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Reductive Coupling of Phthalimides with Ketones and Aldehydes by Low-Valent Titanium: One-Pot Synthesis of Alkylideneisoindolin-1-ones

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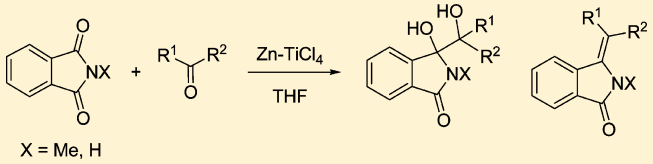
Supporting Information

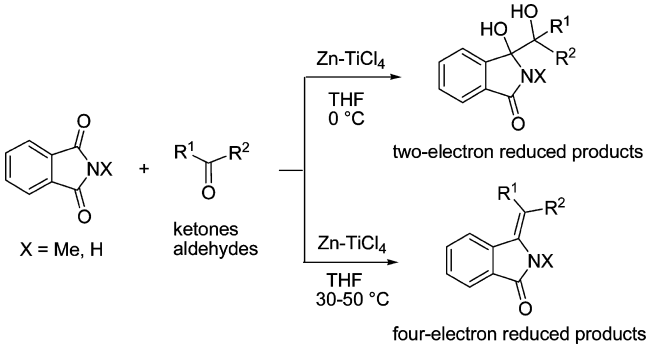
ABSTRACT: The reductive coupling of phthalimides with ketones and aldehydes by Zn-$TiCl_4$ in THF gave two- and four-electron reduced products, 3-hydroxy-3-(1-hydroxyalkyl)-isoindolin-1-ones and alkylideneisoindolin-1-ones, selectively by controlling the reaction conditions. Therefore, the one-pot synthesis of alkylideneisoindolin-1-ones from phthalimides was effected by this reaction. Although the alkylideneisoindolin-1-ones prepared from phthalimides and aldehydes were formed as mixtures of geometric isomers in most cases, the geometric ratios could be increased by reflux in cat. PPTS/toluene. After the isomerization, the *E*-isomers of *N*-methyl substituted alkylideneisoindolin-1-ones (X = Me, R^1 = R, R^2 = H) and the *Z*-isomers of *N*-unsubstituted alkylideneisoindolin-1-ones (X = H, R^1 = H, R^2 = R) were obtained preferentially.



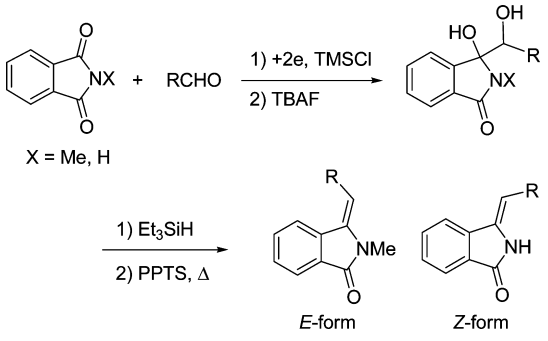
INTRODUCTION

Reductive cross coupling of phthalimides with carbonyl compounds is a useful method for the synthesis of 3-substituted isoindoline-1-ones. To date, this type of reaction has been effected using SmI_2 as a reducing agent[1] and electroreduction,[2] and applied to the synthesis of isoindolone alkaloids.[1b,2c] On the other hand, low-valent titanium is well-known as a powerful reagent for the reductive cross coupling of two different carbonyl compounds.[3,4] Recently, we also reported the reductive coupling of uracils[5] and *N*-methoxycarbonyl lactams[6] with benzophenones by low-valent titanium. In this paper, we report the reductive coupling of phthalimides with ketones and aldehydes by low-valent titanium generated from Zn-$TiCl_4$ (Scheme 1). It is noted that two- and four-electron reduced products could be prepared selectively by controlling the reaction conditions. We previously reported the electroreductive coupling of phthalimides with aldehydes and following transformation of the resulting 3-hydroxy-3-(1-hydroxyalkyl)isoindolin-1-ones to the corresponding alkylideneisoindolin-1-ones (Scheme 2).[2d] However, the substrate were restricted to aldehydes in the electroreductive coupling, thus ketones did not gave adducts with phthalimides. Furthermore, the reductive coupling by low-valent titanium allowed one-pot synthesis of the four-electron reduced products, alkylideneisoindolin-1-ones.[7] In addition, the geometric ratios of the alkylideneisoindolin-1-ones obtained by the one-pot synthesis from phthalimides and aldehydes could be increased by reflux

Scheme 1. Reductive Coupling of Phthalimides with Ketones and Aldehydes by Zn-$TiCl_4$



Scheme 2. Electroreductive Coupling of Phthalimides with Aldehydes and Following Transformation to Alkylideneisoindolin-1-ones



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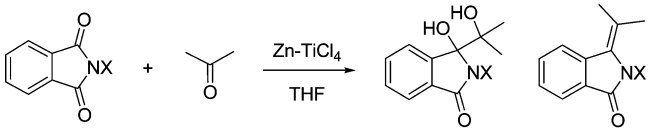
in cat. PPTS/toluene. In particular, the *Z*-isomers of *N*-unsubstituted alkylideneisoindolin-1-ones could be obtained exclusively.

RESULTS AND DISCUSSION

1. Reductive Coupling of Phthalimides with Ketones by Zn-$TiCl_4$. The reaction conditions were investigated using *N*-methylphthalimide (**1a**) and acetone (**2a**) as the substrates and the results are summarized in Table 1. The molar ratio of

Table 1. Reductive Coupling of 1a,b with Acetone by Zn-$TiCl_4$



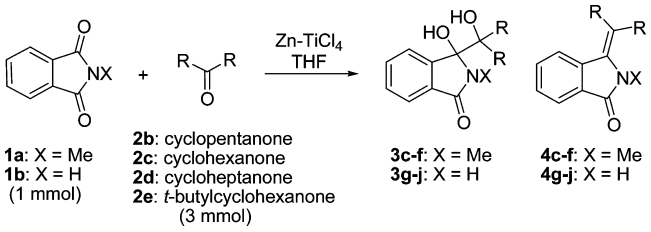
run	1	2a (mmol)	condition[a]	Temp (°C)		% yield[b] 3	4
1	**1a**	1	a	0	**a**	51	-
2	**1a**	2	a	0	**a**	76	-
3	**1a**	3	a	0	**a**	89	-
4	**1a**	5	a	0	**a**	87	-
5	**1a**	3	b	20	**a**	39	47
6	**1a**	3	b	30	**a**	7	83
7	**1a**	3	b	40	**a**	4	78
8	**1a**	3	b	50	**a**	-	70
9	**1b**	3	a	0	**b**	66	-
10	**1b**	3	b	30	**b**	-	58

[a]a: **1**/Zn/$TiCl_4$ = 1/4/2, 12 h. b: **1**/Zn/$TiCl_4$ = 1/8/4, 12 h. [b]Isolated yields.

Zn/$TiCl_4$ was fixed to 2/1. Initially, the reaction was carried out with the molar ratio of **1a**/$TiCl_4$ as 1/2 in THF at 0 °C for 12 h with varying the molar ratio of **1a**/**2a** from 1/1 to 1/5 (runs 1−4). In these cases, 3-hydroxy-3-(2-hydroxypropan-2-yl)-2-methylisoindolin-1-one (**3a**) was produced as a two-electron reduced product. It was shown that the best yield of **3a** (89%) was obtained, when the ratio of **1a**/**2a** was 1/3 (run 3). Therefore, the ratio of **1a**/**2a** was subsequently fixed to 1/3. Next, the reaction was performed with the ratio of **1a**/**2a**/$TiCl_4$ as 1/3/4 in THF at 20−50 °C for 12 h (runs 5−8). Four-electron reduced product 2-methyl-3-(propan-2-ylidene)-isoindolin-1-one (**4a**) was formed at the elevated temperature and the best yield of **4a** (83%) was obtained from the reduction at 30 °C (run 6). When phthalimide (**1b**) was employed in place of **1a**, the reactions under the same conditions as runs 3 and 6 gave **3b** (66%) and **4b** (58%), respectively (runs 9 and 10).

