Chemisty on Isoindoles. Novel Synthesis of Various Functionalized Isoindoles from 2,3-Dicyanobenzaldehyde

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Various isoindoles having carbonyl, imino, cyano, formyl, and hydroxymethyl groups on the pyrrole or benzene ring were synthesized by new reactions of synthetically versatile 2,3-dicyanobenzaldehyde with a variety of nucleophiles. The obtained isoindoles were further converted to some functionalized isoindoles and phthalazine via recyclization with sodium borohydride and hydrazine. Whereas, *N*-(2,3-dicyanobenzylidene)anilines, obtained by treating 2,3-dicyanobenzaldehyde with aniline derivatives reacted with elemental sulfur in liquid ammonia or diethylamine to give 7-cyano-2,3-dihydro-3-(4-substituted phenylimino)-1*H*-isoindole-1-thiones, which were converted into 3-alkylthio-4-cyano-*N*-(4-substituted phenyl)-1*H*-isoindol-1-imines by alkylation with alkyl halides in the presence of phase-transfer catalyst.

Many procedures for the synthesis of indoles or isoindoles have been developed in the viewpoint of the synthesis of natural products and biological active compounds[1] in connection with alkaloids. There have been many reports on the synthesis of isoindoles, e.g., amination-cyclization of 1-chloro-2-(chloromethyl)benzene and 1,2-bis(bromomethyl)benzene,[2] amination-reductive cyclization of 1,2-dibenzoylbenzene,[3] and pyrolysis of triazoles.[4] For preparation of isoindoles having a carbonyl group on a pyrrole ring, numerous methods have been reported, for example, electro-reduction of phthalimide,[5] cyclization-hydrolysis of benzenedicarbonitrile,[6] amination-cyclization of 2-formylbenzoic acid,[7] and ring contraction of naphthyridinium salts.[8] Recently, Leznoff et al. reported the synthesis of isoindoles using 1,3-isoindolinedithione.[9] Thus, much attention has been centered on the synthesis of functionalized isoindoles. We also reported the preparations and reactions of isoindoles which have carbonyl and imino groups on the hetero ring.[10] It is, however, still difficult to introduce a variety of functional groups into the pyrrole and benzene rings of isoindoles. In the course of our investigations on the chemistry of isoindoles, our interests were directed to the synthesis of various isoindoles and the reactions involving recyclization. A recent report on the synthesis of 2,3-dicyanobenzaldehyde dimethylhydrazone by Potts et al. stimulated us to study the synthesis of various isoindoles,[11] since it seems to be possible that 2,3-dicyano benzaldehyde dimethylhydrazone should be hydrolyzed to give 2,3-dicyanobenzaldehyde (**1**), which might cyclize to isoindole having cyano or formyl group. As we could actually obtain **1** effectively from 2,3-dicyanobenzaldehyde *N*,*N*-dimethylhydrazone, synthesis of many heterocycles was examined by the reaction of **1** as a starting material with some nucleophiles such as amines or thiols.[11] In this paper we wish to describe a novel synthesis of various isoindoles and related compounds from **1** with some nucleophiles.

Results and Discussion

Initially, we studied the hydrolysis of 2,3-dicyanobenzaldehyde *N*,*N*-dimethylhydrazone, which was prepared by Potts and coworker.[11] The use of 12M HCl (1 M=1 mol dm^{-3}) in the hydrolysis of 2,3-dicyanobenzaldehyde dimethylhydrazone gave desired **1** in a good yield (66%) as colorless crystals, which were characterized by IR spectra obtained at 1715 (C=O) and

Table 1. Reactions of 2,3-Dicyanobenzaldehyde (**1**) with Various Nucleophiles

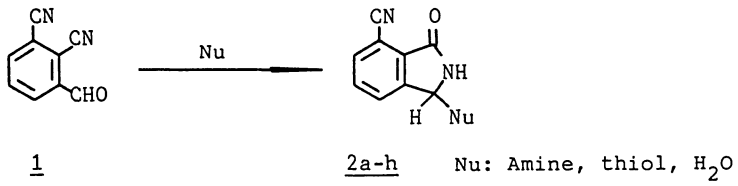
Run[a]	Reagent	Solvent[b]	React.		Yield of product/%[c]
			Temp/°C	Time/h	**2**
1	NH_3	—	20	1	43 **2a**
2	CH_3NH_2	—	20	1	47 **2b**
3	$CH_3CH_2CH_2NH_2$	—	20	1	52 **2c**
4	$CH_3CH_2CH_2NH_2$	$CHCl_3$	20	0.5	93 **2c**
5	$(CH_3)_2CHNH_2$	—	20	4	37 **2d**
6	$(CH_3)_3CNH_2$	—	20	1	46 **2e**
7	Morpholine	—	20	1	89 **2f**
8	Morpholine	$CHCl_3$[d]	20	1	100 **2f**
9	Piperidine	$CHCl_3$	20	0.5	100 **2g**
10	$CH_3C_6H_4SH$	$CHCl_3$	20	4	100 **2h**
11	H_2O	CH_3CN	20	0.5	100 **2i**

a) Substrate: 0.5 mmol. b) Solvent: 10 ml. c) Isolated yield. d) Triethylamine (1 mmol) was added as a base.

2220 (CN) cm^{-1}. Moreover, the yield of 2,3-dicyanobenzaldehyde dimethylhydrazone was improved by the Diels-Alder reaction of furfural dimethylhydrazone with fumaronitrile in the Pott's method (91%). Consequently, we could establish an effective route to **1** from furfural and also succeed in a large scale synthesis of **1**. Compound **1** readily reacted with amines, water, and thiols to give functionalized isoindoles, 3-alkylamino-7-cyano-2,3-dihydro-1*H*-isoindol-1-ones (**2**), as shown in Scheme 1. These results were summarized in Table 1.

