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Novel Alternative for the N−N Bond Formation through a PIFA-Mediated Oxidative Cyclization and Its Application to the Synthesis of Indazol-3-ones†

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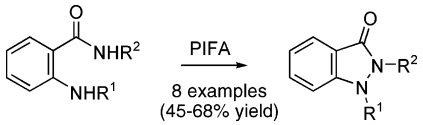

The synthesis of a series of N,N′-disubstituted indazolone derivatives starting from methyl anthranilates is presented. This general approach features a novel and easy way for access to the target *N*-heterocycles by formation of a new N−N single bond. The key cyclization step embraces the formation of an *N*-acylnitrenium intermediate, mediated by the hypervalent iodine reagent PIFA, and its succeeding intramolecular trapping by the amine moiety under rather mild experimental conditions.

Introduction

The maturity of the organic synthesis gained over the decades is the result of significant contributions from all aspects of chemistry, and most of them rely on the discovery of simple reaction conditions for complex transformations.[1] In this context, there is a plethora of tools available for carbon−carbon and carbon−heteroatom bond formation, but the field of heteroatom−heteroatom bond formation remains comparatively less developed. Accordingly, an evident entrance to this area is based on the generation of heteroatom-centered intermediates.

Nitrenium ions are highly reactive intermediates which continue to receive attention not only because of their suspected role in the carcinogenesis initiated by nitro and aminoaromatic compounds[2] but also, particularly, because of their utility in organic synthesis.[3] However, synthetic applications of these electrophilic intermediates remain limited except when such nitrenium ions are stabilized by the electron-donating effect of a proper neighboring group (aryl, alkoxy, or nitrogen, inter alia).[4] In these cases, the so-stabilized nitrenium ions (**I**, **II**, and **III**; see Figure 1) exist for a long enough time to be useful as synthetic intermediates.

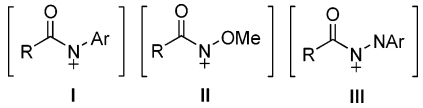

FIGURE 1. Some stabilized acylnitreniun ions.

Despite the fact that *N*-acylnitrenium ions can be generated, for example, by the treatment of *N*-alkoxy-*N*-chloroamides with a variety of Lewis acids, such as silver[4a] or zinc salts,[5] the use of the hypervalent iodine reagent PIFA [phenyliodine(III)bis-(trifluoroacetate)] for this purpose overcomes the limitations associated with those protocols,[6] and therefore, its use has been widely applied to the synthesis of a number of different heterocyclic compounds.[7] In this context, these powerful elec-

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† This paper is dedicated to the memory of our collegue and friend Professor Marcial Moreno-Mañas.

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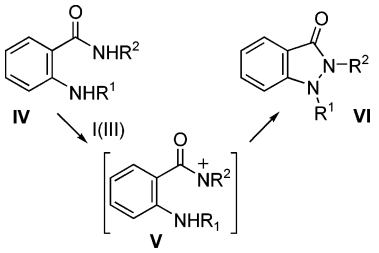


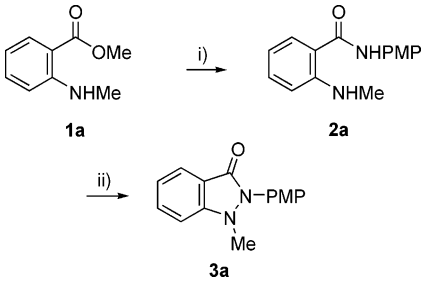
FIGURE 2. Proposed strategy for the synthesis of indazolones.

trophiles readily undergo inter- and intramolecular substitution reactions with a range of nucleophilic species. Nevertheless, as far as we are aware, only the use of carbon nucleophiles as the nucleophilic counterparts, such as (hetero)arene rings and C−C multiple bonds, in an electrophilic amidation reaction[8] and in a novel amidohydroxylation protocol,[9] respectively, has been described. In our hands, these two PIFA-mediated transformations have provided the synthesis of a wide variety of *N*-heterocyclic compounds via C−N bond formation. Herein, we report a novel oxidative cyclization process, which features the first successful intramolecular trapping of *N*-acylnitrenium ions by amine functionalities (**IV** → **V** → **VI** in Figure 2) thus developing a novel approach to the construction of new N−N linkages.

