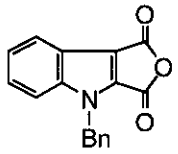
SYNTHESIS AND REACTION OF DIMETHYL 7-BROMO-INDOLE-2,3-DICARBOXYLATES

Yasuyoshi Miki,* Ko-ichi Matsushita, Hajime Hibino, and Hideaki Shirokoshi

Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1, Kowakae, Higashi-Osaka 577-8502, Japan

Abstract - Reaction of 1-(4-benzyloxyphenyl)-2-phenylhydrazine with dimethyl acetylenedicarboxylate (DMAD) gave dimethyl 5-benzyloxyindole-2,3-dicarboxylate and dimethyl indole-2,3-dicarboxylate. However, treatment of 1-(2-bromophenyl)-2-phenylhydrazine with DMAD afforded dimethyl 7-bromoindole-2,3-dicarboxylate, exclusively. In a similar manner, dimethyl 7-bromo-5-methoxyindole-2,3-dicarboxylate was also obtained from 1-(2-bromo-4-methoxyphenyl)-2-phenylhydrazine. The bromo group of dimethyl 7-bromoindole-2,3-dicarboxylate was converted to an 1-ethoxyvinyl or vinyl group by treatment with tributyl-(1-ethoxyvinyl)tin or tributyl(vinyl)tin in the presence of a Pd(0) catalyst.

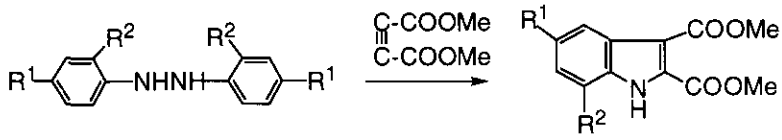
Recently, we have shown that indole-2,3-dicarboxylic anhydride (**1**), prepared from dimethyl indole-2,3-dicarboxylate (**3a**), is a useful synthon for synthesis of natural products,[1-3] 2-acylindoles,[4] and cyclopent[3,4-*b*]indol-3-ones.[5] However, there are many indole natural products having substituents on the benzene ring of an indole.[6] Therefore, we need dimethyl indole-2,3-dicarboxylates, which possess several substituents, e.g., bromo, hydroxy, and alkyl groups, to synthesize natural products.



1

Dimethyl 5-methyl- (**3b**) and 5-chloro- (**3c**) indole-2,3-dicarboxylates were prepared from 4,4'-dimethyl- (**2b**) and 4,4'-dichlorodiphenylhydrazine (**2c**) and dimethyl acetylenedicarboxylate (DMAD) in moderate yield, but dimethyl 4-acetoxyindole-2,3-dicarboxylate (**3d**) was not obtained from 4,4'-diacetoxydiphenylhydrazine (**2d**).[7] **3b** and **3c** were also synthesized from phenylhydroxylamine derivatives and DMAD, but

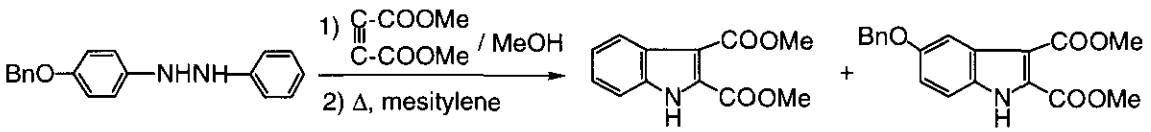
the yields were low.[8] Bare reported that dimethyl 7-chloroindole-2,3-dicarboxylate (**3e**) was obtained from 2,2'-dichlorodiphenylhydrazine (**2e**) and DMAD in moderate yield at high temperature.[9] In this paper we would like to report a synthesis of dimethyl indole-2,3-dicarboxylate derivatives (**3f-h**) and conversion of the bromo group of **3g** to other functional groups.



