

An Investigation of a Palladium Catalysed Biaryl Synthesis of Pyrrolophenanthridine Derivatives. Extension of the Heck Reaction.

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Derivados halogenados de *N*-benzilisatinas ciclizaram facilmente, com eliminação de haletos de hidrogênio, numa reação de síntese de biarilas sob catálise por paládio, na ausência de ligantes fosfinas, levando às oxopirrol[3,2,1-*de*]fenantridinas correspondentes.

N-Benzylisatin derivatives have been found to readily undergo cyclisation *via* hydrogen halide elimination in a biaryl synthesis reaction when using palladium catalysts, in the absence of phosphine ligands, to yield oxopyrrol[3,2,1-*de*]phenanthridine derivatives.

Keywords: Heck reaction (Jeffery's conditions), benzylisatins, pyrrolophenanthridines, biaryl coupling

Introduction

The pyrrolo[3,2,1-*de*]phenanthridine skeleton has been found in a large number of natural products from the plants of almost all of the genera of the family Amaryllidaceae. Examples of these compounds include assoanine¹ (**1**), oxoassoanine² (**2**), hippadine³ (**3**) and ungeremine⁴ (**4**) amongst others⁵. These compounds (Figure 1) are of interest as synthetic targets not only for the development of synthetic methodology but also for their biological activities⁶. An important feature of the pyrrolo[3,2,1-*de*]phenanthridine skeleton is the biaryl linkage and this has often been a central subject of the synthetic methodology employed for the construction of these, and a diverse range of phenanthridine or benzophenanthridine derivatives⁷.

The Heck reaction⁸ is a versatile methodology for the formation of new C-C bonds, particularly for the coupling of an aromatic halide with an olefin⁹. The corresponding biaryl synthesis where hydrogen halide is eliminated from the two aromatic components is a recent extension of the Heck reaction¹⁰, whereas the corresponding biaryl synthesis using an oxidative addition reaction with stoichiometric quantities of palladium salts has been more extensively studied¹¹.

Results and Discussion

In a general approach for the construction of pyrrolo-

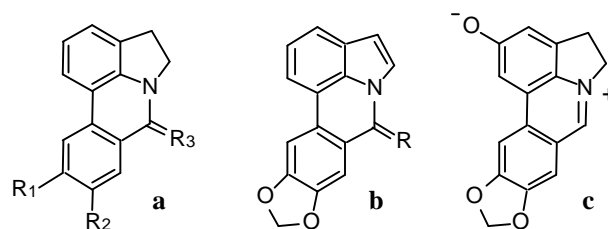
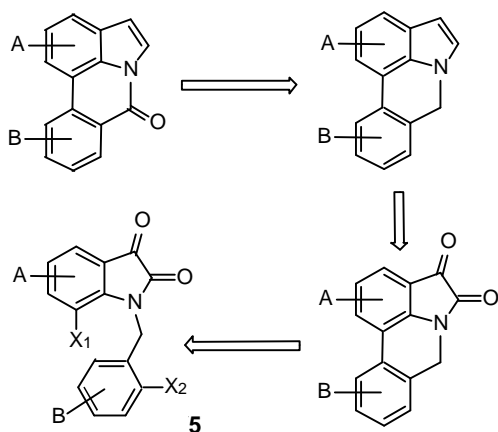


Figure 1. Structures of some naturally occurring pyrrolophenanthridine derivatives. **a)** $R_1 = R_2 = \text{OCH}_3$, $R_3 = 2\text{H}$, Assoanine (**1**); R_1 and R_2 as for **1**, $R_3 = \text{O}$, Oxoassoanine (**2**); $R_1/R_2 = \text{CH}_2(\text{O})_2$, $R_3 = \text{O}$, Anhydrolycorine-7-one (**7**); **b)** $R = \text{O}$, Hippadine (**3**); $R = 2\text{H}$, Dehydroanhydrolycorine (**6**); **c)** Ungeremine (**4**).

phenanthridine alkaloids an appropriately substituted *N*-benzylisatin derivative (**5**), that contained the entire carbon framework, was envisaged as a suitable precursor for the obtention of these natural products and their analogs (Scheme 1).

Subsequent reduction of the cyclised isatin derivatives to indoles would yield, for example, dehydroanhydrolycorine¹² (**6**). Successful cyclization would also furnish substrates to further on going investigations of the use of $\text{BH}_3 \cdot \text{THF}$ for the reduction of isatin derivatives to indoles¹³. Strategically, oxidation of the derivatives of compound **6** could present problems due to oxidation of the indolic double bond. However, Gribble reduction¹⁴ of the indolic double bond and subsequent oxidation of the indoline would seem to be a viable route for the synthesis of, for example, anhydrolycorin-7-one (**7**) and hippadine (**3**), Scheme 1.