Because several indazolone derivatives have gained noteworthy importance in view of their promising pharmacological properties, such as antiinflammatory,[10] antipsychotic,[11] or antihyperlipidemic agents,[12] we decided to focus on the synthesis of indazol-3-one derivatives. The high-pressure transition-metal-catalyzed carbonylation of azobenzenes,[13] the cyclization of *o*-arylhydrazinobenzoic acids,[14] the isomerization of 3-aryl-2-hydroxyindazoles, the base-catalyzed cyclization of *o*-azidobenzanilides, and the reductive cyclization of *o*-nitrobenzanilides[15] can be cited among the most widely used protocols for access to indazolone derivatives.[16] Because the already mentioned synthetic procedures lack generality and require, in some cases, not very accessible substrates, a novel and general approach would be desirable and of high value (see Figure 2).

Thus, as part of our ongoing research for novel applications of the hypervalent iodine reagents in organic chemistry,[17] we would like to report a novel and alternative access to the construction of the indazolone skeleton through a PIFA-mediated oxidative cyclization.

SCHEME 1. Synthesis of Indazolone 3a[a]



[a] Reagents and conditions: (i) $AlMe_3$, *p*-anisidine, CH_2Cl_2, reflux (69%); (ii) see Table 1.

TABLE 1. Selected Assays Performed on Amide 2a

entry	conditions	**3a**[a] (%)
1	PIFA (0.05 M), CH_2Cl_2[b]	51
2	PIDA (0.05 M), CH_2Cl_2[b]	21
3	HTIB (0.05 M), CH_2Cl_2[b]	10
4	PIFA (0.05 M), TFEA[b]	51
5	PIFA (0.05 M), CH_3CN[b]	33
6	PIFA (0.05 M), toluene[b]	36
7	PIFA (0.05 M), DMF[b]	15
8	PIFA (0.05 M), CH_2Cl_2[c]	51
9	PIFA (0.05 M), CH_2Cl_2, TFA[b]	54
10	PIFA (0.01 M), CH_2Cl_2, TFA[b]	68
11	PIFA (0.01 M), CH_2Cl_2, $BF_3{\cdot}OEt_2$[b]	7

[a] Isolated yield after purification by flash chromatography. [b] Reaction carried out at 0 °C. [c] Reaction carried out at −78 °C.

Results and Discussion

Synthesis of Indazolone 3a. On the basis of our previous experience, we selected the *para*-methoxyphenyl-substituted benzamide **2a** as a model system to optimize the experimental conditions for the proposed cyclization step. This substrate was easily prepared by treatment of the commercially available methyl *N*-methylanthranilate (**1a**) with $AlMe_3$ and *para*-anisidine in the conditions depicted below (see Scheme 1).[18] Next, as shown in Table 1, we briefly examined the effect of different solvents, sources of hypervalent iodine, temperature, and additives on the success of the oxidative cyclization step.

The results obtained from these experiments indicated that the hypervalent iodine reagent PIFA was the most efficient oxidant. Indeed, the use of other related I(III) reagents, such as PIDA [phenyliodine(III)diacetate] (entry 2) and HTIB [hydroxytosyloxyiodobenzene] (entry 3), was also tested but, unlike PIFA, rendered the indazolone **3a** in very low yields. On the other hand, the nature of the solvent had a significant influence on the success of the reaction. Thus, whereas the employment of polar aprotic solvents such as CH_3CN (entry 5) or DMF (entry 7) afforded the desired product in low yields, the use of either

(6) When the easily handled and environmentally friendly I(III) reagent is used, an undesirable aromatic chlorination process is avoided because prior chlorination is not required to generate acylnitrenium ions. See: Kikugawa, Y. *Rev. Heteroatom Chem.* **1996**, *15*, 263−299.

