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Regioselective Protection at *N*-2 and Derivatization at *C*-3 of Indazoles

Guanglin Luo,* Ling Chen, and Gene Dubowchik

Department of Neurosciences Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, Connecticut 06443

guanglin.luo@bms.com

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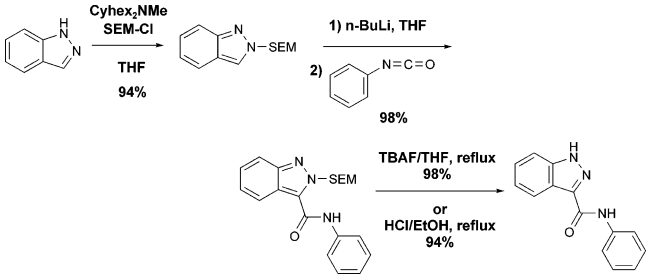
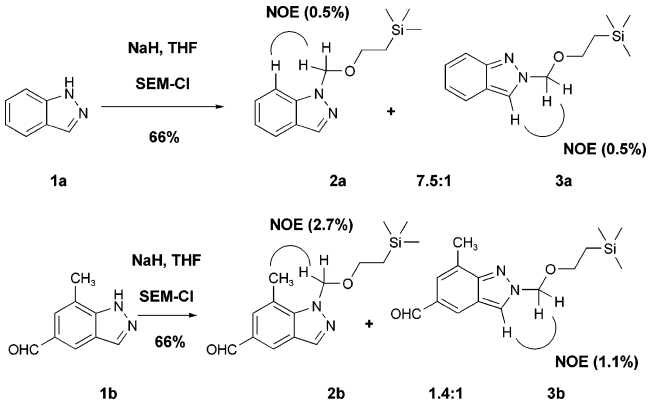


Indazoles are regioselectively protected at *N*-2 by a 2-(trimethylsilyl)ethoxymethyl (SEM) group using novel conditions. The SEM group can efficiently direct regioselective *C*-3 lithiation, and the resulting nucleophile can react with a wide range of electrophiles to generate novel indazole derivatives. The SEM group can be removed by treatment with TBAF in THF or aqueous HCl in EtOH.

Indazoles represent a widely used medicinal chemistry pharmacophore that is found on a number of marketed drugs.[1,2] Most of their syntheses involve construction of either pyrazole or benzene ring systems.[2] During our studies with indazoles, we became interested in derivatizing their *C*-3 positions directly from available simpler indazoles. Unlike their indole counterparts, the *C*-3 position of indazoles is not very nucleophilic. Direct electrophilic substitution reactions of *C*-3 have required harsh conditions resulting in low yields.[3] The synthesis of 3-substituted indazoles has also been reported with indirectly generated *C*-3 nucleophiles reacting with different electrophiles.[4] An alternative pathway would involve selective lithiation at *C*-3, followed by reactions with electrophiles, which requires a lithiation-directing/stabilizing group to be introduced at the *N*-2 position because 3-anionized indazoles generated from *N*-1-substituted indazoles immediately convert into *o*-aminobenzonitriles via a ring-opening process.[5]

SCHEME 1



The 2-(trimethylsilyl)ethoxymethyl (SEM) group is a widely used heterocyclic NH protecting group[6] that is also an excellent directing group for lithiation at a neighboring position. For examples, indoles and pyrroles,[7] imidazoles,[8] and pyrazoles[9] have been protected by SEM with subsequent lithiation and electrophilic quenching taking place at the alpha position. Most protection conditions have employed NaH in THF to deprotonate acidic NHs, followed by reactions with SEM-Cl, resulting in generally good yields.[6] Indazoles, however, contain two nonequivalent nitrogens. Selective protection of either has not been reported. In one report using the conditions described above to protect indazoles, the authors did not specify either yield or regioselectivity.[10]

Using these standard conditions (NaH/THF/SEM-Cl) with indazole **1a**, we found that both regioisomers **2a** and **3a** were formed in good combined yield (66%; Scheme 1). The isomers were separated and characterized, and the regiochemistry was unequivocally assigned through NOE studies. In this case, substitution at the *N*-1 position is favored with a **2a**/**3a** ratio of 7.5:1. Under the same conditions, indazole **1b**,[11] which contains a 7-methyl group, gave a substantially increased ratio of the *N*-2-protected product (**2b**/**3b** ratio of 1.4/1), presumably because of steric blocking of *N*-1. We decided to investigate conditions that might increase the synthetic usefulness of these protections.

