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A novel approach for highly regio- and stereoselective synthesis of (*Z*)-3-methyleneisoindoline-1-ones in aqueous micellar medium

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ABSTRACT

An environmentally benign and operationally simple methodology was developed for the regio- and stereoselective synthesis of (*Z*)-3-methyleneisoindolinones in aqueous micellar medium from 2-iodo-*N*-phenyl-benzamides and terminal alkyne by Cu-free domino Sonogashira reaction followed by 5-exo-dig-cyclization using $Pd(CH_3CN)Cl_2$ as catalyst and 1,4-bis(4-pyridyl)-2,3-diaza-1,3-butadiene as ligand under aerobic condition.

In recent years considerable attention has been perceived among the synthetic organic chemists to execute organic reactions in water[1] because of its abundance in nature, having virtually no cost, and being the safest among all available solvents, leading to environmentally benign chemical processes.[2] But limited solubility of various organic compounds in water actually prevents the execution of reactions in aqueous media. Introduction of aqueous surfactant, in the form of micelles,[3] as the reaction medium has provided a way around this limitation to some extent. In conventional micellar catalysis, the surfactant micelles actually accumulate all reacting molecules within the small volume, both by solubilization due to hydrophobic effect and by counter ion binding due to electrostatic interactions, resulting in high concentration of the molecules with different orientations. It actually influences reaction mechanism, resulting in remarkable differences with respect to reaction rate and selectivity that is observed in homogeneous systems.[4]

Because of the significant biological profile of isoindolin-1-ones and its derivatives,[5] like anti-hypertensive,[6] anti-viral,[7] anti-leukemic,[8] or anti-inflammatory activity,[9] we focused our attention on this scaffold. Isoindolin-1-ones and its derivatives are found in the core structure of a number of naturally occurring and pharmacologically interesting substances like fumaridine,[10] lennoxamine,[11] AKS 186,[12] pictonamine,[13] and pazinaclone.[14] Pazinaclone, pagoclone, and zopiclone showed potent anxiolytic activity, and are of interest as sedatives, hypnotics, and muscle relaxants.[15] The isoindolinone moiety is also found in a group of natural products as exemplified by aristolactam alkaloids.[16]

The varied biological activities of isoindolinone derivatives have attracted the attention of organic chemists and a number of synthetic methodologies have been developed for the preparation of isoindolinone derivatives.[17–25] But many such approaches are plagued by constraints[26,27] like low yield and long time for completion, and if the *o*-iodo benzamides and terminal aryl acetylenes are used as precursors under Pd–Cu catalysis, acyclic Sonogashira product or 6-endo-dig cyclized product, that is, isoquinolinones are formed as side products.

Palladium(II) salts having bidentate *N,P*- or *N,N*-ligands have been established to be efficient catalysts for C–C or C–N bond forming reaction. The most common catalytic systems used in the heteroannulation reaction are mainly $PdCl_2(PPh_3)_2$, $Pd(dba)_4$, and $Pd(dtbpf)Cl_2$ using amines as solvents or co-solvents with CuI as the co-catalyst. Although copper-free Sonogashira cross coupling reactions were reported,[28,29] they generally employed the use of a combination of at least one phosphine as ligand or an amine with *tetra*-butyl ammonium salts as activator. But under these circumstances the use of degassed solvents is essential as phosphine in palladium complexes is often moisture sensitive. We explored a simple, efficient, and green protocol in aqueous micellar medium where a domino Sonogashira-5-exo-dig-cyclization reaction has been used for the complete regio- and stereo-selective synthesis

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of isoindolinones in short reaction time. The method allows domino Sonogashira-cyclization of *o*-bromo or *o*-iodo-*N*-phenylbenzamides and terminal alkyne under aerobic conditions using 1,4-bis(4-pyridyl)-2,3-diaza-1,3-butadiene (**2**) as ligand (Fig. 1). The method excludes the use of copper, organic solvents, phosphine ligands, or the presence of *tetra*-butyl ammonium salts as activator. A library of (*Z*)-3-methyleneisoindoline-1-ones could thus be generated in high yield and short reaction time. The novelty of the methodology lies in its eco-friendly operation, formation of structurally unique molecules, short reaction time, and excellent yield.