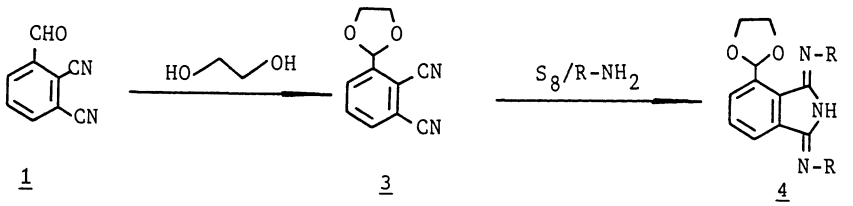
Although many isoindoles **2** were obtained in moderate yields by the reactions of **1** with a variety of amines, such as ammonia, propylamine, morpholine, and bulky amine such as *t*-butylamine without solvent (Runs 1—3 and 5—7), the use of chloroform as a solvent increase the yields of **2** (Runs 4 and 8—11). Reactions of **1** with 4-methylbenzenethiol and water gave also **2h—i** in excellent yields as shown in Table 1 (Runs 10 and 11).

In previous reports on the chemistry of elemental sulfur in liquid ammonia and amines, we have shown some novel synthesis of many heterocycles from 1,2-benzenedicarbonitrile and 2-cyanobenzaldehyde.[10] On the basis of the results, 2,3-dicyanobenzaldehyde ethylene acetal (**3**), obtained by the reaction of **1** with ethylene glycol, was treated with elemental sulfur in liquid ammonia and amines, to give 1,3-bis(alkylimino)-2,3-dihydro-4-(1,3-dioxolan-2-yl)-1*H*-isoindoles (**4**), which were formed by cyclization of two cyano groups, in high yields as shown in Scheme 2. In the absence of elemental sulfur, these reactions were not observed at all. Methyl- and propylamines gave isoindoles **4** in excellent yields (Scheme 2). The role of elemental sulfur may be interpreted in the light of the catalytic action of thiolate species formed from elemental sulfur in liquid ammonia based on our previous results.[10] These results suggest that synthesis of isoindoles having a formyl group on the benzene ring is feasible.



1 2a-h Nu: Amine, thiol, H_2O

Scheme 1.

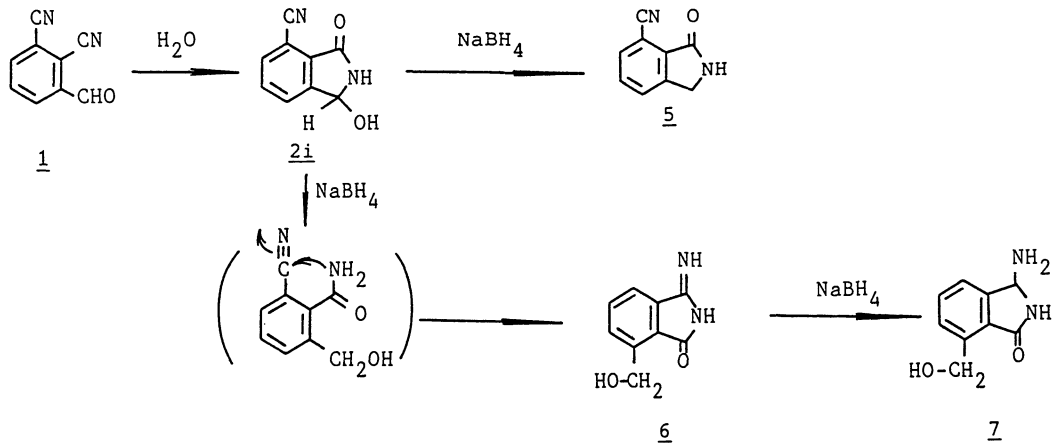


1 3 4

4a: R= CH_3-, 73% (40 °C, 3 h)

4b: R= $CH_3CH_2CH_2$-, 100% (50 °C, 3 h)

Scheme 2.



1 2i 5 6 7

Scheme 3.

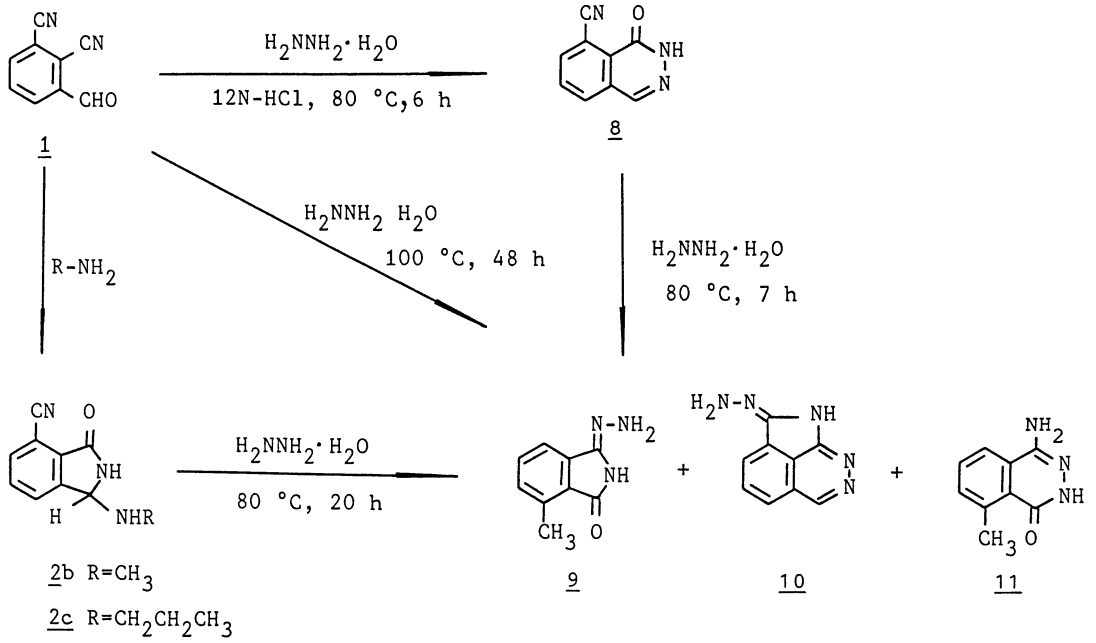
Interestingly, 7-cyano-2,3-dihydro-3-hydroxy-1*H*-isoindol-1-one (**2i**), which was obtained by the reaction of **1** with water in the presence of triethylamine, reacted with sodium borohydride in ethanol at 20 °C for 19 h, to give three new heterocyclic compounds, 7-cyano-2,3-dihydro-1*H*-isoindol-1-one (**5**, 13%), 2,3-dihydro-7-hydroxymethyl-3-imino-1*H*-isoindol-1-one (**6**, 12%), and 3-amino-2,3-dihydro-7-hydroxymethyl-1*H*-isoindol-1-one (**7**, 12%) (Scheme 3).

