Preparation of Alkyl Carbamate of 1-Protected Indole-3-methylamine as a Precursor of Indole-3-methylamine

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Preparation of Alkyl Carbamate of 1-Protected Indole-3-methylamine as a Precursor of Indole-3-methylamine

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Abstract: A series of alkyl carbamates **3** of 1-protected indole-3-methylamines, alkyl carbamates **6** of thiophenylmethylamines, and pyrrolylmethylamines were prepared from the corresponding acetamides **2** and **5** in good to excellent yields via diacetoxyiodobenzene-promoted Hofmann rearrangement. For a successful Hofmann rearrangement, an electron-withdrawing group on position 1 of indolylacetamide and pyrrolylacetamide was required. The alkyl carbamate **3g** was demonstrated to serve well as a stable precursor of 1-protected indole-3-methylamine **1**.

Keywords: Alkyl carbamate, Hofmann arrangement, indole-3-methylamine, precursor

INTRODUCTION

Indole-3-methylamine **1** is an important pharmaceutical intermediate[1] and a starting material for the syntheses of phytoalexins.[2,3] Although its structure is simple, indole-3-methylamine **1** is very unstable under basic conditions and easily becomes deep red by forming polymerized compounds through a 3-methyleneindolenine intermediate when exposed to air. For most cases, indole-3-methylamine **1** has to be used after in situ preparation. Indole-3-methylamine **1** and its 1-protected derivatives were usually prepared by reduction of indole-3-carboxaldehyde oximes or by displacement of gramine methiodide.[3a,3d,4] These methods often encountered difficulties of low yield,

Scheme 1. 1 indole-3-methylamine.

non reproductability, and polymerization. Therefore, development of a simple and practical method for the preparation of stable indole-3-methylamine derivatives is highly desirable in light of the instability and usefulness of indole-3-methylamine **1** (Scheme 1).

Classic Hofmann rearrangement usually requires a harsh basic aqueous condition, which sometimes negates the possible usefulness of Hofmann rearrangement in the preparation of base-sensitive amines. Polyvalent iodine (III) chemistry is a field rapidly developed during the past decade, and it has found numerous applications in organic chemistry.[5] In recent years, diacetoxy-iodobenzene (DIB) has been reported as a mild reagent for Hofmann rearrangement.[6,7] Because indole-3-methylamine **1** is not stable under basic conditions, we were curious to know whether an indole-3-methylamine isocyanate intermediate formed during the Hofmann rearrangement could be captured by a protic solvent under neutral conditions to afford an alkyl carbamate, which should provide an alternative way to synthesize indole-3-methylamine derivatives. Herein we report a convenient method for the preparation of alkyl carbamates **3** of 1-protected indole-3-methylamine from 1-protected indole-3-acetamide **2** via a DIB-promoted Hofmann rearrangement. Furthermore, the synthesized alkyl carbamates **3** could serve as stable precursors of 1-protected indole-3-methylamine **4** (Eq. (1)). The rearrangement studies of thiophenylacetamide and pyrrolylacetamide are also presented in this article.
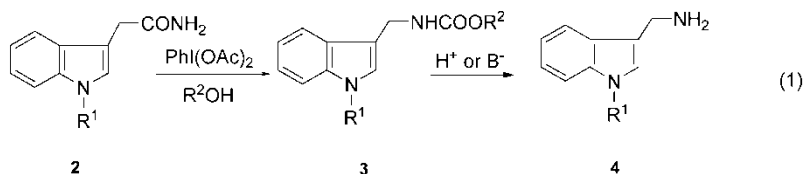
$$\text{(1)}$$

RESULTS AND DISCUSSION

Hofmann Rearrangement of 1-Protected Indole-3-acetamide

Our study first explored the possibility of preparing 1-unsubstituted alkyl carbamate **3a** directly from the commercially available indole-3-acetamide **2a** through Hofmann rearrangement. Unfortunately, when amide **2a** and

DIB (1.2 equiv) were stirred with 10 equiv of methanol at room temperature in different solvents such as methanol, methylene chloride, benzene, acetone, THF, and acetonitrile, **2a** was fully recovered (Table 1, entry 1).

It was reasonable to assume that a protecting group on indole nitrogen could promote the formation of an isocyanate intermediate and stabilize the resulting isocyanate intermediate during the Hoffmann rearrangement. As shown in Table 1, after screening the reactivity of 1-protected indole-3-acetamides **2b**, **2c**, and **2d** with DIB in different solvents, we were able to find that, with an electron-withdrawing group (Boc, Ts) on the indole nitrogen, amides **2c** and **2d** reacted rapidly with DIB in methanol to afford the corresponding methyl carbamate **3c** in 97% yield (entry 3) and methyl carbamate **3d** in 99% yield (entry 4) respectively within 4 h. 1-Protected indole-3-acetamides **2b** and **2c** were synthesized in 76% yield and 96% yield respectively from commercially available indole-3-acetamide **2a** by benzylation and tosylation in a dry CH_2Cl_2/NaOH system catalyzed by 0.05 equiv of tetrabutylammonium hydrogen sulphate.[8] Boc-protected indole-3-acetamide **2d** was prepared in 97% yield by reacting indole-3-acetamide **2a** with Boc_2O in a CH_2Cl_2/Et$_3$N/DMAP system. 1-Ts protected **2f** and **2h** were prepared similar to **2c**. Although methyl carbamate **3b** was isolated in

