Tetrahedron 72 (2016) 5100–5105

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A convenient synthesis of 2-alkyl-3-aryl-2,3-dihydro-1*H*-isoindol-1-ones by the reaction of *N*-alkyl-*N*-[(2-bromophenyl)methyl] benzamides with butyllithium

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ARTICLE INFO

Article history:
Received 23 March 2016
Received in revised form 27 June 2016
Accepted 30 June 2016
Available online 1 July 2016

Keywords:
Isoindolinone
2,3-dihydro-1*H*-isoindol-1-one
Organolithium
Bromine/lithium exchange
Ring closure

ABSTRACT

An unprecedented and convenient synthetic approach to 2,3-dihydro-1*H*-isoindol-1-one (isoindolinone) derivatives has been developed. The key and final step of the method is the reaction of *N*-alkyl-*N*-(*o*-bromobenzyl)benzamides with butyllithium in THF at −78 °C. The corresponding 2-alkyl-3-aryl-2,3-dihydro-1*H*-isoindol-1-ones were produced in moderate-to-fair yields, probably via oxidation of the initially formed corresponding 2*H*-isoindole derivatives with air during workup.

1. Introduction

A large number of 2,3-dihydro-1*H*-isoindol-1-one (isoindolinone) derivatives have been reported to exhibit a variety of biological activities.[1] Recently, some synthetic elaborations of isoindolinone derivatives to more complex and important molecules have been demonstrated.[2] Moreover, many biologically important natural products with the isoindolinone structure have been isolated from nature.[3] Therefore, various synthetic approaches have been recording,[4] and we were interested in developing a method for the preparation of these heterocycles which would not only be unprecedented but also be operationally simple. As one of the studies on our ongoing research program for the preparation of benzene-fused nitrogen heterocycles utilizing *o*-functionalized benzyl azides,[5] we found that 2-alkyl-3-aryl-2,3-dihydro-1*H*-isoindol-1-ones (3-aryl-1-alkylisoindolinones) **4** can be prepared through a sequential reactions induced by the treatment of *N*-alkyl-*N*-(*o*-bromobenzyl)benzamides **3** with butyllithium.[6] Details of the new transformation are reported herein.

2. Results and discussion

Our synthesis of isoindolinones **4** was conducted according to the sequence illustrated in Scheme 1. The requisite precursors **3** were prepared from *o*-bromobenzyl azides **1** as follows. Compounds **1** were treated with triphenylphosphine in dichloromethane at room temperature overnight, and the resulting mixture was then allowed to react with aroyl chloride in the presence of triethylamine to give *N*-(*o*-bromobenzyl)benzamides **2** generally in good yields as compiled in Table 1. Aliphatic acyl chlorides, such as acetyl chloride and propionyl chloride did not work well in this acylation reaction. N-Alkylation of **2** was effected with sodium hydride and alkyl halides in DMF to provide *N*-alkyl-*N*-(*o*-bromobenzyl)benzamides **3** in relatively good yield as listed in Table 2. Compounds **3** were then converted into the desired isoindolinones **4** by treating with butyllithium.

The reaction of *N*-(*o*-bromobenzyl)-*N*-methylbenzamide (**3a**) was first treated with butyllithium in THF at −78 °C for 20 min to give, after quenching by adding water and extractive workup followed by purification using column chromatography on silica gel, 2-methyl-2-phenylisoindolin-1-one (**4a**) in 27% yield. This product exhibited spectral data (IR and ^{1}H NMR) fully identical to those reported previously for this compound.[7] The yield was improved (49%) when the reaction time was prolonged to 2 h (Table 2, Entry 1). Further extended reaction times did not improve the yield. A rise

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http://dx.doi.org/10.1016/j.tet.2016.06.082
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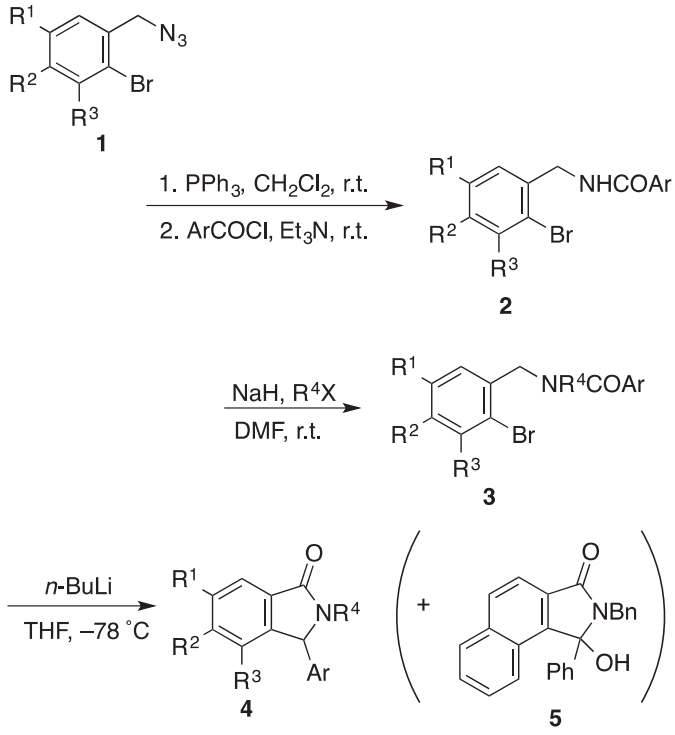


Scheme 1. Preparation of isoindolinones **4**.

