Solvent effect on the reaction of 1-methoxy-3-(2-nitrovinyl)indole with nucleophiles

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SOLVENT EFFECT ON THE REACTION OF 1-METHOXY-3-(2-NITRO-VINYL)INDOLE WITH NUCLEOPHILES[1#]

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Abstract – 1-Methoxy-3-(2-nitrovinyl)indole (**1a**) functions as an electrophile and reacts with various nucleophiles. In THF, nucleophiles undergo conjugate addition to the β-carbon of the nitrovinyl side chain of **1a**, regioselectively. The resultant Michael addition products (**4d** and **8**) cyclize to novel 3-substituted 1-methoxyindoles (**5** and **7**) depending on reaction conditions and a plausible mechanism is discussed. In dipolar aprotic solvent (DMF), nucleophiles react with **1a** at the 2-position predominantly with concomitant liberation of the 1-methoxy group giving 2-substituted indoles.

Solvents are known to exert large effects on reaction rates, equilibrium constants, chemical reactions, and so on.[2] In this paper, we wish to report a novel finding that the solvent can govern the reaction pathway as well in the reaction of 1-methoxy-3-(2-nitrovinyl)indole (**1a**, Scheme 1) with nucleophiles. In THF, nucleophiles undergo regioselective conjugate addition to the β-carbon of the nitrovinyl side chain at the 3-position of **1a**,[3] whereas in dipolar aprotic solvent (DMF) similar reaction with **1a** leads predominantly to nucleophilic substitution reactions at the 2-position with concomitant liberation of the 1-methoxy group.[4] This is a full report of the previous communications.[3,4]

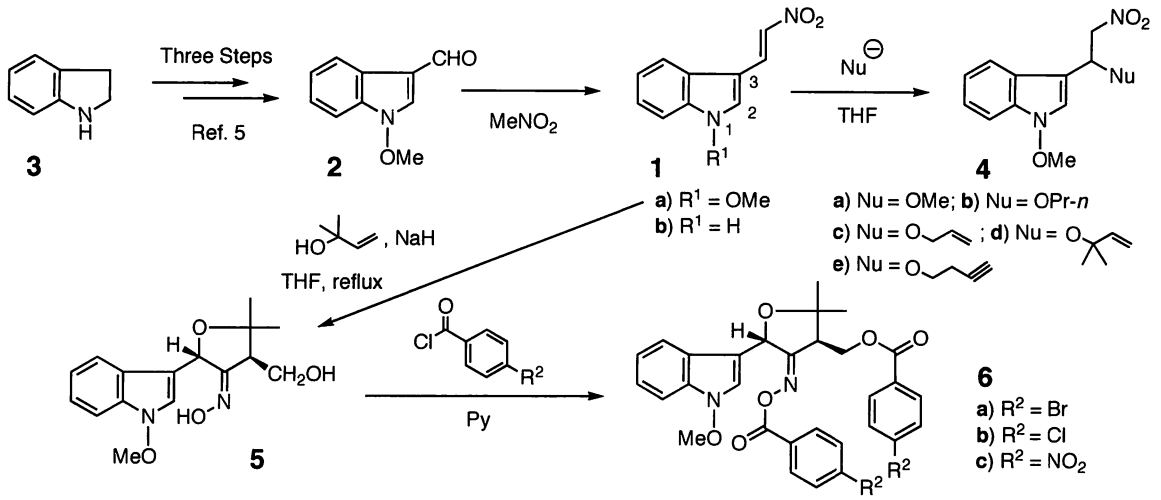
I. Conjugate addition of nucleophiles to the β-carbon of nitrovinyl side chain.

The substrate (**1a**) was prepared in 91% yield by reacting nitromethane with 1-methoxyindole-3-carbaldehyde (**2**), which was readily available from commercially available 2,3-dihydroindole (**3**) in three steps in 49% overall yield according to our procedures.[5] Employing THF as a solvent, the reaction of **1a** was carried out with NaOMe and NaOPr-*n* at 0°C to provide Michael addition products, 1-methoxy-3-(1-methoxy-2-nitroethyl)indole (**4a**) and 1-methoxy-3-(2-nitro-1-*n*-propyloxyethyl)indole

Dedicated to the memory of Dr. Kenji Koga.

(**4b**) in 90 and 92% yields, respectively. Further reactions of **1a** with sodium allyl oxide, potassium 1,1-dimethylallyl oxide, and sodium 3-butyn-1-oxide in THF at 0°C produced **4c**, **4d**, and **4e**[6] in 58, 81, and 95% yields, respectively. Interestingly, when a similar reaction with potassium 1,1-dimethylallyl oxide was carried out at reflux instead of 0°C, formation of novel cyclic product (**5**) was observed in 55% yield probably through the expected intermediate (**4d**).

Scheme 1



In order to determine the structure of **5** by X-Ray single crystallographic analysis, an attempt was made to convert **5** to a crystalline compound. The reactions of **5** with *p*-bromo- and *p*-chlorobenzoyl chlorides afforded **6a** and **6b** in 63 and 82% yields, respectively. They were not suitable crystals though. The reaction with *p*-nitrobenzoyl chloride was finally found to give a 78% yield of **6c** as feasible prisms. Figure 1 shows the ORTEP drawing of **6c**.[7] Consequently, the structures of **6c** and its starting material (**5**) are proved unequivocally.