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CH_2Cl_2 (entries 1 and 8−10) or trifluoroethanol (entry 4) proved to be a better solution because the desired heterocycle **3a** was obtained in slightly higher yields. Because both solvents behaved similarly, the selection of CH_2Cl_2 over TFEA was made on the basis of economical costs. Furthermore, although the results did not improve at all when carrying out the reaction at low temperatures (entry 8), the use of TFA as an additive (entry 9) made the reaction take place much more cleanly, and even the yields were not highly effected. In contrast, the use of other additives, such as the Lewis acid $BF_3{\cdot}OEt_2$ (entry 11), which had been extensively reported to increase the reactivity of this kind of reagents,[19] failed in our case and provided only traces of the desired product. Interestingly, the use of more dilute solutions (entry 10) turned out to be the key for the best conditions leading to indazolone **3a** in 68% yield.

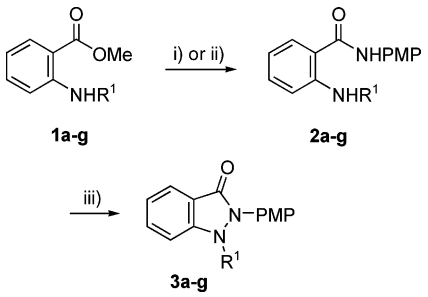
Therefore, we propose that the optimal reaction conditions imply the use of 1.5 equiv of PIFA (0.01 M) in CH_2Cl_2 at 0 °C in the presence of 3 equiv of TFA (entry 10). Besides, these preliminary results suggest that *N*-acylnitrenium ions generated by PIFA, as we presumed before, can also be trapped intramolecularly by amine moieties, featuring consequently an interesting approach to the construction of new N−N linkages.

Synthesis of Indazolones 3a−o. Having established an optimal protocol for the projected process, we performed a more detailed examination of the electronic requirements of the structure of the substrates. Thus, the behavior of a variety of substrates, which include different amine functionalities as well as different amide moieties, under the action of the hypervalent iodine reagent PIFA was examined.

First of all, we analyzed the influence of the nature of the amine moiety on the efficiency of the cyclization step. Thus, a series of the required *p*-methoxyphenylbenzamide derivatives **2a**−**g** were effectively prepared starting from easily accessible or commercially available anthranilates **1a**−**g** either by treatment with $AlMe_3$ and *p*-anisidine or through basic hydrolysis followed by a known amidation protocol (Scheme 2).[20,21] As shown in Table 2, the proposed PIFA-mediated cyclization process proved to be suitable for substrates in which the amine functionality was substituted by either alkyl (entries 1−3) or aryl groups (entry 4). Once again, the positive effect of the presence of TFA as an additive was confirmed in all cases. On the other hand, neither aminobenzamide **2e** (entry 5) nor the ones substituted by an electron-withdrawing group, **2f**,**g** (entries 6 and 7), rendered the desired indazolones **3e**−**g**. Thus, it can be concluded that the scope of this PIFA-promoted oxidative cyclization requires highly nucleophilic amines.

A second part of the research was designed to determine the scope of the cyclization process with respect to the amide functionality. Thus, a series of amides were successfully prepared in a single step by an $AlMe_3$-mediated aminolysis of methylanthranilate **1a** in the presence of different amines

SCHEME 2. Synthesis of Indazolones 3a−g[a]



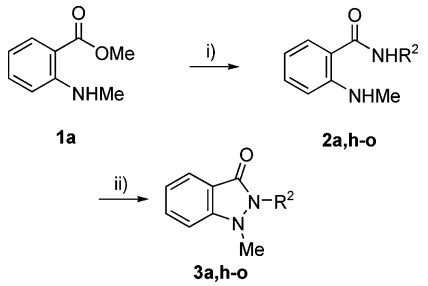
[a] Reagents and conditions: (i) $AlMe_3$, *p*-anisidine, CH_2Cl_2, reflux; (ii) (a) $LiOH{\cdot}H_2O$, THF/H_2O, room temperature, (b) *p*-anisidine, Et_3N, EDC·HCl, HOBt, CH_2Cl_2, 0 °C → room temperature; (iii) PIFA (0.01 M), CH_2Cl_2, TFA, 0 °C.

TABLE 2. Scope of the Cyclization with Respect to Amides 2a−g

entry	R^1	**2** (%)[a]	**3** (%)[b]
1	Me	**2a** (69)[c]	**3a** (68)
2	allyl	**2b** (77)[c]	**3b** (62)
3	$PhCH_2$	**2c** (67)[c]	**3c** (67)
4	Ph	**2d** (68)[c]	**3d** (61)
5	H	**2e** (71)[c]	**3e** (0)
6	CO_2Et	**2f** (85)[d]	**3f** (0)
7	$TolSO_2$	**2g** (86)[d]	**3g** (0)

[a] Isolated yield after purification by crystallization. [b] Isolated yield after purification by flash chromatography. [c] Synthesis through conditions i. [d] Synthesis through conditions ii.

