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# Recyclable Heterogeneous Iron Catalyst for C−N Cross-Coupling under Ligand-Free Conditions

K. Swapna, A. Vijay Kumar, V. Prakash Reddy, and K. Rama Rao*

*Organic Chemistry Division-I, Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad 500607, India*

*kakulapatirama@gmail.com*

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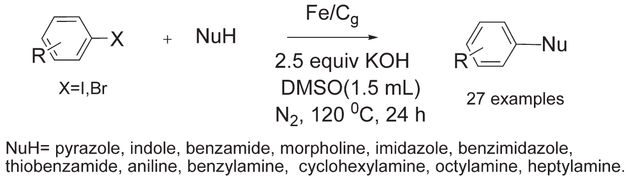
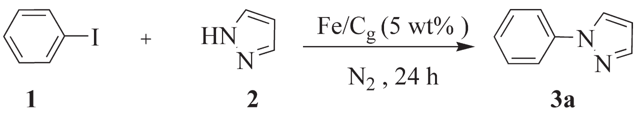


An efficient and ligand-free C−N cross-coupling of aryl halides with various heterocycles using Fe/C$_g$ as a recyclable catalyst is reported. The yields are excellent to moderate.

Sustainable chemistry plays a vital role in chemical industries. As a part of this preoccupation, the search for more economic and eco-friendly synthetic methodologies is our primary concern. Among them, transition-metal-catalyzed C−N cross-coupling reactions are considered to be important in the synthesis of optical devices, pharmaceuticals, and materials.[1] Several metal salts such as Pd,[2] Cu,[3] Ni,[4] Cd,[5] etc. have been reported for the catalysis of N-arylation. Of recent, iron-catalyzed C−N bond formation developed by Liu,[6a] Bolm,[6b−d] and Taillefer[6e] involving different ligands and cocatalysts has attracted considerable attention of chemists due to their inexpensive, nontoxic, and environmentally friendly properties. Though these results are highly encouraging, we felt that there is still scope to further improve these catalytic systems by making them ligand-free with a recyclable catalyst for an efficient access to these highly useful organic compounds.

Herein, we report a highly efficient, reusable graphite-supported iron(III) acetyl acetonate catalytic system for the C−N cross-coupling of aryl halides with amines in the absence of any external ligand. Though many metals dispersed on graphite, viz. M-graphite (M = K, Zn, Sn, Fe, Ti, Pd),[7] were reported, the very tedious preparation of these systems limits their use as catalysts. We have developed a protocol in which Fe$^{III}$(acac)$_3$ was dispersed on graphite by simple procedure. The amount of iron[8] was found to be 4.3% on graphite by ICP-AES analysis. Initially, the reaction between phenyl iodide (**1**) and 1*H*-pyrazole (**2**) in the presence of Fe/C$_g$ catalyst was tested as a model reaction of C−N cross-coupling (Scheme 1).

**SCHEME 1. Heterogeneous Fe/C$_g$-Catalyzed C−N Cross-Coupling**



The reaction was optimized using various reaction parameters such as temperature, solvent, base, catalyst loading, etc. (Table 1). No product formation could be seen in the temperature range of 60−80 °C (Table 1, entries 1 and 2), while lower yield was observed at 100 °C (Table 1, entry 3). The desired C−N product formation was observed (**3a**) in 95% yield when the substrates were stirred for 24 h at 120 °C in the presence of 5 wt % Fe/C$_g$ and KOH in dry DMSO under nitrogen atmosphere (Table 1, entry 4). Among several solvents tested, DMF, toluene, and dioxane were less effective compared to DMSO (Table 1, entries 5−7). DMSO was

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(1) For general reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev*. **2004**, *248*, 2337–2364. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev*. **2007**, *107*, 5318–5365. (c) Corbert, J. P.; Mignani, G. *Chem. Rev*. **2006**, *106*, 2651–2710. (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed*. **2003**, *42*, 5400–5449.