(*o*-lithiobenzyl)-*N*-methylbenzamide and 1-bromobutane after the bromine/lithium exchange, did not be detected in the reaction mixture. In fact, the use of two equivalents of butyllithium did not improve the yields. THF was proved to be a superior solvent to diethyl ether or 1,2-dimethoxyethene (DME); the reactions in these solvents resulted in the formation of considerably intractable mixtures of products, from which only trace amounts of **4a** was obtained. Under these reaction conditions, the other eight *N*-alkyl-*N*-(*o*-bromobenzyl)benzamides (**3b** to **3i**) were similarly converted into the corresponding isoindolin-1-ones (**4b** to **4i**) in comparable yields (Table 2, Entries 2–9). These results indicate that both of electron-donating methoxy and electron-withdrawing chloro substituents on the benzene rings of **3** did not affect the yields of the products so much.

An attempt to prepare a 1,2-dihydro-3*H*-benz[*e*]isoindol-3-one derivative was carried out. However, under typical reaction conditions, *N*-[(2-bromonaphthalen-3-yl)methyl-*N*-(phenylmethyl) benzamide (**3j**) gave 1-hydroxy-1-phenyl-2-(phenylmethyl)-1,2-dihydro-3*H*-benz[*e*]isoindol-3-one (**5**) (32%) together with the desired product, 1-phenyl-2-(phenylmethyl)-1,2-dihydro-3*H*-benz[*e*] isoindol-3-one (**4j**) (19%) (Table 2, Entry 10). This by-product may be arisen from the autoxidation of **4j** probably during aqueous workup. These products could be easily separated by column chromatography on silica gel.

Although the mechanism of the formation of **4** from **3** is unclear, we assumed that the reaction would proceed through the pathway depicted in Scheme 2. Thus, *N*-[(2-lithiophenyl)methyl] benzamide intermediate **6**, generated by the bromine/lithium exchange between **3** and butyllithium, cyclizes intramolecularly to

Table 1
Preparation of *N*-alkyl-*N*-[(2-bromophenyl)methyl]benzamides **3**

Entry	1	Ar	2	Yield/%[a]	R^4X	3	Yield/%[a]
1	**1a** (R^1=R^2=R^3=H)	Ph	**2a**	74	MeI	**3a**	87
2					BnBr	**3b**	92
3					4-$ClC_6H_4CH_2Br$	**3c**	86
4	**1b** (R^1=R^3=H, R^2=Cl)	Ph	**2b**	78	BnBr	**3d**	83
5	**1c** (R^1=Cl, R^2=R^3=H)	Ph	**2c**	84	MeI	**3e**	70
6	**1d** (R^1=OMe, R^2=R^3=H)	Ph	**2d**	90	MeI	**3f**	86
7	**1d**	2-ClC_6H_4	**2e**	64	MeI	**3g**	77
8	**1d**	4-$MeOC_6H_4$	**2f**	90	MeI	**3h**	76
9	**1e** (R^1=R^2=OMe, R^3=H)	Ph	**2g**	75	MeI	**3i**	74
10	**1f** (R^1=H, R^2–R^3=benzo)	Ph	**2h**	87	BnBr	**3j**	73

[a] Yields of isolated products.

Table 2
Preparation of 2-alkyl-3-aryl-2,3-dihydro-1*H*-isoindol-1-ones **4**

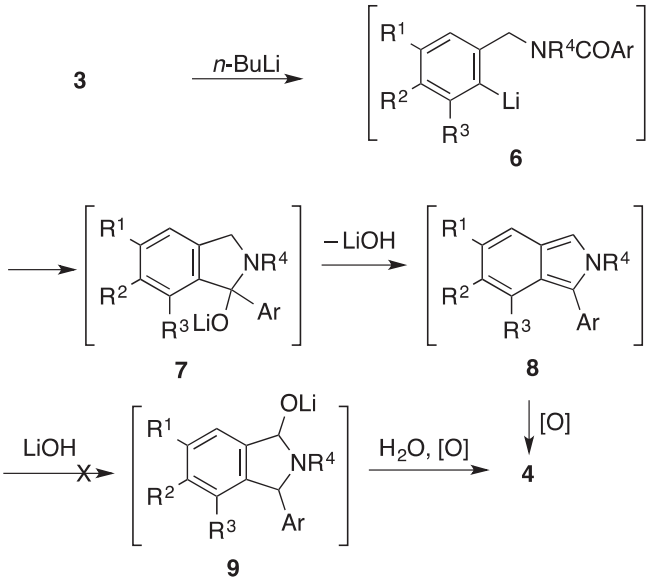
Entry	3	R^1	R^2	R^3	Ar	R^4	4	Yield/%[a]
1	**3a**	H	H	H	Ph	Me	**4a**	49
2	**3b**	H	H	H	Ph	Bn	**4b**	56
3	**3c**	H	H	H	Ph	4-$ClC_6H_4CH_2$	**4c**	51
4	**3d**	H	Cl	H	Ph	Bn	**4d**	50
5	**3e**	Cl	H	H	Ph	Me	**4e**	44
6	**3f**	OMe	H	H	Ph	Me	**4f**	47
7	**3g**	OMe	H	H	2-ClC_6H_4	Me	**4g**	53
8	**3h**	OMe	H	H	4-$MeOC_6H_4$	Me	**4h**	43
9	**3i**	OMe	OMe	H	Ph	Me	**4i**	55
10	**3j**	H	Benzo		Ph	Bn	**4j**	19[b]

[a] Yields of isolated products.
[b] Compound **5** was isolated in 32% yield along with **4j**.

