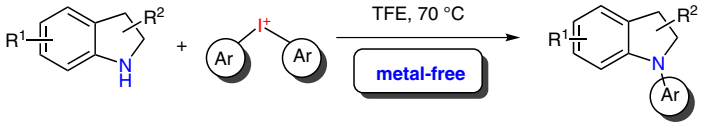
Synlett S. Riedmüller, B. J. Nachtsheim Letter

Metal-Free N-Arylation of Indolines with Diaryliodonium Salts

Stefan Riedmüller[a,b]
Boris J. Nachtsheim[*a]

[a] Institut für Organische Chemie, Eberhard Karls Universität, Auf der Morgenstelle 18, 72076 Tübingen, Germany
boris.nachtsheim@uni-tuebingen.de
[b] Performance Materials Division, Merck KGaA, Frankfurter Straße 250, 64293 Darmstadt, Germany



Received: 05.11.2014
Accepted after revision: 27.11.2014
Published online: 14.01.2015
DOI: 10.1055/s-0034-1379885; Art ID: st-2014-d0922-l

Abstract The N-arylation of indolines using diaryliodonium salts as electrophilic arylating reagents is described. Without the use of any additional additives, the desired *N*-aryl indolines could be obtained in up to 85% yield.

Key words amination, hypervalent iodine, metal-free, arylation, indoline

Indoline (2,3-dihydroindole) and related congeners are widely found as a core structural element in alkaloid natural products[1] or other pharmaceutically interesting molecules.[2] In particular *N*-aryl indolines were found to be interesting structural elements due to their recently explored applications in different areas of organic electronics.[3]

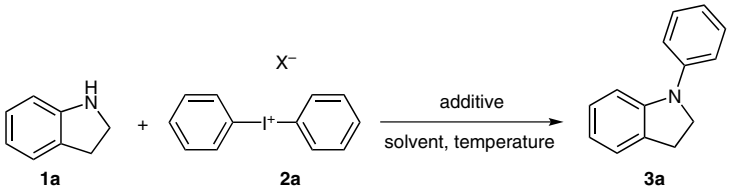
In general, the *N*-aryl indoline framework is accessible via partial hydrogenation of the corresponding fully unsaturated *N*-aryl indole precursor.[4] Another recent methodology is utilizing styrenes as precursors for the introduction of the annelated nitrogen ring.[5] Completely different is the construction of the *N*-aryl indoline via arylation of amines with nonaromatic ketones through a palladium-catalyzed aerobic dehydrogenative aromatization.[6] For late-stage functionalization, the indoline-NH moiety is often used. Here, transition-metal-mediated N-arylation is a common procedure.[7] However, metal-free procedures involving arynes are also known.[8] In the last decade new chemical transformations based on hypervalent iodine reagents have become very popular in organic chemistry.[9] In particular, diaryliodonium salts[10] could demonstrate their great potential as efficient nontoxic, electrophilic arylating reagents which are particularly useful in metal-free arylations.[11] Examples from the literature describe arylation reactions of anilines,[12] oxygen nucleophiles,[13,14] N-protected indoles,[15] pyrroles,[16] carbazoles,[17] benzoazoles,[18] or even ammonia to produce primary aromatic amines.[19]

The research interests of our group are focused on the development of new C–X coupling strategies involving hypervalent iodine reagents or (hypo)iodites.[20] Very recently, we could develop a novel palladium-catalyzed synthesis of *N*-aryl carbazoles using anilines and stable cyclic diaryliodonium salts.[21] As part of our ongoing research projects we were interested in direct metal-free arylation reactions of nitrogen heterocycles utilizing diaryliodonium salts. In this communication we want to present our initial results describing the first metal free N-arylation of indolines.

In an initial attempt, indoline **1a** was treated with 1.1 equivalents of diphenyliodonium triflate in DMF at 130 °C (Table 1, entry 1). We were gratified to observe moderate conversion and isolated 25% of *N*-phenylindoline **3a**. In the same experiment we also detected *N*-formylindoline as a side product in significant amounts which results from an undesired reaction of indoline with the solvent DMF.