The reductive coupling of **1a,b** with aliphatic cyclic ketones **2b−e** was carried out under the same conditions as runs 3 and 6 (conditions a and b) in Table 1 (Table 2). In all cases, 3-(1-hydroxyalkyl)isoindolin-1-ones **3c−j** were produced selectively in satisfactory yields under the condition a. Although alkylideneisoindolin-1-ones **4c−j** were formed under the condition b, the isolated yields were relatively low. The alkylideneisoindolin-1-ones **4**, especially *N*-methyl substituted **4c−f**, were very labile and readily decomposed to **1a** and **2b−e** by air oxidation. Therefore, **4d−f** could not be isolated owing

Table 2. Reductive Coupling of 1a,b with 2b-e by Zn-$TiCl_4$

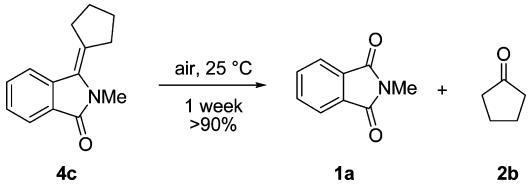


run	1	2	condition[a]		% yield[b] 3	4
1	**1a**	**2b**	a	**c**	82	-
2	**1a**	**2b**	b	**c**	-	28[c]
3	**1a**	**2c**	a	**d**	83	-
4	**1a**	**2c**	b	**d**	-	*d*
5	**1a**	**2d**	a	**e**	66	-
6	**1a**	**2d**	b	**e**	-	*d*
7	**1a**	**2e**	a	**f**	86	-
8	**1a**	**2e**	b	**f**	-	*d*
9	**1b**	**2b**	a	**g**	64	-
10	**1b**	**2b**	b	**g**	-	38
11	**1b**	**2c**	a	**h**	71	-
12	**1b**	**2c**	b	**h**	-	51
13	**1b**	**2d**	a	**i**	65	-
14	**1b**	**2d**	b	**i**	-	37
15	**1b**	**2e**	a	**j**	70	-
16	**1b**	**2e**	b	**j**	-	41

[a]a: **1**/Zn/$TiCl_4$ = 1/4/2, 0 °C, 12 h. b: **1**/Zn/$TiCl_4$ = 1/8/4, 30 °C, 12 h. [b]Isolated yields. [c]Isolated by recrystallization. [d]Could not be isolated.

to their degradation during isolation. While **4c** could be barely isolated by recrystallization, it was completely decomposed in $CDCl_3$ solution within one week by standing at 25 °C under the atmosphere (Scheme 3). Since similar photooxidative

Scheme 3. Decomposition of 4c by Air Oxidation



cleavage of enamines has been reported[8] and the cleavage of **4c** was slow in the dark, it is likely that the oxidative cleavage of **4c−f** requires photochemical activation.

2. Reductive Coupling of Phthalimides with Aldehydes by Zn-$TiCl_4$. The reductive coupling of phthalimides **1a,b** with aldehydes **5** by low-valent titanium were also carried out under the conditions a and b (Table 3). When the aldehydes were aliphatic (**5a,b**), both of 3-(1-hydroxyalkyl)-isoindolin-1-ones **6a−d** and alkylideneisoindolin-1-ones **7a−d** were obtained as mixtures of two stereoisomers in good to high yields (runs 1−8). Since **7** prepared from aldehydes were relatively stable differently from **4** derived from cyclic ketones as describe above, the condition b was performed at 50 °C to shorten the reaction time (2 h). On the other hand, benzaldehyde (**5c**) brought about modest yields of **6e** and **6m** under the condition a (runs 9 and 18). In these cases, pinacols were mainly formed by homocoupling of **5c** (>80%

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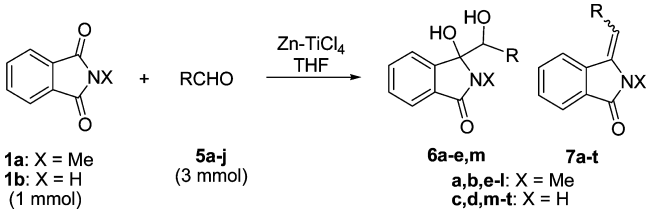
Table 3. Reductive Coupling of 1a,b with 5a−j by Zn-$TiCl_4$

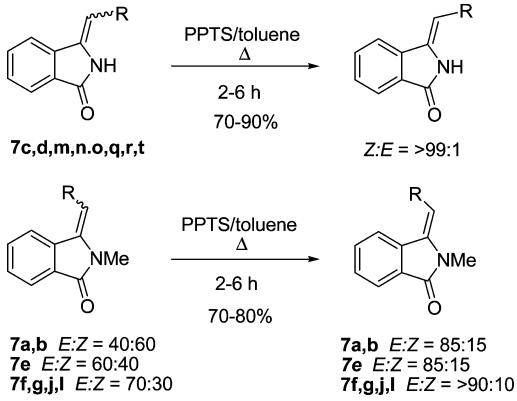


run	1	5	R	Condition[a]		% Yield[b] 6 (dr)[c]	% Yield[b] 7 (E:Z)
1	1a	5a	*n*-C_3H_7	a	a	78 (60:40)	-
2	1a	5a	*n*-C_3H_7	b	a	-	79 (50:50)
3	1a	5b	*i*-C_3H_7	a	b	73 (60:40)	-
4	1a	5b	*i*-C_3H_7	b	b	-	82 (40:60)
5	1b	5a	*n*-C_3H_7	a	c	72 (50:50)	-
6	1b	5a	*n*-C_3H_7	b	c	-	76 (40:60)
7	1b	5b	*i*-C_3H_7	a	d	70 (50:50)	-
8	1b	5b	*i*-C_3H_7	b	d	-	80 (35:65)
9	1a	5c	Ph	a	e	27 (60:40)[d]	-
10	1a	5c	Ph	b	e	-	65 (60:40)
11	1a	5d	*p*-$MeOC_6H_4$	b	f	-	79 (70:30)
12	1a	5e	*m*-$MeOC_6H_4$	b	g	-	61 (70:30)
13	1a	5f	*o*-$MeOC_6H_4$	b	h	-	41 (>99:1)
14	1a	5g		b	i	-	64 (>95:5)
15	1a	5h	*p*-FC_6H_4	b	j	-	65 (70:30)
16	1a	5i	1-Naphthyl	b	k	-	55 (>99:1)
17	1a	5j	2-Naphthyl	b	l	-	63 (70:30)
18	1b	5c	Ph	a	m	26 (50:50)[d]	-
19	1b	5c	Ph	b	m	-	68 (30:70)
20	1b	5d	*p*-$MeOC_6H_4$	b	n	-	69 (40:60)
21	1b	5e	*m*-$MeOC_6H_4$	b	o	-	71 (40:60)
22	1b	5f	*o*-$MeOC_6H_4$	b	p	-	36 (<1:99)
23	1b	5g		b	q	-	58 (30:70)
24	1b	5h	*p*-FC_6H_4	b	r	-	61 (40:60)
25	1b	5i	1-Naphthyl	b	s	-	57 (<1:99)
26	1b	5j	2-Naphthyl	b	t	-	58 (40:60)

