The Heck Reaction of β-Arylacrylamides: An Approach to 4-Aryl-2-quinolones

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Abstract: The Heck reaction of β-arylacrylamides with aryl iodides afforded the corresponding vinylic substitution products usually in high yields. The nature of β-substituents, aryl iodides and substituents at the nitrogen atom influences the stereochemical outcome. *N*,*N*-Dimethyl-β-arylacrylamides gave vinylic substitution products with higher stereoselectivity than the corresponding N-unsubstituted β-arylacrylamides. β-Arylacrylamides containing *ortho*-substituents led to the formation of only one stereoisomer. The procedure was used to prepare 4-aryl-2-quinolones from β-(*o*-bromophenyl)acrylamide through a sequential Heck reaction and copper-catalyzed cyclization process.

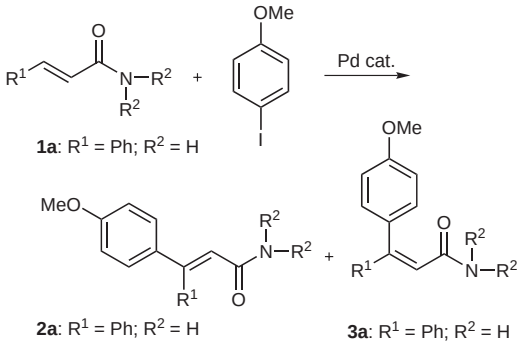
Key words: cinnamamides, 2-quinolones, cyclization, palladium catalysis, copper catalysis

The Heck reaction of β-substituted α,β-unsaturated carbonyl compounds with aryl halides may serve as a valuable method for the preparation of highly functionalized olefin systems. Because of this, the preparation of β,β-disubstituted derivatives from β-substituted α,β-enals and -enones,[1] and α,β-unsaturated esters[2] have been the subject of several investigations, with the achievement of a stereoselective synthesis being a major target. Indeed, whereas excellent regioselectivity was always observed (with vinylic substitution products at the β-position being usually the sole products), the stereochemistry of the reaction was found to depend strongly on reaction conditions.

Surprisingly, very little has been done with β-substituted acrylamides. We described the tendency of cinnamamide to afford preferentially the corresponding vinylic substitution product in the palladium-catalyzed reaction with iodobenzene in the presence of triethylamine and formic acid as compared to cinnamaldehyde and benzalacetone (and a variety of α,β-enones), which gave conjugate addition-type derivatives as the main products under the same conditions.[3] A β,β-diarylacrylamide was prepared adapting the Heck reaction to solid-phase conditions, but the stereochemistry of the Heck product was not established.[4] More recently, Nájera et al. described the preparation of two β,β-diarylacrylamides via vinylic substitution of β-substituted acrylamides in a study devoted to explore Heck reactions of α,β-unsaturated carbonyl compounds in aqueous media.[5] On the other hand, the β,β-diarylacrylamide motif is present in a variety of biologically active molecules.[6] Therefore, it appeared to us of interest to explore in more detail the Heck reaction of this class of compounds.

Herein we report the results of this study.

The reaction of *p*-iodoanisole with cinnamamide[7] (**1a**) in the presence of 0.05 equivalents of $Pd(OAc)_2$ was initially examined as the model system (Scheme 1).



Scheme 1

Part of our optimization work using different bases, solvents and additives is displayed in Table 1. Under a variety of reaction conditions, good chemical yields were observed but the stereochemical outcome was only moderate (Table 1, entries 1–3). Under Jeffery conditions[8] no vinylic substitution product was isolated (Table 1, entry 4). Using KOAc as base and omitting Bu_4NCl produced the vinylic substitution product in good yield and satisfactory stereoselectivity (Table 1, entry 5). Switching to a Bu_4NOAc/Bu_4NBr molten salt mixture (these conditions gave excellent conversions and stereochemical control with cinnamate esters)[2g] led to a moderate conversion and low **2a**:**3a** molar ratio (Table 1, entry 8). The best result in terms of yield and **2a**:**3a** molar ratio was obtained when the reaction was carried out in triethylamine (Table 1, entry 7).

