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SYNTHESIS OF 1*H*-ISOINDOL-3-AMINE DERIVATIVES BY IODINE-MEDIATED CYCLIZATION OF 2-VINYLBENZAMIDINE DERIVATIVES

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Abstract - It has been found that the reaction of 2-vinylbenzamidine derivatives, prepared by reacting 2-vinylbenzonitriles with lithium cyclic secondary amides, with iodine in the presence of sodium hydrogen carbonate in acetonitrile resulted in the formation of the corresponding 1-iodomethyl-1*H*-isoindole-3-amine derivatives in reasonable overall yields based on the starting 2-vinylbenzonitriles. We have also found that transformation of these 1-iodomethyl derivatives into 1-sulfenylmethyl derivatives could be achieved in good yields on treatment with various sodium thiolates.

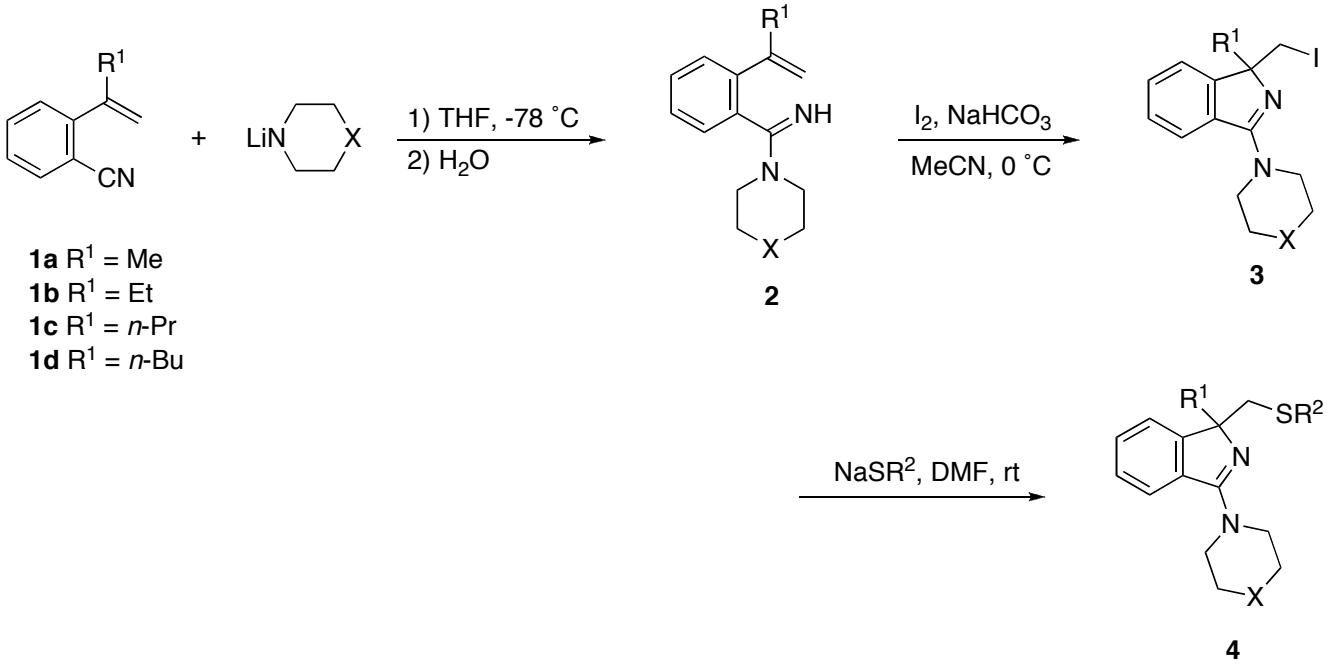
INTRODUCTION

In a recent paper, we described that the reaction of 2-vinylbenzylideneimine derivatives, which were easily prepared by reacting 2-lithiostyrene derivatives with nitriles, with iodine in the presence of sodium hydrogen carbonate afforded the corresponding 3-substituted 1-iodomethyl-1*H*-isoindole derivatives.[1] As an extension of this work, we wish to report here a convenient synthesis of 1*H*-isoindol-3-amine derivatives via iodine-mediated cyclization of 2-vinylbenzamidine derivatives, which can be easily prepared by reacting 2-vinylbenzonitrile derivatives with lithium amides, derived from cyclic secondary amines, such as pyrrolidine, piperidine, and 4-methylpiperazine. To the best of our knowledge, the synthesis of 1*H*-isoindol-3-amine derivatives has only been achieved by ring-contraction of 1*H*-2,4-benzodiazepine derivatives,[2] and no general and simple methods for their preparation have not been available so far.

