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Synthesis of β-carbolines using microwave-assisted aza-Wittig methodology in ionic liquids

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ABSTRACT

The improved preparation of 1-substituted-β-carbolines is reported using microwave-assisted aza-Wittig/electrocyclic ring-closure reaction with ionic liquids as solvent. In all cases an unprecedented *N*-methoxymethyl group (MOM) deprotection is observed.

The β-carboline core is of great interest because it is present in numerous natural and synthetic compounds and has important pharmacological properties.[1] Moreover, the 1-substituted β-carboline alkaloids have antimalarial,[2] antitumoral,[3] anti-Alzheimer,[4] anti-HIV,[5] antitrypanosomal, and antileishmanial[6] properties, they also act as regulators of the dioxin receptor (AhR).[7] Over the years, many synthetic methods have been described for the preparation of 1-substituted β-carbolines, however most of the reported methods involve cyclization and oxidation as separate steps.[8] Recently, based on the domino approach using a bifunctional catalyst Pd/C/K-10 combined with microwave irradiation,[9] via Heck aza Michael methodology,[10] or by intramolecular palladium-catalyzed enolate arylation of 2-iodoindole derivatives have been developed.[11]

In the course of our studies directed toward the synthesis of nitrogen heterocyclic compounds based on the heterocyclization process of 2-aza-1,3,5-hexatriene systems, generated by Staudinger reaction of 1,3-diene azides with triphenylphosphine and the subsequent aza-Wittig reaction with carbonyl compounds or heterocumulenes, we have developed the tandem aza-Wittig/electrocyclic ring-closure strategy for the synthesis of fused pyridines.[12] This methodology has been successfully applied for the synthesis of natural β-carbolines such as eudistomins, lavendamycin, fascaplysin, nitramarin, and xestomanzamine A.[13] However, when toluene or *o*-xylene is used as the solvent, rather long reaction times at high temperatures are required to successfully obtain the carboline core; and milder synthetic methods would be preferable. Since the microwave radiation[14] acts as an alternative heating source and provides an efficient procedure to accelerate organic transformations. Ionic liquids are an environmentally benign reaction medium, due to their polar nature and special properties such as a wide liquid range, good solvating ability, high thermal stability, low vapor pressure, and easy recyclability.[15] We decided to combine the advantages of microwave and ionic liquids to ascertain their combined influence on the preparation of 1-substituted β-carboline (pyrido[3,4-*b*]indole) using the aza-Wittig/electrocyclic ring-closure reaction.

First, iminophosphorane **1**,[16] which is easily prepared from 3-formyl-*N*-methoxymethylindole by sequential treatment with ethyl azidoacetate and triphenylphosphine, and aromatic aldehydes Ar-CHO **2**, were used in a series of experiments involving different combinations of heating modes and ionic liquids: (a) conventional heating, (b) microwave irradiation, (c) conventional heating/ionic liquid, and (d) microwave irradiation/ionic liquid.

When iminophosphorane **1** reacted in an aza-Wittig/electrocyclic cyclization fashion with 4-methoxybenzaldehyde **2a** and 4-chlorobenzaldehyde **2b** in dry toluene by heating in a sealed tube at 160 °C for 48 h, *N*-methoxymethyl-β-carbolines **4a** and **4b** were obtained in yields of 77% and 65%, respectively. However, when the reaction mixture was irradiated with a single-mode microwave, using a pre-selected maximum temperature of 200 °C, (200 W maximum power), in a sealed vessel and using dry toluene as the solvent, compounds **4a** and **4b** were obtained after a shorter reaction time of 8 h, in yields of 87% and 83%, respectively (Scheme 1), (Table 1).