[a]a: **1**/Zn/$TiCl_4$ = 1/4/2, 0 °C, 12 h. b: **1**/Zn/$TiCl_4$ = 1/8/4, 50 °C, 2 h. [b]Isolated yields. [c]Diastereomeric ratio determined by ^{1}H NMR analysis. [d]1,2-Diphenylethane-1,2-diol was mainly obtained.

based on **5c**). However, benzylideneisoindolin-1-ones **7e−t** were obtained in moderate to good yields from aromatic aldehydes **5c−j** under the condition b. The major byproducts under the condition b were McMurry-type adducts of aldehydes, 1,2-diarylethenes (60−70% yields based on **5c−j**). The *E*-isomers of **7e−l** were selectively formed from *N*-methyl substituted **1a** (runs 10−17), whereas the *Z*-isomers of **7m−t** were preferentially produced from **1b** (runs 19−26). As previously reported,[2d] the obtained geometric mixtures of the *N*-unsubstituted benzylideneisoindolin-1-ones **7c,d,m,n,o,q,r,t** were exclusively transformed to the *Z*-isomers alone (*Z*:*E* = >99:1) by reflux in toluene containing a catalytic amount of PPTS, since the *Z*-isomers are thermodynamically much more stable than the *E*-isomers (Scheme 4). Similarly, the *E*:*Z* ratios of *N*-methyl substituted benzylideneisoindolin-1-ones **7a,b,e,f,g,j,l** were increased by reflux in cat. PPTS/toluene. In the *N*-methyl substituted **7**, the *E*-isomers are supposed to be more stable than the *Z*-isomers. This prediction is supported by

Scheme 4. Isomerization of 7 by Reflux in cat. PPTS/Toluene



the DFT calculations of ***E*-7e** and ***Z*-7e** at the B3LYP/6-311+G(2d,p) level in toluene (PCM) at 383 K; ***E*-7e** is more stable (1.14 kcal/mol) than ***Z*-7e** (Figure 1). The *E*:*Z* ratio of

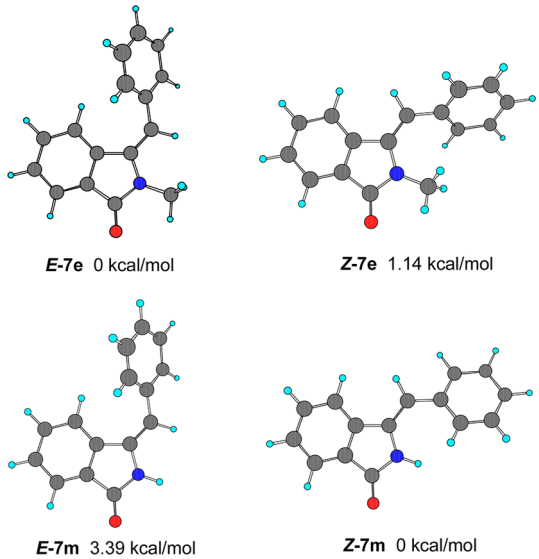


Figure 1. Optimized structures and relative energies of geometric isomers of **7e** and **7m** calculated at the B3LYP/6-311+(2d,p) level in toluene (PCM) at 383 K.

7e derived form the energy difference is 82:18 and agrees well with the experimental result (*E*:*Z* = 85:15). Incidentally, the energy difference between ***E*-7m** and ***Z*-7m** calculated at the same level is 3.39 kcal/mol (Figure 1) and then the *Z*:*E* ratio of **7m** is estimated to be 99:1.

It is noteworthy that the reductive coupling of 4,5-dimethoxyisoindoline-1,3-dione (**1c**) with **5c** under the condition b gave ***Z*-8a** mainly (38%) together with a small amount of its regioisomer ***Z*-8b** (Scheme 5). The major adduct ***Z*-8a** was formed from the addition at the 3-position in **1c**. In contrast, the electroreductive coupling of **1c** with **5c** selectively proceeded at the 1-position in **1c** to give ***Z*-8b**.[2d] The same regioselectivity was reported in the intramolecular coupling of a similar phthalimide substrate using SmI_2 as a reducing agent.[1b]

3. Reaction Mechanism of the Reductive Coupling. The presumed reaction mechanism of the reductive coupling of *N*-methylphthalimide (**1a**) with acetone (**2a**) is exhibited in Scheme 6. Since **1a** is more reducible than **2a**,[2d] **1a** is reduced

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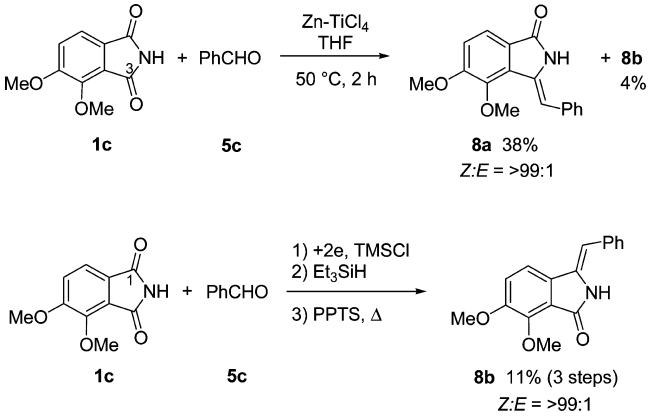
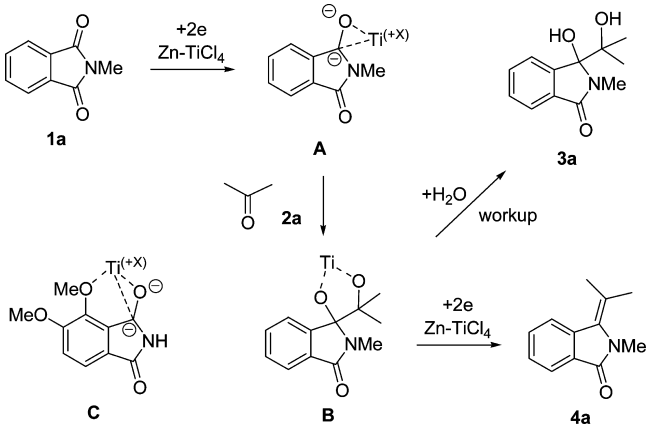
Scheme 5. Reductive Coupling of 1c with 5c by Zn-$TiCl_4$ and Electroreduction



Scheme 6. Presumed Reaction Mechanism of Reductive Coupling of 1a with 2a by Zn-$TiCl_4$



by low-valent titanium to give dianion intermediate A. The nucleophilic addition of **A** to **2a** produces adduct **B**. Since the adduct **B** is stable at 0 °C, the workup of **B** with water gave **3a**. At elevated temperature (>20 °C), further reduction of **B** by low-valent titanium proceeds to afford **4a**. In the reduction of **1c**, dianion intermediate **C** is regioselectively formed owing to the chelation of titanium ion and the 4-methoxy group in **1c**.

CONCLUSION

The reductive coupling of phthalimides **1** with ketones **2** and aldehydes **5** by Zn-$TiCl_4$ gave two-electron reduced products, 3-hydroxy-3-(1-hydroxyalkyl)isoindolin-1-ones **3** and **6**, and four-electron reduced products, alkylideneisoindolin-1-ones **4** and **7**, respectively. The two- and four-electron reduced products could be obtained selectively by controlling the reaction conditions. Therefore, the one-pot synthesis of alkylideneisoindolin-1-ones **4** and **7** was realized by this method. The alkylideneisoindolin-1-ones **4**, especially derived from *N*-methylphthalimide **1a**, were significantly sensitive to air oxidation. Although the alkylideneisoindolin-1-ones **7** were obtained from aldehydes **5** as mixtures of their geometric isomers in most cases, the proportions of the thermodynamically more stable isomers, namely, the *E*-isomers of *N*-methyl substituted **7a,b,e−l** and the *Z*-isomers of *N*-unsubstituted **7c,d,m−t**, could be increased by reflux in cat. PPTS/toluene. Especially, the *Z*-isomers of *N*-unsubstituted **7c,d,m−t** could be obtained exclusively after the isomerization.