Table 1. Hofmann rearrangement of amides **2** promoted by DIB

2a R^1=H; 2b R^1=Bn
2c R^1=Boc; 2d R^1=Ts
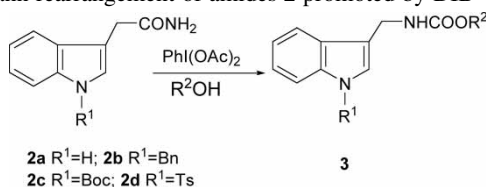
| Entry	2	R^1	R^2	Solvent	Yield (%) of 3^a	Time (h)
1^b	2a	H	Me	MeOH	0 (3a)	24
2	2b	Bn	Me	MeOH	27 (3b)	4
3	2c	Boc	Me	MeOH	97 (3c)	4
4	2d	Ts	Me	MeOH	99 (3d)	4
5^c	2d	Ts	Me	CH$_2$Cl$_2$	70 (3d)	24
6	2d	Ts	Me	PhH	86 (3d)	17
7	2d	Ts	Me	MeCN	88 (3d)	19
8	2d	Ts	Et	EtOH	81 (3e)	20
9	2d	Ts	^{i}Pr	^{i}PrOH	79 (3f)	24
10	2d	Ts	^{t}Bu	^{t}BuOH	75 (3g)	19
11^d	2c	Boc	Bn	PhH	80 (3h)	24
12^d	2d	Ts	Bn	PhH	85 (3i)	24

^{a}Isolated yields.
^{b}Fully recovered amide **2**.
^{c}By-products observed.
^{d}Similar result using acetonitrile.

27% yield (entry 2), the reaction of 1-benzyl amide **2b** with DIB gave a complicated mixture. This might be partly due to the electron-donating characteristics of the *N*-benzyl group. In the case of Ts-protected amide **2d**, Hofmann rearrangement also proceeded smoothly with 5–10 equiv of methanol in methylene chloride, acetonitrile, and benzene, providing methyl carbamate **3d** in good yields (Table 1, entries 5, 6, and 7).

The generality of forming different alkyl carbamates **3** via the DIB-promoted Hofmann rearrangement was then tested in volatile alcohols. With Ts-protected amide **2d**, the rearrangement provided the corresponding alkyl carbamates **3e–g** in moderate to good yields (entries 8–10) by using a variety of alcohols as solvent, but it required a longer reaction time compared with the rearrangement using methanol as solvent. Because benzyl alcohol is not volatile, the reactions of amides **2c** and **2d** with DIB were conducted in benzene in the presence of 5 equiv of benzyl alcohol, affording benzyl carbamates **3h** and **3i** in good yields (entries 11, 12). It was interesting to note that the reaction of acetamide **2c** with DIB in *tert*-butanol afforded predominantly the dimerized di-(1-Boc-indole-3-methylamino) urethane **3k** in 70% yield and 10% of *tert*-butyl carbamate **3j** (Eq. (2)). Methyl amine could fully compete with ethanol to capture the isocyanate to give methyl urea **3l** in 90% yield when **2d** was treated with 30% of MeNH$_2$ in EtOH in the presence of 1.2 equiv of DIB for 10 h (Eq. (3)).

$$(2)$$

$$(3)$$
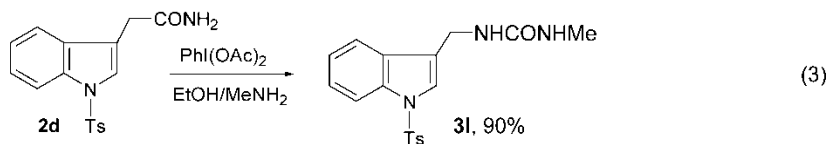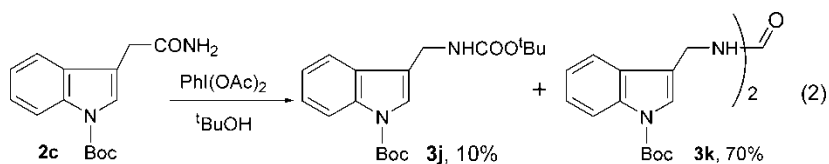
Hofmann Rearrangement of Substituted Indole-3-acetamide

We next carried out the DIB-promoted Hoffmann rearrangement of 2-methyl or 5-methoxy substituted indole-3-acetamides **2e–2h**. The results are shown in Table 2. Like acetamide **2a**, without an electron-withdrawing group on the indole nitrogen, acetamides **2e** and **2g** did not react with DIB (Table 2, entries 1 and 5), whereas the Hofmann rearrangement reactions of **2f** and **2h** with DIB in MeOH proceeded rapidly to give methyl carbamates **3n** and **3r** in greater than 93% yields (Table 2, entries 2 and 6). *tert*-Butyl carbamates **3o** and **3s** were obtained in 55% and 43% yields respectively when **2f** and **2h** were treated with DIB in *tert*-butanol for 24 h (Table 2, entries 3 and 7). The

Table 2. Hoffmann rearrangement of substituted indole-3-acetamide

2e R^1=H, R^2=Me, R^3=H; **2f** R^1=Ts, R^2=Me, R^3=H;
2g R^1=H, R^2=H, R^3=MeO; **2h** R^1=Ts, R^2=H, R^3=MeO
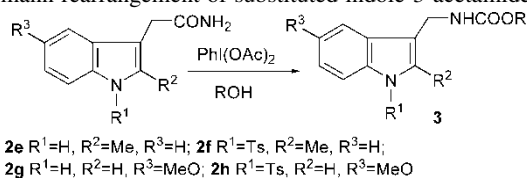
Entry	**2**	R^1	R^2	R^3	R	Solvent	Yield of **3**[a]	Time (h)
1[b]	**2e**	H	Me	H	Me	MeOH	0 (**3m**)	24
2	**2f**	Ts	Me	H	Me	MeOH	93 (**3n**)	3
3	**2f**	Ts	Me	H	^{t}Bu	^{t}BuOH	55 (**3o**)	24
4	**2f**	Ts	Me	H	Bn	PhH	37 (**3p**)	24
5[b]	**2g**	H	H	MeO	Me	MeOH	0 (**3q**)	24
6	**2h**	Ts	H	MeO	Me	MeOH	95 (**3r**)	4
7	**2h**	Ts	H	MeO	^{t}Bu	^{t}BuOH	43 (**3s**)	24
8	**2h**	Ts	H	MeO	Bn	PhH	33 (**3t**)	24