of the reaction temperature to 0 °C conversely diminished the yield slightly. In every reaction, not only the starting material but also *N*-benzyl-*N*-methylbenzamide, arisen from the reaction between *N*-

form the lithium oxide intermediate **7**. Elimination of lithium hydroxide gives 2*H*-isoindole intermediate **8**, which was oxidized with oxygen during workup to give rise to **4**. A similar oxidation of 2*H*-isoindoles to 1,3-dihydro-2*H*-isoindol-1-ones has been recorded previously.[8] Compound **4f** is then further oxidized with air to give **5**. Alternatively, the formation of **4** might be trough addition of lithium hydroxide to **8** at the 3-position producing lithium 1,3-dihydro-2*H*-isoindol-1-olate intermediate **9**, followed by protonation and oxidation. However, since the corresponding protected 1,3-dihydro-2*H*-isoindol-1-ol derivative was not detected at all after addition of di-*tert*-butyl dicarbonate to the mixture obtained from the reaction of **3d** with butyllithium, this pathway could be excluded.

In conclusion, we have developed a novel sequence for the synthesis of 3-aryl-2-alkyl-2,3-dihydro-1*H*-isoindol-1-ones from *o*-bromobenzyl azides. Although the yields of the products in the final step are only moderate-to-fair, the attractiveness of the present procedure lies in its operational simplicity as well as the ready availability of the starting materials.



Scheme 2. A plausible pathway to the products **4**.

3. Experimental

3.1. General

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a Thermo Scientific Exactive spectrometer (ESI, positive) or a JEOL JMS-T100GCV (EI, TOF; 70 eV) spectrometer. Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

3.2. Starting materials

2-Bromo-1-(bromomethyl)-4-chlorobenzene[9] and 1-(azidomethyl)-2-bromobenzenes **1a**,[5f] **1c**[10] and **1e**[10] were prepared by the appropriate reported procedure. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

*3.2.1. Azides **1b**, **1d**,[11] and **1f**.* These compounds were prepared from the respective bromides according to the procedure for the preparation of **1a**.[5f]

*3.2.1.1. 1-(Azidomethyl)-2-bromo-4-chlorobenzene (**1b**).* Yield: 82%; a colorless oil; R_f 0.21 (hexane); IR (neat) 2105 cm^{-1}; ^{1}H NMR δ 4.47 (s, 2H), 7.33 (s, 2H), 7.62 (s, 1H); ^{13}C NMR δ 54.0, 123.9, 128.0, 130.6, 132.6, 133.6, 134.8. Anal. Calcd for $C_7H_5BrClN_3$: C, 34.11; H, 2.04; N, 17.05. Found: C, 33.96; H, 2.23; N, 16.96.

*3.2.1.2. 2-(Azidomethyl)-1-bromonaphthalene (**1f**).* Yield: 81%; a white solid; mp 27–28 °C (pentane); IR (KBr) 2105 cm^{-1}; ^{1}H NMR δ 4.75 (s, 2H), 7.51 (d, J=8.6 Hz, 1H), 7.56 (ddd, J=8.0, 6.9, 1.1 Hz, 1H), 7.63 (ddd, J=8.0, 6.9, 1.1 Hz, 1H), 7.85 (d, J=8.0 Hz, 2H), 8.35 (d, J=8.6 Hz, 1H); ^{13}C NMR δ 55.4, 124.1, 126.6, 127.0, 127.4, 127.79, 127.80, 128.2, 132.3, 132.9, 134.1. Anal. Calcd for $C_{11}H_8BrN_3$: C, 50.41; H, 3.08; N, 16.03. Found: C, 50.36; H, 3.06; N, 15.95.

3.3. General procedure for the preparation of *N*-[(2-bromophenyl)methyl]benzamides 2

A mixture of **1** (3.0 mmol) and PPh_3 (0.79 g, 3.0 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature overnight. Et_3N (0.30 g, 3.0 mmol) and ArCOCl (3.0 mmol) were then added and stirring was continued for an additional 15 min. The mixture was concentrated by evaporation and the residue was subjected to purification using column chromatography on SiO_2 (CH_2Cl_2) to afford **2**.

*3.3.1. N-[(2-Bromophenyl)methyl]benzamide (**2a**).* A white solid; mp 131–133 °C (hexane/CH_2Cl_2) (lit.,[12] 133–134 °C). The spectral (IR and ^{1}H NMR) were identical to those reported previously.[12]

*3.3.2. N-[(2-Bromo-4-chlorophenyl)methyl]benzamide (**2b**).* A white solid; mp 118–119 °C (hexane/CH_2Cl_2); IR (KBr) 3307, 1643 cm^{-1}; ^{1}H NMR δ 4.68 (d, J=6.3 Hz, 2H), 6.64 (br s, 1H), 7.28 (dd, J=8.0, 2.3 Hz, 1H), 7.42–7.46 (m, 3H), 7.52 (t, J=7.4 Hz, 1H), 7.59 (d, J=2.3 Hz, 1H), 7.78 (d, J=7.4 Hz, 2H); ^{13}C NMR δ 43.7, 123.9, 127.0, 128.0, 128.6, 131.3, 131.7, 132.4, 134.0, 134.2, 135.9, 167.3. HRMS (EI) calcd for $C_{14}H_{11}BrClNO$ (M): 322.9713. Found: *m/z* 322.9711.

