N-(2-Aminobenzylidene)-4-methylanilines - stable and cheap alternate for 2-aminobenzaldehydes: concise synthesis of 3-unsubstituted-2-aroylindoles

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Graphical Abstract

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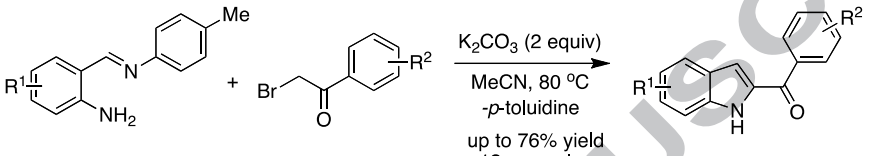

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N-(2-Aminobenzylidene)-4-methylanilines - stable and cheap alternate for 2-aminobenzaldehydes: concise synthesis of 3-unsubstituted-2-aroylindoles

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ABSTRACT

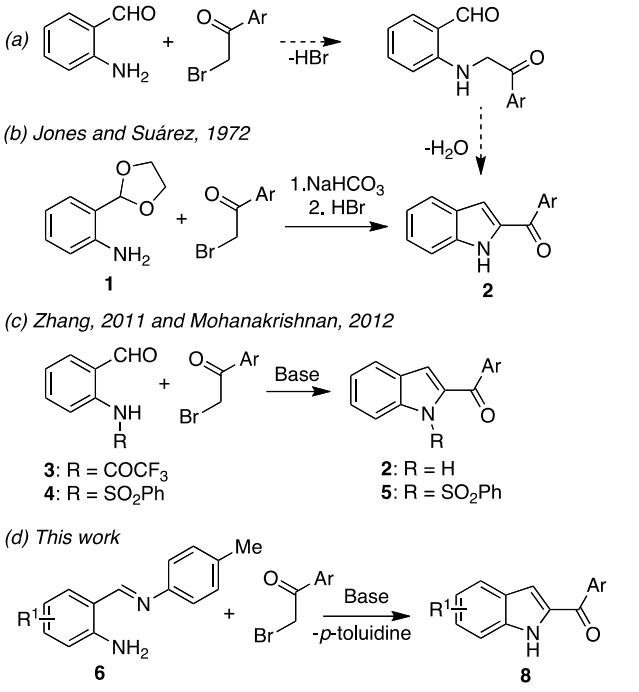
Synthesis of 3-unsubstituted-2-aroylindoles starting from readily available *N*-(2-aminobenzylidene)-4-methylanilines, cheap and stable alternate to 2-aminobenzaldehydes, and α-bromoketones was achieved in moderate to good yields under basic conditions. The reaction proceeded *via* sequential *N*-alkylation-intramolecular nucleophilic cyclization-elimination steps in a single operation.

Nitrogen heterocycles are common structural fragments of countless pharmaceuticals and agrochemicals, indeed, 59% of US FDA approved small molecule drugs contain at least one nitrogen heterocycle.[1] Especially indoles occupy a position in the top-ten most frequent nitrogen ring system present in drug molecules. Furthermore, indoles are one of the most significant scaffold present in large number of natural products[2] and bioactive molecules.[3,4] Consequently, much effort has been devoted to the synthesis of indole derivatives despite the available traditional methods including Fischer, Bischler, Bartoli, Reissert and Nenitzescu reactions.[5]

2-Aroylindoles are particularly important owing to their specific pharmacological properties. For instance, these compounds act as tubulin polymerization inhibitors[6] and autophosphorylation of platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitors.[7] Besides, 2-aroylindoles are potential histone deacetylase (HDAC) class I/II inhibitors with broad cytotoxicity superior to that of the approved drug SAHA[8] and posses antimitotic activity in human cancer cells.[9] Despite the biological significance of these class of compounds, only a limited number of straightforward procedures have been developed for their synthesis.[10]

