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PRELIMINARY STUDY OF PALLADIUM CATALYZED IMINOANNULATION IN AN IMIDAZO[1, 2-*a*]PYRIDINE SERIES

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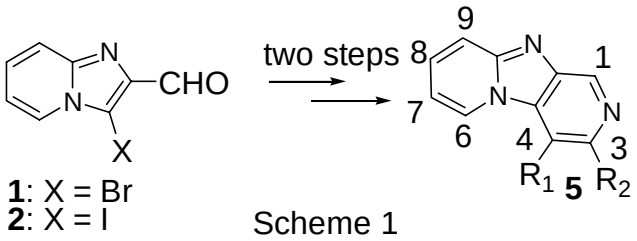
Abstract - Palladium-catalyzed iminoannulation was carried out in an imidazo[1,2-*a*]pyridine (IP) series. *tert*-Butylimine of 3-haloimidazo[1,2-*a*]pyridine-2-carbaldehyde reacted with suitably functionalized alkynes in the presence of a catalytic amount of $Pd(OAc)_2/PPh_3$ and a base to yield dipyrido[1,2-*a*; 3',4'-*d*]imidazoles (**5**).

INTRODUCTION

Pyridoindoles have been screened for a broad range of pharmaceutical activities. β-Carboline derivatives are a representative example that have shown potent CNS[1] and anticancer activities.[2] A number of synthetic approaches to this class of compounds have been described.[3] Classically, these tricyclic systems have been prepared by Bischler-Napieralski reaction[4] or Pictet-Spengler reaction of tryptamine derivatives.[5] More recently, the carboline heterocycle has been synthesized using palladium-catalyzed annulation methods[6] involving the insertion of unsaturated molecules, such as alkynes, into a carbon-metal bond from *ortho*-haloimino compounds. In the course of our work on the development of new synthetic approaches to polycyclic nitrogen heterocycles, we recently reported the synthesis of α,δ-azacarbolines by Pictet-Spengler,[7] heterocyclization of carbodiimides[8] or vinyloximes[9] and modified Skraup[10] methods. To reduce the number of steps, improve the yields and facilitate the access to azacarboline rings, we undertook the synthesis of β–azacarbolines by palladium-catalyzed iminoannulation of alkynes[11] in an formyl-IP[12] series. It was also known that a halogen substituent (bromo or iodo) in the 3-position of the IP structure could be easily replaced by phenyl, alkyl and

heteroatome groups.[13] Leading on from these results, we report here the first synthesis of β-azacarbolines (**5)** by palladium-catalyzed iminoannulation from 3-halo-IP-2-carbaldehydes (**1)** and (**2)** (Scheme 1). This new approach to obtain heterocyclic derivatives of β–carbolines can be useful for the preparation of heterocycles bearing a chemical functionality in search of increased or more specific bioactivity.

