HETEROCYCLES, Vol. 75, No. 7, 2008, pp. 1779 - 1788. © The Japan Institute of Heterocyclic Chemistry
Received, 7th February, 2008, Accepted, 17th March, 2008, Published online, 18th March, 2008. COM-08-11359

SYNTHESIS OF 1*H*-ISOINDOLES BY IODOAMINATION OF 2-VINYLBENZYLIDENAMINES

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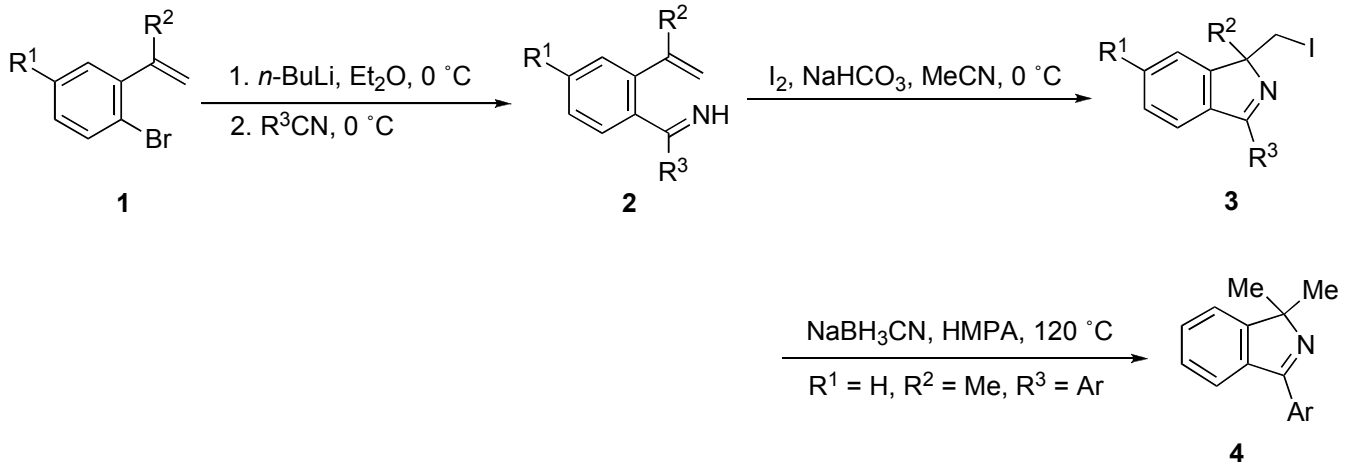
Abstract - An efficient method for the synthesis of 1*H*-isoindole derivatives is described. It is based on iodine mediated cyclization of aryl(or alkyl)(2-vinylbenzyliden)amine derivatives, which can be easily prepared from the reactions of 2-lithiostyrene derivatives with various nitriles, furnishing the corresponding iodoamination products, 3-aryl(or alkyl)-1-iodomethyl-1*H*-isoindole derivatives, in satisfactory overall yields.

Current efforts in our laboratory focus on the development of convenient methods for the synthesis of fused heterocyclic compounds utilizing styrene derivatives carrying an appropriate functional group at the 2-position.[1] We have recently demonstrated that iodine mediated cyclization of styrene derivatives bearing appropriate groups containing an NH moiety at the 2-position affords the corresponding fused nitrogen heterocycles.[2] In studies designed to further explore the utility of the iodine mediated cyclization in the synthesis of fused nitrogen heterocycles, we examined reactions of aryl(or alkyl)(2-vinylbenzyliden)amine derivatives (**2**), which could be easily prepared by treatment of 2-lithiostyrene derivatives with various nitriles, with iodine. We found that the reactions gave 1-iodomethyl-1*H*-isoindole derivatives (**3**). This is a rare example of the cyclization by attack of imino nitrogen on an iodonium ion, though Larock *et al.* have reported a synthesis of 4-iodoisoquinolines by iodine mediated cyclization of *tert*-butylimines of *o*-(1-alkynyl)benzaldehydes.[3] Displacement of the iodo moiety with hydrogen or sulfenyl groups proved to be achieved successfully to afford 1,1-dimethyl-1*H*-isoindole (**4**) or 1-sulfenylmethyl-1*H*-isoindole derivatives (**5**), respectively. The purpose of this paper is to disclose the results of these reactions, which provide a facile method for the construction of 1*H*-isoindole derivatives. Several methods for the preparation of 1*H*-isoindole derivatives have been reported.[4] These are based on electrophilic ring closure of 2-azaallenium salts,[4c] rearrangement of 3-arylisoquinolin-4(1*H*)-ones,[4d] and heat or microwave irradiation of ortho-substituted aryl-oximes.[4e] Therefore, development of any new and simple method is meaningful, because this class of molecules may be of biological interest.

The synthesis of 1*H*-isoindole derivatives (**3**), (**4**), and (**5**) from 2-bromostyrene derivatives **1** were conducted through formation of 2-vinylbenzylidenamine derivatives (**2**), as illustrated in Scheme 1. The 2-vinylbenzylidenamine derivatives (**2**) were prepared by treatment of 2-lithiostyrene derivatives, which were generated from the bromine-lithium exchange between 2-bromostyrene derivatives (**1**) and butyllithium, with various nitriles. After usual aqueous workup, these imine derivatives (**2**) were used in the next iodoamination step without any purification. Thus, treatment of the crude products (**2**) with iodine in acetonitrile in the presence of sodium hydrogencarbonate provided the corresponding 1-iodomethyl-1*H*-isoindoles (**3**) in generally satisfactory overall yields from 2-bromostyrene derivatives (**1**) as summarized in the Table 1. An aliphatic nitrile, such as 2-methylpropanenitrile, was usable in this procedure (Entry 5), but the yield of the desired product (**3e**) was rather lower than those of aryl cyanides, because the iodoamination reaction gave a somewhat complicated mixture of products.