(2) For representative papers on palladium-catalyzed C−N cross-coupling reactions, see: (a) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem*. **2001**, *66*, 3820–3827. (b) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem*. **2003**, *68*, 452–459. (c) Tundel, R. E.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem*. **2006**, *71*, 430–433. (d) Xie, X.; Zhang, T. Y.; Zhang, Z. *J. Org. Chem*. **2006**, *71*, 6522–6529.

(3) For representative papers on copper-catalyzed C−N cross-coupling reactions, see: (a) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 581–584. (b) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 11684–11688. (c) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem*. **2004**, *69*, 5578–5587. (d) Liu, L.; Frohn, M.; Xi, N.; Dominguez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem*. **2005**, *70*, 10135–10138. (e) Kantam, M. L.; Venkanna, G. T.; Sridhar, C.; Sreedhar, B.; Choudary, B. M. *J. Org. Chem*. **2006**, *71*, 9522–9524. (f) Correa, A.; Bolm, C. *Adv. Synth. Catal*. **2007**, *349*, 2673–2676. (g) Zhu, R.; Xing, L.; Wang, X.; Cheng, C.; Su, D.; Hu, Y. *Adv. Synth. Catal*. **2008**, *350*, 1253–1257. (h) Wang, H.; Li, Y.; Sun, F.; Feng, Y.; Jin, K.; Wang, X. *J. Org. Chem*. **2008**, *73*, 8639–8642. (i) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem.—Eur. J*. **2004**, *10*, 5607–5622. (j) Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed*. **2008**, *47*, 1–4. (k) Chen, S.; Huang, H.; Liu, X.; Shen, J.; Jiang, H.; Liu, H. *J. Comb. Chem*. **2008**, *10*, 358–360. (l) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Eur. J. Org. Chem*. **2004**, 695–709. (m) Taillefer, M.; Ouali, A.; Renard, B.; Spindler, J. F. *Chem.—Eur. J*. **2006**, *12*, 5301–5313. (n) Laxmidhar, R.; Saha, P.; Suribabu, J.; Punniyamurthy, T. *Org. Lett*. **2007**, *9*, 3397–3399. (o) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett*. **2001**, *3*, 4315–4317. (p) Ma, D.; Cai, Q. *Acc. Chem. Res*. **2008**, *41*, 1450–1460. (q) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem*. **2005**, *70*, 5164–5173.

(4) (a) Butler, T. A.; Swift, E. C.; Lipshutz, B. H. *Org. Biomol. Chem*. **2008**, *6*, 19–25. (b) Lipshutz, B. H.; Frieman, B. A.; Butler, T.; Kogan, V. *Angew. Chem., Int. Ed*. **2006**, *45*, 800–803.

(5) Laxmidhar, R.; Saha, P.; Suribabu, J.; Punniyamurthy, T. *Adv. Synth. Catal*. **2008**, *350*, 395–398.

(6) (a) Guo, D.; Huang, H.; Xu, J.; Jiang, H.; Liu, H. *Org. Lett*. **2008**, *10*, 4513–4516. (b) Correa, A.; Bolm, C. *Angew. Chem., Int. Ed*. **2007**, *46*, 8862–8865. (c) Correa, A.; Elmore, S.; Bolm, C. *Chem.—Eur. J*. **2008**, *14*, 3527–3529. (d) Correa, A.; Bolm, C. *Adv. Synth. Catal*. **2008**, *350*, 391–394. (e) Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem., Int. Ed*. **2007**, *46*, 934–936.

(7) Savoia, D.; Trombini, C.; Ronchi, A. U. *Pure Appl. Chem*. **1985**, *57*, 1887–1896. and the references cited therein.

(8) (a) Plietker, B. *Iron Catalysis in Organic Chemistry*; Wiley-VCH: Weinheim, Germany, 2008. (b) Bolm, C.; Legros, J.; Paih, J. L.; Zani, L. *Chem. Rev*. **2004**, *104*, 6217–6254. (c) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun*. **2004**, 2822–2823. (d) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun*. **2005**, 4161–4163.

