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1-Aminoisoindole as a useful π-system elongation unit

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ABSTRACT

Nitration of 4,7-ethanoisoindoles gave 1-nitro derivatives in moderate yields. Reduction of a nitro to amino group was successfully performed by sodium hydrosulfite in the case of ethyl 3-nitro-4,7-ethanoisoindole-1-carboxylate. The amino derivative was converted to benzylidenaminoisoindoles based on the retro Diels–Alder reaction. Their UV–vis spectra showed strong absorptions at 500–700 nm.

1. Introduction

Phthalocyanine is one of the most common and important pigments in our life and consists of four units of a 1-aminoisoindole moiety. Two of them adopt a 1-amino-2*H*-isoindole structure and others are 1-iminoisoindolenine (1-imino-1*H*-isoindole). In general, the isoindole moiety can effectively expand its connecting π-system compared with 1*H*-indole, because the π-system of isoindole is fully delocalized over the whole molecule.[1] The isoindole skeleton itself, however, is rarely found in pigments and dyes except that the skeleton is implanted in other π-ring system. The main reasons are paucity of synthetic methods of isoindole derivatives and their instability mainly due to easy tautomerism between highly electron-rich 2*H*-isoindole and electrophilic isoindolenine structures.[2] Preparation of 2*H*-isoindole derivatives with electron-donating substituents is extremely difficult, because such substituents as methoxy groups at α positions of isoindole prompted to shift the equilibrium exclusively to the isoindolenine structure.[3] 1-Hydroxy-2*H*-isoindole and 1-amino-2*H*-isoindole without an *N*-substituent usually existed as their keto and imino forms. Therefore, no synthetic application using these compounds was so far reported. During our continuous studies for the preparation and application of π-expanded porphyrins and their analogues,[4] we planned to introduce an amino group into a bicyclo[2.2.2]octadiene-fused (BCOD-fused) pyrrole derivative in order to prepare soluble precursors of phthalocyanine[5] and *meso*-azatetrabenzoporphyrins. In this paper, we will describe preparation of a 1-amino-4,7-ethano-2*H*-isoindole derivative as the 1-aminoisoindole equivalent and its conversion to arylmethylidenaminoisoindoles.

2. Results and discussion

2.1. Preparation of arylidenaminoisoindole precursors

Ethyl 4,7-dihydro-4,7-ethano-2*H*-isoindole-1-carboxylate (**1**) and 4,7-ethano-2*H*-isoindole (**2**) were prepared according to the literature.[6] We first attempted to prepare a 1-amino 3-bromo derivative, which might be a useful building block for bicyclo[2.2.2]octadiene-fused porphyrazine. Ethanoisoindole **2** was nitrated with concd HNO_3 in acetic anhydride to give 1-nitro-4,7-dihydro-4,7-ethano-2*H*-isoindole (**5**) in 54% yield (Scheme 1). In trifluoroacetic anhydride, concomitant trifluoroacetylation with nitration occurred to give a 1-nitro 3-trifluoroacetyl derivative in 43% yield. Bromination of nitro derivative **5** with NBS gave 1-bromo-4,7-ethano-3-nitro-2*H*-isoindole (**6**) in a 59% yield. Reduction of the nitro group of **6** was attempted under several conditions by using $Na_2S_2O_4$ and $LiAlH_4$. None of identifiable compounds was, however, obtained probably due to very unstable nature of a 2-aminopyrrole derivative under air.[1] Since 2-aminopyrroles were successfully prepared if they had electron-withdrawing groups,[7] the starting compound was changed to ester **1**, reactivity of which was reduced by the electron-withdrawing ester group. As an intractable mixture was obtained in the conventional nitration of **1** using mixed acids (HNO_3, H_2SO_4), the milder nitration conditions were employed. Thus, nitration of pyrrolecarboxylate ester **1** was carried out under the similar conditions (HNO_3, Ac_2O, −10 °C) as used in the nitration of **2** to give nitropyrrolecarboxylate **3** in only a 16% yield. Reduction of the nitro group in **3** was achieved by using $Na_2S_2O_4$ to give aminopyrrole **4**. Isolation of the targeted compound **4** was rather difficult due to its intrinsic instability toward oxidation under air. Thus, the isolated yield of **4** by column chromatography was low (10%), although no obvious by-product formation was detected in the reaction mixture. Therefore, the amino compound was used in the next reaction without purification.

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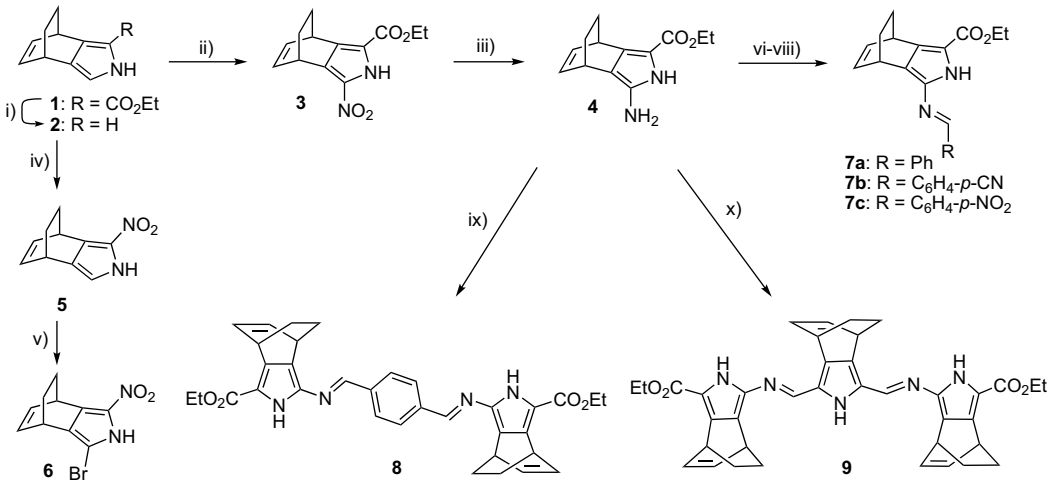

Scheme 1. Reagents, conditions, and yields: (i) KOH, ethylene glycol, 175 °C, 81%; (ii) HNO_3, Ac_2O, −10 °C, 16%; (iii) $Na_2S_2O_4$, aq EtOH, 40 °C, 10%; (iv) HNO_3, Ac_2O, −10 °C, 54%; (v) NBS, DMF/CH_2Cl_2, −10 °C, 59%; (vi) PhCHO, toluene, 120 °C, 19% (from **3**); (vii) *p*-NCC_6H_4CHO, toluene, 120 °C (from **3**), 38%; (viii) *p*-$O_2NC_6H_4CHO$, toluene, 120 °C, 35% (from **3**); (ix) *p*-$C_6H_4(CHO)_2$, toluene, 120 °C, 29% (from **3**); (x) 4,7-ethano-2*H*-isoindole-1,3-dicarbaldehyde, toluene, 120 °C, 64% (from **3**).