*3.3.3. N-[(2-Bromo-5-chlorophenyl)methyl]benzamide (**2c**).* A white solid; mp 129–131 °C (hexane/CH_2Cl_2); IR (KBr) 3295, 1639 cm^{-1}; ^{1}H NMR δ 4.68 (d, J=6.3 Hz, 1H), 6.66 (br s, 1H), 7.15 (dd, J=8.6, 2.3 Hz, 1H), 7.44–7.54 (m, 6H), 7.80 (dd, J=8.6, 1.7 Hz, 2H); ^{13}C NMR δ 44.0, 121.3, 127.0, 128.7 (2 overlapped Cs), 129.2, 130.1, 131.8, 133.8, 133.9, 138.9, 167.4. HRMS (ESI) calcd for $C_{14}H_{12}BrClNO$ (M+H): 323.9791. Found: *m/z* 323.9782.

*3.3.4. N-[(2-Bromo-5-methoxyphenyl)methyl]benzamide (**2d**).*[13] A white solid; mp 100–102 °C (hexane/CH_2Cl_2); IR (KBr) 3310, 1638, 1601 cm^{-1}; ^{1}H NMR δ 3.78 (s, 3H), 4.68 (d, J=5.7 Hz, 2H), 6.63 (br, 1H), 6.73 (dd, J=8.6, 2.9 Hz, 1H), 7.03 (d, J=2.9 Hz, 1H), 7.42–7.46 (m, 4H), 7.51 (t, J=7.4 Hz, 1H), 7.79 (d, J=8.6 Hz, 1H).

*3.3.5. N-[(2-Bromo-5-methoxyphenyl)methyl]-2-chlorobenzamide (**2e**).* A white solid; mp 129–130 °C (hexane/CH_2Cl_2); IR (KBr) 3308, 1631 cm^{-1}; ^{1}H NMR δ 3.80 (s, 3H), 4.70 (d, J=6.3 Hz, 2H), 6.70 (br, 1H), 6.73 (dd, J=8.6, 2.9 Hz, 1H), 7.08 (d, J=2.9 Hz, 1H), 7.33 (td, J=7.4, 1.7 Hz, 1H), 7.37 (td, J=7.4, 1.7 Hz, 1H), 7.40 (dd, J=7.4, 1.7 Hz, 1H), 7.44 (d, J=8.6 Hz, 1H), 7.70 (dd, J=7.4, 1.7 Hz, 1H); ^{13}C NMR δ 44.5, 55.5, 113.9, 115.2, 115.7, 127.1, 130.26, 130.30, 130.7, 131.4, 133.3, 134.6, 137.7, 159.2, 166.3. HRMS (EI) calcd for $C_{15}H_{13}BrClNO_2$ (M): 352.9818. Found: *m/z* 352.9892.

*3.3.6. N-[(2-Bromo-5-methoxyphenyl)methyl]-4-methoxybenzamide (**2f**).* A white solid; mp 129–131 °C (hexane/CH_2Cl_2); IR (KBr) 3339, 1635, 1606 cm^{-1}; ^{1}H NMR δ 3.78 (s, 3H), 3.85 (s, 3H), 4.66 (d, J=6.3 Hz, 2H), 6.55 (br, 1H), 6.72 (dd, J=8.6, 2.9 Hz, 1H), 6.92 (d, J=8.6 Hz, 2H), 7.02 (d, J=2.9 Hz, 1H), 7.44 (d, J=8.6 Hz, 1H), 7.76 (d, J=8.6 Hz, 2H); ^{13}C NMR δ 44.4, 55.4, 55.5, 113.7, 113.8, 114.9, 116.9, 128.8, 132.3, 133.3, 138.3, 159.2, 162.3, 170.9. HRMS (ESI) calcd for $C_{16}H_{17}BrNO_3$ (M+H): 350.0392. Found: *m/z* 350.0386.

*3.3.7. N-[(2-Bromo-4,5-dimethoxyphenyl)methyl]benzamide (**2g**).* A white solid; mp 135–136 °C (hexane/CH_2Cl_2); IR (KBr) 3285, 1635, 1603 cm^{-1}; ^{1}H NMR δ 3.87 (s, 6H), 4.65 (d, J=6.3 Hz, 2H), 6.60 (br s, 1H), 7.03 (s, 2H), 7.43 (t, J=7.4 Hz, 2H), 7.50 (t, J=7.4 Hz, 1H), 7.78 (d, J=7.4 Hz, 2H); ^{13}C NMR δ 44.1, 56.1, 56.2, 113.6, 113.9, 115.4, 126.9, 128.6, 129.4, 131.5, 134.3, 148.5, 149.1, 167.2. HRMS (ESI) calcd for $C_{16}H_{17}BrNO_3$ (M+H): 350.0392. Found: *m/z* 350.0401.

*3.3.8. N-[(1-Bromonaphthalen-2-yl)methyl]benzamide (**2h**).* A white solid; mp 178–180 °C (hexane/CH_2Cl_2); IR (KBr) 3295, 1639 cm^{-1}; ^{1}H NMR δ 4.97 (d, J=6.3 Hz, 2H), 6.73 (br s, 1H), 7.43 (dd,

J=8.0, 7.4 Hz, 2H), 7.49 (t, *J*=7.4 Hz, 1H), 7.53 (dd, *J*=8.0, 7.4 Hz, 1H), 7.60 (d, *J*=8.0 Hz, 2H), 7.79–7.84 (m, 4H), 8.32 (d, *J*=8.6 Hz, 1H); ^{13}C NMR δ 45.3, 124.0, 126.6, 127.0, 127.1, 127.5, 127.6, 128.08, 128.14, 128.6, 131.6, 132.3, 134.0, 134.1, 135.5, 167.4. HRMS (EI) calcd for $C_{18}H_{14}BrBrNO$ (M): 339.0259. Found: *m/z* 339.0254.