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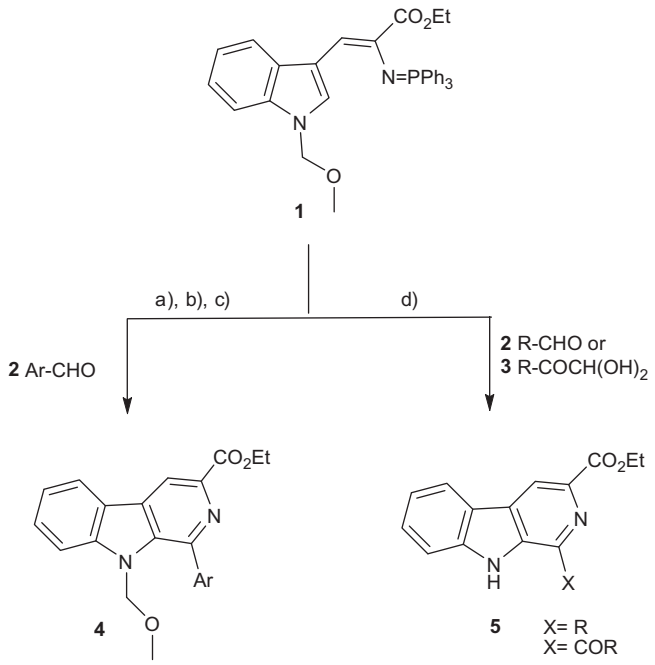
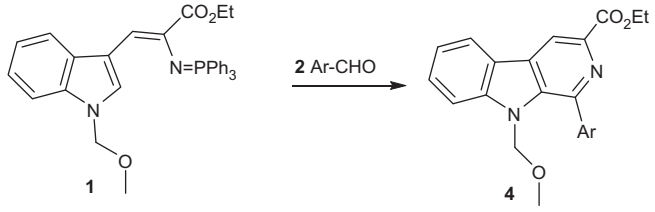


Scheme 1. Synthesis of 1-substituted-β-carbolines **4** and **5** via aza-Wittig/electrocyclic ring-closure reaction. Reagents and conditions: (a) toluene, sealed tube, 160 °C, 48 h; (b) toluene, MW, 200 W, 200 °C, 8 h; (c) (i) [bmim][BF_4], 160 °C, 2 h. (ii) [bmim][PF_6], 160 °C, 2.5 h; (d) [bmim][BF_4], MW, 1 W, 200 °C, 15 min.

Table 1
Synthesis of 1-substituted-β-carboline **4** via aza-Wittig/electrocyclic ring-closure reaction from iminophoshorane **1** and aldehyde **2**

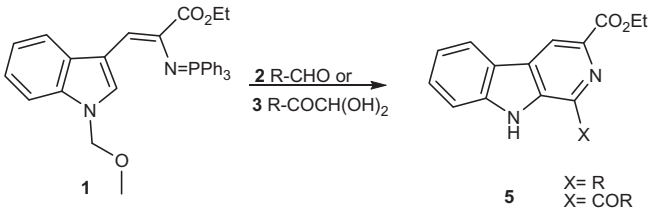


4	ArCHO	Heat[a] yield (%)	MW[b] yield (%)	Heat+IL[c] yield (%)
4a	4-$MeOC_6H_4$	77	87	85/30
4b	4-Cl C_6H_4	65	83	84/25

[a] 1.0 mmol of **1** and 1.2 of **2** were used, toluene, sealed tube, 160 °C, 48 h.
[b] 0.19 mmol of **1** and 0.19 mmol of **2** were used toluene, MW, 200 W, 200 °C, 8 h.
[c] (i) 1 mL, [bmim][BF_4], 160 °C, 2 h/(ii) 1 mL, [bmim][PF_6], 160 °C, 2.5 h.

In order to explore the reaction in ionic liquids, and based on a recent study on the thermal stability of a variety of ionic liquid/solvent combinations under high-temperature microwave conditions,[17] we selected 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4] (290 °C) and 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] (276 °C).[18] The best yields for **4a** and **4b** (85–86%) were obtained when the reaction was performed in [bmim][BF_4] as the solvent and heating at 160 °C for 2–2.5 h. However, when [bmim][PF_6] was used under the same conditions, **4a** and **4b** showed yields of 30% and 25%, respectively.[19] Consequently we decided to use only [bmim][BF_4] as the solvent for the next experiment based on microwave irradiation/ionic liquid. When the reaction mixture was irradiated with a single-mode microwave, using a pre-selected maximum temperature of 200 °C, (1 W maximum power), in a sealed vessel and [bmim][BF_4] as the solvent, unexpectedly β-carbolines **5a** and **5b** with the *N*-methoxymethyl group cleaved were obtained in 79% and 70% yields, respectively after shorter reaction times of 15–20 min.[20]