RESULTS AND DISCUSSION

The synthesis of 1*H*-isoindol-3-amine derivatives (**3**) and (**4**) from 2-vinylbenzonitriles **1** was conducted

as illustrated in Scheme 1. Thus, 2-vinylbenzonitriles (**1**) were allowed to react with lithium amides, derived from cyclic secondary amines, such as pyrrolidine, piperidine, and 4-methylpiperazine, at –78 ˚C in THF to afford the corresponding 2-vinylbenzamidine derivatives (**2**). It should be noted that no reactions were observed for the addition of morpholin-4-yllithium and lithium dialkylamides, such as LDA and lithium diethylamide, to the nitrile carbon of the starting 2-vinylbenzonitriles, and almost quantitative amounts of the starting materials were recovered. Presumably, the lack of nucleophilicity of these lithium amides prevents the addition. Moreover the reactions of 2-(1-arylvinyl)benzonitriles with the above-mentioned lithium amides, derived from cyclic secondary amines, resulted in the formation of intractable mixtures of products. This may be attributable to the liability of these 2-cyanostyrenes to oligomerization under the reaction conditions.



Scheme 1

After usual aqueous work up, these amidines were used in the next step without any purification. Thus, treatment of these crude amidines with iodine (3 molar amounts) in the presence of sodium hydrogencarbonate (3 molar amounts) in acetonitrile at 0 ˚C afforded, after usual aqueous workup followed by purification using column chromatography on neutral alumina, the 5-*exo* cyclization products, 1-iodomethyl-3*H*-isoindol-3-amine derivatives (**3**) in reasonable overall yields from 2-vinylbenzonitriles (**1**), as listed in Table 1. While these products were purified by column chromatography on neutral alumina, no hydrolysis seemed to take place during purification. No traces of the 6-*endo* cyclization products (1-aminoisoquinoline derivatives) were detected.

Next, substitution of the iodo moieties of **3** with various sodium thiolates was examined. The reactions

were conveniently performed by stirring solutions of **3** and various sodium thiolates, generated from the respective thiols and sodium hydride, in DMF at room temperature overnight to afford 1-sulfenylmethyl-1*H*-isoindol-3-amines (**4**) in the yields summarized in Table 1. As can be seen from Entries 4 and 6, heterocyclic thiolates, such as 4,6-dimethylpyrimidine-2-thiolate and pyridin-2-thiolate, exhibited the satisfactory reactivity toward this substitution to yield the corresponding 1-sulfenylmethyl derivatives (**4d**) and (**4f**) in fair-to-good yields.

Table 1. Preparation of 1,1-Disubstituted 1*H*-Isoindol-3-amine Derivatives (**3**) and (**4**)

Entry	**1**	X	**3** (Yield/%)[a]	R^2	**4** (Yield/%)[b]
1	**1a**	nil	**3a** (36)	Bn	**4a** (70)
2	**1a**	CH_2	**3b** (31)	Ph	**4b** (77)
3	**1a**	NMe	**3c** (34)	$(CH_2)_2OH$	**4c** (92)
4	**1b**	nil	**3d** (38)	4,6-dimethylpyrimidin-2-yl	**4d** (62)
5	**1b**	CH_2	**3e** (38)	CH_2CO_2Et	**4e** (80)
6	**1b**	NMe	**3f** (34)	pyridin-2-yl	**4f** (76)
7	**1c**	nil	**3g** (40)	naphthalen-2-yl	**4g** (96)
8	**1c**	CH_2	**3h** (36)	$4\text{-}ClC_6H_4$	**4h** (87)
9	**1c**	NMe	**3i** (36)	*p*-Tol	**4i** (84)
10	**1d**	nil	**3j** (38)	$4\text{-}ClC_6H_4$	**4j** (83)
11	**1d**	CH_2	**3k** (37)	*p*-Tol	**4k** (82)

[a]Isolated yields from **1**. [b]Isolated yields.

In summary, we have developed the first procedure for the general preparation of 1,1-disubstituted 1*H*-isoindol-3-amine derivatives from α-substituted 2-vinylbenzonitriles using iodine mediated cyclization. Although the yields of the cyclization products are not so high, the ease of operations as well as the ready availability of the starting materials 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. ^{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. ^{13}C NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz in $CDCl_3$. Low- and high-resolution mass spectra were recorded on a JEOL JMS-AX505 HA spectrometer. Thin-layer chromatography (TLC) was carried out on Merck Alumina 60 Neutral F_{254} or Merck Kieselgel 60 PF_{254}. Column chromatography was carried out on Merck Alumina, Activated, Neutral, Activity I or Merck Kieselgel 60 (0.063–0.200 mm). All of the solvents used were dried over the appropriate drying agents and distilled under argon prior to use.

