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A FACILE SYNTHESIS OF 1,1-DISUBSTITUTED ISOINDOLINE DERIVATIVES BY INTRAMOLECULAR IODOAMINATION OF 2-VINYLBENZYLAMINE DERIVATIVES

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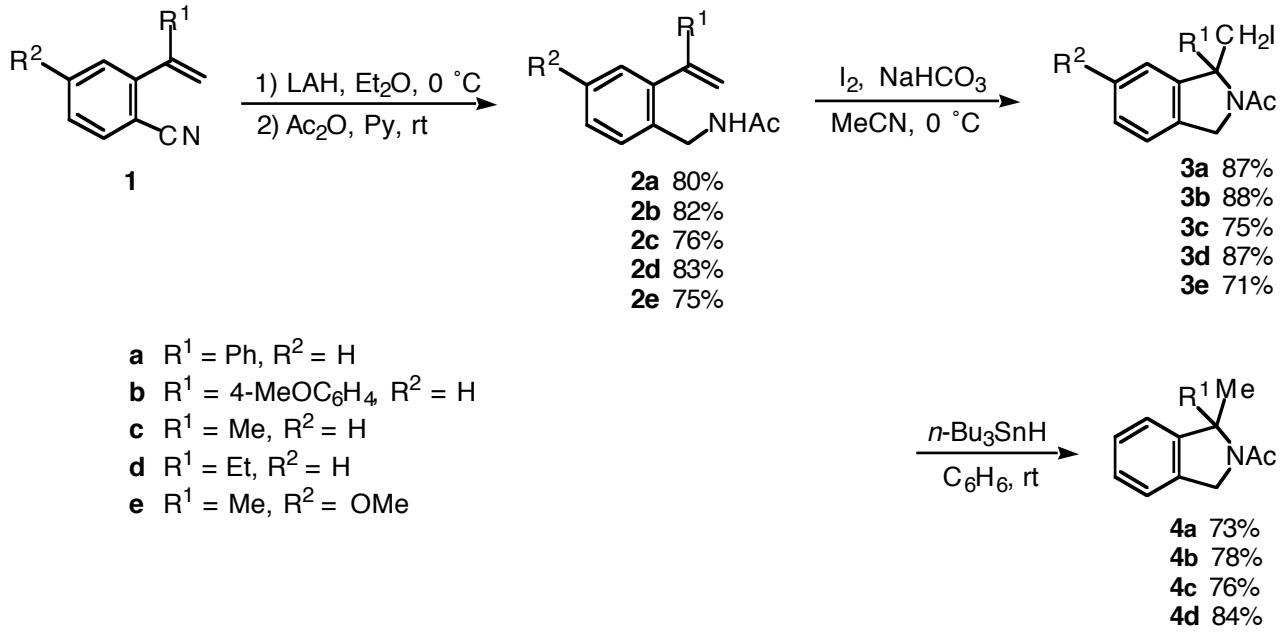
Abstract- The intramolecular iodoamination of *N*-(2-vinylbenzyl)acetamide derivatives, derived from α-substituted 2-vinylbenzonitriles in two steps, afforded the corresponding 2-acetyl-1-iodomethylisoindoline derivatives, which were transformed into the 1-methyl or 1-sulfenylmethyl derivatives by tributyltin hydride reduction or substitution by sodium thiolates, respectively, in reasonable yields.

We have recently demonstrated that 3,3-disubstituted isoindolin-1-ones could be prepared by intramolecular iodoamination[1] of α-substituted secondary 2-vinylbenzamides.[2] As an extension of this synthesis, we now wish to report a new and convenient synthesis of 1,1-disubstituted isoindoline derivatives by iodoamination of *N*-(2-vinylbenzyl)acetamide derivatives, which can be readily prepared from α-substituted 2-vinylbenzonitriles. Isoindoline derivatives have attracted synthetic attention[3] for their biological activities.[4] The derivatives having no substituents both at the 1- and 3-positions have been prepared by reduction of phthalimides with appropriate reducing agents.[5] However, there have been few reports on the synthesis of 1,1-disubstituted isoindoline derivatives, though Buchwald et al. have reported a synthesis of 1-substituted isoindoline-1-carboxylic acid esters by palladium-catalyzed intramolecular α-arylation of *N*-(2-bromobenzyl)-α-amino acid ester derivatives.[3d]