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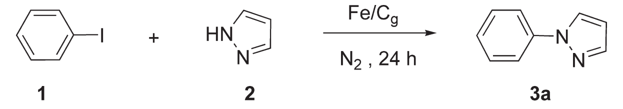
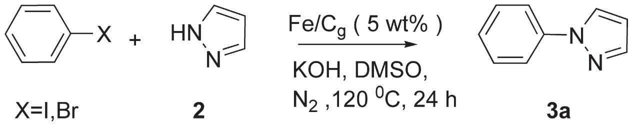
**TABLE 1. Optimization of Reaction Conditions for the C−N Cross-Coupling of 1 and 2 Using Fe/$C_g$ Catalyst**[a]



| entry | catalyst (%) | temp (°C) | solvent | base | yield (%) |
|---|---|---|---|---|---|
| 1 | 5 | 60 | DMSO | KOH | |
| 2 | 5 | 80 | DMSO | KOH | |
| 3 | 5 | 100 | DMSO | KOH | 30 |
| 4 | 5 | 120 | DMSO | KOH | 95 |
| 5 | 5 | 120 | DMF | KOH | 30 |
| 6 | 5 | 120 | Toluene | KOH | 20 |
| 7 | 5 | 120 | Dioxane | KOH | 25 |
| 8 | 5 | 120 | DMSO | $K_2CO_3$ | 15 |
| 9 | 5 | 120 | DMSO | $Cs_2CO_3$ | 10 |
| 10 | 5 | 120 | DMSO | NaOH | 55 |
| 11 | 5 | 120 | DMSO | NaO$^t$Bu | trace |
| 12 | 5 | 120 | DMSO | KO$^t$Bu | trace |
| 13 | 3 | 120 | DMSO | KOH | 85 |
| 14 | 2.5 | 120 | DMSO | KOH | 60 |
| 15 | 1 | 120 | DMSO | KOH | 40 |
| 16[b] | 5 | 120 | DMSO | KOH | 65 |
| 17 | 5 | rt | DMSO | KOH | |
| 18[c] | 5 | 120 | DMSO | KOH | |

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), Fe/$C_g$ (5 wt %), $N_2$. [b] Reaction stopped at 10 h. [c] Reaction conducted in air under the same reaction conditions.

**TABLE 2. Efficiency of Different Iron Sources in the C−N Cross-Coupling**[a]



| entry | X | Fe source | yield (%) |
|---|---|---|---|
| 1 | I | none | |
| 2 | I | $Fe_2O_3$ | 75 |
| 3[b] | I | $Fe_2O_3$ | 20 |
| 4 | Br | $Fe_2O_3$ | 30 |
| 5[c] | I | $Fe_2O_3$ | 15 |
| 6[d] | I | $Fe_2O_3$ | 20 |
| 7 | I | $Fe_3O_4$ | 70 |
| 8[b] | I | $Fe_3O_4$ | 25 |
| 9 | Br | $Fe_3O_4$ | 35 |
| 10 | I | Fe(acac)$_3$ | 20 |
| 11 | I | Fe/$C_g$ | 95 |
| 12 | I | graphite | trace[10] |

[a] Reaction conditions: PhX (1.0 mmol), **2** (1.0 mmol), Fe/$C_g$ (116 mg, 5 wt %), KOH (2.5 equiv), dry DMSO (1.5 mL), $N_2$, 120 °C. [b] DMF as solvent. [c] Reaction carried out under standard conditions by using L-proline as a ligand. [d] Using DMEDA as a ligand.

the solvent of choice in terms of higher yield. It is noteworthy to observe that the choice of KOH as a base with DMSO as the solvent was crucial for our N-arylation of nucleophiles. The reaction with KOH was superior to $K_2CO_3$, $Cs_2CO_3$, and NaOH, whereas only trace amount of product formation takes place with NaO$^t$Bu and KO$^t$Bu (Table 1, entries 8−12). A decrease in catalyst loading from 5 to 3 to 1 wt % afforded the product in decreased yields (Table 1, entries 13−15). Five wt % of the catalyst was found to be optimal.