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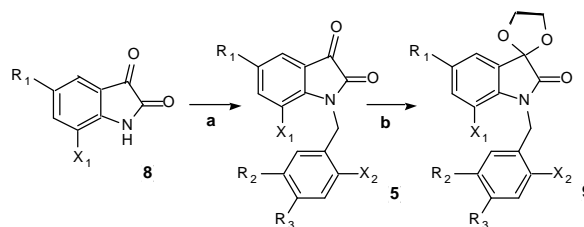


Scheme 1. Retrosynthetic analysis for the synthesis of pyrrolophenanthridine derivatives.

The appropriate *N*-benzylisatin derivatives **5** for investigation of the synthesis of the pyrrolophenanthridines were readily prepared by benzylation of substituted isatin derivatives¹⁵ **8** using basic conditions (Scheme 2).

Initial experiments to determine conditions for the formation of the biaryl linkage focused upon the attempted cyclisations of 7-bromo- and 7-iodo-5-methyl-*N*-benzylisatin (**5a** and **5b**) using 10 mol% Pd(OAc)₂ in the presence of 20 mol% of triphenylphosphine in acetonitrile¹⁶. Substantial substrate consumption was observed but no defined product could be isolated upon workup. It was therefore questioned as to whether the *cis* dicarbonyl system could possibly interfere in the coupling reaction. An inspection of the isatin literature revealed a study by Martinez and Naarmann that reported the Suzuki couplings of a number of heteroarylboronates with 5-bromo- and 5-iodo- isatin using tetrakis-triphenylphosphine palladium as the catalyst, albeit in very modest yields¹⁷. A plausible explanation for the modest yields obtained by Martinez and Naarmann and the poor mass balance in our reactions, where the substrate was recovered in 52-62% yield, was encountered in the work of Lathourakis and Litinas¹⁸, where these authors have shown that PPh₃ reacts with isatin to yield a phosphoranylidene that can undergo Wittig reactions. Therefore, to eliminate this source of interference the ketone was transformed into the corresponding ketal (**9a-i**) using conventional methodology (Scheme 2).

Submission of **9 (a and b)** or *N*-benzyl-5-methyl-7-iodo-2-oxindole, obtained by reduction of **5b** with hydrazine hydrate¹⁹, to the same reaction conditions¹⁶ as used in the first experiments also yielded no defined products but the substrates were recovered in 87-91% yield. The reaction conditions¹⁶ were subsequently modified by replacing acetonitrile with DMF to allow an increased reaction temperature. When **9b** was submitted to the new



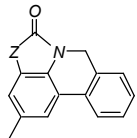
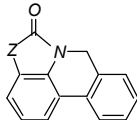
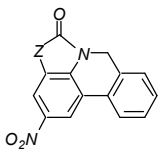
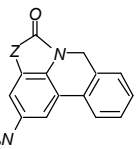
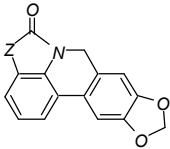
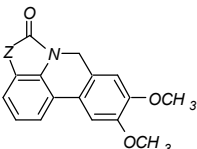
Scheme 2. Synthesis of cyclization substrates. **a)** CaH₂ or K₂CO₃, benzyl halide, DMF; **b)** (CH₂OH)₂, PTSA, toluene; for definition of the substituents (R₁ to R₃) see Table 1, if X₁ is a halogen (I or Br) then X₂ is a hydrogen (or vice versa).