The synthesis of 1,1-disubstituted isoindoline derivatives was conducted by the process illustrated in Scheme 1. Thus, α-substituted 2-vinylbenzonitriles (**1**) were treated with LAH, and the resulting benzylamine derivatives were then acetylated with acetic anhydride in pyridine to give the corresponding α-substituted 2-(acetylaminomethyl)styrenes (**2**) in good overall yields. Treatment of these compounds with iodine in the presence of sodium hydrogencarbonate in acetonitrile resulted in a

clean regioselective conversion to the intramolecular 5-*exo* iodoamination products, 1-iodomethylisoindolines (**3**), in good yields. The resulting 1-iodomethyl derivatives (**3**) thus formed were then reduced with tributyltin hydride to give the 1-methyl derivatives (**4**) in good yields.

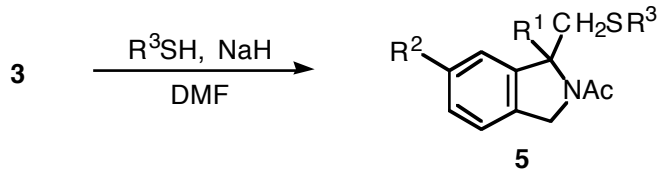


a R^1 = Ph, R^2 = H
b R^1 = 4-$MeOC_6H_4$, R^2 = H
c R^1 = Me, R^2 = H
d R^1 = Et, R^2 = H
e R^1 = Me, R^2 = OMe

Scheme 1

Nucleophilic substitution reactions of the iodomethylisoindoline derivatives (**3**) were then examined. The sulfenylation with sodium thiolates proceeded cleanly to afford the corresponding 1-sufenylmethyl derivatives (**5**),[6] as shown in Scheme 2. The yields and reaction conditions of the sulfenylation are summarized in Table 1, which indicates the yields are generally good. Unfortunately, however, attempted substitution of **3** with sodium acetanilide or sodium acetate resulted in vain.

The structures of the products prepared in this study were assigned from their spectral and analytical data. It was found that in cases where the substituent R^1 was phenyl or 4-methoxyphenyl, each of the ^1H NMR spectra of compounds **3a**, **3b**, **4a**, **4b**, **5a**, and **5b** was observed as a mixture of two rotamers (see Experimental).



Scheme 2

Table 1: Preparation of 1-(Sulfenylmethyl)isoindoline Derivatives (**5**)

Entry	**3**	R^3 in R^3SH	Temp	Time/min	**5** (Yield/%)[a]
1	**3a**	Ph	80 ˚C	45	**5a** (81)
2	**3b**	Ph	100 ˚C	30	**5b** (64)
3	**3c**	Ph	60 ˚C	10	**5c** (79)
4	**3c**	pyridin-2-yl	60 ˚C	40	**5d** (66)
5	**3c**	4,6-dimethylpyrimidin-2-yl	60 ˚C	40	**5e** (69)
6	**3d**	Bn	rt	15	**5f** (90)
7	**3e**	Bn	rt	15	**5g** (69)

[a]Isolated yields.

In conclusion, we have demonstrated herein the utility of the iodoamination strategy for the synthesis of 1,1-disubstituted isoindoline derivatives, which have been hard to prepare by conventional methods. The ready availability of the starting materials and the ease of operations make the present method attractive.

EXPERIMENTAL

The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus 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. Low-resolution mass spectra (EI) were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the solvents used in the reactions were dried over appropriate drying agents and distilled under argon prior to use.

Starting Materials. 2-Bromophenyl(4-methoxyphenyl)methanone[7] and 1-(2-bromo-5-methoxyphenyl)-ethanone[8] were prepared by appropriate reported methods. For the preparation of 2-(1-phenylvinyl)-benzonitrile (**1a**),[9] 2-(1-methylvinyl)benzonitrile (**1c**),[10] and 2-(1-ethylethenyl)benzonitrile (**1d**), see refs. 11 and 12.