Starting Materials. 2-(1-Methylethenyl)benzonitrile (**1a**),[2,4] 2-(1-ethylethenyl)benzonitrile (**1b**),[2,4] 2-pentanoylbenzonitrile,[5] and 1-(2-bromophenyl)-1-butanone[6] were prepared by the appropriate reported procedures. All other chemicals used in this study were commercially available.

2-Butanoylbenzonitrile. This compound was prepared by treating 1-(2-bromophenyl)-1-butanone[4] with CuCN under the conditions reported by Friedman *et al.*[7] in 60% yield; a white solid; mp 42–44 °C (hexane–Et_2O); IR (KBr) 2220, 1693 cm^{-1}; ^1H NMR δ 1.02 (3H, t, *J* = 7.3 Hz), 1.80 (2H, sext, *J* = 7.3 Hz), 3.00 (2H, t, *J* = 7.3 Hz), 7.64 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.70 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.82 (1H, dd, *J* = 7.8, 1.4 Hz), 7.92 (1H, dd, *J* = 7.8, 1.4 Hz). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40, N, 8.09. Found: C, 76.22; H, 6.38; N, 8.08.

2-(1-Butylethenyl)benzonitrile (1c). This compound was prepared by the reaction of 2-butanoylbenzonitrile with methylenetriphenylphosphorane in DME at 0 °C in 51 % yield; R_f 0.47 (1:2 CH_2Cl_2–hexane, silica gel); IR (neat) 2226, 1636 cm^{-1}; ^1H NMR δ 0.93 (3H, t, *J* = 7.3 Hz), 1.42 (2H, sext, *J* = 7.3 Hz), 2.49 (2H, t, *J* = 7.3 Hz), 5.20 (1H, s), 5.36 (1H, d, *J* = 1,4 Hz), 7.32–7.36 (2H, m), 7.53 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.66 (1H, dd, *J* = 7.8, 0.9 Hz). Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65, N, 8.18. Found: C, 84.06; H, 7.72; N, 8.16.

2-(1-Butylethenyl)benzonitrile (1d). This compound was prepared by the reaction of 2-pentanoylbenzonitrile[5] with methylenetriphenylphosphorane in DME at 0 °C in 54% yield; R_f 0.50 (1:1 CH_2Cl_2–hexane, silica gel); IR (neat) 2226, 1634 cm^{-1}; ^1H NMR δ 0.89 (3H, t, *J* = 7.3 Hz), 1.33–1.40 (4H, m), 2.51 (2H, t, *J* = 7.3 Hz), 5.19 (1H, s), 5.35 (1H, d, *J* = 1.4 Hz), 7.33 (1H, d, *J* = 7.8 Hz), 7.35 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.54 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.66 (1H, d, *J* = 7.8 Hz). Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16, N, 7.56. Found: C, 83.97; H, 8.37; N, 7.54.

Typical Procedure for the Preparation of 1-Iodomethyl-1*H*-isoindole Derivatives (3). 1-Iodomethyl-1-methyl-3-(pyrrolidin-1-yl)-1*H*-isoindole (3a). To a stirred solution of pyrrolidine (0.28 g, 4.0 mmol) in THF (8 mL) at –78 °C was added butyllithium (1.6 M in hexane; 4 mmol) dropwise. After 15 min, a solution of **1a** (0.29 g, 2.0 mmol) in THF (3 mL) was added, and stirring was continued for an additional 3 h at the same temperature before the reaction was quenched by adding water (15 mL). The organic materials were extracted with CH_2Cl_2 three times (15 mL each), and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude amidine derivative (**2a**) was used in the next reaction without any purification. Thus, the crude **2a** was dissolved in MeCN (6 mL), and to this solution at 0 °C was added successively $NaHCO_3$ (0.50 g, 6.0 mmol) and iodine (1.5 g, 6.0 mmol) under stirring. After stirring was continued for 1 h at the same temperature, 10% aqueous $Na_2S_2O_3$ was added until the color of iodine disappeared. The solution was adjusted to pH 10 by adding 5% aqueous NaOH and extracted with CH_2Cl_2 three times (15 mL each). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was subjected to column chromatography on alumina to afford **3a** (0.26 mg, 36%); a yellow

solid; mp 75–77 °C (pentane); IR (KBr) 1599 cm^{-1}; ^1H NMR δ 1.62 (3H, s), 1.97 (4H, br s), 3.57 (1H, d, *J* = 9.6 Hz), 3.63 (1H, d, *J* = 9.6 Hz), 3.76 (4H, br s), 7.31 (1H, dd, *J* = 7.8, 7.3 Hz), 7.36 (1H, t, *J* = 7.3 Hz), 7.43 (1H, d, *J* = 7.3 Hz), 7.64 (1H, d, *J* = 7.8 Hz); ^{13}C NMR δ 18.90, 24.86, 25.51, 48.66, 69.85, 121.87, 122.51, 127.49, 128.31, 134.74, 156.96, 161.82; MS (CI) *m*/*z* 341 [$(M+1)^+$, 100]. Anal. Calcd for $C_{14}H_{17}IN_2$: C, 49.43; H, 5.04, N, 8.23. Found: C, 49.28; H, 5.20; N, 8.08.