* Corresponding author. Tel.: +12036776640. Fax: +12036777702.

(1) A search of the indazoles in MDL MDDR 2003.2 resulted in 631 biologically active hit structures, and in MDL CMC 2003.1, a search resulted in 14 hits.

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(7) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723.

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(10) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Greenberg, R. A.; Erickson-Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Rayner, M. M.; Lam, G. N.; Chang, C.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2919.

(11) Synthesized by treating **1d** (Table 2) with NaH in THF and *n*-BuLi, followed by DMF (see Supporting Information). Compound **1d** was prepared from known procedures: Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1994**, *50*, 3529.

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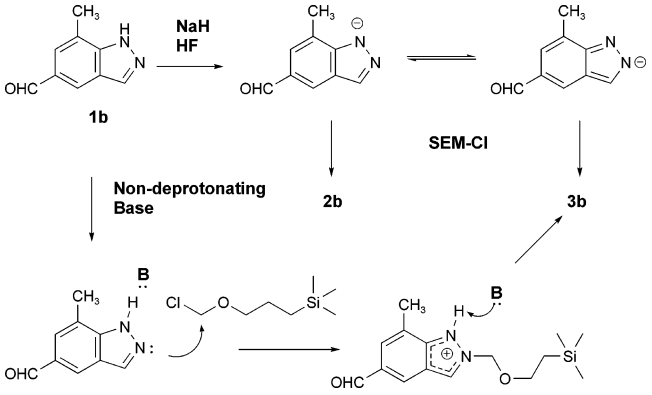
SCHEME 2



SCHEME 3

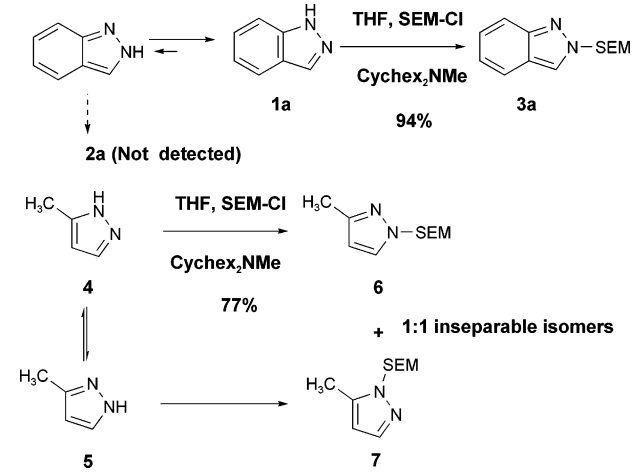


TABLE 1. Protection Conditions for Indazole 1b

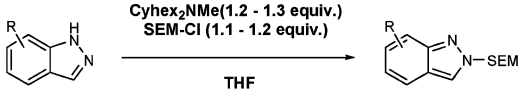
entry	conditions[a]	conversion[b] (%)	ratio[b] (**2b**/**3b**)
1	DMF, K_2CO_3	28	2.2/1
2	DMF, Cs_2CO_3	82	3/1
3	CH_2Cl_2, Et_3N	11	0/1
4	DMF, Ag_2O	30	0/1
5	CH_2Cl_2, Et_3N, 60 °C, 1.0 h	56	0.5/1
6	THF, Et_3N	35	0/1
7	THF, DBU	45	0/1
8	THF, *i*-Pr_2NEt	70[c]	0/1
9	CH_2Cl_2, $Cyhex_2NMe$	>90 (63)	0/1
10	THF, $Cyhex_2NMe$	>90 (87)	0/1