We envisaged using 2-iodo-*N*-substituted benzamides to endow varied acetylenes that could subsequently be used in a one-pot, two-step synthesis of 3-methyleneisoindoline-1-ones (Scheme 1). At the outset, we opted 2-iodo-*N*-phenylbenzamide (**3a**) and phenylethyne (**4a**) as model reactants for the synthesis of 3-methyleneisoindoline-1-one (**5a**) and investigated the feasibility of a copper-free Sonogashira coupling-cycloisomerization domino strategy in aqueous medium (Table 1) to determine the optimal reaction condition using $Pd(CH_3CN)_2Cl_2$ (2 mol %) as the source of palladium. The effect of different hydrazone ligands[29] (Fig. 1) was also investigated. Among the ligands, **1a** and **1b** sound good as it produces a remarkable yield of 73% and 69%, respectively, whereas the use of bishydrazone ligand **1c**, **1d**, or **1e** having a seven-membered ring was not found as effective (gave poor to moderate yield in repetitive experiments). However, the use of ligand **2** (1,4-bis(4-pyridyl)-2,3-diaza-1,3-butadiene) led to an excellent yield of 92% for this reaction.

The effect of micelle has also been noticed in the reaction sequence. The results summarized in Table 1 revealed that, when the reaction was carried out in the absence of a surfactant, no product was isolated even up to 48 h under aerobic condition. An encouraging change in the outcome was noticed when cetyltrimethylammonium bromide (CTAB, 50 mM, cmc 0.92 mM)[30] was introduced in the system. Carrying out the reaction in water at 80 °C for 1 h ensured its completion (monitored by TLC) but gave a low yield (25%; Table 1, entry 2) of **5a**. A drastic change in the reaction yield was observed when the amount of the surfactant is increased. The most prominent result (92%) was obtained when the reaction was performed using CTAB at 80 mM concentration (Table 1, entry 5). However, no significant increase in the yield was observed on enhancement of the concentration of CTAB beyond 80 mM (Table 1, entry 6). Changing to other surfactant, the reaction yielded a decreased amount of product **5a**; with sodium dodecylsulfate (SDS: cmc 8.1 mM)[31] produced 75% (Table 1, entry 8) and with *tetra*-decyltrimethylammonium bromide (TTAB: cmc value 3.8 mM)[32] produced 86% (Table 1, entry 7) both at the concentration of 80 mM. Even the use of a nonionic surface active agent such as Triton X-114 (cmc 0.28 mM)[33] proved less effective compared to CTAB or TTAB (Table 1, entry 9).

Table 1
Effect of different surfactants on the yield of **5a**

Entry[a]	Surfactant	Concentration (mM)	Yield[b] (%)
1	None	—	NR[c]
2	CTAB	50	25
3	CTAB	60	46
4	CTAB	70	72
5	**CTAB**	**80**	**92**
6	CTAB	90	92
7	TTAB	80	86
8	SDS	80	75
9	Triton X-114	80	75

[a] All the reactions were performed using **3a** (1 mmol) and **4a** (1.5 mmol) in water at 80 °C for 1 h under aerobic condition.
[b] Yield of isolated pure product; catalyst used $Pd(CH_3CN)_2Cl_2$ (2 mol %), ligand **2** (2.5 mol %).
[c] No reaction.

The effect of different bases, viz. DBU, Et_3N, DABCO, DMAP, K_2CO_3, and Cs_2CO_3 has also been envisaged (Table 2). DBU appeared to be the most effective when employed in 1.5 mol equiv affording the product in maximum yield. The results concluded that organic bases worked well in comparison to inorganic bases. It is worth mentioning that other Pd-sources [Pd/C-PPh_3, $PdCl_2$, $Pd(PPh_3)_4$, $Pd(dba)_2$, $Pd_2(dba)_3$, Pd-BINAP, Na_2PdCl_4, and $Pd(dtbpf)Cl_2$] however gave either very poor or no yield.