1-Iodomethyl-1-methyl-3-(piperidin-1-yl)-1*H*-isoindole (3b): a yellow oil; R_f 0.37 (CH_2Cl_2); IR (neat) 1598 cm^{-1}; ^1H NMR δ 1.64 (3H, s), 1.74 (6H, br s), 3.60 (4H, br s), 3.66 (2H, s), 7.33–7.41 (2H, m), 7.46 (1H, d, *J* = 7.3 Hz), 7.60 (1H, d, *J* = 7.8 Hz); MS (EI) *m*/*z* 354 (M^+, 13), 227 (37), 213 (100). HR-MS Calcd for $C_{15}H_{19}IN_2$: M, 354.0593. Found: *m*/*z* 354.0585.

1-Iodomethyl-1-methyl-3-(4-methylpiperazin-1-yl)-1*H*-isoindole (3c): a yellow oil; R_f 0.45 (1:1 THF–C_6H_6); IR (neat) 1597 cm^{-1}; ^1H NMR δ 1.65 (3H, s), 2.36 (3H, s), 2.58–2.61 (4H, m), 3.66 (2H, s), 3.69–3.71 (4H, m), 7.36 (1H, td, *J* = 7.3, 1.4 Hz), 7.40 (1H, td, *J* = 7.3, 1.4 Hz), 7.46 (1H, d, *J* = 7.3 Hz), 7.59 (1H, d, *J* = 7.3 Hz); MS (EI) *m*/*z* 369 (M^+, 3.8), 242 (34), 228 (100). HR-MS Calcd for $C_{15}H_{20}IN_3$: M, 369.0702. Found: *m*/*z* 369.0695.

1-Ethyl-1-iodomethyl-3-(pyrrolidin-1-yl)-1*H*-isoindole (3d): a yellow solid; mp 79–81 °C (hexane–THF); IR (KBr) 1597 cm^{-1}; ^1H NMR δ 0.55 (3H, t, *J* = 7.3 Hz), 2.02–2.15 (6H, m), 3.62 (1H, d, *J* = 9.8 Hz), 3.69 (1H, d, *J* = 9.8 Hz), 3.80–3.82 (4H, m), 7.36 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.39 (1H, td, *J* = 7.3, 1.4 Hz), 7.44 (1H, d, *J* = 7.8 Hz), 7.68 (1H, d, *J* = 7.3 Hz); MS (EI) *m*/*z* 354 (M^+, 7.6), 325 (31), 227 (49), 213 (100). Anal. Calcd for $C_{15}H_{19}IN_2$: C, 50.86; H, 5.41; N, 7.91. Found: C, 50.83; H, 5.43; N, 7.90.

1-Ethyl-1-iodomethyl-3-(piperidin-1-yl)-1*H*-isoindole (3e): a yellow oil; R_f 0.38 (CH_2Cl_2); IR (neat) 1597 cm^{-1}; ^1H NMR δ 0.52 (3H, t, *J* = 7.3 Hz), 1.70–1.75 (6H, m), 2.03–2.16 (2H, m), 3.57–3.62 (4H, m), 3.68 (2H, s), 7.33–7.40 (3H, m), 7.59 (1H, d, *J* = 7.3 Hz); MS (EI) *m*/*z* 368 (M^+, 10), 339 (31), 241 (37), 227 (100). HR-MS Calcd for $C_{16}H_{21}IN_2$: M, 368.0749. Found: *m*/*z* 368.0745.

1-Ethyl-1-iodomethyl-3-(4-methylpiperazin-1-yl)-1*H*-isoindole (3f): a yellow oil; R_f 0.44 (1:1 THF–C_6H_6); IR (neat) 1597 cm^{-1}; ^1H NMR δ 0.52 (3H, t, *J* = 7.3 Hz), 2.03–2.17 (2H, m), 2.36 (3H, s), 2.58–2.60 (4H, m), 3.66 (2H, s), 3.68–3.71 (4H, m), 7.34–7.40 (3H, m), 7.58 (1H, d, *J* = 7.3 Hz); MS (EI) *m*/*z* 383 (M^+, 1.7), 326 (7.8), 312 (100). HR-MS Calcd for $C_{16}H_{22}IN_3$: M, 383.0858. Found: *m*/*z* 383.0847.

