Tetrahedron Letters 50 (2009) 5628–5630

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 5 June 2009
Revised 10 July 2009
Accepted 17 July 2009
Available online 24 July 2009

Keywords:
Indole
Indoloisoquinoline
Beckmann rearrangement
Acid-catalyzed cyclization

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.

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 reported[17] 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-Phenylindole[18] **6** was formylated with the Vilsmeier reagent at 0 °C to afford indole-3-carbaldehyde[19] **7** in 89% yield (Scheme 1). Treatment of 3-formylindole **7** with hydroxylamine hydrochloride and potassium hydroxide gave the desired indole-3-carbaldoxime[20] **8** in high yield. However, attempts to cyclize the oxime **8** by the reported procedure were unsuccessful. Instead, 3-cyano-2-phenylindole[21] **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

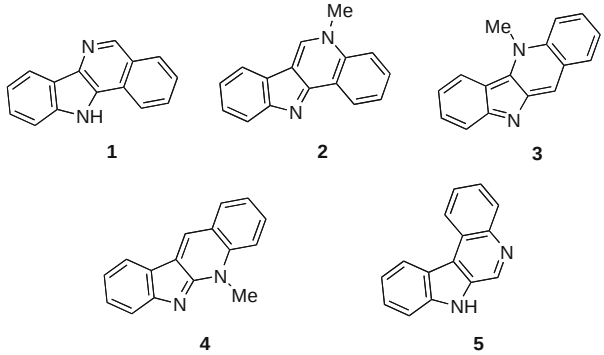

Figure 1. 11*H*-indolo[3,2-*c*]isoquinoline **1**, cryptosanguinolentine **2**, cryptolepine **3**, neocryptolepine **4** and 7*H*-indolo[3,2-*c*]quinoline **5**.

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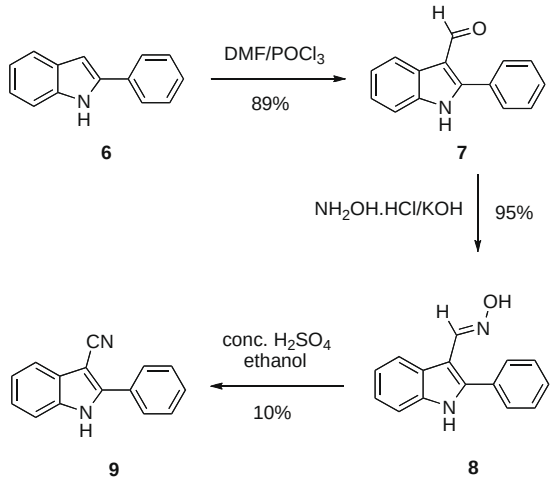
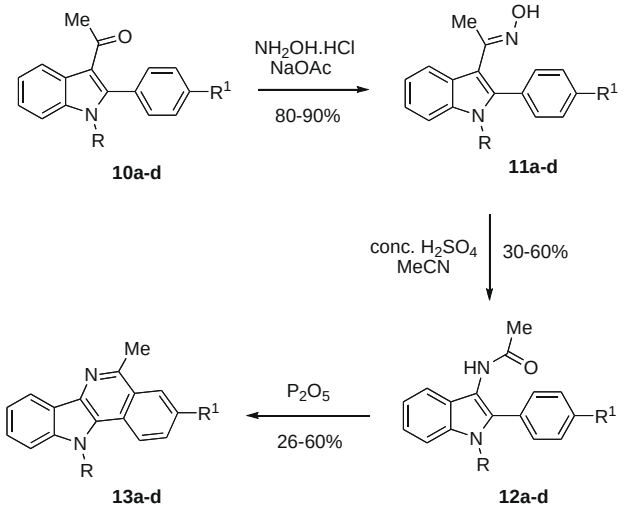
doi:10.1016/j.tetlet.2009.07.107



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 11*H*-indolo[3,2-*c*]isoquinolines **13** (Table 1).

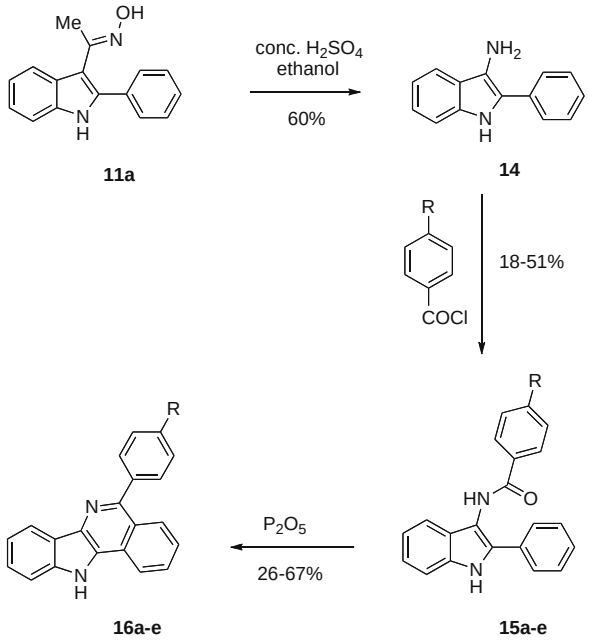
However, the same reaction when carried out on 2-phenylindole-3-acetoxime **11a** with concentrated sulfuric acid in ethanol gave 3-amino-2-phenylindole[26] **14** in 60% yield (Scheme 3). The isolation of the 3-aminoindole rather than the 3-acetamidoindole afforded an opportunity to synthesize differently 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 11*H*-indolo[3,2-*c*]isoquinolines **16** was achieved by heating with P_2O_5 in toluene in moderate yields[28] (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.

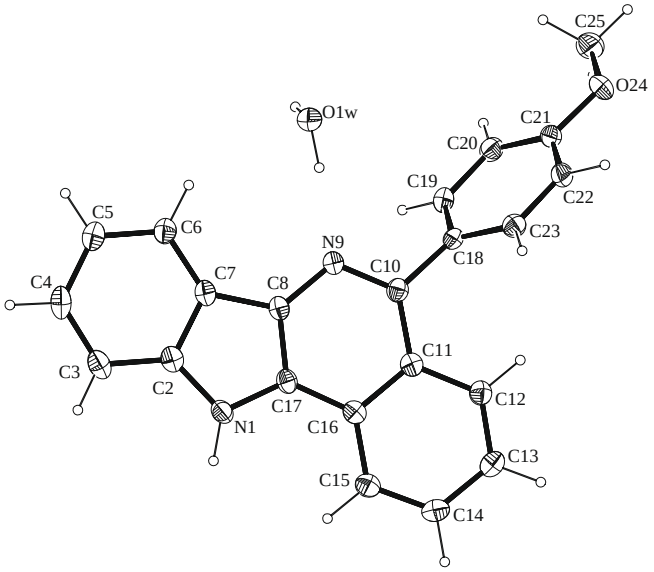


Figure 2. ORTEP diagram of compound **16d**.

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

We thank the Australian Research Council for financial support.

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28. 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 P_2O_5 (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 $C_{21}H_{13}BrN_2.0.5CH_2Cl_2$ 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). ^{1}H 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). ^{13}C 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 ($M+H^+$) $C_{21}H_{14}BrN_2$, requires 373.0335.
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30. 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.