SCHEME 3. Synthesis of Indazolones 3a,h−o[a]



[a] Reagents and conditions: (i) $AlMe_3$, R^2NH_2, CH_2Cl_2, reflux; (ii) PIFA (0.01 M), CH_2Cl_2, TFA, 0 °C.

TABLE 3. Scope of the Cyclization with Respect to Amides 2a,h−o

entry	R^2	**2** (%)[a]	**3** (%)[b]
1	*p*-OMePh	**2a** (69)	**3a** (68)
2	Ph	**2h** (88)	**3h** (60)
3	1-Naph	**2i** (91)	**3i** (61)
4	*p*-EtPh	**2j** (89)	**3j** (60)
5	*p*-BrPh	**2k** (22)	**3k** (45)
6	H	**2l** (90)	**3l** (0)
7	$PhCH_2$	**2m** (88)	**3m** (0)
8	allyl	**2n** (65)	**3n** (0)
9	OMe	**2o** (18)	**3o** (0)

[a] Isolated yield after purification by crystallization. [b] Isolated yield after purification by flash chromatography.

(Scheme 3). When the amides **2a**,**h**−**o** were treated with the trivalent iodine reagent PIFA under the optimized conditions (see Table 3), the effectiveness for this cyclization reaction proved to be restricted to *N*-arylamides (entries 1−5). Although a wide range of experimental conditions was tested on either

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alkyl (entries 7 and 8) or alkoxyamides (entry 9), they all failed to afford the desired indazolone, and a complex mixture of products was obtained in all cases. Similar results were observed with amide **2l**.[22,23] Consequently, it must be pointed out that an aromatic ring seems to be necessary to stabilize the corresponding *N*-acylnitrenium intermediate.

Because of the obtained results and taking into account that a radical mechanism can be discarded, supported by the fact that either an oxygen atmosphere or an addition of a radical trap such as TEMPO or DPPH[24] did not affect the projected reaction at all, it can be proposed that this novel N−N bond formation takes place through an *N*-acylnitrenium ion generated by the action of the mild oxidant PIFA on aromatic amides. These intermediates react intramolecularly with the amine moiety, as the nucleophilic partner of the reaction, giving rise to the highly valued heterocyclic systems **3**.

Conclusions

In conclusion, the powerful potential of the inexpensive and easy-to-handle hypervalent iodine reagent PIFA in organic synthesis, which includes its ability to generate *N*-acylnitrenium ions from adequately substituted amides under rather mild conditions, has been employed satisfactorily in the preparation of a series of N,N′-disubstituted indazolones. Our approach features the first successful intramolecular trapping of *N*-acylnitrenium ions by amine functionalities, developing a novel versatile method for the construction of new N−N linkages and hence offering easy access to a diverse array of *N*-heterocyclic compounds.

Experimental Section

Typical Procedure for the Synthesis of Indazolones 3a−d,h−k. Synthesis of 2-(4-Methoxyphenyl)-1-methyl-1,2-dihydro-*3H*-indazol-3-one (3a). A solution of PIFA (252 mg, 0.78 mmol) in 78 mL of CH_2Cl_2 was added at 0 °C to a solution of benzamide **2a** (100 mg, 0.39 mmol) and TFA (0.09 mL, 1.91 mmol) in 39 mL of the same solvent, and the new solution was stirred for 1 h. Then, the solvent was evaporated at reduced pressure, and the resulting residue was purified by column chromatography (hexanes/EtOAc, 1:1) followed by crystallization from hexanes to afford indazolone **3a** as a white solid (68% yield): mp 117−118 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 3.17 (s, 3H), 3.89 (s, 3H), 7.07 (d, J = 9.1, 2H), 7.29−7.35 (m, 2H), 7.52 (d, J = 9.1, 2H), 7.62−7.68 (m, 1H), 7.95−5.98 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.9, 55.3, 112.1, 114.2, 118.7, 122.6, 124.1, 125.6, 127.6, 132.3, 151.1, 158.1, 161.9; IR (KBr) 1678 cm^{-1}; MS (EI) *m*/*z* (%) 254 (M$^+$, 100), 239 (44), 168 (30), 135 (16), 132 (18), 77 (24); HRMS calcd for $C_{15}H_{14}N_2O_2$ 254.1055, found 254.1057.