3.4. Typical procedure for the preparation of *N*-alkyl-*N*-[(2-bromophenyl)methyl]benzamides 3

*3.4.1. N-[(2-Bromophenyl)methyl]-N-methylbenzamide (**3a**).* To a stirred suspension of NaH (60% in mineral oil; 44 mg, 1.1 mmol) in DMF (3 mL) at room temperature was added a solution of **2a** (0.29 g, 1.0 mmol) in DMF (2 mL) dropwise. After evolution of H_2 gas had ceased, MeI (75 mg, 1.2 mmol) was added. After 1.5 h, H_2O (20 mL) was added and the mixture was extracted with AcOEt (3×10 mL). The combined extracts were washed with H_2O (3×20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to afford **3a** (0.26 g, 87%); a colorless oil; a mixture of rotamers; R_f 0.24 (CH_2Cl_2); IR (neat) 1638, 1602 cm^{-1}; ^{1}H NMR δ 2.91 and 3.08 (2br s, combined 3H), 4.57 and 4.89 (2br s, combined 2H), 7.18–7.60 (m, 9H); ^{13}C NMR δ 33.4, 37.2, 50.5, 55.3, 122.5, 123.6, 126.4, 126.9, 127.4, 127.6, 128.2, 128.8, 129.0, 129.5, 129.60, 129.63, 132.7, 132.9, 135.4, 135.5, 135.7, 171.4, 172.3. HRMS (EI) calcd for $C_{15}H_{14}BrNO$ (M): 303.0259. Found: *m/z* 303.0249.

*3.4.2. N-[(2-Bromophenyl)methyl]-N-(phenylmethyl)benzamide (**3b**).* A colorless oil; a mixture of rotamers; R_f 0.21 (Et_2O/hexane 1:2); IR (neat) 1639, 1602 cm^{-1}; ^{1}H NMR δ 4.47 (br s, 2H), 4.72 and 4.81 (2br s, combined 2H), 7.12–7.53 (m, 14H); ^{13}C NMR δ 47.4, 52.0, 122.7, 123.7, 126.3, 126.6, 127.0, 127.4, 127.5, 127.8, 128.2, 128.5, 128.8, 129.5, 129.6, 131.11, 132.2, 132.8, 133.0, 135.2, 135.5, 135.6, 136.1, 136.4, 172.2. HRMS (EI). calcd for $C_{21}H_{18}BrNO$ (M): 379.0572. Found: *m/z* 379.0588.

*3.4.3. N-[(2-Bromophenyl)methyl]-N-[(4-chlorophenyl)methyl]benzamide (**3c**).* A white solid; mp 91–93 °C (hexane/CH_2Cl_2); a mixture of rotamers; IR (KBr) 1640, 1601 cm^{-1}; ^{1}H NMR δ 4.42 and 4.48 (2br s, combined 2H), 4.67 and 4.80 (2br s, combined 2H), 7.05–7.55 (m, 13H); ^{13}C NMR δ 47.0, 47.5, 51.4, 52.1, 122.9, 123.8, 126.5, 126.6, 127.5, 127.7, 127.9, 128.1, 128.3, 128.4, 128.7, 128.77, 128.79, 129.0, 129.7, 129.8, 131.3, 132.5, 132.9, 133.1, 133.3, 134.7, 135.1, 135.4, 135.5, 137.2, 167.2, 172.3. Anal. Calcd for $C_{21}H_{17}BrClO_2$: C, 60.82; H, 4.13; N, 3.38. Found: C, 60.42; H, 4.08; N, 3.27.

*3.4.4. N-[(2-Bromo-4-chlorophenyl)methyl]-N-(phenylmethyl)benzamide (**3d**).* A colorless oil; a mixture of rotamers; R_f 0.30 (CH_2Cl_2/hexane 2:1); IR (neat) 1642 cm^{-1}; ^{1}H NMR δ 4.43 and 4,47 (2br s, combined 2H), 4.70 and 4.78 (2br s, combined 2H), 7.11–7.58 (m, 13H); ^{13}C NMR δ 47.3, 47.9, 51.9, 52.5, 126.7, 127.0, 127.9, 128.0, 128.1, 128.5, 128.7, 129.0, 130.1, 130.8, 132.7, 133.0, 134.1, 134.7, 135.7, 136.2, 136.6, 171.6. HRMS (EI) calcd for $C_{21}H_{17}BrClNO$ (M): 413.0182. Found: *m/z* 413.0201.

*3.4.5. N-[(2-Bromo-5-chlorophenyl)methyl]-N-methylbenzamide (**3e**).* A pale-yellow oil; R_f 0.29 (CH_2Cl_2/hexane 1:1); a mixture of rotamers; IR (neat) 1639 cm^{-1}; ^{1}H NMR δ 2.95 and 3.09 (2br s, combined 3H), 4.52 and 4.84 (2br s, combined 2H), 7.16–7.51 (m, 8H); ^{13}C NMR δ 33.7, 37.5, 50.6, 53.4, 55.3, 120.3, 121.4, 126.5, 127.0, 127.6, 128.4, 128.8, 128.9, 129.0, 129.8, 133.8, 133.9, 134.1, 135.3, 135.5, 137.6, 171.7, 172.4. HRMS (EI). Calcd for $C_{15}H_{13}BrClNO$ (M): 336.9869. Found: *m/z* 336.9865.