Scheme 1

We next examined the reduction of the iodo moiety of 1-iodomethyl-1*H*-isoindoles (**3**). First, 1-iodomethyl-1-methyl-3-phenyl-1*H*-isoindole (**3a**) was allowed to react with tributyltin hydride in benzene. The reaction, however, resulted in complete recovery of the starting material even in the presence of a catalytic amount of AIBN at reflux temperature. Later, the reduction of **3a** was found to be accomplished by employing sodium cyanoborohydride. Thus, compound (**3a**) was treated with this reagent in HMPA[5] at 120 ˚C to give the desired product, 1,1-dimethyl-3-phenyl-1*H*-isoindole (**4a**), in moderate-to-fair yield (Table 1, Entry 1). In this manner, other 1-iodomethyl-1-methyl-1*H*-isoindoles (**3b-d**) were converted into the corresponding 1,1-dimethyl-1*H*-isoindoles (**4b-d**), respectively, in comparable yields (Table 1, Entries 2–4). It is notable that reduction of 1-aryl-1-iodomethyl-1*H*-isoindole derivatives (**3f-h**) with sodium cyanoborohydride under the same reaction conditions was unsuccessful, affording an intractable mixture of products in each case. However, we have no explanation of the reason

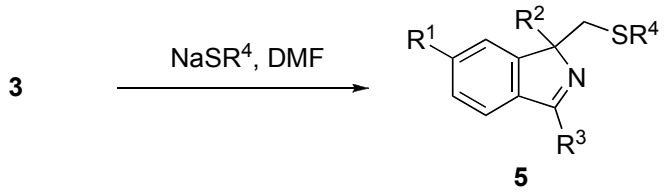
for this.

Table 1. Preparation of 1*H*-Isoindole Derivatives (**3**) and (**4**)

Entry	**1**	R^3 in RCN	**3** (Yield/%)[a]	**4** (Yield/%)[b]
1	**1a** (R^1 = H, R^2 = Me)	Ph	**3a** (68)	**4a** (62)
2	**1a**	2-FC_6H_4	**3b** (59)	**4b** (69)
3	**1a**	4-ClC_6H_4	**3c** (61)	**4c** (75)
4	**1a**	4-$CF_3C_6H_4$	**3d** (55)	**4d** (71)
5	**1a**	*i*-Pr	**3e** (34)	c
6	**1b** (R^1 = H, R^2 = Ph)	Ph	**3f** (59)	d
7	**1c** (R^1 = H, R^2 = 4-ClC_6H_4)	Ph	**3g** (59)	d
8	**1d** (R^1 = H, R^2 = 4-$MeOC_6H_4$)	Ph	**3h** (57)	d
9	**1d**	4-FC_6H_4	**3i** (58)	c
10	**1e** (R^1 = OMe, R^2 = Me)	Ph	**3j** (57)	c

[a]Isolated yields from **1**. [b]Isolated yields. [c]The reduction was not carried out. [d]An intractable mixture of products was obtained.

Subsequently, to explore the utility of the 1-iodomethyl-1*H*-isoindoles (**3**), a series of sulfenylation studies were conducted. It was found that the sulfenyl substitution of **3** proceeded successfully on treatment with sodium thiolates, generated by the reaction of various thiols with sodium hydride, in DMF at the temperature shown in Table 2, to afford the corresponding 1-sulfenylmethyl-1*H*-isoindole derivatives (**5**) in moderate to fair yields (Scheme 2). Heterocyclic thiols, such as pyridine-2-thiol and 4,6-dimethylpyrimidin-2-thiol, proved to be usable in this sulfenylation procedure (Entries 3 and 4, respectively). Unfortunately, however, no reaction was observed in the reaction of **3a** with sodium *N*-methylacetoanilide at 80 ˚C, and raising the reaction temperature resulted in the decomposition of **3a**.



Scheme 2

In conclusion, we have demonstrated a convenient synthesis of 1*H*-isoindole derivatives from readily available starting materials. Since the method is experimentally simple, it may be of value in heterocycle synthesis. Applications of the present methodology to the synthesis of 1*H*-isoindoles carrying various functional groups are currently underway in our laboratory.

EXPERIMENTAL

The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus

Table 2. Substitution of 1-Iodomethyl-1*H*-isoindoles (**3**) with Thiolates Leading to **5**

Entry	**3**	R^4	Temp	Time	**5** (Yield/%)[a]
1	**3a**	Ph	rt	2.5 h	**5a** (77)
2	**3a**	$(CH_2)_2NMe_2$	rt	1 h	**5b** (61)
3	**3c**	pyridin-2-yl	60 ˚C	3 h	**5c** (43)
4	**3c**	4,6-dimethylpyrimidin-2-yl	60 ˚C	4 h	**5d** (67)
5	**3d**	Bn	rt	1 h	**5e** (74)
6	**3f**	$(CH_2)_2OH$	rt	1 h	**5f** (56)
7	**3g**	$(CH_2)_2OH$	rt	2.5 h	**5g** (61)
8	**3h**	Ph	80 ˚C	5 h	**5h** (63)
9	**3i**	$(CH_2)_2OH$	rt	4 h	**5i** (52)
10	**3i**	CH_2CO_2Et	rt	4 h	**5j** (64)
11	**3j**	Ph	rt	12 h	**5k** (75)

[a]Isolated yields.

and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference in $CDCl_3$ with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution mass spectra were recorded on a JEOL JMS-AX505 HA spectrometer. Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}.