1-Iodomethyl-1-propyl-3-(pyrrolidin-1-yl)-1*H*-isoindole (3g): a pale-yellow solid; mp 65–67 °C (hexane–THF); IR (KBr) 1599 cm^{-1}; ^1H NMR δ 0.60–0.71 (1H, m), 0.76 (3H, t, *J* = 7.3 Hz), 1.09–1.19 (1H, m), 1.98–2.11 (6H, m), 3.61 (1H, d, *J* = 9.7 Hz), 3.68 (1H, d, *J* = 9.7 Hz), 3.76–3.84 (4H, m), 7.34–7.40 (3H, m), 7.67 (1H, d, *J* = 7.3 Hz); MS (EI) *m*/*z* 368 (M^+, 2.0), 325 (28), 241 (100). Anal. Calcd for $C_{16}H_{21}IN_2$: C, 52.18; H, 5.75; N, 7.61. Found: C, 52.12; H, 5.80; N, 7.60.

1-Iodomethyl-3-(piperidin-1-yl)-1-propyl-1*H*-isoindole (3h): a yellow oil; R_f 0.31 (CH_2Cl_2); IR (neat)

1597 cm^{-1}; ^1H NMR δ 0.60–0.69 (1H, m), 0.75 (3H, t, *J* = 7.3 Hz), 1.02–1.12 (1H, m), 1.68–1.78 (6H, m), 1.96–2.12 (2H, m), 3.57–3.61 (4H, m), 3.68 (2H, s), 7.33–7.40 (3H, m), 7.58 (1H, d, *J* = 7.3 Hz); ^{13}C NMR δ 14.34, 17.83, 18.18, 24.89, 25.66, 39.86, 49.35, 73.24, 121.70, 122.38, 127.42, 128.23, 135.82, 155.65, 166.42; MS (CI) *m/z* 383 [$(M+1)^+$, 100]. Anal. Calcd for $C_{17}H_{23}IN_2$: C, 53.41; H, 6.06; N, 7.33. Found: C, 53.36; H, 6.14; N, 7.05.

1-Iodomethyl-3-(4-methylpiperazin-1-yl)-1-propyl-1*H*-isoindole (3i): a yellow oil; R_f 0.30 (1:3 THF–C_6H_6); IR (neat) 1597 cm^{-1}; ^1H NMR δ 0.61–0.70 (1H, m), 0.76 (3H, t, *J* = 7.3 Hz); 1.01–1.11 (1H, m), 1.95–2.12 (2H, m), 2.36 (3H, s), 2.56–2.61 (4H, m), 3.66–3.72 (6H, m), 7.34–7.40 (3H, m), 7.57 (1H, d, *J* = 7.3 Hz); MS (CI) *m/z* 398 [$(M+1)^+$, 100]. Anal. Calcd for $C_{17}H_{24}IN_3$: C, 51.39; H, 6.09; N, 10.58. Found: C, 51.37; H, 6.20; N, 10.49.

1-Butyl-1-iodomethyl-3-(pyrrolidin-1-yl)-1*H*-isoindole (3j): a yellow oil; R_f 0.40 (1:3 THF–C_6H_6); IR (neat) 1599 cm^{-1}; ^1H NMR δ 0.59–0.65 (1H, m), 0.77 (3H, t, *J* = 7.3 Hz), 1.07–1.24 (3H, m), 1.99–2.12 (6H, m), 3.61 (1H, d, *J* = 9.6 Hz), 3.68 (1H, d, *J* = 9.6 Hz), 3.80–3.82 (4H, m), 7.36 (1H, td, *J* = 7.3, 1.4 Hz), 7.39 (1H, td, *J* = 7.3, 1.4 Hz), 7.44 (1H, d, *J* = 7.3 Hz), 7.68 (1H, dd, *J* = 7.3, 1.4 Hz); ^{13}C NMR δ 13.90, 19.08, 22.90, 25.50, 26.82, 37.61, 48.67, 72.81, 121.88, 122.27, 127.37, 128.11, 135.77, 155.73, 162.17; MS (CI) *m/z* 383 [$(M+1)^+$, 100]. Anal. Calcd for $C_{17}H_{23}IN_2$: C, 53.41; H, 6.06; N, 7.33. Found: C, 53.28; H, 6.20; N, 7.08.

1-Butyl-1-iodomethyl-3-(piperidin-1-yl)-1*H*-isoindole (3k): a yellow oil; R_f 0.18 (CH_2Cl_2); IR (neat) 1597 cm^{-1}; ^1H NMR δ 0.55–0.64 (1H, m), 0.76 (3H, t, *J* = 7.3 Hz), 0.99–1.07 (1H, m), 1.11–1.21 (2H, m), 1.69–1.76 (6H, m), 1.98–2.13 (2H, m), 3.58–3.62 (4H, m), 3.68 (2H, s), 7.34–7.40 (3H, m), 7.59 (1H, d, *J* = 7.3 Hz); MS (EI) *m/z* 396 (M^+, 0.5), 339 (18), 269 (100). HR-MS Calcd for $C_{18}H_{25}IN_2$: M, 396.1062. Found: *m/z* 396.1077.