Running the reaction at lower temperatures (60 °C) to prevent side-product formation resulted only in trace amounts of **3a** (Table 1, entry 2). Next, *N*,*N*-dimethylacetamide (DMAc) was tested as a solvent, but again, only trace amounts of **3a** were observed (Table 1, entry 3). Acetonitrile showed comparable results to DMF (Table 1, entry 4). Interestingly, we observed a higher product formation with propionitrile giving **3a** in 76% yield (Table 1, entry 5). Using DMSO as another polar aprotic solvent did not improve the outcome of the reaction (Table 1, entry 6). Finally, we investigated fluorinated solvents, in particular 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and 2,2,2-trifluoroethanol (TFE). Here, we observed a further increase in product formation when we used TFE (Table 1, entry 7), while HFIP was completely inefficient in this transformation (Table 1, entry 8).

Table 1 Optimization Studies[a]



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

Entry	X⁻	Solvent	Additive (equiv)	Time (h)	Temp (°C)	Yield (%)[b]
1	OTf	DMF	–	15	130	25
2	OTf	DMF	–	14	60	trace[c]
3	OTf	DMAc	–	66	60	trace[c]
4	OTf	MeCN	–	14	75	27
5	OTf	EtCN	–	16	90	76
6	OTf	DMSO	–	18	110	trace[c]
7	OTf	TFE	–	14	70	83
8	OTf	HFIP	–	23	55	trace[c]
9[d]	OTf	TFE	–	18	70	85
10	OTf	TFE	NaOH (1.5)	15	70	trace[c]
11	OTf	TFE	NaH (1.1)	96	70	trace[c]
12	OTf	TFE	KO*t*-Bu (1.5)	13	75	trace[c]
13	OTs	TFE	–	24	70	44
14	CF_3COO	TFE	–	30	70	81
15	BF_4	TFE	–	42	70	73

[a] Typical reaction conditions: **1a** (0.21 mmol), **2a** (1.1 equiv), solvent (3–4 mL).
[b] Isolated yield after column chromatography.
[c] Product not isolated.
[d] **1a** (0.21 mmol), **2a** (1.3 equiv).

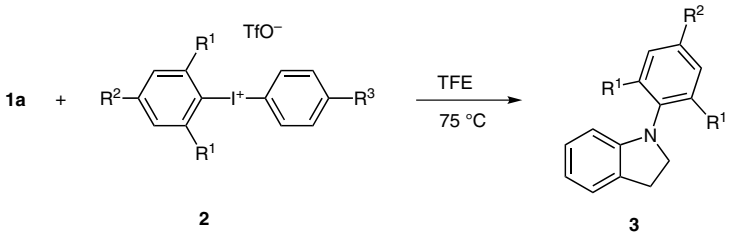
Base additives, such as sodium hydroxide, sodium hydride, and potassium *tert*-butoxide did not improve the product yield (Table 1, entries 10–12). To complete the optimization, we investigated diphenyliodonium salts with other counterions (Table 1, entries 13–15).[22] The tosylate salt of **2a** was not efficient at all (Table 1, entry 13), whereas **2a** associated with trifluoroacetate or tetrafluoroborate performed similiarly to the triflate salt. Diphenyliodonium tetrafluoroborate showed a slightly reduced yield of **3a** of 73%.

Next, we used a variety of iodonium salts with different substituents in 4-position of the arene moiety.[23] Diaryliodonium salts bearing electron-donating (4-Me or 4-MeO) and electron-withdrawing groups (4-Br or 4-F_3C) were selected as arylating reagents. From the results summarized in Table 2, a clear trend in aryl-group-transfer capability is visible. Compared to unsubstituted diphenyliodonium triflate, the more electron-rich 4-methyl-substituted congener reacted in lower yields giving **3b** in 41% (Table 2, entry 1). By using the 4-methoxy-substituted iodonium salt (R^1 = H, R^2 = R^3 = OMe), no *N*-aryl indoline **3c** could be isolated at all. In contrast, electron-deficient diaryliodonium salts bearing 4-bromo or 4-trifluoromethyl substituents furnished *N*-aryl indolines **3d** and **3e** in yields of 65 and 62%, respectively (Table 2, entries 3 and 4).