1-Allyl-2-(4-methoxyphenyl)-1,2-dihydro-*3H*-indazol-3-one (3b). According to the general procedure, indazolone **3b** was obtained from benzamide **2b** in 62% yield as a yellowish oil after purification by column chromatography (hexanes/EtOAc, 1:1): ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 4.15−4.17 (m, 2H), 4.97−5.07 (m, 2H), 5.35−5.51 (m, 1H), 7.00 (d, J = 9.1, 2H), 7.18−7.30 (m, 2H), 7.43 (d, J = 9.1, 2H), 7.53−7.59 (m, 1H), 7.88−7.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 52.9, 55.4, 112.5, 114.4, 119.6, 120.6, 122.7, 124.3, 126.1, 127.7, 129.5, 132.3, 149.5, 158.3, 162.3; IR (KBr) 1679 cm^{-1}; MS (EI) *m*/*z* (%) 280 (M$^+$, 24), 240 (18), 239 (100), 196 (17), 168 (50), 140 (12), 135 (34), 107 (15), 92 (16), 77 (34); HRMS calcd for $C_{17}H_{16}N_2O_2$ 280.1212, found 280.1221.

1-Benzyl-2-(4-methoxyphenyl)-1,2-dihydro-*3H*-indazol-3-one (3c). According to the general procedure, indazolone **3c** was obtained from benzamide **2c** in 67% yield as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 1:1) followed by crystallization from hexanes: mp 148−149 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 4.72 (s, 2H), 6.89−7.28 (m, 9H), 7.45−7.57 (m, 3H), 7.82−7.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 54.2, 55.4, 112.9, 114.4, 119.5, 122.6, 124.3, 125.9, 127.8, 128.2, 128.4, 132.1, 133.5, 149.5, 158.2, 162.3; IR (KBr) 1678 cm^{-1}; MS (EI) *m*/*z* (%) 330 (M$^+$, 20), 239 (100), 196 (15), 168 (35), 135 (27), 107 (12), 91 (35), 77 (38); HRMS calcd for $C_{21}H_{18}N_2O_2$ 330.1368, found 330.1368.

2-(4-Methoxyphenyl)-1-phenyl-1,2-dihydro-*3H*-indazol-3-one (3d). According to the general procedure, indazolone **3d** was obtained from benzamide **2d** in 61% yield as a white solid after purification by column chromatography (hexanes/EtOAc, 1:1) followed by crystallization from hexanes: mp 146−147 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H), 6.86 (d, J = 8.7, 2H), 7.15−7.53 (m, 10H), 7.95−7.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 55.3, 112.2, 114.1, 118.0, 123.1, 124.2, 124.4, 125.2, 127.5, 128.5, 129.5, 132.7, 141.9, 149.7, 157.6, 162.5; IR (KBr) 1678 cm^{-1}; MS (EI) *m*/*z* (%) 316 (M$^+$, 100), 301 (29), 273 (13), 193 (18), 167 (52), 77 (90), 51 (45); HRMS calcd for $C_{20}H_{16}N_2O_2$ 316.1212, found 316.1213.

1-Methyl-2-phenyl-1,2-dihydro-*3H*-indazol-3-one (3h). According to the general procedure, indazolone **3h** was obtained from benzanilide **2h** in 60% yield as a colorless oil after purification by column chromatography (hexanes/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ 3.13 (s, 3H), 7.20−7.29 (m, 3H), 7.44−7.62 (m, 5H), 7.88−7.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 39.5, 112.4, 118.9, 122.9, 123.5, 124.4, 126.2, 129.0, 132.7, 134.9, 151.6, 162.1; IR (KBr) 1684 cm^{-1}; MS (EI) *m*/*z* (%) 224 (M$^+$, 100), 209 (59), 153 (26), 152 (46), 132 (21), 105 (18), 77 (47); HRMS calcd for $C_{21}H_{18}N_2O$ 224.0950, found 224.0950.