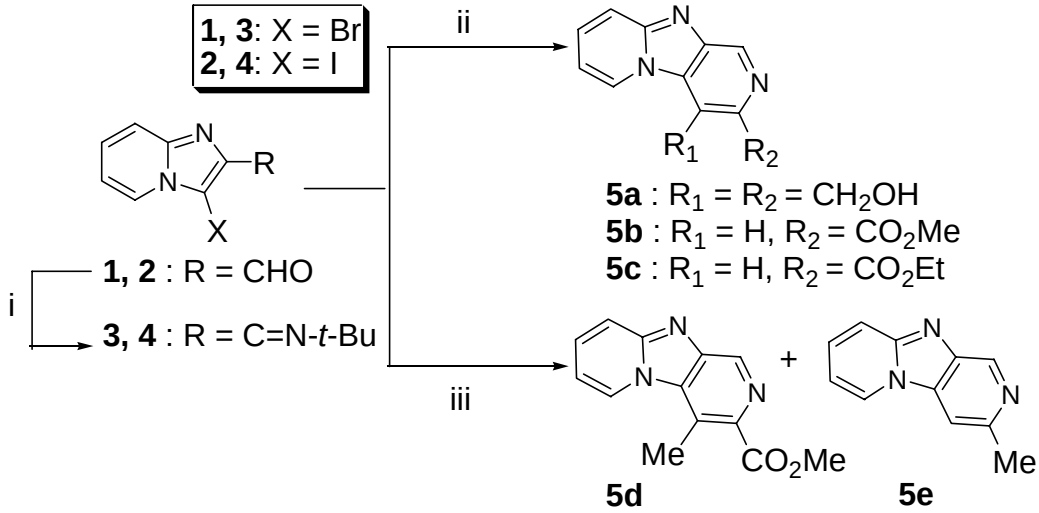


1: X = Br
2: X = I

Scheme 1

RESULTS AND DISCUSSION

Starting material (**1**) was synthetized by the Chavignon procedure.[14] The 3-iodo-IP-2-carbaldehyde (**2**) was easily obtained in 90% yield from 2-formyl-IP[14] using the NIS procedure.[15] At this stage, our synthetic approach required the preparation of imines (**3)** and (**4)**. Condensation of *tert*-$BuNH_2$ with **1** and **2** in dry methylene chloride under reflux gave **3** and **4** respectively, which were used without purification. Referring to palladium-catalyzed iminoannulations previously described by Larock,[16] all the reactions were run with 1 mmol of appropriate imine, 2 equivalents of alkyne, 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3 and 1 equivalent of base in 10 mL of dry DMF at 125° C.



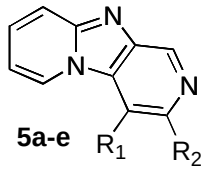
[a]Reagents and conditions : i) *tert*-$BuNH_2/CH_2Cl_2$, Δ; ii) $Pd(OAc)_2$, PPh_3, Base (condition A : Na_2CO_3 or condition B : *n*-Bu_3N), appropriate alkyne (2-butyne-1,4-diol, methyl propiolate, methyl(ethyl) acetylenedicarboxylate), DMF, Δ; iii) $Pd(OAc)_2$, PPh_3, Na_2CO_3 or *n*-Bu_3N), methyl 2-butynoate, DMF, Δ.

Scheme 2[a]

The annulation of 2- butyne-1,4-diol with *ortho*-bromo(iodo)-*tert*-butylimines (**3)** and (**4)** gave the desired disubstituted dipyridoimidazole (**5a**) in moderate yields (Scheme 2; Table 1, Entries 1, 2). The annulation of a terminal alkyne such as methyl propiolate by imines (**3**), (**4**) produced azacarboline (**5b)** in yields comparable to that obtained for alkyne diol (Scheme 2; Table 1, Entries 3, 4). The regiochemistry of the product was confirmed by comparing NMR spectral data with those of 3-ethoxycarbonyldipyrido[1,2-*a*;3',4'-*d*]imidazole described in the literature.[9] The signals in the ^{1}H NMR spectrum included two significant singlets at δ 9.40 and 8.80 for H-1 and H-4, respectively. The ^{13}C NMR spectrum disclosed six tertiary and five quaternary carbons including one characteristic signal (δ 139.0) indicating the presence of an ester group in the 3-position of dipyridoimidazole (**5b**). These findings prompted us to investigate the palladium-catalyzed iminoannulation of symmetrical and unsymmetrical alkynes bearing an ester function. The results are summarized in Scheme 2.

To our surprise, 3-monosubstituted compounds (**5b**) and (**5c**) were obtained by annulation of dimethyl and diethyl acetylenedicarboxylates, in conditions A and B. (Scheme 2; Table 1, Entries 5-7). The structural determination of **5c** is based on analogy with our previous heteroannulation results and comparison of spectral and physical data. [9]

Table 1 : β–Azacarbolines (**5a-e**) obtained by palladium-catalyzed iminoannulation of alkynes.



