Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3775–3778

An approach for quinolines via palladium-catalyzed Heck coupling followed by cyclization

Chan Sik Cho[a,*] and Jun Uk Kim[b]

[a]*Research Institute of Industrial Technology, Kyungpook National University, Daegu 702-701, South Korea*
[b]*Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, South Korea*

Received 22 February 2007; revised 29 March 2007; accepted 2 April 2007
Available online 4 April 2007

Abstract—2-Iodoaniline reacts with α,β-unsaturated carbonyl compounds in DMF at 100 °C in the presence of a catalytic amount of a palladium catalyst along with a base to afford the corresponding quinolones or quinolines in moderate to good yields.

Palladium-catalyzed coupling reaction followed by cyclization has been widely introduced to the synthesis of carbo- and heterocycles, which play an important role as essential building blocks for the design of pharmacologically and biologically active compounds.[1] As part of our continuing studies directed towards transition metal-catalyzed cyclization reactions, we also reported on the synthesis of several cyclic compounds using such an intrinsic transition metal-catalyzed tandem coupling-cyclization protocol. For example, on palladium-catalysis, it is reported that 2-iodoaniline is coupled and cyclized with terminal acetylenic carbinols under palladium-catalyzed Sonogashira coupling conditions along with aqueous tetrabutylammonium hydroxide to give quinolines.[2] It is also reported by us that indazoles and pyrazoles can be synthesized by palladium-catalyzed intramolecular carbon–nitrogen bond forming reaction of 2-bromobenzaldehydes and β-bromovinyl aldehydes with arylhydrazines (Buchwald and Hartwig coupling[3]).[4,5] In connection with this report, several aldehydes such as β-bromovinyl aldehydes, 2-bromobenzaldehydes and 3-bromopyridine-4-carbaldehydes were found to be coupled and cyclized with suitably functionalized alkenes in the presence of a palladium catalyst to give benzenes, naphthalenes and isoquinolines, respectively, via tandem Heck and aldol reactions.[6–8] Under these circumstances, this tandem coupling-cyclization protocol led us to extend to the reaction with 2-iodoaniline. Herein, this report describes a palladium-catalyzed coupling and cyclization of 2-iodoaniline with α,β-unsaturated carbonyl compounds leading to quinolones or quinolines.[9,10]

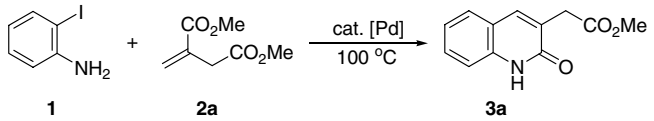
The results of several attempted couplings and cyclizations of 2-iodoaniline (**1**) with dimethyl itaconate (**2a**) for the optimization of conditions are listed in Table 1. Treatment of **1** with 2 equiv of **2a** in DMF in the presence of $Pd(OAc)_2/2PPh_3$ along with NaOAc afforded quinolone **3a** in 69% yield (entry 1).[11] The reaction was monitored until **1** had disappeared on TLC, which occurred within 20 h. From the activity of several palladium precursors examined under the employment of NaOAc as base and DMF as solvent, $PdCl_2(PPh_3)_2$ exhibited nearly the same catalytic activity as $Pd(OAc)_2/2PPh_3$ and other catalyst precursors such as $PdCl_2/2PPh_3$, $Pd(dba)_2/2PPh_3$ and $Pd(PPh_3)_4$ revealed to be moderately effective (entries 1–5). With other bases such as K_2CO_3 and Et_3N combined with $Pd(OAc)_2/2PPh_3$/DMF, the yield of **3a** was lower than that when NaOAc was employed (entries 1, 6 and 7). As a result, after further tuning with several solvents (entries 8–10), the best result in terms of both product yield and complete conversion of **1** is accomplished by the standard set of reaction conditions shown in entry 1 of Table 1.

