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EFFICIENT SYNTHESIS OF *t*-BUTYL 3-ALKYL-*N*-HYDROXY-OXINDOLE-3-CARBOXYLATES FROM DI-*t*-BUTYL 2-NITROPHENYLMALONATES

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Abstract – A selective and efficient synthesis of *t*-butyl 3-alkyl-*N*-hydroxy-oxindole-3-carboxylates from di-*t*-butyl 2-nitrophenylmalonates is described. A tandem reduction-cyclization approach involving reduction of di-*t*-butyl 2-methyl-(2-nitrophenyl)malonate to di-*t*-butyl 2-(2-(hydroxyamino)phenyl)-2-methylmalonate followed by accelerated cyclization reaction using a combination of Rh/C and hydrazine monohydrate smoothly and selectively afforded the *N*-hydroxy-oxindole scaffold. This methodology was successfully applied to gram-scale-synthesis of the *t*-butyl *N*-hydroxy-3-methyl-oxindole-3-carboxylate **1** without silica gel column chromatographic separation step.

A number of bioactive compounds and natural products include 3,3-disubstituted oxindole moieties.[1] In addition, *N*-hydroxy-oxindole scaffolds are common structure among natural products, such as versicolamide C,[2] notoamide A[3] and notoamide H.[4] In spite of the advantages of substituted *N*-hydroxy-oxindoles,[5] there are recently fewer reports on the synthesis of 3,3-disubstituted *N*-hydroxy-oxindoles than on that of 3,3-disubstituted oxindoles.[1] To date, a number of methods for the synthesis of 3,3-disubstituted *N*-hydroxy-oxindoles, including photocyclization reaction,[6] reductive Heck cyclization,[7] transition-metal-free method,[8] oxidation of indoline,[9] nucleophilic reaction to 3,3-dimethyl-3*H*-indole-1-oxide[10] or 2-amino-3*H*-indole-1-oxide,[11] and tandem reduction-cyclization [12] have been developed. In addition, we have previously reported the synthesis of the *N*-hydroxy-oxindole **1** and oxindole **2** using Brønsted acid-catalyzed cyclization reaction.[13] However, it is difficult to use this reaction industrially, because it affords a mixture of **1** and **2**, and separation of **1** from the mixture requires recrystallization. As far as we know, there is no report on selective and efficient syntheses of the

N-hydroxy-oxindole **1** applicable to industrial process chemistry. Here, we describe a selective and efficient synthesis of the *N*-hydroxy-oxindole **1** through tandem reduction-cyclization approach that includes reduction of the nitro group to *N*-hydroxylamine and accelerated cyclization using a combination of Rh/C and hydrazine monohydrate.

In our previous report describing a selective synthesis of the oxindole **2**, addition of a variety of Brønsted acids preferentially gave the oxindole **2** over the *N*-hydroxy-oxindole **1** in spite of the strong nucleophilicity of the nitrogen atom of *N*-hydroxylamine.[14] These results let us to hypothesize that steric repulsion between the *t*-butyl ester and *N*-hydroxylamine averts the cyclization reaction to afford the *N*-hydroxy-oxindole. On the other hand, a less bulky anilinic amine can smoothly attack at the carbonyl carbon atom of the *t*-butyl ester.