EXPERIMENTAL SECTION

General Methods. Column chromatography was performed on silica gel 60. THF was distilled from sodium benzophenone ketyl radical.

Typical Procedure of Reductive Coupling by Ti-$ZnCl_4$. To a solution of **1a** (161 mg, 1.00 mmol), **2a** (174 mg, 3.00 mmol), and zinc powder (0.26 g, 4.0 mmol) in THF (10 mL) was added $TiCl_4$ (0.22 mL, 2.0 mmol) dropwise at 0 °C and then the dark blue suspension was stirred for 12 h at this temperature. To the mixture was added 1 M HCl (20 mL) at 0 °C and the mixture was stirred for 15 min at 25 °C. The mixture was extracted with ethyl acetate three times. The organic layer was washed with aqueous NaCl and dried over $MgSO_4$. After the solvent was removed, the residue was purified by column chromatography on silica gel to give **3a** in 89% yield (197 mg). Compounds **6a**,[2d] **6b**,[2d] **6e**,[2d] **6m**,[2d] *Z*-**7c**,[9] *Z*-**7d**,[7f] *E*-**7e**,[2d,7a] *E*-**7f**,[2d] *E*-**7i**,[2d] *Z*-**7m**,[2d,7b,f,h,i,k] *Z*-**7n**,[7h] *Z*-**7o**,[2d,7h] *Z*-**7p**,[7f,h] *Z*-**7q**,[2d,7f] *Z*-**7r**,[2d] *Z*-**7t**,[2d,7f,h] *Z*-**8a**,[7f] and *Z*-**8b**[2d] were known.

3-Hydroxy-3-(2-hydroxypropan-2-yl)-2-methylisoindolin-1-one (3a). White solid (197 mg, 89%); *Rf* 0.2 (hexanes-ethyl acetate, 1:2); mp 177−178 °C; IR (ATR) 3503, 3215, 1670, 1616, 1474, 959, 932, 818, 768, 700, 677, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.37 (s, 3H), 2.68 (s, 1H), 2.88 (s, 3H), 4.36 (s, 1H), 7.38−7.42 (m, 1H), 7.48−7.52 (m, 1H), 7.53−7.57 (m, 1H), 7.64−7.67 (m, 1H); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 23.7 (q), 25.8 (q), 26.2 (q), 75.6 (s), 93.0 (s), 122.2 (d), 123.7 (d), 128.8 (d), 130.8 (d), 132.3 (s), 146.0 (s), 167.6 (s). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.11; H, 6.88; N, 6.24.

3-Hydroxy-3-(2-hydroxypropan-2-yl)isoindolin-1-one (3b). White solid (137 mg, 66%); *Rf* 0.3 (hexanes-ethyl acetate, 1:5); mp 189−190 °C; IR (ATR) 3372, 3237, 1674, 1616, 1474, 984, 957, 947, 837, 808, 770, 739, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.92 (s, 3H), 1.22 (s, 3H), 4.60 (brs, 1H), 6.22 (brs, 1H), 7.43−7.47 (m, 1H), 7.52−7.57 (m, 2H), 7.63−7.66 (m, 1H), 8.55 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 24.8 (q), 25.2 (q), 73.6 (s), 91.0 (s), 122.1 (d), 124.5 (d), 128.8 (d), 131.5 (d), 132.5 (s), 148.3 (s), 168.7 (s). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.77; H, 6.35; N, 6.64.

3-Hydroxy-3-(1-hydroxycyclopentyl)-2-methylisoindolin-1-one (3c). White solid (203 mg, 82%); *Rf* 0.3 (hexanes-ethyl acetate, 1:5); mp 235 °C; IR (ATR) 3200, 3134, 1672, 1618, 1474, 968, 934, 916, 883, 870, 826, 771, 745, 700, 691, 650 cm^{-1}; ^1H NMR ($CDCl_3$, DMSO-d_6) δ 1.45−1.86 (s, 7H), 2.07−2.15 (m, 1H), 3.12 (s, 3H), 3.44 (s, 1H), 6.20 (s, 1H), 7.44−7.48 (m, 1H), 7.49−7.54 (m, 1H), 7.68−7.71 (m, 1H), 7.73−7.76 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 23.1 (t), 24.3 (t), 26.2 (q), 35.0 (t), 36.5 (t), 84.7 (s), 92.8 (s), 121.8 (d), 123.9 (d), 128.7 (d), 131.0 (d), 133.0 (s), 148.0 (s), 167.3 (s). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.95; H, 6.94; N, 5.60.

3-Hydroxy-3-(1-hydroxycyclohexyl)-2-methylisoindolin-1-one (3d). White solid (217 mg, 83%); *Rf* 0.5 (hexanes-ethyl acetate, 1:5); mp 175 °C; IR (ATR) 3420, 3306, 1655, 1618, 1477, 984, 974, 951, 939, 905, 891, 858, 841, 804, 760, 704, 698, 652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75−0.84 (m, 1H), 0.87−0.99 (m, 1H), 1.44−1.64 (m, 7H), 1.80−1.88 (m, 1H), 2.29 (s, 1H), 2.98 (s, 3H), 3.84 (s, 1H), 7.41−7.45 (m, 1H), 7.49−7.53 (m, 1H), 7.63−7.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.0 (t), 21.1 (t), 25.3 (t), 26.8 (q), 30.3 (t), 32.7 (t), 76.8 (s), 94.0 (s), 122.6 (d), 124.2 (d), 129.2 (d), 131.1 (d), 131.9 (s), 145.6 (s), 168.1 (s). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.91; H, 7.35; N, 5.29.

3-Hydroxy-3-(1-hydroxycycloheptyl)-2-methylisoindolin-1-one (3e). White solid (182 mg, 66%); *Rf* 0.5 (hexanes-ethyl acetate, 1:5); mp 222 °C; IR (ATR) 3489, 3181, 1655, 1616, 1476, 997, 961, 939, 920, 849, 818, 766, 746, 707, 700, 689 cm^{-1}; ^1H NMR ($CDCl_3$, DMSO-d_6) δ 1.09−1.33 (m, 4H), 1.37−1.59 (m, 4H), 1.62−1.72 (m, 2H), 1.84−1.89 (m, 1H), 1.96−2.03 (m, 1H), 3.11 (s, 3H), 3.32 (brs, 1H), 6.19 (s, 1H), 7.45−7.53 (m, 2H), 7.67−7.70 (m, 1H), 7.73−7.77 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 22.0 (t), 22.2 (t), 26.9 (q), 28.5 (t), 28.9 (t), 34.6 (t), 35.6 (t), 79.1 (s), 93.8 (s), 121.9 (d), 124.7 (d), 129.0 (d), 131.1 (d), 132.5 (s), 147.0 (s), 167.1 (s). Anal. Calcd for

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$C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.72; H, 7.68; N, 5.04.

3-(4-*tert*-Butyl-1-hydroxycyclohexyl)-3-hydroxy-2-methylisoindolin-1-one (3f). White solid (273 mg, 86%); *Rf* 0.3 (hexanes-ethyl acetate, 1:2); mp 177 °C; IR (ATR) 3503, 3326, 1655, 1614, 1474, 991, 970, 922, 814, 771, 758, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70−0.84 (m, 2H), 0.80 (s, 9H), 1.26−1.40 (m, 2H), 1.46−1.53 (m, 1H), 1.54−1.66 (m, 3H), 1.87−1.93 (m, 1H), 2.33 (s, 1H), 2.91 (s, 3H), 4.13 (s, 1H), 7.38−7.42 (m, 1H), 7.48−7.52 (m, 1H), 7.55−7.58 (m, 1H), 7.63−7.66 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1 (t), 22.2 (t), 27.1 (q), 27.7 (t), 32.5 (s), 33.6 (t), 47.6 (d), 76.7 (s), 94.2 (s), 123.1 (d), 124.5 (d), 129.7 (d), 131.5 (d), 132.2 (s), 145.7 (s), 168.4 (s). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.86; H, 8.59; N, 4.40.