Typical procedure for the Preparation of 1-Sulfenylmethyl-1*H*-isoindole Derivatives (4). 1-Benzylsulfanylmethyl-1-methyl-3-(pyrrolidin-1-yl)-1*H*-isoindole (4a). To a stirred suspension of NaH (60% in oil; 4.0 mg, 0.10 mmol) in DMF (2 mL) at 0 °C was added BnSH (12 mg, 0.10 mmol); after 15 min, the temperature was raised to rt. To this mixture was added a solution of **3a** (34 mg, 0.10 mmol) in DMF (1 mL), and stirring was continued for 3 h before the reaction was quenched by adding water (10 mL). The organic materials were extracted with CH_2Cl_2 three times (10 mL each), and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was subjected to column chromatography on alumina to afford **4a** (24 mg, 70%); a pale-yellow oil; R_f 0.43 (1:1 THF–hexane); IR (neat) 1597 cm^{-1}; ^1H NMR δ 1.72 (3H, s), 2.01–2.03 (4H, m), 2.93 (1H, d, *J* = 12.8 Hz), 2.97 (1H, d, *J* = 12.8 Hz), 3.63 (2H, s), 3.82 (4H, br s), 7.17–7.21 (3H, m), 7.24 (2H, d, *J* = 7.3 Hz), 7.32–7.36 (2H, m), 7.41 (1H, dd, *J* = 7.3, 1.4 Hz), 7.70 (1H, dd, *J* = 7.8, 1.4 Hz); MS (CI) *m/z* 337 [$(M+1)^+$, 100]. Anal. Calcd for $C_{21}H_{24}N_2S$: C, 74.96; H, 7.19; N, 8.33. Found: C, 74.97; H, 7.40; N, 8.08.

1-Methyl-1-phenylsulfanylomethyl-3-(piperidin-1-yl)-1*H*-isoindole (4b): a pale-yellow oil; R_f 0.29 (CH_2Cl_2); IR (neat) 1595 cm^{-1}; ^1H NMR δ 1.61 (3H, s), 1.68–1.70 (6H, m), 3.45 (2H, s), 3.47–3.52 (4H, m), 7.08 (1H, t, *J* = 7.3 Hz), 7.16 (2H, t, *J* = 7.3 Hz), 7.21 (2H, dd, *J* = 7.3, 1.4 Hz), 7.28–7.33 (2H, m), 7.41 (1H, dd, *J* = 7.8, 1.4 Hz), 7.59 (1H, d, *J* = 7.3 Hz); MS (CI) *m*/*z* 337 [$(M+1)^+$, 100]. Anal. Calcd for $C_{21}H_{24}N_2S$: C, 74.96; H, 7.19; N, 8.33. Found: C, 74.85; H, 7.05; N, 8.26.

2-{[1-Methyl-3-(4-methylpiperazin-1-yl)-1*H*-isoindol-1-yl]methylsulfanyl}ethanol (4c): a pale-yellow oil; R_f 0.32 (2:1 THF–hexane); IR (neat) 3356, 1597 cm^{-1}; ^1H NMR δ 1.48 (3H, s), 2.27 (3H, s), 2.37 (1H, s), 2.48–2.49 (1H, m), 2.59–2.63 (4H, m), 2.73–2.77 (1H, m), 3.18 (1H, d, *J* = 13.7 Hz), 3.26 (1H, d, *J* = 13.7 Hz), 3.67–3.79 (6H, m), 7.24–7.38 (3H, m), 7.62 (1H, d, *J* = 7.8 Hz); MS (CI) *m*/*z* 320 [$(M+1)^+$, 100]. Anal. Calcd for $C_{17}H_{25}N_3OS$: C, 63.91; H, 7.89; N, 13.15. Found: C, 63.76; H, 7.92; N, 13.12.

1-(4,6-Dimethylpyrimidin-2-yl)sulfanylmethyl-1-ethyl-3-(pyrrolidin-1-yl)-1*H*-isoindole (4d): a pale-yellow oil; R_f 0.36 (2:1 THF–hexane); IR (neat) 1597 cm^{-1}; ^1H NMR δ 0.50 (3H, t, *J* = 7.3 Hz), 1.99–2.02 (4H, m), 2.09–2.18 (2H, m), 2.32 (6H, s), 3.61 (1H, d, *J* = 12.8 Hz), 3.78–3.81 (4H, m), 4.07 (1H, d, *J* = 12.8 Hz), 6.56 (1H, s), 7.22 (1H, td, *J* = 7.3, 1.4 Hz), 7.23 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.47 (1H, dd, *J* = 7.3, 1.4 Hz), 7.63 (1H, dd, *J* = 7.8, 1.4 Hz); MS (EI) *m*/*z* 366 (M^+, 5.2), 337 (8.6), 213 (100). Anal. Calcd for $C_{21}H_{26}N_4S$: C, 68.82; H, 7.15; N, 15.29. Found: C, 68.50; H, 7.18; N, 15.03.