[a]Isolated yields.
[b]Fully recovered amide **2e** or **2g**.

reactions of amides **2f** and **2h** with DIB in the presence of 5 equiv of benzyl alcohol in benzene provided the corresponding benzyl carbamates **3p** and **3t** in less than 37% yields (Table 2, entries 4 and 8).

Hofmann Rearrangement of Thiopheneacetamide and Pyrroleacetamide

The possible application of this method to generating the protected hetero-cyclic methyleneamine functional group from related acetamides was also tested. As shown in Table 3, the reactions of both thiophene-2-acetamide **5a** and thiophene-3-acetamide **5b** with DIB (1.2 equiv) in MeOH proceeded smoothly to give methyl carbamate **6a** of thiophene-2-methylamine and methyl carbamate **6b** of thiophene-3-methylamine in moderate yields (Table 3, entries 1 and 2). Pyrrole-2-acetamide **5c** did not react with DIB in MeOH (Table 3, entry 3). Unlike pyrrole-2-acetamide **5c**, the *N*-Boc- and *N*-Ts-substituted pyrrole-2-acetamides **5d** and **5e** reacted with DIB in MeOH to give methyl carbamate **6d** and methyl carbamate **6e** in 80% and 75% yields respectively (Table 3, entries 4 and 5).

## Deprotection of Alkyl Carbamate of Indole-3-methylamine

To demonstrate that the synthesized carbamate **3** could serve as a precursor of indole-3-methylamine, we tried to remove the methylamine protecting group in **3** (Eqs. (4), (5), and (6)). Unexpectedly, all the alkyl carbamate groups on

Table 3. Hofmann rearrangement of amides **5** promoted by DIB

Entry	5	X	R	Solvent	Yield of 6[a]	Time (h)
1	**5a**	S		MeOH	51 (**6a**)	10
2	**5b**	S		MeOH	41 (**6b**)	10
3[b]	**5c**	N	H	MeOH	0 (**6c**)	10
4	**5d**	N	Boc	MeOH	80 (**6d**)	4
5	**5e**	N	Ts	MeOH	75 (**6e**)	6

[a]Isolated yields.
[b]Fully recovered amide **5c**.

methylamine were surprisingly stable under basic conditions, such as hydrazine/MeOH, EtSLi/THF, aqueous NaOH/THF, K_2CO_3/THF, and $NaN(TMS)_2$/THF. The 1-deprotection always occurred dominantly instead of removing the methylamine protecting group when carbamate **3** was treated with these agents. For example, when **3c** and **3d** were hydrolyzed with aqueous NaOH/THF for 1 h, methyl carbamate **7** was produced in 95% and 90% yields respectively (Eq. (4)). Surprisingly, the Cbz group on **3h** was very stable. We failed to remove the Cbz protecting group from compound **3h** by hydrogenolysis under 200-psi pressure of hydrogen in methanol (Eq. (5)). Fortunately, the Boc protecting group in **3g** was easily removed by treatment of **3g** with 20% trifluoroacetic acid (TFA) in CH_2Cl_2 for 0.5 h to afford 1-Ts-indole-3-methylamine **4b** in 94% yield (Eq. (6)). 1-Ts-indole-3-methylamine **4** was reported unstable in pure form (see Ref. 3(d)). In our experiment, **4** was stable enough at room temperature and can survive chromatography. It has been stored at room temperature for three months without decomposition.

(4)

(5)

(6)
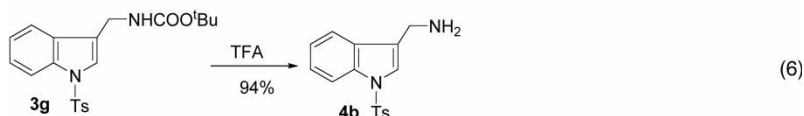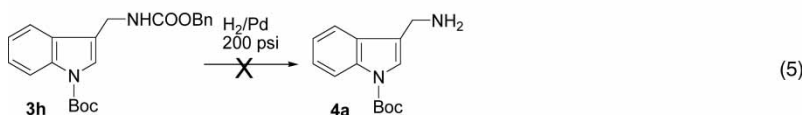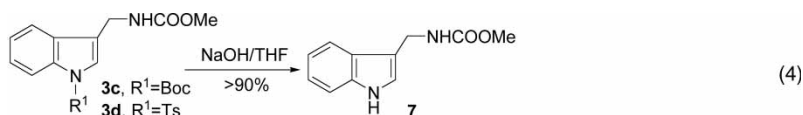
In conclusion, we have described a convenient method for directly converting 1-protected indole-3-acetamides **2** into alkyl carbamates **3** via DIB-promoted Hofmann rearrangement under neutral conditions. DIB also can effectively promote the rearrangements of thiopheneacetamides **5a** and **5b**, and 1-protected pyrroleacetamides **5d** and **5e**, to afford the corresponding alkyl carbamates **6**. Most important, we have demonstrated that the synthesized carbamate **3g** can serve well as a stable precursor of 1-protected indole-3-methylamine **1**.