Unsymmetrically substituted diaryliodonium salts are known to react chemoselectively with different types of nucleophiles. However, the chemoselectivity strongly depends on the nature of the nucleophile[10a,24] and the presence of a transition metal.[11f,12,14a,c,25]

To verify the chemoselectivity for the metal-free arylation of indolines, we reacted **1a** under our standard protocol together with (2,4,6-trimethylphenyl)(phenyl)iodonium triflate.[23c] Here, we isolated a product mixture containing both possible N-arylated indolines, albeit in low yields. Compounds **3a** and **3f** were isolated in 16% and 5% yield. This result matches well with the general observed chemoselectivity trend in nonmetal-catalyzed reactions with hypervalent diaryliodonium salts. Furthermore, a recent report[25a] from Olofsson and coworkers stimulated us to investigate *N*-heteroaryl-containing diaryliodonium triflates. However, a variety of heteroaryl-containing iodonium triflates **4a**–**d** did not react with indoline **1a** under our opti-

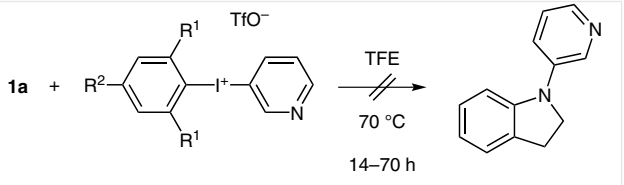
Table 2 Using Different Substituted Symmetrical and Unsymmetrical Iodonium Salts[a]



Entry	R^1	R^2	R^3	Time (h)	*N*-Aryl indoline **3**	Yield (%)[b]
1	H	Me	Me	48	**3b**	41
2	H	OMe	OMe	88	**3c**	0
3	H	Br	Br	22	**3d**	65[c]
4	H	CF_3	CF_3	4	**3e**	62
5[d]	Me	Me	H	24	**3a** R^1, R^2 = H **3f** R^1, R^2 = Me	16 5[e]

[a] Typical reaction conditions: **1a** (0.21 mmol), **2** (1.1 equiv), solvent (3–4 mL).
[b] Isolated yield after column chromatography.
[c] Average of two runs.
[d] Conditions: **1a** (0.36 mmol), **2** (1.1 equiv).
[e] Isolated by column chromatography.

mized reaction conditions (Scheme 1). We generally isolated significant amounts of the corresponding 4-substituted iodoarenes as the sole reaction products.

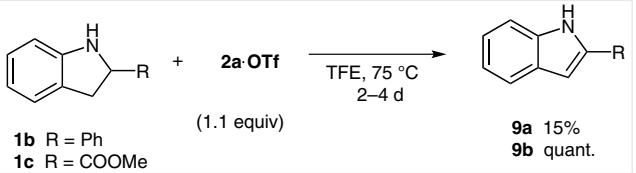


Scheme 1 Attempts using *N*-heteroaryl diaryliodonium triflates as arylating reagents for indoline **1a**

We next concentrated our work on the exploration of the substrate scope using other indolines and other nitrogen heterocycles (Figure 1). Methyl-substituted indolines gave the corresponding products **6a** and **6b** in moderate yields (50% and 41%, respectively). When we used indolines with a hydroxy functionality, we were interested if we could observe a difference in chemoselectivity. However, from the reaction mixture we only isolated **6c** and **6e** as sole N-arylated products in low yields, which indicates that the free hydroxyl group remained untouched. 3-Nitrile-substituted indoline gave **6d** in 18% yield, while the 2-methyl derivative yielded **6f** in 29% yield.

