Synthesis of Tetracyclic 5-Azaindole Analogues by Palladium-Catalyzed Sequential Annulation

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Tetracyclic 5-azaindole analogues were prepared by palladium-catalyzed sequential annulation of benzylidene(3-iodopyridinyl-4-yl)amine and 1-aryl substituted internal alkynes under $Pd(OAc)_2$, *n*-Bu_4NCl, and Et_3N at 120 °C. The synthetic procedure showed possible diversification of tetracyclic 5-azaindole analogues by varying the 1-aryl substituent in internal alkynes.

Key Words : Tetracyclic 5-azaindole analogues, Palladium, Catalyst, Annulation, 1-Aryl alkynes

Introduction

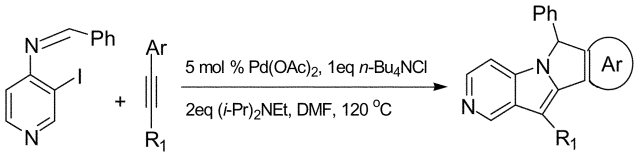
Heteroannulated indole and quinoline alkaloids constitute an important class of natural compounds due to their biological activities, which are based mostly on their affinity toward DNA.[1,2] Therefore, these compounds play crucial roles as potential leads for the discovery of biologically active substances.[3] Although isosteric replacements of tetracyclic indole derivatives have strong antibacterial, antimycotic, and antitumor activities,[4] few synthetic methods for tetracyclic azaindole analogues have been reported in the literature.[5,6] Recently, our group and Larock's group have reported effective annulation methods[7] using internal alkynes to prepare a variety of condensed heterocycles, such as indoles,[8] isoindolo[2,1-*a*]indoles,[9] carbolines,[10] azaindoles,[11] pyrroloquinolines,[12] and pyridopyrrolo[2,1-*a*]isoindoles.[13] Our continued interest is to find prospective bioactive heteroannulated indole analogues. Chemical isosteric replacements of biologically active substances often have improved biological properties, such as potency, selectivity, toxicity, and metabolic stability.[14] In this paper, we describe the facile preparation of tetracyclic 5-azaindole analogues using palladium-catalyzed annulation with internal alkynes.

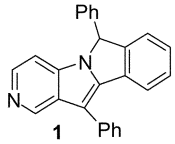
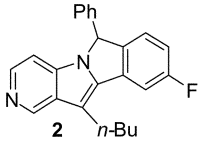
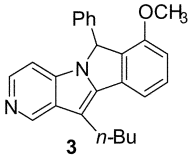
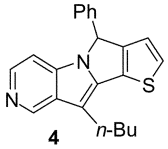
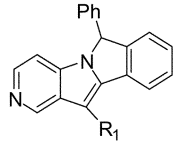
Results and Discussion

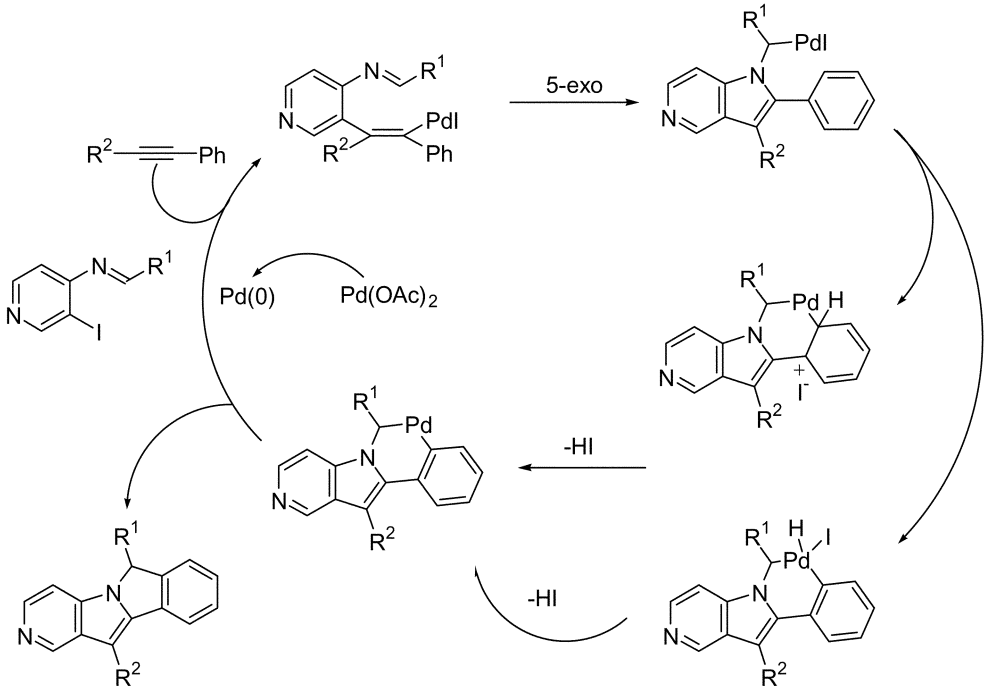
We examined the palladium-catalyzed reaction of benzylidene(3-iodopyridin-4-yl)amine with various 1-aromatic substituted internal alkynes under 5 mol % $Pd(OAc)_2$, 1 eq *n*-Bu_4NCl, 2 eq (*i*-Pr)$_2$NEt, and DMF, at 120 °C. The reactions of benzylidene(3-iodopyridin-4-yl)amine with various functionalized internal alkynes provided reasonable yields of tetracyclic 5-azaindole analogues. The results are summarized in Table 1.