EXPERIMENTAL

All commercially available reagents were used without further purification. All solvents were dried and distilled before use: THF was distilled from sodium/benzophenone ketyl; dichloromethane was distilled from calcium hydride; acetonitrile and acetone were distilled from P_2O_5; methanol and ethanol were distilled from magnesium; *tert*-butanol was distilled from calcium hydride; benzene was distilled from sodium. Chromatography was conducted by using 200–300 mesh silica gel. IR spectra were recorded on a FT IR spectrometer. NMR spectra were acquired on a 400-MHz NMR spectrometer. Chemical shifts are reported in ppm relative to TMS. HRMS spectra were obtained by the electron spray ionization (ESI) method.

General Procedure for the DIB-Promoted Hofmann Rearrangement of 1-Protected Acetamide 2

A mixture of 1 mmol of 1-protected indole-3-acetamide **2** and 1.2 equiv of DIB were stirred in 10 mL of solvent as indicated in Table 1 in the presence of an appropriate alcohol (5 equiv) at room temperature for 4–30 h. After completion of the reaction (checked by TLC), the solvent was removed under vacuum. The residue was purified by chromatography on silica gel to give alkyl carbamate **3**.

3b. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:5) afforded a white solid. Mp: 92°C. IR: 1044, 1261, 1357, 1469, 1534, 1688, 3339 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.69 (s, 3H), 4.50 (d, $J = 6.8$ Hz, 2H), 4.86 (s, 1H), 5.28 (s, 2H), 7.08–7.32 (m, 9H), 7.66 (d, $J = 6.4$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 36.56, 49.92, 52.03, 109.82, 112.25, 119.05, 119.58, 122.16, 126.80, 126.88, 127.09, 127.65, 128.73, 136.74, 137.19, 156.88; EI-MS: m/z (%) 294 (26, M$^+$), 279 (8), 235 (6), 221 (3), 220 (3), 203 (5); ESI-MS: m/z (%) 317 (100, M + Na$^+$); HRMS calcd. for C$_{18}$H$_{18}$N$_2$NaO$_2$: 317.1260; found 317.1247.

3c. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:5) afforded a white solid. Mp: 121°C. IR: 1086, 1152, 1225, 1372, 1455, 1372, 3336 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.67 (s, 9H), 3.71

(s, 3H), 4.50 (d, $J = 5.6$ Hz, 2H), 4.89 (s, br, 1H), 7.26 (dt, $J = 1.2$, 8.4 Hz, 1H), 7.34 (dt, $J = 1.2$, 7.6 Hz, 1H), 7.53 (s, 1H), 7.58 (d, $J = 7.6$ Hz, 1H), 8.13 (d, br, $J = 7.2$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 28.1, 36.3, 52.2, 83.8, 115.3, 117.7, 119.1, 122.7, 123.9, 124.7, 129.1, 135.7, 149.6, 156.9; ESI-MS: m/z (%) 327 (100, M + Na$^+$): HRMS calcd. for C$_{16}$H$_{20}$N$_2$NaO$_4$. 327.1317; found 327.1320.

3d. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:5) afforded a white solid. Mp: 128°C. IR: 965, 1174, 1271, 1365, 1448, 1529, 1701, 3337 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.34 (s, 3H), 3.70 (s, 3H), 4.87 (d, $J = 8.0$ Hz, 2H), 4.89 (s, br, 1H), 7.23 (d, $J = 8.4$ Hz, 3H), 7.27 (t, $J = 7.6$ Hz, 1H), 7.50 (s, 1H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 2H), 8.00 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 21.5, 36.3, 52.3, 113.7, 119.6, 119.8, 123.3, 124.0, 125.0, 126.8, 127.2, 129.4, 129.9, 135.1, 135.3, 145.0, 156.9; ESI-MS: m/z (%) 381 (100, M + K$^+$); HRMS calcd. for C$_{18}$H$_{18}$N$_2$NKO$_4$S: 381.0879; found 381.0868.

3e. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:6) afforded a white solid. Mp: 74°C. IR: 974, 1020, 1119, 1250, 1368, 1448, 1522, 1700 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.27 (t, $J = 7.6$ Hz, 3H), 2.34 (s, 3H), 4.15 (q, $J = 2.0$ Hz, 2H), 4.48 (d, $J = 5.6$ Hz, 2H), 4.85 (s, br, 1H), 7.22 (d, $J = 4.8$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.34 (t, $J = 4.8$ Hz, 1H), 7.49 (s, 1H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 2H), 7.97 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 14.5, 21.4, 36.0, 61.0, 113.6, 119.7, 119.7, 123.2, 123.9, 124.9, 126.7, 129.4, 129.8, 135.0, 135.2, 144.9, 156.2; EI-MS: m/z (%) 372 (14, M$^+$), 343 (2), 217 (19), 189 (7), 145 (10), 118 (16); ESI-MS: m/z (%) 395 (5, M + Na$^+$); HRMS calcd. for C$_{19}$H$_{20}$N$_2$NaO$_4$S: 395.1036; found 395.1048.