When the reaction was stopped at 10 h, the desired C−N product was obtained in 65% yield (Table 1, entry 16). No product formation was observed at rt (Table 1, entry 17) as well as at 120 °C in air (Table 1, entry 18).[9] We have also performed a comparative study of the catalytic activities with other Fe heterogeneous systems viz. Fe/$C_g$, $Fe_2O_3$, and $Fe_3O_4$ and tested with PhBr and PhI for the formation of the coupling partners (Table 2). However, it is observed from these studies that the catalytic activities of other catalysts were lower than Fe/$C_g$. Fe/$C_g$ turned out to be the best catalyst for the coupling reaction.

This catalysis for the C−N cross-coupling reaction was carried out with a diverse range of aryl halides (iodo, bromo) against pyrazole under the optimized conditions (Table 3). In general, aryl iodides were more reactive than aryl bromides, giving the corresponding N-arylated products in high yields (up to 95%). The electronic effects were studied with various aryl halides containing electron-rich and withdrawing groups (Table 3, entries 1−12). The ortho substitution hampered the reaction and led to the formation of the product in lower yields (Table 3, entry 2). With nitro substituent on the aromatic ring (e.g., *p*-nitro-iodobenzene), no formation of the product could be seen. To study the scope of the procedure, the reaction with other N-nucleophiles was next studied. Indole, benzamide, morpholine, imidazole, benzimidazole, thiobenzamide, and aromatic and aliphatic amines were found to be effective N-nucleophiles which underwent reaction to give good to moderate yields (Table 4).

Next, we studied the reusability of the heterogeneous Fe/$C_g$ in the C−N cross-coupling reaction of **1** with **2** (Figure 1). After completion of the reaction, the catalyst was recovered by centrifugation and washed with ethyl acetate followed by acetone then dried in a hot air oven at 80 °C.

The recovered catalyst was employed in the next run, and no substantial loss of activity was observed up to five cycles.[11] It is also observed from the following spectral studies that there is no change in the nature of the catalyst even after the fifth cycle.The binding energy values [(C 1s (283 eV), O 1s (530 eV) and Fe $2p_{3/2}$ (710.6 eV), $2p_{1/2}$ (724.0 eV)] from the X-ray photoelectron spectroscopy (XPS) of the native and the catalyst after the fifth cycle confirmed the +3 oxidation state of iron.[14] The absorption at 1575 $cm^{-1}$ in IR[14] attributed to the formation of anionic acetylacetone complex[12] that was present both in the native and the reused catalyst. Fe−O stretching band[13] at 580 $cm^{-1}$ in IR is absent in all of the cases. This observation strongly confirms that Fe(acac)$_3$ on graphite is intact even after the fifth cycle.

Next, the leaching of iron from the heterogeneous support was checked. After the reaction, the supernatant

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(9) Dimsyl ion produced from DMSO in the presence of KOH acts as a base. However, this dimsyl ion is air-sensitive and reacts rapidly in the presence of water and oxygen. (a) Price, G. G.; Whiting, M. C. *Chem. Ind.* **1963**, 775–776. (b) Ledwith, A.; Mcfarlance, N. *Proc. Chem. Soc.* **1964**, 108–109. (c) Hiller, L. K. Jr. *Anal. Chem.* **1964**, *42*, 30–36.

(10) This catalysis may be due to the presence of iron and oxygen impurities. Nagai, M.; Yoda, T.; Omi, S.; Kodomari, M. *J. Catal.* **2001**, *201*, 105–112.

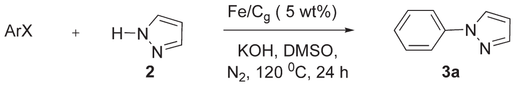
(11) The catalyst, when taken for reaction directly after centrifugation and washing without drying in the oven, did not yield any product.