Ethyl 2-{[1-Ethyl-3-(piperidin-1-yl)-1*H*-isoindol-1-yl]sulfanylmethyl}acetate (4e): a pale-yellow oil; R_f 0.22 (1:10 THF–hexane); IR (neat) 1732, 1595 cm^{-1}; ^1H NMR δ 0.44 (3H, t, *J* = 7.3 Hz), 1.23 (3H, t, *J* = 7.3 Hz), 1.68–1.73 (6H, m), 1.95–2.02 (1H, m), 2.08–2.16 (1H, m), 3.04 (1H, d, *J* = 14.7 Hz), 3.14 (1H, d, *J* = 14.7 Hz), 3.15 (1H, d, *J* = 11.0 Hz), 3.22 (1H, d, *J* = 11.0 Hz), 3.56–3.58 (4H, m), 4.12 (2H, q, *J* = 7.3 Hz), 7.31–7.35 (2H, m), 7.39 (1H, dd, *J* = 7.3, 1.4 Hz), 7.58 (1H, dd, *J* = 7.3, 1.4 Hz); MS (EI) *m*/*z* 360 (M^+, 8.0), 226 (100). Anal. Calcd for $C_{20}H_{28}N_2O_2S$: C, 66.63; H, 7.83; N, 7.77. Found: C, 66.48; H, 7.88; N, 7.80.

1-Ethyl-3-(4-methylpiperazin-1-yl)-1-[(pyridin-2-yl)sulfanylmethyl]-1*H*-isoindole (4f): a pale-yellow oil; R_f 0.31 (2:1 THF–hexane); IR (neat) 1595 cm^{-1}; ^1H NMR δ 0.46 (3H, t, *J* = 7.3 Hz), 2.05–2.12 (1H, m), 2.17–2.24 (1H, m), 2.32 (3H, s), 2.51–2.57 (4H, m), 3.58–3.67 (4H, m), 3.83 (1H, d, *J* = 12.9 Hz), 3.84 (1H, d, *J* = 12.9 Hz), 6.89 (1H, dd, *J* = 7.3, 4.6 Hz), 6.99 (1H, dd, *J* = 8.7, 6.4 Hz), 7.23–7.29 (2H, m), 7.33 (1H, td, *J* = 7.3, 1.8 Hz), 7.40 (1H, d, *J* = 7.3 Hz), 7.54 (1H, d, *J* = 7.3 Hz), 8.36 (1H, d, *J* = 4.6 Hz); MS (EI) *m*/*z* 366 (M^+, 5.3), 284 (100). Anal. Calcd for $C_{21}H_{26}N_4S$: C, 68.82; H, 7.15; N, 15.29. Found: C, 68.76; H, 7.45; N, 14.98.

1-[(Naphthalen-2-yl)sulfanylmethyl]-1-propyl-3-(pyrrolidin-1-yl)-1*H*-isoindole (4g): a pale-yellow oil; R_f 0.30 (1:1 THF–hexane); IR (neat) 1597 cm^{-1}; ^1H NMR δ 0.56–0.66 (1H, m), 0.75 (3H, t, *J* = 7.3 Hz), 1.06–1.16 (1H, m), 1.84–1.90 (4H, m), 1.95–2.15 (2H, m), 3.51 (1H, d, *J* = 12.4 Hz), 3.60–3.70 (5H, m), 7.28–7.42 (6H, m), 7.56 (1H, s), 7.63–7.64 (2H, m), 7.69 (1H, d, *J* = 7.3 Hz), 7.73 (1H, d, *J* =

7.8 Hz); MS (EI) *m/z* 400 (M^+, 1.1), 227 (100). Anal. Calcd for $C_{26}H_{28}N_2S$: C, 77.96; H, 7.05; N, 6.99. Found: C, 77.73; H, 7.00; N, 6.74.