The present reaction, consistent with the product formed, seems to proceed via a pathway shown in Scheme 1. Oxidative addition of a carbon–iodide bond

Keywords: Alkenes; Cyclization; Heck reaction; Quinolines; Quinolones; Palladium catalyst.
* Corresponding author. Tel.: +82 53 950 7318; fax: +82 53 950 6594; e-mail: cscho@knu.ac.kr

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.001

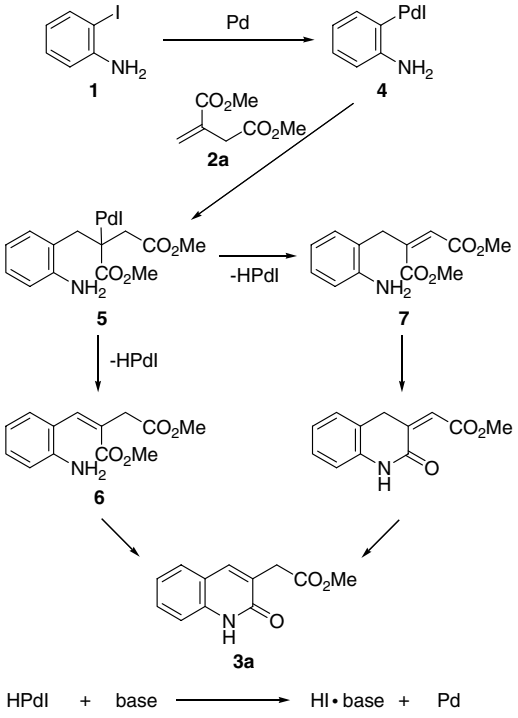
Table 1. Optimization of conditions for the reaction of **1** with **2a**[a]



1 **2a** **3a**

Entry	Pd catalysts	Bases	Solvents	Time (h)	Yield[b] (%)
1	$Pd(OAc)_2/2PPh_3$	NaOAc	DMF	20	69
2	$PdCl_2/2PPh_3$	NaOAc	DMF	20	60
3	$PdCl_2(PPh)_2$	NaOAc	DMF	20	68
4	$Pd(dba)_2/2PPh_3$	NaOAc	DMF	20	46
5	$Pd(PPh_3)_4$	NaOAc	DMF	20	59
6	$Pd(OAc)_2/2PPh_3$	K_2CO_3	DMF	20	13
7	$Pd(OAc)_2/2PPh_3$	Et_3N	DMF	20	59
8	$Pd(OAc)_2/2PPh_3$	NaOAc	MeCN	40	41
9	$Pd(OAc)_2/2PPh_3$	NaOAc	THF	40	41
10	$Pd(OAc)_2/2PPh_3$	NaOAc	Toluene	20	14

[a] Reaction conditions: **1** (0.5 mmol), **2a** (1 mmol), palladium catalyst (0.025 mmol), base (3 mmol), solvent (5 mL), under argon.
[b] Isolated yield.



Scheme 1.

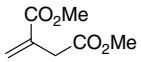
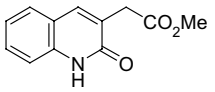
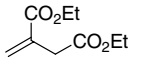
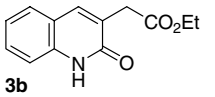
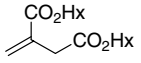
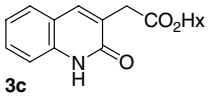
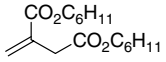
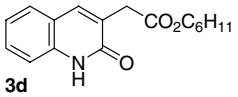
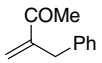
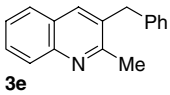
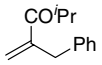
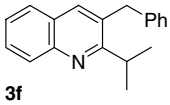
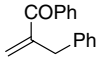
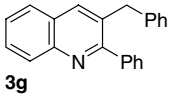
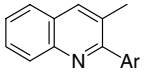
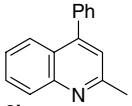
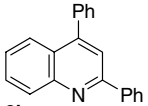
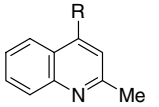
of **1** to palladium(0) produces arylpalladium(II) intermediate **4**, which is followed by the insertion of an olefinic double bond of **2a** into a carbon–palladium bond of **4** to give alkylpalladium species **5**. Subsequent β-hydrogen elimination of **5** produces Heck product **6**, which triggers cyclization to give **3a**. Alternatively, **3a** also seems to be formed by the route via intermediate **7** followed by cyclization and isomerization.