To explore the scope and generality of this approach, we used various aryl or heteroaryl alkynes (Table 3). All the reactions yielded only *Z*-3-methylene isomer and no side product was obtained. The structures of all the products were confirmed by IR, NMR, and MS spectroscopy. Finally, single crystal X-ray analysis

Table 2
Effect of different bases on the yield of **5a**

Entry[a]	Base	Amount (mmol)	Time (h)	Yield[b] (%)
1	Cs_2CO_3	1.0	1	40
2	K_2CO_3	1.0	1	32
3	Et_3N	1.0	1	80
4	DABCO	1.0	1	82
5	DMAP	1.0	1	80
6	DBU	1.0	1	86
7	**DBU**	**1.5**	**1**	**92**
8	DBU	2.0	1	92

[a] All the reactions were performed using **3a** (1 mmol) and **4a** (1.5 mmol) in water at 80 °C for 1 h under aerobic condition in the presence of CTAB (80 mM), $Pd(CH_3CN)_2Cl_2$ (2 mol %), and ligand **2** (2.5 mol %).
[b] Yield of isolated pure product.

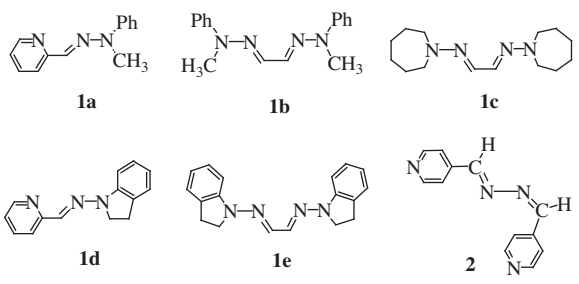
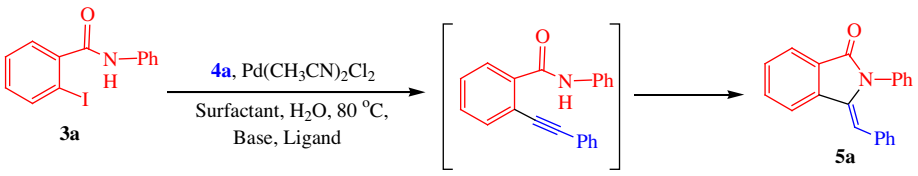
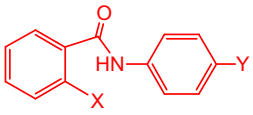
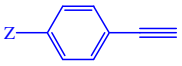
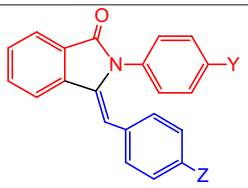
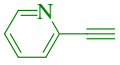
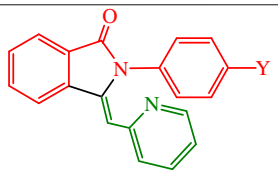
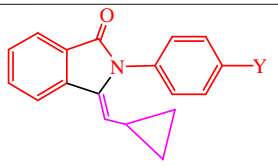


Figure 1. Ligands used in the study.

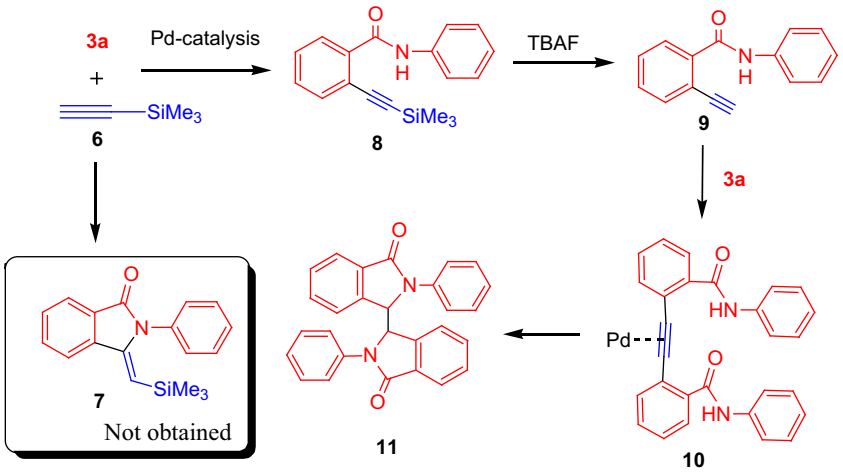


Scheme 1. Synthesis of **5a** in aqueous micellar medium.