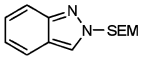
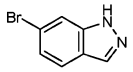
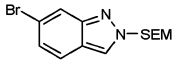
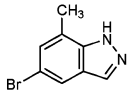
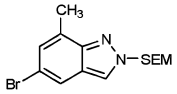
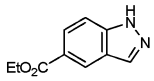
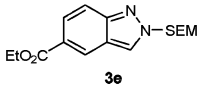
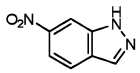
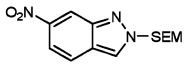
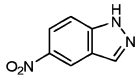
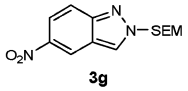
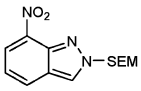
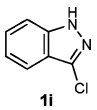
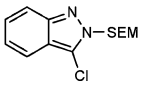
[a] The base (entries 1−5, excess; entries 6−10, 1.2 equiv) was added to the solution of **1b**, followed by SEM-Cl (entries 1−5, 2.2 equiv; entries 6−10, 1.1 equiv) at rt (entry 5, 60 °C) for a period of time (entries 1−4, 3.5 h; entries 6−10, 2 h). [b] Estimated by area integration of LCMS. The yield in parentheses is the isolated yield of **3b**. [c] Greater than 90% after 18 h.

From a mechanistic point of view, after deprotonation of **1b** by NaH, the resulting anion prefers to remain localized on *N*-1 but can apparently transfer to *N*-2 without much of an energy barrier. Therefore, both positions can react with SEM-Cl to afford the respective isomers (Scheme 2). When a nondeprotonating base is used, it should be the electron pair at *N*-2 that is most nucleophilic and, thus, able to react with electrophiles such as SEM-Cl, because the electron pair on *N*-1 is part of the aromatic system. Following cation formation, the N−H becomes acidic enough to be deprotonated by the weaker base. It is also possible that the soft, nondeprotonating base participates in facilitating the nucleophilic reaction of *N*-2 in a concerted fashion, with the cation evenly distributed over the aromatic system. Based on these mechanistic considerations, we screened selected bases and solvents for SEM protection of **1b**, as shown in Table 1.

Entries 1−4 represent our initial attempts. Both entry 3 and entry 4 gave only the desired regioselectivity. However, yields were low, even with longer reaction times. Somewhat better results were obtained when Ag_2O was used to activate the chloride (entry 4), but workups were tedious. Therefore, we focused our efforts on tertiary amine bases. Heating at reflux in CH_2Cl_2 with Et_3N improved conversion but with substantial formation of **2b** (entry 5). The replacement of CH_2Cl_2 with THF resulted in a cleaner conversion (entry 6) whose yield could be improved only by further addition of excess amounts of SEM-

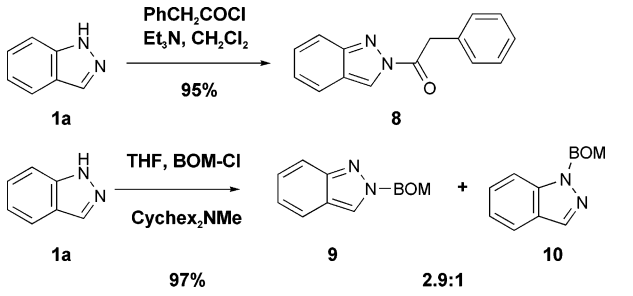
TABLE 2. Regioselective Protection of Various Indazoles[a]



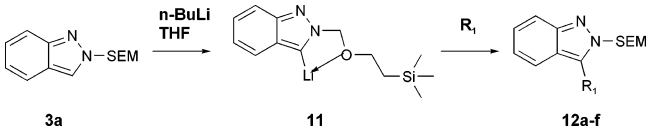
entry	indazole	product	isolated yield (%)
1	 **1a**	 **3a**	94 (3 h)
2	 **1c**	 **3c**	62 (3 h)
3	 **1d**[9]	 **3d**	81 (3 h)
4	 **1e**	 **3e**	89 (3 h)
5	 **1f**	 **3f**	78 (20 h)
6	 **1g**	 **3g**	75 (20 h)
7	 **1h**	 **3h**	56[b] (20 h)
8	 **1i**	 **3i**	61 (20 h) 81 (72 h)

[a] Reaction time is indicated in parentheses. All compounds were purified by silica gel column chromatography and characterized by ^1H NMR, ^{13}C NMR, and HRMS. All yields are isolated yields. [b] 29% starting material recovered, and 14% *N*-1 isomer isolated.