conditions, the formation of defined products could be observed upon TLC analysis. ¹H NMR analysis of the crude product after workup of the reaction revealed the conversion of the reaction to be low, 29% (96% mass balance), and the major product was identified as the reduced *N*-benzyl-5-methylisatin ethylene ketal (25%) from comparison of spectral data with an authentic sample²⁰. The structure of the minor component (4%) was suspected to be the desired cyclised product **10a**; this suspicion being latter confirmed, *vide infra*. Subsequent investigations of the reaction conditions were based upon experimental work first reported by Jeffery²¹. Similarly to the initial experiments using the substrates **5a** and **5b** under Heck conditions, substrate consumption was observed but no defined products could be detected by TLC or upon workup of the reaction. Attention was then focused upon the ketal substrate **9a**, which in the presence of 10% Pd(OAc)₂ (0.1 mol L⁻¹ DMF), 1 mole equivalent of Bu₄NBr, and 5.5 mole equivalents of KOAc at 100°C (bath temp.) resulted in the formation of a single product at 56% conversion of the substrate, Table 1, entry 1 (95% mass balance). This product had the same NMR features as the minor product observed in the previous experiment using this substrate, *vide supra*. In a similar experiment where PdCl₂ was used as the catalyst (table entry 2) a comparable result was obtained with a 98% mass balance. In contrast to the bromide **9a**, the iodide **9b** readily furnished the same product as the previous experiments. Isolation and characterisation of this product identified it as the oxopyrrolophenanthridine **10a**. Investigation of the catalyst loading revealed a reaction time dependance upon the reaction (table entries 4-7). The *ortho*-iodobenzyl derivative **9c** cyclised under similar conditions to yield the parent ring system **10b** (table entry 8). Further evidence for halogen positional versatility can be seen in table entries 9 and 10 where the oxopyrrolophenanthridine derivative **10c** was obtained in 77-78% yield from either substrate **9d** or **9e**. The iodides were found to be superior to the bromides giving better yields and shorter reaction times (compare table entries 1 and 2 with 5, 10 with 11, and 12 with 13). The presence of a nitro group either on the halogenated aromatic

ring or the aromatic ring to be attacked by the intermediate organopalladium species significantly accelerated the reaction giving increased yields in reduced reaction times (compare table entries 1, 2 and 3 with 9 and 10). Little difference in reaction time or yield was observed in the cyclisations of the unsubstituted **9c** and the methylenedioxy substituted **9h** (table entries 8 and 13). However, the dimethoxy substituted **9i** required a significantly longer reaction time to attain an almost equally good yield (table entry 14).

In all successful reactions initiation of the reaction was evidenced by a darkening of the reaction mixture which normally had an onset temperature greater than 80°C (bath temp.). Both aromatic iodides and bromides have been cyclised successfully in the absence of phosphine ligands, though the experiments revealed that the iodides are better substrates²². No special precautions are required for performing these cyclisations which have been routinely performed exposed to the laboratory atmosphere.

Table 1. Palladium catalysed cyclization of N-benzylisatin derivatives

Table entry	Substrate ^a	X	Reaction Time (h) [Modification] ^b	Product ^a (%) ^c	
1	9a	Br	27	(56)	
2	9a	Br	30 [10% PdCl ₂]	(60)	
3	9a	Br	4	(38)	
4	9b	I	2 [15%]	96	10a
5	9b	I	3	98	10a
6	9b	I	7 [5%]	95	10a
7	9b	I	30 [1%]	80	10a
8	9c	I	4	93	
9	9d	Br	3	78	
10	9e	Br	1.5	77	
11	9f	I	1.5	90	
12	9g	Br	24	(76)	
13	9h	I	5-6	90-96	
14	9i	I	9-10	81-87	

a Z = *spiro*-2-(1,3-dioxolane) ring; **b** Reaction conditions used: 10 mole% Pd(OAc)₂, 1.1 equiv. Bu₄NBr, 5.5 equiv. KOAc, DMF (substrate concentration 0.1 mol L⁻¹), 100°C. Modifications to this procedure are indicated within the square brackets, [modification]. All reactions were accompanied by silica gel TLC until substrate was no longer evident or until the reaction appeared to no longer progress; **c** Isolated yield of purified product. Values in parenthesis are conversions to cyclised product based upon isolation of the reaction product(s) and substrate as calculated from analysis of ¹H NMR spectra.

The reaction offers a unique opportunity to investigate structural requirements and substituent effects as it has been found to be tolerant to both activation and deactivation of the aromatic nuclei and therefore, mechanistically relevant information can be delineated. These studies as well as the application of this methodology to the synthesis of a number of natural products are currently being investigated.

Experimental

General

^1H and ^{13}C NMR spectra were recorded using 300 MHz and 200 MHz (^1H) Bruker spectrometers and are referenced to TMS. Coupling constants are quoted in Hz. Mass spectra were recorded at NPPN (Nucleo de Pesquisa de Produtos Naturais, Universidade Federal do Rio de Janeiro) using a Hewlett-Packard GC-MS or by direct insertion using a VG Autospec. Infra-red spectra were recorded using a Perkin Elmer 1600 FT-IR (error $\pm 4\text{cm}^{-1}$) as KBr discs. Melting points were recorded on a hotstage microscope and/or using a MelTemp II capillary apparatus and are reported as uncorrected values. DMF was used as supplied without further treatment.