Entry	R—≡—R'		Cond.[a]	Reaction time (h)		Products[b]	R_1, R_2	Yields (%)	
	R	R'		From **3**	From **4**			From **3**	From **4**
1	CH_2OH	CH_2OH	A	4	5	**5a**	CH_2OH, CH_2OH	42	56
2	CH_2OH	CH_2OH	B	2.5	7	**5a**	CH_2OH, CH_2OH	38	57
3	H	CO_2Me	A	1.5	2.5	**5b**	H, CO_2Me	43	48
4	H	CO_2Me	B	2	2.5	**5b**	H, CO_2Me	32	48
5	CO_2Me	CO_2Me	A	5	6	**5b**	H, CO_2Me	63	23
6	CO_2Me	CO_2Me	B	4	4	**5b**	H, CO_2Me	35	30
7	CO_2Et	CO_2Et	A	8	2.5	**5c**	H, CO_2Et	10	25
8	Me	CO_2Me	A	2	3	**5d**	Me, CO_2Me	40	23
						5e	H, Me	10	ND[c]
9	Me	CO_2Me	B	1.5	3	**5d**	Me, CO_2Me	23	20
						5e	H, Me	ND[c]	ND[c]

a : condition A : base = Na_2CO_3, condition B : base = *n*-Bu_3N.

b : all products have been analyzed by ^{1}H, ^{13}C NMR and MS spectroscopy.

c : Not Detected.

When an unsymmetrical alkyne such as methyl 2-butynoate was used with bromoimine (**3**) in condition A, a 3,4-disubstituted compound (**5d**) was obtained as main product, with a decarboxylated product (**5e**) (Table 1, Entry 8). Surprisingly, with iodoimine (**4**) in condition B, the annulation of this same alkyne gave only regioisomer (**5d**) in low yields (Table 1, Entries 8-9). The regiochemistry of compound (**5d**) was confirmed by its NOESY spectrum. The NMR spectrum of **5e**[19] revealed a singlet at δ 7.57 and confirmed loss of the ester group. The presence of the methyl group in the 3-position was supported by HMBC ^{1}H-^{13}C cross-peaks between the proton H-1 (δ 9.10) and the two quaternary carbons C-3 (δ 149.1) and C-4a (δ 134.4). In addition, the upfield chemical shift at δ 104.4 was consistent with a methine carbon in the 4-position. It was noteworthy that no decarboxylation was observed in the indole system using unsymmetrical alkyne carboxylate.[16] This result suggested that the annulation produced the two regioisomers, but the isomer bearing an ester group in the 4-position underwent decarboxylation, producing compound (**5e**). We easily showed that the CO_2 formation occurred after the addition of the imine, which implies that decarboxylation occurred after the condensation of alkyne with the starting haloimine.

CONCLUSION

A palladium-catalyzed synthesis of substituted dipyridoimidazoles from various alkynes and *tert*-butylimines of 3-bromo(iodo)imidazo[1,2-*a*]pyridine-2-carbaldehydes was developed. When symmetrical alkyne carboxylates were employed, only 3-substituted compounds were isolated. With unsymmetrical alkyne carboxylates, only one regioisomer was observed in most cases.

EXPERIMENTAL

The plates were visualized with UV ligth (254 nm). Melting points were determined on an Electrothermal IA9300 (capillary) and are not corrected. NMR (400 MHz for ^{1}H or 100 MHz for ^{13}C) spectra were recorded on a Bruker Avance 400 spectrophotometer using $CDCl_3$ as solvent unless otherwise spectre specified. Chemical shifts are expressed in part per million (ppm) relative to tetramethylsilane (TMS). IR spectra were recorded on a FTIR Nicolet Impact 410. MS spectral analyses were performed on Hewlett-Packard 5985B instrument. All air-sensitive reactions were run under argon atmosphere. All solvent were dried using common techniques.