The compound **5** is conceivable to be a simple hydride reduction product of hydroxyl group of **2i** by sodium borohydride. The fact that **6** and **7** were obtained in this reaction is very interesting, since a recyclization step should be contained in the transformation from **2i** into **6** and **7** which was formed by further reduction of **6** with sodium borohydride as shown in Scheme 3.

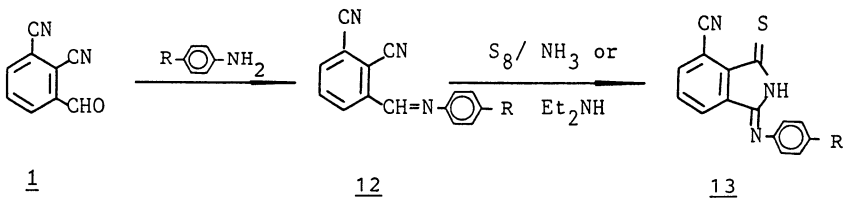
When **1** was allowed to react with hydrazine at 80 °C for 6 h in the presence of hydrochloric acid, 8-cyano-1(2*H*)-phthalazinone (**8**) was obtained in a yield of 66%. The phthalazine **8** further reacted with hydrazine at 80 °C for 7 h to give 3-hydrazono-3,4-dihydro-7-methyl-1*H*-isoindol-1-one (**9**), 1-hydrazono-1,2-dihydropyrrolo[3,4,5-de]phthalazine (**10**), and 4-amino-8-methyl-1 (2*H*)-phthalazinone (**11**) in yields of 20, 12, and 5% respectively. On the other hand, the isoindole **9** and phthalazine derivatives **10** and **11** were also directly obtained by the reaction of **1** with hydrazine at 100 °C for 48 h. These reactions are depicted in Scheme 4.

Since phthalazine derivatives are well-known to show pharmacological activities, the present reaction seems to be a very synthetically useful method.[12] During this reaction, we could observe an interesting fact that isoindoles **2b** and **2c**, which were obtained by the reaction of **1** with methyl- and propylamine, were converted to isoindole **9** and phthalazine derivatives **10** and **11** in yields of 20, 12, and 5% respectively at 80 °C for 20 h (Scheme 5). It is noteworthy that **9**, **10**, and **11** were formed in this reaction, since the conversion of **9** to **11** is the first example of that of isoindole of this type with hydrazine. The formation of **9** and **11** may be interpreted in terms of the Wolff-Kishner like reduction of amino-substituted carbon of **2b** and **2c** with hydrazine.[13]

The formyl group of **1** was readily converted into the Schiff base, *N*-(2,3-dicyanobenzylidene)anilines (**12**), by the reaction with aniline derivatives. Previously, we have shown that when *N*-(2-cyanobenzylidene)anilines[10] were treated with elemental sulfur in liquid ammonia and amines, various 1,3-bis(substituted imino)isoindolines are obtained in



Scheme 4.



Scheme 5.

excellent yields. Based on these results, our next attempt to synthesize many functionalized isoindoles was directed to the reaction of **12** with elemental sulfur in liquid ammonia and amines. Upon treating *N*-(2,3-dicyanobenzylidene)-4-methylaniline (**12a**) with elemental sulfur in liquid ammonia at 20 °C for 3 h, 7-cyano-2,3-dihydro-3-[(4-methylphenyl)imino]-1*H*-isoindole-1-thione (**13a**) was obtained in a yield of 43% (Scheme 5). The results were summarized in Table 2.

It is noteworthy that **13a** was formed by the present reaction, since such thiocarbonyl compounds have never been synthesized even by the reaction of 1,2-benzenedicarbonitrile and the related compounds with elemental sulfur in liquid ammonia and amines.[10] When diethylamine was employed instead of liquid ammonia, **13b—d** were given as reddish yellow crystals in moderate yields. Next, we examined the *S*-alkylation of **13a** with various alkyl halides in the presence of phase-transfer catalyst.[14] 3-Alkylthio-4-cyano-*N*-(4-substituted phenyl)-1*H*-isoindol-1-imines (**14a—e**) were given in moderate to high yields upon treating **13a** with methyl, benzyl, and allyl halides and ethyl bromoacetate in the presence of tetramethylammonium iodide as a phase-transfer catalyst[15] as shown in Scheme 6 and Table 3. No reaction was observed when this *S*-alkylation was

Table 2. Reactions of 4-Substituted *N*-(2,3-Dicyanobenzyliden)anilines (**12**) with Elemental Sulfur in Liquid Ammonia and Diethylamine

