JOC Article

Regioselectivity on the Palladium-Catalyzed Intramolecular Cyclization of Indole Derivatives

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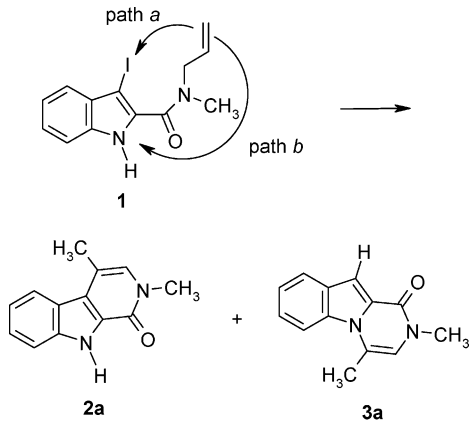
Indole 2-carboxamide derivatives **4** underwent palladium-catalyzed intramolecular cyclization reactions to afford β-carbolinones or pyrazino[1,2-*a*]indoles according to different reaction pathways. The complete regioselectivity of the reactions was obtained in different reaction conditions.

Catalysis by palladium complexes has proven particularly useful in organic synthesis[1] and is successfully applied to the synthesis of complex organic molecules.[2]

During our studies on the reactivity of indole derivatives in the intramolecular Heck reaction, we planned a synthetic route to β- and γ-carbolinones. The intramolecular Heck reaction afforded very good yields of β-carbolinones, by using 3-iodo-1-methoxymethyl-1*H*-indole-2-carboxamide derivatives as starting materials, and of γ-carbolinones starting from 2-iodo-1-methoxymethyl-1*H*-indole-3-carboxamide derivatives.[3] The first attempt to obtain β-carbolinones by intramolecular Heck reaction was carried out on the 3-iodo-1*H*-indole-2-carboxylic acid allylamide **1**. Besides the expected product **2a** derived from the Heck cyclization, we observed the formation of the pyrazino[1,2-*a*]indole derivative **3a**, leaking the iodine atom in position 3, and arising from an intramolecular amination reaction between the indole nitrogen atom and the double bond of the allylic chain (Scheme 1). This unexpected result could be explained by considering the known instability of 3-iodoindoles.[4] In light of the rising interest in the pyrazino[1,2-*a*]indole system[5] due to its therapeutical use as serotonin antagonist and thrombolytic and in a variety of cardiovascular diseases, our goal was to favor the intramolecular cyclization reaction of indole-2-carboxylic acid allylamide, improving the formation of the pyrazino[1,2-*a*]indole skeleton. Reported synthetic routes to this ring system use the condensation of indole-2-carboxylates and *N*-alkylamino acid ethyl esters[6] or *N*-alkylamino alcohol, as well as the reduction and cyclization of 1-(2-nitrophenyl)-indole-2-carboxylates or 1-(2-nitroalkenyl)-indoline-2-carboxylates.[7] Diketopiperazines were prepared by dimerization of indole-2-carboxylic acids.[8] Compared to C−C bond forming reaction, the C−N bond formation is still immature. Moreover, new amination methodologies will have a direct impact on pharmaceutical and fine chemical industries for the synthesis of a variety of commercially interesting compounds.