2-(4-Methoxybenzoyl)benzonitrile. This compound was prepared by treating 2-bromophenyl-(4-methoxyphenyl)methanone[7] with CuCN in DMF under the conditions reported by Friedman et al.[13] in 99% yield; a yellow oil; R_f 0.29 (THF–hexane, 1:2); IR (neat) 2228, 1651 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.90 (s, 3H), 6.97 (d, J = 8.7 Hz, 2H), 7.61–7.65 (m, 2H), 7.69 (ddd, J = 7.8, 7.3, 1.4 Hz, 1H), 7.79–7.84 (m, 3H). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.75; H, 4.73; N, 5.74.

2-[1-(4-Methoxyphenyl)vinyl]benzonitrile (1b). This compound was prepared by treating 2-(4-methoxybenzoyl)benzonitrile with methylenetriphenylphosphorane under conditions for the preparation of **1a** reported by us[12] in 77% yield; a yellow oil; R_f 0.51 (THF–hexane, 1:3); IR (neat) 2226, 1607 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.81 (s, 3H), 5.35 (s, 1H), 5.78 (s, 1H), 6.86 (d, J = 9.1 Hz, 2H), 7.19

(d, J = 9.1 Hz, 2H), 7.37 (d, J = 7.8 Hz, 1H), 7.42 (td, J = 7.3, 1.4 Hz, 1H), 7.57 (ddd, J = 7.8, 7.3, 1.4 Hz, 1H), 7.70 (d, J = 7.3 Hz, 1H). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.59; H, 5.77; N, 5.90.

2-Acetyl-4-methoxybenzonitrile. This compound was prepared by treating 1-(2-bromo-5-methoxyphenyl)ethanone[8] with CuCN in DMF under the conditions for the preparation of 2-propanoylbenzonitrile reported by us[11] in 71% yield; a pale-yellow solid; mp 75–77 °C (hexane–CH_2Cl_2); IR (KBr) 2216, 1680 cm^{-1}; ^1H NMR (400 MHz) δ 2.70 (s, 3H), 3.92 (s, 3H), 7.10 (dd, J = 8.6, 2.6 Hz, 1H), 7.40 (d, J = 2.6 Hz, 1H), 7.73 (d, J = 8.6 Hz, 1H). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.50; H, 5.17; N, 7.98.

4-Methoxy-2-(1-methylvinyl)benzonitrile (1e). This compound was prepared by treating 2-acetyl-4-methoxybenzonitrile with methylenetriphenylphosphorane under conditions for the preparation of **1a** reported by us[12] in 62% yield; a pale yellow oil; R_f 0.15 (CH_2Cl_2–hexane, 1:3); IR (neat) 2220, 1603 cm^{-1}; ^1H NMR (500 MHz) δ 2.18 (dd, J = 1.4, 0.9 Hz, 3H), 3.86 (s, 3H), 5.25 (s, 1H), 5.36 (qd, J = 1.4, 0.9 Hz, 1H), 6.84–6.86 (m, 2H), 7.58 (d, J = 9.2 Hz, 1H). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 75.97; H, 6.55; N, 7.86.

Typical Procedure for the Preparation of *N*-(2-Vinylbenzyl)acetamides (2). *N*-[2-(1-Phenylvinyl)phenylmethyl]acetamide (2a). To a stirred suspension of LAH (93 mg, 2.4 mmol) in Et_2O (2.5 mL) at 0 °C was added a solution of **1a** (0.25 g, 1.2 mmol) in Et_2O (2.5 mL) dropwise. After 1h, five portions of several drops each of saturated aqueous Na_2SO_4 were added at 15 min intervals to decompose excess LAH. After 15 min, anhydrous $MgSO_4$ was added to the mixture and stirring was continued for an additional 20 min. Filtration through a Celite® pad followed by evaporation of the solvent gave a residue (0.23 g), which was dissolved in 0.5 mL each of pyridine and Ac_2O and was allowed to stand overnight at room temperature under stirring. After removal of the excess pyridine and Ac_2O under reduced pressure, the residue was purified by preparative TLC on silica gel (AcOEt–hexane, 1:2) to give **2a** (0.24 g, 80%); a pale-yellow solid; mp 256–257 °C (hexane–CH_2Cl_2); IR (KBr) 3263, 1643, 1611 cm^{-1}; ^1H NMR (500 MHz) δ 1.75 (s, 3H), 4.20 (d, J = 5.5 Hz, 2H), 5.16 (br s, 1H), 5.25 (d, J = 1.4 Hz, 1H), 5.81 (d, J = 1.4 Hz, 1H), 7.26–7.40 (m, 9H). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.40; H, 6.85; N, 5.51.

