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Condensed Heteroaromatic Ring Systems. XXIV.[1,2] Palladium-Catalyzed Cyclization of 2-Substituted Phenylacetylenes in the Presence of Carbon Monoxide

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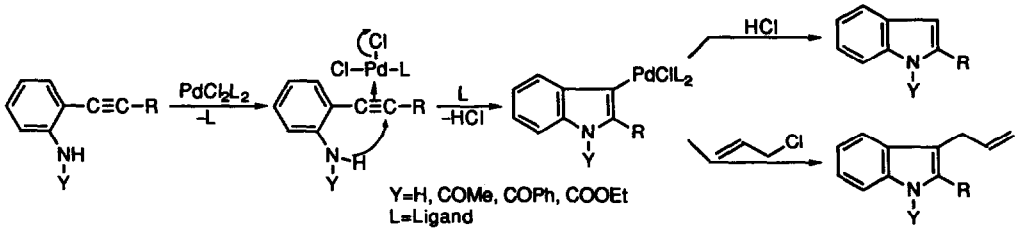
Abstract: The palladium-catalyzed reaction of 2-alkynylanilines and 2-alkynylphenols in the presence of carbon monoxide and methanol under basic conditions gave the sequential cyclization / carbonylation products, methyl 2-substituted indole and benzo[*b*]-furan-3-carboxylates. Similar reaction of 2-alkynylbenzamides gave 3-alkylidenisoindole derivatives.

INTRODUCTION

It has been reported that palladium(II)-catalyzed reaction of *N*-acyl-2-alkynylanilines gave 2-substituted indoles.[3-6] As shown in Scheme 1, the reaction was considered to proceed *via* the indolylpalladium complexes as intermediates which gave indole derivatives and palladium(II) species by protonolysis. When the reaction was carried out in the presence of allyl chloride, the intermediary indolylpalladium complexes were coupled with allyl chloride to give 2-substituted 3-allylindoles.[4]

Similar reaction of 2-hexynyltrifluoroacetanilide with aryl iodides in the presence of a palladium(0) catalyst was reported.[7] In this reaction, arylpalladium iodides formed at first, which reacted with the alkynylaniline to give 3-arylindoles *via* indolylarylpalladium complexes. The palladium-catalyzed reaction was developed to the synthesis of 3-aroylindoles in the presence of carbon monoxide.[8]



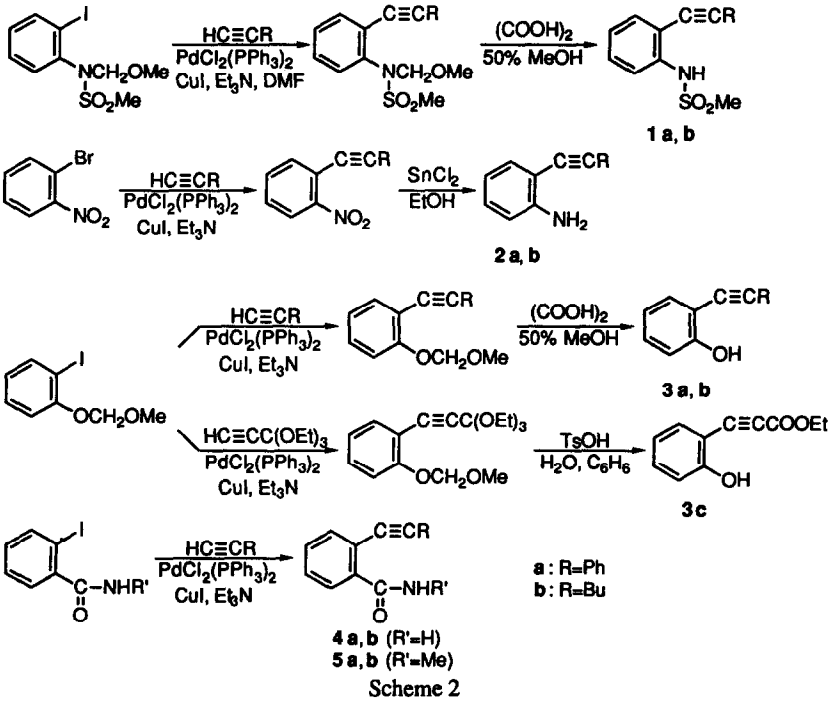
Scheme 1

In this paper, we report the palladium-catalyzed reaction of 2-alkynylanilines and 2-alkynylphenols in the presence of carbon monoxide and methanol to give methyl indole-3-carboxylates and methyl benzo[*b*]furan-3-carboxylates. The carbonylative cyclization reaction of 2-alkynylbenzamides affording 3-alkylidenisoindole derivatives was also described.