SCHEME 1



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SCHEME 2

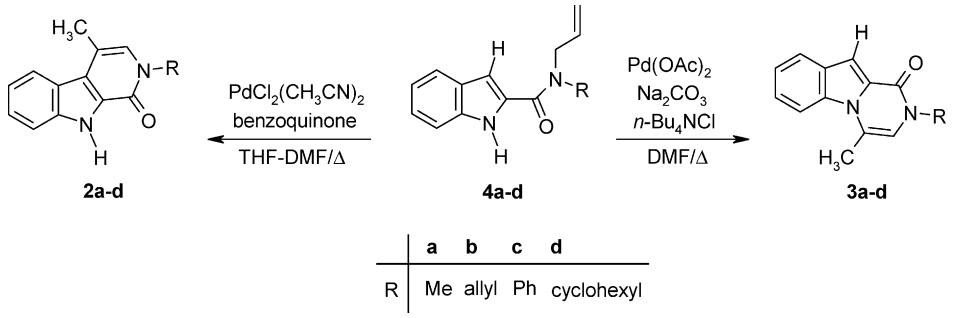

TABLE 1. Reaction Conditions for Cyclization of Compound 4a

entry	catalyst[a]	solvent	base[b]	salt/oxidant[c]	temp (°C)	time (h)	yield (%) 4a	2a	3a
1	$Pd(OAc)_2/Ph_3P$	DMF	AcOK	Pr_4NBr	90	5	35		40
2	$Pd(OAc)_2$	DMA	$NaHCO_3$	Bu_4NCl	90	8	15		55
3	$Pd(OAc)_2$	DMF	Na_2CO_3	Bu_4NCl	100	5			74
4	$Pd(Ph_3P)_4$	THF			65	2	99		
5	$Pd(Ph_3P)_4$	DMF	Na_2CO_3	Bu_4NCl	95	4			67
6	$PdCl_2(CH_3CN)_2$	THF	Na_2CO_3	BQ/LiCl	65	5		60	22
7	$PdCl_2(CH_3CN)_2$	THF		BQ/LiCl	65	24		76	22
8	$PdCl_2(CH_3CN)_2$	DMF/THF		BQ	80	1		98	

[a] $Pd(OAc)_2$, 5 mol %; $PdCl_2(CH_3CN)_2$ and $Pd(Ph_3P)_4$, 10 mol %. [b] Na_2CO_3, 1 equiv; $NaHCO_3$, 3 equiv. [c] BQ and Bu_4NCl, 1 equiv; LiCl, 5 equiv.

Aiming at the selective formation of pyrazino[1,2-*a*]-indole **3a**, the 1*H*-indole-2-carboxylic acid allylmethylamide (**4a**)[9] was reacted with a catalyst system containing $Pd(OAc)_2$ (10 mol %), Ph_3P (15 mol %), tetrapropylammonium bromide (Pr_4NBr) (1.0 equiv), and AcOK (4.0 equiv), in DMF at 90 °C for 5 h. In these conditions compound **3a** was exclusively formed in 40% yield, while 35% of the starting material was recovered (Scheme 2). A variety of conditions were screened to improve the yield of the amination reaction, taking **4a** as a probe. The results are summarized in Table 1. We noticed that the presence of base and tetraalkylammonium salt was crucial to obtain pyrazino[1,2-*a*]indole derivative **3a** in satisfactory yields (entries 1−5). The best yield was achieved by running the reaction with $Pd(OAc)_2$, tetrabutylammonium chloride (Bu_4NCl), and Na_2CO_3 in DMF as solvent at 100 °C for 5 h (entry 3).

When using $PdCl_2(CH_3CN)_2$ as catalyst and benzoquinone (BQ) as reoxidant, according to the conditions reported in the literature for amination reactions,[10] the reaction switched to the alternative cyclization path, giving *β*-carbolinone **2a** as the predominant or exclusive product (entries 6−8). Such a cyclization is explained through an oxidative addition process to form a C−C bond as reported previously.[9] Thus, different results could be obtained in different reaction conditions. The trend for the complete regioselectivity of the reaction was confirmed on the related substrates **4b**−**d** which gave products **3b**−**d** or, under different reaction conditions, products **2b**−**d**.

The process described here represents an intramolecular palladium-catalyzed amination of a double bond. This method was used to synthesize indoles and other aromatic and nonaromatic nitrogen heterocycles.[10] A similar procedure was useful to obtain pyrrolidine and pyrroline derivatives.[11] The role of palladium relies upon its ability to orient and to activate suitable substrates by coordination, and then to mediate further reactions deriving from these activated species.