***N*-{2-[1-(4-Methoxyphenyl)ethenyl]phenylmethyl}acetamide (2b):** a white solid; mp 105–106 °C (hexane–CH_2Cl_2); IR (KBr) 3265, 1647, 1605 cm^{-1}; ^1H NMR (500 MHz) δ 1.78 (s, 3H), 3.80 (s, 3H), 4.21 (d, J = 6.0 Hz, 2H), 5.13 (d, J = 1.4 Hz, 1H), 5.25 (br s, 1H), 5.72 (d, J = 1.4 Hz, 1H), 6.84 (d, J = 9.2 Hz, 2H), 7.20 (d, J = 9.2 Hz, 2H), 7.24–7.39 (m, 4H). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.75; H, 6.93; N, 5.04.

***N*-[2-(1-Methylvinyl)phenylmethyl]acetamide (2c):** a white solid; mp 83–84 °C (hexane–Et_2O); IR (KBr) 3246, 1638 cm^{-1}; ^1H NMR (500 MHz) δ 2.00 (s, 3H), 2.06 (d, J = 0.9 Hz, 3H), 4.46 (d, J = 5.5 Hz,

2H), 4.86 (quint, *J* = 0.9 Hz, 1H), 5.24 (d, *J* = 0.9 Hz, 1H), 5.62 (br s, 1H), 7.14–7.34 (m, 4H). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.97; H, 8.14; N, 7.45.

***N*-[2-(1-Ethylvinyl)phenylmethyl]acetamide (2d):** a white solid; mp 42–43 °C (hexane–Et_2O); IR (KBr) 3256, 1639 cm^{-1}; ^1H NMR (500 MHz) δ 1.05 (t, *J* = 7.3 Hz, 3H), 2.00 (s, 3H), 2.34 (qt, *J* = 7.3, 0.9 Hz, 2H), 4.43 (d, *J* = 5.5 Hz, 2H), 4.87 (q, *J* = 0.9 Hz, 1H), 5.22 (q, *J* = 0.9 Hz, 1H), 5.60 (br s, 1H), 7.09–7.13 (m, 1H), 7.22–7.28 (m, 2H), 7.31–7.34 (m, 1H). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.43; H, 8.32; N, 7.12.

***N*-[4-Methoxy-2-(1-methylvinyl)phenylmethyl]acetamide (2e):** a white solid; mp 77–79 °C (hexane–Et_2O); IR (KBr) 3314, 1632 cm^{-1}; ^1H NMR (400 MHz) δ 1.97 (s, 3H), 2.04 (s, 3H), 3.77 (s, 3H), 4.38 (d, *J* = 5.2 Hz, 2H), 4.86 (s, 1H), 5.22 (s, 1H), 5.54 (br s, 1H), 6.69 (d, *J* = 2.6 Hz, 1H), 6.79 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.20; H, 7.90; N, 6.37.

Typical Procedure for the Preparation of 1-Iodomethylisoindolines (3). 1-(1-Iodomethyl-1-phenylisoindolin-2-yl)ethanone (3a). To a stirred solution of **1a** (0.63 g, 2.5 mmol) in MeCN (15 mL) containing $NaHCO_3$ (0.64 g, 7.6 mmol) at 0 °C was added I_2 (1.9 g, 7.6 mmol) in portions. Stirring was continued for 30 min, and then 10% aqueous $Na_2S_2O_3$ was added until the color of I_2 had disappeared. After the organic solvent was evaporated, the resulting mixture was extracted with Et_2O twice (20 ml each). The combined extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by preparative TLC on SiO_2 (AcOEt–hexane, 1:2) to give **3a** (0.82 g, 87%); a pale-yellow solid; mp 164–165 °C (hexane–CH_2Cl_2); IR (KBr) 1655 cm^{-1}; ^1H NMR (500 MHz; observed as a 9:1 mixture of rotamers) δ 1.79 (s, 0.3H), 2.23 (s, 2.7H), 4.23 (d, *J* = 9.6 Hz, 1H), 4.34 (d, *J* = 11.5 Hz. 0.1H), 4.41 (d, *J* = 11.5 Hz, 0.1H), 4.98 (d, *J* = 13.7 Hz, 0.9H), 5.04 (d, *J* = 13.7 Hz, 0.9 H), 5.25 (d, *J* = 9.6 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 0.1H), 6.94 (d, *J* = 7.8 Hz, 0.9H), 7.17–7.36 (m, 8H). MS *m/z* 377 (M^+, 0.97), 250 (25), 236 (80), 194 (100). Anal. Calcd for $C_{17}H_{16}NOI$: C, 54.13; H, 4.28; N, 3.71. Found: C, 54.11; H, 4.29; N, 3.66.