SYNTHESIS OF STARTING MATERIALS

Since it is known that the palladium-catalyzed reaction of 2-iodo-*N*-(methylsulfonyl)aniline with terminal acetylenes gives no 2-alkynylaniline derivatives but 2-substituted indoles,[9] 2-alkynyl-*N*-(methylsulfonyl)anilines (**1a,b**) were synthesized by the palladium-catalyzed reaction of 2-iodo-*N*-(methoxymethoxy)-*N*-(methylsulfonyl)aniline with terminal acetylenes followed by hydrolysis with oxalic acid in 50% methanol. 2-Alkynylanilines (**2a,b**) were prepared by the reduction of 2-alkynylnitrobenzenes with stannous chloride in ethanol, which were synthesized from 2-bromonitrobenzene with terminal acetylenes in the presence of palladium catalyst.

2-Alkynylphenols (**3a,b**) were synthesized from 2-(methoxymethoxy)iodobenzene analogously to the synthesis of **1a,b**. Preparation of ethyl 3-(2-hydroxyphenyl)propiolate (**3c**) was achieved by hydrolysis of triethyl 2-(methoxymethoxy)orthopropiolate which was derived from the reaction of 2-(methoxymethoxy)iodobenzene and triethyl orthopropiolate in the presence of palladium-catalyst, because the palladium-catalyzed reaction of aryl iodides with ethyl propiolate gave no coupling product.[10]



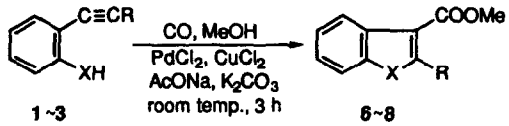
Scheme 2

Finally, 2-alkynylbenzamide derivatives (**4** and **5**) were synthesized by the palladium-catalyzed reaction of 2-iodobenzamides with terminal acetylenes.

CARBONYLATIVE CYCLIZATION OF 2-SUBSTITUTED PHENYLACETYLENES

When *N*-(methylsulfonyl)-2-(2-phenylethynyl)aniline (**1a**) was allowed to react with carbon monoxide in methanol in the presence of palladium dichloride, copper dichloride, sodium acetate, and potassium carbonate at room temperature for 3 h, methyl 1-methylsulfonyl-2-phenylindole-3-carboxylate (**6a**) was obtained in 76% yield. Similarly, methyl 2-butyl-1-methylsulfonylindole-3-carboxylate (**6b**) was yielded in 67% yield. The carbonylative cyclization of 2-alkynylanilines (**2a,b**), however, gave methyl 2-substituted indole-3-carboxylates (**7a,b**) in relatively low yields.

Although the formation of methyl benzo[*b*]furan-3-carboxylates (**8a,b**) from 2-alkynylphenols (**3a,b**) proceeded smoothly, the carbonylative cyclization of ethyl 2-(hydroxyphenyl)propiolate (**3c**) gave the product in low yield. The reason of the low yield may be due to weak coordination of the palladium(II) species to relatively electron-poor triple bond of **3c**.



1~3 **6~8**

Table I. Palladium-Catalyzed Carbonylative Cyclization of **1~3**

Product	X	R	Yield (%)	mp or bp (°C)	Appearance
6a	NSO_2Me	Ph	76[a]	143-144	colorless needles (AcOEt-hexane)
6b	NSO_2Me	Bu	67	75-76	colorless needles (AcOEt-hexane)
7a	NH	Ph	51	150-151	colorless needles ($^iPr_2O$-hexane)
7b	NH	Bu	30	67-68	colorless needles ($^iPr_2O$-hexane)
8a	O	Ph	79	77-78	colorless needles (hexane)
8b	O	Bu	66	145-150/3mmHg	pale yellow liquid
8c	O	COOEt	16[b]	150-151	colorless needles ($^iPr_2O$-hexane)

a) MeCN was used as a co-solvent. b) Recovery of **3c**: 19%.