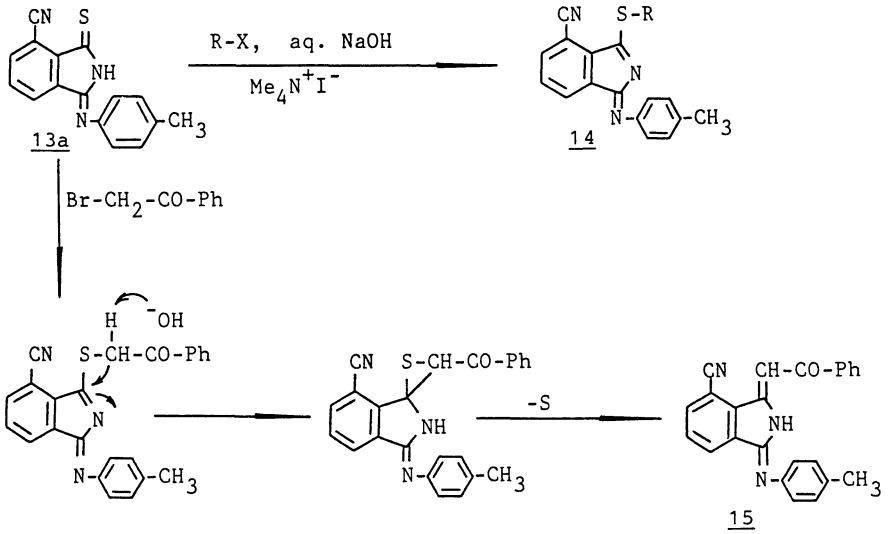
Run[a]	Substrate R		Amine	S_8	React.		Yield of product
				mg-atom	Temp/°C	Time/h	%
1	CH_3-	**12a**	NH_3	0.5	20	3	43 **13a**
2	CH_3O-	**12b**	NH_3	0.5	40	2.5	31 **13b**
3	CH_3O-	**12b**	Et_2NH	0.5	20	20	Trace **13b**
4	H-	**12c**	Et_2NH	0.5	20	10	35 **13c**
5	Cl-	**12d**	Et_2NH	0.5	20	10	32 **13d**

a) Reaction conditions: substrate, 0.5 mmol; NH_3 or Et_2NH, 10 ml.

Table 3. *S*-Alkylation of 7-Cyano-2,3-dihydro-3-[(4-methylphenyl)imino]-1*H*-isoindole-1-thione (**13a**) with Alkyl Halides in the Phase-Transfer Catalyst System

Run[a]	Alkyl halide	React.		Solvent	Yield of **14**
	R-X/R	Temp/°C	Time/min		%
1	CH_3-I	r.t.	30	CH_2Cl_2	94 **14a**
2	$C_6H_5CH_2$-Br	r.t.	45	Benzene	100 **14b**
3	CH_2=CH-CH_2-Br	r.t.	50	Benzene	96 **14c**
4	$C_2H_5OCOCH_2$-Br	r.t.	8	CH_2Cl_2	87 **14d**
5	$C_6H_5COCH_2$-Br	r.t.	3(h)	CH_2Cl_2	(45 **15**)[b]

a) Reaction conditions: substrate, 0.5 mmol; R-X, 0.8 mmol; tetramethylammonium iodide, 0.08 mmol; solvent, 15 ml. b) 4-Cyano-3-[(4-methylbenzoyl)carbonylmethylene]-*N*-(4-methylphenyl)-1*H*-isoindol-1-imine (**15**) was obtained.



Scheme 6.

carried out by using triethylamine as a base in homogeneous system.

The similar treatment of **13a** with bromomethyl phenyl ketone gave 4-cyano-3-[(4methylbenzyl)carbonylmethylene]-*N*-(4-methylphenyl)-1*H*-isoindol-1-imine (**15**) instead of *S*-alkylated product in a yield of 45%. The formation of **15** may be illustrated as follows. Thus, deprotonation of methylene proton of S-alkylated product with base, intramolecular nucleophilic addition of carbanion and then desulfurization of the resulted thiirane afford product **15** as shown in Scheme 6.[16]

In conclusion, we succeeded in a novel synthesis of many isoindoles and related compounds from 2,3-dicyanobenzaldehyde (**1**). These results suggest the synthetic versatility of 2,3-dicyanobenzaldehyde.

Experimental

Melting points are uncorrected. IR spectra were obtained on a Hitachi 295 spectrophotometer and ^{1}H NMR spectra were obtained on a Hitachi R-22 spectrometer using tetramethylsilane as an internal standard. Mass spectra and high-resolution mass spectra were taken with a Hitachi RMU-6M mass spectrometer and Hitachi M-2000 respectively. Elemental analyses were carried out with a Yanagimoto MT-3.

Materials. All reagents were obtained from Wako Pure Chemical Industries Ltd., Tokyo Kasei Co., Ltd., or Aldrich Chemical Co. The reagents were used without further purification. Wako gel C-200 was employed as silica gel for column chromatography.

Preparation of 1. Furfural dimethylhydrazone (80.8 g, 0.64 mol), prepared by the reaction of furfural with *N,N*-dimethylhydrazine according to the method described by Potts,[11] was added to the stirred solution of fumaronitrile (50 g, 0.64 mol), magnesium sulfate anhydride (10 g), and tin(IV) chloride (5.1 g) in degassed chloroform (1000 ml), which was purified by distillation on diphosphorus pentoxide, under nitrogen atmosphere. After reflux of the solution for 78 h, the mixture was cooled at room temperature, washed three times with aq. sodium hydrogencarbonate, and dried over sodium sulfate, and then the solvent was removed by evaporation under vacuum. Column chromatography of the residue on silica gel using dichloromethane as an eluent gave yellow crystals, 2,3-dicyanobenzaldehyde dimethylhydrazone, 101 g (88%). Mp 163 °C (from ethanol) (lit,[11] green needle, 165—166 °C from ethanol).

To a solution of 2,3-dicyanobenzaldehyde dimethylhydrazone (0.992 g, 5 mmol) in acetonitrile (200 ml) was added dropwise 150 ml of aq. 12 M HCl at room temperature. After completion of addition, the reaction was immediately quenched with dichloromethane (700 ml) and the organic layer was washed with aq. sodium hydrogencarbonate (200 ml) and water (200 ml×2) and then dried over sodium sulfate. Evaporation of the solvent followed by column chromatography of the residue on silica gel (Wako gel C-200) using dichloromethane as an eluent gave colorless crystals (**1**, 0.765 g, 98%).