Table 3
Reactions of 2-halobenzamides (**3a–c**) with terminal alkynes (**4a–e**) leading to isoindolinones (**5a–j**) in aqueous micellar medium

Entry[a]	Amide	Acetylene	Product	Yield[b] (%)	Ref.
					
1	**3a:** X = I, Y = H	**4a:** Z = H	**5a:** Y = H, Z = H	92	25b
2	**3b:** X = I, Y = CH_3	**4a**	**5b:** Y = CH_3, Z = H	94	25b
3	**3c:** X = Br, Y = H	**4a**	**5a**	83	25b
4	**3a**	**4b:** Z = OCH_3	**5c:** Y = H, Z = OCH_3	90	25b
5	**3b**	**4b**	**5d:** Y = CH_3, Z = OCH_3	87	-
6	**3a**	**4c:** Z = C_5H_{11}	**5e:** Y = H, Z = C_5H_{11}	80	-
7	**3b**	**4c**	**5f:** Y = CH_3, Z = C_5H_{11}	82	-
					-
8	**3a**	**4d**	**5g:** Y = H	74	-
9	**3b**	**4d**	**5h:** Y = CH_3	72	-
					-
10	**3a**	**4e**	**5i:** Y = H	66	-
11	**3b**	**4e**	**5j:** Y = CH_3	68	-

[a] Reactions were performed using **3a–c** (10 mmol), alkyne (15 mmol), $Pd(CH_3CN)_2Cl_2$ (2 mol %), ligand **2** (2.5 mol %), and DBU (15 mmol) in water at 80 °C for 1 h under aerobic condition in the presence of CTAB. Products were characterized by spectroscopic and analytical data.
[b] Isolated yield.



Scheme 2. Synthesis of dimer **11**.

of product **5b** (see Supplementary data) confirmed the stereochemistry and structure simultaneously.

It is notable that, when the aryl substituent on the nitrogen atom of the benzamide moiety is replaced by hydrogen atom, that is for 2-iodobenzamide, only Sonogashira product is formed. However, the presence of aryl substituent on the terminal alkyne, which was found to be the essential requirement for one-pot synthesis of isoindolinones from corresponding 2-iodobenzamides and terminal alkynes via Pd-mediated synthesis,[25b] is no longer mandatory in our case (Table 3, entry 10–11). Another major advantage of the protocol is that no dimerized product, which normally occurs during heteroannulation reaction and leads to the reduced reaction yield of the product, was observed in our case. Moreover, the corresponding bromides **3c**, which are less prone to participate in such a reaction, are found to be equally good in our reaction condition (Table 3, entry 3).

It is interesting to note that with *o*-iodo benzamide **3a** and trimethylsilyl acetylene (**6**) under the above condition, the reaction yielded the desired cyclized product **7**.[25b] But when *tetra*-butylammonium fluoride (50 mol %) was added to the system dimer **11**[34] was formed as the sole product (Scheme 2).

A plausible mechanism for the formation of **11** in cationic surfactant medium is also envisaged. It is presumed that in aqueous micellar medium **3a** and trimethylsilyl acetylene **6** are in very close proximity leading to the formation of 2-(trimethylsilyl)ethynyl benzamide **8** by Sonogashira reaction as predicted. Now fluoride ion (from *tetra*-butylammonium fluoride) being negatively charged lies in the immediate vicinity of the cationic surfactant, and acts as a desilylating agent to give intermediate **9**. The intermediate immediately undergoes a consecutive Sonogashira reaction to give the dimer **10**, which undergoes an easy cyclization in the presence of Pd-catalyst to afford dimer **11**.

In summary, we have demonstrated an efficient, economical, environmentally benign, and rapid process for the synthesis of (*Z*)-3-methyleneisoindoline-1-one scaffold[35,36] in aqueous micellar medium. We found that, 1,4-bis(4-pyridyl)-2,3-diaza-1,3-butadiene was useful as phosphine-free ligand for this reaction. The green reaction condition, complete regio- and stereo-selectivity, and excellent yields of products, made this protocol a convenient one for the preparation of (*Z*)-3-methyleneisoindoline-1-ones.