The carbonylative cyclization of 2-alkynylbenzamide (**4** and **5**) gave 3-alkylidenisoindole derivatives (**9** and **10**). Another possible structure for **9b**, methyl 3-butyl-1,2-dihydro-1-oxoisoquinoline-4-carboxylate, was excluded by alternative synthesis of **11** from 3-butyl-1(2*H*)-isoquinolinone as described in experimental section.

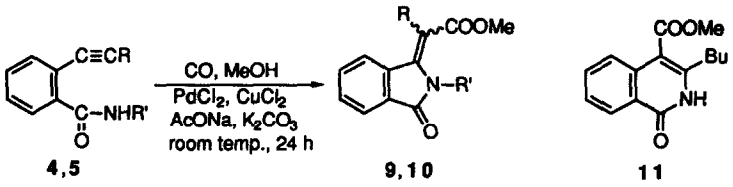
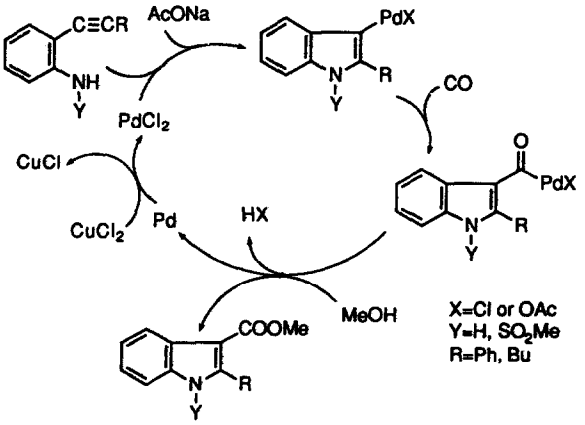


Table II. Palladium-Catalyzed Carbonylative Cyclization of **4** and **5**

Product	R'	R	Yield (%)	mp or bp (°C)	Appearance
9a	H	Ph	25	168-170	colorless needles ($^{i}Pr_2O$-hexane)
9b	H	Bu	29	130/3mmHg	pale yellow liquid
10a	Me	Ph	55	125-126	colorless needles ($^{i}Pr_2O$-hexane)
10b	Me	Bu	30	—	pale yellow viscous liquid

DISCUSSION

The pathway of the palladium-catalyzed carbonylative cyclization is conceivably as follows taking indole formation as an example. The indolylpalladium complex generated from the reaction of ethynylanilines and palladium dichloride reacts with carbon monoxide to form the indolylacylpalladium species. The palladium complexes react with methanol to give the final products. The palladium(0) species formed in this step are oxidized with copper dichloride to palladium dichloride. The use of 1,4-benzoquinone, disodium peroxysulfate, or molecular oxygen as an oxidant of the palladium(0) species was inefficient for the regeneration of the palladium(II) species. In addition to the above, it was founded that the addition of sodium acetate to the reaction mixture improved the yields of the products. The results suggest that the indolylpalladium acetate is much smoothly carbonylated than the indolylpalladium chloride.



Scheme 3

In conclusion, the results described above may provide a new method for the one-step synthesis of condensed heterocycles such as indole or benzo[*b*]furan with an alkoxycarbonyl group at the 3-position.

EXPERIMENTAL

Melting points are uncorrected. Boiling points are bath temperature of Kugelrohr apparatus. IR spectra were measured on a JASCO IR-A1 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL PMX-60 (60 MHz) spectrometer using tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. MS were recorded on a JEOL JMS-PX303 spectrometer.

2-Iodo-N-(methoxymethyl)-N-(methylsulfonyl)aniline

A mixture of 2-iodo-*N*-(methylsulfonyl)aniline (2.97 g, 10 mmol) and 60% NaH (0.45 g, 11 mmol) in THF (15 ml) was stirred at room temperature for 15 min. To the mixture, $MeOCH_2Cl$ (0.76 g, 10 mmol) was added, and the whole was stirred at room temperature for 16 h. After dilution with H_2O, the reaction mixture was extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and evaporated to give a colorless solid. Yield 3.00 g (88%). bp 220°C / 0.6 mmHg. mp 79-81°C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.07 (3H, s), 3.40 (3H, s), 4.7-5.3 (2H, br), 7.2-7.9 (4H, m). *Anal.* Calcd for $C_9H_{12}INO_4S$: C, 31.69; H, 3.55; N, 4.11. Found: C, 31.69; H, 3.34; N, 4.10.