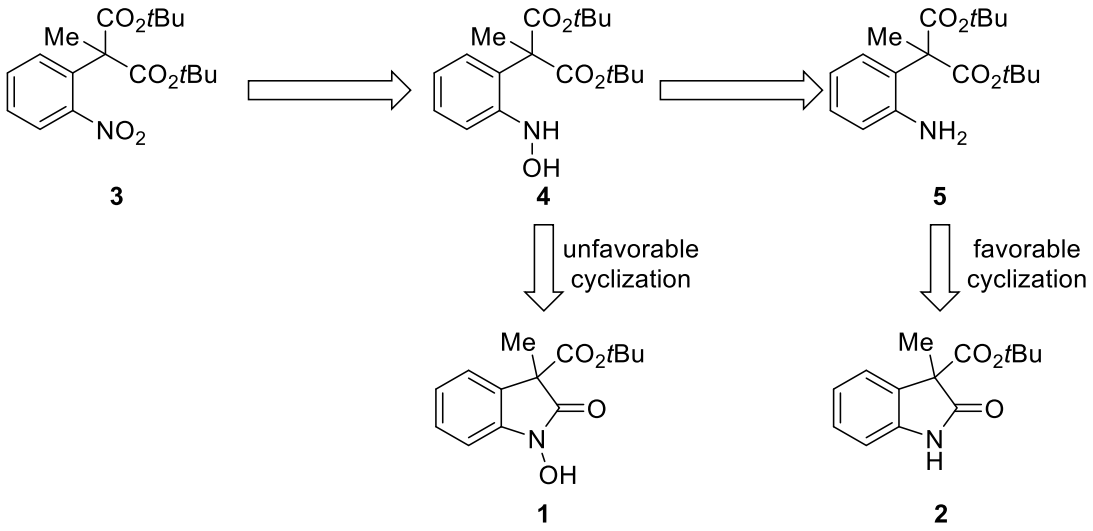
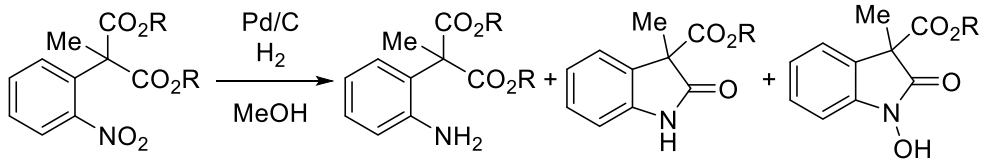


Figure 1. Our hypothesis of the reaction mechanism

First, we examined the relationship between bulkiness of the ester moiety and the *N*-hydroxy-oxindole/oxindole ratio. The results are summarized in Table 1. Use of dimethyl and diethyl malonate as starting materials afforded *N*-hydroxy-oxindoles and oxindoles to nearly the same extent (entries 1 and 2). As the ester moiety became bulkier, more oxindoles were produced than *N*-hydroxy-oxindoles (entries 3 and 4). These results indicate that steric repulsion between the ester and *N*-hydroxylamine hampers the cyclization reaction that produces oxindoles.

Table 1. Cyclization reaction of malonates to afford oxindole derivatives



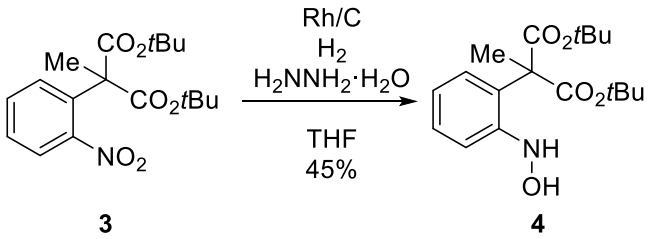
3: R = *t*Bu
3a: R = Me
3b: R = Et
3c: R = *i*Pr

5, 5a-c **2, 2a-c** **1, 1a-c**

			Product Ratio (%)		
entry	R	time (h)	aniline	oxindole	*N*-hydroxy-oxindole
1	Me (**3a**)	2	N.D.	52[a] (52)	48[a] (46)
2	Et (**3b**)	12	N.D.	50[a] (50)	50[a] (45)
3	*i*Pr (**3c**)	18	N.D.	64[a] (55)	36[a] (32)
4	*t*Bu (**3**)	168	46[b]	54[b]	N.D.

N.D. = Not detected.
The number in the parentheses is isolated yield.
[a] Ratio between oxindole and *N*-hydroxy-oxindole determined by ^{1}H NMR analysis of the reaction mixture.
[b] Ratio between aniline and oxindole determined by ^{1}H NMR analysis of the reaction mixture.

Second, we screened Brønsted acids to accelerate the cyclization reaction of *N*-hydroxylamine and obtain the *N*-hydroxy-oxindole **1**. Based on a report describing the reduction of the nitro group to *N*-hydroxylamine using a combination of Rh/C and hydrazine monohydrate,[15] we prepared the *N*-hydroxyaniline **4** as starting material (Scheme 1).