The effect of substituents on the aryl group was first examined with several different aryl internal alkynes (entries 1-4). The reaction using the 3-fluorophenyl internal alkyne provided a somewhat higher yield of the desired product as compared to the reaction using 3-methoxyphenyl internal alkyne. However, the total reaction time was quite dependent

Table 1. Synthesis of tetracyclic 5-azaindole analogues by palladium-catalyzed annulation



Entry	Ar	R_1	Product	Reaction time (h)	Isolated yields (%)
1	Ph	Ph	 **1**	8	68
2	3-FPh	*n*-Bu	 **2**	24	45
3	3-CH_3OPh		 **3**	12	34
4	2-Thiophene	*n*-Bu	 **4**	24	20
5	Ph	CH_3	 **5** (R_1 = CH_3)	10	55
6	Ph	CH_2CH_2OH	**6** (R_1 = CH_2CH_2OH)	20	43
7	Ph	CH_2OCH_3	**7** (R_1 = CH_2OCH_3)	20	51
8	Ph	CO_2Et	**8** (R_2 = CO_2Et)	27	45



Scheme 1

on the substituent in the phenyl group. Although single tetracyclic 5-azaindole analogues were obtained from the reactions using meta-substituted phenyl internal alkynes, the regioselectivity of the second annulation was quite dependent on the phenyl substituent. Conversely, the reaction using 1-(2-thiophenyl)-1-hexyne provided 20% of the tetracyclic product owing to deactivation of the palladium catalyst. Finally, the reactions using various alkyl-substituted 1-aryl internal alkynes afforded moderate yields of tetracyclic 5-azaindole analogues (entries 5-8). Considering previous annulation results,[8,12] the annulation might proceed *via* the route illustrated in Scheme 1. The actual catalyst Pd(0) could be formed from $Pd(OAc)_2$ by the reaction medium. Pd(0) reacts with aryl halides *via* oxidative addition. The aryl-palladium complex coordinates and adds the triple bond of an internal alkyne.

The resulting vinyl palladium intermediate adds the carbon-nitrogen double bonds sequentially. The tetracyclic 5-azaindole analogues are formed by either electrophilic palladation of the resulting π-palladium intermediate onto the adjacent aromatic ring or oxidative addition of the neighboring aryl carbon-hydrogen bond of the aromatic ring to the π-palladium intermediate to form a Pd intermediate, with sequential elimination of HI by the base, and regeneration of the Pd(0) catalyst by reductive elimination.

Conclusion

The palladium-catalyzed annulation of benzylidene(3-iodopyridin-4-yl)amine with aryl substituted internal alkynes provided tetracyclic 5-azaindole analogues in moderate yields. The annulation reaction showed possible diversification of tetracyclic 5-azaindole analogues with various aryl imines and internal alkynes.

Experimental Section

IR spectra were obtained using a JASCO FT-IR 410 spectrometer. All the ^{1}H- and ^{13}C-NMR spectra were recorded on a JNM-AL 400-MHz spectrometer at Chungnam National University. Chemical shifts are given as values relative to tetramethylsilane (TMS) as an internal standard. The GC/MS spectra were obtained on a Shimadzu QP 1000. Melting points were determined on a Mut-TEM apparatus and are uncorrected. Microanalyses were performed at Chungnam National University with a CE Instrument EA 1110. The products were purified by flash chromatography on 230-400-mesh ASTM 60 silica gel. All the bases, *n*-Bu_4NCl, and palladium species were purchased from Aldrich Chemical Co. The other chemicals were used as obtained from commercial sources, unless otherwise noted.