1-[1-Iodomethyl-1-(4-methoxyphenyl)isoindolin-2-yl]ethanone (3b): a white solid; mp 134–135 °C (hexane–CH_2Cl_2); IR (KBr) 1653, 1609 cm^{-1}; ^1H NMR (500 MHz; observed as a 9:1 mixture of rotamers) δ 1.81 (s, 0.3H), 2.20 (s, 2.7H), 3.75 (s, 2.7 H), 3.79 (s, 0.3H), 4.16 (d, *J* = 10.1 Hz, 1H), 4.31 (d, *J* = 10.5 Hz, 0.1H), 4.36 (d, *J* = 10.5 Hz, 0.1H), 4.94 (d, *J* = 13.3 Hz, 0.9H), 5.00 (d, *J* = 13.3 Hz, 0.9H), 5.27 (d, *J* = 10.1 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1.8 H), 6.85 (d, *J* = 8.7 Hz, 0.2H), 6.93 (d, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.25–7.36 (m, 3H); MS *m/z* 407 (M^+, 5.3), 266 (34), 224 (100). Anal. Calcd for $C_{18}H_{18}NO_2I$: C, 53.09; H, 4.46; N, 3.44. Found: C, 53.08; H, 4.51; N, 3.38.

1-(1-Iodomethyl-1-methylisoindolin-2-yl)ethanone (3c): a white solid; mp 123–124 °C (hexane–Et_2O); IR (KBr) 1638 cm^{-1}; ^1H NMR (500 MHz) δ 1.95 (s, 3H), 2.20 (s, 3H), 3.56 (d, *J* = 10.1 Hz, 1H), 4.74 (d, *J* = 13.7 Hz, 1H), 4.79 (d, *J* = 10.1 Hz, 1H), 4.85 (d, *J* = 13.7 Hz, 1H), 7.11–7.15 (m,

1H), 7.24–7.27 (m, 1H), 7.33–7.39 (m, 2H); MS *m/z* 315 (M^+, 0.10), 300 (0.62), 258 (4.4), 174 (87), 132 (100). Anal. Calcd for $C_{12}H_{14}INO$: C, 45.73; H, 4.48; N, 4.44. Found: C, 45.59; H, 4.78; N, 4.39.

1-[1-Ethyl-1-(iodomethyl)isoindolin-2-yl]ethanone (3d): a white solid; mp 71–72 °C (hexane–Et_2O); IR (KBr) 1645 cm^{-1}; ^1H NMR (500 MHz) δ 0.62 (t, *J* = 7.3 Hz, 3H), 1.79 (dq, *J* = 14.6, 7.3 Hz, 1H), 2.22 (s, 3H,), 2.89 (dq, *J* = 14.6, 7.3 Hz, 1H), 3.53 (d, *J* = 9.6 Hz, 1H), 4.69 (d, *J* = 13.7 Hz, 1H), 4.74 (d, *J* = 9.6 Hz, 1H), 4.85 (d, *J* = 13.7 Hz, 1H), 7.07 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.26 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.33–7.39 (m, 2H); MS *m/z* 329 (M^+, 0.38), 300 (93), 258 (100). Anal. Calcd for $C_{13}H_{16}INO$: C, 47.43; H, 4.90; N, 4.26. Found: C, 47.08; H, 4.86; N, 4.35.

1-(1-Iodomethyl-6-methoxy-1-methylisoindolin-2-yl)ethanone (3e): a white solid; mp 134–135 °C (hexane–Et_2O); IR (KBr) 1648 cm^{-1}; ^1H NMR (500 MHz) δ 1.94 (s, 3H), 2.18 (s, 3H), 3.53 (d, *J* = 10.1 Hz, 1H), 3.83 (s, 3H), 4.67 (d, *J* = 13.3 Hz, 1H), 4.76 (d, *J* = 10.1 Hz, 1H), 4.77 (d, *J* = 13.3 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 1H), 6.90 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H); MS *m/z* 345 (M^+, 4.5), 288 (4.6), 204 (88), 162 (100). Anal. Calcd for $C_{13}H_{16}INO_2$: C, 45.23; H, 4.67; N, 4.06. Found: C, 45.21; H, 4.73; N, 3.75.