Table 2
Microwave-assisted synthesis of 1-substituted-β-carbolines **5** in [bmim][BF_4][a]



5	R-CHO **2a–d**	R-COCH(OH)$_2$ **3a–c**	Time (min)	Yield (%)
5a	4-$MeOC_6H_4$		15	79
5b	4-Cl C_6H_4		20	70
5c	C_6H_5		20	73
5d	C_6H_5-$(CH_2)_2$		20	65
5e		C_6H_5	15	88
5f		4-$MeOC_6H_4$	15	90
5g		*N*-MOM-indol-3-yl	25	76

[a] 0.19 mmol of **1** and 0.19 mmol of **2** or **3** were used, 1 mL, [bmim][BF_4], MW, power = 1 W, T = 200 °C.

Although several reagents, including HCO_2H-reflux,[21] CF_3SO_3H/MeOH/$HC(OCH_3)_3$, nitromethane/100 °C,[22] HCl (EtOH, THF, and dioxane)[23] and HCl-dioxane/MW,[24] have been used for deprotection of the *N*-MOM group, however their use in conjunction with ionic liquids and microwave energy has not been reported in the literature.

To establish the generality and viability of this method, the same conditions were successfully applied to several R-CHO **2** aldehydes, benzaldehyde **2c**, 3-phenylpropanal **2d**, and RCO-$CH(OH)_2$ **3**, aryl/heteroaryl glyoxals,[21d,25] phenylglyoxal **3a**, 4-methoxyphenylglyoxal **3b**, 2-(*N*-methoxymethyl-3-indolyl)glyoxal **3c**, to give the corresponding aryl/aroyl 1-substituted-9*H*-pyrido[3,4-*b*]indoles **5e**–**5g** in yields ranging from 65% to 90% and in shorter reaction times of 15–25 min (Scheme 1), (Table 2).[26]

In summary, we have developed a useful and an efficient method for the preparation of aryl/aroyl 1-substituted-9*H*-pyrido[3,4-*b*]indoles through the tandem aza-Wittig/electrocyclic ring-closure reaction using microwave irradiation in combination with an ionic liquid [bmim][BF_4] as the solvent. In addition, we describe here, for the first time a pyridoannulation process involving the simultaneous deprotection of *N*-methoxymethyl group using ionic liquid/microwave-assisted irradiation with good yields (65–90%) and short reaction times (15–25 min). The advantage of this method is that it uses microwave radiation and a non-contaminating, reusable solvent [bmim][BF_4], in addition, the fact that the starting material is readily accessible, it is easily manipulated, and the few steps necessary mean that the method is suitable for preparing new β-carbolines.