Starting Materials. 1-Bromo-2-(1-methylethenyl)benzene (**1a**),[6] 1-bromo-2-(1-phenylethenyl)benzene (**1b**),[7] 1-bromo-2-[1-(4-chlorophenyl)ethenyl]benzene (**1c**),[1h] 1-bromo-4-methoxy-2-(1-methylethenyl)benzene (**1e**),[2a] and (2-bromophenyl)(4-methoxyphenyl)methanone[8] were prepared by the appropriate reported procedures. All other chemicals used in this study were commercially available.

1-Bromo-2-[1-(4-methoxyphenyl)ethenyl]benzene (1d). This compound was prepared by treating (2-bromophenyl)(4-methoxyphenyl)methanone[8] with methylenetriphenylphosphorane in THF at 0 ˚C in 74% yield; a colorless oil; R_f 0.47 (1:3 CH_2Cl_2–hexane); IR (neat) 1605 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.80 (3H, s), 5.15 (1H, d, J = 0.9 Hz), 5.74 (1H, d, J = 0.9 Hz), 6.83 (2H, d, J = 8.7 Hz), 7.19–7.22 (3H, m), 7.30–7.35 (2H, m), 7.59 (1H, dd, J = 7.8, 1.4 Hz). Anal. Calcd for $C_{15}H_{13}BrO$: C, 62.30; H, 4.53. Found: C, 62.03; H, 4.60.

Typical Procedure for the Preparation of 1-Iodomethylisoindoles (3). 1-Iodomethyl-1-methyl-3-phenyl-1*H*-isoindole (3a). To a stirred solution of 1-bromo-2-(1- methylethenyl)benzene (**1a**) (0.54 g, 2.7 mmol) in Et_2O (5 mL) at 0 ˚C was added *n*-BuLi (1.6 M in hexane; 2.7 mmol) dropwise. After 1 h stirring, PhCN (0.28 g, 2.7 mmol) was added, and stirring was continued for an additional 20 min before saturated aqueous NH_4Cl (15 mL) was added. The organic materials were extracted with Et_2O three times (10 mL each), and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave crude *C*-[2-(1-methylethenyl)phenyl]-*C*-phenylmethylenamine (0.54 g),

which was dissolved in MeCN (5 mL) and $NaHCO_3$ (0.62 g, 7.4 mmol) was added. Then, I_2 (1.9 g, 7.4 mmol) was added in portions under stirring at 0 ˚C. After 20 min, 10% aqueous $Na_2S_2O_3$ was added until the color of iodine disappeared. Acetonitrile was evaporated, and the resulting mixture was extracted with Et_2O three times (10 mL each). The combined extracts were washed with saturated aqueous $NaHCO_3$ twice and brine once, and dried over anhydrous K_2CO_3. Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel to afford **3a** (0.64 g, 68%); a yellow oil; R_f 0.40 (1:3 THF–hexane); IR (neat) 1595 cm^{-1}; ^1H NMR (500 MHz) δ 1.77 (3H, s), 3.74 (1H, d, *J* = 10.1 Hz), 3.79 (1H, d, *J* = 10.1 Hz), 7.44–7.50 (2H, m), 7.52–7.55 (3H, m), 7.57 (1H, dd, *J* = 6.9, 1.4 Hz), 7.74 (1H, dd, *J* = 6.9, 1.4 Hz), 7.93–7.95 (2H, m); MS (EI) *m*/*z* 347 (M^+, 5.7), 220 (100). Anal. Calcd for $C_{16}H_{14}IN$: C, 55.35; H, 4.06; N, 4.03. Found: C, 55.25; H, 4.15; N, 3.76.

3-(2-Fluorophenyl)-1-iodomethyl-1-methyl-1*H*-isoindole (3b): a yellow oil; R_f 0.26 (1:4 AcOEt–hexane); IR (neat) 1618 cm^{-1}; ^1H NMR (500 MHz) δ 1.78 (3H, s), 3.74 (1H, d, *J* = 9.6 Hz), 3.80 (1H, d, *J* = 9.6 Hz), 7.24 (1H, ddd, *J* = 8.2, 7.3, 1.4 Hz), 7.30 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.43 (1H, td, *J* = 7.3, 0.9 Hz), 7.47 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.50–7.57 (3H, m), 7.79 (1H, td, *J* = 7.3, 1.8 Hz); MS (EI) *m*/*z* 365 (M^+, 17), 238 (100). Anal. Calcd for $C_{16}H_{13}FIN$: C, 52.62; H, 3.59; N, 3.84. Found: C, 55.61; H, 3.62; N, 3.77.