1-[(4-Chlorophenyl)sulfanylmethyl]-1-propyl-3-(pyrrolidin-1-yl)-1*H*-isoindole (4h): a pale-yellow oil; R_f 0.29 (1:7 THF–hexane); IR (neat) 1595 cm^{-1}; ^1H NMR δ 0.56–0.65 (1H, m), 0.74 (3H, t, *J* = 7.3 Hz), 1.00–1.08 (1H, m), 1.64–1.73 (6H, m), 1.90–2.11 (2H, m), 3.41 (1H, d, *J* = 12.8 Hz), 3.45–3.51 (5H, m), 7.12 (4H, s), 7.28–7.33 (3H, m), 7.58 (1H, d, *J* = 7.3 Hz); ^{13}C NMR δ 14.18, 16.80, 24.74, 25.60, 40.50, 44.81, 49.15, 75.25, 121.81, 122.26, 127.03, 127.97, 128.48, 130.82, 131.38, 135.98, 136.79, 155.41, 166.22; MS (CI) *m/z* 399 [$(M+1)^+$, 100]. Anal. Calcd for $C_{23}H_{27}ClN_2S$: C, 69.24; H, 6.82; N, 7.02. Found: C, 69.23; H, 6.85; N, 6.86.

1-[(4-Methylphenyl)sulfanylmethyl]-3-(4-methylpiperazin-1-yl)-1-propyl-1*H*-isoindole (4i): a pale-yellow oil; R_f 0.34 (1:2 THF–hexane); IR (neat) 1595 cm^{-1}; ^1H NMR δ 0.57–0.68 (1H, m), 0.74 (3H, t, *J* = 7.3 Hz), 0.98–1.08 (1H, m), 1.91–2.11 (2H, m), 2.26 (3H, s), 2.34 (3H, s), 2.54 (4H, t, *J* = 5.0 Hz), 3.43 (1H, d, *J* = 12.8 Hz), 3.45 (1H, d, *J* = 12.8 Hz), 3.54–3.65 (4H, m), 6.97 (2H, d, *J* = 7.8 Hz), 7.10 (2H, d, *J* = 7.8 Hz), 7.28–7.33 (2H, m), 7.37 (1H, dd, *J* = 7.3, 1.4 Hz), 7.56 (1H, d, *J* = 7.3 Hz); MS (CI) *m/z* 394 [$(M+1)^+$, 100]. Anal. Calcd for $C_{24}H_{31}N_3S$: C, 73.24; H, 7.94; N, 10.68. Found: C, 73.14; H, 8.22; N, 10.58.

1-Butyl-1-[(4-chlorophenyl)sulfanylmethyl]-3-(pyrrolidin-1-yl)-1*H*-isoindole (4j): a pale-yellow oil; R_f 0.32 (1:3 THF–C_6H_6); IR (neat) 1597 cm^{-1}; ^1H NMR δ 0.51–0.62 (1H, m), 0.74 (3H, t, *J* = 7.3 Hz), 1.05–1.22 (3H, m), 1.93–2.09 (6H, m), 3.41 (1H, d, *J* = 12.8 Hz), 3.51 (1H, d, *J* = 12.8 Hz), 3.69–3.81 (4H, m), 7.10 (2H, d, *J* = 8.7 Hz), 7.14 (2H, d, *J* = 8.7 Hz), 7.29–7.38 (3H, m), 7.68 (1H, d, *J* = 7.3 Hz); ^{13}C NMR δ 13.94, 22.87, 25.45, 25.65, 38.49, 45.41, 48.51, 75.03, 121.92, 122.23, 127.08, 128.02, 128.30, 128.40, 130.94, 131.31, 136.93, 155.64, 161.93; MS (CI) *m/z* 399 [$(M+1)^+$, 100]. Anal. Calcd for $C_{23}H_{27}ClN_2S$: C, 69.24; H, 6.82; N, 7.02. Found: C, 69.05; H, 6.65; N, 7.03.

1-Butyl-1-[(4-methylphenyl)thiomethyl]-3-(piperidin-1-yl)-1*H*-isoindole (4k): a pale-yellow oil; R_f 0.21 (1:2 Et_2O–hexane); IR (neat) 1595 cm^{-1}; ^1H NMR δ 0.44–0.53 (1H, m), 0.67 (3H, t, *J* = 7.3 Hz), 0.89–0.97 (1H, m), 1.02–1.12 (2H, m), 1.60–1.65 (6H, m), 1.87–2.01 (2H, m), 2.19 (3H, s), 3.35 (1H, d, *J* = 12.4 Hz), 3.38 (1H, d, *J* = 12.4 Hz), 3.40–3.45 (4H, m), 6.90 (2H, d, *J* = 7.8 Hz), 7.03 (2H, d, *J* = 7.8 Hz), 7.19–7.26 (2H, m), 7.29 (1H, d, *J* = 7.3 Hz), 7.50 (1H, d, *J* = 7.8 Hz); MS (EI) *m/z* 392 (M^+, 2.4), 255 (100). Anal. Calcd for $C_{25}H_{32}N_2S$: C, 76.48; H, 8.22; N, 7.14. Found: C, 76.38; H, 8.26; N, 7.07.

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