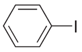
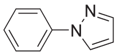
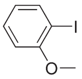
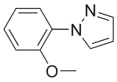
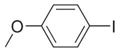
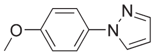
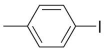
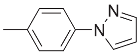
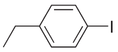
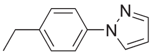
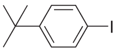
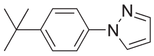
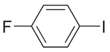
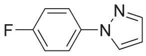
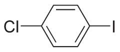
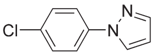
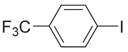
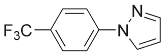
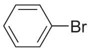
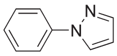
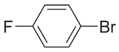
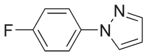
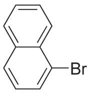
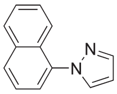
(12) Sohn, J. R.; Lee, S. II. *J. Ind. Eng. Chem.* **1997**, *3*, 198–202.

(13) Maity, D.; Kale, S. N.; Ghanekar, R. K.; Xue, J. M.; Ding, J. *J. Magn. Magn. Mater.* **2009**, *321*, 3093–3098.

(14) See Supporting Information.

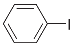
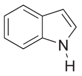
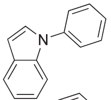
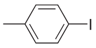
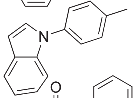
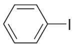
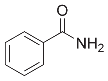
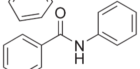
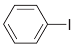
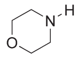
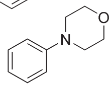
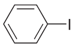
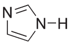
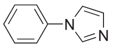
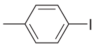
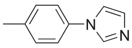
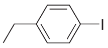
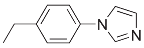
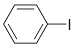
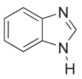
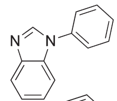
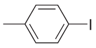
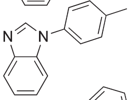
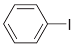
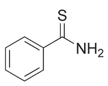
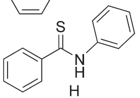
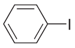
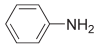
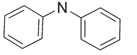
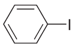
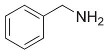
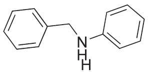
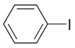
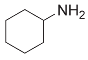
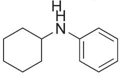
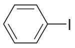
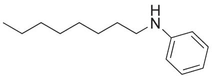
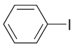
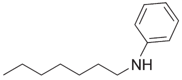
**TABLE 3.** Fe/C$_g$ Catalyzed C−N Cross-Coupling of Pyrazole (**2**) with Aryl Halides[a]



| entry | ArX | product | | yield (%) |
|---|---|---|---|---|
| 1 |  |  | **3a** | 95 |
| 2 |  |  | **3b** | 41 |
| 3 |  |  | **3c** | 58 |
| 4 |  |  | **3d** | 87 |
| 5 |  |  | **3e** | 72 |
| 6 |  |  | **3f** | 60 |
| 7 |  |  | **3g** | 62 |
| 8 |  |  | **3h** | 58 |
| 9 |  |  | **3i** | 52 |
| 10 |  |  | **3a** | 60 |
| 11 |  |  | **3g** | 51 |
| 12 |  |  | **3j** | 52 |

[a] Reaction conditions: aryl halide (1.0 mmol), **2** (1.0 mmol), Fe/C$_g$ (5 wt %), N$_2$.

**TABLE 4.** Fe/C$_g$ Catalyzed C−N Cross-Coupling of Aryl Iodides with Various Amines[a]

| entry | ArI | nucleophile | product | | yield (%) |
|---|---|---|---|---|---|
| 1 |  |  |  | **4a** | 78 |
| 2 |  | |  | **4b** | 80 |
| 3 |  |  |  | **5a** | 51 |
| 4 |  |  |  | **6a** | 52 |
| 5 |  |  |  | **7a** | 75 |
| 6 |  | |  | **7b** | 94 |
| 7 |  | |  | **7c** | 88 |
| 8 |  |  |  | **8a** | 70 |
| 9 |  | |  | **8b** | 68 |
| 10 |  |  |  | **9a** | 58 |
| 11 |  |  |  | **10a** | 62 |
| 12 |  |  |  | **11a** | 60 |
| 13 |  |  |  | **12a** | 61 |
| 14 |  | octylamine |  | **13a** | 65 |
| 15 |  | heptylamine |  | **14a** | 68 |