Scheme 2

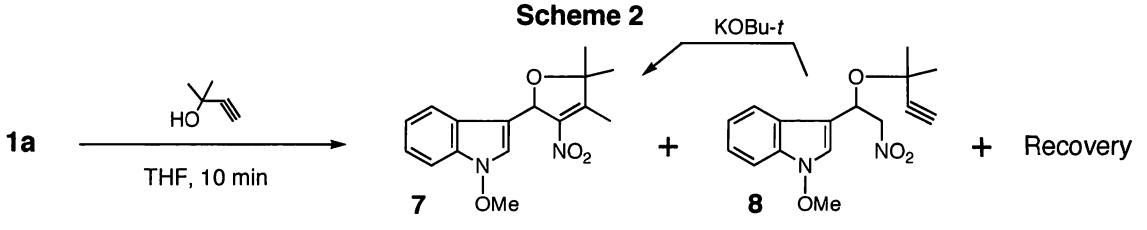


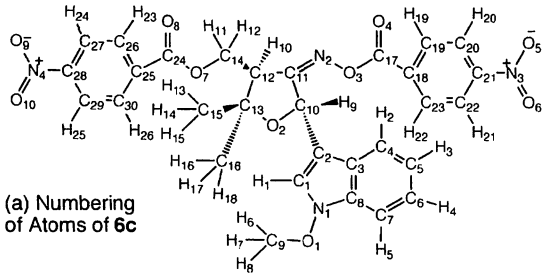
Table 1

Entry	Base (mol eq.)	Reaction Temperature (°C)	Yield (%) of 7	8	Recovery
1	KOBu-*t* (10)	rt	35	0	11
2	NaH (5)	0	0	75	0

Taking the formation of **5** into consideration, we next planned to react **1a** with 1,1-dimethylpropargyl

alcohol (Scheme 2). As expected, employing KOBu-*t* as a base, the reaction proceeded smoothly in THF at room temperature and provided a novel cyclic product (**7**) in 35% yield as shown in Table 1 (Entry 1). A similar reaction using NaH as a base in THF at 0°C provided conjugate addition product (**8**) in 75% yield (Entry 2). Although the structure of **7** was determined based on its spectral data, further confirmation was obtained by the fact that **7** was produced in 60% yield from **8** by treatment with KOBu-*t* at 0°C for 30 min.

Figure 1



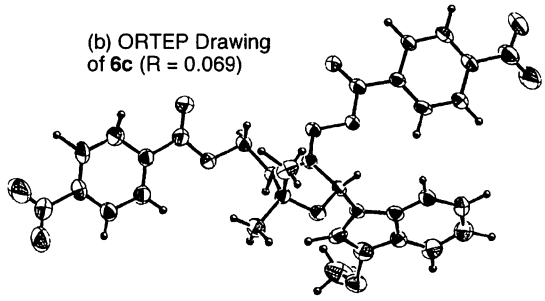
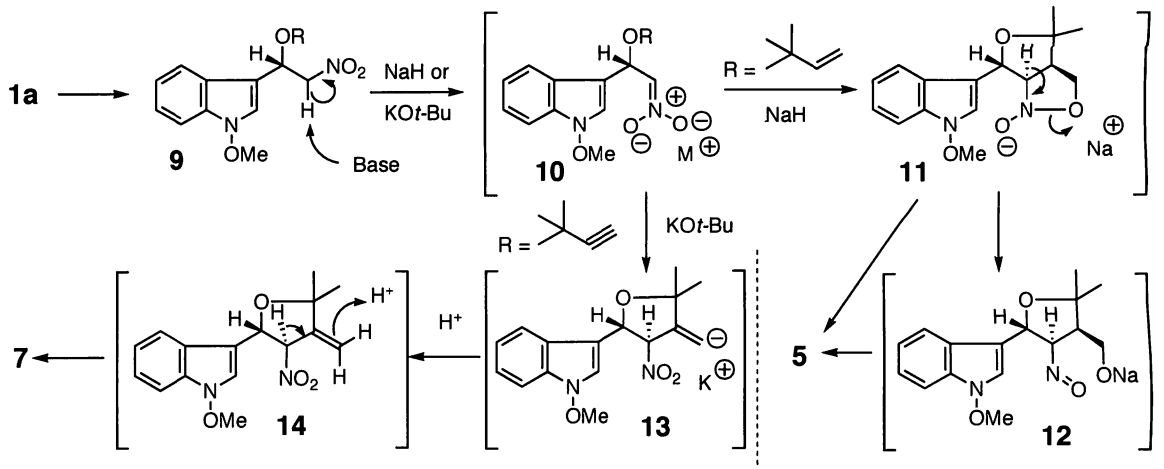