The stereochemistry of **2a** and **3a** [obtained as an approximately 20:80 mixture when prepared from iodobenzene and β-(*p*-methoxyphenyl)acrylamide] was assigned by

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Table 1 Bases, Additives, and Solvents in the Palladium-Catalyzed Reaction of Cinnamamide (**1a**) with *p*-Iodoanisole[a]

Entry	Base	Additive	Solvent	Time (h)	Overall yield (%)	**2a**:**3a**	Yield (%) of recovered **1a**
1	Et_3N (3 equiv)	–	DMF	48	82	76:24	15
2	Et_3N (3 equiv)	–	THF	24	70	74:26	25
3	Et_3N (3 equiv)	–	EtOAc	24	67	74:26	27
4	K_2CO_3 (2 equiv)	Bu_4NCl (1 equiv)	DMF	96	–		68
5	KOAc (2 equiv)	–	DMF	96	71	84:16	20
6	Bu_4NOAc (2 equiv)	–	DMF	48	54	68:32	18
7	Et_3N (5 equiv)	–	–	12	92	83:17	–
8	Bu_4NOAc (3 equiv)	Bu_4NBr (3 equiv)	–	24	60	70:30	20

[a] All reactions were carried out on a 0.5-mmol scale at 100 °C under an argon atmosphere using 1 equiv of **1a**, 1.5 equiv of *p*-iodoanisole and 0.05 equiv of $Pd(OAc)_2$ in 1.5 mL of solvent.

NOE experiments. That of the other vinylic substitution products (vide infra) has been assigned based on these data.

Thus, these conditions were used when the procedure was extended to the reaction of other β-arylacrylamides[9] with *p*-iodoanisole (Table 2) and ethyl *p*-iodobenzoate (Table 3), models of electron-rich and electron-poor aryl iodides, respectively.

Using *p*-iodoanisole as the aryl partner, β,β-diarylacrylamides were produced in high yields and with satisfactory stereoselectivity, the highest stereoselectivity being observed with the *N*,*N*-dimethyl-β-arylacrylamides (Table 2, entries 2, 3, 6, 9, 11, 13, 14) and β-(*o*-substituted aryl)acrylamides (Table 2, entries 4, 7–9).

Reactions with ethyl *p*-iodobenzoate, under the conditions used with *p*-iodoanisole, showed a strong tendency to give

Table 2 The Palladium-Catalyzed Heck Reaction of β-Arylacrylamides **1** with *p*-Iodoanisole[a]

Entry	β-Arylacrylamide **1**			Time (h)	Yield of **2** (%)[b]	Yield of **3** (%)[b]
	R^1	R^2				
1	Ph	H	**1a**	24	**2a**, 66	**3a**, 16
2	Ph	Me	**1b**	12	**2b**, 74	**3b**, 8
3	*p*-Me-C_6H_4	Me	**1c**	48	**2c**, 79	**3c**, 17
4	*o*-MeO-C_6H_4	H	**1d**	12	**2d**, 91	–
5	*m*-MeO-C_6H_4	H	**1e**	24	**2e**, 56	**3e**, 14
6	*m*-MeO-C_6H_4	Me	**1f**	48	**2f**, 64	**3f**, 24
7	*o*-Me-C_6H_4	H	**1g**	24	**2g**, 74	–
8	*o*-Br-C_6H_4	H	**1h**	12	**2h**, 87	–
9	*o*-Br-C_6H_4	Me	**1i**	24	**2i**, 70	–
10	*m*-F-C_6H_4	H	**1j**	24	**2j**, 57	**3j**, 18
11	*m*-F-C_6H_4	Me	**1k**	48	**2k**, 80	**3k**, 8
12	*m*-CF_3-C_6H_4	H	**1l**	24	**2l**, 68	**3l**, 12
13	*m*-CF_3-C_6H_4	Me	**1m**	48	**2m**, 83	**3m**, 9
14	*p*-MeCO-C_6H_4	Me	**1n**	36	**2n**, 84	**3n**, 10

[a] All reactions were carried out on a 0.5-mmol scale at 100 °C under an argon atmosphere using 1 equiv of **1**, 1.5 equiv of *p*-iodoanisole, 3 equiv of Et_3N and 0.05 equiv of $Pd(OAc)_2$.
[b] Yields are given for isolated products.

p,*p*′-diethoxycarbonyl biphenyl, the biaryl product formed via a homocoupling process. With the N-unsubstituted β-arylacrylamides that we have tested, *p*,*p*′-diethoxycarbonyl biphenyl was isolated in 20–37% yields and the desired vinylic substitution products were obtained in moderate yields (Table 3, entries 2, 5 and 10).