One of the simplest routes to access 2-aroylindoles includes the reaction between 2-aminobenzaldehydes and α-bromoketones under basic conditions involving *N*-substitution-intramolecular aldol condensation steps (Scheme 1a). Nonetheless, 2-aminobenzaldehyde is highly unstable; it undergoes polymerization rapidly under ambient conditions due to the intermolecular condensation between the reactive amino and aldehyde functionalities. Besides polymerization, 2-aminobenzaldehyde is known to undergo trimerization in nucleophilic solvents or in the presence of moisture.[11] Moreover, 2-aminobenzaldehyde is rather expensive, for instance, one gram of unsubstituted 2-aminobenzaldehde costs 180 USD. Hence it is highly essential to find out a cheap and stable alternate for 2-aminobenzaldehydes to access 3-unsubstituted-2-aroylindoles. Jones and Suárez reported the synthesis of 2-aroylindoles **2** starting from amino acetal **1** and phenacyl bromide in moderate yield (Scheme 1b).[12] Alternatively, the relatively stable *N*-trifluoroacetyl or *N*-phenylsulfonyl-2-aminobenzaldehydes (**3**[13] and **4**[14]) were used as 2-aminobenzaldehyde equivalents to obtain the products **2** and **5**, respectively, in good to moderate yields (Scheme 1c). However, compound **3** was prepared from the corresponding 2-aminobenzaldehydes, again with the difficulties associated with handling of 2-aminobenzaldehydes, on the other hand, compound **4** was prepared from 2-aminobenzyl alcohol in two steps. Notwithstanding these protocols, it would be convenient if we could protect the aldehyde group instead of the amino functionality of 2-aminobenzaldehyde to obtain *N*-unsubstituted indoles. With this background, we envisioned to utilize the readily available and stable *N*-(2-aminobenzylidene)-4-methylanilines **6** as alternate to 2-aminobenzaldehydes to synthesize 3-unsubstituted-2-aroylindoles **8** (Scheme 1d). Importantly, compound **6** could be derived from the stable and economical 2-nitrobenzaldehydes (25 g = 51 USD) in two simple steps involving imine formation and sodium sulfide-mediated reduction.[15]

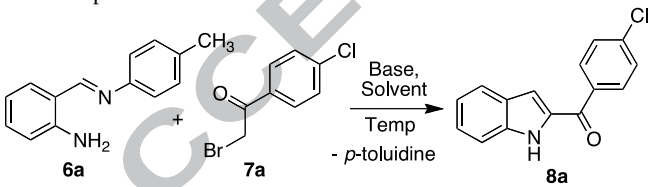
Our initial optimization study began with the reaction of *N*-(2-aminobenzylidene)-4-methylaniline **6a** and *p*-chlorophenacyl bromide **7a**. The reaction was carried out at 25 ^{o}C in a variety of



Scheme 1 Synthesis of 2-aroylindoles from 2-aminobenzaldehyde equivalents and α-bromoketones.

solvents including ethanol, DCM, DCE, dioxane, toluene, DMF, acetonitrile and water in the presence of two equivalents of potassium carbonate. Virtually, in all these solvents no product formation was observed and in few cases the intermediate *N*-alkylation product was noticed in small quantities. Increase of the reaction temperature led to the product formation albeit in low yields in most of the tested solvents. Although the starting materials were completely consumed within four hours in ethanol, DCM, DCE and dioxane only 15-30% product was isolated (Table 1, entries 1 to 4). Toluene was completely ineffective and DMF furnished only 36% of isolated product (entries 5 and 6). Eventually, we found that acetonitrile was effective to afford 71% of indole **8a** in three hours reaction time at 80 °C (entry 7). Neither increase of the amount of base nor the α-bromoketone improved the yield significantly. A green alternate, water, was also tested for the reaction and merely 24% of product was isolated (entry 8). When other bases including Cs_2CO_3, triethylamine, pyrrolidine and piperidine were tested in acetonitrile, the yields were decreased considerably, in fact, only traces of the product was observed in the presence of Cs_2CO_3 (entries 9-12). Ultimately, we reserved the combination of acetonitrile and potassium carbonate at 80 °C for further studies.

Table 1 Optimization of reaction conditions.[a]