3-Iodoimidazo[1,2-*a*]pyridine-2-carbaldehyde (2):To a solution of imidazo[1,2-*a*]pyridine-2-carbaldehyde[14] (1.00 g, 6.85 mmol) in acetonitrile (25 mL), the *N*-iodosuccinimide (1.85 g, 8.22 mmol) was added portionwise. The reaction mixture was heated at reflux for 3 h. After cooling, the solvent was evaporated under reduced pressure, 20 mL of water was added and the solution was basified with Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (30 mL x 3), dried over Na_2SO_4, filtered and

evaporated under reduced pressure. The product was purified by chromatography on a alumina gel column eluated with CH_2Cl_2/EtOH (99/1, v/v) to give brown crystals (1.67 g, 90%). Rf = 0.68 (Al_2O_3/AcOEt/hexanes, 8/2, v/v). mp 161-163 °C (from EtOAc/hexanes: 9/1). IR (KBr, cm^{-1}) 1695, 1512, 1067, 852, 749. ^{1}H NMR δ 7.00 (t, 1H, *J* = 7 Hz, H-6), 7.30 (m, 1H, H-7), 7.58 (d, 1H, *J* = 9 Hz, H-8), 8.20 (d, 1H, *J* = 7 Hz, H-5), 10.10 (s, 1H, CHO). ^{13}C NMR δ 67.2 (C-3), 115.2 (C-6), 119.5 (C-8), 126.7 (C-7), 127.5 (C-5), 142.9 (C-2), 148.4 (C-8a), 187.0 (CHO). MS (m/z, %) 272 (M^+, 100), 244 (24), 116 (12), 90 (9), 78 (39), 51 (17). Anal. Calcd for $C_8H_5N_2OI$: C, 35.32; H, 1.85; N, 10.30. Found: C, 34.98; H, 1.45; N, 10.24.

General procedure for preparation of imines (3-4): To a solution of the appropriate carboxaldehyde (1.1 mmol) in dry CH_2Cl_2 (10 mL), a solution of *tert*-butylamine (0.17 mL, 1.64 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred at reflux for 4 h. Removal of the solvent afforded the imine.

(3-Bromoimidazo[1,2-*a*]pyridin-2-ylmethylene)-*tert*-butylamine (3): (0.31 g) as an oil; Rf = 0.43 (Al_2O_3/CH_2Cl_2). IR (CCl_4, cm^{-1}) 1697, 1650, 1520, 1358, 1226, 755. ^{1}H NMR δ 1.30 (s, 9H, 3xCH_3), 6.85 (t, 1H, *J* = 7 Hz, H-6), 7.18 (m, 1H, H-7), 7.59 (d, 1H, *J*= 9 Hz, H-8), 8.05 (d, 1H, *J* = 7 Hz, H-5), 8.40 (s, 1H, H-C=N). ^{13}C NMR δ 28.4 (3xCH_3), 58.4 (C-(CH_3)$_3$), 97.6 (C-3), 113.6 (C-6), 118.7 (C-8), 123.9 (C-5), 126.0 (C-7), 140.2 (C-2), 146.1(C-8a), 147.3 (H-C=N). MS (m/z, %) 281 [(M+2, 27)]$^+$, 279 (M^+, 27), 225 (43), 223 (60), 198 (43), 196 (43), 184 (35), 144 (22), 143 (20), 116 (12), 90 (27), 78 (100), 51 (48).

(3-Iodoimidazo[1,2-*a*]pyridin-2-ylmethylene)-*tert*-butylamine (4): (from compound **2**). (0.34 g). Rf =0.43 (Al_2O_3/CH_2Cl_2). IR (KBr, cm^{-1}) 1706, 1650, 1520, 1225, 725. ^{1}H NMR δ 1.30 (s, 9H, 3xCH_3), 6.84 (t, 1H, *J* = 6.5 Hz, H-6), 7.19 (m, 1H, H-7), 7.55 (d, 1H, *J* = 9 Hz, H-8), 8.09 (d, 1H, *J* = 6.5 Hz, H-5), 8.36 (s, 1H, H-C=N). ^{13}C NMR ($CDCl_3$) δ 29.8 (3xCH_3), 58.3 (C(CH_3)$_3$), 63.5 (C-3), 113.7 (C-6), 118.6 (C-8), 126.2 (C-5), 126.4 (C-7), 142.0 (C-2), 146.3 (C-8a), 146.4 (H-C=N). MS (m/z, %) 327 (M^+, 4), 312 (4), 272 (100), 244 (28), 116 (17), 78 (40), 51 (16).