Since it has been reported that formation of homocoupling biaryl products – a competitive side reaction assumed to require a bimolecular transmetalation of σ-arylpalladium intermediates – can be limited by decreasing the catalyst loading,[10] we decided to conduct the reaction using lower amounts of catalyst. Indeed, decreasing the catalyst loading to 0.01 equivalent led to a remarkable increase of yields at the expense of biaryl formation (Table 3, compare entries 3, 6, 11 with entries 2, 5, 10, respectively).[11]

As to the stereochemical outcome, equilibration following the Heck arylation might account for the formation of mixtures of stereoisomers. In the present reaction, however, it appears that stereoisomers are generated during the vinylic substitution event through the well-known elimination–reverse-addition–elimination of HPd species and that no equilibration occurs after the vinylic substitution products are formed.

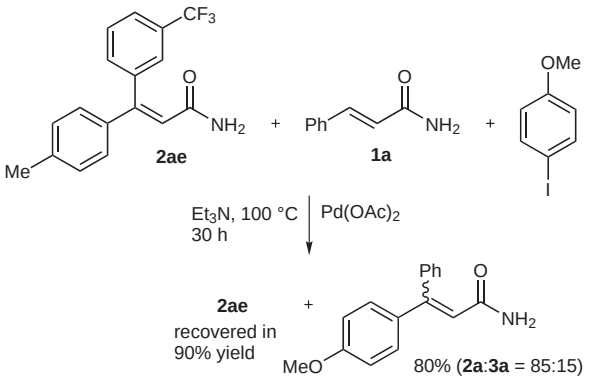
This view is supported by the following experiment. A pure sample of **2ae**, prepared via the reaction of **1l** with *p*-iodotoluene, was subjected to the conditions producing vinylic substitution products in the presence of **1a** and *p*-iodoanisole (Scheme 2). The 3,3-diarylacrylamide product, formed via the reaction of **1a** with *p*-iodoanisole, was isolated in 80% yield as an approximately 85:15 *E*/Z mixture (a result similar to that reported in Table 2, entry 1). Compound **2ae** was recovered in almost quantitative isolated yield and its stereochemistry was maintained, even under prolonged heating.

Electronic effects due to the β-aryl groups in the carbopalladation adduct appear to play a role in controlling the stereochemical outcome. In particular, it seems that β-substituents containing electron-withdrawing groups tend

Table 3 The Palladium-Catalyzed Heck Reaction of β-Arylacrylamides **1** with Ethyl *p*-Iodobenzoate[a]

Entry	β-Arylacrylamide **1**			Yield of **2** (%)	Yield of **3** (%)[b,c]
	R^1	R^2			
1	*o*-MeO-C_6H_4	H	**1d**	**2o**, 78	–
2[d]	*m*-MeO-C_6H_4	H	**1e**	**2p**, 56	**3p**, 14 (5)
3	*m*-MeO-C_6H_4	H	**1e**	**2p**, 68	**3p**, 13 (–)
4	*m*-MeO-C_6H_4	Me[e]	**1f**	**2q**, 74	**3q**, 6
5[d]	*p*-MeO-C_6H_4	H	**1j**	**2r**, 37	**3r**, 11 (20)
6	*p*-MeO-C_6H_4	H	**1j**	**2r**, 62	**3r**, 14 (–)
7	*p*-MeO-C_6H_4	Me[e]	**1o**	**2s**, 88	**3s**, 7
8[d]	*o*-Me-C_6H_4	H	**1g**	**2t**, 90	–
9	*o*-Me-C_6H_4	H	**1g**	**2t**, 91	–
10[d]	Ph	H	**1a**	**2u**, 36	**3u**, 16 (30)
11	Ph	H	**1a**	**2u**, 74	**3u**, 13 (–)
12	Ph	Me[e]	**1b**	**2v**, 91	**2v**, 6
13[d]	*m*-F-C_6H_4	H	**1j**	**2w**, 60	**3w**, 10 (32)
14	*m*-F-C_6H_4	Me	**1k**	**2y**, 86	**3y**, 10
15[d]	*m*-CF_3-C_6H_4	H	**1l**	**2z**, 48	**3z**, 9 (37)
16	*m*-CF_3-C_6H_4	Me[e]	**1m**	**2ab**, 82	**3ab**, 8
17	*o*-Br-C_6H_4	H	**1h**	**2ac**, 82	–
18	*p*-MeCO-C_6H_4	Me[e]	**1n**	**2ad**, 65	–