In order to extend the chromophore of **4**, the amino group of **4** was transformed into an imino group. The crude aminopyrrole **4** was reacted with aromatic aldehydes to give imino derivatives **7** in moderate yields. These imino compounds were considered as good precursors giving the targeted 1-benzylidenaminoisoindole derivatives by heat treatment. Amino derivative **4** also reacted with aromatic dialdehydes such as *p*-phthalaldehyde and 4,7-dihydro-4,7-ethano-2*H*-isoindole-1,3-dicarbaldehyde[6a] to give bis-imino derivatives **8** and **9** in respective yields of 29 and 64%.

2.2. Thermal behavior of BCOD-fused arylmethylidenaminopyrroles

Before examination of the thermal conversion of BCOD-fused compounds, X-ray crystallographic analysis was tried because we often experienced co-crystallization of BCOD-fused compounds with solvent molecules. Unfortunately, no suitable single crystal of BCOD-fused benzylidenaminopyrrole **7**, **8**, or **9** was obtained, although X-ray analysis was successfully done in two of BCOD-fused nitro compounds **3** and **6**.[8] Hydrogen-bonding network of these crystal structures were worthy to note (Figs. 1 and 2). In both crystal structures, mean planes of five pyrroles and three nitro atoms were almost coplanar: 8.04(6)° for **3** and 3.07(10)° for **6**. In the case of **3**, the pyrrole and carboxyl planes were also coplanar (2.39(7)°) and this pyrrole-2-carboxylate moiety formed a planar dimer by two hydrogen bonds (Fig. 1; N–H···O: N···O distance, 2.927(3) Å; N–H, 0.826 Å; H···O, 2.156 Å; ∠N–H···O, 155.1°). The dimeric pairs were stacked at the nitro group by the static electronic attraction between positively charged nitrogen and negatively charged oxygen atoms (3.010(2) Å). Contrarily to **3**, a zigzag cyclic tetrameric motif was observed in the crystal structure of **6** (Fig. 2). The hydrogen-bonding angle of ∠N–H···O was 127.1° and the N···O distance was 2.970(4) Å.

Molecular compositions of BCOD-fused benzylidenaminopyrroles **7**, **8**, and **9** were determined by combustion analysis. One-eighth to half water molecule per a pyrrole molecule was contained in the samples of **7** and **8** and one toluene molecule was included in the sample of **9**. Thermal behavior of BCOD-fused benzylidenaminopyrroles was then examined by thermogravimetric (TG) analysis (10 °C/min) and the results are summarized in Table 1.

In all cases except for **9**, extrusion of ethylene from the BCOD moiety started around 170 °C with concomitant loss of water. In the case of **9**, co-solvent toluene was first lost during two temperature ranges (114–151 and 151–180 °C) and then ethylene was

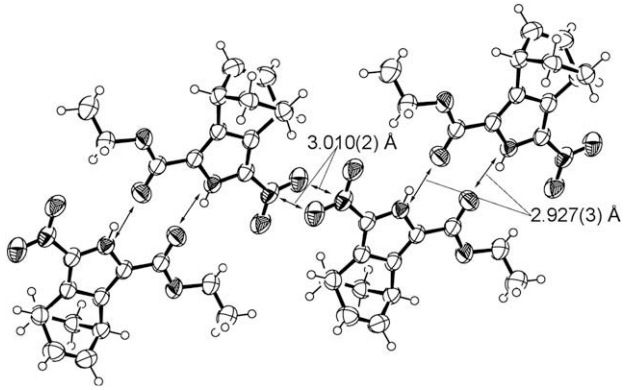

Figure 1. Ortep drawing of two pairs of dimeric hydrogen-bonding molecules **3**. N···O=C distance, 2.927(3) Å; ∠N–H···O angle, 155.1°.

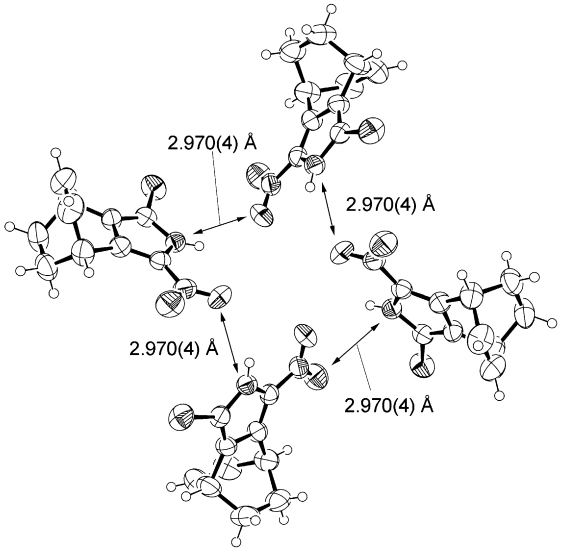

Figure 2. Ortep drawing of four hydrogen-bonding molecules of **6**. Dihedral angle of pyrrole mean planes, 106.29(15)°; N···O distance, 2.970(4) Å; ∠N–H···O angle, 127.1°.