3-(4-Chlorophenyl)-1-iodomethyl-1-methyl-1*H*-isoindole (3c): a pale-yellow solid; mp 145–149 ˚C (hexane–Et_2O); IR (KBr) 1595 cm^{-1}; ^1H NMR (500 MHz) δ 1.76 (3H, s), 3.72 (1H, d, *J* = 9.6 Hz), 3.79 (1H, d, *J* = 9.6 Hz), 7.44–7.50 (2H, m), 7.52 (2H, d, *J* = 8.7 Hz), 7.56 (1H, d, *J* = 6.9 Hz), 7.70 (1H, d, *J* = 6.9 Hz), 7.90 (2H, d, *J* = 8.7 Hz); ^{13}C NMR δ 13.59, 23.44, 75.12, 121.77, 122.64, 128.20, 128.98, 129.00, 129.66, 132.56, 136.48, 137.50, 156.75, 169.27; MS (EI) *m*/*z* 381 (M^+, 14), 254 (100). Anal. Calcd for $C_{16}H_{13}ClIN$: C, 50.35; H, 3.43; N, 3.67. Found: C, 50.27; H, 3.45; N, 3.51.

1-Iodomethyl-1-methyl-3-(4-trifluoromethylphenyl)-1*H*-isoindole (3d): a white solid; mp 150–152 ˚C (hexane–Et_2O); IR (KBr) 1601 cm^{-1}; ^1H NMR (500 MHz) δ 1.78 (3H, s), 3.73 (1H, d, *J* = 10.1 Hz), 3.82 (1H, d, *J* = 10.1 Hz), 7.48 (1H, td, *J* = 7.3, 1.4 Hz), 7.51 (1H, t, *J* = 7.3 Hz), 7.58 (1H, d, *J* = 7.3 Hz), 7.69 (1H, d, *J* = 7.3 Hz), 7.81 (2H, d, *J* = 8.2 Hz), 8.06 (2H, d, *J* = 8.2 Hz); MS (CI) *m*/*z* 416 ($[M+1]^+$, 100). Anal. Calcd for $C_{17}H_{13}F_3IN$: C, 49.18; H, 3.16; N, 3.37. Found: C, 49.07; H, 3.15; N, 3.26.

1-Iodomethyl-1-methyl-3-(1-methylethyl)-1*H*-isoindole (3e): a yellow oil; R_f 0.43 (1:4 AcOEt–hexane); IR (neat) 1603 cm^{-1}; ^1H NMR (500 MHz) δ 1.40 (3H, d, *J* = 6.9 Hz), 1.43 (3H, d, *J* = 6.9 Hz), 1.65 (3H, s), 3.23 (1H, hept, *J* = 6.9 Hz), 3.68 (1H, d, *J* = 10.1 Hz), 3.70 (1H, d, *J* = 10.1 Hz), 7.40–7.42 (2H, m), 7.47 (1H, dd, *J* = 7.8, 1.4 Hz), 7.55 (1H, dd, *J* = 7.8, 1.4 Hz); MS (EI) *m*/*z* 313 (M^+, 34), 186 (100). Anal. Calcd for $C_{13}H_{16}IN$: C, 49.86; H, 5.15; N, 4.47. Found: C, 49.59; H, 5.40; N, 4.50.

1-Iodomethyl-1,3-diphenyl-1*H*-isoindole (3f): a white solid; mp 102–103 ˚C (hexane–Et_2O); IR (KBr) 1597 cm^{-1}; ^1H NMR (500 MHz) δ 4.10 (1H, d, *J* = 10.1 Hz), 4.23 (1H, d, *J* = 10.1 Hz), 7.29 (1H, tt, *J* = 7.3, 1.4 Hz), 7.34 (2H, dd, *J* = 7.8, 7.3 Hz), 7.46–7.56 (5H, m), 7.63–7.67 (2H, m), 7.73 (1H, d, *J* = 7.3

Hz), 7.76 (1H, d, *J* = 7.3 Hz), 7.99–8.01 (2H, m); MS (EI) *m/z* 409 (M^+, 0.9), 282 (100). Anal. Calcd for $C_{21}H_{16}IN$: C, 61.63; H, 3.94; N, 3.42. Found: C, 61.46; H, 3.34; N, 3.93.

1-(4-Chlorophenyl)-1-iodomethyl-3-phenyl-1*H*-isoindole (3g): a yellow oil; R_f 0.30 (1:7 THF–hexane); IR (neat) 1597 cm^{-1}; ^1H NMR (500 MHz) δ 4.03 (1H, d, *J* = 10.1 Hz), 4.14 (1H, d, *J* = 10.1 Hz), 7.30 (2H, d, *J* = 8.7 Hz), 7.48–7.59 (7H, m), 7.69 (1H, d, *J* = 6.9 Hz), 7.77 (1H, d, *J* = 6.9 Hz), 7.97–7.99 (2H, m); MS (CI) *m/z* 444 ($[M+1]^+$, 100). Anal. Calcd for $C_{21}H_{15}ClIN$: C, 56.84; H, 3.41; N, 3.16. Found: C, 56.82; H, 3.50; N 3.10.