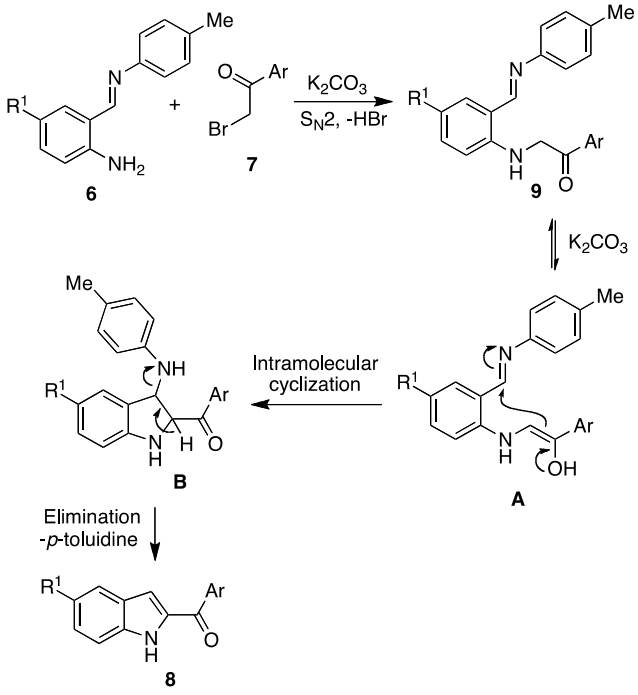


Entry	Base (2 equiv)	Solvent	Temp. (°C)[b]	Time (h)	Yield (%)[c]
1	K_2CO_3	EtOH	80	4	15
2	K_2CO_3	DCM	40	2.5	13
3	K_2CO_3	DCE	45	2.5	24 (29)[e]
4	K_2CO_3	Dioxane	100	3	30
5	K_2CO_3	Toluene	100	15	trace
6	K_2CO_3	DMF	100	3	36
7[d]	**K_2CO_3**	**MeCN**	**80**	**3**	**71 (70,[f] 74[g])**
8	K_2CO_3	Water	80	3	24
9	Cs_2CO_3	MeCN	80	3	trace
10	Et_3N	MeCN	80	2	18
11	Pyrrolidine	MeCN	80	3.5	15
12	Piperidine	MeCN	80	3.5	23

[a] Unless otherwise noted, all reactions were carried out with **6a** (1 mmol), **7a** (1 mmol) and base (2 mmol) in 5 mL solvent. [b] No product formation was observed for reactions 1 to 8 at 25 °C. [c] Isolated yield. [d] Use of 3 equiv of base did not improve the yield. [e] Reaction was carried out at 80 °C. [f] 1.3 equiv of **7a** was used. [g] 1.5 equiv of **7a** was used.

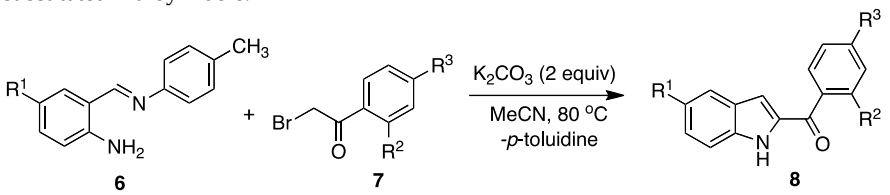
Having established the optimal reactions conditions, we then studied the scope and limitations of the methodology involving a couple of *N*-(2-aminobenzylidene)-4-methylanilines **6** and a large number of α-bromoketones **7** to access 3-unsubstituted-2-aroylindoles **8** and the results are summarized in Table 2.[16] The reaction showed high functional group tolerance in both the reactants. α-Bromoketones bearing electron-donating group (Me, entry 4), moderately electron-withdrawing groups (Cl, Br entries 2, 3, 6 and 11) and strongly electron-withdrawing group (NO_2, entries 5 and 10) afforded the corresponding 3-unsubstituted-2-aroylindoles **8** in moderate to good yields. 2-Acetylnaphthalene derived α-bromoketone (entries 7 and 12) and 2-furfuryl derivative (entry 8) were also effective to afford the corresponding 2-aroylindoles in good yields. Furthermore, 2,4-dichlorophenacyl bromide was also reacted with compound **7** to yield 76% of the product (entry 6). To our delight, *N*-(2-aminobenzylidene)-4-methylaniline also tolerated bromo-substituent with no significant change in the reactivity (entries 9-12).

