COMMUNICATION

A versatile synthesis of benzo[*c*]phenanthridine alkaloids

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Suzuki coupling between 2-bromo-1-formamidonaphthalenes and arylboronic acids is the key step in a versatile synthesis of benzo[*c*]phenanthridine alkaloids, illustrated by the synthesis of norallonitidine, nornitidine, noravicine, allonitidine, nitidine and avicine.

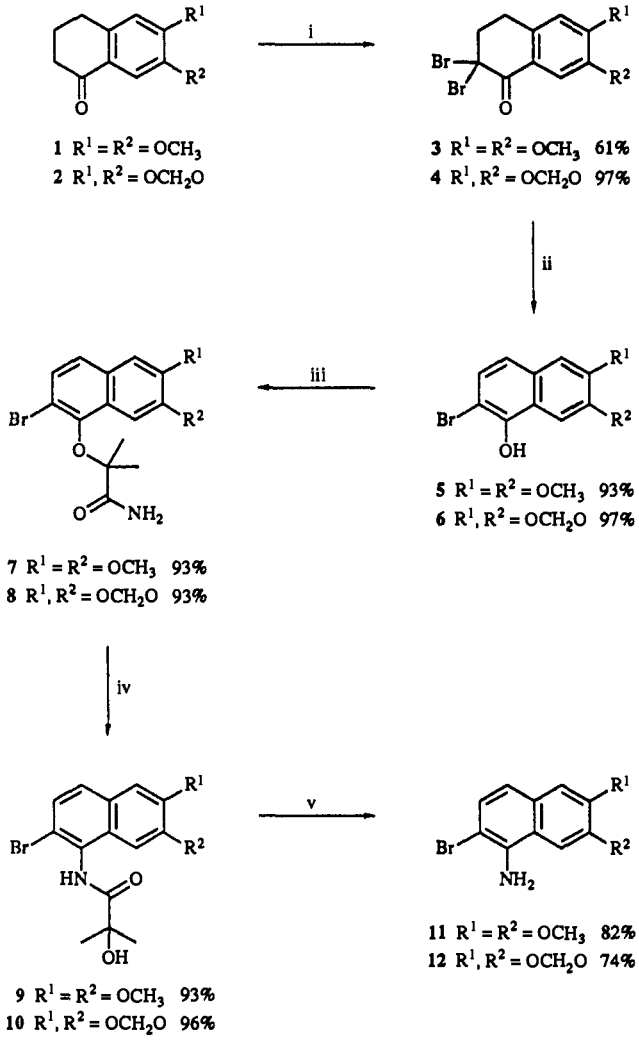
The benzo[*c*]phenanthridines are an important group of alkaloids, certain members of which exhibit antileukaemic activity, and are inhibitors of DNA topoisomerases and both HIV-1 and HIV-2 reverse transcriptases.[1] They have been the subject of a number of syntheses, but many of these join the components which become the A and D rings early in the sequence.[2] Since most of these alkaloids are differentiated by the sites and nature of oxygenation within these two rings, such a synthetic strategy necessitates an individually tailored sequence for each target molecule. We sought to design a synthesis which included a late stage fusion of these components, thereby allowing easy access to a number of such alkaloids from a few key synthetic intermediates.

In planning this strategy, we envisaged a Suzuki coupling between appropriately substituted 2-halogeno-1-naphthylamines and arylboronic acids as the key step.[3] The boronic acids were readily prepared from the corresponding bromides, but the 2-halogeno-1-naphthylamines were less readily accessible.

Preparation of 2-bromo-6,7-dioxygenated-1-naphthylamines

Strategies based on electrophilic bromination or *ortho*-directed metallation of 1-naphthylamine derivatives either failed or gave unacceptably low yields of the desired products. We therefore reversed the order of introduction of these functionalities, and commenced with bromination of the readily available tetralones **1** and **2** using bromine in chloroform (Scheme 1).[4] Although both reactions were easily conducted, bromination of the dimethoxy tetralone **1** was not as efficient as the methylenedioxy analogue **2**, and the product **3** required purification by trituration with dichloromethane after removal of the reaction solvent. The 2,2-dibromides **3** and **4** were then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in warm acetonitrile for 20 min to give the 2-bromo-1-naphthols **5** and **6** in excellent yield.