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19. *General procedure in ionic liquids. Preparation of ethyl N-methoxymethyl-1-substituted-9H-pyrido[3,4-b]indole-3 carboxylate* (**4**). A mixture of iminophosphorane **1** (100 mg, 0.19 mmol) and 4-methoxybenzaldehyde **2a**, or 4-chlorobenzaldehyde **2b** (0.19 mmol) was dissolved in [bmim][BF_4] or [bmim][PF_6] (1 mL), dried previously during 4 h at 80 °C, under nitrogen. The solution was stirred at 160 °C during 2 h. After cooling, the mixture was extracted with EtOAc (10 × 5 mL) and dried over anhydrous Na_2SO_4. The solvent was concentrated to dryness under reduced pressure. The residue was chromatographed on a silica gel column using EtOAc/CH_2Cl_2/*n*-hexane (2:3:6) as the eluent to give **4a** (85% and 30%) or **4b** (84% and 25%) yields.
Ethyl N-methoxymethyl-1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**4a**). Yield 85%, 62 mg, white prisms, mp 167–168 °C (CH_2Cl_2/n-hexane, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.47 (t, *J* = 7.2 Hz, 3H), 2.94 (s, 3H), 3.90 (s, 3H), 4.52 (q, *J* = 7.2 Hz, 2H), 5.29 (s, 2H), 7.05 (dd, *J* = 8.8, 2.4 Hz, 2H), 7.40 (td, *J* = 7.4, 1.2 Hz, 1H), 7.58–7.65 (m, 4 H), 8.22 (d, *J* = 7.6 Hz, 1H), 8.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.5, 55.4, 61.6, 74.6, 111.3, 113.9, 116.3, 121.6, 122.1, 129.1, 130.8, 131.1, 131.6, 136.2, 138.5, 142.5, 144.3, 160.2, 166.1. IR (nujol): υ = 1707, 1610, 1456, 1241 cm^{-1}. MS (EI): *m*/*z* (%): 390 (54), $[M]^+$, 345 (6), $[M-CH_2OCH_3]^+$, 283 (7), $[M-PhOCH_3]^+$. Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68, N, 7.17. Found: C, 70.67; H, 5.75; N, 7.23.
Ethyl N-methoxymethyl-1-(4-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**4b**). Yield 84%, 62 mg, white prisms, mp 189–191 °C, (CH_2Cl_2/*n*-hexane, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.48 (t, *J* = 7.2 Hz, 3H), 2.97 (s, 3H), 4.53 (q, *J* = 7.2 Hz, 2H), 5.24 (s, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.64–7.67 (m, 3H), 8.24 (d, *J* = 7.6 Hz, 1H), 8.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.5, 55.4, 61.8, 74.7, 111.2, 116.8, 121.0, 121.9, 122.0, 128.7, 129.9, 130.9, 131.1, 135.1, 135.8, 137.6 138.7, 142.7, 143.1, 165.9. IR (nujol): υ = 1712, 1458, 1376, 1083 cm^{-1}. MS (EI): *m*/*z* (%): 396 (16), $[M+2]^+$, 394 (42), $[M]^+$, 323 (37), $[M-COOEt]^+$. Anal. Calcd for $C_{22}H_{19}ClN_2O_4$: C, 66.92; H, 4.85; Cl, 8.98; N, 7.09. Found: C, 66.89; H, 4.93; Cl, 8.92; N, 7.17.
20. *General procedure in ionic liquid/microwave irradiation. Preparation of ethyl 1-substituted-9H-pyrido[3,4-b]indole-3 carboxylate* (**5**). A mixture of iminophosphorane **1** (100 mg, 0.19 mmol) and aryl/alkylaldehyde **2** or arylglyoxal **3** (0.19 mmol) was dissolved in [bmim][BF_4] (1 mL), contained in a sealed tube. The reaction mixture was irradiated with a single-mode microwave (1 W, 200 °C) under nitrogen for 15–20 min. After cooling, the mixture was extracted with ethyl acetate (10 × 5 mL) and dried over anhydrous Na_2SO_4. To the residual material was added dichloromethane (10 mL) and active carbon, filtrated over celite, and concentrated to dryness to give [bmim][BF_4], which was re-used. The filtrate was concentrated under reduced pressure and the residue was chromatographed on a silica gel column using ethyl acetate/dichloromethane/*n*-hexane (2:3:6) as the eluent to give **5** in 65–90% yield.