Experimental procedure

The appropriate isatin derivative (1.00 mmol), $\text{Pd}(\text{OAc})_2$ (0.10 mmol), Bu_4NBr (1.10 mmol), KOAc (5.50 mmol) and DMF (10 mL) were added to a round bottom flask. The reaction mixture was heated on an oil bath ($100 \pm 5^\circ\text{C}$, bath temp.) and the reaction accompanied by TLC. On complete reaction, distilled water (50ml) or aqueous HCl (0.2mol L^{-1} , 50mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (3 x 15 mL). The organic phase was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was then chromatographed on a silica gel column using hexane/ethyl acetate (4:1, V/V) as eluent. Physical and spectroscopic data of compounds **10** follow:

spiro-4-(ethylenedioxy)-2-methyl-7-hydropyrrolo [3,2,1-de]phenanthridin-5-one (10 a)

mp. $190\text{--}193^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3058, 2975, 2889, 1719, 1636, 1449, 1349, 1204, 1029, 1000, 948, 864, 773, 741 (KBr), Mass [m/z (abun.)] 293(33%), 264(100), 220(29), 193(27), 178(4), 165(17), 110(31), 96(29), 96(29), 82(28); ^1H NMR (300 MHz, CDCl_3) δ 2.34 (s, 3H, CH_3), 4.29–4.34 (m, 2H, CH_2), 4.56–4.61 (m, 2H, CH_2), 4.88 (s, 2H, CH_2), 7.06 (d, 1H, CH, J 0.6 Hz), 7.10 (dd, 1H, CH, J 0.9, 6.3 Hz),

7.24 (dt, 1H, CH, J 1.4, 7.4, 7.4 Hz), 7.26 (dt, 1H, CH, J 0.7, 7.4, 7.4 Hz), 7.43 (s, 1H, CH), 7.67 (d, 1H, CH, J 7.5 Hz); ^{13}C NMR PENDANT (75 MHz, CDCl_3) δ 21.6 (CH_3), 44.5 (CH_2), 66.0 (CH_2), 103.4 (C), 117.2 (C), 122.4 (CH), 122.7 (C), 124.6 (CH), 125.1 (CH), 127.8 (CH), 128.1 (CH), 128.2 (C), 128.5 (CH), 128.9 (C), 133.3 (C), 137.1 (C), 172.9 (C=O). Found: C, 73.23; H, 5.04; N, 4.62. Calc. for $\text{C}_{18}\text{H}_{15}\text{NO}_3$: C, 73.71; H, 5.15; N, 4.76%.

spiro-4-(ethylenedioxy)-7-hydropyrrolo[3,2,1-de]phenanthridin-5-one (10 b)

mp. $161\text{--}162^\circ\text{C}$, IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3060, 2986, 2903, 1721, 1633, 1489, 1440, 1367, 1312, 1283, 1194, 1148, 1002, 950, 756; Mass [m/z (abun.)] 279(32%), 250(100), 220(3), 206(53), 190(4), 178(37), 151(36), 126(6), 103(28), 89(62), 76(71), 63(19); ^1H NMR (300 MHz, CDCl_3) δ 4.31–4.39 (m, 2H, CH_2), 4.57–4.62 (m, 2H, CH_2), 4.93 (s, 2H, CH_2), 7.04 (t, 1H, CH, J 7.7), 7.13 (d, 1H, CH, J 7.2 Hz), 7.22–7.31 (m, 3H, CH), 7.65 (dd, 1H, CH, J 0.6, 8.0 Hz), 7.73 (dd, 1H, CH, J 1.4, 7.3 Hz); ^{13}C NMR PENDANT (75 MHz, CDCl_3) δ 42.3 (CH_2), 65.8 (CH_2), 103.1 (C), 117.4 (C), 122.4 (CH), 122.7 (C), 123.5 (CH), 124.1 (CH), 124.3 (CH), 127.6 (CH), 127.7 (C), 128.0 (C), 128.0 (CH), 128.5 (CH), 139.3 (C), 172.8 (C=O). Found: C, 73.03; H, 4.42; N, 5.08. Calc. for $\text{C}_{17}\text{H}_{13}\text{NO}_3$: C, 72.94; H, 4.64; N, 5.01%.