1-Iodomethyl-1-(4-methoxyphenyl)-3-phenyl-1*H*-isoindole (3h): a pale-yellow solid; mp 104–105 °C (hexane–Et_2O); IR (KBr) 1607 cm^{-1}; ^1H NMR (500 MHz) δ 3.78 (3H, s), 4.06 (1H, d, *J* = 10.1 Hz), 4.19 (1H, d, *J* = 10.1 Hz), 6.86 (2H, d, *J* = 8.7 Hz), 7.47 (1H, t, *J* = 7.3 Hz), 7.51 (1H, t, *J* = 7.3 Hz), 7.52–7.56 (3H, m), 7.57 (2H, d, *J* = 8.7 Hz), 7.71 (1H, d, *J* = 7.3 Hz), 7.75 (1H, d, *J* = 7.3 Hz), 7.96–8.00 (2H, m); MS (CI) *m/z* 440 ($[M+1]^+$, 100). Anal. Calcd for $C_{22}H_{18}INO$: C, 60.14; H, 4.13; N, 3.19. Found: C, 60.26; H, 4.13; N, 3.24.

3-(4-Fluorophenyl)-1-iodomethyl-1-(4-methoxyphenyl)-1*H*-isoindole (3i): a yellow oil; R_f 0.41 (1:3 THF–hexane); IR (neat) 1607 cm^{-1}; ^1H NMR (500 MHz) δ 3.78 (3H, s), 4.04 (1H, d, *J* = 10.1 Hz), 4.18 (1H, d, *J* = 10.1 Hz), 6.86 (2H, d, *J* = 8.7 Hz), 7.23 (2H, t, *J* = 8.7 Hz), 7.48 (1H, td, *J* = 7.3, 0.9 Hz), 7.52 (1H, td, *J* = 7.3, 1.4 Hz), 7.55 (2H, d, *J* = 8.7 Hz), 7.70 (1H, d, *J* = 7.3 Hz), 7.71 (1H, d, *J* = 7.3 Hz), 7.99 (2H, dd, *J* = 8.7, 5.5 Hz); MS (CI) *m/z* 458 ($[M+1]^+$, 100). Anal. Calcd for $C_{22}H_{17}FINO$: C, 57.78; H, 3.75; N, 3.06. Found: C, 57.68; H, 3.84; N,3.05.

1-Iodomethyl-6-methoxy-1-methyl-3-phenyl-1*H*-isoindole (3j): a yellow-solid; mp 121–123 °C (hexane–CH_2Cl_2); IR (KBr) 1600 cm^{-1}; ^1H NMR (400 MHz) δ 1.74 (3H, s), 3.69 (1H, d, *J* = 9.9 Hz), 3.73 (1H, d, *J* = 9.9 Hz), 3.91 (3H, s), 6.96 (1H, dd, *J* = 8.4, 2.2 Hz), 7.08 (1H, d, *J* = 2.2 Hz), 7.50–7.53 (3H, m), 7.62 (1H, d, *J* = 8.4 Hz), 7.91–7.94 (2H, m); ^{13}C NMR δ 14.08, 23.77, 55.70, 74.34, 107.55, 114.04, 123.81, 128.27, 128.66, 130.21, 131.07, 134.31, 159.15, 160.78, 169.82; MS (EI) *m/z* 377 (M^+, 14), 250 (100). Anal. Calcd for $C_{17}H_{16}INO$: C, 54.13; H, 4.28; N, 3.71. Found: C, 54.07; H, 4.28; N, 3.77.

Typical Procedure for the Preparation of 1,1-Dimethylisoindole Derivatives (4). 1,1-Dimethyl-3-phenyl-1*H*-isoindole (4a). A solution of **3a** (0.24 g, 0.69 mmol) and $NaCNBH_4$ (0.17 g, 2.8 mmol) in HMPA (3 mL) was heated at 120 °C for 12 h. Brine (10 mL) was added to the cooling reaction mixture, and the resulting mixture was extracted with Et_2O three times (10 mL each). The combined extracts were washed with water twice and brine once, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel to afford **4a** (94 mg, 62%); a yellow oil; R_f 0.35 (1:4 AcOEt–hexane); IR (neat) 1607 cm^{-1}; ^1H NMR (500 MHz) δ 1.57 (6H, s), 7.39 (1H, td, *J* = 7.3, 0.9 Hz), 7.43 (1H, td, *J* = 7.3, 0.9 Hz), 7.50–7.54 (4H, m), 7.73 (1H, d, *J* = 7.3 Hz), 7.92 (2H, dd, *J* = 7.8, 0.9 Hz); MS (EI) *m/z* 221 (M^+, 82), 206 (100). Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.78; H, 6.94; N, 6.26.

3-(2-Fluorophenyl)-1,1-dimethyl-1*H*-isoindole (4b): a pale-yellow oil; R_f 0.22 (1:4 AcOEt–hexane); IR (neat) 1618 cm^{-1}; ^1H NMR (500 MHz) δ 1.58 (6H, s), 7.22 (1H, ddd, *J* = 8.2, 7.3, 1.4 Hz), 7.28 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.37 (1H, td, *J* = 7.3, 0.9 Hz), 7.42 (1H, td, *J* = 7.3, 1.4 Hz), 7.46–7.54 (3H, m), 7.71 (1H, td, *J* = 7.3, 1.8 Hz); MS (EI) *m*/*z* 239 (M^+, 80), 224 (100). Anal. Calcd for $C_{16}H_{14}FN$: C, 80.31; H, 5.90; N, 5.85. Found: C, 80.28; H, 6.05; N, 5.58.