Ethyl 1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**5a**). Yield 79%, 51 mg, white prisms, mp 222–224 °C, (CH_2Cl_2/*n*-hexane, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.48 (t, *J* = 7.2 Hz, 3H), 3.83 (s, 3H), 4.53 (q, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.37 (td, 1H), 7.57–7.59 (m, 2H),7.85 (d, *J* = 8.8 Hz, 2H), 8.21 (d, *J* = 8 Hz, 1H), 8.80 (s, 1H), 8.99 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.5, 55.0, 61.1, 111.5, 114.1, 115.9, 120.6, 121.5, 121.8, 128.3, 129.2, 129.3, 130.0, 134.5, 138.1, 140.1, 142.3, 160.0, 166.0. IR (nujol): υ = 3252, 1703, 1458 cm^{-1}. MS (EI): *m*/*z* (%): 346 (54), $[M]^+$, 345 (6), 283 (7), $[M-PhOCH_3]^+$, 273 (100), $[M-COOEt]^+$. Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 7.09. Found: C 72.74, H 5.30, N 7.02.
Ethyl 1-(4-methoxybenzoyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**5f**). Yield 90%, 63 mg, yellow prisms, mp 211 °C (d), (CH_2Cl_2/*n*-hexane, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.54 (t, *J* = 7.2 Hz, 3H), 3.93 (s, 3H) 4.54 (q, *J* = 7.2 Hz, 2H), 7.05 (d, *J* = 8.8 H, 2H) 7.38–7.42 (m, 1H), 7.60–7.65 (m, 2H), 8.24 (d, *J* = 7.6 Hz, 1H), 8.83 (d, *J* = 8.8 Hz, 2H), 9.02 (s, 1H), 10.72 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.5, 55.6, 61.7, 112.4, 120.3, 121.3, 121.6, 122.1, 129.7, 129.8, 132.0, 134.6, 136.2, 136.5, 138.3, 141.3, 163.7, 165.8, 191.6. IR (nujol): υ = 3420,1707, 1596 cm^{-1}. MS (EI): *m*/*z* (%): 374 (66), $[M]^+$, 315 (58), $[M-Et]^+$, 301 (41), $[M-COOEt]^+$. Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.50; H, 4.93; N, 7.39.
Ethyl 1-[(1H-indole-3-yl)carbonyl]-9H-pyrido[3,4-b]indole-3-carboxylate (**5g**). Yield 76%, 55 mg, yellow prisms, after chromatographed on a silica gel column using ethyl acetate/*n*-hexane/aqueous NH_3 (3.5:6:0.5) as the eluent, and recrystallization from CH_2Cl_2/*n*-hexane (4:1), mp 159–161 °C. ^{1}H NMR (400 MHz, [D_6]acetone, 25 °C): δ = 1.53 (t, *J* = 7.2 Hz, 3H), 4.51 (q, *J* = 7.2 Hz, 2H), 7.25–7.35 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.58–7.68 (m, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 8.45 (d, *J* = 7.8 Hz, 1H), 8.68 (dd, *J* = 2.16, 7.7 Hz, 1H), 9.10 (s, 1H), 10.02 (s, 1H), 11.33 (br s, 1H), 11.82 (br s, 1H). ^{13}C NMR (100 MHz, [D_6]acetone, 25 °C): δ = 13.5, 60.5, 111.3, 112.8, 116.8, 119.0, 120.6, 120.7, 121.5, 121.8, 121.9, 122.6, 127.6, 128.8, 131.4, 131.5, 135.5, 135.8, 136.5, 138.7, 141.8, 165.0, 186.6. IR (nujol): υ = 3385, 1697, 1603 cm^{-1}. MS (EI): *m*/*z* (%): 383 (87), $[M]^+$, 315 (4), $[M-Et]^+$, 301 (37), $[M-COOEt]^+$. Anal. Calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 72.16; H, 4.54; N, 10.88.
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26. *General Methods*: All reactions were carried out under N_2 and the solvent was dried by standard procedures. Column chromatography purification was performed using silica gel (60 Å, 70–200 μm, SDS) as stationary phase. All melting points were determined on a hot-plate melting point apparatus and are uncorrected. IR spectra were recorded with a Nicolet 380 FT-IR instrument. NMR spectra (Bruker Avance 300 MHz and 400 MHz) were determined using tetramethylsilane as an internal standard. The proton (^{1}H NMR) and carbon (^{13}C NMR) signals were assigned by DEPT or two-dimensional NMR experiments. Mass spectra were recorded with Agilent 5973 (EI) mass spectrometers. Elemental analyses were performed with a Carlo Erba EA-1108 elemental analyzer. Microwave irradiation was carried out with a single-mode microwave CEM Discover Focused Synthesizer with standard IR temperature sensor. Ethyl-2-[(triphenylphosphoranylideneamino]-3-[(*N*-methoxymethyl) indole-3-yl]acrylate was prepared according to our previously described method.[16] Arylglyoxals were prepared according to the published procedure.[21d,25]