The Smiles rearrangement[5] was highly effective for transformation of the naphthols **5** and **6** into the naphthylamines **11** and **12**. Use of the published conditions for phenol *O*-alkylation with 2-bromo-2-methylpropanamide (NaH, 1,4-dioxane)[5b] gave poor results when applied to **5** and **6**, and yields of the alkylated products **7** and **8** were typically below 30%. However, reaction in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) in the presence of solid sodium hydroxide was clean and efficient, affording both **7** and **8** in 93% yield. Smiles rearrangement of **7** and **8** using sodium hydride in DMF–DMPU at 100 °C gave the hydroxy amides **9** and **10** in yields of 93 and 96% respectively. Amide hydrolysis required heating with an excess of sodium hydroxide in aqueous methanol, but cleanly furnished the desired amines **11** and **12**

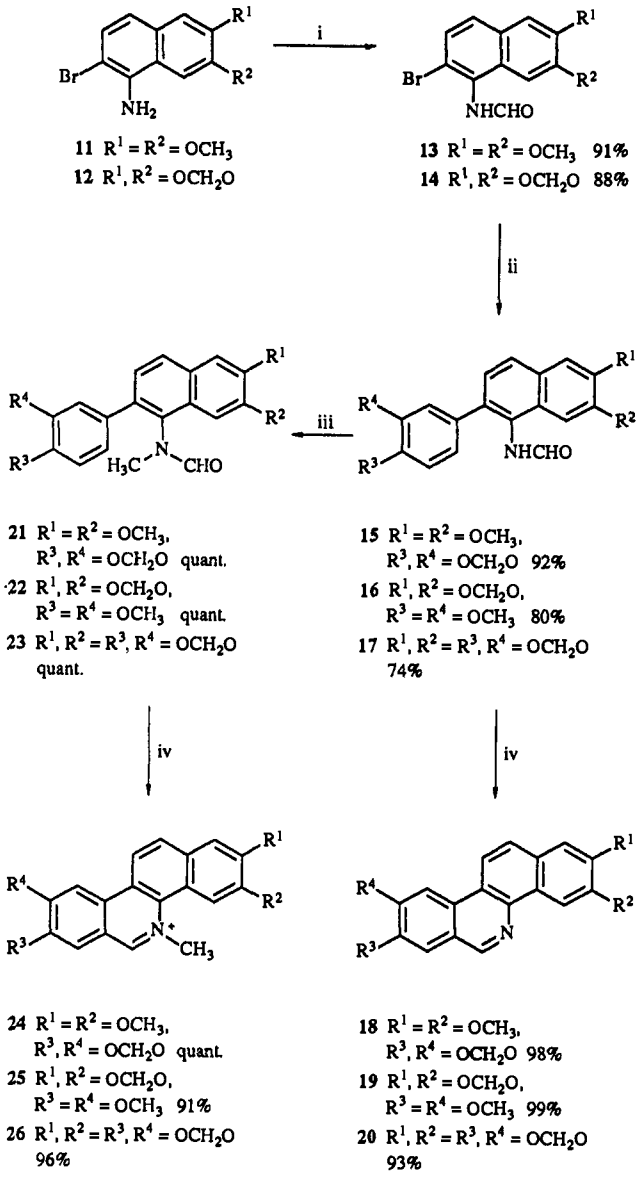


Scheme 1 *Reagents and conditions:* i, Br_2, $CHCl_3$, 25 °C, 18 h; ii, DBU, MeCN, 45–60 °C, 20 min; iii, 2-bromo-2-methylpropanamide, granular NaOH, DMPU, 25 °C, 3 h; iv, NaH, 4:1 DMF–DMPU, 100 °C, 2 h; v, 80% aq. NaOH, MeOH, reflux, 2–4 d

in 82 and 74% yields. Both compounds were purified by recrystallisation from ethanol, and were suitably stable for use as stock intermediates.