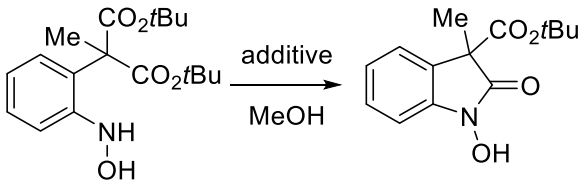
3 **4**

Scheme 1. Preparation of the *N*-hydroxyaniline **4**

As a result, addition of Brønsted acids (Table 2, entries 2–5) and Lewis acids (Table 2, entries 6 and 7) produced the *N*-hydroxy-oxindole **1** quantitatively. On the other hand, cyclization reaction of the *N*-hydroxyaniline **4** hardly proceeded without acids (Table 2, entry 1). As shown in our previous report on

cyclization that affords the oxindole **2**,[13] addition of acids increased reactivity of the *N*-hydroxyaniline **4**. Interestingly, addition of hydrazine monohydrate also accelerated the cyclization reaction of *N*-hydroxyaniline **4** in MeOH (Table 2, entry 8), indicating that both acids and bases promote the cyclization reaction of *N*-hydroxyaniline **4**.

Table 2. Screening of acids for *N*-hydroxy-oxindole cyclization



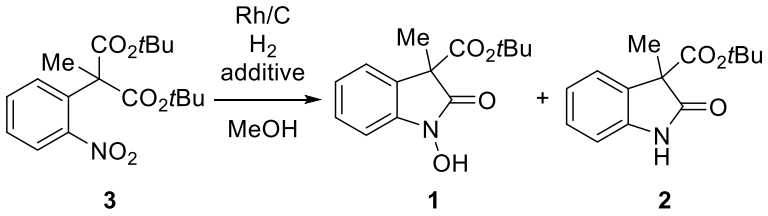
4 **1**

entry	additive	time (h)	yield (%)
1	–	168	20[a]
2	AcOH	168	91[b]
3	citric acid	24	93[b]
4	$TsOH·H_2O$	0.25	98[b]
5	PPTS	2	97[b]
6	$BF_3·OEt_2$	0.5	99[b]
7	$AlCl_3$	1	95[b]
8	$H_2NNH_2·H_2O$	6	92[b]

[a] Conversion ratio determined by ^1H NMR analysis of the reaction mixture.
[b] Isolated yield.

Third, we applied these reaction conditions to the tandem reduction-cyclization reaction to produce the *N*-hydroxy-oxindole **1** using compound **3** as substrate (Table 3). Addition of AcOH did not produce the *N*-hydroxy-oxindole **1** at all (entry 1). Addition of citric acid produced the oxindole **2** as a major product (entry 2). On the other hand, the *N*-hydroxy-oxindole **1** was obtained as a main product using $BF_3·OEt_2$, $AlCl_3$, or $TsOH·H_2O$ (entries 3–5). These results suggest that reduction of the *N*-hydroxyaniline **4** to aniline **5** is promoted by either Brønsted acids or Lewis acids to produce oxindole **2**. By contrast, addition of hydrazine monohydrate selectively afforded *N*-hydroxy-oxindole **1** without production of oxindole **2** (Table 3, entry 6).

Table 3. Tandem reduction-cyclization reaction using a combination of Rh/C and Brønsted acids, Lewis acids or hydrazine monohydrate



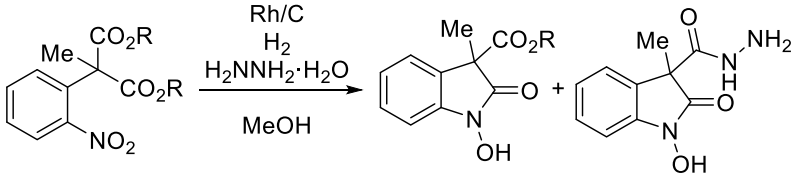
3 **1** **2**

entry	additive	time (h)	**1** (%)[a]	**2** (%)[a]
1	AcOH	61	N.D.	54
2	citric acid	24	6	71
3	$BF_3 \cdot OEt_2$	3	8	16
4	$AlCl_3$	5	80	16
5	$TsOH \cdot H_2O$	1	56	27
6	$H_2NNH_2 \cdot H_2O$	3	quant.	N.D.

N.D. = Not detected.
[a] Isolated yield.

Next, we applied the optimized reaction condition to the dimethyl malonate **3a**, diethyl malonate **3b** and diisopropyl malonate **3c** (Table 4).