Typical Procedure for the Preparation of 1,1-Disubstituted Isoindolines (4). 1-(1-Methyl-1-phenylisoindolin-2-yl)ethanone (4a). A solution of **3a** (0.28 g, 0.74 mmol) and *n*-Bu_3SnH (0.45 g, 1.5 mmol) in benzene (4 mL) was stirred at rt for 40 min before the solvent was evaporated. The residue was purified by column chromatography on silica gel (AcOEt–hexane, 1:2) to give **4a** (0.14 g, 73%); a white solid; mp 148–150 °C (hexane–Et_2O); IR (KBr) 1645 cm^{-1}; ^1H NMR (500 MHz; observed as a 6:4 mixture of rotamers) δ 1.75 (s, 1.2H), 2.07 (s, 1.2H), 2.150 (s, 1.8H), 2.155 (s, 1.8H), 4.98 (d, *J* = 11.9 Hz, 0.4H), 4.99 (d, *J* = 16.5 Hz, 0.6H), 5.06 (d, *J* = 11.9 Hz, 0.4H), 5.14 (d, *J* = 16.5 Hz, 0.6H), 6.82 (d, *J* = 7.8 Hz, 0.6H), 6.92 (d, *J* = 7.3 Hz, 0.4H), 7.15–7.34 (m, 8H); MS *m/z* (%) 251 (M^+, 100). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.11; H, 6.81; N, 5.55.

1-[1-(4-Methoxyphenyl)-1-methylisoindolin-2-yl)ethanone (4b): a white solid; mp 137–138 °C (hexane–CH_2Cl_2); IR (KBr) 1641, 1614 cm^{-1}; ^1H NMR (500 MHz; observed as a 6:4 mixture of rotamers) δ 1.77 (s, 1.2H), 2.03 (s, 1.2H), 2.13 (s, 1.8H), 2.14 (s, 1.8H), 3.75 (s, 1.2H), 3.79 (s, 1.8H), 4.94 (d, *J* = 13.7 Hz, 0.4H), 4.95 (d, *J* = 16.5 Hz, 0.6H), 5.02 (d, *J* = 13.7 Hz, 0.4H), 5.12 (d, *J* = 16.5 Hz, 0.6H), 6.79 (d, *J* = 9.2 Hz, 0.8H), 6.80 (d, *J* = 7.8 Hz, 0.4H), 6.85 (d, *J* = 8.7 Hz, 1.2H), 6.92 (d, *J* = 7.3 Hz, 0.6H), 7.15–7.33 (m, 5H); MS *m/z* 281 (M^+, 100). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.63; H, 6.74; N, 4.88.

1-(1,1-Dimethylisoindolin-2-yl)ethanone (4c): a white solid; mp 74–75 °C (hexane–Et_2O); IR (KBr) 1653 cm^{-1}; ^1H NMR (500 MHz) δ 1.75 (s, 6H), 2.15 (s, 3H), 4.78 (s, 2H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.28 (td, *J* = 7.3, 1.4 Hz, 1H), 7.32 (td, *J* = 7.3, 1.4 Hz, 1H); MS *m/z* 189 (M^+, 4.2), 174 (41), 132 (100). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.05; H, 8.06; N, 7.41.

1-(1-Ethyl-1-methylisoindolin-2-yl)ethanone (4d): a pale-yellow oil; R_f = 0.23 (AcOEt–hexane, 1:2); IR (neat) 1651 cm^{-1}; ^1H NMR (500 MHz) δ 0.50 (t, *J* = 7.3 Hz, 3H), 1.68 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.71 (s, 3H), 2.17 (s, 3H), 2.82 (dq, *J* = 14.6, 7.3 Hz, 1H), 4.72 (d, *J* = 13.7 Hz, 1H), 4.80 (d, *J* = 13.7 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.28 (td, *J* = 7.3, 1.4 Hz, 1H), 7.32 (dd, *J* = 7.8, 7.3 Hz, 1H); MS *m/z* 203 (M^+, 0.17), 174 (50), 132 (100). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.79; H, 8.50; N, 6.51.