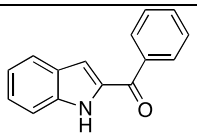
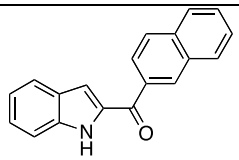
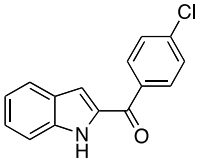
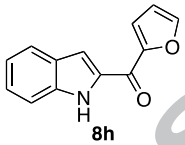
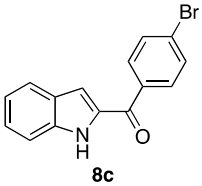
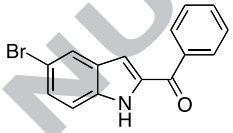
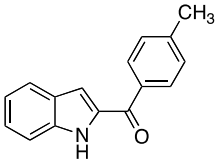
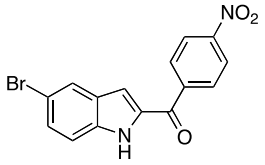
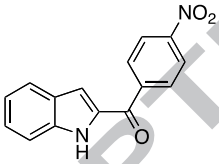
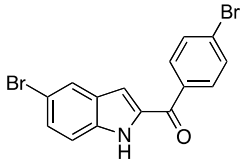
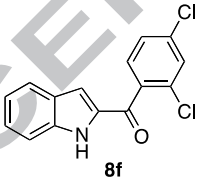
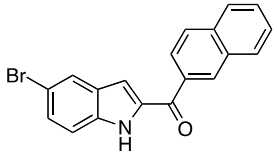
The proposed mechanism for the formation of 2-aroylindoles is depicted in Scheme 2. A base mediated initial *N*-alkylation of imines **6** with α-bromoketones **7** affords *N*-phenacylanilines **9**.[17] Subsequently, intermediate **9** undergoes an intramolecular nucleophilic cyclization *via* its enolic form **A** to generate the 3-aminoindoline species **B**. Final elimination of *p*-toluidine from intermediate **B** at elevated temperature furnishes the products **8**.[11b,12] High temperature is essential for the intramolecular cyclization and the subsequent elimination steps. Among the tested solvents, acetonitrile was the best presumably due to its polar aprotic nature to facilitate the initial S_N2 reaction and the subsequent intramolecular nucleophilic cyclization. Potassium carbonate, a weak base, promotes the initial *N*-alkylation in a controlled manner and facilitates the subsequent cyclization *via* enolization.



Scheme 2 Plausible mechanism.

Table 2 Synthesis of 3-unsubstituted-2-aroylindole.[a]



Entry	Product **8**	Yield (%)[b]	Entry	Product **8**	Yield (%)[b]
1	 **8a**	74	7	 **8g**	67
2	 **8b**	71	8	 **8h**	69
3	 **8c**	74	9	 **8i**	65
4	 **8d**	70	10	 **8j**	60
5	 **8e**	68	11	 **8k**	57
6	 **8f**	76	12	 **8l**	66

[a] Reaction conditions: unless otherwise noted all reactions were carried out with **6** (1 mmol), **7** (1 mmol) and K_2CO_3 (2 mmol) in 5 mL acetonitrile at 80 °C for 3 h. [b] Isolated yield

In summary, we have developed a facile synthetic procedure for the synthesis of 3-unsubstituted-2-aroylindoles starting from readily available *N*-(2-aminobenzylidene)-4-methylanilines and α-bromoketones under basic conditions. The base-mediated sequential *N*-alkylation-intramolecular nucleophilic cyclization-elimination reactions afforded the products in moderate to good yields in a single operation. The reaction tolerated a variety of substituents on both the reactants. We believe that this method would be a good addition to the existing methods to access 3-unsubstituted-2-aroylindoles. This protocol demonstrated that *N*-(2-aminobenzylidene)-4-methylanilines derived from easily accessible 2-nitrobenzaldehydes, remain the stable and cheap alternate to 2-aminobenzaldehydes.

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Supplementary data

Supplementary data associated with this article (characterization data and copies of NMR spectra) can be found, in the online version at http://dx.doi.org/10.1016/j.tetlet.2015

References and notes

1. For a miniperspective, see: Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.
2. For selected reviews of indole natural products, see: (a) Xu, W.; Gavia, D. J.; Tang, Y. *Nat. Prod. Rep*. **2014**, *31*, 1474; (b) Marcos, I. S.; Moro, R. F.; Costales, I.; Basabe, P.; Díez, D. *Nat. Prod. Rep*. **2013**, *30*, 1509; (c) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep*. **2013**, *30*, 694; (d) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev*. **2010**, *110*, 4489; (e) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev*. **2009**, *109*, 3080.
3. For selected reviews of biological importance of indoles, see: (a) Sidhu, J. S.; Singla, R.; Mayank, E. Y.; Jaitak, V. *Anticancer Med.*