1-Methyl-2-(1-naphthyl)-1,2-dihydro-*3H*-indazol-3-one (3i). According to the general procedure, indazolone **3i** was obtained from benzamide **2i** in 61% yield as a brown solid after purification by column chromatography (hexanes/EtOAc, 1:1) followed by crystallization from hexanes: mp 160−161 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 3.06 (s, 3H), 7.25−7.31 (m, 2H), 7.50−7.67 (m, 5H), 7.78−8.02 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 37.9, 111.8, 118.1, 122.4, 123.4, 124.4, 125.2, 126.4, 126.5, 127.0, 128.1, 129.4, 130.4, 130.9, 132.5, 134.3, 150.9, 162.7; IR (KBr) 1678 cm^{-1}; MS (EI) *m*/*z* (%) 274 (M$^+$, 100), 257 (14), 245 (22), 202 (21), 144 (27), 132 (28), 127 (28), 104 (19); HRMS calcd for $C_{18}H_{14}N_2O$ 274.1106, found 274.1106.

2-(4-Ethylphenyl)-1-methyl-1,2-dihydro-*3H*-indazol-3-one (3j). According to the general procedure, indazolone **3j** was obtained from benzamide **2j** in 60% yield as a brown solid after purification by column chromatography (hexanes/EtOAc, 1:1) followed by crystallization from hexanes: mp 101−103 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.1, 3H), 2.67 (q, J = 7.1, 2H), 3.12 (s, 3H), 7.19−7.31 (m, 4H), 7.45−7.58 (m, 3H), 7.88−7.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.5, 28.4, 39.3, 112.3, 112.8, 118.9, 123.8, 124.3, 128.5, 132.5, 142.6, 151.4, 161.9; IR (KBr) 1684 cm^{-1}; MS (EI) *m*/*z* (%) 252 (M$^+$, 100), 237 (49), 165 (17), 132 (22), 105 (14), 77 (30); HRMS calcd for $C_{16}H_{16}N_2O$ 252.1263, found 252.1262.

2-(4-Bromophenyl)-1-methyl-1,2-dihydro-*3H*-indazol-3-one (3k). According to the general procedure, indazolone **3k** was obtained from benzamide **2k** in 45% yield as a brown solid after purification by column chromatography (hexanes/EtOAc, 1:1) followed by crystallization from hexanes: mp 112−114 °C (hexanes); ^{1}H NMR

(22) Because the $AlMe_3$-mediated aminolysis of methylanthranilate **1a** in the presence of NH_3 failed to afford the desired primary amide, it was prepared by treating the commercially available *N*-methylanthranilamide with methyl iodide at 100 °C following a described protocol in: Chatterjee, A.; Majudmar, S. G. *J. Am. Chem. Soc.* **1953**, *75*, 4365−4366.

(23) Primary amides have been reported to suffer Hofmann-type rearrangements using various iodine(III) reagents. However, in our case, such types of products were not detected. See: Prakash, O.; Batra, H.; Kaur, H.; Sharma, P. K.; Sharma, V.; Singh, S. P.; Moriarty, R. M. *Synthesis* **2001**, 541−543.

(24) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394−3403.

($CDCl_3$) δ 3.14 (s, 3H), 7.23−7.62 (m, 7H), 7.88−7.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 39.9, 112.6, 118.8, 119.5, 123.3, 124.6, 124.8, 132.2, 133.1, 134.2, 151.9, 162.2; IR (KBr) 1688 cm^{-1}; MS (EI) *m*/*z* (%) 304 (M + 2, 99), 302 (M^+, 100), 289 (54), 287 (53), 180 (65), 157 (24), 155 (23), 152 (62), 132 (27), 86 (30), 84 (44); HRMS calcd for $C_{12}H_{11}BrN_2O$ 302.0055, found 302.0053.

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Note Added after ASAP Publication. There was an error in the spectra of the Supporting Information in the version published ASAP March 21, 2006; the corrected version was published ASAP March 29. 2006.

Supporting Information Available: Experimental details for compounds **2a**−**o** and ^1H NMR and ^{13}C NMR spectra of all new compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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