Table 1
Thermal behavior of BCOD-fused arylmethylidenaminopyrroles

Sample[a]	Decomp./°C		Weight loss		Assignment
	Start	End	Obsd[b]/%	Calcd[c]/%	
7a·1/2H_2O	167	275[d]	31.5	33.1	2CH_2=CH_2, CO_2, 1/2H_2O
7b·1/8H_2O	171	252[e]	13.5	8.7	CH_2=CH_2, 1/8H_2O
	252[e]	328[d]	31.8(18.3)	28.4(20.7)	CH_2=CH_2, CO_2
7c·1/4H_2O	170	245	8.5	8.8	CH_2=CH_2, 1/4H_2O
	245	289[d]	29.7(21.2)	28.3(19.5)	CH_2=CH_2, CO_2
8·1/4H_2O	170	248	10.9	10.7	2CH_2=CH_2, 1/4H_2O
	281	320[e]	24.5(12.5)	23.4(12.7)	CH_2=CH_2, CO_2
	320[e]	410[d]	36.6(12.1)	36.1(12.7)	CH_2=CH_2, CO_2
9·C_7H_8	114	151[e]	6.4	6.4	1/2C_7H_8
	151[e]	180[e]	12.4(6.0)	12.8(6.4)	1/2C_7H_8
	180[e]	255[e]	32.2(19.8)	30.6(17.8)	3CH_2=CH_2, CO_2
	255[e]	318[d]	42.3(10.1)	40.6(10.0)	CH_2=CH_2, CO_2

[a] The sample composition was determined by combustion analysis.
[b] Percentage of weight loss was calculated from the initial weight and the observed weight at the end temperature. Numerals in parentheses were percentage of weight loss during the start and end temperatures versus the initial weight.
[c] Calculated percentage of weight loss was based on the assignment molecules.
[d] Slow weight loss continued after the end temperature probably due to decomposition of the isoindole moiety.
[e] The start and end temperatures were determined by differential TG diagram.

extruded. Decomposition of the ester group of **7a** occurred almost simultaneously with loss of ethylene from the BCOD moiety, while the ester group of **7c** and **8** started to decompose completely after the extrusion of ethylene. In the TG curves of **7b** and **9**, there was no obvious rate change during the weight-losing temperature ranges. These decomposition temperatures, however, could be obviously distinguished by differential TG data. From these TG data, we concluded that extrusion of ethylene from the BCOD-fused moiety was hardly affected by the substituent at the pyrrole ring and the starting temperature was around 170 °C as previously reported.[9] On the other hand, decomposition temperature of the ester group was quite sensitive to the electronic structure of the pyrrole ring. The more electron-withdrawing the substituent at α-position was, the higher the decomposition temperature became.

Bulk conversion of BCOD-fused pyrroles **7c**, **8**, and **9** were successfully performed at 230, 240, and 220 °C under a reduced pressure (ca. 0.05 mmHg) for 30 min. Benzylidenaminoisoindoles **10c**, **11**, and **12** were obtained in quantitative yields (Chart 1). In the thermal treatment of **7a** and **7b**, however, we failed to obtain pure samples of **10a** and **10b** probably due to the partial decomposition of ester group mentioned above, partial sublimation, and oxidative decomposition.

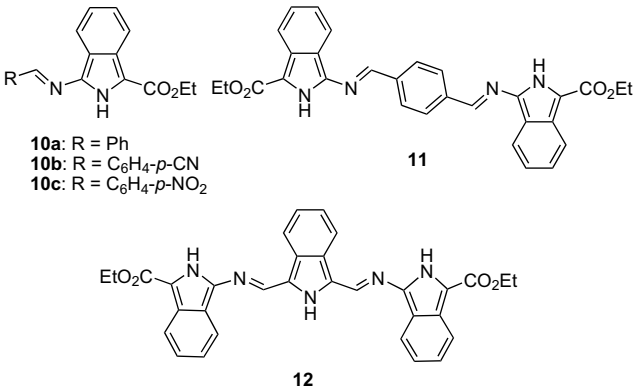

Chart 1. Arylmethylidenaminoisoindoles.

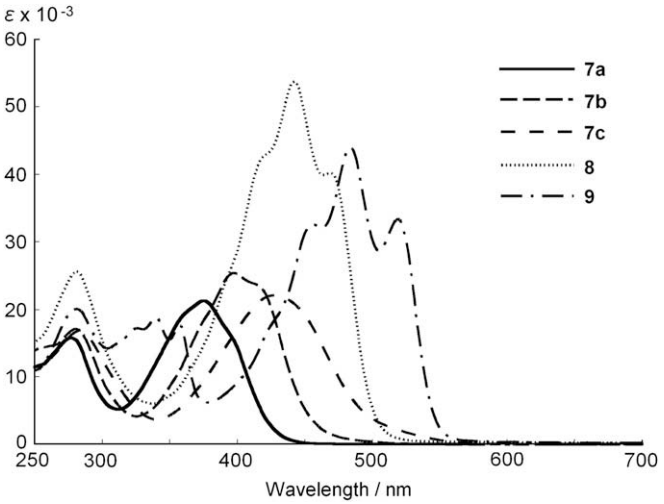

Figure 3. UV–vis spectra of BCOD-fused pyrroles in $CHCl_3$.

2.3. UV–vis measurement of BCOD-fused pyrroles and isoindoles

UV–vis spectra of the BCOD-fused pyrroles and the corresponding isoindoles were measured in $CHCl_3$ and are shown in Figures 3 and 4. From Figure 3, broad absorption bands of monobenzylidenaminopyrroles **7a–c** in the visible region showed