2 **3**

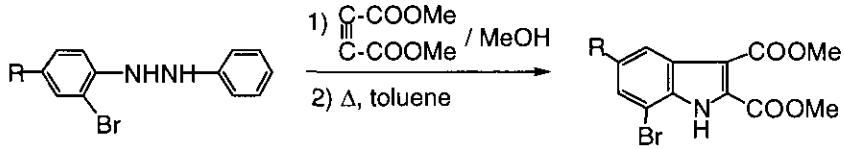
a; $R^1 = R^2 = H$, **b**; $R^1 = Me$, $R^2 = H$, **c**; $R^1 = Cl$, $R^2 = H$,
d; $R^1 = OAc$, $R^2 = H$, **e**; $R^1 = H$, $R^2 = Cl$, **f**; $R^1 = BnO$, $R^2 = H$,
g; $R^1 = H$, $R^2 = Br$, **h**; $R^1 = MeO$, $R^2 = Br$

Reaction of 1-(4-benzyloxyphenyl)-2-phenylhydrazine (**4**)[10] with DMAD in hot methanol gave adducts, which were heated in xylene to afford a mixture of dimethyl indole-2,3-dicarboxylate (**3a**)[11] and dimethyl 5-benzyloxyindole-2,3-dicarboxylate (**3f**) in 15% and 13% yields, respectively. This result shows that preparation of **3f** from **4** is very difficult.



4 ***3a*** ***3f***

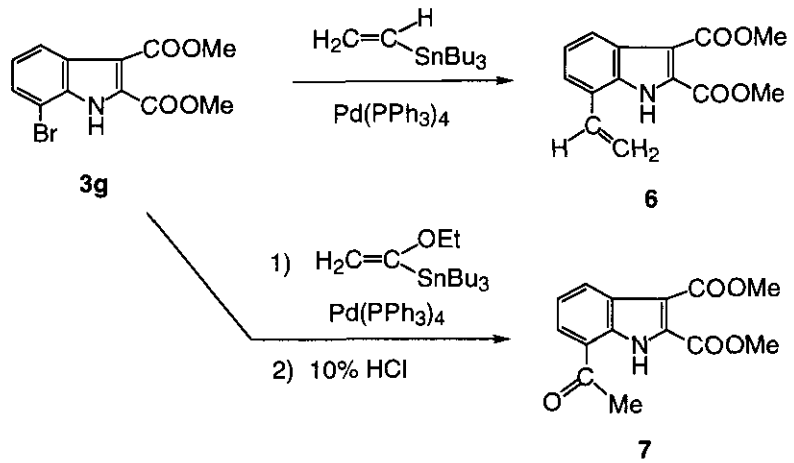
Next, we investigated the reactivity of bromo-substituted diphenylhydrazines. A mixture of 2,2'-dibromodiphenylhydrazine (**2g**)[12] and DMAD in methanol was refluxed, but the starting materials were recovered. This fact suggests that steric hindrance is a significantly important factor in this reaction. We treated 1-(2-bromophenyl)-2-phenylhydrazine (**5a**) with DMAD in hot methanol to give the corresponding adduct, which was heated in mesitylene to afford dimethyl 7-bromoindole-2,3-dicarboxylate (**3g**) in 62% yield. In a similar manner, dimethyl 7-bromo-5-methoxyindole-2,3-dicarboxylate (**3h**) was obtained in 45% yield from 1-(2-bromo-4-methoxyphenyl)-2-phenylhydrazine (**5b**).



5 **a**; R = H
b; R = OMe

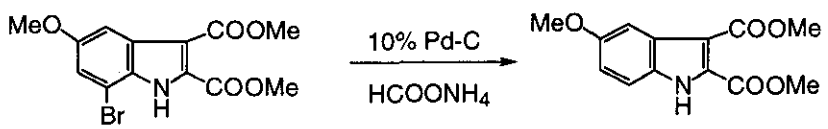
3 **g**; R = H,
h; R = OMe

When dimethyl 7-bromoindole-2,3-dicarboxylate (**3g**) was treated with tributyl(vinyl)tin in the presence of $Pd(PPh_3)_4$, dimethyl 7-vinylindole-2,3-dicarboxylate (**6**) was isolated in 71% yield. In a similar manner, reaction of **3g** with tributyl(1-ethoxyvinyl)tin provided dimethyl 7-(1-ethoxyvinyl)indole-2,3-dicarboxylate, which was converted to dimethyl 7-acetylindole-2,3-dicarboxylate (**7**) by hydrochloric acid treatment in 78% yield.