Nitrogen heterocycles, such as 1*H*-indole, 1*H*-benzo[*d*]imidazole gave trace amounts of product. 1,2,3,4-Tetrahydroquinoline did not react at all. With 1*H*-indazole at least 12% of the N-arylated product **7** was observed. Next, we submitted 1*H*-benzotriazole together with a variety of diaryliodonium salts. Under optimized reaction conditions (see Supporting Information) we observed a high N2-selectivity[26] and isolated the N2-arylated products **8a**–**d** in moderate yields (25–46%).

Indolines with a phenyl or ester group in the 2-position of the indoline underwent reoxidation in the presence of the hypervalent iodine arylating reagent. In both cases the corresponding indoles **9a** and **9b** were isolated (Scheme 2).



Scheme 2 Arylation of 2-substituted indolines **1b** and **1c** yield the corresponding indoles

To conclude, we have demonstrated for the first time the transition-metal-free N-arylation of indolines by utilizing diaryliodonium salts as mild and nontoxic arylating reagents. Beside other indolines, 1*H*-benzotriazole could be used as well in our N-arylation procedure. The corresponding N-arylated products could be isolated in moderate to acceptable yields. In future research we want to look deeper

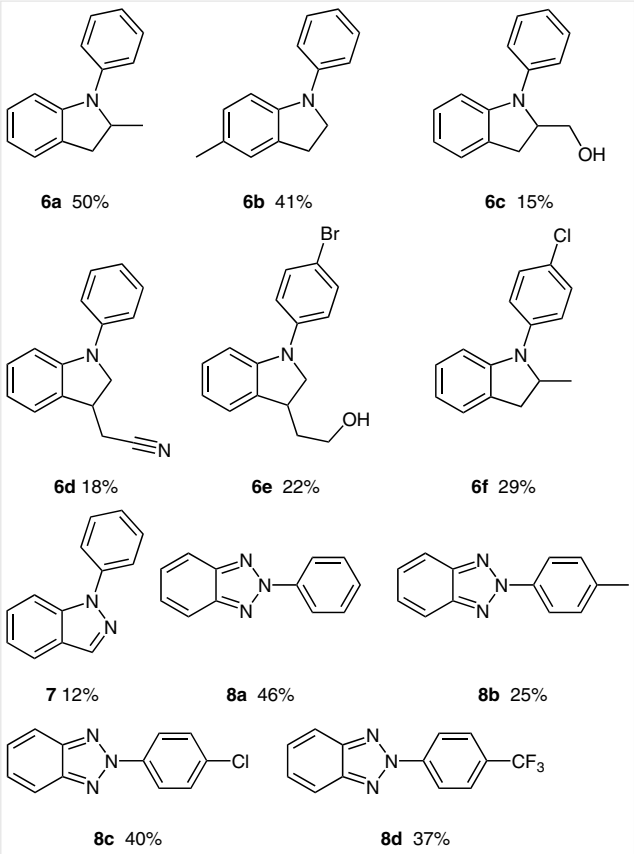


Figure 1 Scope of isolated N-arylated indolines and 2-arylated benzotriazoles in our investigation

into the side-product portfolio of this transformation to get a better idea about its mechanism and improve product yields, also for a more rational design of metal-free arylations of other N-heterocyclic nucleophiles.

Acknowledgment

Financial support by the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie (Sachkostenzuschuss) is acknowledged. S.R. gratefully acknowledges Merck KGaA for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379885.