[a] Unless otherwise stated, reactions were carried out on a 0.5-mmol scale at 100 °C for 24 h under an argon atmosphere using 1 equiv of **1**, 2.5 equiv of ethyl *p*-iodobenzoate, 5 equiv of Et_3N and 0.01 equiv of $Pd(OAc)_2$.
[b] Yields are given for isolated products.
[c] Figures in parentheses refer to isolated homocoupling products.
[d] In the presence of 1.5 equiv of ethyl *p*-iodobenzoate, 3 equiv of Et_3N and 0.05 equiv of $Pd(OAc)_2$.
[e] 36 h.



Scheme 2

to afford higher stereoselectivity. For example, a relatively low stereoselectivity was observed in the reaction of **1c** with *p*-iodoanisole – the carbopalladation adduct contains two electron-rich β-substituents (Table 2, entry 3) – whereas **2ad** was formed as the sole stereoisomer in the reaction of **1n** with ethyl *p*-iodobenzoate (Table 3, entry 18). In the latter case, the carbopalladation adduct contains two electron-poor β-substituents.

The general higher diastereoselectivity observed with *N*,*N*-dimethyl-β-arylacrylamides as compared to N-unsubstituted β-arylacrylamides may be due to the stronger tendency of the disubstituted amide group to coordinate to palladium[12] (Figure 1). This coordinating effect could disfavor the reverse addition of HPdX generating the carbopalladation adduct with the palladium atom close to the β-substituents.

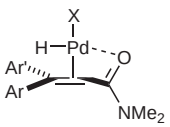


Figure 1

The exclusive formation of the trisubstituted olefin containing the original β-substituent on the same side of the carbon–carbon double bond as the amide group when β-(*o*-substituted aryl)acrylamides are used as substrates is also remarkable. Most probably it is due to the relative instability of the adduct **B**, which would form from **A** via elimination–reverse-addition of HPdX, in the presence of an *ortho*-substituent (Figure 2).

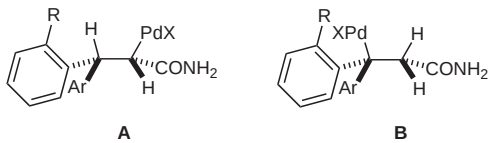
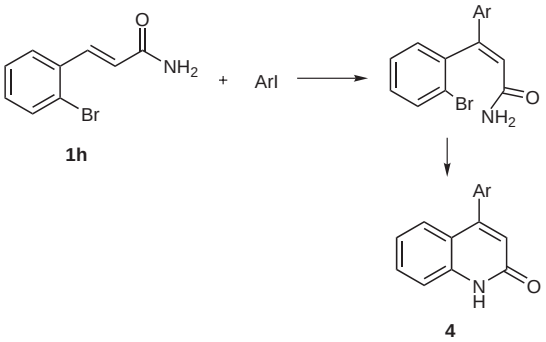


Figure 2

The results obtained with 3-(*o*-bromophenyl)acrylamide **1f** (Table 2, entry 8; Table 3, entry 17) prompted us to investigate the utilization of this chemistry for the preparation of 2-quinolone derivatives, a class of compounds abundant in many biologically active compounds,[13] through a process involving a Heck reaction followed by an intramolecular carbon–nitrogen bond-forming step (Scheme 3).



Scheme 3

With regard to the cyclization step, the economic attractiveness of copper-based methods and the growing interest in copper-catalyzed syntheses[14] stimulated us to develop a copper-catalyzed protocol.

Using the vinylic substitution product **2h** as the model system, the cyclization reaction was attempted under a variety of reaction conditions. As shown in Table 4, the highest yield was obtained in the presence of 0.2 equivalent of CuI, 2 equivalents of NaI,[15] 2 equivalents of K_3PO_4, 0.4 equivalent *N*,*N*-dimethylethylendiamine (DMEDA) in dioxane at 120 °C.