Table 4. One-pot reaction for *N*-hydroxy-oxindole cyclization



3: R = *t*Bu
3a: R = Me
3b: R = Et
3c: R = *i*Pr

1, **1a-c** **6**

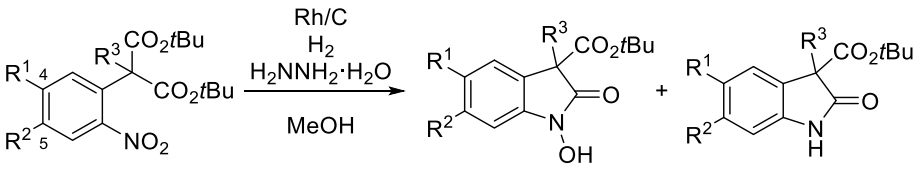
entry	compound	time (h)	*N*-hydroxy-oxindole (%)[a]	**6** (%)[a]
1	**3**	3	quant.	N.D.
2	**3a**	2	54	23
3	**3b**	2	61	22
4	**3c**	2	70	18

N.D. = Not detected.
[a] Isolated yield.

These reactions afforded the *N*-hydroxy-oxindoles **1a**–**1c** in relatively low yield in spite of the complete reaction of the starting materials (entries 2–4). This result was explained by assuming that the less hindered malonates in **3a**, **3b** and **3c** than in **3** facilitated nucleophilic attack of hydrazine to their carbonyl carbon atoms, leading to production of by-product **6**.

Finally, we applied this optimized methodology for selective synthesis of *N*-hydroxy-oxindole to prepare a variety of substituted *N*-hydroxy-oxindoles (Table 5). Replacement of the methyl group at the α-position of malonate by an ethyl group or a benzyl group afforded the *N*-hydroxy-oxindoles **1d** and **1e** (entries 1 and 2). Likewise, introduction of a substituent at the 4- or 5-position of the benzene ring provided the *N*-hydroxy-oxindoles **3f**–**3i** (entries 3–6).

Table 5. Synthesis of various *N*-hydroxy-oxindoles



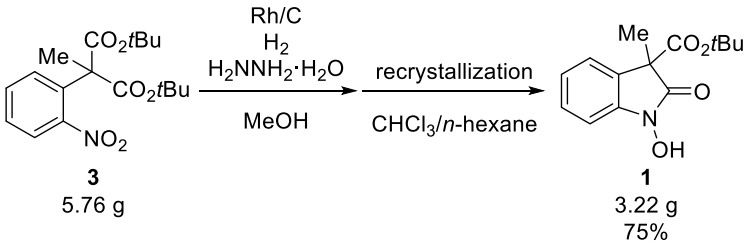
3d: R^1 = H, R^2 = H, R^3 = Et
3e: R^1 = H, R^2 = H, R^3 = Bn
3f: R^1 = F, R^2 = H, R^3 = Me
3g: R^1 = OMe, R^2 = H, R^3 = Me
3h: R^1 = H, R^2 = Me, R^3 = Me
3i: R^1 = H, R^2 = CF_3, R^3 = Me

1d-i **2d-i**

entry	compound	time (h)	*N*-hydroxy-oxindole (%)[a]	oxindole (%)
1	**3d**	3.5	73	N.D.
2	**3e**	3.5	80	N.D.
3	**3f**	1.5	75	N.D.
4	**3g**	6	74	N.D.
5	**3h**	3	76	N.D.
6	**3i**	2	78	N.D.

N.D. = Not detected.
[a] Isolated yield.

For industrial use, we challenged the synthesis of *t*-butyl *N*-hydroxy-3-methyl-oxindole-3-carboxylate **1** without use of column chromatography (Scheme 2). Purification of compound **1** was accomplished by recrystallization using $CHCl_3$/*n*-hexane as solvents.



Scheme 2. Column-less synthesis of compound **1**

In summary, we have developed a selective synthesis for the *N*-hydroxy-oxindole **1** from di-*t*-butyl 2-methyl-2-(2-nitrophenyl)malonate **3** through tandem reduction-cyclization of the nitro group to *N*-hydroxylamine followed by accelerated cyclization using a combination of Rh/C and hydrazine monohydrate. In addition, we have successfully expanded this methodology to the synthesis of substituted *N*-hydroxy-oxindole derivatives. Moreover, we have established a column-less synthesis of *N*-hydroxy-oxindole **1** suitable for industrial use.