3-(4-Chlorophenyl)-1,1-dimethyl-1*H*-isoindole (4c): a pale-yellow oil; R_f 0.37 (1:6 THF–hexane); IR (neat) 1599 cm^{-1}; ^1H NMR (500 MHz) δ 1.56 (6H, s), 7.40 (1H, td, *J* = 7.3, 1.4 Hz), 7.44 (1H, t, *J* = 7.3 Hz), 7.50 (2H, d, *J* = 8.2 Hz), 7.53 (1H, d, *J* = 7.3 Hz), 7.68 (1H, d, *J* = 7.3 Hz), 7.88 (2H, d, *J* = 8.2 Hz); MS (EI) *m*/*z* 255 (M^+, 78), 240 (100). Anal. Calcd for $C_{16}H_{14}ClN$: C, 75.14; H, 5.52; N, 5.48. Found: C, 75.08; H, 5.75; N, 5.51.

1,1-Dimethyl-3-(4-trifluoromethylphenyl)-1*H*-isoindole (4d): a pale-yellow solid; mp 104–105 °C (hexane–Et_2O); IR (KBr) 1620 cm^{-1}; ^1H NMR (500 MHz) δ 1.58 (6H, s), 7.41 (1H, td, *J* = 7.3, 0.9 Hz), 7.46 (1H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.55 (1H, d, *J* = 7.3 Hz), 7.69 (1H, d, *J* = 7.8 Hz), 7.79 (2H, d, *J* = 7.8 Hz), 8.04 (2H, d, *J* = 7.8 Hz); MS (EI) *m*/*z* 289 (M^+, 73), 274 (100). Anal. Calcd for $C_{17}H_{14}F_3N$: C, 70.58; H, 4.88; N, 4.84. Found: C, 70.33; H, 5.13; N, 4.54.

Typical Procedure for the Preparation of 1-Sufenylmethylisoindoles (5). 1-Methyl-3-phenyl-1-phenylthiomethyl-1*H*-isoindole (5a). To a stirred suspension of NaH (60% in oil; 18 mg, 0.45 mmol) in DMF (2 mL) at rt was added PhSH (50 mg, 0.45 mmol). After stirring for 15 min, a solution of **3a** (0.14 g, 0.41 mmol) in DMF (3 mL) was added, and stirring was continued for an additional 2.5 h at the same temperature. Saturated aqueous NH_4Cl (10 mL) was added and the resulting mixture was extracted with Et_2O three times (10 mL each). The combined extracts were washed with water twice and brine once, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel to afford **5a** (0.11 g, 77%); a yellow oil; R_f 0.32 (1:4 AcOEt–hexane); IR (neat) 1605 cm^{-1}; ^1H NMR (500 MHz) δ 1.68 (3H, s), 3.58 (1H, d, *J* = 12.8 Hz), 3.59 (1H, d, *J* = 12.8 Hz), 7.11 (1H, t, *J* = 7.3 Hz), 7.17 (2H, dd, *J* = 7.8, 7.3 Hz), 7.22 (2H, d, *J* = 7.8 Hz), 7.35 (1H, t, *J* = 7.3 Hz), 7.40 (1H, t, *J* = 7.3 Hz), 7.49–7.52 (4H, m), 7.75 (1H, d, *J* = 7.3 Hz), 7.85 (2H, dd, *J* = 7.3, 1.8 Hz); MS (EI) *m*/*z* 329 (M^+, 46), 283 (65), 206 (100). Anal. Calcd for $C_{22}H_{19}NS$: C, 80.20; H, 5.81; N, 4.25. Found: C, 80.12; H, 5.74; N, 4.22.

1-[2-(Dimethylamino)ethylthiomethyl]-1-methyl-3-phenyl-1*H*-isoindole (5b): a yellow oil; R_f 0.10 (THF); IR (neat) 1607 cm^{-1}; ^1H NMR (500 MHz) δ 1.66 (3H, s), 2.15 (6H, s), 2.33–2.40 (2H, m), 2.52–2.55 (2H, m), 3.12 (1H, d, *J* = 13.3 Hz), 3.19 (1H, d, *J* = 13.3 Hz), 7.40–7.45 (2H, m), 7.51–7.53 (3H, m), 7.61 (1H, dd, *J* = 6.9, 1.8 Hz), 7.75 (1H, dd, *J* = 6.9, 2.3 Hz), 7.93–7.95 (2H, m); MS (EI) *m*/*z* 325 ($[M+1]^+$, 0.28), 253 (42), 207 (100). Anal. Calcd for $C_{20}H_{24}N_2S$: C, 74.03; H, 7.46; N, 8.63. Found: C, 74.02; H, 7.71; N, 8.52.

3-(4-Chlorophenyl)-1-methyl-1-(pyridin-2-yl)thiomethyl-1*H*-isoindole (5c): a yellow oil; R_f 0.33 (1:5

THF–hexane); 1599 cm^{-1}; ^1H NMR (500 MHz) δ 1.70 (3H, s), 3.91 (1H, d, *J* = 13.3 Hz), 3.98 (1H, d, *J* = 13.3 Hz), 6.92 (1H, ddd, *J* = 7.3, 5.0, 0.9 Hz), 6.99 (1H, dd, *J* = 7.8, 0.9 Hz), 7.30–7.38 (3H, m), 7.47 (2H, d, *J* = 8.7 Hz), 7.56 (1H, d, *J* = 7.3 Hz), 7.66 (1H, d, *J* = 7.8 Hz), 7.81 (2H, d, *J* = 8.7 Hz), 8.39 (1H, dd, *J* = 5.0, 0.9 Hz); ^{13}C NMR δ 23.44, 37.93, 77.14, 119.37, 122.22, 122.35, 122.51, 127.65, 128.44, 128.85, 129.65, 132.88, 135.65, 136.19, 137.47, 149.01, 157.31, 158.70, 168.62; MS (EI) *m*/*z* 364 (M^+, 25), 252 (100). Anal. Calcd for $C_{21}H_{17}ClN_2S$: C, 69.12; H, 4.70; N, 7.68. Found: C, 68.99; H, 4.81; N, 7.48.