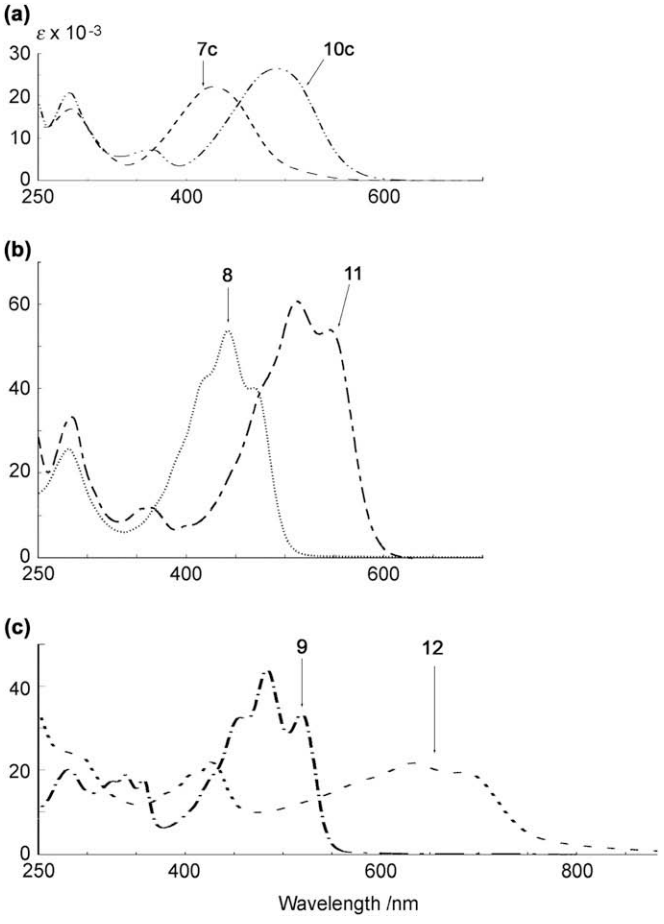

Figure 4. UV–vis spectra of BCOD-fused pyrroles and the corresponding isoindoles in $CHCl_3$: (a) spectra of **7c** and **10c**; (b) spectra of **8** and **11**; and (c) spectra of **9** and **12**.

a sequential bathochromic shift corresponding to electron-withdrawing nature of the *p*-substituents on aryl groups (**7a**: 375 nm, **7b**: 397 nm, and **7c**: 427 nm) and their molecular extinction coefficients were almost similar. This is well understood by considering strong electron-donating nature of α-aminopyrrole. In the spectrum of *p*-xylene-α,α′-bis(ylidenaminopyrrole) **8**, the molecular extinction coefficients of the absorption bands were nearly doubled compared to the mono-benzylidenaminopyrroles and the absorption maxima (281 and 442 nm) are similar to that of **7c**. A further bathochromic shift and obvious splitting (456, 484, and 519 nm) were observed in the spectrum of pyrrole-2,5-bis(methylidenaminopyrrole) **9**.

In Figure 4, spectra of isoindoles are shown with the corresponding BCOD-fused pyrroles. Conversion of BCOD-fused pyrrole to isoindole (Fig. 4a, **7c** to **10c**) brought about 65 nm bathochromic shift. In the cases of **8** to **11** and **9** to **12**, larger bathochromic shifts were recorded corresponding to the multiple π-system expansion of pyrrole to isoindole. Especially, the absorption end of **12** exceeded the visible range and reached to 1000 nm. These isoindole dyes were stable under air and no special precaution was needed although slow decomposition was observed in protic solvents.

In conclusion, ethyl 1-amino-4,7-dihydro-4,7-ethano-isoindolecarboxylate (**4**) as a 1-aminoisoindole equivalent was prepared and was derivatized to benzylidenamino compounds, which were converted to benzylidenaminoisoindoles by the retro-Diels–Alder reaction. The isoindole moiety was shown to be a good π-elongating moiety. In the case of isoindole-1,3-bis(methylidenaminoisoindole) **12**, the absorption end went beyond the visible region.

3. Experimental

3.1. General

Melting points were measured on a Yanagimoto micromelting point apparatus and are uncorrected. NMR spectra were obtained with a JEOL AL-300, JEOL AL-400 or EX-400 spectrometer at ambient temperature. IR spectra were measured with a Horiba FT-720 infrared spectrophotometer. EI and FAB spectra were measured with a JEOL JMS-700. The MALDI-TOF MS spectrum was measured with a Voyager DE Pro instrument. Elemental analyses were performed with a Yanaco MT-5 elemental analyzer. UV–vis spectra were measured with a HITACHI U-2810 spectrophotometer. All solvents and chemicals were reagent grade quality, obtained commercially, and used without further purification except as noted. Dry dichloromethane and THF were purchased from Kanto Chemical Co. Toluene, triethylamine, and pyridine were distilled from calcium hydride and then stored on appropriate Molecular Sieves 4 Å. Solvents for chromatography were purified by distillation. For spectral measurements, spectral grades of chloroform were purchased from Nacalai Tesque Co. Thin-layer (TLC) and column chromatography were performed on Art. 5554 (Merck KGaA) and Silica Gel 60N (Kanto Chemical Co.), respectively. Ethyl 4,7-dihydro-4,7-ethano-2*H*-isoindole-1-carboxylate (**1**),[6] 4,7-dihydro-4,7-ethano-2*H*-isoindole (**2**),[6] and 4,7-dihydro-4,7-ethano-2*H*-isoindole-1,3-dicarbaldehyde[6a] were prepared according to the literature procedures.

3.2. Ethyl 3-nitro-4,7-dihydro-4,7-ethano-2*H*-isoindole-1-carboxylate (3)

To a stirred solution of ethyl pyrrolecarboxylate (**1**; 6.00 g, 27.6 mmol) in Ac_2O (750 mL) was slowly added concd HNO_3 (3.82 mL) at −10 °C under argon and the mixture was stirred for 1 h. After being stirred overnight, the mixture was poured into ice-water. The mixture was extracted with CH_2Cl_2. The organic extract was successively washed with a satd $NaHCO_3$ solution, water, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (CH_2Cl_2) to give 1.18 g (16%) of the title compound as pale yellow crystals: mp 150–151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (t, 3H, *J*=7.1 Hz), 1.47–1.66 (m, 4H), 4.40 (q, 2H, *J*=7.1 Hz), 4.41 (m, 1H), 4.58 (m, 1H), 6.47–6.56 (m, 2H), 9.37 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.23, 25.44, 25.62, 33.04, 33.38, 61.48, 115.88, 130.65, 131.90, 134.41, 135.34, 136.89, 160.44; IR (KBr) ν_{max} 3273 (NH), 1693, 1588, 1520, 1364, 1307, 1293, 1242 cm^{-1}; MS (EI) 262 (M^+, 3%), 235 (12), 234 (100), 206 (10). Anal. Calcd for $C_{13}H_{14}N_2O_4$+1/8H_2O: C, 59.03; H, 5.43; N, 10.59%. Found: C, 58.87; H, 5.27; N, 10.51%. The single crystals were obtained by slow vapor diffusion of methanol into a solution of **3** in $CHCl_3$. Crystal formula, $C_{13}H_{14}N_2O_4$, 0.30×0.25×0.20 mm, triclinic, space group *P*-1, *a*=7.7064(8), *b*=8.4775(6), *c*=11.1885(12) Å, α=69.979(12)°, β=75.454(13)°, γ=67.811(12)°, *V*=629.65(12) Å^3, Mo Kα, *T*=296 K, *Z*=2, ρ_{calcd}=1.383 g cm^{-3}, μ=0.104 mm^{-1}, *F*(000)=276. 11,480 measured, 2874 unique, 2146 observed [$I>2\sigma(I)$]; R_1=0.0625 [$I>2\sigma(I)$], wR_2=0.1997 (all); GOF=1.094. CCDC no. 721549.