The above putative mechanistic explanation shows that the starting alkene should contain a carbonyl group attached to vinyl carbon for final N-heteroannulation. Thus, under the controlled conditions, various α,β-unsaturated carbonyl compounds **2** were subjected to react with **1** in order to investigate the reaction scope and several representative results are summarized in Table 2. With dialkyl itaconates (**2a–d**),[12] alkyl 3-butenoates, which have carboalkoxy substituents at position 3, quinolones (**3a–d**) were formed in the range of 67–76% yields without any identifiable side products. However, when the reaction was carried out with α,β-unsaturated ketones, the corresponding quinolines were produced. With α,β-unsaturated ketones (**2e–g**),[13–15] which have benzyl substituent at α-position, the corresponding 2,3-disubstituted quinolines (**3e–g**) were formed in 63–68% yields. The reaction proceeds likewise with α,β-unsaturated ketones (**2h** and **2i**)[14,15] having methyl substituent at α-position to give 2-aryl-3-methylquinolines (**3h** and **3i**) in similar yields. From the reactions between **1** and α,β-unsaturated ketones (**2j–m**) having no substituent at α-position, the corresponding 1,3-disubstituted quinolines (**3j–m**) were produced and the product yield was lower than that when compared to the reaction with α,β-unsaturated carbonyl compounds having a substituent at α-position.

General experimental procedure: To a 50 mL pressure vessel were added 2-iodoaniline (0.5 mmol), α,β-unsaturated carbonyl compound (1 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol), NaOAc (3 mmol) and DMF (5 mL). After the system was flushed with argon, the reaction mixture was allowed to react at 100 °C for 20 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–hexane) to eliminate black precipitate. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate–hexane mixture) to give quinolones or quinolines.[16]

In summary, it has been shown that 2-iodoaniline undergoes coupling and cyclization with an array of α,β-unsaturated carbonyl compounds in the presence of a palladium catalyst along with a base to afford quinolones or quinolines according to the kind of carbonyl group attached to vinyl carbon of the starting alkenes. The present reaction is applicable to the synthesis of

Table 2. Palladium-catalyzed synthesis of quinolones and quinolines[a]

α,β-Unsaturated carbonyl compounds	Quinolines	Yield (%)
 **2a**	 **3a**	69
 **2b**	 **3b**	76
 **2c**	 **3c**	67
 **2d**	 **3d**	75
 **2e**	 **3e**	67
 **2f**	 **3f**	68
 **2g**	 **3g**	63
 **2h** Ar = Ph **2i** Ar = 4-OMe	 **3h** Ar = Ph **3i** Ar = 4-OMe	65 56
 **2j**	 **3j**	46
 **2k**	 **3k**	44
 **2l** R = Pr **2m** R = heptyl	 **3l** R = Pr **3m** R = heptyl	40 40

[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol), NaOAc (3 mmol), DMF (5 mL), 100 °C, for 20 h, under argon.

2,3- and 2,4-disubstituted quinolines by the variation of the starting α,β-unsaturated ketones.

Acknowledgement

This work was supported by a Research Professor Grant of Kyungpook National University (2006).