Table 2. Positional parameters and *B* (eq) for **6c**

atom	x	y	z	*B* (eq)	atom	x	y	z	*B* (eq)
O (1)	-0.3048(6)	0.1165(6)	0.1842(7)	7.2(4)	C (22)	-0.152(1)	0.414(1)	0.941(1)	6.4(5)
O (2)	0.1331(5)	0.2236(5)	0.3161(5)	4.7(3)	C (23)	-0.0965(9)	0.3362(9)	0.856(1)	5.6(5)
O (3)	0.0328(5)	0.1994(4)	0.6881(5)	4.8(3)	C (24)	0.374(1)	-0.1221(8)	0.351(1)	5.7(5)
O (4)	0.0838(7)	0.1257(6)	0.8553(6)	8.0(4)	C (25)	0.4172(8)	-0.1911(7)	0.226(1)	5.1(5)
O (5)	-0.1747(7)	0.5326(6)	1.2894(8)	9.4(4)	C (26)	0.500(1)	-0.252(1)	0.246(1)	11.6(9)
O (6)	-0.244(1)	0.566(1)	1.130(1)	26(1)	C (27)	0.553(2)	-0.312(1)	0.136(2)	15(1)
O (7)	0.2858(5)	-0.0729(5)	0.3193(5)	5.7(3)	C (28)	0.512(1)	-0.320(1)	0.008(1)	7.9(6)
O (8)	0.4093(7)	-0.1116(6)	0.4656(7)	8.4(4)	C (29)	0.426(1)	-0.262(1)	-0.014(1)	6.3(5)
O (9)	0.526(1)	-0.397(1)	-0.219(1)	12.6(7)	C (30)	0.379(1)	-0.1985(9)	0.097(1)	6.4(6)
O (10)	0.628(2)	-0.438(2)	-0.094(1)	31(2)	H (1)	-0.09(1)	0.067(8)	0.23(1)	11.1(1)
N (1)	-0.2216(8)	0.1702(7)	0.2922(8)	6.6(4)	H (2)	-0.034(6)	0.434(7)	0.601(9)	5.79(5)
N (2)	0.0891(6)	0.1147(5)	0.5996(6)	4.4(3)	H (3)	-0.200(7)	0.546(8)	0.66(1)	7.55(6)
N (3)	-0.1907(9)	0.514(1)	1.172(1)	8.4(5)	H (4)	-0.381(7)	0.477(7)	0.547(9)	7.96(6)
N (4)	0.562(1)	-0.387(1)	-0.114(1)	11.1(7)	H (5)	-0.4037	0.2937	0.3575	9.1
C (1)	-0.112(1)	0.148(1)	0.297(1)	5.6(5)	H (6)	-0.4276	0.0149	0.2370	12.0
C (2)	-0.0515(8)	0.2307(8)	0.4024(9)	4.3(4)	H (7)	-0.3687	-0.0447	0.1091	12.0
C (3)	-0.127(1)	0.3080(8)	0.4573(9)	5.0(4)	H (8)	-0.3059	-0.0165	0.2539	12.0
C (4)	-0.114(1)	0.4092(9)	0.556(1)	6.0(6)	H (9)	0.111(6)	0.309(6)	0.507(7)	4.81(5)
C (5)	-0.207(1)	0.467(1)	0.586(1)	7.2(6)	H (10)	0.102(6)	0.018(6)	0.319(8)	4.53(5)
C (6)	-0.310(1)	0.426(1)	0.517(1)	7.5(7)	H (11)	0.302(7)	0.037(7)	0.50(1)	6.02(7)
C (7)	-0.328(1)	0.325(1)	0.413(1)	7.4(6)	H (12)	0.184(6)	-0.057(7)	0.472(8)	5.48(5)
C (8)	-0.234(1)	0.2686(9)	0.387(1)	5.1(5)	H (13)	0.317(9)	0.247(8)	0.49(1)	7(3)
C (9)	-0.361(1)	0.017(1)	0.200(1)	10.2(7)	H (14)	0.349(7)	0.278(8)	0.36(1)	6.85(7)
C (10)	0.0734(8)	0.2352(7)	0.4386(8)	4.0(4)	H (15)	0.415(8)	0.178(7)	0.415(8)	7(2)
C (11)	0.1011(7)	0.1370(7)	0.4860(8)	3.8(4)	H (16)	0.319(8)	0.078(7)	0.156(9)	7(3)
C (12)	0.166(1)	0.0661(8)	0.3791(8)	4.5(4)	H (17)	0.285(9)	0.188(8)	0.13(1)	10.5(1)
C (13)	0.2214(8)	0.1545(8)	0.3136(9)	4.7(4)	H (18)	0.174(7)	0.055(7)	0.119(8)	6(3)
C (14)	0.240(1)	-0.0002(8)	0.436(1)	5.3(5)	H (19)	0.031(8)	0.238(7)	1.084(8)	8.32(9)
C (15)	0.330(1)	0.222(1)	0.398(2)	6.7(7)	H (20)	-0.059(5)	0.378(6)	1.232(7)	4.11(4)
C (16)	0.242(1)	0.108(1)	0.164(1)	6.8(6)	H (21)	-0.203(9)	0.460(7)	0.90(1)	8.7(1)
C (17)	0.0360(9)	0.1920(8)	0.8202(9)	5.4(5)	H (22)	-0.115(5)	0.323(6)	0.758(8)	4.43(4)
C (18)	-0.0267(8)	0.2757(7)	0.9067(8)	4.3(4)	H (23)	0.540(7)	-0.22(1)	0.33(1)	9.02(5)
C (19)	-0.013(1)	0.2916(8)	1.0476(9)	5.3(5)	H (24)	0.60(1)	-0.38(1)	0.16(1)	15.6(1)
C (20)	-0.069(1)	0.3682(8)	1.134(1)	5.1(5)	H (25)	0.39(1)	-0.278(8)	-0.10(1)	9.5(1)
C (21)	-0.1345(8)	0.4287(8)	1.0810(9)	5.2(4)	H (26)	0.32(1)	-0.160(9)	0.08(1)	10.7(1)

A possible reaction mechanism for the formation of **5** and **7** is shown in Scheme 3. The base abstracts an active methylene proton of the conjugate addition product (**9**) giving nitronate intermediate (**10**). In the case that the R substituent is a 1,1-dimethylallyl group, cycloaddition[8] of nitronate to the alkene side chain occurs to give **11**. Subsequent elimination of the alkoxy part produces **5** directly or *via* a nitroso intermediate (**12**).

Scheme 3



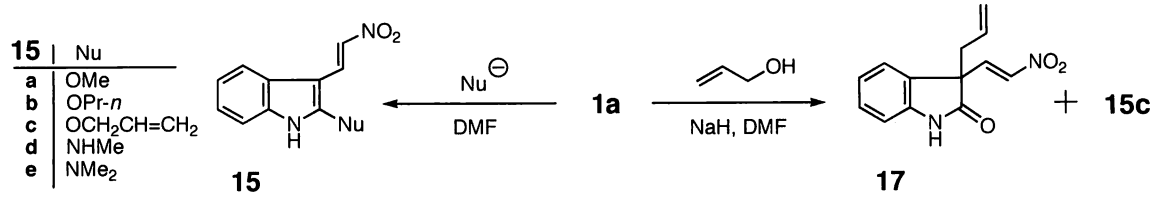
On the other hand, when the R substituent of **10** is a 1,1-dimethylpropargyl group, cycloaddition of nitronate to the alkyne side chain, followed by protonation, affords **14** through **13**. Subsequent isomerization of **14** leads to **7**.

Thus, novel types of 3-substituted 1-methoxyindoles (**4**—**8**) are produced for the first time.

II. Nucleophilc substitution reaction of 1a at the 2-position with concomitant liberation of the 1-methoxy group

Nucleophilic substitution reactions are rarely observed in the indole chemistry.[4,9] We have disclosed that 1-methoxyindole-3-carbaldehyde (**2**) undergoes nucleophilic substitution reactions[9] in sharp contrast with indole-3-carbaldehyde which does not react with nucleophiles under forcing reaction conditions.

Scheme 4



In dipolar aprotic solvents, **1a** was also found to react with nucleophiles regioselectively at the 2-position with concomitant liberation of the 1-methoxy group (Scheme 4). When **1a** was treated with either NaOMe or NaOPr-*n* in DMF at around 80—92 °C, **15a** and **15b** were obtained in 85 and 45% yields,

respectively. In these reactions, formation of conjugate addition products to the β-carbon atom of the nitrovinyl side chain was not observed at all. In addition, **1b** did not produce the corresponding 2-substituted indoles under the same and forcing reaction conditions.