To make this overall approach to 2-quinolones more attractive from a synthetic standpoint, we explored the vinylic substitution and cyclization of **1f** through a process that would omit the isolation of vinylic substitution intermediates. After some experimentation, we were pleased to find that adding CuI, NaI, K_3PO_4, *N*,*N*-dimethylethylendiamine and dioxane to the crude mixture derived from the Heck reaction after work-up gave quinolone products in good to high overall isolated yields with neutral, electron-rich and electron-poor aryl iodides (Table 5).[16] None of the quinolone derivative was obtained when the vinylic substitution–cyclization protocol was attempted under optimized conditions omitting CuI.

In conclusion, we have shown that the palladium-catalyzed reaction of β-arylacrylamides with aryl iodides in the presence of triethylamine affords vinylic substitution products usually in high yield. The nature of β-substituents, aryl iodides and substituents at the nitrogen atom was found to influence the stereochemical outcome of the reaction. In particular, the presence of β-substituents containing electron-withdrawing groups in the carbopalladation adduct appear to afford higher diastereoselectivity; *N*,*N*-dimethyl-β-arylacrylamides tend to give a higher diastereoselectivity than the corresponding N-unsubstituted β-arylacrylamides; β-arylacrylamides containing *ortho*-substituents lead to the formation of only one ste-

Table 4 Examination of the Copper-Catalyzed Cyclization of **2h** to the Quinolone Product **4b**[a]

Entry	Catalyst system	Base	Additive	Ligand	Temp (°C)	Time (h)	Yield of **4b** (%)[b,c]
1	$CuCl(PPh_3)$	K_3PO_4	–	–	110	20	50 (–)
2	CuI	K_3PO_4	NaI	1,3-DAP[d]	110	96	50 (50)
3	CuI	K_3PO_4	–	DMEDA	110	48	66 (34)
4	CuI	K_3PO_4	–	DMEDA	120	96	56 (40)
5	CuI	–	NaI	DMEDA	120	48	16 (83)
6	CuI	K_3PO_4	NaI	DMEDA	120	24	85 (–)

[a] All reactions were carried out on a 0.5-mmol scale using 1 equiv of **1h**, 0.2 equiv of the copper catalyst, 2 equiv of NaI (when added), 2 equiv of K_2CO_3 (when added), 0.4 equiv of 1,3-DAP or DMEDA (when added) in 2 mL of dioxane.
[b] Yields are given for isolated products.
[c] Figures in parentheses refer to the recovered starting material.
[d] 1,3-Diaminopropane.

Table 5 Synthesis of 4-Aryl-2-quinolones **4** through a Sequential Heck Reaction–Copper-Catalyzed Cyclization of β-(*o*-Bromophenyl)acrylamide **1h**[a]

Entry	ArI	Time (h)		Overall yield of **4** (%, procedure)[b]
		Heck reaction	Cyclization	
1	*m*-MeO-C_6H_4-I	48	24	**4a**, 71 (A)
2	*p*-MeO-C_6H_4-I	12	24	**4b**, 77 (A)
3	Ph-I	48	24	**4c**, 77 (A)
4	*m*-F-C_6H_4-I	48	24	**4d**, 71 (B)
5	*p*-EtOOC-C_6H_4-I	48	24	**4e**, 60 (B)

[a] Reactions were carried out on a 0.5-mmol scale as follows. Procedure A: 1 equiv of **1**, 1.5 equiv of aryl iodide, 3 equiv of Et_3N and 0.05 equiv of $Pd(OAc)_2$ at 100 °C, work-up, and then 0.2 equiv of CuI, 2 equiv of NaI, 2 equiv of K_2CO_3, 0.4 equiv of DMEDA and 2 mL of dioxane at 120 °C; procedure B: 1 equiv of **1**, 2.5 equiv of aryl iodide, 5 equiv of Et_3N and 0.01 equiv of $Pd(OAc)_2$ at 100 °C, work-up, and then as for procedure A.
[b] Yields are given for isolated products.

reoisomer. The procedure was used to develop an efficient approach to 4-aryl-2-quinolones from β-(*o*-bromophenyl)acrylamide through a sequential Heck-reaction–copper-catalyzed-cyclization process.