3g **6** **7**

Reduction of dimethyl 7-bromo-5-methoxyindole-2,3-dicarboxylate (**3h**) with 10% Pd-C and ammonium formate in hot methanol gave dimethyl 5-methoxyindole-2,3-dicarboxylate (**8**) in 95% yield.



3h **8**

In conclusion, we have demonstrated an efficient synthesis of dimethyl indole-2,3-dicarboxylates by using 2-bromodiphenylhydrazine.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ^{1}H-NMR spectra were determined on a JEOL JNM-GSX 270 spectrometer using tetramethylsilane as an internal standard. The IR spectra were recorded with a JASCO FT/IR-7000 spectrophotometer. The high MS were recorded on a JOEL JMS-HX100 spectrometer. Column chromatography was performed on E. Merck silica gel 60 (70-230 mesh or 230-400 mesh). Tetrahydrofuran (THF) was distilled from sodium and benzophenone prior to use.

Dimethyl Indole-2,3-dicarboxylate(3a) and 5-Benzyloxyindole-2,3-dicarboxylate(3f) from 4

Dimethyl acetylenedicarboxylate (DMAD)(50 mg, 0.35 mmol) was added to a suspension of 1-(4-benzyloxyphenyl)-2-phenylhydrazine (**4**)[10](102 mg, 0.35 mmol) in MeOH (1 mL) and the mixture was refluxed for 1 h. Then, DMAD (50 mg, 0.35 mmol) was added to the reaction mixture and the mixture was refluxed for 0.5 h. The solvent was evaporated off to give an oil, which was dissolved in xylene (1 mL). The xylene solution was refluxed for 0.5 h and concentrated to afford a residue, which was purified by preparative thin-layer chromatography (*n*-hexane : $CHCl_3$: AcOEt = 10 : 10 : 1) to give dimethyl indole-2,3-dicarboxylate (**3a**)[11] (12 mg, 15%) as colorless crystals and dimethyl 5-benzyloxyindole-2,3-dicarboxylate (**3f**) (15 mg, 13%) as pale yellow crystals.

3a; mp 110-112°C (lit.,[11] mp 114°C)(MeOH-H_2O). IR (Nujol) 3300, 1735, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 4.00 (6H, s, $COOCH_3$), 7.24-7.46 (6H, m, aromatic protons), 8.05 (1H, dd, *J* = 8, 1 Hz, H-4), 9.23-9.35 (1H, br s, NH).

3f; mp 152-153°C (*n*-hexane-AcOEt). IR (Nujol) 3300, 1726, 1683 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.97 (3H, s, $COOCH_3$), 3.98 (3H, s, $COOCH_3$), 5.13 (2H, s, OCH_2Ph), 7.12 (1H, dd, *J* = 9, 2.5 Hz, H-6), 7.30-7.51 (6H, m, aromatic protons), 7.59 (1H, d, *J* = 2.5 Hz, H-4), 9.20-9.28 (1H, br s, NH). *Anal.* Calcd for $C_{19}H_{17}N_2O_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.03; H, 5.14; N, 4.16. MS *m/z* : 339. HRMS *m/z* (M^+) calcd for $C_{19}H_{17}NO_5$: 339.1107. Found: 339.1075.