1: Colorless crystals, mp 117 °C (from $CHCl_3$-hexane); IR (KBr) 1715 and 2220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.90 (t, 1H, J=7.7, arom), 8.07 (dd, 1H, J=7.7 and 1.5 Hz, arom), 8.29 (dd, 1H, J=7.7 and 1.5 Hz, arom), and 10.31 (s, 1H, CHO); MS (70 eV) m/z 156 (M^+). Found: C, 69.25; H, 2.47; N, 18.05%. Calcd for $C_9H_4N_2O$: C, 69.23; H, 2.58; N, 17.94%.

Reaction of 1 with Ammonia and Amines. To an evacuated all titanium autoclave containing **1** (156 mg) was charged 10 ml of ammonia or methylamine from needle valve to needle valve. The mixture in the autoclave was allowed to react at 20 °C for 1 h with stirring magnetically. After completion of the reaction, ammonia or methylamine was removed by evaporation and the residue was chromatographed on silica gel using chloroform as an eluent, to give two products **2a** or **2b**. In the case of other amine, a usual flask was employed as a reaction vessel.

2a: Colorless crystals; mp 260 °C (decomp); IR (KBr) 1600, 1700, 2220, and 3000 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=4.04 (brs, 2H, NH_2), 5.41 (S, 1H, CH), and 7.68—8.00 (m, 4H, arom); MS (70 eV) m/z 173 (M^+). Found: C, 62.22; H, 4.11; N, 24.28%. Calcd for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.26%.

2b: Colorless crystals; mp 155 °C (from $CHCl_3$-MeOH); IR (KBr) 1720, 2220, 2900, 3170, and 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.00 (s, 1H, NH), 2.40 (s, 3H, CH_3), 5.70 (s, 1H, CH), 7.70—8.03 (m, 3H, arom), and 8.55 (brs, 1H, NH); MS (70 eV) m/z 187 (M^+). Found: C, 63.78; H, 4.99; N, 22.27%. Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45%.

2c: Colorless crystals; mp 150 °C (from $CHCl_3$-hexane); IR (KBr) 1720, 2220, 2925, 3175, and 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.90 (t, 3H, J=7.3 Hz, CH_3), 1.46 (sext, 2H, J=7.3 Hz, CH_2), 1.90 (s, 1H, NH), 2.60 (q, 2H, J=7.3 Hz, CH_2), 5.63 (s, 1H, CH), and 7.60—7.96 (m, 4H, arom and NH); MS (70 eV) m/z 215 (M^+). Found: C, 66.58; H, 5.99; N, 19.58%. Calcd for $C_{12}H_{12}N_3O$: C, 66.96; H, 6.09; N, 19.52%.

2d: Colorless crystals; mp 203 °C (decomp); IR (KBr) 1700, 2245, 2975, and 3180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.08 (d, 3H, J=7.0 Hz, CH_3), 1.20 (d, 3H, J=7.0 Hz, CH_3), 1.66 (brs, 1H, NH), 3.10 (hept, 1H, J=7.0 Hz, CH), 5.53 (brs, 1H, CH), and 7.55—7.95 (m, 4H, arom and NH); MS (70 eV) m/z 215 (M^+). Found: C, 67.02; H, 6.08; N, 19.63%. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52%.

2e: Colorless crystals; mp 188 °C (decomp); IR (KBr) 1735, 2245, 2970, and 3200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.30 (s, 9H, CH_3), 5.53 (brs, 1H, CH), and 7.53—8.20 (m, 4H, arom and NH); MS (70 eV) m/z 229 (M^+). Found: C, 68.47; H, 6.66; N, 18.17%. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33%.

Reaction of 1 with Morpholine or Piperidine. To a solution of 78 mg (5 mmol) of **1** in dried chloroform (1 ml) was added morpholine or piperidine (0.1 ml, ca. 1 mmol) and then the mixture was stirred at 20 °C for 1 h. After evaporation of the solvent, the residue was chromatographed on silica gel using chloroform-methanol (v/v, 15/1) as an eluent, giving **2f** or **2g** as colorless crystals.

2f: Mp 216 °C (from AcOEt); IR (KBr) 1712, 2235, 2850, and 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.55 (t, 4H, J=5.0 Hz, CH_2), 3.70 (t, 4H, J=5.0 Hz, CH_2), 5.45 (s, 1H, CH), and 7.53—7.93 (m, 4H, arom and NH); MS (70 eV) m/z 243 (M^+). Found: C, 63.94; H, 5.28; N, 17.25%. Calcd for $C_{13}H_{13}N_3O$: C, 64.19; H, 5.39; N, 17.27%.

2g: Mp 193 °C (decomp) (from AcOEt); IR (KBr) 1600, 2230, 2855, 2940, and 3175 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.30—

1.71 (m, 6H, $-CH_2CH_2CH_2-$), 2.16—2.80 (m, 4H, CH_2), 5.42 (s, 1H, CH), 7.55 (brs, 1H, NH), and 7.60—7.92 (m, 3H, arom); MS (70 eV) m/z 241 (M^+). Found: C, 69.68; H, 6.29; N, 17.38%. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41%.

Reaction of 1 with 4-Methylbenzenethiol. The mixture of **1** (78 mg, 0.5 mmol), 4-methylbenzenethiol (124 mg, 1 mmol), and triethylamine (101 mg, 1 mmol) in chloroform (2 ml) was stirred at 20 °C for 4 h under nitrogen atmosphere. After evaporation of triethylamine and chloroform, chromatography of the residue on silica gel gave colorless crystals, **2h**.

