



A versatile synthetic route to 11*H*-indolo[3,2-*c*]isoquinolines

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ABSTRACT

A wide variety of indoloisoquinoline derivatives are prepared from the acid-catalyzed cyclization of 3-amido-2-phenylindoles, which in turn were obtained from the Beckmann rearrangement of 2-phenylindole-3-oximes.

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Indoles exhibit potent biological activity and there is a continuing demand for novel synthetic methods to prepare new indole derivatives.^{1–3} The tetracyclic structures related to the indoloisoquinolines have received considerable attention due to their interesting biological properties including anti-tumour, fungicidal, analgesic, anti-inflammatory, anthelmintic and antibacterial activities.^{4–6} The parent compound 11*H*-indolo[3,2-*c*]isoquinoline **1** has not yet been found in Nature. However, the related indoloquinoline and quindoline ring systems constitute important structural moieties in natural products, as exemplified by the biologically active compounds cryptosanguinolentine **2**, cryptolepine **3** and neocryptolepine **4** (Fig. 1).^{7,8} We have recently described the synthesis of 7*H*-indolo[2,3-*c*]quinolines^{9,10} **5**. Although the parent 11*H*-indolo[3,2-*c*]isoquinoline **1** and its 5-substituted analogues are known,^{11–14} further functionalized derivatives are rare. Therefore a general synthetic route to substituted 11*H*-indolo[3,2-*c*]isoquinolines **1** is of particular interest.

Syntheses of isoquinolines have been extensively reported in the literature and typically involve Pomeranz–Fritsch, Bischler–Napieralski and Pictet–Spengler reactions.¹⁵ However, recently, 11*H*-indolo[3,2-*c*]isoquinoline **1** has been prepared via a selective Buchwald–Hartwig reaction followed by a Pd-catalyzed intramolecular direct arylation reaction.¹⁶ Hiremath et al. have reported¹⁷ the formation of indolo[3,2-*c*]isoquinolines by cyclization of indole-3-carbaldoximes with alcoholic sulfuric acid. This reaction proceeds through Beckmann rearrangement followed by Bischler–Napieralski cyclization of the 3-amidoindole to the indoloisoquinoline. Here we describe an efficient synthesis of 11*H*-

indolo[3,2-*c*]isoquinolines **1**, employing the Beckmann rearrangement of a variety of 2-phenylindole-3-oximes and cyclization of the intermediate amides.

2-Phenylindole¹⁸ **6** was formylated with the Vilsmeier reagent at 0 °C to afford indole-3-carbaldehyde¹⁹ **7** in 89% yield (Scheme 1). Treatment of 3-formylindole **7** with hydroxylamine hydrochloride and potassium hydroxide gave the desired indole-3-carbaldoxime²⁰ **8** in high yield. However, attempts to cyclize the oxime **8** by the reported procedure were unsuccessful. Instead, 3-cyano-2-phenylindole²¹ **9** and 2-phenylindole **6** were obtained as the only products. The Beckmann rearrangement reaction conditions were varied with respect to solvent but again led to the formation of the 3-cyano-indole **9**.

Treatment of 3-acetyl-2-phenylindoles **10** with hydroxylamine hydrochloride in 95% ethanol containing sodium acetate gave the