As expected, the reaction of **1a** with allyl alcohol/NaH in DMF at 86 °C produced 2-allyloxy-3-(2-nitrovinyl)indole (**15c**) and (±)-3-allyl-3-(2-nitrovinyl)-2-oxindole (**17**) in 65 and 6% yields, respectively. Subsequent heating of **15c** at 144°C on celite underwent Claisen-type rearrangement resulting in the formation of **17** in 95% yield. On the basis of the results, we examined the reaction of **1a** with sodium allyl oxide in *N*-methylformamide or DMF at around 105°C in order to obtain **17** in a one-pot reaction. In both cases, formation of **17** was not detected; instead, formation of **15d** and **15e** was observed in 58 and 49% yields, respectively. The formation of these compounds through **15c** might be one of the possible reaction pathways.

In summary, we have disclosed that 1-methoxy-3-(2-nitrovinyl)indole (**1a**) has two reaction sites on the reaction with nucleophiles, and the choice of the solvent governs the position to which the nucleophiles add. In addition, conjugate addition products undergo interesting cyclization depending on the bases giving novel 3-substituted 1-methoxyindoles.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and ^{1}H-NMR spectra with a JEOL GSX-500 spectrometer, with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A spectrometer. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF_{254} (Type 60)(SiO_2). Column chromatography was performed on silica gel (SiO_2, 100-200 mesh, from Kanto Chemical Co. Inc.).

1-Methoxy-3-(2-nitrovinyl)indole (1a) from 1-Methoxyindole-3-carbaldehyde[5] (2) — A mixture of **2** (149.8 mg, 0.86 mmol) and ammonium acetate (149.8 mg, 0.86 mmol) in $MeNO_2$ (9.0 mL) was heated at 100 °C for 2.5 h with stirring. After addition of H_2O, the whole was extracted with CH_2Cl_2–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed with CH_2Cl_2–hexane (2:3, v/v) to give **1a** (169.3 mg, 91%). **1a**: mp 109—111 °C (lit.,[5a] mp 105—106 °C, no spectral data are reported, yellow fine needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 1626, 1518, 1470 (br), 1328 (br) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.18 (3H, s), 7.34 (1H, ddd, *J*=8.3, 7.2, 1.1 Hz), 7.40 (1H, ddd, *J*=8.3, 7.2, 1.1 Hz), 7.53 (1H, dt, *J*=8.3, 1.1 Hz), 7.73 (1H, s), 7.75 (1H, d, *J*=13.3 Hz), 7.77 (1H, dt, *J*=8.3, 1.1 Hz), 8.21 (1H, d, *J*=13.3 Hz). *Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.46; H, 4.59; N, 12.63.

General Procedure for Michael Addition of 1a to give Products (4a—d): An alcohol was added to a

suspension of NaH (60% suspension in paraffin oil) in anhydrous THF (1.5 mL) and the mixture was stirred at 0 °C for 10 min. To the resulting mixture, a solution of **1a** in anhydrous THF (1.5 mL) was added and the mixture was stirred at 0 °C for 10 min. After addition of AcOH, the whole was filtered through SiO_2 and the pad was rinsed with AcOEt. The filtrate was evaporated under reduced pressure to leave a residue, which was column-chromatographed with AcOEt–hexane (1:10 or 1:5, v/v) to give product.

1-Methoxy-3-(1-methoxy-2-nitroethyl)indole (4a) from 1a — According to the general procedure, methanol (0.20 mL, 4.70 mmol), NaH (48.0 mg, 1.20 mmol), and **1a** (51.3 mg, 0.24 *mmol) were used.* After column-chromatography 53.2 mg (90%) of **4a** was obtained. **4a**: mp 101—102 °C (yellow plates, recrystallized from CCl_4–hexane). IR (KBr): 1558, 1383, 1107 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.31 (3H, s), 4.11 (3H, s), 4.52 (1H, dd, *J*=12.7, 3.7 Hz), 4.87 (1H, dd, *J*=12.7, 10.0 Hz), 5.25 (1H, dd, *J*=10.0, 3.7 Hz), 7.17 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.30 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.32 (1H, s), 7.46 (1H, dt, *J*=8.1, 1.0 Hz), 7.71 (1H, dt, *J*=8.1, 1.0 Hz). *Anal.* Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.37; H, 5.66; N, 10.96.

1-Methoxy-3-(1-propoxy-2-nitroethyl)indole (4b) from 1a — According to the general procedure, 1-propanol (0.36 mL, 4.82 mmol), NaH (48.2 mg, 1.21 mmol), and **1a** (52.2 mg, 0.24 mmol) were used. After column-chromatography 61.3 mg (92%) of **4b** was obtained. **4b**: pale yellow viscous oil. IR (film): 2964, 2937, 1558, 1379 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, *J*=7.6 Hz), 1.55 (2H, tq, *J*=6.5, 7.6 Hz), 3.33 (1H, dt, *J*=9.0, 6.5 Hz), 3.44 (1H, dt, *J*=9.0, 6.5 Hz), 4.10 (3H, s), 4.51 (1H, dd, *J*=12.7, 3.7 Hz), 4.85 (1H, dd, *J*=12.7, 10.0 Hz), 5.34 (1H, dd, *J*=10.0, 3.7 Hz), 7.16 (1H, ddd, *J*=8.3, 7.5, 1.0 Hz), 7.29 (1H, ddd, *J*=8.3, 7.5, 1.0 Hz), 7.30 (1H, s), 7.45 (1H, dt, *J*=8.3, 1.0 Hz), 7.72 (1H, dt, *J*=8.3, 1.0 Hz). HRMS *m/z*: Calcd for $C_{14}H_{18}N_2O_4$: 278.1266. Found: 278.1270.