In the literature two possible mechanisms for this reaction are suggested. Although we cannot rule out the possibility of a coordinative binding of the olefin to the central atom of the electron-poor metal complex followed by direct attack of the amine, our results suggest an alternative mechanism. We propose the preliminary activation of the N−H bond, by way of oxidative addition of the indolo moiety R_2NH to the coordinatively unsaturated metal center in a low oxidation state.[12] The reaction produces a hydrido−amido complex H−[Pd]−NR_2. The formation of amido complexes directly from amines has seldom been observed, and confirmed reports of oxidative additions of R_2N−H to a coordinatively unsaturated metal center are rare.[13] Then, the reaction occurs at the Pd−N bond with the insertion of the olefin, generating a 2-aminoalkyl complex (**a**) (Scheme 3). The most common decomposition of the latter is by *β*-hydride elimination, leading to an unsaturated amine as the oxidative amination product. Probably, dehydrogenation reaction takes place to convert the resulting dihydride metal species into

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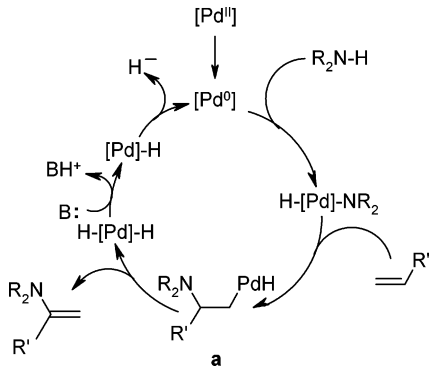
SCHEME 3



the active catalyst species, but there is no experimental evidence for this reaction. The base and the tetrabutylammonium chloride salt are essential to assist in the regeneration of zerovalent palladium catalyst, and several possible mechanisms could be envisaged.[14] The salt might act as a stabilizing agent by its chlorine anion when there is no phosphine ligand in the reaction mixture and as an accelerating agent by its onium cation.

In conclusion, in this paper we describe a catalytic approach to aminations of nonactivated double bonds which are still rare reactions. Furthermore, we have demonstrated a high regioselectivity in a palladium-catalyzed reaction of indole derivatives and focused on a very efficient method to synthesize β-carbolinones **2** and pyrazino[1,2-*a*]indole derivatives **3**. Starting from olefin derivatives of different nitrogen heterocycles, further developments in this area are foreseen.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in Nujol mull for solids and as a liquid film for oils. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution unless otherwise stated. Chemical shifts are given in parts per million downfield from $SiMe_4$. Colum chromatography was performed on Kieselgel 60, 0.063−0.2 mm.

Reaction of 3-Iodo-1*H*-indole-2-carboxylic Acid Allylmethylamide (1). To a solution of **1** (340 mg, 1 mmol) in DMF (4 mL) were added AcOK (393 mg, 4 mmol), $Pd(OAc)_2$ (11 mg, 5 mol %), and tetrapropylammonium bromide (266 mg, 1 mmol), Ph_3P (39 mg, 15 mol %), and the mixture was heated at 90 °C with stirring for 5 h. The mixture was then washed with brine and extracted with Et_2O (2 × 20 mL). The organic layer was dried with Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluent CH_2Cl_2/Et_2O, 1:1, to afford **2a** (62%) and **3a** (17%).

Synthesis of β-Carbolinones 2a−d: General Procedure. To a solution of **4a−d** (1 mmol) in DMF (6 mL) and THF (12 mL) were added $PdCl_2(CH_3CN)_2$ (26 mg, 10 mol %) and benzoquinone (108 mg, 1 mmol) under N_2. The mixture was stirred for 45 min at 80 °C and then concentrated in vacuo, and the residue was poured into brine to give the β-carbolinones **2a−d**. The filtrate was extracted with Et_2O (2 × 20 mL) and the solvent evaporated to give a residue which was chromatographed on a silica gel column, eluent Et_2O, to give an additional amount of compounds **2a−d**.