References and Notes

(1) Gan, Z.; Reddy, P. T.; Quevillon, S.; Couve-Bonnaire, S.; Arya, P. *Angew. Chem.* **2005**, *117*, 1390.
(2) Mathvink, R. J.; Barritta, A. M.; Candelore, M. R.; Cascieri, M. A.; Liping, D.; Tota, L.; Strader, C. D.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1869.
(3) Kuang, D.; Uchida, S.; Humphry-Baker, R.; Zakeeruddin, S. M.; Grätzel, M. *Angew. Chem.* **2008**, *120*, 1949.
(4) (a) Gribble, G. W.; Hoffman, J. H. *Synthesis* **1977**, 859. (b) Heath-Brown, B. *Chem. Ind. (London)* **1969**, 1595.
(5) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403.
(6) Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M.-O.; Deng, G.-J.; Li, C.-J. *Org. Lett.* **2012**, *14*, 5606.
(7) Basolo, L.; Bernasconi, A.; Borsini, E.; Broggini, G.; Beccalli, E. M. *ChemSusChem* **2011**, *4*, 1637.
(8) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198.
(9) (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Finkbeiner, P.; Nachtsheim, B. J. *Synthesis* **2013**, *45*, 979. (c) Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, *26*, 5769. (d) Wirth, T. *Hypervalent Iodine Chemistry*; Springer: Berlin/Heidelberg, **2003**. (e) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271. (f) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (g) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (h) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (i) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656.
(10) (a) Merritt, E. A.; Olofsson, B. *Angew. Chem.* **2009**, *121*, 9214. (b) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *ARKIVOC* **2011**, *(i)*, 370.
(11) (a) Kumar, D.; Arun, V.; Pilania, M.; Shekar, K. P. C. *Synlett* **2013**, *24*, 831. (b) Umierski, N.; Manolikakes, G. *Org. Lett.* **2012**, *15*, 188. (c) Eastman, K.; Baran, P. S. *Tetrahedron* **2009**, *65*, 3149. (d) Castro, S.; Fernandez, J. J.; Vicente, R.; Fananas, F. J.; Rodriguez, F. *Chem. Commun.* **2012**, *48*, 9089. (e) Umierski, N.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 4972. (f) Wagner, A. M.; Sanford, M. S. *J. Org. Chem.* **2014**, *79*, 2263.
(12) Carroll, M. A.; Wood, R. A. *Tetrahedron* **2007**, *63*, 11349.
(13) Norrby, P.-O.; Petersen, T. B.; Bielawski, M.; Olofsson, B. *Chem. Eur. J.* **2010**, *16*, 8251.
(14) (a) Petersen, T. B.; Khan, R.; Olofsson, B. *Org. Lett.* **2011**, *13*, 3462. (b) Jalalian, N.; Ishikawa, E. E.; Silva, L. F.; Olofsson, B. *Org. Lett.* **2011**, *13*, 1552. (c) Jalalian, N.; Petersen, T. B.; Olofsson, B. *Chem. Eur. J.* **2012**, *18*, 14140.
(15) Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. *Org. Lett.* **2011**, *13*, 2358.
(16) Wen, J.; Zhang, R.-Y.; Chen, S.-Y.; Zhang, J.; Yu, X.-Q. *J. Org. Chem.* **2012**, *77*, 766.
(17) Guo, F.; Wang, L.; Wang, P.; Yu, J.; Han, J. *Asian J. Org. Chem.* **2012**, *1*, 218.
(18) Wang, F.-Y.; Chen, Z.-C.; Zheng, Q.-G. *J. Chem. Res.* **2004**, 206.
(19) Li, J.; Liu, L. *RSC Adv.* **2012**, *2*, 10485.
(20) (a) Kloeckner, U.; Weckenmann, N. M.; Nachtsheim, B. J. *Synlett* **2012**, *23*, 97. (b) Hempel, C.; Weckenmann, N. M.; Maichle-Moessmer, C.; Nachtsheim, B. J. *Org. Biomol. Chem.* **2012**, *10*, 9325. (c) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754.
(21) Riedmueller, S.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2013**, *9*, 1202.
(22) When diaryliodonium salts with more nucleophilic counterions (e.g., halogens) were used, in some cases they have a negative influence on the specific reaction due to the nucleophilic nature of the counterion; cf. ref. 12 and 14b.

(23) (a) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, 592. (b) Bielawski, M.; Olofsson, B. *Chem. Commun.* **2007**, 2521. (c) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610. (d) Kuriyama, M.; Hamaguchi, N.; Onomura, O. *Chem. Eur. J.* **2012**, *18*, 1591.

(24) Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B. *Chem. Eur. J.* **2013**, *19*, 10334.