EXPERIMENTAL

Melting points were recorded on Yanaco MP-500D and are uncorrected. IR spectra were recorded on SHIMADZU FT-IR-8400 or SHIMADZU IRPrestige-21. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL AL-400 or JEOL ECS-400 spectrometer in the stated solvents using tetramethylsilane or residual nondeuterated solvent peak as an internal standard. Chemical shifts (δ) are expressed in parts per million. High resolution MS spectra were recorded on Thermo Fisher Scientific Q Exactive orbitrap LC-MS/MS or AB SCIEX Triple TOF 5600. Reactions were followed by TLC on silica gel 60 F_{254} (E. Merck) or silica gel 70 F_{254} (Wako) using precoated TLC plates. Column chromatography was carried out on a Yamazen W-prep system using prepacked silica gel or amino silica gel. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All solvents were of the commercially available grade. Reactions requiring anhydrous conditions were performed under nitrogen atmosphere.

General procedure for di-alkyl 2-methyl-2-(2-nitrophenyl)malonate derivatives (Table 1). Di-alkyl 2-(2-nitrophenyl)malonate was dissolved in DMF (0.7 M). K_2CO_3 (1.3 eq.) and methyl iodide (1.2 eq.) were added to the reaction mixture. The resultant mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with EtOAc/*n*-hexane (2/1). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 100/0 – 40/60).

Diisopropyl 2-methyl-2-(2-nitrophenyl)malonate (3c): Yield; quant. as a colorless oil; IR ($CHCl_3$):

1733, 1541, 1094, 1047 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.03 (1H, dd, *J* = 8.3, 1.4 Hz), 7.58 (1H, td, *J* = 8.3, 1.4 Hz), 7.47 (1H, td, *J* = 8.3, 1.4 Hz), 7.32 (1H, dd, *J* = 8.3, 1.4 Hz), 5.08 (2H, sep, *J* = 6.0 Hz), 1.99 (3H, s), 1.23 (6H, d, *J* = 6.0 Hz), 1.22 (6H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 169.2, 148.8, 134.8, 133.1, 129.3, 128.4, 126.0, 70.1, 59.8, 23.5, 21.5, 21.3; HRMS (ESI): *m/z* calcd. for $C_{16}H_{22}NO_6$: 324.1442 $[M+H]^+$; found: 324.1444.

General procedure for tandem reduction-cyclization reaction of di-alkyl 2-methyl-2-(2-nitrophenyl)malonate (Table 1 and 3). Di-alkyl 2-methyl-2-(2-nitrophenyl)malonate (100 mg) was dissolved in MeOH (0.3 M). Catalyst 10% Pd/C (w/w = 1/10) was added to the reaction mixture in Table 1, whereas catalyst 5% Rh/C (w/w = 1/10) and additive (1.0 eq.) were added in Table 3. The resultant mixture was stirred at room temperature under H_2 atmosphere. The reaction was followed by ^1H NMR. After confirming the completion of the cyclization reaction by ^1H NMR, the mixture was passed through a pad of Celite with MeOH and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 30/70 – 0/100) to afford alkyl 3-methyl-oxindole-3-carboxylate and alkyl 1-hydroxy-3-methyl-oxindole-3-carboxylate.

Methyl 1-hydroxy-3-methyl-oxindole-3-carboxylate (1a): Yield; 46% as a brownish oil; IR ($CHCl_3$): 3112, 1746, 1615, 1245, 1116 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 10.70 (br s, 1H), 7.25 (1H, t, *J* = 7.2 Hz), 7.20 (1H, d, *J* = 7.2 Hz), 6.99 (1H, t, *J* = 7.2 Hz), 6.90 (1H, d, *J* = 7.2 Hz), 3.58 (3H, s), 1.50 (3H, s); ^{13}C NMR ($CDCl_3$) δ: 171.6, 169.4, 141.0, 129.4, 126.3, 124.0, 122.8, 109.0, 53.9, 53.3, 19.8; HRMS (ESI): *m/z* calcd. for $C_{11}H_{12}NO_4$: 222.0761 $[M+H]^+$; found: 222.0761.

Isopropyl 1-hydroxy-3-methyl-oxindole-3-carboxylate (1c): Yield; 32% as a colorless solid; mp 112–115 °C; IR ($CHCl_3$): 3116, 1731, 1614, 1249, 1098 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 11.06 (1H, s), 7.34 (1H, t, *J* = 7.3 Hz), 7.25 (1H, d, *J* = 7.3 Hz), 7.06 (1H, t, *J* = 7.3 Hz), 6.98 (1H, d, *J* = 7.3 Hz), 4.87 (1H, sep, *J* = 6.1 Hz), 1.51 (3H, s), 1.10 (3H, d, *J* = 6.1 Hz), 1.02 (3H, d, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 171.7, 168.3, 141.0, 129.2, 126.7, 123.8, 122.6, 109.0, 70.0, 54.3, 21.4, 21.2, 19.7; HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NO_4$: 250.1074 $[M+H]^+$; found: 250.1074.

