$(PhO)_3P{\cdot}Cl_2$-Promoted Bischler–Napieralski-Type Cyclization: a Mild Access to β-Carbolines

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Abstract: A novel mild access to the β-carboline skeleton is described. The reaction is a Bischler–Napieralski-type cyclocondensation, promoted by $(PhO)_3P{\cdot}Cl_2$, which is performed in dichloromethane at –30 °C. The products are easily obtained in good yields and do not require further chromatographic purification.

Key words: triphenyl phosphite, chlorine, indoles, alkaloids, Bischler–Napieralski cyclizations

The demand for milder methods to carry on reactions, which are generally performed under severe conditions, has become an attractive challenge when new modifications of existing procedures are proposed. In this respect, our recent efforts in providing a new, mild and simple method for deacylation of amides have been oriented accordingly.[1] In the course of that study, we also disclosed a preliminary report of the first and mildest example of a Bischler–Napieralski-type cyclization at low temperature promoted by the triphenyl phosphite–chlorine complex, $(PhO)_3P{\cdot}Cl_2$.[1–3]

Along this line, we wish herein to follow up this kind of chemistry and report its natural extension to indolamides for the synthesis of β-carboline derivatives, a fascinating class of naturally occurring alkaloids endowed with a variety of biological and psychotropic properties.[4] Classically, cyclization of *N*-β-arylethylamides through Bischler–Napieralski reaction[5,6] proceeds via formation of an iminochloride intermediate, which is formed by exposure of the substrate to a suitable halogenating reagent.[7] Subsequently, the iminochloride undergoes an intramolecular electrophilic substitution, thus affording the cyclic product.[7] It is likely, as already suggested, that, once formed, the iminochloride rearranges into a nitrilium intermediate,[7,8] which is more willing to be trapped by the electron-rich aromatic ring.

To the best of our knowledge, literature reports formation of the iminochloride usually by means of harsh reagents and often by heating the reaction mixture to high temperatures. In particular, the most widespread conditions involve $POCl_3$,[9] or $SnCl_4/POCl_3$[10] in high boiling solvents, such as toluene or xylene; alternatively, other approaches can be employed to prime cyclization, the more often employed being exposure to dehydrating agents, like P_2O_5,[11] polyphosphoric acid[12] or esters thereof.[13] Two remarkable exceptions exist, namely the recent and intriguing Tf_2O/DMAP protocol developed in Banwell's group,[14] and the $(COCl)_2/FeCl_3$-promoted procedure by Larsen and coworkers.[15] Although both these high-yielding methods have well demonstrated their usefulness in promoting Bischler–Napieralski-type reactions, either on urethanes[14] or β-arylethylamines,[15] respectively, it is worth noting that they exhibit limitations towards cyclization of indoles. Most recently, for instance, Li and colleagues failed in applying them satisfactorily to indole urethanes[16] and were forced to move back to the classical Bischler–Napieralski reaction, which still represents, as yet, the only straightforward route to 3,4-dihydro-β-carbolines from indoles, whereas the perhaps most exploited Pictet–Spengler reaction leads to 1,2,3,4-tetrahydro-β-carbolines.[6] Awkward reagents and harsh conditions, however, may preclude successful application of Bischler–Napieralski cyclization when sensitive functional groups are present.[6] Hence, with the aim to bridge this gap and encouraged by preliminary results in our hands,[1] we were prompted to apply our $(PhO)_3P{\cdot}Cl_2$ methodology for the cyclocondensation of a variety of indolamides.

For our purposes, commercially available tryptamine was envisaged as a convenient starting material for the construction of the β-carboline skeleton. Firstly, conversion into variously substituted tryptamides was achieved, on multigram scale, by classical acylation with the appropriate acyl chloride in dichloromethane, affording the corresponding amides **1a**–**d** in 70–92% yield.[17] In contrast, **1e** was prepared from commercially available L-tryptophan according to standard procedures. When tryptamides **1a**–**e** were treated with a slight excess of $(PhO)_3P{\cdot}Cl_2$ at –30 °C in dichloromethane in the presence of triethylamine,[18] the expected cyclic products **2a**–**e** were obtained in good to excellent yields, as depicted in Scheme 1.

According to a typical experimental procedure, chlorine is bubbled through a glass septum in a solution of $(PhO)_3P$ in anhydrous dichloromethane at –30 °C under Ar atmosphere, until the solution appears intensely yellow. The color is discharged by addition of a few further drops of $(PhO)_3P$, thus obtaining an almost colorless and clear mixture. Substrate and base are added and the mixture is

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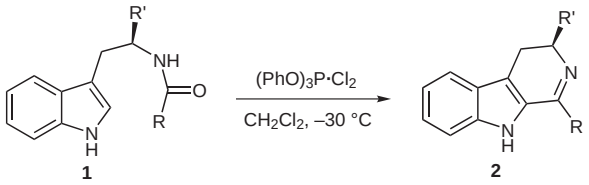
left to stir at the same temperature over two hours. The cold bath is then removed and the mixture stirred for an additional 12 hours. Meanwhile, precipitation of β-carboline as hydrochloride may occur, thus facilitating recovery by simple filtration (as for **2a**).[19] Should this not be the case, a final extraction step is performed, and the desired product is recovered as free base.[20] Nonetheless, no additional chromatographic purification is strictly required, since major by-products are completely removed during acid–base extraction. The results are summarized in Table 1.