Alkaloid preparation

Direct Suzuki coupling–ring closure between **11** or **12** and appropriately substituted 2-formylarylboronic acids gave low to moderate yields of the desired benzo[*c*]phenanthridines, with deboronation a major side reaction despite rigorous exclusion of oxygen.[6,7] However, coupling of 2-bromo-1-formamidonaphthalenes with arylboronic acids worked well, and allowed simple incorporation of the formamido carbon atom as C-6 into the final tetracyclic structures.



11 $R^1 = R^2 = OCH_3$
12 $R^1, R^2 = OCH_2O$

13 $R^1 = R^2 = OCH_3$ 91%
14 $R^1, R^2 = OCH_2O$ 88%

21 $R^1 = R^2 = OCH_3$, $R^3, R^4 = OCH_2O$ quant.
22 $R^1, R^2 = OCH_2O$, $R^3 = R^4 = OCH_3$ quant.
23 $R^1, R^2 = R^3, R^4 = OCH_2O$ quant.

15 $R^1 = R^2 = OCH_3$, $R^3, R^4 = OCH_2O$ 92%
16 $R^1, R^2 = OCH_2O$, $R^3 = R^4 = OCH_3$ 80%
17 $R^1, R^2 = R^3, R^4 = OCH_2O$ 74%

24 $R^1 = R^2 = OCH_3$, $R^3, R^4 = OCH_2O$ quant.
25 $R^1, R^2 = OCH_2O$, $R^3 = R^4 = OCH_3$ 91%
26 $R^1, R^2 = R^3, R^4 = OCH_2O$ 96%

18 $R^1 = R^2 = OCH_3$, $R^3, R^4 = OCH_2O$ 98%
19 $R^1, R^2 = OCH_2O$, $R^3 = R^4 = OCH_3$ 99%
20 $R^1, R^2 = R^3, R^4 = OCH_2O$ 93%

Scheme 2 *Reagents and conditions:* i, HCO_2H, $(CH_3CO)_2O$, 25 °C, 45 min; ii, **27**, or **28**, $Pd(OCOCH_3)_2$, PPh_3, DME, aq. Na_2CO_3, 1.25–4 h; iii, MeI, NaH, THF, 0–25 °C; iv, $POCl_3$, MeCN, reflux, 50 min

Treatment of **11** and **12** with formic acid and acetic anhydride gave the formamides **13** and **14** in yields of 91 and 88% (Scheme 2). These were then efficiently coupled with 3,4-dimethoxyphenyl- (**27**) or 3,4-methylenedioxyphenyl-boronic acid (**28**) using catalyst prepared *in situ* from 1:2 palladium acetate:triphenylphosphine. The resulting 2-aryl-1-formamidonaphthalenes **15–17** were then either directly subjected to the Bischler–Napieralski reaction to give the alkaloid norbases norallonitidine **18**, nornitidine **19** and noravicine **20**, or methylated using NaH–MeI–THF and the resulting *N*-methylformamidonaphthalenes **21–23** cyclised to give the quaternised alkaloids allonitidine **24**, nitidine **25** and avicine **26** as their chloride salts.[2b] All the cyclisations and methylations proceeded in >90% yield. The final products were obtained directly from the Bischler–Napieralski reactions in good purity, but could be further purified by recrystallisation from pyridine–methanol (norbases) or methanol (quaternary compounds).

The simple methodology described above is particularly appropriate for the preparation of benzo[*c*]phenanthridine alkaloids having the 8,9-dioxygenation pattern in the D-ring. Studies are continuing into the similarly based synthesis of alkaloids having 7,8-dioxygenation or 7,8,10-trioxygenation (*e.g.* chelerythrine and chelilutine) from 2-bromonaphthylamines such as **11** and **12**.