References and notes

1. (a) Tsuji, J. *Palladium Reagents and Catalysis*; Wiley: Chichester, 1995; (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002.
2. Cho, C. S. *J. Organomet. Chem.* **2005**, *690*, 4094.
3. For reviews, see: (a) Hartwig, J. P. *Synlett* **1997**, 329; (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805; (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 805; (d) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2064; (e) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417; (f) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
4. Cho, C. S.; Lim, D. K.; Heo, N. H.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2004**, 104.
5. Cho, C. S.; Patel, D. B. *Tetrahedron* **2006**, *62*, 6388.
6. Cho, C. S.; Patel, D. B.; Shim, S. C. *Tetrahedron* **2005**, *61*, 9490.
7. Cho, C. S.; Lim, D. K.; Zhang, J. Q.; Kim, T.-J.; Shim, S. C. *Tetrahedron Lett.* **2004**, *45*, 5653.
8. Cho, C. S.; Patel, D. B. *J. Mol. Cat. A: Chem.* **2006**, *260*, 105.
9. For our recent report on palladium catalysis: (a) Cho, C. S. *J. Mol. Cat. A: Chem.* **2005**, *240*, 55; (b) Cho, C. S.; Shim, H. S. *Tetrahedron Lett.* **2006**, *47*, 3835.
10. For our recent report on transition metal-catalyzed synthesis of quinolines: (a) Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Lett.* **1999**, *40*, 1499; (b) Cho, C. S.; Oh, B. H.; Shim, S. C. *J. Heterocycl. Chem.* **1999**, *36*, 1175; (c) Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2000**, 1885; (d) Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2000**, *56*, 7747; (e) Cho, C. S.; Kim, T. K.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Organomet. Chem.* **2002**, *650*, 65; (f) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2001**, 2576; (g) Cho, C. S.; Kim, B. T.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2003**, *59*, 7997; (h) Cho, C. S.; Ren, W. X.; Shim, S. C. *Tetrahedron Lett.* **2006**, *47*, 6781.
11. Similar treatment of 2-bromoaniline with **2a** under the same conditions afforded **3a** in only 15% yield.
12. Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Tetrahedron Lett.* **2002**, *43*, 879.
13. Ayed, T. B.; Amri, H. *Synth. Commun.* **1995**, *25*, 3813.
14. Zook, H. D.; Rellahan, W. L. *J. Am. Chem. Soc.* **1957**, *79*, 881.
15. Rodrigues, J. A. R.; Siqueira-Filho, E. P.; Mancilha, M.; Moran, P. J. S. *Synth. Commun.* **2003**, *33*, 331.
16. Spectroscopic data for **3a**–**m**. Compound **3a**: IR (KBr) *v* 1712 (CO_2Me), 1673 (CONH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.31 (s, 2H), 3.86 (s, 3H), 7.11 (d, $J = 7.5$ Hz, 1H), 7.19–7.23 (m, 1H), 7.39–7.43 (m, 2H), 7.86 (s, 1H), 8.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.52, 52.93, 122.15, 124.64, 126.11, 127.37, 130.88, 131.84, 137.06, 138.68, 166.20, 171.98; MS *m*/*z* (relative intensity) 217 (M^+, 100). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.15; H, 5.11; N, 6.35. Compound **3b**: IR (KBr) *v* 1704 (CO_2Et), 1675 (CONH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, $J = 7.0$ Hz, 3H), 3.31 (s, 2H), 4.32 (q, $J = 7.0$ Hz, 2H), 7.17–7.22 (m, 2H), 7.39–7.42 (m, 2H), 7.85 (s, 1H), 9.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.69, 34.53, 61.92, 122.32, 124.54, 126.28,