3.3. Ethyl 3-amino-4,7-dihydro-4,7-ethano-2*H*-isoindole-1-carboxylate (4)

To a stirred solution of ethyl nitropyrrolecarboxylate (**3**; 50 mg, 0.191 mmol) in 60% aq EtOH (10 mL) was added $Na_2S_2O_4$ (143 mg, 0.82 mmol) at room temperature. After being stirred at 40 °C for 1 h, the mixture was poured into ice-water. The mixture was extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (CH_2Cl_2/EtOAc=2/1) to give 4.4 mg (10%) of the title compound as a brown oil. This compound was very labile. Therefore, no satisfactory analytical data were obtained. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, 3H, *J*=7.1 Hz), 1.44–1.55 (m, 4H), 3.64 (br, 2H), 3.73 (m, 1H), 4.25 (q, 2H, *J*=7.1 Hz), 4.28 (m, 1H), 6.43–6.50 (m, 2H), 8.72 (br, 1H).

3.4. 1-Nitro-4,7-dihydro-4,7-ethano-2*H*-isoindole (5)

To a stirred solution of ethanoisoindole (**2**; 4.00 g, 27.5 mmol) in Ac_2O (500 mL) was added slowly concd HNO_3 (1.93 mL) at −10 °C under argon and the mixture was stirred for 7 h. The mixture was poured into ice-water. The mixture was extracted with CH_2Cl_2. The organic extract was successively washed with a satd $NaHCO_3$ solution, water, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (CH_2Cl_2) to give 2.85 g (54%) of the title compound as pale yellow crystals: mp 108–109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38–1.61 (m, 4H), 3.90 (m, 1H), 4.56 (m, 1H), 6.42–6.51 (m, 2H), 6.64 (d, 1H, *J*=2.9 Hz), 9.45 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.42, 26.17, 33.09, 33.20, 114.50, 129.84, 132.54, 133.24, 133.89, 135.84; IR (KBr) ν_{max} 3386 (NH), 2955, 1586, 1363, 1092, 915, 846, 816, 680, 612 cm^{-1}; MS (EI) 190 (M^+, 41%), 162 (100), 132 (83), 116 (63), 89 (73). Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73%. Found: C, 63.06; H, 5.28; N, 14.77%.

3.5. 1-Bromo-3-nitro-4,7-dihydro-4,7-ethano-2*H*-isoindole (6)

To a stirred solution of the nitro compound (**5**; 1.00 g, 5.26 mmol) in DMF (100 mL) was added NBS (0.936 g, 5.26 mmol) at −10 °C and the mixture was stirred for 30 min. After the mixture was warmed up to 5 °C, additional NBS (240 mg, 1.35 mmol) was added. After 3 h, the mixture was poured into ice-water. The mixture was extracted with CH_2Cl_2. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was successively chromatographed on silica gel (CH_2Cl_2) and alumina (EtOAc) to give 830 mg (59%) of the title compound as pale yellow crystals: mp>158 °C (decomp.); ^{1}H NMR ($CDCl_3$,

400 MHz) δ 1.41–1.64 (m, 4H), 3.85 (m, 1H), 4.58 (m, 1H), 6.44–6.53 (m, 2H), 9.21 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.30, 25.71, 32.51, 33.52, 98.21, 130.26, 132.60, 133.91, 134.01, 135.44; IR (KBr) ν_{max} 3291 (NH), 2960, 1588, 1372, 1063, 851, 746, 694, 558 cm^{-1}; MS (EI) 270 (M^++1, 15%), 268 (15), 242 (99), 240 (100), 169 (11), 167 (11), 130 (43). Anal. Calcd for $C_{10}H_9BrN_2O_2$: C, 44.63; H, 3.37; N, 10.41%. Found: C, 44.57; H, 3.62; N, 10.43%. The single crystals were obtained by slow vapor diffusion of methanol into a solution of **6** in $CHCl_3$. Crystal formula, $C_{10}H_9BrN_2O_2$, 0.30×0.20×0.20 mm, tetragonal, space group $I4_1/a$, a=19.359(3), b=19.359(3), c=10.845(2) Å, V=4064.4(12) $Å^3$, Mo Kα, T=296 K, Z=16, ρ_{calcd}=1.759 g cm^{-3}, μ=4.025 mm^{-1}, $F(000)$=2144. 10,465 measured, 2281 unique, 1838 observed [$I>2\sigma(I)$]; R_1=0.0471 [$I>2\sigma(I)$], wR_2=0.1265 (all); GOF=1.168. CCDC no. 721548.