General Procedure for the Preparation of 1-(Sulfenylmethyl)isoindolines (5). To a stirred suspension of NaH (60% in oil; 1.0 mmol) in DMF (2 mL) at 0 ˚C was added a thiol (1.0 mmol). After 15 min, one of compounds **3** (1.0 mmol) in DMF (6 mL) was added and the mixture was stirred for the time at the temperature indicated in Table 1. The resulting mixture was treated with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O four times (10 mL each). The combined extracts were washed with water three times (10 mL each) and then brine once (10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel (AcOEt–hexane, 1:2) to give pure product.

1-(1-Phenyl-1-phenylthiomethylisoindolin-2-yl)ethanone (5a): a white solid; mp 100–101 ˚C (hexane–CH_2Cl_2); IR (KBr) 1657 cm^{-1}; ^1H NMR (500 MHz; observed as a 8:2 mixture of rotamers) δ 1.61 (s, 0.6H), 1.93 (s, 2.4H), 3.90 (d, *J* = 12.8 Hz, 1H), 4.95 (d, *J* = 13.3 Hz, 0.8H), 5.00 (d, *J* = 13.3 Hz, 0.8H), 5.01 (d, *J* = 12.8 Hz, 1H), 5.08 (d, *J* = 16.1 Hz, 0.2H), 5.18 (d, *J* = 16.1 Hz, 0.2 Hz), 6.79 (d, *J* = 7.8 Hz, 0.2H), 6.83 (d, *J* = 7.8 Hz, 0.8H), 7.09 (m, 13H); MS *m/z* 359 (M^+, 4.1), 250 (14), 209 (36), 191 (100). Anal. Calcd for $C_{23}H_{21}NOS$: C, 76.85; H, 5.89; N, 3.90. Found: C, 76.77; H, 5.90; N, 3.90.

1-[1-(4-Methoxyphenyl)-1-phenylthiomethylisoindolin-2-yl)ethanone (5b): a white solid; mp 120–121 ˚C (hexane–CH_2Cl_2); IR (KBr) 1651, 1611 cm^{-1}; ^1H NMR (500 MHz; observed as a 8:2 mixture of rotamers) δ 1.63 (s, 0.6H), 1.92 (s, 2.4H), 3.75 (s, 2.4H), 3.78 (s, 0.6H), 3.84 (d, *J* = 12.8 Hz, 1H), 4.92 (d, *J* = 13.8 Hz, 0.8H), 4.98 (d, *J* = 13.8 Hz, 0.8H), 5.01 (d, *J* = 12.8 Hz, 1H), 5.05 (d, *J* = 16.0 Hz, 0.2H), 5.16 (d, *J* = 16.0 Hz, 0.2H), 6.76–6.85 (m, 3H), 7.09–7.35 (m, 10H); MS *m/z* 389 (M^+, 0.04), 266 (51), 224 (100). Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N, 3.60; S, 8.23. Found: C, 73.64; H, 6.01; N, 3.58; S, 8.14.

1-[1-Methyl-1-(phenylthiomethyl)isoindolin-2-yl]ethanone (5c): a white solid; mp 94–95 ˚C (hexane–Et_2O); IR (KBr) 1659 cm^{-1}; ^1H NMR (500 MHz) δ 1.85 (s, 3H), 1.88 (s, 3H), 3.25 (d, *J* = 13.3 Hz, 1H), 4.54 (d, *J* = 13.3 Hz, 1H), 4.72 (s, 2H), 7.07 (d, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 6.9, 2.3 Hz, 1H), 7.15–7.21 (m, 4H), 7.23–7.27 (m, 2H), 7.30 (td, *J* = 7.3, 0.9 Hz, 1H); MS *m/z* 297 (M^+, 0.27), 174 (62), 132 (100). Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71; S, 10.78. Found: C, 72.43; H, 6.43; N, 4.71; S, 10.76.