3f. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:5) afforded a white solid. Mp: 135°C. IR: 970, 1119, 1175, 1253, 1364, 1532, 1681, 1703, 3303 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.23 (d, $J = 6.3$ Hz, 6H), 2.33 (s, 3H), 4.46 (d, $J = 5.6$ Hz, 2H), 4.87 (s, br, 1H), 4.94 (m, $J = 6.4$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.25 (t, $J = 8.0$ Hz, 1H), 7.32 (t, $J = 8.0$ Hz, 1H), 7.48 (s, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.97 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 21.52, 22.13, 29.68, 36.14, 68.47, 113.72, 119.68, 120.00, 121.85, 123.30, 123.97, 125.01, 126.82, 129.47, 129.90, 135.39, 144.98, 156.13; ESI-MS: m/z (%) 409 (7, M + Na$^+$); HRMS calcd. for C$_{20}$H$_{22}$N$_2$NaO$_4$S: 409.1192; found 409.1203.

3g. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:7) afforded a white solid. Mp: 86°C. IR: 937, 967, 1092, 1172, 1293, 1366, 1448, 1526, 1683, 2978, 3334 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.46 (s, 9H), 2.34 (s, 3H), 4.42 (d, $J = 5.6$ Hz, 2H), 4.72 (s, br, 1H), 7.23 (d, $J = 5.6$ Hz, 2H), 7.24 (d, $J = 1.2$ Hz, 1H), 7.33 (t, $J = 8.0$ Hz, 1H), 7.48 (s, 1H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 2H), 7.97 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 21.4, 28.3, 35.7, 79.5,

113.6, 119.7, 120.2, 123.2, 123.8, 124.8, 126.7, 129.4, 129.8, 130.2, 135.1, 135.3, 144.9, 155.7; ESI-MS: m/z (%) 423 (5, M + Na$^+$); HRMS calcd. for $C_{21}H_{24}N_2NaO_4S$: 423.1349; found 423.1338.

3h. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:10) afforded a white solid. Mp: 120°C. IR: 910, 1087, 1158, 1259, 1371, 1454, 1731, 3341 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.66 (s, 9H), 4.52 (d, $J = 5.6$ Hz, 2H), 4.99 (s, br, 1H), 5.14 (s, 2H), 7.23 (d, $J = 7.6$ Hz, 1H), 7.31 (d, $J = 1.2$ Hz, 1H), 7.33 (s, 2H), 7.35 (d, $J = 4.0$ Hz, 2H), 7.37 (s, 1H), 7.52 (s, 1H), 7.56 (d, $J = 7.6$ Hz, 1H), 8.12 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 27.9, 36.1, 64.7, 66.6, 83.6, 115.1, 117.6, 118.9, 122.5, 123.7, 124.5, 126.7, 127.2, 128.2, 127.8, 127.9, 128.2, 128.3, 140.8, 149.4, 156.3; ESI-MS:m/z (%) 403 (4, M + Na$^+$); HRMS calcd. for $C_{22}H_{24}N_2NaO_4S$: 403.1628; found 403.1628.

3i. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:10) afforded a white solid. Mp: 95°C. IR: 969, 1097, 1173, 1267, 1372, 1530, 1694, 3325 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.34 (s, 3H), 4.50 (d, $J = 5.6$ Hz, 2H), 4.95 (s, br, 1H), 5.14 (s, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.25 (m, 1H), 7.31 (m, 6H), 7.49 (s, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.97 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 21.49, 29.65, 36.28, 113.66, 119.66, 123.30, 124.01, 125.00, 126.77, 126.92, 127.56, 128.05, 128.14, 128.50, 129.34, 129.87, 135.11, 135.29, 144.98, 156.22; ESI-MS: m/z (%) 457 (5, M + Na$^+$); HRMS calcd. for $C_{24}H_{22}N_2NaO_4S$: 457.1192; found 457.1182.

3j. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:7) afforded a white solid. Mp: 80°C. IR: 1099, 1152, 1283, 1371, 1458, 1717, 1750, 1802, 2990 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.45 (s, 9H), 1.66 (s, 9H), 4.44 (d, $J = 5.6$ Hz, 2H), 4.75 (s, br, 1H), 7.26 (dt, $J = 1.2$, 7.6 Hz, 1H), 7.33 (dt, $J = 1.2$, 7.6 Hz, 1H), 7.51 (s, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 8.12 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 27.8, 27.9, 29.6, 84.0, 115.0, 117.1, 119.4, 122.5, 124.3, 124.84, 129.3, 135.2, 149.0, 149.4, 154.6; EI-MS: m/z (%) 346 (3, M$^+$), 230 (2); HRMS calcd. for $C_{19}H_{26}N_2NaO_4$: 369.1893; found 369.1889.

3k. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:5) afforded a white solid. Mp: 230°C. IR: 973, 1120, 1173, 1367, 1448, 1559, 1596, 1636, 3410 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 1.60 (s, 18H), 4.37 (d, $J = 5.6$ Hz, 4H), 6.31 (t, $J = 5.6$ Hz, 2H), 7.18 (t, $J = 7.2$ Hz, 2H), 7.33 (t, $J = 7.2$ Hz, 2H), 7.51 (s, 2H), 7.66 (d, $J = 8.0$ Hz, 2H), 8.02 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d$_6$) δ 27.9, 34.5, 83.8, 114.9, 119.9, 120.3, 122.7, 123.4, 124.6, 129.4, 135.2, 148.3, 158.1; ESI-MS: m/z 541 (100, M + Na$^+$); HRMS calcd for $C_{29}H_{34}N_4NaO_5$: 541.2421; found 541.2435.