3-(1-Allyloxy-2-nitroethyl)-1-methoxyindole (4c) from 1a — According to the general procedure, allyl alcohol (0.32 mL, 4.69 mmol), NaH (48.3 mg, 1.21 mmol), and **1a** (50.3 mg, 0.23 mmol) were used. After column-chromatography 58.2 mg (91%) of **4c** was obtained. **4c**: pale yellow viscous oil. IR (film): 1558, 742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.89 (1H, ddt, *J*=12.7, 6.4, 1.5 Hz), 4.05 (1H, ddt, *J*=12.7, 5.1, 1.5 Hz), 4.11 (3H, s), 4.53 (1H, dd, *J*=12.7, 3.8 Hz), 4.90 (1H, dd, *J*=12.7, 10.0 Hz), 5.17 *(1H, dq, J=10.5,* 1.5 Hz), 5.20 (1H, dq, *J*=17.3, 1.5 Hz), 5.42 (1H, dd, *J*=10.0, 3.8 Hz), 5.84 (1H, dddd, *J*=17.3, 10.5, 6.4, 5.1 Hz), 7.17 (1H, ddd, *J*=8.1, 7.3, 1.0 Hz), 7.30 (1H, ddd, *J*=8.1, 7.3, 1.0 Hz), 7.31 (1H, s), 7.46 (1H, dt, *J*=8.1, 1.0 Hz), 7.71 (1H, dt, *J*=8.1, 1.0 Hz). HRMS *m/z*: Calcd for $C_{14}H_{16}N_2O_4$: 276.1110. Found: 276.1109.

1-Methoxy-3-[1-(2-methyl-3-buten-2-oxy)-2-nitroethyl]indole (4d) from 1a — According to the general procedure, 2-methyl-3-buten-2-ol (0.50 mL, 4.78 mmol), NaH (48.3 mg, 1.21 mmol), and **1a** (52,1 mg, 0.24 mmol) were used. After column-chromatography 58.6 mg (81%) of **4d** was obtained. **4d**:

mp 85—86 °C (colorless plates, recrystallized from hexane). IR (KBr): 1545 (br), 1384, 1362, 734 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.13 (3H, s), 1.23 (3H, s), 4.06 (3H, s), 4.55 (1H, dd, *J*=12.0, 3.9 Hz), 4.74 (1H, dd, *J*=12.0, 9.7 Hz), 5.02 (1H, dd, *J*=10.7, 1.0 Hz), 5.13 (1H, dd, *J*=17.5, 1.0 Hz), 5.49 (1H, dd, *J*=9.7, 3.9 Hz), 5.73 (1H, dd, *J*=17.5, 10.7 Hz), 7.10 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.22 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.41 (1H, dt, *J*=8.1, 1.0 Hz), 7.42 (1H, s), 7.70 (1H, dt, *J*=8.1, 1.0 Hz). *Anal.* Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.14; H, 6.72; N, 9.12.

Preparation of 4e was already reported in our literature.[6]

2,4-*trans*-4,5-Dihydro-4-hydroxymethyl-2-(1-methoxyindol-3-yl)-5,5-dimethyl-3(2*H*)-furanone (*Z*)-oxime (5) from 1a — 2-Methyl-3-buten-2-ol (2.23 mL, 21.3 mmol) was added to a suspension of NaH (60% suspension in paraffin oil, 291.4 mg, 7.29 mmol) and the mixture was stirred for 5 min at rt. To the resulting mixture, a solution of **1a** (309.7 mg, 1.42 mmol) in anhydrous THF (5.0 mL) was added and the mixture was refluxed for 1 h with stirring. After addition of H_2O, the whole was made acidic with 6% HCl under ice cooling and extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed with AcOEt–hexane (1:2, v/v) and then on Al_2O_3 with AcOEt–MeOH (95:5, v/v) to give **5** (235.8 mg, 55%). **5**: yellow viscous oil. IR (film): 3290 (br), 2928, 1448, 1367, 736 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, s), 1.51 (3H, s), 2.83 (1H, br d, *J*=11.0 Hz, disappeared on addition of D_2O), 3.19 (1H, ddd, *J*=8.0, 4.5, 1.6 Hz), 3.72 (1H, br dt, *J*=4.5, 11.0 Hz, collapsed to dd, *J*=11.0, 4.5 Hz on addition of D_2O), 3.92 (1H, br dd, *J*=11.0, 8.0 Hz), 4.07 (3H, s), 5.85 (1H, d, *J*=1.6 Hz) , 7.09 (1H, br s, disappeared on addition of D_2O), 7.12 (1H, ddd, *J*=8.3, 7.3, 1.0 Hz), 7.24 (1H, ddd, *J*=8.3, 7.3, 1.0 Hz), 7.31 (1H, s), 7.41 (1H, dt, *J*=8.3, 1.0 Hz), 7.71 (1H, dt, *J*=8.3, 1.0 Hz). HRMS *m/z*: Calcd for $C_{16}H_{20}N_2O_4$: 304.1423. Found: 304.1421.

General Procedure for the Preparation of Products (6a—c) from 5: An aroyl chloride was added to a solution of **5** in pyridine (1.0 mL) and the mixture was stirred at rt for 1 h. The solvent was evaporated under reduced pressure to leave a residue, which was column-chromatographed with $CHCl_3$–hexane (2:1, v/v) to give products.

2,4-*trans*-3-(*Z*)-(*p*-Bromobenzoyloxyimino)-4-(*p*-bromobenzoyloxymethyl)-2-(1-methoxyindol-3-yl)-4,5-dihydro-5,5-dimethyl-3(2*H*)-furanone (6a) from 5 — According to the general procedure, *p*-bromobenzoyl chloride (92.7 mg, 0.42 mmol) and **5** (21.2 mg, 0.07 mmol) were used. After column-chromatography 29.4 mg (63%) of **6a** was obtained. **6a**: mp 209—212 °C (decomp, colorless powder, recrystallized from $CHCl_3$–AcOEt). IR (KBr): 1743, 1720, 1591 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, s), 1.60 (3H, s), 3.71 (1H, ddd, *J*=9.3, 5.1, 1.2 Hz), 4.01 (3H, s), 4.56 (1H, dd, *J*=12.0, 9.3 Hz), 5.09 (1H, dd, *J*=12.0, 5.1 Hz), 5.93 (1H, d, *J*=1.2 Hz), 7.15 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.26—7.30 (3H, m), 7.32 (2H, m), 7.33 (1H, s), 7.42 (1H, dt, *J*=8.1, 1.0 Hz), 7.63 (2H, m), 7.66 (1H, dt, *J*=8.1, 1.0 Hz), 7.96

(2H, m). MS (FAB$^+$) *m/z*: 673 (M^++1), 671 (M^++1), 669 (M^++1). *Anal.* Calcd for $C_{30}H_{26}N_2O_6Br_2 \cdot H_2O$: C, 52.34; H, 4.10; N, 4.07. Found: C, 52.61; H, 3.88; N, 4.05.