1-(2-Bromophenyl)-2-phenylhydrazine(5a)

A mixture of 2-bromoazobenzene[13] (13.10 g, 50 mmol), zinc powder (3.25 g, 50 mmol), and sodium hydroxide (6.00 g, 150 mmol) in EtOH (100 mL) and H_2O (1 mL) was refluxed for 5 h and the insoluble material was filtrated off. The filtrate was added to 1% Na_2SO_3 aqueous solution and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 50 : 1) to afford a solid, which was recrystallized from *n*-hexane to give 1-(2-bromophenyl)-2-phenylhydrazine (**5a**) (9.32 g, 71 %) as colorless crystals, mp 66-67°C. IR ($CHCl_3$) cm^{-1} 3378; ^{1}H-NMR ($CDCl_3$) δ: 5.68 (1H, s, NH), 6.18 (1H, s, NH), 6.64-7.27 (8H, m, aromatic protons), 7.47 (1H, dd, *J* = 8, 2 Hz, H-3). *Anal.* Calcd for $C_{12}H_{11}N_2Br$: C, 54.77; H, 4.21; N, 10.65. Found: C, 54.86; H, 4.27; N, 10.57.

2-Bromo-4-methoxyazobenzene

Nitrosobenzene (24.4 g, 28 mmol) was added to a solution of 2-bromo-4-methoxyaniline[14] (46.0 g, 28 mmol) in acetic acid (137 mL) and the mixture was stirred overnight at rt. The mixture was added to water, then neutralized with sodium hydrogen carbonate and extracted with ether. The ether extracts were treated with ethereal hydrogen chloride to afford precipitates, which were removed by filtration. The filtrate was evaporated off to give a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 50 : 1) to yield 2-bromo-4-methoxyazobenzene (16.0 g, 57%), mp 67-68°C (from *n*-hexane). IR ($CHCl_3$) 1486 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.89 (3H, s, OCH_3), 6.93 (1H, dd, *J* = 9, 3 Hz, H-5), 7.28 (1H, d, *J* = 3 Hz, H-3), 7.45-7.56 (3H, m, aromatic protons), 7.76 (1H, d, *J* = 9 Hz, H-6), 7.97 (2H, dd, *J* = 9, 2 Hz, aromatic protons). HRMS *m/z* (M^+) calcd for $C_{13}H_{11}N_2OBr$: 290.0055. Found : 290.0025.

1-(2-Bromo-4-methoxyphenyl)-2-phenylhydrazine(5b)

A mixture of 2-bromo-4-methoxyazobenzene (146 mg, 0.5 mmol), zinc powder (33 mg, 0.5 mmol), and sodium hydroxide (63 mg, 1.5 mmol) in EtOH (1 mL) and H_2O (0.01 mL) was refluxed for 20 min and the insoluble material was filtered off. The filtrate was added to 1% Na_2SO_3 aqueous solution and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was washed with *n*-hexane to afford 1-(2-bromo-4-methoxyphenyl)-2-phenylhydrazine (**5b**) (110 mg, 75%) as an brown oil. IR (Neat) 3362 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ: 3.74 (3H, s, OCH_3), 5.63-5.68 (1H, br s, NH), 5.90-5.95 (1H, br s, NH), 6.74-6.84 (5H, m, aromatic protons), 6.97 (1H, d, J = 9 Hz, H-6), 7.06 (1H, d, J = 3 Hz, H-3), 7.22 (1H, dt, J = 9, 1 Hz, H-5). HRMS *m/z* (M^+) calcd for $C_{13}H_{13}N_2OBr$: 292.0211. Found: 292.0208.

Dimethyl 7-Bromoindole-2,3-dicarboxylate(3g)

DMAD (4.26 g, 40 mmol) was added to a suspension of 1-(2-bromophenyl)-2-phenylhydrazine (**5a**)(7.89 g, 30 mmol) in hot MeOH (12 mL) and the mixture was refluxed for 3 h. Then, DMAD (4.26 g, 40 mmol) was added to the reaction mixture and the mixture was refluxed for 1 h. The solvent was evaporated off to give an oil, which was dissolved in mesitylene (30 mL). The mesitylene solution was refluxed for 1 h and concentrated to afford a residue, which was purified by column chromatography ($CHCl_3$) to yield dimethyl 7-bromoindole-2,3-dicarboxylate (**3g**) (5.80 g, 62%), mp 78°C (*n*-hexane) as pale yellow crystals. IR ($CHCl_3$) 3436, 1747, 1709 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.99 (3H, s, $COOCH_3$), 4.02 (3H, s, $COOCH_3$), 7.16 (1H, dd, J = 9, 8 Hz, H-5), 7.54 (1H, dd, J = 8, 1 Hz, H-6), 8.01 (1H, dd, J = 9, 1 Hz, H-4), 9.22-9.32 (1H, br s, NH). *Anal.* Calcd for $C_{12}H_{10}NO_4Br$: C, 46.18; H, 3.28; N, 4.49. Found: C, 46.16; H, 3.34; N, 4.32.