SCHEME 4



SCHEME 5



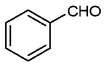
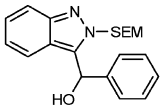
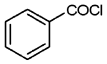
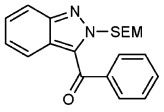
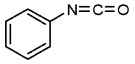
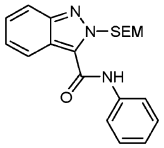
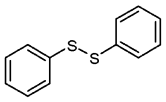
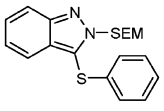
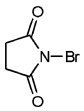
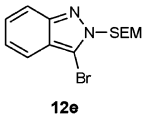
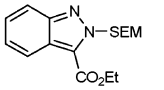
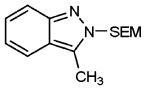
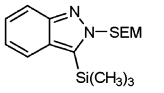
Cl and Et_3N. Apparently, SEM-Cl was being consumed by Et_3N at a rate competitive with the protection reaction. DBU in THF gave similar results (entry 7). A recent publication has shown that alkoxymethyl chlorides can efficiently form a quaternary ammonium salt in CH_2Cl_2.[12] Therefore, a more hindered tertiary amine should be more inert to a direct reaction with SEM-Cl, avoiding excessive reagent consumption. Indeed, use of *i*-Pr_2-NEt resulted in good conversion and regioselectivity after 2 h (entry 8). However, when dicyclohexylmethylamine ($Cyhex_2$-NMe), a bulky tertiary amine successfully used in Pd-catalyzed Heck coupling reactions,[13] was employed in either CH_2Cl_2 or THF, regioselective protection took place with excellent conversions (>90%) within 2 h (entries 9 and 10). The reaction in CH_2Cl_2 was not as clean as that in THF, resulting in lower isolated yields.

The mechanism shown in Scheme 2 for indazole **1b** assumed that, in the presence of nondeprotonating bases, there should be little generation of the 2-*H* tautomer. The fact that only one regioisomer **3b** was formed strongly supports this assumption. However, one might also argue that the presence of the 7-methyl group might significantly slow protection at *N*-1 by steric hindrance. However, when the same conditions were applied to indazole **1a**, excellent regioselectivity was also achieved and only isomer **3a** was detected and isolated (Scheme 3).[14] For indazole **1a**, the calculated energy difference between the 1-*H* tautomer and the 2-*H* tautomer in the ground state is 2.3 kcal/mol, indicating that the 1-*H* tautomer is significantly more stable than the 2-*H* tautomer.[15] This is in full agreement with our proposed mechanism and experimental results.

To further verify the mechanism, we applied the same protection conditions to 3-methylpyrazole, in which the theoretical energy difference between the two tautomers **4** and **5** is comparatively small such that both tautomers should coexist in solution.[16] Not surprisingly, a 1:1 mixture of inseparable regioisomers **6** and **7** were produced in good combined yield (Scheme 3).

These protection conditions work well with other indazole derivatives, as documented in Table 2. Various substituents have some effect on reaction rates, but all gave good yields (entries 1−8). For strong electron-withdrawing nitro substituents (entries 5−7), a longer reaction time was needed for better conversions. Only with 7-nitroindazole (entry 7) was a substantial amount of the *N*-1 isomer also detected and isolated, presumably as a result of a reduction in the energy difference between the

TABLE 3. Selective Lithiation of 1a at *C*-3 and Subsequent Electrophilic Reactions[a]

entry	electrophile	product	isolated yield (%)
1		 **12a**	89
2		 **12b**	94
3		 **12c**	98
4		 **12d**	85
5		 **12e**	72 (98)
6		 **12f**	77 (91)
7		 **12g**	90
8		 **12h**	80

[a] All compounds were purified by silica gel column chromatography and characterized by ^1H NMR, ^{13}C NMR, and HRMS. All yields are isolated yields (yield in parentheses are relative to recovered **1a**).