127.36, 130.82, 131.77, 137.24, 138.45, 165.76, 172.38; MS *m*/*z* (relative intensity) 231 (M^+, 100). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.19; H, 5.98; N, 5.74. Compound **3c**: IR (KBr) *v* 1713 (CO_2Hx), 1673 (CONH) cm^{-1}; H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, $J = 7.0$ Hz, 3H), 1.31–1.45 (m, 6H), 1.70–1.77 (m, 2H), 3.31 (s, 2 H), 4.25 (t, $J = 6.8$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 1H), 7.21 (dt, $J = 1.0$ and 7.5 Hz, 1H), 7.39–7.43 (m, 2H), 7.84 (s, 1H), 9.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.99, 22.50, 25.60, 28.54, 31.40, 34.08, 65.71, 121.76, 124.15, 125.97, 126.96, 130.38, 131.38, 136.65, 137.92, 165.37, 171.73. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 69.87; H, 7.18; N, 4.67. Compound **3d**: IR (KBr) *v* 1703 ($CO_2C_6H_{11}$), 1671 (CONH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28–1.59 (m, 6H), 1.76–1.93 (m, 4H), 3.31 (s, 2H), 4.90–4.94 (m, 1H), 7.18–7.22 (m, 2H), 7.38–7.42 (m, 2H), 7.82 (s, 1H), 9.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.09, 25.80, 31.98, 34.58, 74.17, 122.35, 124.47, 126.71, 127.39, 130.74, 131.74, 137.28, 138.12, 165.15, 172.55. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.69; H, 6.66; N, 4.80. Compound **3e**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H), 4.11 (s, 2H), 7.14 (d, $J = 7.0$ Hz, 2H), 7.21–7.24 (m, 1H), 7.28–7.32 (m, 2H), 7.41–7.45 (m, 1H), 7.60–7.64 (m, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.73 (s, 1H), 8.01 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.00, 39.58, 126.20, 126.90, 127.51, 127.66, 128.74, 129.08, 129.21, 129.28, 133.15, 136.26, 139.30, 147.10, 159.28. Compound **3f**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, $J = 7.0$ Hz, 6H), 3.32–3.42 (m, 1H), 4.20 (s, 2H), 7.13 (d, $J = 7.0$ Hz, 2H), 7.20–7.31 (m, 3H), 7.43 (t, $J = 7.5$ Hz, 1H), 7.59–7.64 (m, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.75 (s, 1H), 8.05 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.54, 32.22, 39.04, 126.05, 126.80, 127.37, 127.42, 128.93, 129.02, 129.21, 131.91, 136.83, 140.23, 147.47, 167.04. Anal. Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.35; H, 7.30; N, 5.27. Compound **3g**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 2H), 6.99 (d, $J = 7.0$ Hz, 2H), 7.15–7.24 (m, 3H), 7.40–7.51 (m, 6H), 7.64–7.68 (m, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.91 (s, 1H), 8.14 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.52, 126.67, 126.89, 127.52, 127.94, 128.60, 128.71, 128.90, 129.27, 129.41, 129.56, 129.72, 132.92, 137.41, 140.37, 141.07, 147.06, 161.16. Compound **3h**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.40–7.51 (m, 4H), 7.57–7.59 (m, 2H), 7.62–7.66 (m, 1H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.97 (s, 1H), 8.13 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.03, 126.81, 127.12, 128.00, 128.59, 128.71, 129.14, 129.27, 129.61, 129.71, 137.14, 141.29, 147.05, 160.93. Compound **3i**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.86 (s, 3H), 7.01 (d, $J = 8.5$ Hz, 2H), 7.48 (t, $J = 7.3$ Hz, 1H), 7.54–7.58 (m, 2H), 7.62–7.66 (m, 1H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.97 (s, 1H), 8.11 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.24, 55.78, 114.11, 126.61, 127.08, 127.84, 129.07, 129.61, 129.68, 130.71, 133.79, 137.14, 147.09, 160.04, 160.52. Compound **3j**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 7.23 (s, 1H), 7.41–7.53 (m, 6H), 7.68 (t, $J = 7.5$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 8.09 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.98, 124.86,127.70, 128.27, 128.37, 130.94, 131.15, 131.62, 131.94, 132.11, 140.76, 151.01, 151.15, 161.11. Compound **3k**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.58 (m, 9H), 7.74 (t, $J = 7.3$ Hz, 1H), 7.82 (s, 1H), 7.91 (d, $J = 8.5$ Hz, 1H), 8.19 (d, $J = 7.6$ Hz, 2H), 8.25 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.39, 125.64, 125.74, 126.33, 127.58, 128.41, 128.59, 128.84, 129.34, 129.53, 129.57, 130.10, 138.37, 139.64, 148.78, 149.16, 156.90. Compound **3l**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, $J = 7.3$ Hz, 3H), 1.75–1.84 (m, 2H), 2.71 (s, 3H), 3.00 (t, $J = 7.8$ Hz, 2H), 7.13 (s, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 8.02 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.60, 23.63, 25.73, 34.53, 122.07, 123.81, 125.70, 126.26, 129.34, 129.70, 148.43, 148.75, 159.00. Compound **3m**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, $J = 6.3$ Hz, 3H), 1.26–1.46 (m, 8H), 1.70–1.78 (m, 2H), 2.71 (s, 3H), 3.01 (t, $J = 7.8$ Hz, 2H), 7.12 (s, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.51, 23.06, 25.72, 29.54, 30.12, 30.52, 32.18, 32.54, 121.99, 123.80, 125.71, 126.24, 129.34, 129.69, 148.41, 149.10, 159.02. Anal. Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.78; H, 9.85; N, 5.60.