2h: Mp 168 °C (from AcOEt); IR (KBr) 1700, 2250, 2900, and 3200 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.25 (s, 3H, CH_3), 6.00 (s, 1H, CH), 6.50 (d, 2H J=8.0 Hz, arom), 7.21 (d, 2H, J=8.0 Hz, arom), 7.50 (m, 2H, arom and NH), and 7.85 (dd, 2H, J=8.0 Hz and 8.0 Hz, arom); MS (70 eV) m/z 157 (M^+−-S-C_6H_4-CH_3). Found: C, 68.48; H, 4.28; N, 9.79%. Calcd for $C_{11}H_{12}N_2OS$: C, 68.55; H, 4.31; N, 9.99%.

Reaction of 1 with Water. To a solution of **1** (78 mg, 0.5 mmol) in acetonitrile (1 ml) was added 18 mg of water (1 mmol) and 101 mg of triethylamine (1 mmol). The mixture was stirred at 20 °C for 30 min and then the solvent was removed under vacuum. Chromatography of the residue on silica gel using chloroform-methanol, (v/v 10/1) as eluent gave **2i** (colorless crystals).

2i: Mp. 283 °C (from EtOH); IR (KBr) 1720, 2230, and 3400 cm^{-1}; ^1H NMR (DMSO-d_6) δ=5.91 (d, 1H, J=9.0 Hz, CH), 6.50 (d, 1H, J=9.0 Hz, OH), 7.65—8.20 (m, 3H, arom), and 9.24 (brs, 1H, NH); MS (70 eV) m/z 174 (M^+). Found: C, 61.77; H, 3.59; N, 15.89%. Calcd for $C_9H_6N_2O_2$: C, 62.07; H, 3.47; N, 16.08%.

Preparation of 3. The mixture of 0.350 g (2.24 mmol) of **1**, 0.278 g (4.48 mmol) of ethyleneglycol, and 5 mg (0.03 mmol) of 4-methylbenzenesulfonic acid in 20 ml of benzene was heated under reflux using Dean-Stark trap for 2 h. After cooling to room temperature, the benzene solution was washed with aq. sodium bicarbonate (10%) and water (10 ml×3) and then dried over sodium sulfate. Evaporation of the solvent gave **3** as colorless crystals.

3: Mp 118 °C (from EtOH); IR (KBr) 2235, 2240, and 1880 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.05—4.32 (m, 4H, $-CH_2-$), 6.00 (s, 1H, CH), and 7.62—7.95 (m, 3H, arom); MS (70 eV) m/z 200 (M^+). Found: C, 66.14; H, 4.02; N, 14.06%. Calcd for $C_{11}H_8N_2O_2$: C, 66.00; H, 4.03; N, 13.99%.

Reaction of 3 with Elemental Sulfur in Amines. Typical procedure: The mixture of 100 mg (0.5 mmol) of **3**, 16 mg (0.5 mg-atom) of elemental sulfur, and 10 ml of propylamine was allowed to react at 50 °C for 3 h. After removal of propylamine under vacuum, chromatography of the reaction mixture on silica gel using chloroform-methanol (v/v, 30/1) as an eluent gave colorless crystals, 1,3-di-(propylimino)-2,3-dihydro-4-ethyleneglycoxymethyl-1*H*-isoindole (**4b**) (0.193 g, 100%).

4a: Mp 169 °C (decomp) (from EtOAc); IR (KBr) 1525, 1660, 2900, and 3250 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.30 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 4.15 (s, 4H, $-CH_2CH_2-$), 6.26 (brs, 1H, CH), and 7.35—7.90 (m, 4H, arom and NH); MS (70 eV) m/z 245 (M^+). Found: C, 63.76; H, 6.22;, N, 16.88%. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13%.

4b: Mp 116 °C (decomp) (EtOH-ether); IR (KBr) 1580, 1660, 2950, and 3225 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90—1.10 (m, 6H, CH_3), 1.50—2.00 (m, 4H, CH_2), 3.60—3.90 (m, 4H, CH_2), 4.10 (s, 4H, $-CH_2CH_2-$), 6.28 (brs, 1H, CH), and 7.30—8.13 (m, 4H, arom and NH); MS (20 eV) m/z 301 (M^+). Found: C, 67.61; H, 7.78; N, 13.84%. Calcd for $C_{13}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94%.

Reaction of 2i with Sodium Borohydride. To a suspension of 0.595 g (3.4 mmol) of **2i** in dry methanol (35 ml) was added slowly 1.034 g (27.4 mmol) of sodium borohydride for 30 min. The mixture was stirred at room temperature for 19 h, neutralized with 12M HCl, and then filtered. Evaporation of the solvent of filtrate followed by chromatography on silica gel gave three products, **5** (71 mg, 13%) , **6** (73 mg, 12%), and **7** (73 mg, 12%).

5: Mp 140 °C (from AcOEt); IR (KBr) 1700, 2220, and 3270 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.35 (s, 2H, CH_2) and 7.60—8.20 (m, 4H, arom and NH); MS (70 eV) m/z 158 (M^+). Found: C, 68.51; H, 3.81; N, 17.64%. Calcd for $C_9H_6N_2O$: C, 68.35; H, 3.82; N, 17.71%.

6: Mp 196 °C (decomp) (from EtOH); IR (KBr) 1670, 1740, and 3240 cm^{-1}; ^1H NMR (DMSO-d_6) δ=4.96 (s, 2H, CH_2), 5.31 (brs, 1H, OH), 6.32 (brs, 1H, NH), 7.45—8.06 (m, 3H, arom) , and 9.00 (brs, 1H, NH); MS (70 eV) m/z 176 (M^+). Elemental analysis for **6** was not available because of the lability and difficulty of further purification.

7: Mp 245 °C (decomp) (from EtOH); IR (KBr) 1660, 2880, 3240, 3350, and 3450 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.30 (brs, 2H, NH_2), 4.93 (d, 2H, J=7.5 Hz, $-CH_2-O-$), 5.35 (s, 1H, CH), and 5.46 (t, 1H, J=7.5 Hz, OH), 7.40—7.70 (m, 3H, arom), and 8.60 (brs, 1H, NH); MS (70 eV) m/z 178 (M^+). Found: C, 60.47; H, 5.65; N, 15.25%. Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.66; N, 15.72%.