3-Hydroxy-3-(1-hydroxycyclopentyl)isoindolin-1-one (3g). White solid (149 mg, 64%); *Rf* 0.3 (hexanes-ethyl acetate, 1:5); mp 179−180 °C; IR (ATR) 3200, 3134, 1672, 1618, 1474, 968, 934, 916, 883, 870, 826, 771, 745, 700, 691, 650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.20−1.29 (m, 1H), 1.41−1.71 (m, 6H), 2.00−2.08 (m, 1H), 4.39 (brs, 1H), 6.27 (brs, 1H), 7.42−7.46 (m, 1H), 7.50−7.56 (m, 2H), 7.61−7.65 (m, 1H), 8.56 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 24.3 (t), 24.5 (t), 35.3 (t), 35.8 (t), 84.7 (s), 90.5 (s), 122.1 (d), 124.1 (d), 128.7 (d), 131.6 (d), 132.7 (s), 148.8 (s), 168.9 (s). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.87; H, 6.44; N, 5.92.

3-Hydroxy-3-(1-hydroxycyclohexyl)isoindolin-1-one (3h). White solid (175 mg, 71%); *Rf* 0.35 (hexanes-ethyl acetate, 1:5); mp 207 °C; IR (ATR) 3578, 3385, 3183, 1701, 1686, 1614, 1470, 974, 955, 909, 878, 853, 835, 806, 795, 750, 733, 696, 667 cm^{-1}; NMR (DMSO-d_6) δ 0.90−1.02 (m, 1H), 1.07−1.15 (m, 1H), 1.20−1.56 (m, 7H), 1.76−1.84 (m, 1H), 4.30 (brs, 1H), 6.22 (brs, 1H), 7.42−7.46 (m, 1H), 7.50−7.56 (m, 2H), 7.62−7.66 (m, 1H), 8.52 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 21.0 (t), 21.1 (t), 25.5 (t), 30.5 (t), 30.8 (t), 74.4 (s), 91.6 (s), 122.2 (d), 124.8 (d), 128.8 (d), 131.5 (d), 132.6 (s), 148.3 (s), 168.9 (s). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.78; H, 6.94; N, 5.64.

3-Hydroxy-3-(1-hydroxycycloheptyl)isoindolin-1-one (3i). White solid (170 mg, 65%); *Rf* 0.4 (hexanes-ethyl acetate, 1:5); mp 204−205 °C; IR (ATR) 3285, 1665, 1614, 1470, 989, 961, 939, 912, 839, 799, 764, 729, 700, 654 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.18−1.60 (m, 10H), 1.65−1.74 (m, 1H), 1.83−1.91 (m, 1H), 4.32 (brs, 1H), 6.22 (brs, 1H), 7.42−7.46 (m, 1H), 7.50−7.56 (m, 2H), 7.65−7.68 (m, 1H), 8.55 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 22.0 (t), 22.5 (t), 29.0 (t), 29.2 (t), 34.8 (t), 35.5 (t), 78.0 (s), 92.0 (s), 122.1 (d), 124.9 (d), 128.8 (d), 131.6 (d), 132.6 (s), 148.5 (s), 168.8 (s). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.96; H, 7.32; N, 5.33.

3-(4-*tert*-Butyl-1-hydroxycyclohexyl)-3-hydroxyisoindolin-1-one (3j, 70:30 diastereomeric mixture). White solid (212 mg, 70%); *Rf* 0.5 (hexanes-ethyl acetate, 1:5); mp 222−223 °C; IR (ATR) 3420, 3270, 1676, 1614, 1468, 982, 957, 930, 880, 797, 773, 754, 710, 694, 660 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.78 (q, 3H), 1.04−1.56 (m, 7.7H), 1.61−1.69 (m, 0.3H), 1.81−1.89 (m, 0.7H), 2.02−2.10 (m, 0.3H), 4.26 (brs, 0.3H), 4.27 (brs, 0.7 H), 6.20 (s, 0.3H), 6.21 (brs, 0.7H), 7.42−7.46 (m, 1H), 7.50−7.56 (m, 2H), 7.63−7.66 (m, 1H), 8.50 (brs, 0.7H), 8.51 (brs, 0.3H); ^{13}C NMR (DMSO-d_6) δ 21.7 (t), 21.9 (t), 22.0 (t), 27.5 (q), 27.7 (q), 30.9 (t), 31.3 (t), 32.1 (t), 32.4 (t), 32.7 (t), 73.7 (s), 74.0 (s), 91.3 (s), 92.0 (s), 121.97 (d), 122.04 (d), 124.6 (d), 124.7 (d), 128.6 (d), 128.7 (d), 131.2 (d), 131.4 (d), 132.5 (s), 132.7 (s), 148.3 (s), 148.6 (s), 168.6 (s). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.22; H, 8.35; N, 4.53.

2-Methyl-3-(propan-2-ylidene)isoindolin-1-one (4a). Pale yellow solid (155 mg, 83%); *Rf* 0.25 (hexanes-ethyl acetate, 5:1); mp 110−112 °C; IR (ATR) 1682, 1638, 1609, 943, 822, 760, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 2.32 (s, 3H), 3.54 (s, 3H), 7.40−7.44 (m, 1H), 7.53−7.57 (m, 1H), 7.81−7.83 (m, 1H), 7.87−7.89 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.7 (q), 23.3 (q), 30.9 (q), 118.4 (s), 122.7 (d), 123.1 (d), 127.0 (d), 129.1 (s), 131.2 (d), 131.2 (d), 132.4 (s), 133.6 (s), 167.8 (s). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.83; H, 6.95; N, 7.36.

3-(Propan-2-ylidene)isoindolin-1-one (4b). Pale yellow solid (100 mg, 58%); *Rf* 0.3 (hexanes-ethyl acetate, 2:1); mp 223 °C; IR (ATR) 3157, 1682, 1665, 1611, 1472, 799, 777, 762, 739, 691, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.26 (s, 3H), 7.42−7.46 (m, 1H), 7.56−7.61 (m, 1H), 7.82−7.85 (m, 1H), 7.89−7.92 (m, 1H), 8.81 (brs, 1H); ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 20.0 (q), 21.5 (q), 117.4 (q), 122.8 (d), 123.0 (d), 126.9 (d), 129.0 (s), 130.6 (s), 131.4 (d), 136.5 (s), 167.8 (s). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.17; H, 6.34; N, 8.01.

3-Cyclopentylidene-2-methylisoindolin-1-one (4c). White solid (60 mg, 28%); *Rf* 0.4 (hexanes-ethyl acetate, 2:1); mp 174−175 °C; IR (ATR) 1684, 1647, 1611, 1472, 804, 772, 689, 669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78−1.90 (m, 4H), 2.87−2.91 (m, 2H), 2.95−2.99 (m, 2H), 3.59 (s, 3H), 7.40−7.45 (m, 1H), 7.53−7.58 (m, 1H), 7.69−7.72 (m, 1H), 7.86−7.89 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.4 (t), 27.0 (t), 29.5 (q), 32.7 (t), 33.7 (t), 122.9 (d), 123.1 (d), 127.2 (s), 129.0 (s), 129.3 (s), 129.5 (s), 131.3 (d), 136.6 (s), 167.6 (s). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.55; H, 7.03; N, 6.46.