Isopropyl 3-methyl-oxindole-3-carboxylate (2c): Yield; 55% as a brownish solid; mp 114–119 °C; IR ($CHCl_3$): 3208, 1728, 1619, 1195, 1103 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 10.62 (1H, s), 7.23 (1H, t, *J* = 7.9 Hz), 7.17 (1H, d, *J* = 7.9 Hz), 6.97 (1H, t, *J* = 7.9 Hz), 6.87 (1H, d, *J* = 7.9 Hz), 4.85 (1H, sep, *J* = 6.1 Hz), 1.47 (3H, s), 1.09 (3H, d, *J* = 6.1 Hz), 1.00 (3H, d, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 178.0, 168.8, 141.0, 130.9, 128.9, 123.1, 122.8, 110.3, 69.6, 55.8, 21.5, 21.3, 20.0; HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NO_3$: 234.1130 $[M+H]^+$; found: 234.1126.

Preparation of di-*t*-butyl 2-(2-(hydroxyamino)phenyl)-2-methylmalonate (4) (Scheme 1). Di-*t*-butyl 2-methyl-2-(2-nitrophenyl)malonate **3** (502 mg, 1.43 mmol) was dissolved in THF (4.8 mL, 0.3 M). 5% Rh/C (50.0 mg, w/w = 1/10) and hydrazine monohydrate (416 μL, 8.58 mmol, 6.0 eq.) were added to the

reaction mixture. The reaction mixture was stirred at 0 °C. After 1 h, the mixture was passed through a pad of Celite with THF and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 30/70) to afford compound **4** (217 mg, 45%) as a pale yellow solid; mp 105–107 °C; IR ($CHCl_3$): 3576, 3327, 1717, 1281, 1258, 1163, 1113 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.22 (1H, br s), 7.53 (1H, br s), 7.32 (1H, d, J = 7.6 Hz), 7.23 (1H, t, J = 7.6 Hz), 7.08 (1H, d, J = 7.6 Hz), 6.83 (1H, t, J = 7.6 Hz), 1.67 (3H, s), 1.41 (18H, s); ^{13}C NMR ($CDCl_3$) δ: 171.1, 148.6, 128.4, 127.5, 126.4, 122.2, 117.2, 82.1, 58.8, 27.8, 22.5; HRMS (ESI): *m/z* calcd. for $C_{18}H_{28}NO_5$: 338.1962 $[M+H]^+$; found: 338.1967.

Cyclization reaction of di-*t*-butyl 2-(2-(hydroxyamino)phenyl)-2-methylmalonate (4) (Table 2). Di-*t*-butyl 2-(2-(hydroxyamino)phenyl)-2-methylmalonate **4** (100 mg) was dissolved in MeOH (1.0 mL, 0.3 M). Additive (1.0 eq.) was added to the reaction mixture. The reaction mixture was stirred at room temperature. The reaction was followed by ^1H NMR. After confirming the completion of the cyclization reaction by ^1H NMR, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 30/70 – 0/100) to afford compound **1**.

General procedure for alkyl 1-hydroxy-3-methyl-oxindole-3-carboxylate (Table 4). Di-alkyl 2-methyl-(2-nitrophenyl)malonate was dissolved in MeOH (0.3 M). 5% Rh/C (w/w = 1/10) and hydrazine monohydrate (6.0 eq.) were added to the reaction mixture. The resultant mixture was stirred at room temperature. The reaction was followed by ^1H NMR. After confirming the completion of the reduction reaction by ^1H NMR, the mixture was passed through a pad of Celite with MeOH and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 30/70 – 0/100).