2,4-*trans*-3-(*Z*)-(*p*-Chlorobenzoyloxyimino)-4-(*p*-chlorobenzoyloxymethyl)-2-(1-methoxyindol-3-yl)-4,5-dihydro-5,5-dimethyl-3(2*H*)-furanone (6b) from 5 — According to the general procedure, *p*-chlorobenzoyl chloride (0.075 mL, 0.59 mmol) and **5** (60.1 mg, 0.20 mmol) were used. After column-chromatography 94.4 mg (82%) of **6b** was obtained. **6b**: mp 217—222 °C (decomp, colorless prisms, recrystallized from $CHCl_3$–MeOH). IR (KBr): 1741, 1720, 1593, 1400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, s), 1.60 (3H, s), 3.71 (1H, ddd, *J*=9.3, 5.1, 1.2 Hz), 4.01 (3H, s), 4.56 (1H, dd, *J*=12.0, 9.3 Hz), 5.09 (1H, dd, *J*=12.0, 5.1 Hz), 5.93 (1H, d, *J*=1.2 Hz), 7.13—7.16 (3H, m), 7.28 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.32 (1H, s), 7.36 (2H, m), 7.42 (1H, dd, *J*=8.1, 1.0 Hz), 7.46 (2H, m), 7.66 (1H, dd, *J*=8.1, 1.0 Hz), 8.03 (2H, m). MS *m/z*: 584 (M^+), 582 (M^+), 580 (M^+). *Anal.* Calcd for $C_{30}H_{26}N_2O_6Cl_2 \cdot 1/4\ H_2O$: C, 61.49; H, 4.56; N, 4.78. Found: C, 61.52; H, 4.47; N, 4.78.

2,4-*trans*-4,5-Dihydro-2-(1-methoxyindol-3-yl)-5,5-dimethyl-3-(*Z*)-(*p*-nitrobenzoyloxyimino)-4-(*p*-nitrobenzoyloxymethyl)-3(2*H*)-furanone (6c) from 5 — According to the general procedure, *p*-nitrobenzoyl chloride (166.7mg, 0.90 mmol) and **5** (90.6 mg, 0.30 mmol) were used. After column-chromatography with $CHCl_3$, 139.5 mg (78%) of **6c** was obtained. **6c**: mp 176.5—177.0 °C (yellow prisms, recrystallized from $CHCl_3$–MeOH). IR (KBr): 1749, 1728, 1603, 1525 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, s), 1.63 (3H, s), 3.75 (1H, ddd, *J*=8.5, 5.4, 1.5 Hz), 4.06 (3H, s), 4.64 (1H, dd, *J*=12.0, 8.5 Hz), 5.11 (1H, dd, *J*=12.0, 5.4 Hz), 5.96 (1H, d, *J*=1.5 Hz), 7.15 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.30 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.36 (1H, s), 7.45 (1H, dd, *J*=8.1, 1.0 Hz), 7.54 (2H, m), 7.65 (1H, dd, *J*=8.1, 1.0 Hz), 8.00 (2H, m), 8.29 (2H, m), 8.35 (2H, m). *Anal.* Calcd for $C_{30}H_{26}N_4O_{10}$: C, 59.80; H, 4.35; N, 9.30. Found: C, 59.60; H, 4.23; N, 9.21.

2,5-Dihydro-5-(1-methoxyindol-3-yl)-2,2,3-trimethyl-4-nitrofuran (7) from 1a — 2-Methyl-3-butyn-2-ol (0.50 mL, 5.16 mmol) was added to a suspension of KOBu-*t* (158.2 mg, 1.41 mmol) in anhydrous THF (1.5 mL) and the mixture was stirred at 0 °C for 20 min. To the resulting mixture, a solution of **1a** (30.7 mg, 0.14 mmol) in anhydrous THF (1.5 mL) was added and the mixture was stirred at rt for 10 min. After addition of H_2O, the whole was made acidic with 6% HCl under ice cooling and extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed with benzene to give unreacted **1a** (3.4 mg, 11%) and **7** (14.7 mg, 35%) in the order of elution. **7**: pale yellow viscous oil. IR (film): 2978, 1670, 1508, 1360 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.47 (3H, s), 1.50 (3H, s), 2.27 (3H, d, *J*=1.7 Hz), 4.07 (3H, s), 6.30 (1H, q, *J*=1.7 Hz), 7.06 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.21 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.41 (1H, dt, *J*=8.1, 1.0 Hz), 7.50 (1H, s), 7.59 (1H, dt, *J*=8.1, 1.0 Hz). HRMS *m/z*: Calcd for $C_{16}H_{18}N_2O_4$: 302.1267. Found: 302.1271.

1-Methoxy-3-[1-(2-methyl-3-butyn-2-oxy)-2-nitroethyl]indole (8) from 1a — 2-Methyl-3-butyn-2-ol (0.46 mL, 4.75 mmol) was added to a suspension of NaH (60% suspension in paraffin oil, 48.5 mg, 1.21 mmol) in anhydrous THF (1.5 mL) and the mixture was stirred at 0 °C for 10 min. To the resulting mixture, a solution of **1a** (51.5 mg, 0.24 mmol) in anhydrous THF (1.5 mL) was added and the mixture was stirred at 0 °C for 10 min. After addition of AcOH (0.07 mL, 1.22 mmol), the whole was filtered through SiO_2 and the pad was rinsed with AcOEt. The filtrate was evaporated under reduced pressure to leave a residue, which was column-chromatographed with AcOEt–hexane (1:10, v/v) to give **8** (53.8 mg, 75%). **8**: mp 91.0—91.5 °C (pale yellow prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 3280, 2112, 1552, 1381, 1068 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s), 1.50 (3H, s), 2.41 (1H, s), 4.08 (3H, s), 4.53 (1H, dd, *J*=12.1, 4.2 Hz), 4.79 (1H, dd, *J*=12.1, 9.3 Hz), 5.86 (1H, dd, *J*=9.3, 4.2 Hz), 7.16 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.28 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.30 (1H, s), 7.43 (1H, dt, *J*=8.1, 1.0 Hz), 7.75 (1H, dt, *J*=8.1, 1.0 Hz). *Anal.* Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.49; H, 6.02; N, 9.10.