3-Cyclopentylideneisoindolin-1-one (4g). Pale yellow solid (76 mg, 38%); *Rf* 0.4 (hexanes-ethyl acetate, 1:1); mp 247 °C; IR (ATR) 3144, 1682, 1672, 1611, 1474, 802, 772, 737, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80−1.96 (m, 4H), 2.59−2.65 (s, 2H), 2.77−2.83 (m, 2H), 7.42−7.47 (m, 1H), 7.56−7.62 (m, 1H), 7.65−7.68 (m, 1H), 7.87−7.91 (m, 1H), 8.04 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 26.1 (t), 27.3 (t), 30.9 (t), 32.0 (t), 122.4 (d), 123.5 (d), 126.2 (s), 127.3 (d), 128.5 (s), 130.2 (s), 131.7 (d), 136.9 (s), 168.4 (s). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.27; H, 7.00; N, 6.96.

3-Cyclohexylideneisoindolin-1-one (4h). Pale yellow solid (109 mg, 51%); *Rf* 0.35 (hexanes-ethyl acetate, 2:1); mp 214−215 °C; IR (ATR) 3167, 1678, 1609, 1474, 800, 773, 762, 735, 692, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64−1.79 (m, 6H), 2.43−2.49 (m, 2H), 2.79−2.84 (m, 2H), 7.40−7.46 (m, 1H), 7.54−7.60 (m, 1H), 7.88−7.96 (m, 2H), 8.65 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 26.2 (t), 27.5 (t), 27.7 (t), 29.8 (t), 31.3 (t), 123.5 (d), 123.6 (d), 126.1 (s), 127.2 (s), 127.4 (d), 131.3 (s), 131.8 (d), 137.0 (s), 168.0 (s). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.70; H, 7.03; N, 6.49.

3-Cycloheptylideneisoindolin-1-one (4i). Pale yellow solid (84 mg, 37%); *Rf* 0.35 (hexanes-ethyl acetate, 2:1); mp 164−166 °C; IR (ATR) 3174, 1680, 1647, 1611, 1472, 962, 858, 799, 758, 748, 727, 687, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49−2.03 (m, 8H), 2.56−2.67 (m, 2H), 2.80−2.89 (m, 2H), 7.40−7.48 (m, 1H), 7.54−7.61 (m, 1H), 7.79−7.85 (m, 1H), 7.88−7.94 (m, 1H), 8.96 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 27.3 (t), 28.8 (t), 29.3 (t), 31.2 (t), 32.4 (t), 123.4 (d), 123.5 (d), 127.3 (d), 128.6 (s), 129.0 (s), 130.8 (s), 131.8 (d), 136.6 (s), 168.3 (s). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.15; H, 7.49; N, 6.08.

3-(4-*tert*-Butylcyclohexylidene)isoindolin-1-one (4j). White solid (110 mg, 41%); *Rf* 0.8 (hexanes-ethyl acetate, 1:5); mp 200−201 °C; IR (ATR) 3190, 1676, 1665, 1605, 1470, 988, 800, 770, 758, 735, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (s, 9H), 1.20−1.37 (m, 3H), 2.00−2.08 (m, 2H), 2.15−2.28 (m, 2H), 2.71−2.78 (m, 1H), 3.42−3.49 (m, 1H), 7.42−7.46 (m, 1H), 7.55−7.59 (m, 1H), 7.90−7.92 (m, 1H), 7.93−7.95 (m, 1H), 8.35 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 27.5 (q), 28.1 (t), 28.3 (t), 29.6 (t), 31.1 (t), 32.5 (s), 47.7 (d), 123.4 (d), 123.6 (d), 125.9 (s), 127.0 (s), 127.4 (d), 131.4 (s), 137.0 (s), 168.0 (s). Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.08; H, 8.53; N, 5.11.

3-Hydroxy-3-(1-hydroxybutyl)isoindolin-1-one (6c, 50:50 diastereomeric mixture). Colorless paste (159 mg, 72%); *Rf* 0.5 (ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.75 (t, 1.5H, J = 7.2 Hz), 0.85 (t, 1.5H, J = 7.2 Hz), 1.16−1.61 (m, 4H), 3.35 (brs, 0.5H), 3.85 (brs, 0.5H), 3.88 (d, 0.5H, J = 10.0 Hz), 4.10−4.13 (m, 0.5H), 4.82 (brs, 0.5H), 5.00 (brs, 0.5H), 7.36−7.42 (m, 1H), 7.46−7.57 (m, 3H), 7.63−7.68 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6 (q), 13.7 (q), 18.9 (t), 19.2 (t), 32.3 (t), 32.6 (t), 74.9 (d), 75.1 (d), 89.8 (s), 90.1 (s), 122.1 (d), 123.2 (d), 123.4 (d), 123.6 (d), 129.2 (d), 129.4 (d), 130.9 (s),

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131.1 (s), 132.3 (d), 132.6 (d), 146.2 (s), 146.4 (s), 170.5 (s), 171.1(s); HRMS (ESI, ion trap) calcd for $C_{12}H_{16}NO_3$ $(M + H)^+$ 222.1130, found 222.1128.

3-Hydroxy-3-(1-hydroxy-2-methylpropyl)isoindolin-1-one (6d, 50:50 diastereomeric mixture). Colorless paste (155 mg, 70%); *Rf* 0.55 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.63 (d, 1.5H, J = 6.9 Hz), 0.80 (d, 1.5H, J = 6.9 Hz), 0.82 (d, 1.5H, J = 6.9 Hz), 0.91 (d, 1.5H, J = 6.9 Hz), 1.38−1.47 (m, 0.5H), 1.84−1.93 (m, 0.5H), 3.73 (brs, 1H), 3.96 (d, 0.5H, J = 4.0 Hz), 4.19 (brs, 0.5H), 5.32 (brs, 0.5H), 5.50 (brs, 0.5H), 7.32−7.48 (m, 3.5H), 7.62−7.67 (m, 0.5H), 7.99−8.07 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.6 (q), 17.0 (q), 21.6 (q), 21.7 (q), 29.0 (d), 29.1 (d), 79.2 (d), 79.5 (d), 89.9 (s), 90.0 (s), 122.5 (d), 123.4 (d), 123.6 (d), 124.2 (d), 129.5 (d), 129.6 (d), 130.8 (s), 131.1 (s), 132.4 (d), 132.6 (d), 146.4 (s), 147.0 (s), 170.40 (s), 170.42 (s); HRMS (ESI, ion trap) calcd for $C_{12}H_{16}NO_3$ $(M + H)^+$ 222.1130, found 222.1127.

3-Butylidene-2-methylisoindolin-1-one (7a, 50:50 geometric mixture). Colorless paste (159 mg, 79%); *Rf* 0.45 (hexanes-ethyl acetate, 5:1); ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 1.5H, J = 7.3 Hz), 1.06 (t, 1.5H, J = 7.3 Hz), 1.56−1.71 (m, 2H), 2.56−2.66 (m, 2H), 3.26 (s, 1.5H), 3.53 (s, 1.5H), 5.54 (t, 0.5H, J = 7.6 Hz), 5.63 (t, 0.5H, J = 8.0 Hz), 7.40−7.44 (m, 0.5H), 7.44−7.48 (m, 0.5H), 7.50−7.54 (m, 0.5H), 7.54−7.58 (m, 0.5H), 7.59−7.62 (m, 0.5H), 7.79−7.82 (m, 1H), 7.86−7.88 (m, 0.5H); ^{13}C NMR ($CDCl_3$) δ 13.7 (q), 13.8 (q), 23.2 (t), 23.7 (t), 25.7 (q), 28.3 (t), 29.07 (q), 29.14 (t), 108.9 (d), 112.0 (d), 118.5 (d), 122.8 (d), 123.0 (d), 123.1 (d), 128.0 (d), 128.3 (d), 130.6 (s), 131.3 (d), 131.5 (d), 134.8 (s), 135.2 (s), 136.0 (s), 137.6 (s), 166.2 (s), 167.9 (s); HRMS (ESI, ion trap) calcd for $C_{13}H_{16}NO$ $(M + H)^+$ 202.1232, found 202.1231.