1-Hydroxy-3-methyl-oxindole-3-carbohydrazide (6): As a colorless solid; mp 58–60 °C; IR ($CHCl_3$): 3276, 1686, 1611, 1508, 1463 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 10.40 (1H, br s), 9.09 (1H, br s), 7.29 (1H, t, J = 7.2 Hz), 7.28 (1H, d, J = 7.3 Hz), 7.03 (1H, t, J = 7.2 Hz), 6.93 (1H, d, J = 7.3 Hz), 4.29 (2H, br s), 1.51 (3H, s); ^{13}C NMR (DMSO-d_6) δ: 170.7, 167.6, 142.2, 128.6, 127.7, 123.2, 122.5, 107.3, 53.0, 19.9; HRMS (ESI): *m/z* calcd. for $C_{10}H_{12}N_3O_3$: 222.0873 $[M+H]^+$; found: 222.0873.

Preparation of di-*t*-butyl 2-substituted-2-(2-nitrophenyl)malonate derivatives (Table 5). See general procedure for di-alkyl 2-methyl-2-(2-nitrophenyl)malonate derivatives (Table 1).

Di-*t*-butyl 2-benzyl-2-(2-nitrophenyl)malonate (3e): Yield; 99% as a colorless solid; mp 96–98 °C; IR ($CHCl_3$): 1733, 1538, 1275, 1131 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.94 (1H, dd, J = 8.0, 1.2 Hz), 7.43 (1H, td, J = 8.0, 1.2 Hz), 7.35 (1H, td, J = 8.0, 1.2 Hz), 7.05–7.00 (3H, m), 6.95–6.91 (2H, m), 6.51 (1H, dd, J = 8.0, 1.2 Hz), 3.75 (2H, s), 1.37 (18H, s); ^{13}C NMR (DMSO-d_6) δ: 167.3, 149.2, 136.7, 132.2, 131.9, 131.3, 130.4, 128.6, 127.5, 126.3, 125.0, 82.8, 79.2, 66.1, 27.1; HRMS (ESI): *m/z* calcd. for $C_{24}H_{29}NO_6Na$: 450.1887 $[M+Na]^+$; found: 450.1891.

General procedure for *t*-butyl 1-hydroxy-3-methyl-oxindole-3-carboxylate derivatives (Table 5). Di-*t*-butyl 2-methyl-(2-nitrophenyl)malonate derivative was dissolved in MeOH (0.3 M). 5% Rh/C (w/w = 1/10) and hydrazine monohydrate (6.0 eq.) were added to the reaction mixture. The resultant mixture was stirred at room temperature. The reaction was followed by ^{1}H NMR. After confirming the completion of the reduction reaction by ^{1}H NMR, the mixture was passed through a pad of Celite with MeOH and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 30/70 – 0/100).

***t*-Butyl 3-ethyl-1-hydroxy-oxindole-3-carboxylate (1d):** Yield; 73% as a colorless solid; mp 131–133 °C; IR ($CHCl_3$): 3138, 1734, 1699, 1221, 1155 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 10.97 (1H, br s), 7.35 (1H, t, *J* = 7.6 Hz), 7.24 (1H, d, *J* = 7.6 Hz), 7.08 (1H, t, *J* = 7.6 Hz), 6.98 (1H, d, *J* = 7.6 Hz), 2.09 (2H, q, *J* = 7.3 Hz), 1.30 (9H, s), 0.57 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ: 168.3, 167.6, 142.8, 129.0, 124.3, 122.7, 122.7, 107.2, 81.7, 58.9, 27.3, 26.3, 7.9; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}NO_4Na$: 300.1206 $[M+Na]^+$; found: 300.1207.

***t*-Butyl 3-benzyl-1-hydroxy-oxindole-3-carboxylate (1e):** Yield; 80% as a colorless solid; mp 187–189 °C; IR ($CHCl_3$): 3020, 1738, 1618, 1215, 1153 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 10.82 (1H, s), 7.37 (1H, d, *J* = 7.9 Hz), 7.21 (1H, t, *J* = 7.9 Hz), 7.05-7.01 (4H, m), 6.88-6.84 (2H, m), 6.72 (1H, d, *J* = 7.9 Hz), 3.47 (1H, d, *J* = 13.4 Hz), 3.35 (1H, d, *J* = 13.4 Hz), 1.31 (9H, s); ^{13}C NMR (DMSO-d_6) δ: 167.7, 167.4, 142.5, 134.7, 129.8, 128.9, 127.7, 126.6, 123.8, 123.5, 122.3, 107.1, 82.1, 59.7, 37.9, 27.3; HRMS (ESI): *m/z* calcd. for $C_{20}H_{21}NO_4Na$: 362.1363 $[M+Na]^+$; found: 362.1359.