2,5-Dihydro-5-(1-methoxyindol-3-yl)-2,2,3-trimethyl-4-nitrofuran (7) from 8 — KOBu-*t* (20.1 mg, 0.18 mmol) was added to a solution of **8** (36.0 mg , 0.12 mmol) in anhydrous THF (5 mL) and the mixture was stirred at 0 °C for 30 min. After addition of H_2O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was purified by p-TLC on SiO_2 developed with benzene. Extraction of the band having an Rf value of 0.50—0.37 with $CHCl_3$ gave **1a** (3.2 mg, 12%). Extraction of the band having an Rf value of 0.37—0.17 with $CHCl_3$ gave **7** (22.7 mg, 63%).

2-Methoxy-3-(2-nitrovinyl)indole (15a) from 1a — A solution of **1a** (32.7 mg, 0.15 mmol) in DMF (3.0 mL) was added to a solution of NaOMe [prepared with sodium (113.6 mg, 4.90 mg atom) and anhydrous MeOH (2.0 mL)]. The mixture was heated at 92 °C for 1.5 h with stirring. After addition of saturated NH_4Cl, the whole was extracted with CH_2Cl_2–MeOH (9:1, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed repeatedly with CH_2Cl_2–MeOH (99:1, v/v) to give **15a** (27.0 mg, 85%). **15a**: mp 209—212 °C (decomp, red powder, recrystallized from CH_2Cl_2–MeOH). IR (KBr): 1597, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.21 (3H, s), 7.15 (1H, dt, *J*=1.5, 7.3 Hz), 7.18 (1H, dt, *J*=1.5, 7.3 Hz), 7.35—7.38 (1H, m), 7.66—7.69 (1H, m), 7.70 (1H, d, *J*=13.0 Hz), 8.25 (1H, d, *J*=13.0 Hz). MS *m/z*: 218 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_2O_3 \cdot 1/8H_2O$: C, 59.93; H, 4.69; N, 12.70. Found: C, 60.09; H, 4.58; N, 12.76.

3-(2-Nitrovinyl)-2-*n*-propoxyindole (15b) from 1a — 1-Propanol (0.35 mL, 4.68 mmol) was added to a suspension of NaH (60% suspension in paraffin oil, 48.8 mg, 1.22 mmol) in anhydrous THF (1.5 mL) and the mixture was stirred at 0 °C for 10 min. After evaporation of the solvent, the residue was

dissolved in DMF (1.5 mL). Then a solution of **1a** (51.4 mg, 0.24 mmol) in anhydrous DMF (1.5 mL) was added under ice cooling. The mixture was heated at 80 °C for 1 h with stirring. After addition of H_2O, the whole was made acidic with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed successively with $CHCl_3$ and $CHCl_3$–MeOH (99:1, v/v) to give unreacted **1a** (13.4 mg, 26%) and **15b** (31.7 mg, 55%). **15b**: mp 191—198 °C (decomp, red powder recrystallized from CH_2Cl_2–hexane). IR (KBr): 3188 (br), 1597, 1156 (br) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 60 °C) δ: 1.04 (3H, t, *J*=7.1 Hz), 1.87 (2H, sex, *J*=7.1 Hz), 4.42 (2H, t, *J*=7.1 Hz), 7.13 (1H, dt, *J*=1.5, 7.7 Hz), 7.16 (1H, dt, *J*=1.5, 7.7 Hz), 7.31—7.34 (1H, m), 7.62—7.65 (1H, m), 7.66 (1H, d, *J*=13.2 Hz), 8.24 (1H, d, *J*=13.2 Hz). MS *m/z*: 246 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O_3 \cdot 1/2H_2O$: C, 61.17; H, 5.53; N, 10.97. Found: C, 61.23; H, 5.53; N, 10.91.

2-Allyloxy-3-(2-nitrovinyl)indole (15c) and 3-Allyl-3-(2-nitrovinyl)-2-oxindole (17) from 1a — A solution of **1a** (61.3 mg, 0.28 mmol) in DMF (2.0 mL) was added to sodium allyl oxide [prepared with NaH (60% suspension in paraffin oil, 98.5 mg, 2.46 mmol) and allyl alcohol (0.30 mL, 4.40 mmol)]. The mixture was heated at 86 °C for 2 h with stirring. After addition of H_2O, the whole was made neutral with 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed with AcOEt–hexane (1:4, v/v) to give **15c** (39.1 mg, 57%) and **17** (12.6 mg, 18%). **15c**: mp 124—129 °C (decomp, pink powder, recrystallized from acetone–hexane). IR (KBr): 3193 (br), 1593, 1576, 1558 cm^{-1}. ^{1}H-NMR ($CDCl_3$:CD_3OD = 1:1, v/v) δ: 4.93 (2H, dt, *J*=5.5, 1.4 Hz), 5.43 (1H, dq, *J*=10.7, 1.4 Hz), 5.54 (1H, dq, *J*=17.3, 1.4 Hz), 6.14 (1H, ddt, *J*=17.3, 10.7, 5.5 Hz), 7.18 (1H, dt, *J*=1.1, 7.7 Hz), 7.22 (1H, dt, *J*=1.1, 7.7 Hz), 7.29—7.32 (1H, m), 7.54—7.58 (1H, m), 7.71 (1H, d, *J*=13.2 Hz), 8.42 (1H, d, *J*=13.2 Hz). MS *m/z*: 244 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O_3 \cdot 1/8H_2O$: C, 63.34; H, 5.01; N, 11.36. Found: C, 63.19; H, 4.84; N, 11.24. **17**: mp 124.0—127.5 °C (decomp, colorless prisms, recrystallized from AcOEt–hexane). IR ($CHCl_3$): 1714, 1615, 1525 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.73 (1H, br dd, *J*=13.0, 7.9 Hz), 2.82 (1H, br dd, *J*=13.0, 6.9 Hz), 4.99 (1H, br d, *J*=10.0 Hz), 5.06 (1H, dq, *J*=16.7, 1.1 Hz), 5.40—5.48 (1H, m), 6.96 (1H, dt, *J*=7.7, 1.1 Hz), 7.09 (1H, d, *J*=13.6 Hz), 7.12 (1H, dt, *J*=1.1, 7.7 Hz), 7.31 (1H, dt, *J*=1.1, 7.7 Hz), 7.37 (1H, br d, *J*=7.7 Hz), 7.38 (1H, d, *J*=13.6 Hz). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.84; H, 4.95; N, 11.41.