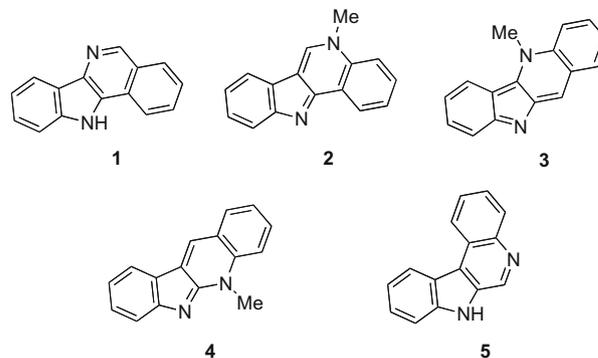
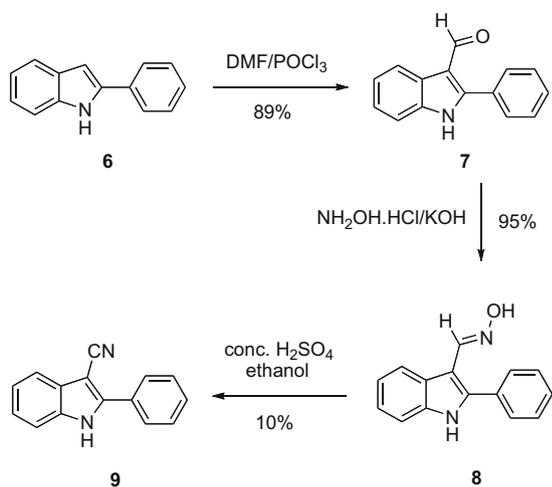
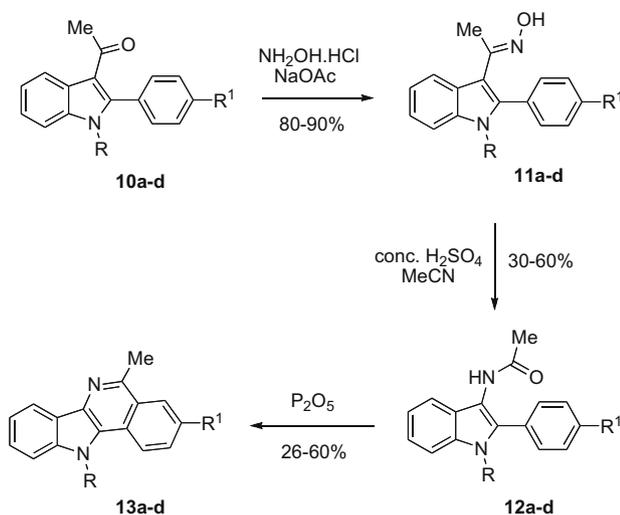


Figure 1. 11*H*-indolo[3,2-*c*]isoquinoline **1**, cryptosanguinolentine **2**, cryptolepine **3**, neocryptolepine **4** and 7*H*-indolo[2,3-*c*]quinoline **5**.

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Scheme 1.



Scheme 2.

corresponding 2-phenylindole-3-acetoximes **11** in 80–90% yield (Scheme 2). 3-Acetamido-2-phenylindoles **12** were produced by Beckmann rearrangement of 2-phenylindole-3-acetoximes **11** with concentrated sulfuric acid in acetonitrile under reflux for 2–6 h in 30–60% yields. The final cyclization step was carried out by heating with P_2O_5 in toluene, to afford the 11H-indolo[3,2-c]isoquinolines **13** (Table 1).

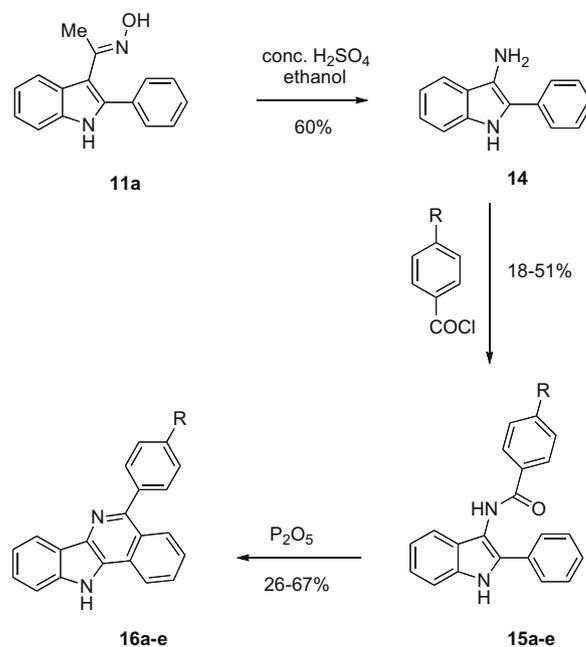
However, the same reaction when carried out on 2-phenylindole-3-acetoxime **11a** with concentrated sulfuric acid in ethanol gave 3-amino-2-phenylindole²⁶ **14** in 60% yield (Scheme 3). The isolation of the 3-aminoindole rather than the 3-acetamidoindole afforded an opportunity to synthesize differently substituted indoloisoquinolines, without the need to start from 2-phenylindole **6** in each case. Furthermore, this synthesis of the known 3-amino-2-phenylindole **14** is more efficient than the previously reported method, which utilized hydrogenation of the related 3-nitroindole with a palladium catalyst.²⁶