Chem. **2015**, **DOI:** 10.2174/1871520615666150520144217; (b) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620; (c) Olgen, S. *Mini-Rev. Med. Chem*. **2013**, *13*, 1700; (d) Biersack, B.; Schobert, R. *Curr. Drug Targets* **2012**, *13*, 1705; (e) Lal, S.; Snape, T. J. *Curr. Med. Chem*. **2012**, *19*, 4828; (f) Ahmad, A.; Sakr, W. A.; Rahman, K. M. *Curr. Drug Targets* **2010**, *11*, 652; (g) Xu, H.; Lv, M. *Curr. Pharm. Des*. **2009**, *15*, 2120; (h) Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem*. **2009**, *16*, 2531.

4. For selected, recent examples, see: (a) Revenga, M. F.; Fernández-Sáez, N.; Herrera-Arozamena, C.; Morales-García, J. A.; Alonso-Gil, S.; Pérez-Castillo, A.; Caignard, D.-H.; Rivara, S.; Rodríguez-Franco, M. I. *J. Med. Chem.* **2015**, *58*, **DOI:** 10.1021/acs.jmedchem.5b00245; (b) Boyd, S.; Brookfield, J. L.; Critchlow, S. F.; Cumming, I. A.; Curtis, N. J.; Debreczeni, J.; Degorce, S. J.; Donald, C.; Evans, N. J.; Groombridge, S.; Hopcroft, P.; Jones, N. P.; Kettle, J. G.; Lamont, S.; Lewis, H. J.; MacFaull, P.; McLoughlin, S. B.; Rigoreau, L. J. M.; Smith, J. M.; St-Gallay, S.; Stock, J. K.; Turnbull, A. P.; Wheatley, E. R.; Winter, J.; Wingfield, J. *J. Med. Chem.* **2015**, *58*, 3611; (c) Aksenov, A. V.; Smirnov, A. N.; Magedov, I. V.; Reisenauer, M. R.; Aksenov, N. A.; Aksenova, I. V.; Pendleton, A. L.; Nguyen, G.; Johnston, R. K.; Rubin, M.; De Carvalho, A.; Kiss, R.; Mathieu, V.; Lefranc, F.; Correa, J.; Cavazos, D. A.; Brenner, A. J.; Bryan, B. A.; Rogelj, S.; Kornienko, A.; Frolova, L. V. *J. Med. Chem.* **2015**, *58*, 2206.
5. For selected reviews on indole synthesis, see: (a) Guo, T.; Huang, F.; Yu, L.; Yu, Z. *Tetrahedron Lett*. **2015**, *56*, 296; (b) Shiri, M. *Chem. Rev*. **2012**, *112*, 3508; (c) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J. C. *Chem. Soc. Rev*. **2012**, *41*, 3929; (d) Cacchi, S.; Fabrizi, G. *Chem. Rev*. **2011**, *111*, 215; (e) Cacchi, S.; Fabrizi, G. *Chem. Rev*. **2005**, *105*, 2873.
6. Brancale, A.; Silvestri, R. *Med. Chem. Rev*. **2007**, *27*, 209.
7. Mahboobi, S.; Teller, S.; Pongratz, H.; Hufsky, H.; Sellmer, A.; Botzki, A.; Uecker, A.; Beckers, T.; Baasner, S.; Schächtele, C.; Überall, F.; Kassack, M. U.; Dove, S.; Böhmer, F.-D. *J. Med. Chem*. **2002**, *45*, 1002.
8. Mahboobi, S.; Sellmer, A.; Höcher, H.; Garhammer, C.; Pongratz, H.; Maier, T.; Ciossek, T.; Beckers, T. *J. Med. Chem*. **2007**, *50*, 4405.
9. Mahboobi, S.; Pongratz, H.; Hufsky, H.; Hockemeyer, J.; Frieser, M.; Lyssenko, A.; Paper, D. H.; Bürgermeister, J.; Böhmer, F.-D.; Fiebig, H.-H.; Burger, A. M.; Baasner, S.; Beckers, T. *J. Med. Chem*. **2001**, *44*, 4535.
10. For methods to access 2-aroylindoles, see: (a) Goriya, Y.; Ramana, C. V. *Chem. Commun*. **2014**, *50*, 7790; (b) Pan, C.; Jin, H.; Liu, X.; Cheng, Y.; Zhu, C. *Chem. Commun*. **2013**, *49*, 2933; (c) Reddy, B. V. S.; Reddy, M. R.; Rao, Y. G.; Yadav, J. S.; Sridhar, B. *Org. Lett*. **2013**, *15*, 464; (d) Gao, W.-C.; Jiang, S.; Wang, R.-L.; Zhang, C. *Chem. Commun*. **2013**, *49*, 4890; (e) Arthuis, M.; Pontikis, R.; Florent, J.-C. *Org. Lett*. **2009**, *11*, 4608.