3l. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 2:1) afforded a white solid. Mp: 170°C. IR: 970, 1171, 1369, 1619, 2924, 3328 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.34 (s, 3H), 2.76 (s, 3H), 4.48 (d, $J = 5.2$ Hz, 2H), 4.50 (s, br, 1H), 4.70 (s, br, 1H), 7.21 (d, $J = 8.0$ Hz,

2H), 7.25 (d, $J = 0.8$ Hz, 1H), 7.32 (t, $J = 5.6$ Hz, 1H), 7.48 (s, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.95 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 21.5, 27.3, 35.7, 113.6, 119.8, 120.5, 123.3, 123.8, 125.0, 126.8, 129.5, 129.9, 135.1, 135.3, 145.0, 158.5; EI-MS: m/z (%) 357 (29, M$^+$), 202 (30), 145 (100); HRMS calcd. for C$_{18}$H$_{19}$N$_3$NaO$_3$S: 380.1039; found 380.1032.

3n. Purification by chromatography on silica gel (acetone/petroleum ether 2:3) afforded a light yellow solid. Mp: 104;°C. IR: 1000, 1176, 1238, 1365, 1455, 1522, 1702, 3333 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.35 (s, 3H), 2.60 (s, 3H), 3.69 (s, 3H), 4.40 (d, $J = 5.2$ Hz, 2H), 4.71 (s, br, 1H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 5.2$ Hz, 1H), 7.30 (td, $J = 1.2$, 7.6 Hz, 1H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 2H), 8.20 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 12.5, 21.4, 34.9, 52.1, 114.5, 116.5, 118.3, 123.5, 124.3, 125.4, 126.3, 129.1, 129.8, 130.0, 134.8, 136.2, 144.8, 156.8. ESI-MS: m/z(%) 395 (100, M + Na$^+$); HRMS calcd. for C$_{19}$H$_{20}$N$_2$NaO$_4$S: 395.1036; found 395.1045.

3o. Purification by chromatography on silica gel (acetone/petroleum ether 1:8) afforded a light yellow solid. Mp: 85°C. IR: 911, 1007, 1176, 1238, 1455, 1508, 1701, 2930, 2976 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.43 (s, 9H), 2.35 (s, 3H), 2.59 (s, 3H), 4.35 (d, $J = 5.2$ Hz, 2H), 4.52 (s, br, 1H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.25 (dd, $J = 1.2$, 7.6 Hz, 1H), 7.30 (td, $J = 1.2$, 7.2 Hz, 1H), 7.49 (d, $J = 7.6$ Hz, 1H), 7.66 (d, $J = 8.0$ Hz, 2H), 8.20 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 12.5, 21.4, 28.3, 29.6, 34.4, 79.5, 114.4, 116.8, 116.4, 123.4, 124.2, 126.3, 126.3, 129.2, 129.8, 134.6, 136.2, 144.7, 155.6. ESI-MS: m/z 437 (100, M + Na$^+$); HRMS calcd. for C$_{22}$H$_{26}$N$_2$NaO$_4$S: 437.1505; found 437.1497.

3p. Purification by chromatography on silica gel (acetone/petroleum ether 1:10) afforded a light yellow solid. Mp: 130°C. IR: cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.34 (s, 3H), 2.59 (s, 3H), 4.41 (d, $J = 5.6$ Hz, 2H), 4.80 (s, br, 1H), 5.10 (s, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.23-7.35 (m, 7H), 7.47 (d, $J = 7.2$ Hz, 1H), 7.65 (d, $J = 8.4$ Hz, 2H), 8.19 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 12.6, 21.5, 34.9, 66.9, 114.5, 118.3, 123.5, 124.4, 126.3, 128.0, 128.1, 128.5, 129.9, 136.3, 144.8; EI-MS: m/z (%) 448 (4, M$^+$), 357 (15), 203 (11); HRMS calcd. for C$_{25}$H$_{24}$N$_2$NaO$_4$S: 471.1349; found 471.1327.

3r. Purification by chromatography on silica gel (acetone/petroleum ether 2:3) afforded a light yellow solid. Mp: 95°C. IR: 1033, 1119, 1265, 1370, 1476, 1518, 1721, 2926 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.35 (s, 3H), 3.71 (s, 3H), 3.82 (s, 3H), 4.44 (d, $J = 5.6$ Hz, 2H), 4.87 (s, br, 1H), 6.94 (dd, $J = 2.4$, 8.8 Hz, 1H), 7.01 (s, 1H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.44 (s, 1H), 7.73 (d, $J = 7.6$ Hz, 2H), 7.86 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 21.5, 36.2, 52.3, 55.6, 101.9, 114.1, 114.5, 119.9, 124.7, 126.7, 129.8, 129.9, 130.3, 135.0, 144.9, 156.9; EI-MS: m/z (%) 388 (19, M$^+$), 233 (71), 174 (6), 159 (11); HRMS calcd. for C$_{19}$H$_{20}$N$_2$NaO$_5$S: 411.0985; found 411.0976.

3s. Purification by chromatography on silica gel (acetone/petroleum ether 1:4) afforded a light yellow solid. Mp: 90°C. IR: 1033, 1173, 1265, 1369, 1507, 1710, 2852, 2925 3055 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.46 (s, 9H), 2.38 (s, 3H), 3.82 (s, 3H), 4.38 (d, $J = 5.6$ Hz, 2H), 4.70 (s, br, 1H), 6.93 (dd, $J = 2.4, 9.2$ Hz, 1H), 7.02 (s, 1H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.42 (s, 1H), 7.73 (d, $J = 8.8$ Hz, 2H), 7.85 (d, $J = 9.2$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 21.5, 28.7, 36.3, 52.3, 83.4, 101.8, 114.1, 114.5, 119.9, 124.7, 126.7, 129.8, 129.9, 130.3, 135.0, 144.9, 156.4, 156.9; EI-MS: m/z (%) 430 (31, M$^+$), 329 (6), 314 (15), 219 (100), 175 (43); HRMS calcd. for C$_{22}$H$_{26}$N$_2$NaO$_5$S: 453.1562; found 453.1569.