General procedure for the synthesis of the aryl alkynes[9b]**.** To a solution of an iodo- or bromoarene (10.0 mmol) and a terminal alkyne (12.0 mmol) in Et_3N (40 mL) was added $PdCl_2(PPh_3)_2$ (140 mg, 2 mol %) in Et_3N (40 mL). The mixture was then stirred for 5 min, and CuI (20 mg, 1 mol %) was added. The resulting mixture was heated under a nitrogen atmosphere at 50 ºC. The reaction mixture was allowed to cool to rt, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure, and then the residue was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the pure alkynes.

Preparation of benzylidene(3-iodo-pyridin-4-yl)amine. A mixture of 4-amino-3-iodopyridine[15] (1.2 g, 5.5 mmol), benzaldehyde (0.58 g, 5.5 mmol), and a molecular sieve (1

g) in benzene (40 mL) was refluxed for 24 h using the Dean-Stark apparatus to remove the water produced. The reaction mixture was monitored by TLC to establish completion. The reaction mixture was then cooled to rt, and the solvent was removed under reduced pressure. The oily residue was dissolved in a minimal amount of ethanol and cooled. The resulting solid was collected to afford 1.23 g (73%) of the imine as a yellow solid. mp 96-97 °C; IR (KBr) 1644 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.81 (s 1H, -N=CH-), 8.43 (d, J = 4.8 Hz, 1H Ar-H), 8.22 (s, J = 4.8 Hz, 1H, ArH), 7.94-7.92 (m, 1H, ArH), 7.52-7.47 (m, 4H, ArH), 6.83 (d, J = 4.8 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$) δ 162.8, 159.7, 157.1, 149.9, 134.7, 132.4, 129.4, 129.2, 128.7, 113.8; MS (EI) (*m/z*) 309 (M^++1, 11), 308 (M^+, 79), 204 (17), 181 (56), 91 (31), 77 (23), 43 (100); Anal. Calcd for $C_{12}H_9N_2I$: C, 46.78; H, 2.94; N, 9.09. Found: C, 46.81; H, 2.90; N, 9.05.

General procedure for the synthesis of tetracyclic 5-azaindole derivatives by palladium-catalyzed annulation. Palladium acetate (6 mg, 0.025 mmol), *n*-Bu_4NCl (139 mg, 0.5 mmol), Et_3N (101 mg, 1.0 mmol), benzylidene(3-iodo-pyridin-4-yl)amine (154 mg, 0.5 mmol), diphenylacetylene (178 mg, 1.0 mmol), and DMF (10 mL) were added to a pressure tube equipped with a stirring bar. After heating the reaction mixture for 11 h at 120 °C, the resulting solution was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography using hexane-ethyl acetate (1 : 1). 6,11-Diphenyl-6*H*-pyrido[3',4':4,5]pyrrolo-[2,1-*a*]isoindole (**1**) (120 mg, 67%) was obtained as a yellow solid. mp 149-150 °C; IR (KBr) 3025, 1602, 1455 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.04 (s, 1H, ArH), 8.13 (d, J = 5.6 Hz, 1H, ArH), 7.83 (d, J = 7.6 Hz, 1H, ArH), 7.74 (d, J = 4.8 Hz, 2H, ArH), 7.37 (t, J = 7.3 Hz, 1H, ArH), 7.29-7.24 (m, 3H, ArH), 7.22-7.08 (m, 5H, ArH), 6.75 (d, J = 6.0 Hz, 1H, ArH), 5.98 (s, 1H, ArCH); ^{13}C-NMR ($CDCl_3$) δ 147.9, 142.2, 140.9, 139.6, 137.6, 136.5, 133.2, 130.4, 128.9, 128.8, 129.0, 128.9, 128.5, 128.2, 128.2, 126.8, 123.8, 121.0, 109.0, 104.9, 63.9; MS (EI) (*m/z*) 358 (M^+, 100), 281 (55), 64 (17); Anal. Calcd for $C_{26}H_{18}N_2$: C, 87.12; H, 5.06; N, 7.82. Found: C, 87.09; H, 5.07; N, 7.83.

The following compounds were obtained using the above general procedure.