Data for 2a. Yield: 98%. Mp: 295 °C dec from CH_2Cl_2. ^{1}H NMR (acetone-d_6): δ 2.60 (d, J = 0.7 Hz, 3H), 3.66 (s, 3H), 7.08 (d, J = 0.7 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 11.8 (br s, exch with D_2O, 1H). ^{13}C NMR (DMSO): δ 16.9, 36.4 (CH_3), 113.3, 120.4, 123.0, 126.5, 127.6 (CHAr), 111.4, 123.2, 124.1, 128.1, 140.0, 155.4 (C). IR: 3150, 1651, 1589 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.55; H, 5.86; N, 13.07.

Data for 2b. Yield: 88%. Mp: 202−205 °C dec from CH_2Cl_2. ^{1}H NMR: δ 2.65 (d, J = 0.7 Hz, 3H), 4.86 (d, J = 5.5 Hz, 2H), 5.25 (dd, J = 1.5, 16.8 Hz, 1H), 5.33 (dd, J = 1.5, 10.2 Hz, 1H), 6.04 (ddt, J = 10.2, 16.8, 5.5 Hz, 1H), 6.89 (d, J = 0.7 Hz, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 10.95 (br s, exch with D_2O, 1H). ^{13}C NMR: δ 16.9 (CH_3), 50.6 (CH_2), 113.2, 120.5, 122.5, 124.6, 126.5 (CHAr), 117.9 (CH_2=), 133.4 (CH=), 113.9, 122.9, 125.1, 127.7, 140.3, 155.1 (C). IR: 3100, 1645, 1589 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.51; H, 6.11; N, 11.75.

Data for 2c. Yield: 80%. Mp: >320 °C from CH_2Cl_2. ^{1}H NMR (DMSO): δ 2.55 (d, J = 1.1 Hz, 3H), 7.14 (d, J = 1.1 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 7.40−7.52 (m, 6H), 7.57 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 12.16 (br s, exch with D_2O, 1H). ^{13}C NMR (DMSO): δ 17.0 (CH_3), 112.3, 124.4, 127.6, 127.8, 140.3, 142.0, 155.1 (C), 113.6, 120.8, 123.2, 127.0, 127.3, 128.6 (CHAr), 128.1, 129.9 (2CHAr). IR: 3416, 1666, 1456 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.74; H, 5.23; N, 10.12.

Data for 2d. Yield: 94%. Mp: 241−243 °C from Et_2O. ^{1}H NMR: δ 1.45 (m, 2H), 1.67 (m, 4H), 2.01 (m, 4H), 2.66 (s, 3H), 5.19 (m, 1H), 6.96 (s, 1H), 7.26 (t, J = 7.0 Hz, 1H), 7.50 (t, J = 7.0 Hz, 1H), 7.65 (d, J = 7.0 Hz, 1H), 8.11 (d, J = 7.0 Hz, 1H), 10.56 (br s, exch with D_2O, 1H). ^{13}C NMR: δ 17.4 (CH_3), 25.9 (CH_2), 26.4, 33.2 ($2CH_2$), 54.0 (CH), 113.2, 123.2, 124.1, 126.1, 140.2, 155.1 (C), 112.9, 120.1, 121.1, 122.7, 126.3 (CHAr). IR: 3106, 1651, 1582 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.00; H, 7.26; N, 9.86.

Synthesis of 2,4-Disubstituted 2*H*-Pyrazino[1,2-*a*]indol-1-ones 3a−d: General Procedure. To a solution of **4a−d** (1 mmol) in DMF (5 mL) were added $Pd(OAc)_2$ (12 mg, 5 mol %), tetrabutylammonium chloride (276 mg, 1 mmol), and Na_2CO_3 (106 mg, 1 mmol). The mixture was heated at 100 °C with stirring for the reported time. After completation of the reaction the mixture was washed with brine and extracted with Et_2O (2 × 20 mL). The organic layer was dried with Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography to give compounds **3a−d** (eluent see below).