3.6. 1-Nitro-3-trifluoroacetyl-4,7-dihydro-4,7-ethano-2*H*-isoindole

To a stirred solution of ethyl pyrrolecarboxylate (**1**; 73 mg, 0.50 mmol) in trifluoroacetic anhydride (10 mL) was added slowly concd HNO_3 (0.035 mL) at −10 °C under argon and the mixture was stirred for 1 h. After being stirred for 1 h, the mixture was poured into ice-water. The mixture was extracted with CH_2Cl_2. The organic extract was successively washed with a satd $NaHCO_3$ solution, water, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (CH_2Cl_2) to give 61.5 mg (43%) of the title compound as pale yellow crystals: mp 111–114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46–1.70 (m, 4H), 4.40 (m, 1H), 4.65 (m, 1H), 6.48–6.59 (m, 2H), 9.80 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.04, 25.38, 32.78, 33.93, 114.69, 117.37, 117.55, 132.00, 133.24, 134.40, 134.60, 134.82, 136.15, 140.93, 170.24, 170.63, 171.02, 171.40; IR (KBr) ν_{max}; 3321 (NH), 1678, 1529, 1271, 1211, 1161, 1020, 930 cm^{-1}; MS (FAB) 287 (M^++1); HRMS (FAB) calcd for $C_{12}H_9F_3N_2O_3$+H^+: M_r=287.0644. Found: 287.0645.

3.7. Ethyl 3-benzylidenamino-4,7-dihydro-4,7-ethano-2*H*-isoindole-1-carboxylate (7a)

To a stirred solution of ethyl nitropyrrolecarboxylate (**3**; 200 mg, 0.763 mmol) in 60% aq EtOH (28 mL) was added $Na_2S_2O_4$ (532 mg, 3.06 mmol) at room temperature. After being stirred at 40 °C for 1 h, the mixture was poured into ice-water. The mixture was extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. To the residue was added a solution of benzaldehyde (71.3 mg, 0.7 mmol) in toluene (40 mL) and then the mixture was stirred at 120 °C overnight. When the mixture was cooled to room temperature, yellow precipitates were formed. Filtration gave 45.4 mg (19%) of the title compound as yellow crystals: mp 190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (t, 3H, J=7.1 Hz), 1.53–1.61 (m, 4H), 4.20 (m, 1H), 4.33 (q, 2H, J=7.1 Hz), 4.40 (m, 1H), 6.54 (m, 2H), 7.45–7.47 (m, 3H), 7.85 (m, 2H), 8.45 (br, 1H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.55, 26.15, 26.72, 33.22, 33.66, 59.99, 111.53, 122.17, 128.28, 128.78, 131.17, 134.35, 135.36, 135.60, 136.37, 138.33, 156.92, 161.56; IR (KBr) ν_{max} 3274 (NH), 1667, 1444, 1371, 1345, 1250, 1153, 756, 693 cm^{-1}; UV–vis ($CHCl_3$): λ_{max}/nm ($\log_{10}\varepsilon$): 375 (4.33), 277 (4.20); MS (EI) 320 (M^+, 28%), 293 (20), 292 (100), 246 (27), 245 (12), 219 (19), 218 (89), 90 (14). Anal. Calcd for $C_{20}H_{20}N_2O_2$+1/2H_2O: C, 72.93; H, 6.43; N, 8.50%. Found: C, 72.75; H, 6.11; N, 8.63%.

3.8. Ethyl 3-*p*-cyanobenzylidenamino-4,7-dihydro-4,7-ethano-2*H*-isoindole-1-carboxylate (7b)

To a stirred solution of ethyl nitropyrrolecarboxylate (**3**; 200 mg, 0.763 mmol) in 60% aq EtOH (28 mL) was added $Na_2S_2O_4$ (532 mg, 3.06 mmol) at room temperature. After being stirred at 40 °C for 1 h, the mixture was poured into ice-water. The mixture was extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. To the residue was added a solution of 4-cyanobenzaldehyde (91.8 mg, 0.7 mmol) in toluene (40 mL) and then the mixture was stirred at 120 °C overnight. When the mixture was cooled to room temperature, orange precipitates were formed. Filtration gave 100 mg (38%) of the title compounds as orange crystals: mp>210 °C (decomp.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, 3H, J=7.1 Hz), 1.52–1.66 (m, 4H), 4.22 (m, 1H), 4.34 (q, 2H, J=7.1 Hz), 4.40 (m, 1H), 6.54 (m, 2H), 7.72 (m, 2H), 7.94 (m, 2H), 8.54 (br, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.51, 26.03, 26.59, 33.37, 33.61, 60.25, 112.72, 113.76, 118.55, 124.27, 128.36, 132.48, 133.33, 135.30, 135.46, 138.22, 140.35, 153.14, 161.50; IR (KBr) ν_{max} 3309 (NH), 2224, 1666, 1455, 1372, 1346, 1250, 1145, 551 cm^{-1}; UV–vis ($CHCl_3$): λ_{max}/nm ($\log_{10}\varepsilon$): 397 (4.41), 280 (4.23); MS (EI) 345 (M^+, 23%), 318 (22), 317 (100), 271 (33), 244 (19), 243 (84), 115 (21). Anal. Calcd for $C_{21}H_{19}N_3O_2$+1/8H_2O: C, 72.55; H, 5.58; N, 12.09%. Found: C, 72.58; H, 5.64; N, 11.88%.

3.9. Ethyl 3-*p*-nitrobenzylidenamino-4,7-dihydro-4,7-ethano-2*H*-isoindole-1-carboxylate (7c)

To a stirred solution of ethyl nitropyrrolecarboxylate (**3**; 400 mg, 1.53 mmol) in 60% aq EtOH (56 mL) was added $Na_2S_2O_4$ (1.06 g, 6.09 mmol) at room temperature. After being stirred at 40 °C for 1 h, the mixture was poured into ice-water. The mixture was extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. To the residue was added a solution of 4-nitrobenzaldehyde (211 mg, 1.40 mmol) in toluene (80 mL) and then the mixture was stirred at 120 °C overnight. When the mixture was cooled to room temperature, orange precipitates were formed. Filtration gave 192 mg (35%) of the title compound as orange crystals: mp>225 °C (decomp.); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (t, 3H, J=7.1 Hz), 1.48–1.64 (m, 4H), 4.24 (m, 1H), 4.35 (q, 2H, J=7.1 Hz), 4.41 (m, 1H), 6.53–6.55 (m, 2H), 8.00 (m, 2H), 8.30 (m, 2H), 8.53 (br, 1H), 8.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.52, 26.04, 26.60, 33.43, 33.63, 60.31, 112.97, 124.04, 124.61, 128.58, 133.31, 135.27, 135.49, 138.26, 142.01, 148.86, 152.48, 161.48; IR (KBr) ν_{max} 3314 (NH), 3277, 1671, 1518, 1450, 1335, 1245, 1100, 844, 748, 688 cm^{-1}; UV–vis ($CHCl_3$): λ_{max}/nm ($\log_{10}\varepsilon$): 427 (4.34), 283 (4.23); MS (EI) 365 (M^+, 19%), 338 (21), 337 (100), 291 (28), 263 (31), 217 (26), 190 (17), 89 (12). Anal. Calcd for $C_{20}H_{19}N_3O_4$+1/4H_2O: C, 64.94; H, 5.31; N, 11.36%. Found: C, 64.73; H, 5.09; N, 11.40%.