Scheme 1 General scheme for Bischler–Napieralski reaction promoted by $(PhO)_3P{\cdot}Cl_2$ reagent

Noteworthily, **2a** (harmalane)[21a] is a pharmacologically active compound,[21b] whilst β-carboline **2d** is closely related to the fungal alkaloid infractin, originally isolated from *Cortinarius infractus*.[22] In addition, derivative **2e** bears structural resemblance to a metabolite present in the entheogenic mushroom *Amanita muscaria*.[4a,23]

Table 1 Cyclization Results

Substrate	R	R′	Product	Yield (%)
1a	Me	H	**2a**	98
1b	Ph	H	**2b**	51
1c	CH_2Ph	H	**2c**	65
1d	CH_2CH_2COOMe	H	**2d**	50
1e	Me	COOMe	**2e**	62

When compared to available methodologies[24] for the synthesis of β-carbolines, our $(PhO)_3P{\cdot}Cl_2$-primed protocol offers an alternative route to perform similar cyclocondensations and is well tolerated by the sensitive indole skeleton. Most interestingly, this method represents the mildest procedure ever described in the literature for Bischler–Napieralski-type cyclizations.

Furthermore, preliminary attempts to assess whether this approach can be extended to the synthesis of 3,4-dihydroisoquinolines, yet another important class of bioactive alkaloids, would suggest that this chemistry can be successfully applied also to a variety of substituted β-phenylethylamides, albeit with less satisfactory yields. A painstaking investigation along this direction and application of this methodology to the total synthesis of natural alkaloids are currently representing a central issue in our laboratory and further developments will be reported in due course.

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(17) **Synthesis of Tryptamine Amides (1a–d); General Procedure.**
Tryptamine (4500 mg, 28 mmol) was dissolved in dry CH_2Cl_2 (20 mL) in a two-necked 100 mL flask, and Et_3N

(4.3 mL, 30.8 mmol) was added. The appropriate acyl chloride (1.1 equiv) dissolved in CH_2Cl_2 (10 mL) was then cautiously dropped in, under vigorous stirring. The reaction mixture was heated to reflux for 90 min, until TLC showed disappearance of starting tryptamine. Thereafter, the mixture was washed with 10% HCl, sat. NaCl and finally with H_2O, each time extracting with CH_2Cl_2. The organic phases were pooled, dried over $MgSO_4$ and evaporated in vacuo, to provide a thick foam which was triturated with light petroleum, thus affording the desired amide as a reddish-brown fine powder (70–92% yield).

(18) The role of the base is to shield $(PhO)_3P{\cdot}Cl_2$ from the action of adventitious HCl, which is reported to enhance its degradation into an inactive form. For more detailed mechanistic insights, see Ref. 1,2a.

(19) **Synthesis of Harmalane Hydrochloride (2a).**
In a three-necked 50 mL round bottom flask, anhyd CH_2Cl_2 (15 mL) was cooled to –30 °C under argon atmosphere. Triphenyl phosphite (1.2 mL, 4.6 mmol) was added and Cl_2 was bubbled in, until the solution became bright yellow. The color was discharged by addition of a few drops of triphenyl phosphite, and tryptamine acetamide **1a** (850 mg, 4.2 mmol) was then added, quickly followed by Et_3N (671 μL, 4.83 mmol). The reaction was stirred over a 2-hour period, then the cold bath was removed and the mixture left to stir at r.t. After 12 h, a conspicuous yellow solid had precipitated and was recovered by centrifugation, thus affording 909 mg (98%) of harmalane (**2a**) as hydrochloride. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.79 (3 H, s, Me), 3.19 (2 H, t, J = 8.1 Hz, CH_2CH$_2$N), 3.88 (2 H, t, J = 8.1 Hz, CH$_2$CH_2N), 7.78–8.14 (4 H, m, arom.), 12.87 (1 H, br, NH), 13.07 (1 H, br, HCl). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 19.0, 19.1, 42.1 113.7, 121.6, 122.2, 123.0, 124.3, 126.8, 128.5, 140.9, 167.2. MS: m/z = 221 (M^+), 207, 182, 154, 128, 91, 77, 63, 44. Anal. Calcd for $C_{12}H_{13}ClN_2$: C, 65.31; H, 5.94; N, 12.69. Found: C, 65.42; H, 6.05; N, 12.73.

(20) **Synthesis of 1-Phenyl-4,9-dihydro-3*H*-β-carboline (2b).**
By close analogy to the procedure described above, triphenyl phosphite (1.16 mL, 4.3 mmol) was dissolved in anhyd CH_2Cl_2 (14 mL) at –30 °C under argon atmosphere. Then, Cl_2 was bubbled in, until the solution turned intensely yellow. The color was discharged by addition of a few further drops of triphenyl phosphite and tryptamine benzamide **1b** (1000 mg, 3.9 mmol) was added, quickly followed by Et_3N (637 μL, 4.58 mmol), and the system was maintained under vigorous stirring over 2 h at –30 °C before removing the cold bath. After an additional 12 h period at r.t., the dark mixture was treated with 10% HCl and extracted with CH_2Cl_2 (4 × 10 mL). The aqueous phase was then basified to pH 10 with 20% NaOH and repeatedly extracted with CH_2Cl_2 (4 × 15 mL). The organic phases were pooled, dried and rotary evaporated, to afford **2b** (505 mg, 51%) as a yellow fine powder (mp 196–198 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.99 (2 H, t, J = 8.5 Hz, CH_2CH$_2$N), 4.06 (2 H, t, J = 8.5 Hz, CH$_2$CH_2N), 7.10–7.85 (9 H, m, arom.), 8.24 (1 H, br, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.2, 48.8, 111.9, 117.9, 119.9, 120.4, 124.6, 127.8, 128.8, 129.9, 136.5, 137.6, 159.4. Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.85; H, 5.64; N, 11.49.

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