*3.4.6. N-[(2-Bromo-5-methoxyphenyl)methyl]-N-methylbenzamide (**3f**).* A pale-yellow oil; R_f 0.38 (CH_2Cl_2/hexane 3:1); a mixture of rotamers; IR (neat) 1638 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.92 and 3.08 (2br s, combined 3H), 3.81 (br s, 3H), 4.52 and 4.84 (2br s, combined 2H), 6.74 (dd, *J*=8.6, 2.9 Hz, 1H), 6.85 and 6.92 (2br s, combined 1H), 7.35–7.48 (m, 6H); ^{13}C NMR δ 33.5, 37.2, 50.6, 55.3, 112.7, 113.8, 114.0, 114.8, 126.5, 126.8, 128.2, 129.6, 129.7, 133.3, 133.5, 135.5, 135.8, 136.6, 159.1, 170.8, 172.3. HRMS (EI) calcd for $C_{16}H_{16}BrNO_2$ (M): 333.0364. Found: *m/z* 333.0361.

*3.4.7. N-[(2-Bromo-5-methoxyphenyl)methyl]-2-chloro-N-methylbenzamide (**3g**).* A pale-yellow oil; R_f 0.28 (CH_2Cl_2/hexane 5:1); a mixture of rotamers; IR (neat) 1646 cm^{-1}; ^{1}H NMR δ 2.82 and 3.09 (2br s, combined 3H), 3.80 (s, 3H), 4.43, 4.76, and 5.04 (3br, combined 2H), 6.71 and 6.74 (2dd, *J*=9.2, 2.9 Hz each, combined 1H), 6.81 and 7.04 (2d, *J*=2.9 Hz each, combined 1H), 7.26–7.46 (m, 5H); ^{13}C NMR δ 32.7, 35.8, 50.1, 54.2, 55.4, 113.1, 113.9, 114.1, 114.6, 115.2, 127.0, 127.2, 127.6, 127.7, 129.6, 129.7, 130.1, 130.2, 130.3, 130.4, 133.3, 133.6, 135.9, 136.0, 159.29, 159.33, 168.7, 169.0. HRMS (EI) calcd for $C_{16}H_{15}BrClNO_2$ (M): 366.9975. Found: *m/z* 366.9983.

*3.4.8. N-[(2-Bromo-5-methoxyphenyl)methyl]-4-methoxy-N-methylbenzamide (**3h**).* A pale-yellow oil; R_f 0.25 (CH_2Cl_2); a mixture of rotamers; IR (neat) 1634, 1609 cm^{-1}; ^{1}H NMR δ 3.05 (br, 3H), 3.81 (s. 3H), 3.82 (s, 3H), 4.56 and 4.81 (2br, combined 2H), 6.73 (dd, *J*=8.6, 2.9 Hz, 1H), 6.89 (br, 3H), 7.45 (br, 3H); ^{13}C NMR δ 34.5, 38.3, 50.1, 55.1, 55.3, 113.5, 114.1, 127.7, 128.7, 128.8, 128.86, 128.92, 128.96, 129.00, 129.1, 133.47, 133.49, 136.9, 159.3, 160.7, 170.9, 172.0. HRMS (EI) calcd for $C_{17}H_{18}BrNO_3$ (M): 363.0470. Found: *m/z* 363.0464.

*3.4.9. N-[(2-Bromo-4,5-dimethoxyphenyl)methyl]-N-methylbenzamide (**3i**).* A pale-yellow oil; R_f 0.23 (CH_2Cl_2); a mixture of rotamers; IR (neat) 1636, 1602 cm^{-1}; ^{1}H NMR δ 2.89 and 3.06 (2br s, combined 3H), 3.88 (s, 6H), 4.52 and 4.85 (2br s, combined 2H), 6.72–7.45 (m, 7H); ^{13}C NMR δ 33.1, 36.8, 49.7, 99.6, 110.3, 112.3, 112.6, 113.8, 115.0, 115.5, 123.8, 125.9, 126.6, 126.7, 127.9, 128.2, 129.4, 129.6, 135.8, 148.5, 148.7, 170.8, 172.1. HRMS (EI) calcd for $C_{17}H_{18}BrNO_3$ (M): 363.0470. Found: *m/z* 363.0471.

*3.4.10. N-[(2-Bromonaphthalen-3-yl)methyl]-N-(phenylmethyl)benzamide (**3j**).* A white solid; mp 98–100 °C (hexane/CH_2Cl_2); a mixture of rotamers; IR (neat) 1630 cm^{-1}; ^{1}H NMR δ 4.47 (br s, 1H), 4.73 and 4.75 (2br s, combined 2H), 5.09 (br s, 1H), 7.13–8.33 (m, 16H); ^{13}C NMR δ 47.7, 48.2, 52.0, 52.9, 123.0, 124.0, 124.4, 126.5, 126.67, 126.71, 126.8, 127.1, 127.5, 127.7, 127.9, 127.96, 128.02, 128.1, 128.2, 128.4, 128.6, 129.7, 132.2, 133.3, 133.7, 134.0, 135.6, 135.7, 136.2, 136.5, 172.4. HRMS (ESI) calcd for $C_{25}H_{21}BrNO$ (M+H): 430.0807. Found: *m/z* 430.0805.