3.10. *p*-Xylene-α,α'-bis(ylidenamino-3-ethoxycarbonyl-4,7-dihydro-4,7-ethano-2*H*-isoindole) (8)

To a stirred solution of ethyl nitropyrrolecarboxylate (**3**; 200 mg, 0.763 mmol) in 60% aq EtOH (28 mL) was added $Na_2S_2O_4$ (532 mg, 3.06 mmol) at room temperature. After being stirred at 40 °C for 1 h, the mixture was poured into ice-water. The mixture was extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. To the residue was added a solution of *p*-phthalaldehyde (33.5 mg, 0.25 mmol) in toluene (20 mL) and then the mixture was stirred at 120 °C overnight. When the mixture was cooled to room temperature, orange precipitates were formed. Filtration gave 40.8 mg (29%) of the title compound as orange crystals: mp>210 °C (decomp.); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (t, 6H, J=7.1 Hz), 1.56–1.64 (m, 8H), 4.24 (m, 2H), 4.35 (q, 4H, J=7.1 Hz), 4.41 (m, 2H), 6.53–6.56 (m, 4H), 7.94 (s, 4H), 8.45 (br, 2H), 8.69 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, diastereomer mixture, typical signals) δ 14.56, 26.12, 26.70, 33.38, 33.66, 38.12, 60.09, 112.05, 123.00, 128.55, 134.15, 135.42, 135.50, 138.70, 149.44, 149.75, 155.35, 166.51; IR (KBr) ν_{max}

3306 (NH), 1672, 1446, 1371, 1342, 1247, 1142, 1045, 953, 687, 526 cm^{-1}; UV–vis ($CHCl_3$): λ_{max}/nm ($\log_{10}\varepsilon$): 469 (4.60), 442 (4.73), 281 (4.41); MS (MALDI-TOF) 583 (M^++1). Anal. Calcd for $C_{34}H_{34}N_4O_4$+1/4H_2O: C, 72.00; H, 6.13; N, 9.88%. Found: C, 71.98; H, 6.09; N, 9.65%.

3.11. 4,7-Dihydro-4,7-ethano-2*H*-isoindole-1,3-bis(methylidenamino-3-ethoxycarbonyl-4,7-dihydro-4,7-ethano-2*H*-isoindole) (9)

To a stirred solution of ethyl nitropyrrolecarboxylate (**3**; 1.00 g, 3.80 mmol) in 60% aq EtOH (140 mL) was added $Na_2S_2O_4$ (2.66 g, 15.3 mmol) at room temperature. After being stirred at 40 °C for 1 h, the mixture was poured into ice-water. The mixture was extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. To the residue was added a solution of 4,7-dihydro-4,7-ethano-2*H*-isoindole-1,3-dicarbaldehyde (250 mg, 1.25 mmol) in toluene (105 mL) and then the mixture was stirred at 120 °C overnight. When the mixture was cooled to room temperature, orange precipitates were formed. The precipitates were collected by filtration and then chromatographed on silica gel (EtOAc/hexane=1/1) to give 500 mg (64%) of the title compound as red crystals: mp 165 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (t, 6H, J=7.1 Hz), 1.48–1.64 (m, 12H), 4.14 (m, 4H), 4.33 (q, 4H, J=7.1 Hz), 4.46 (m, 2H), 6.53–6.54 (m, 6H), 8.46 (m, 2H), 9.02 (br, 2H), 9.57 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, diastereoisomer mixture, typical signals) δ 14.44, 25.62, 26.16, 26.22, 26.76, 26.90, 32.78, 33.47, 33.50, 33.70, 33.71, 60.10, 111.34, 120.58, 125.65, 135.25, 135.44, 135.52, 135.62, 135.85, 137.96, 139.08, 144.74, 161.94; IR (KBr) ν_{max} 3293 (NH), 2952, 1659, 1433, 1245, 1145, 1044, 1024, 845, 689 cm^{-1}; UV–vis ($CHCl_3$): λ_{max}/nm ($\log_{10}\varepsilon$): 519 (4.52), 484 (4.64), 456 (4.51), 357 (4.25), 339 (4.28), 325 (4.24), 281 (4.30); MS (FAB) 629 (M^+). Anal. Calcd for $C_{38}H_{39}N_5O_4$+C_7H_8: C, 74.87; H, 6.56%; N, 9.70. Found: C, 75.10; H, 6.62; N, 9.28%.

3.12. Ethyl 3-*p*-nitrobenzylidenamino-2*H*-isoindole-1-carboxylate (10c)

p-Nitrobenzylidenaminoisoindole **7c** (5 mg) was heated at 230 °C under a reduced pressure (ca. 0.05 mmHg) for 30 min to give the title compound in quantitative yield: mp 261–264 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.39 (t, 3H, J=6.8 Hz), 4.38 (q, 2H, J=6.8 Hz), 7.23 (m, 1H), 7.33 (m, 1H), 8.02 (m, 2H), 8.12 (m, 4H), 9.29 (s, 1H), 13.53 (br, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.52, 59.78, 110.59, 120.60, 120.62, 120.73, 123.62, 124.15, 125.95, 127.56, 128.79, 133.97, 142.45, 148.20, 153.91, 160.72; IR (KBr) ν_{max} 3209 (NH), 1662, 1508, 1450, 1330, 1205, 1099, 838, 744 cm^{-1}; UV–vis ($CHCl_3$): λ_{max}/nm ($\log_{10}\varepsilon$): 492 (4.42), 366 (3.86), 282 (4.31); MS (FAB) 338 (M^++1), 337 (M^+). Anal. Calcd for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46%. Found: C, 63.16; H, 4.48; N, 12.23%.