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(9) **Typical Procedure for the Reaction of β-Arylacrylamides with *p*-Iodoanisole.**
To a stirred solution of **1h** (0.113 g, 0.50 mmol), *p*-iodoanisole (0.093 mg, 0.75 mmol) and Et_3N (348 μL, 2.5 mmol), $Pd(OAc)_2$ (0.006 g, 0.025 mmol) was added. The reaction mixture was stirred for 12 h at 100 °C. Then, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane–EtOAc, 30:70) to give 0.144 g (87% yield) of **2h**: mp 163–165 °C. IR (KBr): 3294, 3177, 1654 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.69 (dd, *J* = 8.4, 1.33 Hz, 1 H), 7.43 (m, 1 H), 7.32–7.27 (m, 3 H), 7.23–7.21 (m, 2 H), 6.87–6.85 (m, 2 H), 6.49 (s, 1 H) 5.28–5.16 (d, 2 H),1.61 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ = 167.2, 160.1, 148.6, 139.0, 132.8, 130.3, 130.2, 129.4, 128.1, 127.4, 122.3, 119.7, 113.6, 54.8. MS: *m/z* (rel. int.) = 332 (100) [M^+], 334 (73), 252 (54). Anal. Calcd for $C_{16}H_{14}BrNO_2$: C, 57.85; H, 4.25; Br, 24.05; N; 4.22. Found: C, 57.77; H, 4.28; Br, 24.02; N, 4.26.
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(11) **Typical Procedure for the Reaction of β-Arylacrylamides with Ethyl *p*-Iodobenzoate.**
To a stirred solution of **1h** (0.113 g, 0.50 mmol), ethyl *p*-iodobenzoate (209 μL, 1.25 mmol) and Et_3N (348 μL, 2.5 mmol), $Pd(OAc)_2$ (0.001 g, 0.005 mmol) was added. The reaction mixture was stirred for 24 h at 100 °C. Then, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane–EtOAc, 25:75) to give 0.152 g (82% yield) of **2ac**: mp 235–237 °C. IR (KBr): 3338, 3181, 1668 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.03 (d, *J* = 8.3 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.35–7.30 (m, 4 H), 6.61 (s, 1 H) 5.32–5.25 (d, 2 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 1.38 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 166.5, 165.5, 147.9, 142.1, 138.2, 132.9, 130.4, 130.3, 129.8, 129.3, 127.5, 126.6, 123.5, 122.2, 60.6, 13.8. MS: *m/z* (rel. int.) = 374 (50) [M^+], 376 (100), 294 (34). Anal. Calcd for $C_{18}H_{16}BrNO_3$: C, 57.77; H, 4.31; Br, 21.35; N; 3.74. Found: C, 57.69; H, 4.35; Br, 21.38; N, 3.70.
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(16) **Typical Procedure for the Preparation of 2-Quinolones 4.**
To a stirred solution of **1h** (0.113 g, 0.50 mmol), *p*-iodoanisole (0.093 g, 0.75 mmol) and Et_3N (348 μL, 2.5 mmol), $Pd(OAc)_2$ (0.006 g, 0.025 mmol) was added. The reaction mixture was stirred for 12 h at 100 °C. Then, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Then, 2 mL of dioxane, CuI (0.019 g, 0.1 mmol), NaI (0.149 g, 1 mmol), K_3PO_4 (0.212 g, 1 mmol), *N*,*N*-dimethylethylendiammine (21.3 μL, 0.2 mmol) and were added to the crude mixture. The mixture was stirred for 24 h at 120 °C. Then, the mixture was diluted with EtOAc and washed with a sat. NH_4Cl solution. The organic layer was dried over Na_2SO_4 concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane–EtOAc, 30:70) to give 0.97 g (77% yield) of **4b**: mp 196–198 °C. IR (KBr): 3131, 1672 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 11.82 (s, 1 H), 7.51 (t, *J* = 8 Hz, 1 H), 7.44–7.36 (m, 4 H), 7.13–7.07 (m, 3 H), 6.34 (s, 1 H), 3.82 (s, 3 H). ^{13}C NMR (DMSO-d_6): δ = 161.3, 159.6, 151.1, 139.3, 130.4, 130.1, 128.8, 126.2, 121.7, 120.9, 118.5, 115.8, 114.1, 55.2. MS: *m/z* (rel. int.) = 251 (100) [M^+], 252 (25), 236 (25) 220 (12). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N; 5.57. Found: C, 76.55; H, 5.18; N, 5.53.