General Procedure for the Palladium-Catalyzed Formation of Azacarbolines (5a-e): To a suspension of dry DMF (5 mL), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Na_2CO_3 (1 mmol, condition A) or *n*-Bu_3N (1 mmol, condition B) was added the appropriate alkyne (2 mmol). After stirring for 5 min at rt a solution of imine (1 mmol) in dry DMF (5 mL) was added and the contents heated in an oil bath at 125 °C for the indicate time. The completion of the reaction was established by the observation of the palladium black. The reaction mixture was cooled, diluted with ether (20 mL), washed with saturated aqueous NH_4Cl solution (30 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure and the product was purified by chromatography on a silica gel column eluated with $CHCl_3$/MeOH /NH_4OH (8/1/0.2, v/v/v).

3,4-Bis(hydroxymethyl)dipyrido[1,2-*a*;3',4'-*d*]imidazole (5a): Rf = 0.3 (SiO_2/$CHCl_3$/MeOH, 8/1, v/v). mp 161-163 °C (from $CHCl_3$, brown crystals). IR (KBr, cm^{-1}) 3250-3100, 2923, 1643, 1502, 1372, 1023, 1005. ^{1}H NMR (DMSO-d_6) δ 4.08 (d, 2H, *J* = 5.5 Hz, C$\underline{H}_2$-OH), 4.87 (d, 2H, *J* = 5 Hz, C$\underline{H}_2$-OH), 5.3 (t, 1H, *J* = 5 Hz, OH), 5.70 (t, 1H, *J* = 5.5 Hz, OH), 7.08 (t, 1H, *J* = 7 Hz, H-7), 7.65 (m, 1H, H-8), 7.75 (d, 1H, *J* = 9 Hz, H-9), 9.06 (s, 1H, H-1), 9.10 (d, 1H, *J* = 7 Hz, H-6). ^{13}C NMR (DMSO-d_6) δ 55.1 ($\underline{C}H_2$-OH), 63.3 ($\underline{C}H_2$-OH), 111.0 (C-7), 117.6 (C-9), 120.9 (C-4), 130.4 (C-6), 131.3 (C-8), 133.0 (C-4a), 140.3 (C-1), 140.5 (C-3), 148.2 (C-10a), 149.1 (C-9a). MS (m/z, %) 229 (M^+, 17), 211 (9), 200 (16), 198 (8), 183 (100), 170 (19), 168 (56), 155 (24), 78 (12), 51 (6). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.80; H, 4.44; N, 18.30.

Methyl dipyrido[1,2-*a*;3',4'-*d*]imidazole-3-carboxylate (5b): Rf = 0.71 **(**SiO_2/$CHCl_3$/MeOH, 8/1, v/v). mp 229-231 °C (from EtOAc/hexanes : 7/3, brown powder). IR (KBr, cm^{-1}) 1742, 1645, 1426, 1290, 1225, 1093. ^{1}H NMR δ 4.01 (s, 3H, CH_3), 7.05 (t, 1H, *J* = 7 Hz, H-7), 7.62 (m, 1H, H-8), 7.82 (d, 1H, *J* = 9 Hz, H-9), 8.60 (d, 1H, *J* = 7 Hz, H-6), 8.80 (s, 1H, H-4), 9.40 (s, 1H, H-1). ^{13}C NMR δ 53.1 (CH_3), 108.9 (C-4), 112.5 (C-7), 119.2 (C-9), 126.1 (C-6), 132.4 (C-8), 133.3 (C-4a), 139.0 (C-3), 143.1 (C-10a), 143.3 (C-1), 151.2 (C-9a), 166.2 (C=O). MS (m/z, %) 227 (M^+, 34), 169 (100), 141 (10), 78 (24), 51 (15). Anal. Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.30; H, 3.59; N, 18.40.