3.5. Typical procedure for the preparation of 2,3-dihydro-1*H*-isoindol-1-ones 4

*3.5.1. 2-Methyl-3-phenyl-2,3-dihydro-1H-isoindol-1-one (**4a**).* To a stirred solution of **3a** (0.23 g, 0.76 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (1.6 M in hexane; 0.76 mmol) dropwise. After 2 h, H_2O (15 mL) was added and the mixture was extracted with AcOEt (3×10 mL). The combined extracts were washed with H_2O and brine (15 mL each), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 (AcOEt/hexane 1:2) to afford **4a** (83 mg, 49%); white solid; mp 100–102 °C (hexane/CH_2Cl_2) (lit.,[7] mp 101 °C). The spectral data (IR and ^{1}H NMR) were identical to those reported previously.[7]

*3.5.2. 3-Phenyl-2-(phenylmethyl)-2,3-dihydro-1H-isoindol-1-one (**4b**).* A white solid; mp 133–135 °C (hexane/CH_2Cl_2) (lit.,[7] mp 136 °C). The spectral data (IR and ^{1}H NMR) were identical to those reported previously.[7]

*3.5.3. 2-[(4-Chlorophenyl)methyl]-3-phenyl-2,3-dihydro-1H-isoindol-1-one (**4c**).* A pale-yellow solid; mp 120–125 °C (hexane/

CH_2Cl_2); IR (KBr) 1694, 1640 cm^{-1}; ^1H NMR δ 3.74 (d, J=14.9 Hz, 1H), 5.22 (s, 1H), 5.31 (d, J=14.9 Hz, 1H), 7.05–7.06 (m, 2H), 7.10 (d, J=8.6 Hz, 2H), 7.25 (d, J=8.6 Hz, 2H), 7.29–7.39 (m, 4H), 7.43–7.50 (m, 2H), 7.94 (dd, J=8.6, 2.3 Hz, 1H); ^{13}C NMR δ 43.2, 63.6, 123.2, 123.7, 127.7, 128.4, 128.76, 128.81, 129.2, 129.8, 131.1, 132.0, 133.4, 135.6, 136.5, 146.2, 168.5. HRMS (EI) calcd for $C_{21}H_{16}ClNO$ (M): 333.0920. Found: m/z 333.0927. Anal. Calcd for $C_{21}H_{16}ClNO$: C, 75.56; H, 4.83; N, 4.20. Found: C, 75.43; H, 5.06; N, 4.12.

*3.5.4. 5-Chloro-3-phenyl-2-(phenylmethyl)-2,3-dihydro-1H-isoindol-1-one (**4d**).* A white solid; mp 148–151 °C (hexane/CH_2Cl_2); IR (KBr) 1698, 1611 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.72 (d, J=14.9 Hz, 1H), 5.21 (s, 1H), 5.37 (d, J=14.9 Hz, 1H), 7.05–7.09 (m, 3H), 7.16 (d, J=6.9 Hz, 2H), 7.26–7.31 (m, 3H), 7.36–7.39 (m, 3H), 7.43 (dd, J=8.0, 1.1 Hz, 1H), 7.86 (d, J=8.0 Hz, 1H); ^{13}C NMR δ 43.9, 63.2, 123.6, 125.0, 127.67, 127.70, 128.4, 128.7, 129.0, 129.3, 129.83, 129.84, 135.9, 136.8, 138.2, 147.8, 167.4. HRMS (EI) calcd for $C_{21}H_{16}ClNO$ (M): 333.0920. Found: m/z 333.0913. Anal. Calcd for $C_{21}H_{16}ClNO$: C, 75.56; H, 4.83; N, 4.20. Found: C, 75.38; H, 4.96; N, 4.02.

*3.5.5. 6-Chloro-2-methyl-3-phenyl-2,3-dihydro-1H-isoindol-1-one (**4e**).* A yellow solid; mp 94–96 °C (hexane/CH_2Cl_2); IR (KBr) 1686 cm^{-1}; ^1H NMR δ 2.96 (s, 3H), 5.31 (s, 1H), 7.09–7.13 (m, 3H), 7.34–7.38 (m, 3H), 7.42 (dd, J=8.0, 1.7 Hz, 1H), 7.83 (d, J=1.7 Hz, 1H); ^{13}C NMR δ 27.6, 66.3, 123.6, 124.2, 127.3, 128.9, 129.3, 131.8, 133.4, 134.6, 136.2, 144.2, 167.3. HRMS (EI) calcd for $C_{15}H_{12}ClNO$ (M): 257.0607. Found: m/z 257.0612. Anal. Calcd for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.69; N, 5.43. Found: C, 69.56; H, 4.56; N, 5.33.

*3.5.6. 6-Methoxy-2-methyl-3-phenyl-2,3-dihydro-1H-isoindol-1-one (**4f**).* A white solid; mp 115–116 °C (hexane/CH_2Cl_2); IR (KBr) 1682, 1617 cm^{-1}; ^1H NMR δ 2.96 (s, 3H), 3.86 (s, 3H), 5.27 (s, 1H), 7.01 (dd, J=8.6, 2.9 Hz, 1H), 7.05 (d, J=8.6 Hz, 1H), 7.13 (dd, J=7.4, 1.1 Hz, 2H), 7.31–7.36 (m, 3H), 7.37 (d, J=2.9 Hz, 1H); ^{13}C NMR δ 27.6, 55.7, 66.2, 106.2, 119.9, 123.8, 127.3, 128.6, 129.8, 133.0, 137.2, 138.4, 160.1, 168.7. HRMS (EI) calcd for $C_{16}H_{15}NO_2$ (M): 253.1103. Found: m/z 253.1103. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.82; H, 6.05; N, 5.42.