11-*n*-Butyl-9-fluoro-6-phenyl-6*H*-pyrido[3',4':4,5]pyrrolo-[2,1-*a*]isoindole (2). The compound (**2**) was obtained as brown oil in 45% yield with a 24 h reaction (Table1, entry 2). IR (KBr) 3029, 1604, 1467 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.81 (s, 1H, ArH), 8.00 (s, 1H, ArH), 7.48 (d, J = 7.2 Hz, 1H, ArH), 7.36-7.20 (m, 4H, ArH), 7.07-6.09 (m, 2H, ArH), 6.86-6.81 (m, 2H, ArH), 5.99 (s, 1H, ArCH), 2.98 (d, J = 7.6 Hz, 2H, CH_2), 1.71 (q, 2H, CH_2), 1.39 (m, 2H, CH_2), 0.89 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 162.9, 142.6, 142.1, 140.2, 137.8, 136.6, 132.9, 131.0, 128.9, 128.6, 126.9, 125.2, 117.1, 114.5, 114.2, 108.3, 108.1, 63.7, 33.2, 24.1, 22.6, 14.0; MS (EI) (*m/z*) 356 (M^+, 6), 313 (22), 149 (13), 70 (18), 43 (100); Anal. Calcd for $C_{24}H_{21}N_2F$: C, 80.87; H, 5.94; N, 7.86. Found: C, 80.85; H, 5.96; N, 7.86

11-*n*-Butyl-7-methoxy-6-phenyl-6*H*-pyrido[3',4':4,5]-pyrrolo[2,1-*a*]isoindole (3). The compound (**3**) was obtained as yellow solid in 34 % yield with a 12 h reaction (Table 1, entry 3). mp = 150-151 °C; IR (KBr) 2928, 1466 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H, ArH), 8.10 (d, J = 5.6 Hz, 1H, ArH), 7.33-7.30 (m, 3H, ArH), 7.11-7.09 (m, 2H, ArH), 6.79-6.74 (m, 2H, ArH), 6.04 (s, 1H, ArCH), 3.87 (s, 3H, OCH_3), 3.09 (t, J = 7.6 Hz, 2H, CH_2), 1.82 (q, J = 7.6 Hz, 2H, CH_2), 1.49 (m, 2H, CH_2), 0.99 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 160.1, 142.9, 140.6, 139.8, 139.2, 138.6, 136.6, 132.6, 129.7, 129.1, 128.5, 126.9, 124.7, 113.1, 108.1, 106.8, 104.8, 63.7, 55.5, 33.3, 24.1, 22.6, 14.0; MS (EI) (*m/z*) 368 (M^+, 27), 325 (100), 293 (26), 281 (17), 205 (13), 140 (11); Anal. Calc. for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.46; H, 6.59; N, 7.61

Compound 4. The compound (**4**) was obtained as brown oil in 20% yield with with a 24 h reaction (Table 1, entry 4). IR (KBr) 3041, 2925, 1552, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H, ArH), 8.07 (d, J = 5.6 Hz, 1H, ArH), 7.35-7.32 (m, 4H, ArH), 7.18-7.14 (m, 2H, ArH), 6.88 (d, J = 4.8 Hz, 1H, ArH), 6.75 (d, J = 5.6 Hz, 1H, ArH), 6.10 (s, 1H, $ArCH_2$), 2.95 (t, J = 7.6 Hz, 2H, CH_2), 1.84 (q, J = 7.6 Hz, 2H, CH_2), 1.46 (m, 2H, CH_2), 0.99 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 141.7, 139.8, 137.7, 137.2, 129.6, 129.1, 128.6, 128.4, 126.8, 126.7, 125.8, 121.3, 107.3, 105.5, 104.9, 63.3, 32.6, 24.6, 22.7, 14.1; MS (EI) (*m/z*) 344 (M^+, 17), 301 (40), 149 (10), 105 (15), 43 (100); Anal. Calcd for $C_{22}H_{20}N_2S$: C, 76.71; H, 5.85; N, 8.13. Found: C, 76.69; H, 5.83; N, 8.15.

11-Methyl-6-phenyl-6*H*-pyrido[3',4':4,5]pyrrolo[2,1-*a*]-isoindole (5). The compound (**5**) was obtained as a yellow solid in 55% yield with a 10 h reaction (Table 1, entry 5). mp 162-163 °C; IR (KBr) 2916, 1449 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.26 (s, 1H, ArH), 8.18 (d, J = 5.6 Hz, 1H, ArH), 7.84 (d, J = 7.6 Hz, 1H, ArH), 7.48-7.43 (m, 2H, ArH), 7.33-7.26 (m, 5H, ArH), 7.14-7.12 (m, 2H, ArH), 6.15 (s, 1H, ArCH), 2.58 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 147.3, 143.0, 138.4, 138.3, 138.2, 132.6, 131.4, 130.1, 129.2, 128.7, 128.5, 128.0, 127.0, 124.1, 121.5, 113.9, 101.7, 64.6, 8.8; MS (EI) (*m/z*) 297 (M^++1, 12), 296 (M^+, 100), 219 (39), 146 (14); Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.07; H, 5.46; N, 9.47.