Treatment of 3-amino-2-phenylindole **14** with 4-substituted benzoyl chlorides in the presence of sodium bicarbonate gave the corresponding 3-benzamido-2-phenylindoles **15** (Scheme 3). The amides **15a,b,e** have been prepared previously by Przheval'skii et al. via the Fischer synthesis of the phenylhydrazones of benzamidoacetophenones.²⁷ The cyclization of 3-benzamido-2-phenylindoles **15** to give

Table 1
Synthesis of compounds **10–13**

Entry	R	R ¹	Product	Yield ^a (%)	Mp (°C)
1	H	H	10a	93	220–222 ²²
2	Me	H	10b	80	66–68 ²³
3	H	Me	10c	88	208–211
4	H	MeO	10d	93	227–230 ²⁴
5	H	H	11a	96	177–180
6	Me	H	11b	95	212–214
7	H	Me	11c	72	184–187
8	H	MeO	11d	72	186–188
9	H	H	12a	64	203–205 ¹¹
10	Me	H	12b	60	171–174 ²⁵
11	H	Me	12c	44	135–138
12	H	MeO	12d	42	247–250
13	H	H	13a	43	238–241 ¹¹
14	Me	H	13b	48	115–117
15	H	Me	13c	65	232–235
16	H	MeO	13d	30	233–236

^a Yield of isolated pure product.



Scheme 3.

the 11H-indolo[3,2-c]isoquinolines **16** was achieved by heating with P_2O_5 in toluene in moderate yields²⁸ (Table 2).

The structures of the indoloisoquinolines were established on the basis of NMR spectroscopy and on reported spectroscopic data. Also, an X-ray crystal structure (Fig. 2) of compound **16d** was ob-

Table 2
Synthesis of compounds **15–16**

Entry	R	Product	Yield ^a (%)	Mp (°C)
1	Br	15a	32	195–198 ²⁷
2	Cl	15b	18	208–211 ²⁷
3	F	15c	51	178–181
4	MeO	15d	31	188–190
5	H	15e	44	199–203 ²⁷
6	Br	16a	67	291–293
7	Cl	16b	32	300–302
8	F	16c	26	296–298
9	MeO	16d	53	256–258
10	H	16e	43	234–237 ²⁹

^a Yield of isolated pure product.

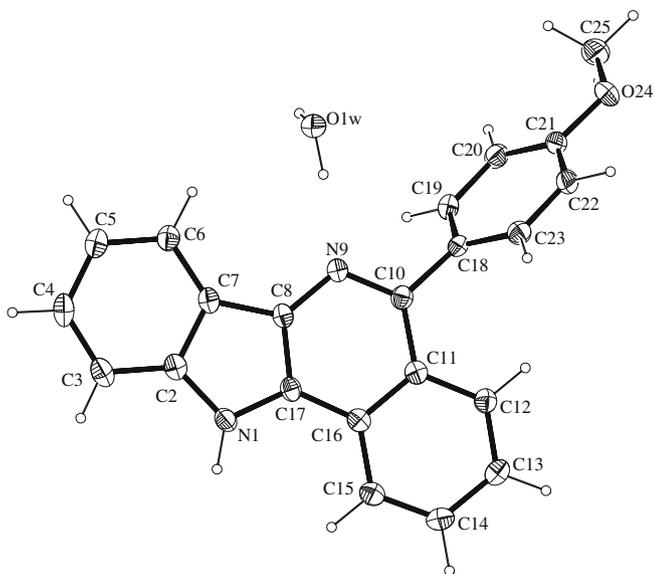


Figure 2. ORTEP diagram of compound **16d**.