3.13. *p*-Xylene-α,α′-bis(ylidenamino-3-ethoxycarbonyl-2*H*-isoindole) (11)

p-Xylylidenamino compound **8** (5 mg) was heated at 240 °C under a reduced pressure (ca. 0.05 mmHg) for 30 min to give the title compound in quantitative yield: mp 284–286 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.40 (t, 6H, J=7.1 Hz), 4.38 (q, 4H, J=7.1 Hz), 7.20 (m, 4H), 7.32 (m, 4H), 8.03 (m, 4H), 9.25 (s, 2H), 13.47 (br, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.62, 59.60, 109.31, 120.23, 120.39, 120.58, 122.95, 125.84, 127.53, 128.49, 134.64, 138.65, 156.08, 160.58; IR (KBr) ν_{max} 3203 (NH), 1654, 1484, 1407, 1358, 1269, 1232, 1193, 1901, 1307, 752 cm^{-1}; UV–vis ($CHCl_3$): λ_{max}/nm ($\log_{10}\varepsilon$): 544 (4.73), 512 (4.78), 365 (4.07), 284 (4.52); MS (FAB) 507 (M^++1), 506 (M^+). Anal. Calcd for $C_{30}H_{26}N_4O_4$: C, 71.13; H, 5.17; N, 11.06%. Found: C, 70.55; H, 5.15; N, 10.95%.

3.14. 2*H*-Isoindole-1,3-bis(methylidenamino-3-ethoxycarbonyl-2*H*-isoindole) (12)

Tris-isoindole derivative **9** (5 mg) was heated at 220 °C under a reduced pressure (ca. 0.05 mmHg) for 30 min to give the title compound in quantitative yield: 235–238 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.41 (t, 6H, J=7.3 Hz), 4.38 (q, 4H, J=7.3 Hz), 7.19 (m, 2H), 7.31 (m, 2H), 7.43 (m, 2H), 7.99 (m, 2H), 8.09 (m, 2H), 8.52 (m, 2H), 9.46 (s, 2H), 13.28 (br, 3H); IR (KBr) ν_{max} 2360, 1654, 1446, 1207, 1186, 1088, 1030, 754 cm^{-1}; UV–vis ($CHCl_3$): λ_{max}/nm ($\log_{10}\varepsilon$): 684 (4.29), 632 (4.33), 426 (4.34); MS (FAB) 545 (M^+); HRMS (FAB) calcd for $C_{32}H_{27}N_5O_4$+H^+: M_r=546.2141. Found: 546.2140.

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References and notes

1. For reviews, see: *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4; *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2.
2. Donohoe, T. J. 1H- and 2H-Isoindoles. In *Hetarenes and Related Ring Systems, Fused Five-membered Hetarenes with One Heteroatom*; Thomas, E. J., Ed.; Science of Synthesis; George Thieme: Stuttgart, 2001; Vol. 10, Chapter 14, pp 653–692.
3. Chacko, E.; Bornstein, J.; Sadella, D. J. *Tetrahedron* **1979**, *35*, 1055–1058.
4. For recent examples, see: Okujima, T.; Hashimoto, Y.; Jin, G.; Uno, H.; Ono, N. *Tetrahedron* **2008**, *64*, 2405–2411; Mack, J.; Bunya, M.; Shimizu, Y.; Uoyama, H.; Komobuchi, N.; Okujima, T.; Uno, H.; Ito, S.; Stillman, M. J.; Ono, N.; Kobayashi, N. *Chem.—Eur. J.* **2008**, *14*, 5001–5020; Uno, H.; Shimizu, Y.; Uoyama, H.; Tanaka, Y.; Okujima, T.; Ono, N. *Eur. J. Org. Chem.* **2008**, 87–98; Yamada, H.; Kuzuhara, D.; Takahashi, T.; Shimizu, Y.; Uota, K.; Uno, H.; Ono, N. *Org. Lett.* **2008**, *10*, 2947–2950.
5. Akiyama, T.; Hirao, A.; Okujima, T.; Yamada, H.; Uno, H.; Ono, N. *Heterocycles* **2007**, *74*, 835–842; Hirao, A.; Akiyama, T.; Okujima, T.; Yamada, H.; Uno, H.; Sakai, Y.; Aramaki, S.; Ono, N. *Chem. Commun.* **2008**, 4714–4716.
6. (a) Ito, S.; Ochi, N.; Murashima, T.; Uno, H.; Ono, N. *Heterocycles* **2000**, *52*, 399–411; (b) Okujima, T.; Komobuchi, N.; Uno, H.; Ono, N. *Heterocycles* **2006**, *67*, 255–267; (c) Okujima, T.; Jin, G.; Hashimoto, Y.; Uno, H.; Ono, N. *Heterocycles* **2006**, *70*, 619–626.
7. Pantoş, G. D.; Rodríguez-Morgade, M. S.; Torres, T.; Lynch, V. M.; Sessler, J. L. *Chem. Commun.* **2006**, 2132–2134 and references cited therein.
8. X-ray data were processed by CrystalClear Ver. 1.3.6. The processed data were treated with the WinGX program. Structures were solved by SIR-97, expanded by DIRDIF, and then refined by SHELXL-97. The final structures were validated by the PLATON cif check. WinGX 1.80.03: Suite for small-molecule single-crystal crystallography, University of Glasgow, Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838; SIR-97: A package for crystal structure solution and refinement, Istituto di Gristallografia, Italy; Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119; SHELXL-97: Program for the refinement of crystal structures from diffraction data, University of Göttingen, Göttingen, Germany; 'A short history of SHELX' Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122; DIRDIF2008 program system: Beurskens, P. T.; Beurskens, G.; de Gelder, R.; Garcia-Granda, S.; Gould, R. O.; Smits, J. M. M. Crystallography Laboratory, University of Nijmegen: The Netherlands, 2008. PLATON: A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherland; Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7–13.
9. Uno, H.; Ito, S.; Wada, M.; Watanabe, H.; Nagai, M.; Hayashi, A.; Murashima, T.; Ono, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4347–4355.