3-(4-Chlorophenyl)-1-(4,6-dimethylpyrimidin-2-yl)thiomethyl-1-methyl-1*H*-isoindole (5d): a white solid; mp 150–151 ˚C (hexane–CH_2Cl_2); IR (KBr) 1582 cm^{-1}; ^1H NMR (500 MHz) δ 1.71 (3H, s), 2.34 (6H, s), 3.67 (1H, d, *J* = 13.3 Hz), 4.15 (1H, d, *J* = 13.3 Hz), 6.62 (1H, s), 7.32 (1H, t, *J* = 7.3 Hz), 7.35 (1H, t, *J* = 7.3 Hz) 7.48 (2H, d, *J* = 8.7 Hz), 7.65 (1H, d, *J* = 7.3 Hz), 7.66 (1H, d, *J* = 7.3 Hz), 7.86 (2H, d, *J* = 8.7 Hz); ^{13}C NMR δ 23.34, 23.75, 38.35, 77.00, 115.49, 122.42, 122.49, 127.64, 128.30, 128.84, 129.66, 132.87, 136.16, 137.46, 157.21, 166.61, 168.78, 170.69; MS (EI) *m*/*z* 393 (M^+, 64), 252 (100). Anal. Calcd for $C_{22}H_{20}ClN_3S$: C, 67.08; H, 5.12; N, 10.67. Found: C, 66.82; H, 5.07; N, 10.55.

1-Methyl-1-(phenylmethyl)thiomethyl-3-(4-trifluoromethylphenyl)-1*H*-isoindole (5e): a yellow oil; R_f 0.28 (1:4 AcOEt–hexane); IR (neat) 1601 cm^{-1}; ^1H NMR (500 MHz) δ 1.63 (3H, s), 3.02 (1H, d, *J* = 13.3 Hz), 3.08 (1H, d, *J* = 13.3 Hz), 3.56 (1H, d, *J* = 13.3 Hz), 3.59 (1H, d, *J* = 13.3 Hz), 7.18 (2H, dd, *J* = 7.8, 1.4 Hz), 7.20 (1H, tt, *J* = 7.3, 1.4 Hz), 7.24 (2H, dd, *J* = 7.8, 7.3 Hz), 7.42–7.47 (2H, m), 7.54 (1H, dd, *J* = 6.9, 1.8 Hz), 7.71 (1H, dd, *J* = 6.9, 1.8 Hz), 7.79 (2H, d, *J* = 7.8 Hz), 8.07 (2H, d, *J* = 7.8 Hz); MS (EI) *m*/*z* 412 ($[M+1]^+$, 23), 289 (100). Anal. Calcd for $C_{24}H_{20}F_3NS$: C, 70.05; H, 4.90; N, 3.40. Found: C, 69.77; H, 5.16; N, 3.46.

1-[(2-Hydroxyethyl)thiomethyl]-1,3-diphenyl-1*H*-isoindole (5f): a yellow oil; R_f 0.53 (1:1 AcOEt–hexane); IR (neat) 3254, 1599 cm^{-1}; ^1H NMR (500 MHz) δ 2.48 (1H, ddd, *J* = 14.7, 5.5, 3.2 Hz), 2.69 (1H, ddd, *J* = 14.7, 8.2, 3.7 Hz), 3.48–3.53 (1H, m), 3.64 (1H, d, *J* = 13.7 Hz), 3.65–3.70 (1H, m), 3.82 (1H, d, *J* = 13.7 Hz), 4.47 (1H, br s), 7.27 (1H, t, *J* = 7.3 Hz), 7.33 (2H, dd, *J* = 7.8, 7.3 Hz), 7.45–7.51 (2H, m), 7.55–7.59 (5H, m), 7.68 (1H, dd, *J* = 6.9, 1.8 Hz), 7.82 (1H, dd, *J* = 6.9, 1.8 Hz), 7.82–7.86 (2H, m); MS (EI) *m*/*z* 359 (M^+, 27), 268 (100). Anal. Calcd for $C_{23}H_{21}NOS$: C, 76.85; H, 5.89; N, 3.90. Found: C, 76.74; H, 6.02; N, 3.73.

1-(4-Chlorophenyl)-1-[(2-hydroxyethyl)thiomethyl]-3-phenyl-1*H*-isoindole (5g): a yellow oil; R_f 0.39 (1:1 AcOEt–hexane); IR (neat) 3265, 1605 cm^{-1}; ^1H NMR (500 MHz) δ 2.48 (1H, ddd, *J* = 14.2, 5.0, 3.2 Hz), 2.70 (1H, ddd, *J* = 14.2, 8.7, 3.7 Hz), 3.51–3.56 (1H, m), 3.58 (1H, d, *J* = 13.7 Hz), 3.65–3.71 (1H, m), 3.76 (1H, d, *J* = 13.7 Hz), 4.29 (1H, t, *J* = 6.2 Hz), 7.29 (2H, d, *J* = 8.7 Hz), 7.46–7.52 (4H, m), 7.56–7.59 (3H, m), 7.65 (1H, dd, *J* = 6.9, 1.8 Hz), 7.83 (1H, dd, *J* = 6.9, 1.8 Hz), 8.02–8.05 (2H, m); MS (EI) *m*/*z* 393 (M^+, 28), 302 (100). Anal. Calcd for $C_{23}H_{20}ClNOS$: C, 70.13; H, 5.12; N, 3.56. Found: C, 69.97; H, 5.16; N, 3.67.