spiro-4-(ethylenedioxy)-2-nitro-7-hydropyrrolo [3,2,1-de]phenanthridin-5-one (10 c)

mp. $238\text{--}240^\circ\text{C}$ (decomp.); IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3083, 2971, 2909, 1739, 1613, 1527, 1493, 1339, 1252, 1175, 1031, 946, 781, 753, 729; Mass [m/z (abun.)] 324(24%), 295(100), 251(39), 224(16), 205(26), 177(45), 150(32), 126(5), 103(16), 86(66), 75(79), 63(16); ^1H NMR (200 MHz, $\text{CDCl}_3/\text{DMSO-d}_6$) δ 4.16–4.22 (m, 2H, CH_2), 4.35–4.41 (m, 2H, CH_2), 4.81 (s, 2H, CH_2), 7.02 (d, 1H, CH, J 5.3 Hz), 7.20 (m, 2H, CH), 7.67 (d, 1H, CH, J 5.4 Hz), 7.91 (s, 1H, CH), 8.42 (s, 1H, CH); ^{13}C NMR PENDANT (50 MHz, $\text{CDCl}_3/\text{DMSO-d}_6$) δ 42.1 (CH_2), 65.9 (CH_2), 101.5 (C), 117.7 (C), 119.4 (CH), 119.9 (CH), 122.7 (CH), 123.2 (C), 125.6 (C), 127.6 (CH), 128.2 (C), 128.4 (CH), 129.8 (CH), 144.2 (C), 144.6 (C), 172.9 (C=O)*. Found: C, 63.13; H, 3.45; N, 8.81. Calc. for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_5$: C, 62.94; H, 3.55; N, 8.86%. *Signal observed in the normal ^1H decoupled ^{13}C spectrum recorded in $\text{C}_6\text{D}_6/\text{CDCl}_3$.

spiro-4-(ethylenedioxy)-9,10-(methylenedioxy)-7-hydropyrrolo[3,2,1-de]phenanthridin-5-one (10 d)

mp. $226\text{--}228^\circ\text{C}$ (decomp.); IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3047, 2969, 2900, 1716, 1638, 1508, 1475, 1369, 1238, 1188, 1153,

1042, 939, 787, 744; Mass [m/z (abun.)] 323(42%), 294(100), 264(25), 250(37), 223(27), 164(23), 138(14), 124(30), 110(14), 96(43), 82(39), 69(25), 63(14); ^1H NMR (300 MHz, CDCl_3) δ 4.31-4.39 (m, 2H, CH_2), 4.54-4.61 (m, 2H, CH_2), 4.88 (s; 2H, CH_2), 6.00 (s, 2H, CH_2), 6.61 (s, 1H, CH), 7.03 (t, 1H, CH, J 7.5 Hz), 7.18 (s, 1H, CH), 7.19 (dd, 1H, CH, J 0.7, 7.5 Hz), 7.50 (d, 1H, CH, J 7.5 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 42.9 (CH_2), 66.0 (CH_2), 101.8 (CH_2), 102.9 (CH), 103.5 (C), 107.8 (CH), 117.8 (C), 122.3 (C), 122.6 (C), 122.7 (C), 123.7 (CH), 123.8 (2 x CH), 139.0 (C), 148.1 (C), 148.3 (C), 173.1 (C=O).

spiro-4-(ethylenedioxy)-9,10-dimethoxy-7- hydroxy-pyrrolo[3,2,1-de]phenanthridin-5-one (10 e)

mp. 188-190°C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3067, 2966, 2839, 1719, 1635, 1467, 1358, 1217, 1185, 1149, 1048, 1002, 940, 854, 780, 737; Mass [m/z (abun.)] 339(42%), 310(100), 266(21), 239(28), 153(8), 134(8), 126(5), 63(3); ^1H NMR (300 MHz, CDCl_3) δ 3.89 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 4.31-4.35 (m, 2H, CH_2), 4.57-4.62 (m, 2H, CH_2), 4.88 (s, 2H, CH_2), 6.60 (s, 1H, CH), 7.03 (t, 1H, CH, J 7.4 Hz), 7.16 (s, 1H, CH), 7.19 (d, 1H, CH, J 7.4 Hz), 7.53 (d, 1H, CH, J 7.4 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 42.0 (CH_2), 55.9 (2 x CH_3), 65.7 (CH_2), 101.2 (C), 105.1 (CH), 109.9 (CH), 117.5 (C), 120.5 (C), 121.0 (CH), 122.3 (C), 123.2 (CH), 123.2 (CH), 123.4 (CH), 138.4 (C), 148.6 (C), 149.3 (C), 172.8 (C=O); HRMS. Found: 339.1107. Calc. for $\text{C}_{19}\text{H}_{17}\text{NO}_5$: 339.1107.

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