1-[1-Methyl-1-(pyridin-2-yl)thiomethylisoindolin-2-yl]ethanone (5d): a pale-yellow solid; mp 85–88 ˚C (hexane–CH_2Cl_2); IR (KBr) 1651 cm^{-1}; ^1H NMR (500 MHz) δ 1.91 (s, 3H), 2.10 (s, 3H), 3.87 (d, *J* =

13.3 Hz, 1H), 4.57 (d, *J* = 13.3 Hz, 1H), 4.77 (d, *J* = 13.7 Hz, 1H), 4.83 (d, *J* = 13.7 Hz, 1H), 6.87 (ddd, *J* = 6.9, 5.0, 0.9 Hz, 1H), 6.94 (dd, *J* = 6.9, 1.4 Hz, 1H), 7.12–7.22 (m, 4H), 7.31 (ddd, *J* = 8.2, 7.3, 1.8 Hz, 1H), 8.33 (dt, *J* = 3.7, 0.9 Hz, 1H); MS *m/z* 298 (M^+, 0.27), 174 (62), 132 (100). Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39; S, 10.75. Found: C, 68.17; H, 6.05; N, 9.36; S, 10.50.

1-[1-(4,6-Dimethylpyrimidin-2-yl)thiomethyl-1-methylisoindolin-2-yl]ethanone (5e): a white solid; mp 152–154 ˚C (hexane–CH_2Cl_2); IR (KBr) 1643 cm^{-1}; ^1H NMR (500 MHz) δ 1.93 (s, 3H), 2.14 (s, 3H), 2.31 (s, 6H), 3.97 (d, *J* = 13.3 Hz, 1H), 4.53 (d, *J* = 13.3 Hz, 1H), 4.76 (d, *J* = 13.3 Hz, 1H), 4.87 (d, *J* = 13.3 Hz, 1H), 6.54 (s, 1H), 7.12–7.20 (m, 3H), 7.23 (dd, *J* = 6.4, 1.8 Hz, 1H); MS *m/z* 327 (M^+, 0.16), 174 (55), 132 (100). Anal. Calcd for $C_{18}H_{21}N_3OS$: C, 66.02; H, 6.46; N, 12.83; S, 9.79. Found: C, 66.02; H, 6.44; N, 12.82; S, 9.54.

1-(1-Benzylthiomethyl-1-ethylisoindolin-2-yl)ethanone (5f): a white solid; mp 104–105 ˚C (hexane–Et_2O); IR (KBr) 1647 cm^{-1}; ^1H NMR (500 MHz) δ 0.53 (t, *J* = 7.3 Hz, 3H), 1.69 (dq, *J* = 14.6, 7.3 Hz, 1H,), 2.18 (s, 3H), 2.80 (dq, *J* = 14.6, 7.3 Hz, 1H), 2.86 (d, *J* = 13.3 Hz, 1H), 3.33 (d, *J* = 13.3 Hz, 1H), 3.34 (d, *J* = 13.3 Hz, 1H), 3.93 (d, *J* = 13.3 Hz, 1H), 4.74 (d, *J* = 13.7 Hz, 1H), 4.88 (d, *J* = 13.7 Hz, 1H), 7.03 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.12 (d, *J* = 8.2, 1.4 Hz, 2H), 7.19 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.22–7.27 (m, 3H), 7.29–7.33 (m, 2H); MS *m/z* 325 (M^+, 0.40), 188 (95), 146 (100). Anal. Calcd for $C_{20}H_{23}NOS$: C, 73.81; H, 7.12; N, 4.30. Found: C, 73.66; H, 7.14; N, 4.28.

1-(1-Benzylthiomethyl-6-methoxyisoindolin-2-yl)ethanone (5g): a white solid; mp 104–105 ˚C (hexane–CH_2Cl_2); IR (KBr): 1650 cm^{-1}; ^1H NMR (500 MHz) δ 1.77 (s, 3H), 2.15 (s, 3H), 2.84 (d, *J* = 13.3 Hz, 1H), 3.34 (d, *J* = 13.3 Hz, 1H), 3.39 (d, *J* = 13.3 Hz, 1H), 3.79 (s, 3H), 3.93 (d, *J* = 13.3 Hz, 1H), 4.72 (d, *J* = 12.8 Hz, 1H), 4.81 (d, *J* = 12.8 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.87 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.14–7.25 (m, 6H); MS *m/z* 341 (M^+, 0.28), 204 (94), 162 (100). Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10. Found: C, 70.28; H, 7.01; N, 3.98.

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