(*E*)-2-Methyl-3-(2-methylpropylidene)isoindolin-1-one (*E*-7b). White solid (66 mg, 33%); *Rf* 0.45 (hexanes-ethyl acetate, 5:1); mp 111−112 °C; IR (ATR) 1692, 1655, 1647, 1614, 1473, 968, 825, 804, 777, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 6H, J = 6.7 Hz), 3.25 (s, 3H), 3.28−3.36 (m, 1H), 5.30 (d, 1H, J = 9.5 Hz), 7.44−7.48 (m, 1H), 7.54−7.59 (m, 1H), 7.80−7.84 (m, 1H), 7.85−7.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6 (q), 25.8 (q), 26.6 (d), 119.6 (d), 123.1 (d), 123.3 (d), 128.4 (d), 130.8 (s), 131.6 (d), 134.7 (s), 135.1 (s), 166.2 (s). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.57; H, 7.51; N, 6.91.

(*Z*)-2-Methyl-3-(2-methylpropylidene)isoindolin-1-one (*Z*-7b). White solid (99 mg, 49%); *Rf* 0.5 (hexanes-ethyl acetate, 5:1); mp 138−139 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 6H, J = 6.8 Hz), 3.24−3.33 (m, 1H), 3.53 (s, 3H), 5.47 (d, 1H, J = 10.6 Hz), 7.39−7.44 (m, 1H), 7.50−7.54 (m, 1H), 7.59−7.62 (m, 1H), 7.79−7.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.1 (q), 25.7 (d), 28.9 (q), 116.2 (d), 118.7 (d), 122.9 (d), 128.1 (d), 128.2 (s), 131.4 (d), 132.8 (s), 137.9 (s), 167.9 (s); HRMS (ESI, ion trap) calcd for $C_{13}H_{16}NO$ $(M + H)^+$ 202.1232, found 202.1230.

(*E*)-3-(3-Methoxybenzylidene)-2-methylisoindolin-1-one (*E*-7g). White solid (113 mg, 43%); *Rf* 0.6 (hexanes-ethyl acetate, 2:1); mp 145−147 °C; IR (ATR) 1697, 1655, 1595, 1584, 1489, 1474, 858, 814, 799, 773, 739, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 3H), 3.83 (s, 3H), 6.48 (s, 1H), 6.91−6.94 (m, 1H), 6.98−7.00 (m, 1H), 7.03−7.06 (m, 1H), 7.30−7.43 (m, 4H), 7.82−7.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.1 (q), 55.3 (q), 110.0 (d), 113.6 (d), 114.7 (d), 121.9 (d), 123.1 (d), 123.2 (d), 129.2 (d), 129.7 (d), 130.6 (s), 131.4 (d), 134.8 (s), 136.5 (s), 137.6 (s), 159.8 (s), 166.6 (s). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.90; H, 5.73; N, 5.20.

(*E*)-3-(2-Methoxybenzylidene)-2-methylisoindolin-1-one (*E*-7h). Pale yellow solid (109 mg, 41%); *Rf* 0.5 (hexanes-ethyl acetate, 2:1); mp 141−143 °C; IR (ATR) 1713, 1636, 1599, 1578, 1487, 1472, 824, 764, 739, 712, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 3H), 3.86 (s, 3H), 6.47 (s, 1H), 6.96−7.02 (m, 2H), 7.28−7.33 (m, 1H), 7.35−7.43 (m, 3H), 7.46−7.50 (m, 1H), 7.80−7.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.2 (q), 55.5 (q), 106.8 (d), 110.7 (d), 120.4 (d), 122.9 (d), 123.0 (d), 123.7 (s), 129.0 (d), 129.6 (d), 130.6 (s), 131.3 (d), 135.0 (s), 137.0 (s), 157.5 (s), 166.5 (s). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.89; H, 5.75; N, 5.22.

(*E*)-3-(4-Fluorobenzylidene)-2-methylisoindolin-1-one (*E*-7j). White solid (115 mg, 46%); *Rf* 0.55 (hexanes-ethyl acetate, 2:1); mp 155−157 °C; IR (ATR) 1694, 1645, 1618, 1596, 1506, 1474, 847, 822, 812, 772, 746, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 3H), 6.44 (s, 1H), 7.11−7.16 (m, 2H), 7.23−7.26 (m, 1H), 7.30−7.34 (m, 1H), 7.39−7.45 (m, 3H), 7.82−7.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.1 (q), 108.8 (d), 115.7 (d, J_{CCF} = 21.5 Hz), 122.8 (d), 123.2 (d), 129.3 (d), 130.6 (s), 131.1 (s, J_{CCCCF} = 3.6 Hz), 131.2 (d, J_{CCCF} = 7.2 Hz), 131.5 (s), 134.7 (s), 137.8 (s), 162.3 (s, J_{CF} = 247.3 Hz), 166.5 (s). Anal. Calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78; N, 5.53. Found: C, 75.89; H, 4.76; N, 5.47.

(*E*)-2-Methyl-3-(naphthalen-1-ylmethylene)isoindolin-1-one (*E*-7k). Yellow paste (157 mg, 55%); *Rf* 0.5 (hexanes-ethyl acetate, 2:1); ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 6.81 (s, 1H), 6.89 (d, 1H, J = 6.9 Hz), 7.13−7.17 (m, 1H), 7.33−7.37 (m, 1H), 7.48−7.57 (m, 3H), 7.61−7.64 (m, 1H), 7.83 (d, 1H, J = 7.5 Hz), 7.91−7.96 (m, 2H), 8.02 (d, 1H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 26.1 (q), 107.7 (d), 122.9 (d), 123.1 (d), 125.0(d), 125.4 (d), 126.3 (d), 126.4 (d), 127.7 (d), 128.5 (d), 129.0 (d), 130.5 (s), 131.4 (d), 132.0 (s), 132.2 (s), 133.6 (s), 134.9 (s), 138.3 (s), 166.6 (s); HRMS (ESI, ion trap) calcd for $C_{20}H_{16}NO$ $(M + H)^+$ 286.1232, found 286.1231.

(*E*)-2-Methyl-3-(naphthalen-2-ylmethylene)isoindolin-1-one (*E*-7l). Pale yellow solid (126 mg, 44%); *Rf* 0.65 (hexanes-ethyl acetate, 2:1); mp 164−166 °C; IR (ATR) 1695, 1638, 1595, 1506, 1474, 862, 824, 810, 772, 750, 741, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.43 (s, 3H), 6.65 (s, 1H), 7.22−7.28 (m, 1H), 7.34−7.37 (m, 1H), 7.39−7.43 (m, 1H), 7.51−7.57 (m, 3H), 7.81−7.95 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.2 (q), 110.2 (d), 123.0 (d), 123.1 (d), 126.3 (d), 126.5 (d), 127.5 (d), 127.8 (d), 127.9 (d), 128.3 (d), 128.5 (d), 129.3 (d), 130.6 (s), 131.5 (d), 132.6 (s), 132.7 (s), 133.3 (s), 134.9 (s), 137.7 (s), 166.6 (s). Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.15; H, 5.30; N, 4.88.