Reaction of 1 with Hydrazine Hydrate in the Presence of Acid. A mixture of **1** (78 mg, 0.5 mmol), hydrazine hydrate (89 mg, 1.78 mmol), and 12 M HCl (100 mg, 2.7 mmol) in benzene (1 ml) was heated under reflux at 6 h. The precipitate obtained upon quenching with water (1.25 ml) was filtered and washed with aq. 5% sodium hydrogencarbonate and water (20 ml). Compound **8** (56 mg, 66%) was obtained as colorless crystals by recrystallization from ethanol.

8: Mp 274 °C (from EtOH); IR (KBr) 1675, 2220, 2900, 3020, 3170, and 3400 cm^{-1}; ^1H NMR (DMSO-d_6) δ=7.95—8.40 (m, 3H, arom), 8.43 (s, 1H, -CH=), and 12.95 (brs, 1H, NH); MS (70 eV) m/z 171 (M^+). Found: C, 63.14; H, 2.87; N, 24.29%. Calcd for $C_9H_5N_3O$: C, 63.16; H, 2.94; N, 24.55%.

Reaction of 1 with Hydrazine Hydrate in the Absence of Acid. A mixture of **1** (78 mg, 0.5 mmol) and hydrazine hydrate (5 ml) was heated at 100 °C for 24 h and cooled at room temperature. Removal of hydrazine hydrate under vacuum and chromatography on silica gel using chloroform-methanol (v/v, 5/1) gave two products **9** (34 mg, 40%), **10** (14 mg, 15%), and **11** (4 mg, 5%).

9: Mp 281 °C (from MeOH); IR (KBr) 1480, 1560, 1590, 1640, 2920, 3200, and 3325 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.90 (s, 3H, CH_3), 5.80 (brs, 2H, NH_2), 7.50—8.00 (m, 3H, arom), and 11.26 (brs, 1H, NH); MS (20 eV) m/z 175 (M^+). Found: C, 61.70; H, 5.21; N, 23.93%. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99%.

10: Mp 315 °C (from MeOH); IR (KBr) 1475, 1540, 1610, 1620, 2850, 3100, and 3410 cm^{-1}; ^1H NMR (DMSO-d_6) δ=5.98 (brs, 2H, NH_2), 7.45—7.90 (m, 3H, arom), 8.06 (s, 1H, =CH), and 11.72 (brs, 1H, NH); MS (20 eV) m/z 185 (M^+). Found: m/z 185.0702. Calcd for $C_9H_7N_5$: M, 185.1880.

11: Mp 281 °C (decomp) (from MeOH); IR (KBr) 1480,

1560, 1640, 2920, 3200, and 3325 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.90 (s, 3H, CH_3), 5.80 (brs, 2H, NH_2), 7.50—8.00 (m, 3H, arom), and 11.26 (brs, 1H, NH); MS (70 eV) m/z 175 (M^+). Found: C, 61.70; H, 5.21; 23.93%. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99%.

Reaction of 2b or 2c with Hydrazine Hydrate. A mixture of 0.576 mmol of **2b** or **2c** and 2 ml of hydrazine hydrate (100%) was heated at 80 °C for 20 h. After cooling the mixture and removal hydrazine under vacuum, chromatography of the mixture on silica gel gave **9** (20 mg, 20%), **10** (13 mg, 12%), and **11** (5 mg, 5%).

Preparation of 12 from 1. Typical Procedure: To a solution of **1** (156 mg, 1 mmol) in benzene (10 ml) was added 4-methylaniline (107 mg, 1 mmol) and the mixture was allowed to react with stirring at room temperature for 6 h under monitoring by tlc. After completion of the reaction, benzene was removed by evaporation under vacuum. Column chromatography of the residue on silica gel using dichloromethane afforded pale yellow crystals, **12a** (181 mg, 74%).

12a: Mp 161 °C (from EtOH); IR (KBr) 1505 and 2248 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.38 (s, 3H, CH_3), 7.22 (s, 4H, arom), 7.63—7.93 (m, 2H, arom), 8.43—8.63 (m, 1H, arom), and 8.82 (s, 1H, CH); MS (70 eV) m/z 245 (M^+). Found: C, 78.77; H, 4.44; N, 16.79%. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13%.

12b: Mp 168 °C (from EtOH); IR (KBr) 1240, 1500, and 2225 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.85 (s, 3H, CH_3), 6.81—7.48 (m, 4H, arom), 7.66—7.93 (m, 2H, arom), 8.51—8.66 (m, 1H, arom), and 8.86 (s, 1H, CH); MS (70 eV) m/z 261 (M^+). Found: C, 73.81 ; H, 4.24; N, 16.15%. Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08%.

12c: Mp 149 °C (from EtOH); IR (KBr) 810, 1480, and 2225 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.13—7.56 (m, 5H, arom), 7.65—7.97 (m, 2H, arom), 8.52—8.67 (m, 1H, arom), and 8.85 (s, 1H, CH); MS (70 eV) m/z 231 (M^+). Found: C, 78.03; H, 3.77; N, 18.28%. Calcd for $C_{15}H_9N_3$: C, 77.91; H, 3.92; N, 18.17%.

12d: Mp 184 °C (from EtOH); IR (KBr) 1090, 1480, and 2225 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.15—7.55 (m, 4H, arom), 7.72—8.03 (m, 2H, arom), 8.52—8.66 (m, 1H, arom), and 8.83 (s, 1H, CH); MS (70 eV) m/z 266 (M^+). Found: C, 68.14; H, 2.99; N, 15.78%. Calcd for $C_{15}H_8N_3Cl$: C, 67.81; H, 3.03; N, 15.81%.