N-(Methylsulfonyl)-2-(2-phenylethynyl)aniline (1a)

A mixture of 2-iodo-*N*-(methoxymethyl)-*N*-(methylsulfonyl)aniline (3.41 g, 10 mmol), phenylacetylene (1.22 g, 12 mmol), $PdCl_2(PPh_3)_2$ (160 mg, 0.23 mmol), CuI (80 mg, 0.4 mmol), Et_3N (20 ml), and DMF (5 ml) was stirred at 50°C for 6 h. To the reaction mixture, H_2O and Et_2O was added, and the whole was filtered through Celite® pad. The filtrated was extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and evaporated. A mixture of the residue and $(COOH)_2 \cdot 2H_2O$ (1.00 g, 8 mmol) in 50% aq. MeOH (20 ml) was refluxed for 2 h. After removal of the solvent, the residue was diluted with H_2O and extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography using hexane-AcOEt (4:1) as an eluent to give colorless needles which were recrystallized from $^iPr_2O$. Yield 1.84 g (68%). mp 128-130°C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.03 (3H, s), 6.8-7.8 (10H, m). IR ν ($CHCl_3$) cm^{-1}: 3340, 2220. *Anal.* Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.30; H, 4.97; N, 5.20; S, 11.90.

2-(1-Hexynyl)-N-(methylsulfonyl)aniline (1b)

1-Hexyne (0.98 g, 12 mmol) was allowed to react for 8 h under the same conditions as described as the preparation of **1a** to give a viscous pale yellow liquid. Yield 1.03 g (65%). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.95 (3H, t, *J*=7 Hz), 1.2-2.0 (4H, m), 2.2-2.8 (2H, m), 3.00 (3H, s), 6.9-8.1 (5H, m). IR ν

($CHCl_3$) cm^{-1}: 3340, 2225. MS *m/z*: 251.0947 (Calcd for $C_{18}H_{17}NO_2S$: 251.0979).

2-(2-Phenylethynyl)aniline (2a)

A mixture of 2-bromonitrobenzene (2.02 g, 10 mmol), phenylacetylene (1.22 g, 12 mmol), $PdCl_2(PPh_3)_2$ (160 mg, 0.23 mmol), CuI (80 mg, 0.4 mmol), and Et_3N (20 ml) was stirred at 70°C for 3 h. To the reaction mixture, H_2O and Et_2O were added and the whole was filtered through Celite® pad. The filtrated was extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and evaporated. A mixture of the residue and $SnCl_2$ (9.48 g, 50 mmol) and EtOH (20 ml) was stirred for 1 h. After evaporating of the solvent, the residue was made alkaline with 3N KOH and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography using hexane-AcOEt (4:1) as an eluent to give colorless solid. Yield 1.25 g (65%). bp 156-158°C / 2 mmHg. mp 87.5-88°C (lit.[11] mp 92°C). ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.10 (2H, br s), 6.6-7.7 (9H, m). IR ν ($CHCl_3$) cm^{-1}: 3480, 3340, 2220.

2-(1-Hexynyl)aniline (2b)

1-Hexyne (0.98 g, 12 mmol) was allowed to react under the same conditions as described as the preparation of **2a** to give a pale yellow liquid. Yield 0.99 g (57%). bp 130°C / 3 mmHg. ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.95 (3H, t, *J*=7 Hz), 1.2-1.9 (4H, m), 2.90 (2H, t, *J*=7 Hz), 4.83 (2H, br s), 6.5-7.5 (4H, m). IR ν ($CHCl_3$) cm^{-1}: 3480, 3340, 2220. MS *m/z*: 173.1204 (Calcd for $C_{12}H_{15}N$: 173.1204).

2-(2-Phenylethynyl)phenol (3a)

A mixture of 2-(methoxymethoxy)iodobenzene (2.64 g, 10 mmol), phenylacetylene (1.22 g, 12 mmol), $PdCl_2(PPh_3)_2$ (160 mg, 0.23 mmol), CuI (80 mg, 0.4 mmol), and Et_3N (20 ml) was stirred at room temperature for 3 h. To the reaction mixture, H_2O and Et_2O were added and the whole was filtered through Celite® pad. The filtrated was extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and evaporated. A solution of the residue and $(COOH)_2 \cdot 2H_2O$ (1.00 g, 8 mmol) in 50% aq. MeOH (20 ml) was refluxed for 2 h. After evaporating of the solvent, the residue was diluted with H_2O and extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography using hexane-AcOEt (4:1) as an eluent. The crude product was distilled under reduced pressure to give a colorless solid. Yield 1.75 g (89%). bp 180°C / 6 mmHg. mp 68-70°C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.77 (1H, s), 6.8-7.7 (9H, m). IR ν ($CHCl_3$) cm^{-1}: 3510, 2220. *Anal.* Calcd for $C_{14}H_{10}O$: C, 86.57; H, 5.19. Found: C, 86.83; H, 5.17.