Dimethyl 7-Bromo-5-methoxyindole-2,3-dicarboxylate(3h)

DMAD (0.03 mL, 0.2 mmol) was added to a suspension of 1-(2-bromo-4-methoxyphenyl)-2-phenylhydrazine (**5b**)(57 mg, 0.2 mmol) in MeOH (2 mL) and the mixture was refluxed for 2 h. The solvent was evaporated off to give an oil, and a solution of the oil in xylene (2 mL) was refluxed for 1 h. The reaction mixture was concentrated to afford a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to yield dimethyl 7-bromo-5-methoxyindole-2,3-dicarboxylate (**3h**) (31 mg, 45%), mp 113-114°C (from *n*-hexane-AcOEt). IR ($CHCl_3$) 3310, 1708, 1686 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.87 (3H, s, OCH_3), 3.98 (3H, s, $COOCH_3$), 4.07 (3H, s, $COOCH_3$), 7.23 (1H, d, J = 2 Hz, H-6), 7.45 (1H, d, J = 2 Hz, H-4), 9.13-9.23 (1H, br s, NH). *Anal.* Calcd for $C_{13}H_{12}NO_5Br$: C, 45.61; H, 3.53; N, 4.07. Found: C, 45.47; H, 3.54; N, 3.90. HRMS *m/z* (M^+) calcd for $C_{13}H_{12}NO_5Br$: 340.9899. Found : 340.9896.

Dimethyl 7-Vinylindole-2,3-dicarboxylate(6)

A mixture of dimethyl 7-bromoindole-2,3-dicarboxylate (**3g**)(218 mg, 0.7 mmol), tributyl(vinyl)tin (444 mg, 1.4 mmol), and tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.017 mmol) in toluene (3.5 mL) was refluxed for 2 h under Ar. The solvent was evaporated off to give a residue, which was mixed with 8% potassium fluoride solution and stirred for 1 h at rt. The insoluble precipitate was filtered off through Celite and the filtrate was extracted with ether. The ether extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 5 :

1) to yield dimethyl 7-vinylindole-2,3-dicarboxylate (**6**) (128 mg, 71%), mp 124-125°C (from *n*-hexane-AcOEt). IR (Nujol) 3314, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.99 (3H, s, COOMe), 4.00 (3H, s, COOMe), 5.52 (1H, dd, *J* = 11, 1 Hz, CH=C*H*$_2$), 5.85 (1H, dd, *J* = 17.5, 1 Hz, CH=C*H*$_2$), 7.00 (1H, dd, *J* = 17.5, 11, Hz, C*H*=CH$_2$), 7.26 (1H, dd, *J* = 8, 7.5 Hz, H-5), 7.42 (1H, dt, *J* = 7.5, 1 Hz, H-6), 7.98 (1H, d, *J* = 8 Hz, H-4), 9.28-9.43 (1H, br s, NH). *Anal.* Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.60; H, 5.08; N, 5.38.

Dimethyl 7-Acetylindole-2,3-dicarboxylate(7)