Reaction of 12 with Elemental Sulfur in Liquid Ammonia or Diethylamine. **12a** (123 mg, 0.5 mmol) and elemental sulfur (16 mg, 0.5 mg atom) were taken into an all-titanium autoclave. After evacuation of the autoclave, liquid ammonia (10 ml) was charged or diethylamine (10 ml) was taken into the autoclave directly. The mixture was stirred at 0 °C for 8 h by magnetic mean. Evaporation of ammonia or diethylamine followed by chromatography of the residue on silica gel using dichloromethane as an eluent gave reddish yellow crystals, **13a** (111 mg, 80%).

13a: Mp 225 °C (from EtOH); IR (KBr) 1660, 2240, and 3200 cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.39 (s, 3H, CH_3), 6.80—7.63 (m, 4H, arom), 7.65—8.80 (m, 3H, arom), and 12.91 (brs, 1H, NH); MS (70 eV) m/z 277 (M^+). Found: C, 69.29; H, 3.92; N, 14.96%. Calcd for $C_{16}H_{11}N_3S$: C, 69.29; H, 4.00; N, 15.15%.

13b: Mp 237 °C (from $CHCl_3$); IR (KBr) 1650, 2220, and 3250 cm^{-1}; ^1H NMR (DMSO-d_6) δ=4.80 (s, 3H, CH_3), 6.90—7.33 (m, 4H, arom), 7.62—8.37 (m, 3H, arom), and 12.74 (brs, 1H, NH); MS (70 eV) m/z 293 (M^+). Found: C, 65.39; H, 3.66; N, 14.01%. Calcd for $C_{16}H_{11}N_3OS$: C, 65.51; H, 3.78; N, 14.32%.

13c: Mp 225 °C (from EtOH); IR (KBr) 1680, 2240, and 3200 cm^{-1}; ^1H NMR (DMSO-d_6) δ=6.75—7.80 (m, 5H, arom), 7.83—8.39 (m, 3H, arom), and 12.91 (brs, 1H, NH); MS (70 eV) m/z 263 (M^+). Found: C, 68.58; H, 3.26; N, 15.98%. Calcd for $C_{15}H_9N_3S$: C, 68.42; H, 3.45; N, 15.96%.

13d: Mp 226 °C (from EtOH); IR (KBr) 1670, 2230, and 3200 cm^{-1}; ^1H NMR (DMSO-d_6) δ=6.90—7.63 (m, 4H, arom), 7.70—8.40 (m, 3H, arom), and 12.89 (brs, 1H, NH); MS (70 eV) m/z 298 (M^+). Found: C, 60.36; H, 2.73; N, 13.75%. Calcd for $C_{15}H_8N_3SCl$: C, 60.51; H, 2.71; N, 14.11%.

***S*-Alkylation of 13a with Alkyl Halide in the Phase-Transfer System.** Typical Procedure: To a solution of **13a** (111 mg, 0.4 mmol) and tetramethylammonium iodide (29 mg, 0.08 mmol) in dichloromethane (15 ml) was added methyl iodide (114 mg, 0.8 mmol) and aq. 20% sodium hydroxide (3 ml). The solution was stirred vigorously at room temperature for 30 min. Water (10 ml) was added to the solution followed by extracted with dichloromethane (10 ml×5). Washing with water and drying of the organic layer on sodium sulfate and evaporation of dichloromethane and subsequent chromatography of the residue on silica gel using chloroform as an eluent gave colorless crystals, 4-cyano-*N*-(4-methylphenyl)-3-(methylthio)-1*H*-isoindol-1-imine (**14a**) (109 mg, 94%).

14a: Mp 178 °C (from hexane-AcOEt)); IR (KBr) 1345, 1445, and 2230 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.38 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 6.66—7.80 (m, 6H, arom), and 8.02—8.26 (m, 1H, arom); MS (70 eV) m/z 291 (M^+). Found: C, 70.37; H, 4.45; N, 14.32%. Calcd for $C_{17}H_{13}N_3S$: C, 70.08; H, 4.50; N, 14.42%.

14b: Mp 184 °C (from hexane-AcOEt); IR (KBr) 1220, 1340, 1440, and 2225 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.39 (s, 3H, CH_3), 4.58 (s, 2H, CH_2), 7.10—7.78 (m, 11H, arom), and 8.06—8.23 (m, 1H, arom); MS (70 eV) m/z 367 (M^+). Found: C, 75.04; H, 4.60; N, 11.25%. Calcd for $C_{23}H_{17}N_3S$: C, 75.18; H, 4.66; N, 11.44%.

14c: Mp 139 °C (from hexane-AcOEt); IR (KBr) 1440, 1580, and 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.39 (s, 3H, CH_3), 4.04 (d, 2H, J=7.5 Hz, CH_2), 5.23 (d, 1H, J=10.5 Hz, =CH), 5.38 (d, 1H, J=16.5 Hz, =CH), 5.01—6.30 (m, 1H, =CH), 7.08—7.81 (m, 6H, arom); 8.10—8.30 (m, 1H, arom); MS (70 eV) m/z 317 (M^+). Found: C, 72.34; H, 4.71; N, 12.86%. Calcd for $C_{19}H_{15}N_3S$: C, 71.90; H, 4.76; N, 13.24%.

14d: Mp 165 °C (from hexane-AcOEt); IR (KBr) 1445, 1740, 2225 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.22 (t, 3H, J=7.5 Hz, CH_3), 2.36 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 4.18 (q, 2H, J=7.5 Hz, CH_2), 7.06—7.83 (m, 6H, arom), and 8.06—8.26 (m, 1H, arom); MS (70 eV) 363 (M^+). Found: C, 66.41; H, 4.72; N, 11.38%. Calcd for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.72; N, 11.56%.

15: Mp 225 °C (from EtOH); IR (KBr) 1260, 1650, 2225, and 3325 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.36 (s, 3H, CH_3), 6.83—8.40 (m, 13H, arom and CH), and 11.46 (brs, 1H, NH); MS (70 eV) m/z 363 (M^+). Found: C, 79.44; H, 4.65; N, 11.44%. Calcd for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.72; N, 11 56%.

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