11. (a) Richers, M. T.; Deb, I.; Platonova, A. Y.; Zhang, C.; Seidel, D. *Synthesis* **2013**, 1730; (b) Sridharan, V.; Ribelles, P.; Ramos, M. T.; Menéndez, J. C. *J. Org. Chem*. **2009**, *74*, 5715; (c) Xiao, X. S.; Fanwick, P. E.; Cushman, M. *Synth. Commun*. **2004**, *34*, 3901.
12. Jones, C. D.; Suárez, T. *J. Org. Chem.* **1972**, *23*, 3622.
13. Zhao, Y.; Li, D.; Zhao, L.; Zhang, J. *Synthesis* **201**1, 873.
14. Dhayalan, V.; Panchapakesan, G.; Mohanakrishnan, A. K. *Synth. Commun*. **2012**, *42*, 402.
15. (a) Leleu, S.; Papamicaël, C.; Marsais, F.; Dupas, G.; Lavacher, *Tetrahedron: Asymmetry* **2004**, *15*, 3919.
16. General procedure for the synthesis of 3-unsubstituted-2-aroylindoles **8**: To a solution of (*E*)-*N*-(2-aminobenzylidene)-4-methylbenzenamines **6** (1 mmol) and α-bromoketones **7** (1 mmol) in dry acetonitrile (5 mL) was added potassium carbonate (2 mmol) and the mixture was stirred at 80 ^{o}C for 3 h. After completion of the reaction, as indicated by TLC, the mixture was diluted with water and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layer was washed with water followed by brine solution, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude mixture was purified through silica column chromatography eluting with petroleum ether and ethyl acetate mixture (98:2 v/v). Characterization data for representative compounds. **8a**: Off-white solid, mp. 146-147 ^{o}C (147-148 ^{o}C);[12] Yield: 74%; IR (KBr) 3313.6, 3057.2, 2924.9, 1619.7, 1516.0, 1259.6, 1126.0, 1011.4 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15-7.20 (m, 2H), 7.39 (td, *J* = 8.4, 1. 2 Hz, 1H), 7.49 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.63 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.73 (dd, *J* = 8.1, 0.6 Hz, 1H), 8.00 (dd, *J* = 8.4, 1.2 Hz, 2H), 9.32 (s, 1H); ^{13}C NMR (CDCl3, 75 MHz): δ 112.2, 112.9, 121.1, 123.3, 126.6, 127.8, 128.5, 129.2, 132.4, 134.4, 137.6, 138.3, 187.3; **8c:** Pale yellow solid, mp. 202-204 ^{o}C; Yield: 74%; IR (KBr) 3309.1, 3051.5, 2924.9, 1619.9, 1514.5, 1259.9, 1126.3, 1067.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14 (d, *J* = 1.2 Hz, 1H), 7.17 (td, *J* = 7.2, 0.9 Hz, 1H), 7.39 (td, *J* = 8.1, 0.9 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 2H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.6, 112.8, 121.0, 123.1, 126.5, 127.1, 127.5, 130.7, 131.7, 134.1, 137.0, 138.1, 186.1; **8f:** Pale yellow solid, mp. 176-178 ^{o}C; Yield: 76%; IR (KBr) 3313.0, 3079.5, 2925.4, 1621.1, 1514.2, 1254.1, 1128.2, 1103.0 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.89 (d, *J* = 1.2 Hz, 1H), 7.16 (td, *J* = 7.2, 0.9 HZ, 1H), 7.37-7.43 (m, 2H), 7.47-7.52 (m, 2H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.6, 114.6, 121.4, 123.4, 126.8, 127.4, 127.5, 130.4, 130.5, 132.9, 134.5, 136.1, 136.9, 138.5, 185.2**.**
17. Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Synlett* **2006**, 91.