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(14) When **1a** was treated with SEM-Cl (1.1 equiv) in THF without any base, 88% conversion was achieved with a **2a**/**3a** ratio of 2:3 in 3 h. Further reaction for 24 h did not improve conversion, but the **2a**/**3a** ratio was greatly increased to 9.4:1, indicating **2a** is the thermodynamically more stable product. When pyridine (1.2 equiv) was used as a base, 85% conversion was achieved with a **2a**/**3a** ratio of 1:30 in 3 h. Further reaction for 24 h gave >90% conversion with a **2a**/**3a** ratio of 1:18. These results indicate that the base is not simply an acid scavenger, and the base strength also affects the selectivity of the SEM protection.
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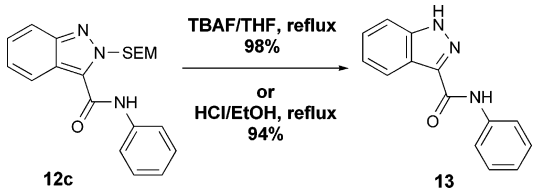
SCHEME 6



tautomers. Similarly, chlorine substitution at *C*-3 also slowed the reaction rate (entry 8), and the longer reaction time afforded better yields. In all cases, starting indazoles could be recovered.

The mechanism using nondeprotonating base should also apply to the acylation of indazoles as well as protection with benzyloxymethyl chloride (BOM-Cl) (Scheme 4). While acylation did occur exclusively at *N*-2, protection with BOM-Cl showed somewhat diminished selectivity with a **9**/**10** ratio of 2.9:1. A recent publication,[17] in which regioselective methylation and ethylation of indazoles at *N*-2 was achieved at room temperature by using strong methyl- and ethyl-donating reagents, further indicates that the energy difference between indazole tautomers along with carefully chosen electrophiles can be utilized for synthetic purposes.

Following SEM protection at *N*-2, we were now able to selectively lithiate *C*-3 (Scheme 5), a well-documented process using other SEM-protected nitrogen heterocycles.[7−9] Thus, treatment of **1** with 1.1 equiv of *n*-BuLi in THF at −70 °C resulted in a yellow solution, presumably the oxygen-directed lithiation product **11**. The addition of various carbon, sulfur, halogen, and silicon electrophiles resulted in a diverse set of 3-subsituted indazole derivatives (Table 3).

The SEM group is stable to a wide variety of reaction conditions, but it could be removed using either basic (TBAF, THF, reflux) or acidic (H^+) conditions, as reported for other SEM-protected heterocycles.[6] For example, when **12c** was treated with TBAF in THF at reflux or HCl in EtOH at reflux, **13**[18] was obtained in 98 and 94% yields, respectively (Scheme 6).

In conclusion, the work described here presents a useful regioselective protection of indazoles at *N*-2 by the SEM group. SEM-directed regioselective lithiation at *C*-3 and subsequent substitution with a variety of electrophiles was also achieved. In addition, the SEM group could easily be removed by treatment with TBAF or aqueous HCl.