tained,³⁰ and the 11*H*-indolo[3,2-*c*]isoquinoline structure was confirmed. All new compounds were fully characterized by ¹H and ¹³C NMR spectroscopies, IR spectra, mass spectra and elemental analyses, and several by X-ray crystallographic analysis. Known products were characterized by comparison of their ¹H NMR spectra and melting points with those reported in the literature.

In summary, a series of new indolo[3,2-*c*]isoquinolines has been produced by the acid-catalyzed cyclization of 3-acetamido-2-phenylindoles and 3-benzamido-2-phenylindoles, which in turn were obtained by the Beckmann rearrangement of the related oximes. However, 2-phenylindole-3-carbaldoxime did not undergo the Beckmann rearrangement, but gave a 3-cyanoindole. This methodology provides an effective and flexible route to synthesize a variety of indolo[3,2-*c*]isoquinolines, and opens the way for their systematic biological evaluation.

Acknowledgement

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- Representative procedure for indolo[3,2-*c*]isoquinoline **16a**. To a solution of 3-benzamido-2-phenylindole **15a** (70 mg, 0.2 mmol) in toluene (20 mL) was added P₂O₅ (0.5 g, 3.5 mmol). The yellow mixture was heated at 120–130 °C overnight. The reaction mixture was cooled to room temperature and poured into ice-cold water (20 mL). The solution was neutralized with 2 M NaOH, and extracted with EtOAc (3 × 30 mL). The organic layer was collected and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel using dichloromethane/light petroleum (70:30) as eluent to yield indoloisoquinoline **16a** as a yellow solid (45 mg, 67%). Mp 291–293 °C. Elem. Anal. Calcd for C₂₁H₁₃BrN₂·0.5CH₂Cl₂ requires C, 62.1; H, 3.4; N, 6.7. Found: C, 62.3; H, 3.6; N, 6.9. ν_{max} (KBr): 3430, 1620, 1500, 1490, 1460, 1390, 1350, 1280, 1240, 1160, 1100, 1070, 970, 830, 740 cm⁻¹. λ_{max} (MeOH): 211 nm (ε 30,600 cm⁻¹ M⁻¹), 238 (32,300), 288 (28,900), 371 (10,200). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.28 (1H, t, *J* 7.4 Hz, ArH), 7.48 (1H, t, *J* 7.5 Hz, ArH), 7.62–7.78 (6H, m, ArH), 7.92 (1H, t, *J* 7.6 Hz, ArH), 8.08 (1H, d, *J* 8.3 Hz, ArH), 8.19 (1H, d, *J* 7.5 Hz, ArH), 8.53 (1H, d, *J* 7.9 Hz, ArH), 12.42 (1H, s, NH). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 112.3, 119.7, 120.3, 122.2, 126.2, 126.8, 128.2, 130.3, 131.6, 132.6 (Ar-CH), 121.8, 123.0, 124.4, 124.5, 127.5, 133.1, 139.2, 139.8, 151.3 (Ar-C). HRMS (+ESI) *m/z* 373.0316 (M+H⁺) C₂₁H₁₄BrN₂, requires 373.0335.
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- Crystallographic data for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 718540. X-ray crystal structures were obtained by Mohan Bhadbhade, Crystallography Laboratory, Analytical Centre, The University of New South Wales, Sydney, Australia.