11-Hydroethyl-6-phenyl-6*H*-pyrido[3',4':4,5]pyrrolo[2,1-*a*]isoindole (6). The compound (**6**) was obtained as a yellow solid in 43% yield with a 20 h reaction (Table 1 entry 6). mp = 145-148 °C; IR (KBr) 3397, 2924, 2854 cm^{-1}; ^{1}H NMR (DMSO) δ 8.95 (s, 1H, ArH), 8.09 (d, J = 5.2 Hz, 1H, ArH), 7.95 (d, J = 7.2 Hz, 1H, ArH), 7.56 (d, J = 5,2 Hz, 2H, ArH), 7.29-7.27 (m, 4H, ArH), 7.13 (d, J = 5.6 Hz, 2H, ArH), 6.82 (d, J = 6.0 Hz, ArH), 6.47 (s, 1H, $ArCH_2$), 4.97 (br, 1H, -OH), 3.83 (t, J = 7.2 Hz, 2H, CH_2), 3.27 (t, J = 6.8 Hz, 2H, CH_2OH); ^{13}C NMR (DMSO) δ 146.8, 142.5, 140.4, 139.9, 138.5, 135.7, 130.5, 129.0, 128.9, 128.5, 128.4, 128.1, 127.7, 126.7, 124.0, 121.3, 103.9, 63.1, 61.7, 27.9; MS (EI) (*m/z*) 326 (M+, 26), 295 (100), 218 (8), 147 (8); Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.94; H, 5.58; N, 8.58.

11-Methoxymethyl-6-phenyl-6*H*-pyrido[3',4':4,5]pyrrolo-[2,1-*a*]isoindole (7). The compound (**7**) was obtained as a yellow solid in 51% yield with a 20 h reaction. mp = 134-135 °C; IR (KBr) 2930, 1454 cm^{-1}; ^1H NMR (DMSO) δ 8.94 (s, 1H, Ar-H), 8.07 (d, J = 6.0 Hz, 1H, ArH), 8.01 (d, J = 7.6 Hz, 1H, ArH), 7.48 (t, 1H, ArH), 7.37-7.28 (m, 5H, ArH), 7.13-7.11 (m, 2H, ArH), 6.85 (d, J = 6.0 Hz, 1H, ArH), 6.58 (s, 1H, ArCH), 4.97 (s, 2H, CH_2O), 3.38 (s, 3H, OCH_3); ^{13}C NMR (DMSO) δ 147.3, 142.6, 141.7, 140.4, 138.2, 135.7, 129.8, 128.9, 128.7, 128.6, 128.4, 128.3, 126.7, 124.1, 122.1, 105.1, 103.0, 63.9, 63.3, 56.9; MS (EI) (*m/z*) 326 (M^+, 50), 295 (100), 147 (26), 77 (14), 51 (10); Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.94; H, 5.57; N, 8.59.

6-Phenyl-6*H*-pyrido[3',4':4,5]pyrrolo[2,1-*a*]isoindole-11-carboxylic acid ethyl ester (8). The compound (**8**) was obtained as a brown solid in 45% yield with a 27 h reaction. mp = 152-155 °C; IR (KBr) 1684 cm^{-1}; ^1H NMR (DMSO) δ 8.68 (d, J = 7.6 Hz, 1H, ArH), 8.60 (d, J = 7.6 Hz, 1H, ArH), 8.19 (s, 1H, ArH), 8.01 (d, J = 5.6 Hz, 1H, ArH), 7.59 (t, J = 7.2 Hz, 1H, ArH), 7.51 (t, J = 7.2 Hz, 1H, ArH), 7.41-7.31 (m, 3H, ArH), 7.23 (d, J = 7.2 Hz, 1H, ArH), 7.19-7.15 (m, 2H, ArH), 6.74 (s, 1H, $ArCH_2$), 4.47 (q, J = 7.2 Hz, 2H, OCH_2), 1.47 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (DMSO) δ 164.2, 150.9, 147.8, 141.1, 136.1, 129.8, 129.1, 129.0, 128.7, 128.6, 128.5, 128.2, 127.4, 126.7, 125.6, 125.2, 123.2, 64.6, 60.1, 49.8, 14.4; MS (EI) (*m/z*) 355 (M^++ 1, 34), 354 (M^+, 100), 325 (58), 309 (29), 282 (38), 281 (46), 140 (23), 126 (20).

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