Experimental

General procedure for the O-alkylation of 2-bromo-6,7-dioxygenated-1-naphthols with 2-bromo-2-methylpropanamide
Sodium hydroxide (40–60 mesh granules) (0.3 mol) was added to a solution of the naphthol (0.05 mol) in DMPU (100 ml) at room temperature, and the resultant mixture was stirred for 20 min. 2-Bromo-2-methylpropanamide (0.3 mol) was added and the mixture vigorously stirred for 2 h. Water (100 ml) was then added, together with sufficient 5M HCl to bring the pH of the mixture to 0. The resulting suspension was added to water (2 l), and the mixture allowed to stand overnight. The product was collected by filtration, washed with water (3 × 500 ml) and dried under vacuum at 60 °C for 48 h.

General procedure for the Suzuki coupling between 2-bromo-6,7-dioxygenated-1-formamidonaphthalenes and arylboronic acids
Palladium(II) acetate (0.02 mmol) and triphenylphosphine (0.04 mmol) were added to a suspension of the 2-bromo-1-formamidonaphthalene (0.68 mmol) in 1,2-dimethoxyethane (3 ml). The resulting mixture was degassed and stirred at ambient temperature for 10 min before the addition of 2 M aq. sodium carbonate solution (1.0 ml). The mixture was again degassed, and then stirred in an atmosphere of argon for 1 h. The arylboronic acid (1.0 mmol) was then added, and the resulting mixture was heated under reflux with stirring in an atmosphere of argon for 1.25–4 h.

The cooled mixture was diluted with dichloromethane (40 ml) and water (20 ml), the organic phase was separated, and the aqueous layer was extracted with further dichloromethane (10 ml). The combined extracts were washed with water (2 × 10 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to leave a pale grey solid. Purification by column chromatography on silica gel (10 g), eluting firstly with 1:1 ethyl acetate–hexane and then with neat ethyl acetate, gave the product as a colourless solid.†

†Physical properties and spectroscopic data for known compounds were in complete agreement with literature data. Analytical and spectroscopic data for all new products were fully consistent with the assigned structures.

References

1 (*a*) W. M. Suffness and G. A. Gordell, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1985, vol. 25, p. 333; (*b*) S.-D. Fang, L.-K. Wang and S. M. Hecht, *J. Org. Chem.*, 1993, **58**, 5025; (*c*) G. T. Tan, J. F. Miller, A. D. Kinghorn, S. M. Hughes and J. M. Pezzuto, *Biochem. Biophys. Res. Commun.*, 1992, **185**, 370.
2 (*a*) V. Šimánek, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1985, vol. 26, p. 185; (*b*) H. Ishi, Y.-I. Ichikawa, E. Kawanabe, M. Ishikawa, T. Ishikawa, K. Kuretani, M. Inomata and A. Hoshi, *Chem. Pharm. Bull.*, 1985, **33**, 4139; (*c*) R. D. Clark and Jahangir, *J. Org. Chem.*, 1988, **53**, 2378; (*d*) R. Beugelmans and M. Bois-Choussy, *Tetrahedron*, 1992, **48**, 8285; (*e*) N. Sotomayor, E. Domínguez and E. Lete, *Tetrahedron Lett.*, 1994, **35**, 2973; (*f*) M. Hanaoka and C. Mukai, in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, 1994, vol. 14, p. 769; (*g*) D. Sèraphin, M. A. Lynch and O. Duval, *Tetrahedron Lett.*, 1995, **36**, 5731.
3 For synthesis of the phenanthridine and benzo[*c*]phenanthridine ring systems using Suzuki coupling methodology see: A. R. Martin and Y. Yang, *Acta Chem. Scand.*, 1993, **47**, 221 and references cited therein.
4 Tetralone **1** is commercially available. For the preparation of **2** see: W. J. Begley and J. Grimshaw, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2324.
5 (*a*) R. Bayles, M. C. Johnson, R. F. Maisey and R. W. Turner, *Synthesis*, 1977, 33; (*b*) I. G. C. Coutts and M. R. Southcott, *J. Chem. Soc., Perkin Trans. 1*, 1990, 767.
6 T. Watanabe, N. Miyaura and A. Suzuki, *Synlett*, 1992, 207.
7 S. Gronowitz, A.-B. Hörnfeldt and Y.-H. Yang, *Chem. Scr.*, 1986, **26**, 311.

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