Acknowledgment

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all new compounds associated with this article can be found in the online version. Crystallographic data in CIF format are available free of charge via the Internet at CCDC **866283**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.001. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Manabe, K. S.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971; (b) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley: New York, 1997; (c) Shiri, M.; Zolfigol, M. A. *Tetrahedron* **2009**, *65*, 587.
2. (a) Anastas, P.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998; (b) Polshettiwar, V.; Varma, R. S. *J. Org. Chem.* **2007**, *72*, 7420.
3. Dwars, T.; Paetzold, E.; Oehme, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7174.
4. Fendler, J. H.; Fendler, E. J. *Catalysis in Micellar and Macromolecular Systems*; Academic Press: New York, 1975.
5. Tanenbaum, S. W. In *Frontiers of Biology*; Tanenbaum, S. W., Ed.; North Holland Publishing Co: New York, 1980; Vol. 46,.
6. Ferland, J. M.; Demerson, C. A.; Humber, L. G. *Can. J. Chem.* **1985**, *63*, 361.
7. Clercq, E. D. *J. Med. Chem.* **1995**, *38*, 2491.
8. Taylor, E. C.; Zhou, P.; Jenning, L. D.; Mao, Z.; Hu, B.; Jun, J. G. *Tetrahedron Lett.* **1997**, *38*, 521.
9. Li, S.; Wang, X.; Guo, H.; Chen, L. *Yiyano Gongye* **1985**, *16*, 543.
10. Blasko, G.; Guha, D. J.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 105.
11. (a) Weinstock, J.; Hieble, J. P.; Wilson, J. W. *Drugs Future* **1985**, *10*, 645; (b) Cordell, G. A. In *The Alkaloids: Chemistry and Pharmacology*; Academic: San Diego, 1998; Vol. 50,
12. (a) Achinami, K.; Ashizawa, N.; Kobayashi, F. *Jpn Patent JP 03* **1991**, *133*, 955; (b) *Chem. Abstr.* **1991**, *115*, 255977.
13. Valencia, E.; Fajardo, V.; Firdous, S.; Freyer, A. J.; Shamma, M. *Tetrahedron Lett.* **1985**, *26*, 993.
14. Wada, T.; Fukuda, N. *Psychopharmacology* **1991**, *103*, 314.
15. Kavoussi, R. J.; Pande, A. C.; Lydiard, R. B.; Pap, L.; Pigott, T. A.; Rickels, K. *Int. J. Neuropsychopharmacol.* **2000**, 3. Abst. P. 09.042.
16. Chang, Z.-L.; Zhu, D.-Y. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1978; Vol. 31, p 29.
17. Gabriel, S. *Ber* **1985**, *18*, 3470.
18. Ang, W. S.; Halton, B. B. *Aust. J. Chem.* **1971**, *24*, 851.
19. Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1997**, *53*, 10313.
20. Gutierrez, A. J.; Shea, K. J.; Svoboda, J. J. *J. Org. Chem.* **1989**, *54*, 4335.
21. (a) Mali, R. S.; Yeola, S. *Synthesis* **1986**, 755; (b) Epsztajn, J.; Grzelak, R.; Jozwiak, A. *Synthesis* **1996**, 1212.
22. (a) Weidner-Wells, M. A.; Oda, K.; Mazzochi, P. H. *Tetrahedron* **1997**, *53*, 3475; (b) Griesbeck, A. G.; Hirt, J.; Kramer, W.; Dallakian, P. *Tetrahedron* **1998**, *54*, 3169.
23. Milewska, M. J.; Bytner, T.; Polonski, T. *Synthesis* **1996**, 1485.
24. (a) Yamamoto, I.; Tabo, Y.; Gotoh, H. *Tetrahedron Lett.* **1971**, *12*, 2295; (b) Dominh, T.; Johnson, A. L.; Jones, J. E.; Senise, P. P., Jr. *J. Org. Chem.* **1977**, *42*, 4217; (c) Nefkens, G. H. L.; Zwanenburg, B. *Tetrahedron* **1985**, *41*, 6063; (d) Rowe, F. M.; McFadyen, W. T.; Peters, A. T. *J. Chem. Soc.* **1947**, 468; (e) Takeuchi; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2149.