(25) (a) Bielawski, M.; Malmgren, J.; Pardo, L. M.; Wikmark, Y.; Olofsson, B. *ChemistryOpen* **2014**, *3*, 19. (b) Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. *Org. Lett.* **2011**, *13*, 2358. (c) Ghosh, R.; Olofsson, B. *Org. Lett.* **2014**, *16*, 1830. (d) Oh, C. H.; Kim, J. S.; Jung, H. H. *J. Org. Chem.* **1999**, *64*, 1338. (e) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (f) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924. (g) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13778. (h) Walkinshaw, A. J.; Xu, W.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 12532. (i) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (j) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773.

(26) (a) Beletskaya, I. P.; Davydov, D. V.; Moreno-Mañas, M. *Tetrahedron Lett.* **1998**, *39*, 5621. (b) Tomas, F.; Abboud, J. L. M.; Laynez, J.; Notario, R.; Santos, L.; Nilsson, S. O.; Catalan, J.; Claramunt, R. M.; Elguero, J. *J. Am. Chem. Soc.* **1989**, *111*, 7348. (c) Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389.

(27) **General Procedure for the N-Arylation of Indoline (1a) with Diphenyliodonium Triflate (2a) to 1-Phenylindoline (3a)**

Diphenyliodonium triflate (**2a**, 0.1 g, 0.23 mmol, 1.1 equiv) was charged in a vial and sealed with a septum. After adding TFE (3 mL), indoline (**1a**, 0.024 mL, 0.21 mmol) was added dropwise slowly to the solution, which was then heated to 70 °C for 14 h. After the solution was cooled to r.t., the mixture was diluted with H_2O and sat. $NaHCO_3$. The aqueous phase was extracted several times with CH_2Cl_2. The organic phase is washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel, eluting with cyclohexane–CH_2Cl_2 (2:1, v/v) giving 34 mg (83%) of **3a** as a colorless solid.

2,3-Dihydro-1-(4-methylphenyl)-1*H*-indole (3b)

Pale yellow oil, partially crystalline (18 mg, 41%); eluent: cyclohexane–CH_2Cl_2 (20:1 → 15:1 → 10:1, v/v); mp 66–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.13 (m, 5 H), 7.07–7.04 (m, 2 H), 6.75–6.69 (m, 1 H), 3.93 (t, 2 H, *J* = 8.5 Hz), 3.12 (t, 2 H, *J* = 8.5 Hz), 2.33 (s, 3 H). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 147.7, 141.9, 131.2, 130.8, 129.8, 127.2, 125.1, 118.6, 118.3, 108.0, 52.5, 28.3, 20.9. IR (neat): 2360, 2341, 1770, 1742, 1597, 1515, 1482, 1456, 1384, 1312, 1296, 1246, 1166, 1127, 1063, 1049, 924, 869, 815, 742, 703 cm^{-1}. HRMS (APCI): *m/z* calcd for $C_{15}H_{15}N$: 209.12045; found [M + H]$^+$: 210.12714.

1-(4-Chlorophenyl)-2-methylindoline (6f)

Pale yellow oil (15 mg, 29%); eluent: cyclohexane–CH_2Cl_2 (5:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (d, 2 H, *J* = 8.8 Hz), 7.18 (d, 2 H, *J* = 8.8 Hz), 7.14 (d, 1 H, *J* = 7.2 Hz), 7.03 (t, 1 H, *J* = 7.5 Hz), 6.78 (d, 1 H, *J* = 7.9 Hz), 6.74 (t, 1 H, *J* = 7.4 Hz), 4.36–4.30 (m, 1 H), 3.33 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 15.5 Hz), 2.76 (dd, 1 H, J_1 = 7.4 Hz, J_2 = 15.4 Hz), 1.31 (d, 3 H, *J* = 6.1 Hz). ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 148.4, 142.3, 129.7, 129.4, 127.7, 127.3, 125.1, 122.9, 119.3, 108.5, 60.1, 37.3, 20.1. HRMS (APCI): *m/z* calcd for $C_{15}H_{14}ClN$: 243.08148 (100%), found [M + H]$^+$: 244.08851.