2-Methylamino-3-(2-nitrovinyl)indole (15d) from 1a — Sodium (98.9 mg, 4.3 mg atom) was added to anhydrous allyl alcohol (3.0 mL) with stirring. To the resultant solution, a solution of **1a** (40.4 mg, 0.19 mmol) in anhydrous *N*-methylformamide (1.5 mL) was added and the mixture was heated at 103 °C for 2 h with stirring. Brine was added to the reaction mixture and the whole was made neutral by adding 6% HCl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated

under reduced pressure to leave an oil, which was column-chromatographed with CH_2Cl_2–MeOH (97:3, v/v) to give **15d** (23.2 mg, 58%). **15d**: mp 229.5-231.0 °C (decomp, red purple powder recrystallized from acetone–hexane). IR (KBr): 3175, 1649, 1585 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.98 (3H, d, J = 4.7 Hz, collapsed to s on addition of D_2O), 7.01—7.09 (2H, m), 7.16 (1H, d, J = 7.0 Hz), 7.44 (1H, d, J = 7.0 Hz), 7.51 (1H, d, J = 12.1 Hz), 8.44 (1H, d, J = 12.1 Hz), 8.51 (1H, br s). MS *m/z*: 217 (M^+), 201, 170, 155, 115. *Anal.* Calcd for $C_{11}H_{11}N_3O_2 \cdot 1/4H_2O$: C, 59.59; H, 5.23; N, 18.95. Found: C, 59.34; H, 5.07; N, 18.68.

2-Dimethylamino-3-(2-nitrovinyl)indole (15e) from 1a — Sodium (145.2 mg, 6.3 mg atom) was added to anhydrous allyl alcohol (4.0 mL) with stirring. To the resultant solution, a solution of **1a** (51.2 mg, 0.24 mmol) in anhydrous DMF (1.0 mL) was added and the mixture was heated at 105 °C for 1 h with stirring. The reaction mixture was made neutral by adding 6% HCl and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed with CH_2Cl_2–MeOH (97:3, v/v) to give **15e** (26.7 mg, 49%). **15e**: mp 236—239 °C (decomp, dark purple prisms, recrystallized from MeOH). IR (KBr): 1580, 1568, 1256, 1171 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.32 (6H, s), 7.07—7.11 (2H, m), 7.18—7.22 (1H, m), 7.51—7.55 (1H, m), 7.59 (1H, d, J = 12.3 Hz), 8.52 (1H, d, J = 12.3 Hz). MS *m/z*: 231 (M^-). *Anal.* Calcd for $C_{12}H_{13}N_3O_2 \cdot 1/8\ H_2O$: C, 61.72; H, 5.61; N, 18.00. Found: C, 62.10; H, 5.67; N, 17.81.

REFERENCES AND NOTES

1. a) This report is Part 127 of a series entitled "The Chemistry of Indoles". b) Part 126: F. Yamada, Y. Fukui, T. Iwaki, S. Ogasawara, M. Okigawa, S. Tanaka, and M. Somei, *Heterocycles*, 2006, **67**, 129.
2. C. Reichardt, "Solvent Effects in Organic Chemistry," 3, Verlag Chemie GmbH, Weinheim, 1979.
3. K. Yamada, F. Yamada, and M. Somei, *Heterocycles*, 2002, **57**, 1231.
4. M. Somei, F. Yamada, T. Izumi, and M. Nakajou, *Heterocycles*, 1997, **45**, 2327 and references related to nucleophilic substitution reactions in indole chemistry are cited therein.
5. a) R. M. Acheson, P. G. Hunt, D. M. Littlewood, B. A. Murrer, and H. E. Rosenberg, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1117; b) M. Somei, H. Ohnishi, and Y. Shoken, *Chem. Pharm. Bull.*, 1986, **34**, 677; c) M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251.
6. K. Yamada, F. Yamada, and M. Somei, *Heterocycles*, 2003, **59**, 685.
7. The reflection data were collected on a Rigaku AFC5R diffractometer over the range of $62.19° < 2\theta < 80.04°$ using Cu$K\alpha$ radiation (λ=1.54178 Å) and the ω–2θ scan method at a 2θ scan speed of 6°/min. The structure of **6c** was solved by the direct method using MITHRIL[10] and refined by the full-matrix least-squares method with anisotropic thermal factors for non-hydrogen atoms and with isotropic ones for hydrogen atoms. The final R- and Rw-factors were 0.069 and 0.074 for

1771 observed reflections [$I>3.00\sigma(I)$], respectively. Crystal data for **6c**: $C_{30}H_{26}N_4O_{10}$, M=602.56; triclinic, space group $P\bar{1}$ (#2); a=11.779 (3) Å, b=12.640 (3) Å, c=10.196 (2) Å, α=106.15 (1)°, β=92.30 (2)°, γ=97.29 (2)°; V=1441.8 (6) Å^3, Z=2, D_{calc}=1.388 g/cm^3.

8. Related cycloadditions of nitronates: S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137; G. Broggini and G. Zecchi, *Synthesis*, 1999, 905 and references cited therein.
9. a) Review: M. Somei, *J. Synth. Org. Chem.*, 1991, **49**, 205; b) Review: M. Somei, *Heterocycles*, 1999, **50**, 1157; c) M. Somei, Advances in Heterocyclic Chemistry, Vol. 82, ed. by A. R. Katrizky, Elsevier Science, USA, 2002, pp. 101—155.
10. C. J. Gilmore, *J. Appl. Cryst.*, 1984, **17**, 42.