***t*-Butyl 5-fluoro-1-hydroxy-3-methyl-oxindole-3-carboxylate (1f):** Yield; 75% as a brownish oil; IR ($CHCl_3$): 3138, 1738, 1701, 1261, 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 9.88 (1H, br s), 7.12 (1H, dd, *J* = 8.4, 4.4 Hz), 7.06 (1H, td, *J* = 8.4, 2.4 Hz), 7.00 (1H, dd, *J* = 7.6, 2.4 Hz), 1.58 (3H, s), 1.34 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 171.6, 167.1, 159.8 (d, *J* = 242.8 Hz), 137.1, 128.5 (d, *J* = 7.7 Hz), 115.5 (d, *J* = 24.1 Hz), 110.7 (d, *J* = 26.0 Hz), 109.7 (d, *J* = 8.7 Hz), 83.2, 55.1, 27.6, 19.4; HRMS (ESI): *m/z* calcd. for $C_{14}H_{15}FNO_4$: 280.0991 $[M–H]^–$; found: 280.0985.

***t*-Butyl 1-hydroxy-5-methoxy-3-methyl-oxindole-3-carboxylate (1g):** Yield; 74% as a brownish oil; IR ($CHCl_3$): 3146, 1734, 1697, 1223, 1207, 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 10.21 (1H, br s), 7.09 (1H, d, *J* = 7.9 Hz), 6.86 (1H, d, *J* = 7.9 Hz), 6.84 (1H, s), 3.79 (3H, s), 1.57 (3H, s), 1.33 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 171.3, 167.7, 156.8, 134.6, 128.4, 113.2, 109.8, 109.4, 82.8, 55.8, 55.1, 27.6, 19.5; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}NO_5Na$: 316.1155 $[M+Na]^+$; found: 316.1155.

***t*-Butyl 1-hydroxy-3,6-dimethyl-oxindole-3-carboxylate (1h):** Yield; 76% as a colorless solid; mp 130–131 °C; IR ($CHCl_3$): 3153, 1734, 1701, 1223, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 10.22 (1H, br s), 7.10 (1H, d, *J* = 7.3 Hz), 7.01 (1H, s), 6.89 (1H, d, *J* = 7.3 Hz), 2.39 (3H, s), 1.55 (3H, s), 1.32 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 172.1, 167.9, 141.1, 139.4, 124.1, 124.1, 122.1, 109.6, 82.6, 54.7, 27.6, 21.7, 19.4; HRMS

(ESI): *m/z* calcd. for $C_{15}H_{19}NO_4Na$: 300.1206 $[M+Na]^+$; found: 300.1206.

***t*-Butyl 1-hydroxy-3-methyl-6-(trifluoromethyl)oxindole-3-carboxylate (1i):** Yield; 78% as a pale yellow oil; IR ($CHCl_3$): 3140, 1738, 1711, 1319, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 10.14 (1H, br s), 7.42 (1H, s), 7.40 (1H, d, J = 7.9 Hz), 7.36 (1H, d, J = 7.9 Hz), 1.62 (3H, s), 1.33 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 171.9, 166.8, 141.7, 131.7 (q, J = 32.8 Hz), 130.6, 123.7 (q, J = 272.1 Hz), 122.9, 120.8 (d, J = 3.8 Hz), 105.9 (q, J = 3.8 Hz), 83.6, 55.1, 27.5, 19.3; HRMS (ESI): *m/z* calcd. for $C_{15}H_{15}F_3NO_4$: 330.0959 $[M-H]^-$; found: 330.0954.

Synthesis of *t*-butyl 1-hydroxy-3-methyl-oxindole-3-carboxylate 1 without column chromatography (Scheme 2). Di-*t*-butyl 2-methyl-(2-nitrophenyl)malonate **3** (5.76 g, 16.4 mmol) was dissolved in MeOH (55 mL, 0.3 M). 5% Rh/C (578 mg, w/w = 1/10) and hydrazine monohydrate (4.78 mL, 98.3 mmol, 6.0 eq.) were added to the reaction mixture. The mixture was stirred at room temperature. The reaction was followed by ^1H NMR. After confirming the completion of the reduction reaction, the mixture was passed through a pad of Celite with MeOH and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with sat. NH_4Cl aq., brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Crystallization of the residue from $CHCl_3$/*n*-hexane (1/2) afforded compound **1** (3.22 g, 75%) as a colorless solid.

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