1-(4-Methoxyphenyl)-3-phenyl-1-phenylthiomethyl-1*H*-isoindole (5h): a yellow oil; R_f 0.27 (1:4

THF–hexane); IR (neat) 1609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 (3H, s), 3.95 (1H, d, *J* = 12.8 Hz), 4.00 (1H, d, *J* = 12.8 Hz), 6.84 (2H, d, *J* = 8.7 Hz), 7.08–7.18 (5H, m), 7.35 (1H, t, *J* = 7.3 Hz), 7.41 (1H, t, *J* = 7.3 Hz), 7.50–7.54 (5H, m), 7.60 (1H, d, *J* = 7.3 Hz), 7.76 (1H, d, *J* = 7.3 Hz), 7.89–7.93 (2H, m); MS (EI) *m*/*z* 421 (M^+, 32), 298 (100). Anal. Calcd for $C_{28}H_{23}NOS$: C, 79.78; H, 5.50; N, 3.32. Found: C, 79.71; H, 5.30; N, 3.22.

3-(4-Fluorophenyl)-1-[(2-hydroxyethyl)thiomethyl]-1-(4-methoxyphenyl)-1*H*-isoindole (5i): a yellow oil; R_f 0.35 (1:1 AcOEt–hexane); IR (neat) 3310, 1607 cm^{-1}; ^1H NMR (500 MHz) δ 2.46 (1H, ddd, *J* = 14.2, 5.0, 3.2 Hz), 2.69 (1H, ddd, *J* = 14.2, 8.2, 3.7 Hz), 3.46–3.50 (1H, m), 3.60 (1H, d, *J* = 13.7 Hz), 3.67–3.70 (1H, m), 3.77 (1H, d, *J* = 13.7 Hz), 3.78 (3H, s), 4.38 (1H, br s), 6.85 (2H, d, *J* = 8.7 Hz), 7.25 (2H, dd, *J* = 8.2, 7.8 Hz), 7.45–7.52 (4H, m), 7.67 (1H, d, *J* = 7.3 Hz), 7.79 (1H, d, *J* = 7.3 Hz), 8.05 (2H, dd, *J* = 8.2, 5.5 Hz); MS (EI) *m*/*z* 407 (M^+, 23), 316 (100). Anal. Calcd for $C_{24}H_{22}FNO_2S$: C, 70.74; H, 5.44; N, 3.44. Found: C, 70.59; H, 5.47; N, 3.28.

Ethyl 2-[3-(4-Fluorophenyl)-1-(4-methoxyphenyl)-1*H*-isoindol-1-yl]methylthioacetate (5j): a yellow oil; R_f 0.20 (1:4 AcOEt–hexane); IR (neat) 1732, 1607 cm^{-1}; ^1H NMR (500 MHz) δ 1.22 (3H, t, *J* = 7.3 Hz), 2.98 (1H, d, *J* = 14.7 Hz), 3.06 (1H, d, *J* = 14.7 Hz), 3.63 (1H, d, *J* = 13.3 Hz), 3.74 (1H, d, *J* = 13.3 Hz), 3.77 (3H, s), 4.12 (2H, q, *J* = 7.3 Hz), 6.85 (2H, d, *J* = 8.7 Hz), 7.22 (2H, t, *J* = 8.7 Hz), 7.43–7.46 (2H, m), 7.49 (2H, d, *J* = 8.7 Hz), 7.71–7.74 (2H, m), 8.00 (2H, dd, *J* = 8.7, 5.5 Hz); MS (EI) *m*/*z* 449 (M^+, 23), 316 (100). Anal. Calcd for $C_{26}H_{24}FNO_3S$: C, 69.47; H, 5.38; N, 3.12. Found: C, 69.36; H, 5.42; N, 2.99.

6-Methoxy-1-methyl-3-phenyl-1-phenylthiomethyl-1*H*-isoindole (5k): a yellow oil; R_f 0.35 (1:4 THF–hexane); IR (neat) 1606 cm^{-1}; ^1H NMR (400 MHz) δ 1.65 (3H, s), 3.54 (1H, d, *J* = 13.2 Hz), 3.56 (1H, d, *J* = 13.2 Hz), 3.80 (3H, s), 6.90 (1H, dd, *J* = 8.4, 2.2 Hz), 6.97 (1H, d, *J* = 2.2 Hz), 7.08–7.22 (4H, m), 7.46–7.52 (4H, m), 7.63 (1H, d, *J* = 8.4 Hz), 7.83–7.86 (2H, m); MS (EI) *m*/*z* 359 (M^+, 16), 313 (46), 236 (100). Anal. Calcd for $C_{23}H_{21}NOS$: C, 76.85; H, 5.89; N, 3.90. Found: C, 76.73; H, 6.01; N, 3.86.

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