*3.5.7. 3-(2-Chlorophenyl)-6-methoxy-2-methyl-2,3-dihydro-1H-isoindol-1-one (**4g**).* A white solid; mp 131–134 °C (hexane/CH_2Cl_2); IR (KBr) 1693, 1620 cm^{-1}; ^1H NMR δ 2.99 (s, 3H), 3.86 (s, 3H), 6.02 (s, 1H), 6.77 (dd, J=8.0, 1.7 Hz, 1H), 7.01 (dd, J=8.0, 2.3 Hz, 1H), 7.17 (t, J=7.4 Hz, 1H), 7.16–7.25 (m, 2H), 7.36 (d, J=2.3 Hz, 1H), 7.49 (d, J=7.4 Hz, 1H); ^{13}C NMR δ 27.7, 55.7, 61.7, 106.4, 120.0, 123.7, 127.4, 127.8, 129.5, 130.0, 133.0, 134.0, 135.0, 137.9, 160.3, 168.9. HRMS (EI) calcd for $C_{16}H_{14}ClNO_2$ (M): 287.0713. Found: m/z 287.0719. Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.69; H, 4.86; N, 4.79.

*3.5.8. 6-Methoxy-3-(4-methoxyphenyl)-2-methyl-2,3-dihydro-1H-isoindol-1-one (**4h**).* A white solid; mp 133–135 °C (hexane/CH_2Cl_2); IR (KBr) 1686, 1611 cm^{-1}; ^1H NMR δ 2.93 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 5.22 (s, 1H), 6.87 (d, J=9.2 Hz, 2H), 7.00–7.05 (m, 4H), 7.36 (d, J=2.3 Hz, 1H); ^{13}C NMR δ 27.4, 55.3, 55.7, 65.7, 106.1, 113.9, 114.4, 119.8, 123.8, 128.7, 129.0, 133.1, 138.6, 159.8, 160.1. HRMS (EI) calcd for $C_{17}H_{17}NO_3$ (M): 283.1208. Found: m/z 283.1218. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.93; H, 5.82; N, 4.84.

*3.5.9. 5,6-Dimethoxy-2-methyl-3-phenyl-2,3-dihydro-1H-isoindol-1-one (**4i**).* A colorless viscous oil; R_f 0.29 (AcOEt/hexane 2:1); IR (neat) 1685, 1615 cm^{-1}; ^1H NMR δ 2.94 (s, 3H), 3.82 (s, 3H), 3.96 (s, 3H), 5.23 (s, 1H), 6.61 (s, 1H), 7.14 (dd, J=7.4, 1.1 Hz, 2H), 7.35–7.39 (m, 4H); ^{13}C NMR δ 27.5, 56.1, 56.3, 66.3, 105.0, 124.0, 126.0, 127.5, 128.6, 129.1, 137.2, 139.6, 149.8, 152.8, 168.9. HRMS (EI) calcd for $C_{17}H_{17}NO_3$ (M): 283.1208. Found: m/z 283.1208. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.92; H, 6.12; N, 4.66.

*3.5.10. 1-Phenyl-2-(phenylmethyl)-1,2-dihydro-3H-benz[e]isoindol-3-one (**4j**).* A white solid; mp 175–177 °C (hexane/CH_2Cl_2); IR (KBr) 1689 cm^{-1}; ^1H NMR δ 3.69 (d, J=14.9 Hz, 1H), 5.40 (d, J=14.9 Hz, 1H), 5.60 (s, 1H), 7.13–7.38 (m, 11H), 7.46–7.50 (m, 2H), 7.92 (d, J=8.6 Hz, 1H), 7.98 (d, J=8.6 Hz, 1H), 8.01 (d, J=8.6 Hz, 1H); ^{13}C NMR δ 43.5, 63.3, 119.9, 123.6, 127.0, 127.4, 127.5, 127.7, 128.3, 128.4, 128.7, 128.8, 129.1, 129.2, 129.7, 129.7, 135.5, 136.9, 137.4, 143.9, 168.6. HRMS (EI) calcd for $C_{25}H_{19}NO$ (M): 349.1467. Found: m/z 349.1483. Anal. Calcd for $C_{25}H_{19}NO$: C, 85.93; H, 5.48; N, 4.01. Found: C, 85.63; H, 5.42; N, 3.92.

*3.5.11. 1-Hydroxy-1-phenyl-2-(phenylmethyl)-1,2-dihydro-3H-benz[e]isoindol-3-one (**5**).* A white solid; mp 187–189 °C (hexane/CH_2Cl_2); IR (KBr) 3262, 1675 cm^{-1}; ^1H NMR δ 2.96 (s, 1H), 4.09 (d, J=15.5 Hz, 1H), 4.79 (d, J=15.5 Hz, 1H), 7.15–7.20 (m, 2H), 7.24–7.27 (m, 6H), 7.36–7.41 (m, 3H), 7.50 (dd, J=8.0, 6.9 Hz, 1H), 7.85 (d, J=8.6 Hz, 1H), 7.88 (d, J=8.6 Hz, 1H), 7.90 (d, J=8.6 Hz, 1H), 7.97 (d, J=8.6 Hz, 1H); ^{13}C NMR δ 42.6, 91.7, 119.2, 124.6, 126.3, 126.9, 127.3, 127.6, 127.9, 128.2, 128.4, 128.5, 128.6, 128.8, 128.9, 130.9, 136.1, 138.25, 138.32, 145.3, 167.9. HRMS (EI) calcd for $C_{25}H_{19}NO_2$ (M): 365.1416. Found: m/z 365.1425. Anal. Calcd for $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 82.00; H, 5.30; N, 3.66.

Acknowledgements

This work was founded by a grant from Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant No. 26410051). The authors gratefully acknowledge Mrs. Miyuki Tanmatsu of our university for recording mass spectra and performing combustion analyses.

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