2-(1-Hexynyl)phenol (3b)

1-Hexyne (0.98 g, 12 mmol) was allowed to react for 4 h under the conditions as described as the preparation of **3a** to give a pale yellow liquid. Yield 1.03 g (59%). bp 130°C / 5 mmHg. ^{1}H-NMR ($CDCl_3$) δ (ppm):0.95 (3H, t, *J*=7 Hz), 1.2-2.0 (4H, m), 2.97 (2H, t, *J*=7 Hz), 5.87 (1H, s), 6.7-7.7 (4H, m). IR ν ($CHCl_3$) cm^{-1}: 3500, 2220. MS *m/z*: 174.1045 (Calcd for $C_{12}H_{14}O$: 174.1044).

Ethyl (2-Hydroxyphenyl)propiolate (3c)

A mixture of 2-(methoxymethoxy)iodobenzene (2.64 g, 10 mmol), ethyl orthopropiolate (2.06 g, 12 mmol), $PdCl_2(PPh_3)_2$ (160 mg, 0.23 mmol), CuI (80 mg, 0.4 mmol), and Et_3N (20 ml) was stirred at room temperature for 2 h. To the reaction mixture, H_2O and Et_2O were added and the whole was filtered through Celite® pad. The filtrate was extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and evaporated. The crude product obtained from the Et_2O extract was stirred with *p*-toluenesulfonic acid (TsOH) (1.00 g, 5.8 mmol), H_2O (1 ml), and C_6H_6 (20 ml) at room temperature for 12 h. The reaction mixture was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and evaporated. A solution of the residue and $(COOH)_2 \cdot 2H_2O$ (1.00 g, 8 mmol) in 50% aq. MeOH (20 ml) was refluxed for 2 h. After evaporating of the solvent, the residue was diluted with H_2O and extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography using hexane-AcOEt (4:1) as an eluent. The crude product was distilled under reduced pressure to give a colorless solid. Yield 0.55 g (29%). bp 130°C / 2 mmHg. mp 54-56°C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.35 (3H, t, *J*=7 Hz), 4.30 (2H, q, *J*=7 Hz), 6.5-7.6 (5H, m). IR ν ($CHCl_3$) cm^{-1}: 3500, 2200, 1700. MS *m/z*: 190.0630 (Calcd for $C_{11}H_{10}O_3$: 190.0629).

General Procedure of the Preparation of 2-Ethynylbenzamides

A mixture of a 2-iodobenzamide (10 mmol), a terminal acetylene (12 mmol), $PdCl_2(PPh_3)_2$ (160 mg, 0.23 mmol), CuI (80 mg, 0.4 mmol), Et_3N (20 ml), and DMF (5 ml) was stirred at the temperature for the time shown in the experimental section of individual compounds. To the reaction mixture, H_2O and Et_2O were added, and the whole was filtered through Celite® pad. The filtrate was extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography using hexane-AcOEt (1:1) as an eluent.

2-(Phenylethynyl)benzamide (4a)

Reaction at 50°C for 2 h. Yield 1.22 g (55%). Colorless needles (hexane-AcOEt). mp 153-155°C (lit.[12] 155-157°C).

2-(1-Hexynyl)benzamide (4b)

Reaction at 50°C for 6 h. Yield 1.01 g (50%). Colorless needles (hexane-AcOEt). mp 103-105°C (lit.[12] 105-107°C).

N-Methyl-2-(phenylethynyl)benzamide (5a)

Reaction at room temperature for 2 h. Yield 1.55 g (66%). Colorless needles (hexane-AcOEt). mp 105-107°C (lit.[12] 105-107°C).