Data for 3a. Reaction time: 5.30 h. Eluent: CH_2Cl_2. Yield: 74%. Mp: 183 °C from Et_2O−hexane. ^{1}H NMR: δ 2.77 (d, J = 1.1 Hz, 3H), 3.50 (s, 3H), 6.08 (d, J = 1.1 Hz, 1H), 7.30−7.40 (m, 2H), 7.51 (s, 1H), 7.85 (d, J = 7.3 Hz, 1H), 8.02 (d, J = 7.3 Hz, 1H). ^{13}C NMR: δ 18.3, 34.6 (CH_3), 104.1 (CH=), 113.8, 114.1, 122.3, 122.9, 124.0 (CHAr), 118.5, 128.9, 129.3, 134.1, 157.0 (C). IR: 1640, 1463 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.51; H, 5.68; N, 13.34.

Data for 3b. Reaction time: 2 h. Eluent: hexanes−Et_2O, 1:1. Yield: 77%. Mp: 142−145 °C from Et_2O−hexane. ^{1}H NMR: δ 2.77 (s, 3H), 4.54 (dd, J = 1.1, 5.9 Hz, 2H), 5.26 (dd, J = 1.5, 14.7 Hz, 1H), 5.27 (dd, J = 1.5, 11.3 Hz, 1H), 5.94 (m, 1H), 6.07 (s, 1H), 7.34 (m, 2H), 7.53 (s, 1H), 7.86 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H). ^{13}C NMR: δ 18.5 (CH_3), 48.7 (CH_2), 104.7, 112.2, 114.1, 122.3, 123.0, 124.2 (CHAr), 132.9 (CH=), 118.5 (CH_2=), 118.8, 128.9, 129.3, 134.1, 156.5 (C). IR:1651, 1582 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.02; H, 5.78; N, 11.84.

Data for 3c. Reaction time: 36 h. Eluent: hexanes−Et_2O, 1:3. Yield: 65%. Mp: 150−153 °C from Et_2O−hexane. ^{1}H NMR: δ 2.81 (s, 3H), 6.32 (s, 1H), 7.33−7.46 (m, 3H), 7.48−7.56 (m, 4H), 7.61 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H). ^{13}C NMR: δ 18.6 (CH_3), 106.0, 114.0, 114.2, 122.5, 123.3, 124.6, 126.9, 127.2, 128.2, 129.5, 129.7 (CHAr), 99.5, 118.9, 129.1, 134.5, 140.3, 156.5 (C). IR: 1716, 1640, 1460

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cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81, H, 5.14; N, 10.21. Found: C, 78.68; H, 5.09; N, 10.30.

Data for 3d. Reaction time: 3 h. Eluent: CH_2Cl_2–Et_2O, 10:1. Yield: 79%. Mp: 151−154 °C from Et_2O−hexane. ^1H NMR: δ 1.25 (m, 2H), 1.55 (m, 4H), 1.90 (m, 4H), 2.79 (d, J = 1.1 Hz, 3H), 4.90 (m, 1H), 6.15 (d, J = 1.1 Hz, 1H), 7.26−7.39 (m, 2H), 7.50 (s, 1H), 7.84 (t, J = 7.3 Hz, 1H), 8.02 (t, J = 7.3 Hz, 1H). ^{13}C NMR: δ 18.9 (CH_3), 25.8 (CH_2), 26.1, 32.2 ($2CH_2$), 52.5 (CH), 104.4, 108.7, 114.2, 122.2, 123.3, 124.0 (CHAr), 98.6, 118.7, 129.0, 134.0, 156.5 (C). IR: 1648, 1465 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.98; H, 7.02; N, 10.07.

Synthesis of 1*H*-Indole-2-carboxylic Acid Allylamides 4a−d: General Procedure. To a solution of indole-2-carboxylic acid (1 mmol) in CH_2Cl_2 (20 mL) were added oxalyl chloride (0.3 mL, 3 mmol) and DMF (0.05 mL). The reaction was heated to reflux for the reported time, and then the solvent was evaporated to dryness in vacuo. The residue was taken up with CH_2Cl_2 (20 mL) and the suitable allylamine (3 mmol) added at 0 °C. After 30 min at rt the mixture was washed with 1 N HCl. The organic layer was dried with Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography (except **4d**).