3t. Purification by chromatography on silica gel (acetone/petroleum ether 1:4) afforded a light yellow solid. Mp: 128°C. IR: 979, 1034, 1173, 1227, 1370, 1476, 1516, 1717, 2917 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.34 (s, 3H), 3.81 (s, 3H), 4.44 (d, $J = 6.0$ Hz, 2H), 5.00 (s, br, 1H), 5.15 (s, 2H), 6.94 (dt, $J = 2.8, 9.6$ Hz, 1H), 6.99 (s, 1H), 7.21 (m, 2H), 7.33 (m, 5H), 7.44 (s, 1H), 7.73 (m, 2H), 7.86 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 21.5, 36.3, 55.6, 66.9, 101.9, 102.0, 114.2, 114.3, 114.6, 124.7, 124.8, 126.8, 128.0, 128.2, 128.5, 129.9, 134.4, 144.9, 156.45; EI-MS: m/z (%) 464 (14, M$^+$), 373 (27), 314 (4), 309 (10), 218 (19); HRMS calcd. for C$_{25}$H$_{24}$N$_2$NaO$_4$S: 487.1306; found 487.1306.

General Procedure for the DIB-Promoted Hofmann Rearrangement of Acetamides 5a, 5b, 5d, and 5e

A mixture of 1 mmol of acetamide **5** and 1.2 equiv of DIB were stirred in 10mL of methanol at room temperature for 4–10h. The solvent was removed under vacuum. The residue was purified by chromatography on silica gel to give alkyl carbamate **6**.

6a. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:10) afforded a white solid. Mp: 102 °C. IR: 1239.1, 1465.9, 1569.3, 1611.1, 2871.4, 3335.2 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.70 (s, 3H), 4.54 (d, $J = 5.6$ Hz, 2H), 5.11 (s, br, 1H), 6.96 (m, 2H), 7.2 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d$_6$) δ 38.4, 52.3, 121.3, 126.4, 127.8, 142.0, 158.1; EI-MS: m/z (%) 112 (100, M$^+$-COOCH$_3$); anal. calcd. for C$_7$H$_9$N$_1$O$_2$S$_1$: C, 49.10; H, 5.30; N, 8.18. Found: C, 49.14; H, 5.26; N, 8.22.

6b. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:10) afforded a white solid. Mp: 105°C. IR: 1263.9, 1423.8, 1617.4, 2924.5, 3353.2 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.70 (s, 3H), 4.53 (d, $J = 5.6$ Hz, 2H), 5.10 (s, br, 1H), 6.92 (m, 2H), 7.2 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d$_6$) δ 38.32, 52.00, 124.9, 126.8, 127.9, 144.4, 157.6; EI-MS: m/z (%) 112 (100, M$^+$-COOCH$_3$); anal. calcd. for C$_7$H$_9$N$_1$O$_2$S$_1$: C, 49.10; H, 5.30; N, 8.18. Found: C, 49.07; H, 5.33; N, 8.15.

6d. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:10) afforded a white solid. Mp: 125°C. IR: 1131, 1339, 1508, 1734,

2924, 3345 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.60 (s, 9H), 3.65 (s, 3H), 4.46 (d, J = 6.4 Hz, 2H), 5.63 (s, br, 1H), 6.08 (t, J = 3.2 Hz, 1H), 6.21 (s, 1H), 7.25 (t, J = 2.0 Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 28.0, 38.3, 52.0, 84.1, 110.3, 113.6, 121.5, 127.3, 131.9, 158.7; EI-MS: m/z (%) 254 (2, M$^+$), 154 (18); HRMS calcd. for C$_{12}$H$_{18}$N$_2$NaO$_4$: 277.1159; found 277.1142.

6e. Purification by chromatography on silica gel (ethyl acetate/petroleum ether 1:10) afforded a white solid. Mp: 105 °C. IR: 1052, 1155, 1264, 1367, 1515, 1716, 2924, 3445 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.41 (s, 3H), 3.64 (s, 3H), 4.35 (d, J = 6.4 Hz, 2H), 5.41 (s, br, 1H), 6.21 (t, J = 3.2 Hz, 1H), 6.27 (s, 1H), 7.25 (t, J = 1.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 21.6, 37.3, 52.1, 111.9, 115.1, 123.3, 126.5, 130.1, 131.7, 136.0, 145.2; EI-MS: m/z (%) 308 (2, M$^+$), 234 (9), 153 (100); HRMS calcd. for C$_{14}$H$_{16}$N$_2$NaO$_4$S: 331.0723; found 331.0733.

1-Deprotection of Alkyl Carbamate 3c and 3d to Give 7

Carbamate **3c** or **3d** (0.5 mmol) was stirred with 2 mL of 1 M of NaOH in 2 mL of THF for 1 h. The reaction mixture was extracted with EtOAc (2 × 5 mL). The organic layers were dried and evaporated to give a residue. The residue was purified by chromatography on silica gel (ethyl acetate/petroleum ether 1:3) to afford **7** as a white solid in 95% yield and 90% yield respectively. Mp: 85°C. IR: 1073, 1253, 1457, 1523, 1698, 2925, 3325 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.7 (s, 3H), 4.56 (d, J = 5.2 Hz, 2H), 4.89 (s, br, 1H), 7.16 (m, 2H), 7.22 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 8 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 8.19 (s, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 36.7, 52.1, 111.5, 112.6, 118.7, 119.6, 122.2, 123.2, 126.4, 136.5, 157.2; EI-MS: m/z (%) 204 (100, M$^+$), 189 (29), 145 (14), 130 (75), 118 (28); HRMS calcd. for C$_{11}$H$_{12}$N$_2$NaO$_2$: 224.0799; found 224.0807.