Experimental Section

General Procedure of Regioselective Protection of Indazoles. Preparation of 2-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-indazole (3a): To the solution of indazole (119 mg, 1.0 mmol) in THF (10 mL) in an oven-dried flask was added dicyclohexylmethylamine (0.26 mL, 1.2 mmol, 1.2 equiv), followed by SEM-Cl (0.21 mL, 1.2 mmol, 1.2 equiv) via syringe. The mixture was stirred at room temperature for 3 h. The mixture was diluted with ethyl acetate and quenched with 0.5 N NaOH. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified using silica gel column chromatography (step gradient: 0−50% hexane/ethyl acetate) to afford 236 mg (94% yield) of **3a** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (1H, s), 7.73 (1H, d, J = 8.8 Hz), 7.66 (1H, d, J = 8.8 Hz), 7.28 (1H, t, J = 8.4 Hz), 7.08 (1H, t, J = 8.4 Hz), 5.71 (2H, s), 3.62 (2H, t, J = 8.0 Hz), 0.93 (2H, t, J = 8.0 Hz), −0.04 (9H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.9, 126.4, 122.6, 122.3, 122.1, 120.5, 118.0, 81.8, 67.5, 17.9, −1.2; HRMS *m*/*e* calcd, 249.1423; found, 249.1423 $(M + H)^+$.

General Procedure of Selective Lithiation and Subsequent Electrophilic Reactions of 3a. Preparation of *N*-Phenyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazole-3-carboxamide (12c): To a solution of **3a** (80 mg, 0.32 mmol) in THF (2 mL) at −70 °C under nitrogen was added *n*-BuLi (2.5 M in hexanes, 0.14 mL, 0.35 mmol, 1.1 equiv) dropwise via syringe. After the resulting bright yellow solution was stirred at the same temperature for 10 min, it was briefly warmed to room temperature for 5 min and re-cooled to −70 °C. Phenyl isocyanate (0.039 mL, 0.35 mmol, 1.1 equiv) was added via syringe. The cooling bath was removed, and after 30 min, the reaction was quenched by NH_4Cl solution. THF was stripped off, and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified using silica gel column chromatography (linear gradient up to 1:4 hexane/ethyl acetate) to afford 117 mg (98% yield) of **12c** as a colorless oil. R_f = 0.40 (20% ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (1H, s), 8.10 (1H, d, J = 12.0 Hz), 7.75 (1H, d, J = 8.4 Hz), 7.71 (1H, s), 7.69 (1H, s), 7.42−7.30 (3H, m), 7.23 (1H, t, J = 8.0 Hz), 7.16 (1H, t, J = 7.4 Hz), 5.99 (2H, s), 3.79 (2H, t, J = 10.0 Hz), 1.02 (2H, t, J = 10.0 Hz), −0.04 (9H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.4, 147.6, 137.9, 129.5, 129.2, 127.2, 124.9, 124.7, 124.0, 121.1, 120.1, 118.3, 81.0, 67.9, 18.0, −1.5; HRMS *m*/*e* calcd, 366.1638; found, 366.1628 $(M - H)^+$.

General Procedures of the SEM Group Deprotection. Preparation of *N*- Phenyl-1*H*-indazole-3-carboxamide (13): To a solution of **12c** (23 mg, 0.062 mmol) in THF (1 mL) was added TBAF (1 M in THF, 0.3 mL, 0.3 mmol), and the mixture was refluxed at 80 °C for 5 h. THF was stripped off, and the residue was partitioned between water and ethyl acetate. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified using silica gel column chromatography (linear gradient up to 1:1 hexane/ethyl acetate) to afford 14 mg (98% yield) of **13** as a colorless oil. Alternatively, **12c** (15 mg, 0.041 mmol) was treated with 3 N HCl (0.5 mL) in EtOH (2 mL) at 90 °C for 1 h. Workup and purification following the above procedures afforded 9.2 mg (94% yield) of **13** as a colorless oil. R_f = 0.74 (50% ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (1H, br), 8.89 (1H, s), 8.46 (1H, d, J = 8.3 Hz), 7.74 (2H, d, J = 7.6 Hz), 7.56−7.28 (5H, m), 7.13 (1H, t, J = 7.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.5, 141.5, 139.7, 137.9, 129.1, 127.7, 124.2, 123.2, 122.7, 122.1, 119.8, 109.9; MS *m*/*e* 238 $(M + H)^+$.

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Supporting Information Available: Experimental procedures for the new reactions and full characterization of new compounds **1b**, **2a**, **2b**, **3b**−**3i**, **8**−**10**, **12b**−**12h**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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