Ethyl dipyrido[1,2-*a*;3',4'-*d*]imidazole-3-carboxylate (5c): Rf = 0.68 **(**SiO_2/$CHCl_3$/MeOH, 8/1, v/v). mp 171-172 °C (from EtOAc/hexanes : 7/3 yellow powder) (lit.,[9] 172-174 °C). ^{1}H NMR δ 1.50 (t, 3H, *J* = 7 Hz, CH_3), 4.55 (q, 2H, *J* = 7 Hz, CH_2), 7.04 (t, 1H, *J* = 7 Hz, H-7), 7.64 (m, 1H, H-8), 7.81 (d, 1H, *J* = 9 Hz, H-9), 8.58 (d, 1H, *J* = 7 Hz, H-6), 8.79 (s, 1H, H-4), 9.40 (s, 1H, H-1). ^{13}C NMR δ 14.6 (CH_3), 62.1 (CH_2), 108.8 (C-4), 112.6 (C-7), 119.2 (C-9), 126.1 (C-6), 132.3 (C-8), 133.4 (C-4a), 138.8 (C-3), 143.1 (C-10a), 143.4 (C-1), 151.0 (C-9a), 165.8 (C=O).

Methyl 4-methyldipyrido[1,2-*a*;3',4'-*d*]imidazole-3-carboxylate (5d): Rf = 0,68 (SiO_2/$CHCl_3$/MeOH, 8/1, v/v). mp 100-102 °C (from EtOAc/hexanes : 7/3, yellow powder). IR (KBr, cm^{-1}) 1713, 1643, 1255, 1220, 1079; ^{1}H NMR δ 3.17 (s, 3H, CH_3), 4.03 (s, 3H, $CO_2C\underline{H}_3$), 6.98 (t, 1H, *J* = 7 Hz, H-7), 7.57 (m, 1H, H-8), 7.79 (d, 1H, *J* = 9 Hz, H-9), 8.89 (d, 1H, *J* = 7 Hz, H-6), 9.20 (s, 1H, H-1). ^{13}C NMR δ 15.0 (CH_3), 52.7 ($CO_2\underline{C}H_3$), 112.3 (C-7), 119.0 (C-9), 122.5 (C-4), 128.3 (C-6), 131.2 (C-8), 133.0 (C-4a), 139.0 (C-3), 141.0 (C-1), 141.8 (C-10a), 150.6 (C-9a), 167.0 (C=O). MS (m/z, %) 241 (M^+, 82), 226 (9), 209 (43), 183 (100), 182 (59), 181 (89), 155 (35), 78 (43), 51 (28). Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.32; H, 4.25; N, 17.03.

3-Methyldipyrido[1,2-*a*;3',4'-*d*]imidazole (5e) : Rf = 0.55 (SiO_2/$CHCl_3$/MeOH, 8/1, v/v). mp 155-157 °C (from EtOAc/hexanes : 7/3, white powder). IR (KBr, cm^{-1}) 2923, 2852, 1642, 1499, 1469. ^{1}H NMR δ 2.71 (s, 3H, CH_3), 6.81 (t, 1H, *J* = 7 Hz, H-7), 7.40 (m, 1H, H-8), 7.57 (s, 1H, H-4), 7.60 (d, 1H, *J* = 9.5 Hz, H-9), 8.30 (d, 1H, *J* = 7 Hz, H-6), 9.10 (s, 1H, H-1). ^{13}C NMR δ 24.6 (CH_3), 104.4 (C-4), 111.4 (C-

7), 119.2 (C-9), 125.8 (C-6), 130.8 (C-8), 134.4 (C-4a), 139.4 (C-10a), 142.8 (C-1), 149.1 (C-9a), 149.2 (C-3). MS (m/z, %) 183 (100), 155 (23), 78 (17), 51 (9). Anal. Calcd for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.95. Found: C, 72.01; H, 4.55; N, 22.65.

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