Data for 4a. Reaction time: 1 h, then allylmethylamine. Eluent: CH_2Cl_2–Et_2O, 10:1. Yield: 99%. Mp: 101 °C from Et_2O. ^1H NMR: δ 3.29 (s, 3H), 4.34 (br s, 2H), 5.32 (m, 2H), 5.97 (m, 1H), 6.89 (s, 1H), 7.15 (dt, J = 1.1, 8.1 Hz, 1H), 7.29 (dt, J = 1.1, 8.1 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 9.48 (br s, exch with D_2O, 1H). ^{13}C NMR: δ 36.5 (CH_3), 53.5 (CH_2), 105.5 (CH═), 117.6 (CH_2═), 112.0, 120.4, 122.0, 124.4, 132.8 (CHAr), 127.8, 129.5, 135.9, 164.0 (C). IR: 3230, 1605, 1459 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.72; H, 7.29; N, 14.26.

Data for 4b. Reaction time: 2 h, then diallylamine. Eluent: from CH_2Cl_2. Yield: 95%. Mp: 118−120 °C from CH_2Cl_2–hexane. ^1H NMR ($CDCl_3$): δ 4.30 (br s, 4H), 5.35 (m, 4H), 5.97 (m, 2H), 6.90 (s, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.1, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 9.46 (br s, exch with D_2O, 1H). ^{13}C NMR ($CDCl_3$): δ 49.7 (2 CH_2), 105.3, 112.0, 120.5, 122.1, 124.5 (CHAr), 117.8 (2 CH_2═), 132.9 (2 CH═), 127.8, 129.2, 136.0, 163.6 (C). IR: 3225, 1607, 1531 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71, N, 11.66. Found: C, 74.80; H, 6.80; N, 11.72.

Data for 4c. Reaction time: 2 h, then *N*-allylaniline. Eluent: from CH_2Cl_2. Yield 86%. Mp: 145−146 °C from CH_2Cl_2–hexane. ^1H NMR: δ 4.53 (dd, J = 1.1, 6.3 Hz, 2H), 5.18 (dd, J = 1.1, 6.3 Hz, 2H), 6.05 (m, 1H), 7.02 (dt, J = 1.1, 8.4 Hz, 1H), 7.20−7.42 (m, 7H), 7.50 (m, 2H), 9.44 (br s, exch with D_2O, 1H). ^{13}C NMR: δ 54.0 (CH_3), 107.4, 111.9, 120.3, 122.3, 124.6, 128.6, (CHAr), 129.0, 129.7 (2 CHAr), 118.4 (CH_2═), 132.9 (CH═), 127.8, 129.8, 135.8, 142.8, 162.0 (C). IR: 3190, 1580, 1466 cm^{-1}. Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84, N, 10.14. Found: C, 78.13; H, 5.93; N, 10.28.

Data for 4d. Reaction time: 1.45 h, then allylcyclohexylamine. Yield: 80%. Mp: 198−200 °C from CH_2Cl_2. ^1H NMR: δ 1.15−1.78 (m, 6H), 1.89 (m, 4H), 4.27 (m, 2H), 4.53 (m, 1H), 5.31 (m, 2H), 6.02 (m, 1H), 6.84 (s, 1H), 7.14 (t, J = 1.1, 8.1 Hz, 1H), 7.29 (dd, J = 1.1, 7.7, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 9.29 (br s, exch with D_2O, 1H). ^{13}C NMR: δ 25.7, 31.5 (CH_2), 26.2 (2 CH_2), 46.1, 57.1 (CH_2), 116.6 (CH_2═), 128.1, 130.2, 135.7, 163.3 (C), 105.0 (CH═), 111.9, 120.6, 122.2 (CH), 124.5 (2CH), 136.0 (CHAr). IR: 3257, 1596, 1458 cm^{-1}. Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.42; H, 7.98; N, 9.98.

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