benzocinnoline derivative **25** in high overall yield (61% from **22**)

In conclusion, we have demonstrated the utility of this simple and high yielding three step procedure for the synthesis of diverse tricyclic scaffolds bearing a central pyridazine motif. The base-catalysed cyclisation of appropriate 2-amino-2′-nitrobiaryls is a versatile ring closure method, and difficult cases are easily overcome by altering either the reaction temperature or base catalyst and solvent. The use of potassium *tert*-butoxide is especially appealing in this respect since milder reaction conditions are required and sluggish substrates are rapidly cyclised. Furthermore, the *N*-oxides produced by ring closure are interesting compounds in their own right since the regioselective *N*-oxidation of diazines is non-trivial. Lastly, the limited commercial availability

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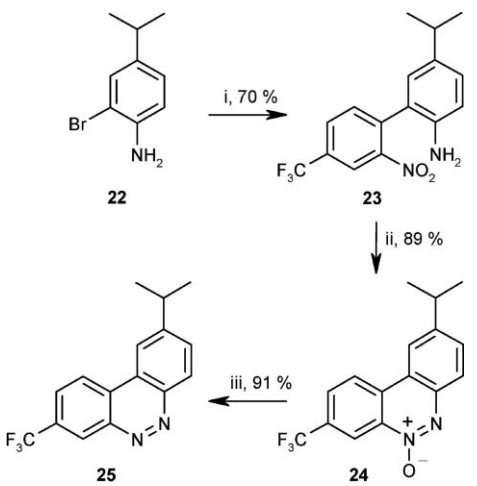


**Scheme 4** *Reagents and conditions*: i, pinacolborane, $Et_3N$, $Pd(OAc)_2$ (5 mol%), 2-(dicyclohexylphosphino)biphenyl (20 mol%), dioxane, 80 °C, 1 h, then water, $Ba(OH)_2$, **6b**, 100 °C, 1 h; ii, methanolic NaOH (1 M), 70 °C, 2 h; iii, In, $NH_4Cl$ (aq.), EtOH, 80 °C, 1 h.

of 2-aminobenzeneboronic acids can be enriched by the use of a tandem borylation and Suzuki coupling protocol prior to base-catalysed cyclisation.[9]

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9 Since completion of this work, a range of 2-aminobenzeneboronic acid derivatives, bearing different substituents on the aryl ring, are now commercially available.



 