2-(1-Hexynyl)-N-methylbenzamide (5b)

Reaction at room temperature for 20 h. Yield 1.03 g (48%). Pale yellow liquid. bp 160°C / 4 mmHg. ^{1}H-

NMR ($CDCl_3$) δ (ppm): 0.95 (3H, t, *J*=7 Hz), 1.2-1.8 (4H, m), 2.50 (2H, *J*=7 Hz), 3.00 (3H, d, *J*=5 Hz), 7.3-8.2 (5H, m). IR ν ($CHCl_3$) cm^{-1}: 3400, 2220, 1650. MS *m/z*: 215.1310 (Calcd for $C_{14}H_{17}NO$: 215.1309).

General Procedure for the Palladium-Catalyzed Cyclization of 2-Substituted Phenylacetylenes in the Presence of Carbon Monoxide in Methanol

A mixture of a 2-substituted phenylacetylene (3 mmol), NaOAc (0.50 g, 6 mmol), K_2CO_3 (0.83 g, 6 mmol), $PdCl_2$ (30 mg, 0.2 mmol), $CuCl_2 \cdot 2H_2O$ (1.53 g, 9 mmol), and MeOH (20 ml) was vigorously stirred under CO atmosphere at room temperature for the time shown in Tables I and II. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography using hexane-AcOEt (4:1) as an eluent.

Methyl 1-Methylsulfonyl-2-phenylindole-3-carboxylate (6a)

MeCN (10 ml) was used as co-solvent. ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.06 (3H, s), 3.76 (3H, s), 7.3-7.8 (6H, m), 8.1-8.5 (3H, m). IR ν ($CHCl_3$) cm^{-1}: 1705, 1385. *Anal.* Calcd for $C_{17}H_{15}NO_3S$: C, 61.99; H, 4.59; N, 4.25; S, 9.73. Found: C, 62.02; H, 4.75; N, 4.24; S, 9.70.

Methyl 2-Butyl-1-methylsulfonylindole-3-carboxylate (6b)

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.95 (3H, t, *J*=7 Hz), 1.2-2.0 (4H, m), 3.10 (3H, s), 3.3-3.7 (2H, t, *J*=7 Hz) 3.96 (3H, s) 7.2-7.5 (1H, m), 8.0-8.2 (3H, m). IR ν ($CHCl_3$) cm^{-1}: 1705, 1375. *Anal.* Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.05; H, 6.10; N, 4.52.

Methyl 2-Phenylindole-3-carboxylate (7a)

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.86 (3H, s), 7.1-7.8 (8H, m), 8.0-8.3 (1H, m), 8.80 (1H, br s). IR ν ($CHCl_3$) cm^{-1}: 3440,1690. *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.61; H, 5.48; N, 5.60.

Methyl 2-Butylindole-3-carboxylate (7b)

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.96 (3H, t, *J*=7 Hz), 1.2-2.0 (4H, m), 3.16 (2H, t, *J*=7 Hz), 3.93 (3H, s), 7.1-7.5 (3H, m), 7.9-8.3 (1H, m), 8.60 (1H, br s). IR ν ($CHCl_3$) cm^{-1}: 3440, 1685. *Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.83; H, 7.63; N, 6.04.

Methyl 2-Phenylbenzo[b]furan-3-carboxylate (8a)

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.92 (3H, s), 7.2-7.7 (6H, m), 7.9-8.2 (3H, m). IR ν ($CHCl_3$) cm^{-1}: 1710. *Anal.* Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.48; H, 4.72.

Methyl 2-Butylbenzo[b]furan-3-carboxylate (8b)

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.95 (3H, t, *J*=7 Hz), 1.2-2.0 (4H, m), 3.20 (2H, t, *J*=7 Hz), 3.95 (3H, s), 7.2-7.5 (3H, m), 7.8-8.1 (1H, m). IR ν ($CHCl_3$) cm^{-1}: 1705. *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.46; H, 7.14.

Ethyl 3-Methoxycarbonylbenzo[b]furan-2-carboxylate (8c)

^{1}H-NMR ($CDCl_3$) δ (ppm):1.40 (3H, t, *J*=7 Hz), 3.97 (3H, s), 4.47 (2H, q, *J*=7 Hz), 7.3-7.7 (3H, m), 7.8-8.0 (1H, m). IR ν ($CHCl_3$) cm^{-1}: 1720. *Anal.* Calcd for $C_{11}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.75; H, 4.89.