A mixture of dimethyl 7-bromoindole-2,3-dicarboxylate (**3g**) (218 mg, 0.7 mmol), tributyl(1-ethoxyvinyl)tin (505 mg, 1.4 mmol), and tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.017 mmol) in toluene (3.5 mL) was refluxed for 1 h under Ar. The solvent was evaporated off to give a residue, which was dissolved in 10% hydrochloric acid (1 mL) and tetrahydrofuran (2 mL) and stirred for 0.5 h at rt. The insoluble precipitate was filtered off through Celite and the filtrate was extracted with ether. The ether extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to yield dimethyl 7-acetylindole-2,3-dicarboxylate (**7**) (150 mg, 78%), mp 80°C (from *n*-hexane-AcOEt). IR (Nujol) 3416, 1712, 1695, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 2.75 (3H, s, COMe), 4.00 (3H, s, COOMe), 4.02 (3H, s, COOMe), 7.36 (1H, dd, *J* = 8, 7.5 Hz, H-5), 7.95 (1H, dd, *J* = 7.5, 1 Hz, H-6), 8.35 (1H, dd, *J* = 8, 1 Hz, H-4), 11.06-11.21 (1H, br s, NH). *Anal.* Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.02; H, 4.83; N, 4.93.

Dimethyl 7-Methoxyindole-2,3-dicarboxylate(8)

A mixture of dimethyl 7-bromo-5-methoxyindole-2,3-dicarboxylate (**3h**)(205 mg, 0.6 mmol), ammonium formate (227 mg, 3.6 mmol), and 10% Pd-C (48 mg) in MeOH (12 mL) was refluxed for 20 min. The mixture was filtered through Celite and the filtrate was concentrated. The residue was purified by column chromatography (*n*-hexane : $CHCl_3$ = 1 : 10) to yield dimethyl 7-methoxyindole-2,3-dicarboxylate (**8**) (151 mg, 95%), mp 165-166°C (from *n*-hexane-AcOEt). IR (Nujol) 3284, 1721, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.88 (3H, s, OCH_3), 3.98 (3H, s, $COOCH_3$), 3.99 (3H, s, $COOCH_3$), 7.03 (1H, dd, *J* = 9, 2 Hz, H-6), 7.33 (1H, d, *J* = 9 Hz, H-7), 7.48 (1H, d, *J* = 2 Hz, H-4), 9.24-9.46 (1H, br s, NH). *Anal.* Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.30; H, 4.98; N, 5.33.

REFERENCES AND NOTE

1. Y. Miki and H. Hachiken, *Synlett*, 1993, 333.
2. Y. Miki, Y. Tada, N. Yanase, H. Hachiken, and K. Matsushita, *Tetrahedron Lett.*, 1996, **37**, 7753.
3. Y. Miki, Y. Tada, and K. Matsushita, *Heterocycles*, 1998, **48**, 1593.
4 Y. Miki, H. Hachiken, and I. Yoshikawa, *Heterocycles*, 1997, **45**, 1143.
5. Y. Miki, H. Hachiken, Y. Sugimoto, and N. Yanase, *Heterocycles*, 1997, **45**, 1759.
6 M. Alvarez, M. Sala, and J. A. Joule, *Heterocycles*, 1991, **32**, 1391.
7. E. H. Huntress, J. Bornstein, and W. M. Hearon, *J. Am. Chem. Soc.*, 1956, **78**, 2225.
8 T. Sheradsky, E. Nov, S. Segal, and A. Frank, *J. Chem. Soc., Perkin Trans. I*, 1977, 1827.

9. T. Bare, *Eur. Pat.*, 0512817 (*Chem. Abstr.*, 1993, **118**, 101975g).
10. R. Pfister and F. Häfliger, *Helv. Chim. Acta*, 1957, **40**, 395.
11. O. Diels and J. Reese, *Ann.*, 1934, **511**, 168.
12. H. R. Snyder, C. Weaver, and C. D. Marshall, *J. Am. Chem. Soc.*, 1949, **71**, 289.
13. R. Belcher, A. J. Nutten, and W. I. Stephen, *J. Chem. Soc.*, 1958, 2336.
14. C. Wright, M. Shulkind, K. Jones, and M. Thompson, *Tetrahedron Lett.*, 1987, **28**, 6389.
15. We could not examine the reactivity of 4,4'-dibenzyloxydiphenylhydrazine (**2f**) with DMAD to obtain dimethyl 7-benzyloxyindole-2,3-dicarboxylate (**3f**), because **2f** was not prepared by a reductive self-coupling of 4-benzyloxy-1-nitrobenzene by using zinc and sodium hydroxide.

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