25. (a) Hellal, M.; Cuny, G. D. *Tetrahedron Lett.* **2011**, *52*, 5508; (b) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777; (c) Wilkinson, G.; Stone, F. G. A.; Abel, E. W. In *Comprehensive Organometallic Chemistry*; Pergamon: Oxford, 1982; Vol. 1, 1st ed.; (d) Kundu, N. G.; Khan, M. W.; Mukhopadhyay, R. *Tetrahedron* **1999**, *55*, 12361; (e) Khan, M. W.; Kundu, N. G. *Synlett.* **1997**, 1435.
26. (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.
27. (a) Yi, C. Y.; Hua, R. M. *J. Org. Chem.* **2006**, *71*, 2535; (b) Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191.
28. For copper and amine-free condition using phosphine follow: (a) Yi, C.; Hua, R. *J. Org. Chem.* **2006**, *71*, 2535; For copper and phosphine-free condition using amines or *tetra*-butyl ammonium salts follow: (b) Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391.
29. (a) Mino, T.; Shirae, Y.; Saito, T.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2006**, *71*, 9499; (b) Dang, D.; Zheng, Y.; Bai, Y.; Guo, X.; Ma, P.; Niu, J. *Cryst. Growth Des.* **2012**, *12*, 3856.
30. Kalyanasundaram, K. *Photochemistry in Microheterogeneous Systems*; Academic Press: San Diego, 1987.
31. Israelachvili, J. *Intermolecular and Surface Forces*; Academic Press: San Diego, 1997.
32. Evans, D. F.; Allen, M.; Ninham, B. W.; Fouda, A. *J. Solution Chem.* **1984**, *13*, 87.
33. McCarroll, M.; Toerne, K.; Wandruszka, R. V. *Langmuir* **1998**, *14*, 2965.
34. Cho, C. S.; Jiang, L. H.; Lee, D. Y.; Shim, S. C. *J. Heterocycl. Chem.* **1997**, *34*, 1371.
35. *General reaction procedure for the synthesis of isoindolinones:* In a round-bottomed flask filled with 50 mL of water, aryl amide (**3a**–**c**, 1.0 equiv), alkyne (**4a**–**e**, 1.5 equiv), $Pd(CH_3CN)_2Cl_2$ (0.02 equiv), ligand **2** (0.025 equiv), and DBU (1.5 equiv) were stirred vigorously at 80 °C for 1 h under aerobic condition in the presence of CTAB (4 mmol). After completion of the reaction (monitored by TLC), the contents of the reaction mixture were extracted with ethyl acetate (3 × 25 mL) and washed thoroughly with water until free from CTAB and base. Column chromatography produced pure products (**5a**–**j**).
36. *Spectral data of Z-3-(2-Pyridinyl)methylidene-N-(4-methylphen-yl)isoindolin-1-one (***5h***):* Yellow needles (yield: 72%); mp 164–166 °C; IR ν_{max} (KBr): 3001, 1700, 1650, 1559, 1455, 1287, 1175, 1015, 856, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.44 (s, 3H, CH_3), 6.26 (s, 1H), 7.19–7.23 (m, 1H), 7.26–7.37 (m, 5H), 7.54–7.6 (m, 2H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.94–7.98 (m, 1H), 8.47-8.5 (m, 1H), 8.72 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.24 (CH_3), 111.64 (CH), 121.94 (CH), 123.37 (CH), 125.30 (CH), 125.34 (CH), 128.89 (2 × CH), 128.89 (C), 130.10 (2 × CH), 130.22 (CH), 131.84 (C), 132.18 (CH), 134.60 (C), 136.37 (CH), 138.57 (C), 140.88 (C), 149.29 (CH), 154.42 (C), 166.75 (C); HRMS (ESI): *m*/*z* calcd for $C_{21}H_{16}ON_2$ $[M+Na]^+$ 335.1160; found: 335.1172.