Methyl 2-(2,3-Dihydro-1-oxo-1H-isoindol-3-ylidene)phenylacetate (9a)

^{1}H-NMR ($CDCl_3$) δ (ppm): 377 (3H, s), 7.2-8.0 (10H, m). IR ν ($CHCl_3$) cm^{-1}: 3350, 1715, 1675. *Anal.* Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.03; H, 4.65; N, 4.99.

Methyl 2-(2,3-Dihydro-1-oxo-1H-isoindol-3-ylidene)hexanoate (9b)

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.95 (3H, t, *J*=7 Hz), 1.2-2.0 (4H, m), 2.3-2.6 (2H, m), 3.67 (3H, s), 6.9-7.6 (5H, m). IR ν ($CHCl_3$) cm^{-1}: 3350, 1715, 1650. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H,6.61; N, 5.40. Found: C, 69.26; H, 6.57; N, 5.24.

Methyl 2-(2,3-Dihydro-2-methyl-1-oxo-1H-isoindol-3-ylidene)phenylacetate (9a)

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.21 (3H, s), 3.87 (3H, s), 7.1-8.3 (9H, m). IR ν ($CHCl_3$) cm^{-1}: 1710, 1670. *Anal.* Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 74.00; H, 5.22; N, 4.83.

Methyl 2-(2,3-Dihydro-2-methyl-1-oxo-1H-isoindol-3-ylidene)hexanoate (9b)

^{1}H-NMR ($CDCl_3$) δ (ppm): 0.95 (3H, t, *J*=7 Hz), 1.2-2.0 (4H, m), 2.4-2.6 (2H, m), 3.18 (3H, s), 3.89 (3H, s), 7.2-8.3 (4H, m). IR ν ($CHCl_3$) cm^{-1}: 1710, 1660. MS *m/z*: 273.1358 (Calcd for $C_{16}H_{19}NO_3$: 273.1365).

3-Butyl-4-bromo-1(2H)-isoquinolinone

To a solution of 3-butyl-1(2*H*)-isoquinolinone[12] (2.0 g, 10 mmol) in AcOH (50 ml), was added Br_2 (1.6 g, 10 mmol) at room temperature with stirring, and the mixture was heated on a water bath for 30 min. After removal of the solvent, the residue was made alkaline with 3N Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to give colorless needles which were recrystallized from EtOH. Yield 2.4 g (86%). mp 180-181°C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.00 (3H, t, *J*=7 Hz), 1.1-2.0 (4H, m), 2.95 (2H, t, *J*=7 Hz), 7.3-8.1 (3H, m), 8.3-8.5 1H, m), 11.5-12.0 (1H, br). IR ν ($CHCl_3$) cm^{-1}: 3390, 1660. *Anal.* Calcd for $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00. Found: C, 55.58; H, 5.28; N, 5.28.

Methyl 3-Butyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (11)

Butyllithium in hexane (1.39 M; 2.9 ml, 4 mmol) was added to a solution of 3-butyl-4-bromo-1(2*H*)-iso-

quinolinone (560 mg, 2 mmol) in dry THF (2 ml) at -78°C. After stirring at -78°C for 2 h, the mixture was poured into a mixture of solid CO_2 and dry Et_2O (50 ml). The reaction mixture was concentrated in vacuo, and the residue was made alkaline with 1N $NaHCO_3$ and washed with $CHCl_3$. The aqueous layer was acidified with 3N HCl and the resulting precipitate was filtered and dried *in vacuo*. A mixture of the precipitate and $SOCl_2$ (20 ml) was heated at 50-60°C for 3 h. The excess $SOCl_2$ was evaporated *in vacuo*. The residue was dissolved in MeOH (20 ml), and the mixture was refluxed for 2 h. After removal of the MeOH, the residue was made alkaline with 3N Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated. The residue was recrystallized from acetone-hexane to give colorless needles. Yield 250 mg (48%). mp 186°C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.00 (3H, t, *J*=7 Hz), 1.1-2.1 (4H, m), 2.95 (2H, t, *J*=7 Hz), 4.00 (3H, s), 7.3-8.0 (3H, m), 8.3-8.6 1H, m), 11.6-12.0 (1H, br). IR ν ($CHCl_3$) cm^{-1}: 3390, 1720, 1660. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H,6.61; N, 5.40. Found: C, 69.41; H, 6.54; N, 5.33.

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