(*Z*)-3-(Naphthalen-1-ylmethylene)isoindolin-1-one (*Z*-7s). Yellow solid (154 mg, 57%); *Rf* 0.45 (hexanes-ethyl acetate, 2:1); mp 224−225 °C; IR (ATR) 3171, 1707, 1655, 1647, 1612, 1591, 1508, 866, 824, 797, 775, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.09 (s, 1H), 7.51−7.62 (m, 5H), 7.68−7.72 (m, 1H), 7.82−7.96 (m, 5H), 8.05−8.11 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 103.3 (d), 120.0 (d), 123.6 (d), 124.4 (d), 125.6 (d), 126.4 (d), 126.6 (d), 128.6 (d), 128.8 (d), 129.3 (s), 129.4 (d), 131.6 (s), 131.8 (s), 132.3 (d), 133.9 (s), 134.8 (s), 137.6 (s), 168.4 (s). Anal. Calcd for $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 84.07; H, 4.83; N, 5.13.

(*E*)-3-(Naphthalen-2-ylmethylene)isoindolin-1-one (*E*-7t). Pale yellow solid (63 mg, 23%); *Rf* 0.35 (hexanes-ethyl acetate, 2:1); mp 196−198 °C; IR (ATR) 3189, 1697, 1653, 1611, 1506, 1472, 864, 843, 818, 748, 739, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.82 (s, 1H), 7.31−7.37 (m, 1H), 7.44−7.50 (m, 1H), 7.50−7.59 (m, 4H), 7.80−7097 (m, 5H), 9.17 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 112.3 (d), 123.36 (d), 123.43 (d), 126.4 (d), 126.5 (d), 127.3 (d), 127.8 (d), 128.0 (d), 128.3 (d), 128.4 (d), 129.5 (d), 131.4 (s), 131.9 (d), 132.4 (s), 132.8 (s), 133.3 (s), 134.8 (s), 135.5 (s), 168.6 (s); HRMS (ESI, ion trap) calcd for $C_{19}H_{14}NO$ $(M + H)^+$ 272.1075, found 272.1073.

Typical Procedure of Isomerization of 7. A solution of **7m** (*Z*:*E* = 70:30, 0.5 mmol) and PPTS (10 mg) in toluene (10 mL) was refluxed using Dean−Stark apparatus under nitrogen atmosphere for 12 h. After the solvent was removed *in vacuo*, the residue was purified by column chromatography on silica gel (hexanes-EtOAc) to give **7m** in 85% yield (188 mg, *Z*:*E* = >99:1).

X-ray Crystallographic Analysis. All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods with SIR-97 and refined with SHELXL-97. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. All calculations were performed using the YADOKARI-XG software package.

Crystal Data of 3d. $C_{15}H_{19}NO_3$, FW = 261.31, mp 175 °C, monoclinic, $P2_{1/a}$ (no 14), colorless block, a = 11.830(2) Å, b = 8.916(2) Å, c = 12.804(2) Å, β = 99.082(9), V = 1333.6(5) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.302 g/cm^3, μ = 0.90 cm^{-1}, GOF = 1.054.

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Crystal Data of 3f. $C_{19}H_{27}NO_3$, FW = 317.42, mp 177 °C, monoclinic, $P2_{1/c}$ (no 14), colorless block, a = 13.919(11) Å, b = 9.284(6) Å, c = 14.029(9) Å, β = 88.10(3), V = 1812(2) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.164 g/cm^3, μ = 0.78 cm^{-1}, GOF = 1.048.

Crystal Data of 4b. $C_{11}H_{11}NO$, FW = 173.21, mp 223 °C, monoclinic, $P2_{1/n}$ (no 14), pale yellow block, a = 8.7086(12) Å, b = 5.7304(6) Å, c = 17.984(2) Å, β = 101.455(6), V = 879.60(19) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.308 g/cm^3, μ = 0.84 cm^{-1}, GOF = 1.066.

Crystal Data of *E*-7b. $C_{13}H_{15}NO$, FW = 201.26, mp 111−112 °C, monoclinic, $P2_{1/c}$ (no 14), colorless block, a = 7.7636(7) Å, b = 16.5858(11) Å, c = 9.1023(7) Å, β = 107.742(4), V = 1116.32(5) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.198 g/cm^3, μ = 0.76 cm^{-1}, GOF = 1.103.

Crystal Data of *Z*-7d. $C_{12}H_{13}NO$, FW = 187.23, mp 188−190 °C, monoclinic, $P2_{1/n}$ (no 14), colorless block, a = 10.642(5) Å, b = 19.168(12) Å, c = 11.125(4) Å, β = 111.89(2), V = 2105.7(18) Å^3, T = 298 K, Z = 8, D_{calcd} = 1.181 g/cm^3, μ = 0.75 cm^{-1}, GOF = 0.898.

Crystal Data of *E*-7g. $C_{17}H_{15}NO_2$, FW = 265.30, mp 145−147 °C, triclinic, P_{-1} (no 2), colorless block, a = 8.5149(12) Å, b = 8.6262(13) Å, c = 10.788(2) Å, α = 110.318(9), β = 103.934(7), γ = 101.948(8), V = 683.5(2) Å^3, T = 298 K, Z = 2, D_{calcd} = 1.289 g/cm^3, μ = 0.85 cm^{-1}, GOF = 0.956.

Crystal Data of *E*-7i. $C_{17}H_{13}NO_3$, FW = 279.28, mp 144−145 °C, monoclinic, $P2_{1/a}$ (no 14), yellow block, a = 7.9701(9) Å, b = 16.241(2) Å, c = 10.4629(11) Å, β = 87.440(5), V = 1353.0(3) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.371 g/cm^3, μ = 0.95 cm^{-1}, GOF = 1.019.

Crystal Data of *E*-7j. $C_{16}H_{12}FNO$, FW = 253.27, mp 155−157 °C, monoclinic, $P2_{1/c}$ (no 14), colorless block, a = 9.5792(7) Å, b = 11.4148(9) Å, c = 11.4639(7) Å, β = 93.012(4), V = 1251.78(15) Å^3, T = 298 K, Z = 4, D_{calcd} = 1.344 g/cm^3, μ = 0.94 cm^{-1}, GOF = 1.069.

Crystal Data of *Z*-7p. $C_{16}H_{13}NO_2$, FW = 251.27, mp 160−162 °C, triclinic, P_{-1} (no 2), colorless block, a = 7.1350(9) Å, b = 9.5257(15) Å, c = 10.5396(18) Å, α = 101.925(6), β = 109.686(7), γ = 104.211(5), V = 620.11(16) Å^3, T = 298 K, Z = 2, D_{calcd} = 1.346 g/cm^3, μ = 0.89 cm^{-1}, GOF = 1.063.

Crystal Data of *Z*-8a. $C_{13}H_{15}NO_2$, FW = 217.26, mp 169−170 °C, monoclinic, $C2/c$ (no 15), colorless block, a = 19.315(19) Å, b = 15.066(15) Å, c = 7.783(9) Å, β = 103.62(4), V = 2201(4) Å^3, T = 298 K, Z = 8, D_{calcd} = 1.311 g/cm^3, μ = 0.88 cm^{-1}, GOF = 1.027.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

A PDF file of ^{1}H and ^{13}C NMR spectra of products, X-ray crystallographic data (ortep) of **3d**, **3f**, **4b**, ***E*-7b**, ***Z*-7d**, ***E*-7g**, ***E*-7i**, ***E*-7j**, ***Z*-7p**, and ***Z*-8a** and the results of DFT calculations for **7e** and **7m**. Crystallographic CIF files for **3d**, **3f**, **4b**, ***E*-7b**, ***Z*-7d**, ***E*-7g**, ***E*-7i**, ***E*-7j**, ***Z*-7p**, and ***Z*-8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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