Deprotection of Alkyl Carbamate 3g to Give 4b

A solution of carbamate **3g** (0.398 g, 1 mmol) in 5 ml of CH$_2$Cl$_2$ was stirred at room temperature for 0.5 h in the presence of 20% TFA. The reaction mixture was quenched with saturated Na$_2$CO$_3$ and was extracted with CH$_2$Cl$_2$. The combined organic layers were dried by Na$_2$SO$_4$. The solvent was removed under vacuum. The residue was purified by chromatography on silica gel (ethyl acetate/methanol 10:1) to afford 0.283 g of amine **4b** (94% yield) as a white solid. Mp: 85°C. IR: 972, 1122, 1174, 1368, 1684, 2924 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.88 (s, 2H), 2.31 (s, 3H), 3.98 (s, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.24 (m, 3H), 7.47 (s, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.98 (d, J = 8.0 Hz, 1H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 21.4, 37.3, 113.7,

119.4, 122.7, 123.1, 124.4, 124.8, 126.7, 129.7, 129.8, 130.0, 135.5, 144.8; EI-MS: m/z (%) 300 (68, M$^+$), 284 (17), 145 (84), 129 (15); HRMS calcd. for $C_{16}H_{16}KN_2O_2S$: 339.0564; found 339.0572.

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REFERENCES

1. (a) Gfesser, G.; Bayburt, E.; Cowart, M.; DiDomenico, S.; Gomtsyan, A.; Lee, Ch; Stewart, A.; Jarvis, M.; Kowaluk, E.; Bhagwat, S. *Euro. J. Med. Chem.* **2003**, *38*, 245; (b) Remiszewski, S. W.; Sambucetti, L. C.; Bair, K. W.; Bontempo, J.; Cesarz, D.; Chandramouli, N.; Chen, R.; Cheung, M.; Cornell-Kennon, S.; Dean, K.; Diamantidis, G.; France, D.; Green, M. A.; Howell, K. L.; Kashi, R.; Kwon, P.; Lassota, P.; Martin, M. S.; Mou, Y.; Perez, L. B.; Sharma, S.; Smith, T.; Sorensen, E.; Taplin, F.; Trogani, N.; Versace, R.; Walker, H.; Weltchek-Engler, S.; Wood, A.; Wu, A.; Atadja, P. *J. Med. Chem.* **2003**, *46*, 4609; (c) Lapinsh, M.; Prusis, P.; Mutule, I.; Mutulis, F.; Wikberg, J. E. S. *J. Med. Chem.* **2003**, *48*, 2572.

2. Daniel, M.; Purkayastha, R. *Eds. Handbook of Phytoalexins Metabolism and Action*; Marcel Dekker: New York, 1995 and references cited therein.

3. For the latest syntheses of phytoalexins, see (a) Pedras, M. S. C.; Zaharia, I. L. *Organic Lett.* **2001**, *3*, 1213; (b) Suchy, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentova, E. *J. Org. Chem.* **2001**, *66*, 3940; (c) Kutschy, P.; Dzurilla, M.; Torok, M.; Achbergerova, I.; Homzova, R.; Racova, M. *Tetrahedron* **1998**, *54*, 3549; (d) Kutschy, P.; Achbergerova, I.; Dzurilla, M.; Takasugi, M. *Synlett* **1997**, 289; (e) Takasugi, M.; Monde, K.; Katsui, N.; Shirata, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 285.

4. (a) Yamada, F.; Kobayashi, K.; Shimizu, A.; Aoki, N.; Somei, M. *Heterocycles* **1993**, *36*, 2783; (b) Pedras, M. S. C.; Taylor, J. L. *J. Nat. Prod.* **1993**, *56*, 731; (c) Kawasaki, T.; Somei, M. *Heterocycles* **1990**, *31*, 1605; (d) Schallenberg, J.; Meyer, E. Z. *Naturforsch.* **1983**, *38b*, 108; (e) Gower, B. G.; Leete, E. *J. Am. Chem. Soc.* **1963**, *85*, 3683; (f) Walker, G.; Moore, M. *J. Org. Chem.* **1961**, *26*, 432.

5. For recent reviews on polyvalent iodine chemistry, see: (a) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905; (b) Zhdankin, V.; Stang, P. *Chem. Rev.* **2002**, *102*, 2523; (c) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179.

6. (a) Prakash, O.; Batra, H.; Kaur, H.; Sharma, P. K.; Sharma, V.; Singh, S. P.; Moriarty, R. M. *Synthesis* **2001**, 541; (b) Erdelmeier, I.; Tailhan-Lomont, C.; Yadan, J. *J. Org. Chem.* **2000**, *65*, 8152; (c) Zhang, L.; Kauffman, G.; Pesti, J.; Yin, J. *J. Org. Chem.* **1997**, *62*, 6918; (d) Zhang, L.; Chung, J.; Costello, T.; Valvis, I.; Ma, P.; Kauffman, S.; Ward, R. *J. Org. Chem.* **1997**, *62*, 2466.

7. DIB was used to prepare methyl carbamates from primary alkyl- andaryl-
   carboxamides under strong basic condition via Hofmann rearrangement; see
   Moriarty, R. M.; Chany, C. J., II; Vaid, R. K.; Prakash, O.; Tuladhar, S. M.
   J. Org. Chem. **1993**, *58*, 2478.
8. Gribble, G.; Jiang, J.; Liu, Y. *J. Org. Chem.* **2002**, *67*, 1001.