[a] Reaction conditions: aryl iodide (1.0 mmol), nucleophile (1.0 mmol), Fe/C$_g$ (5 wt %), N$_2$, 120 °C, 24 h.

was collected by filtration of the catalyst, and the filtrate was tested for iron by ICP-AES technique. It was found that 0.001% iron leached into the solution. This study clearly demonstrated that iron was intact to a considerable extent with the heterogeneous support, and there is no significant amount of leaching.

In conclusion, we have developed a robust recyclable heterogeneous iron catalytic system for the N-arylation of nucleophiles under ligand-free conditions, contributing to the progress of sustainable chemistry in the field of iron-catalyzed reactions.

## Experimental Section

**Preparation of Graphite-Supported Iron Catalyst.** Graphite (10 g) was charged in a round-bottom flask containing THF solution (250 mL) of Fe(acac)$_3$ (1 g) and stirred under nitrogen atmosphere for 24 h. The resultant catalyst was filtered off and washed two (or three) times with THF. The residue was dried in a hot air oven for 24 h to afford the catalyst (i.e., heterogeneous Fe/C$_g$ catalyst). The loading of iron was determined to be 4.3% as analyzed by ICP-AES technique.

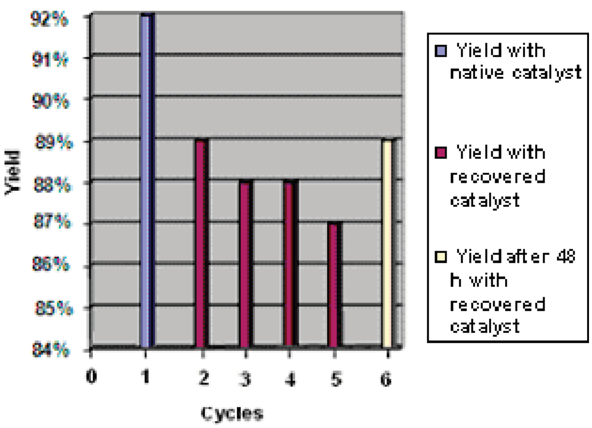


**FIGURE 1.** Reusability study of heterogeneous Fe/C$_g$ in the cross-coupling of **1** and **2**.

**General Procedure for the Iron-Catalyzed C−N Cross-Coupling.** 1*H*-Pyrazole (**2**; 68 mg, 1.0 mmol), Fe/$C_g$ (116 mg, 5 wt %), KOH (2.5 equiv), and iodobenzene (**1**; 0.1 mL, 1.0 mmol) were charged in a 25 mL round-bottom flask with a condenser under nitrogen atmosphere, followed by dry DMSO (1.5 mL). The round-bottom flask was flushed and sealed under nitrogen atmosphere, and the mixture was heated in an oil bath at 120 °C and stirred at this temperature for 24 h. After completion of the reaction as monitored by TLC, the heterogeneous mixture was then cooled to room temperature and treated with water (2 mL). The aqueous layer was separated and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$ and concentrated under reduced pressure to yield the product, which was purified by silica gel column chromatography (with ethyl acetate and hexane as eluent) to get **3a** (134 mg, 95%) as a pale yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.89−7.88 (m, 1H), 7.69−7.65 (m, 3H), 7.45−7.39 (m, 2H), 7.27−7.20 (m, 1H), 6.42 (t, 1H, $J$ = 2.26 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 140.9, 140.1, 129.4, 126.8, 126.5, 119.2, 107.5. All of the products were characterized by $^1$H and $^{13}$C NMR and MS and compared with the literature values.[14]

**Acknowledgment.** We are grateful to UGC, New Delhi, for the research fellowships to K.S. and A.V.K., and CSIR, New Delhi, for V.P.R.

**Supporting Information Available:** Synthetic procedures, characterization data, and copies of $^1$H NMR and $^{13}$C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.