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SYNTHESIS OF SUBSTITUTED *t*-BUTYL 3-ALKYLOXINDOLE-3-CARBOXYLATES FROM DI-*t*-BUTYL (2-NITROPHENYL)MALONATES

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Abstract – Using a novel tandem reduction-cyclization, we synthesized *t*-butyl 3-alkyloxindole-3-carboxylates from the di-*t*-butyl 2-alkyl-2-(2-nitrophenyl)malonate. Introduction of an α-substituent to the di-*t*-butyl 2-(2-nitrophenyl)malonates and addition of acid promoted reactivity. This methodology was successfully applied to gram-scale-synthesis of the *t*-butyl 3-methyloxindole-3-carboxylate **1** and 3-hydroxymethyl-3-methyloxindole **2** without silica gel column chromatography.

INTRODUCTION

3,3-Disubstituted oxindoles are common scaffolds in a number of biologically active compounds.[1] Among them, alkyl 3-alkyloxindole-3-carboxylates have attracted much attention due to their asymmetric quaternary carbon atom at the 3-position of the oxindole and valuable properties in the synthesis of natural products.[2] In fact, various synthetic routes for these oxindoles are described in the literature.[3-9] Especially, tandem reduction-lactamization, which uses dimethyl or diethyl 2-alkyl-2-(2-nitrophenyl)malonates, is considered one of the most efficient method for preparing these oxindoles. For example, Acheson and co-workers reported that Raney nickel catalyzed hydrogenation of the nitro group of the diethyl 2-methyl-2-(2-nitrophenyl)malonate produces oxindole **3**.[9b] On the other hand, Bunce and co-workers reported that tandem reduction-cyclization of the dimethyl

2-methyl-2-(2-nitrophenyl)malonate via the nitro group using a combination of Fe and AcOH affords compound **4**.[2hf]

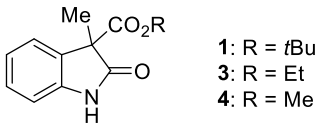


Figure 1. Chemical structures of methyl, ethyl, and *t*-butyl esters of alkyl 3-methyloxindole-3-carboxylic acid

Although a number of synthetic routes for the above oxindoles have been reported, there are only few reports describing the synthesis of *t*-butyl 3-alkyloxindole-3-carboxylates.[7a,7d,9a] The known methodologies are based on cyclization of *t*-butyl diphenylmethyl 2-alkyl-2-(2-nitrophenyl)malonate via reduction of its nitro group.[9a] As far as we know, there is no report on the use of tandem reduction-lactamization of di-*t*-butyl 2-alkyl-2-(2-nitrophenyl)malonates to produce *t*-butyl 3-alkyloxindole-3-carboxylates. Finding this cyclization reaction leads to developing asymmetric construction of quaternary carbon center at 3-position of oxindole compounds because bulky *t*-butyl moiety is effective for asymmetric desymmetrization.[10] Here, we describe a new synthetic route to 3-alkyl-substituted *t*-butyl oxindole-3-carboxylates via Pd and Brønsted acid catalyzed reduction-lactamization. This route enhances interaction between carbonyl carbon atoms of the malonates and the anilinic nitrogen atom (Figure 2). In addition, we refer to the use of this method for a concise and efficient synthesis of alkyl *t*-butyl 3-alkyloxindole-3-carboxylates.

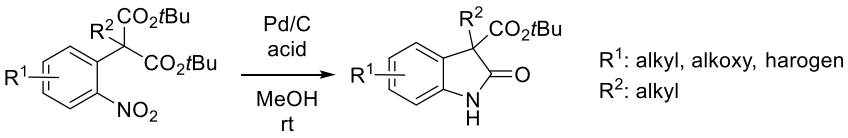


Figure 2. Tandem reduction-lactamization of di-*t*-butyl 2-alkyl-2-(2-nitrophenyl)malonates to produce *t*-butyl 3-alkyloxindole-3-carboxylates

RESULTS AND DISCUSSION

To prepare *t*-butyl 3-alkyloxindole-3-carboxylates, we considered increasing the reactivity of the di-*t*-butyl 2-(2-aminophenyl)malonate **5**[11] via the reactive rotamer effect (Figure 3).[12] Although some reports suggest that cyclization of compound **6** may not occur due to low reactivity of the *t*-butyl ester,[11,13] we speculate that steric repulsion elicited by introduction of α-substituents, such as a methyl group, rotates C-C bond, leading to nucleophilic attack of the anilinic nitrogen atom on the carbonyl

carbon atom of *t*-butyl esters of compound **6**. On the other hand, nucleophilic attack does not occur in compound **5**, because the two ester groups of compound **5** are positioned far from the anilinic nitrogen atom to avoid steric repulsion (Figure 3).

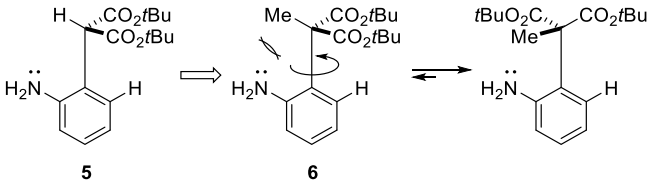
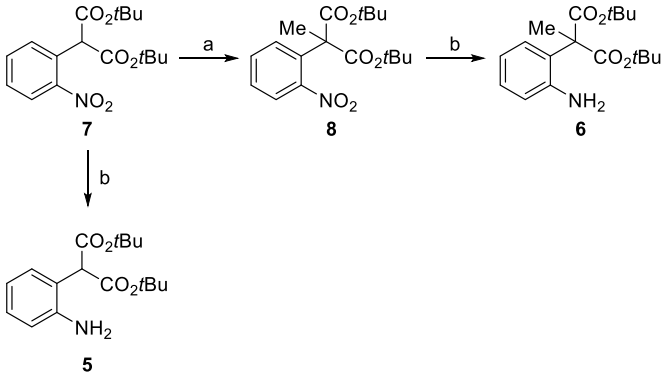


Figure 3. Reactive rotamer effect induced by α-substituent

First, we carried out an X-ray crystal analysis and estimated the steric repulsion induced by the α-methyl group. In the process of synthesizing compounds **5** and **6** (Scheme 1), we fortunately obtained the respective single crystals of compounds **7**[11] and **8**.



Scheme 1. Reagents and conditions: (a) K_2CO_3, MeI, rt, 73%; (b) Pd/C, H_2, MeOH, rt, **5**: 98%, **6**: 81%

Figure 4 shows X-ray crystal structure of compounds **7** and **8**. As suggested, both esters of compound **7** keep distance from the nitrogen atom of the nitro group to avoid mutual steric repulsion (Figures 4A and B). On the other hand, compound **8** possessing a methyl group at the α-position is in a conformation where one carbonyl carbon atom is in the proximity of the nitro group (Figures 4C and D). These findings support our hypothesis that introduction of α-substituent to compound **5** shortens the distance between the carbonyl carbon atom and the anilinic nitrogen atom, resulting in enhanced reactivity for cyclization.

For further estimation of the reactivity, we determined the activation energies for compounds **5** and **6** as substrates for the cyclization reaction by DFT[14] calculation using Gaussian 09 package.[15] The hybrid functional B3LYP[16] combined with 6-31G(d),[17] indicating that 6d was used to fully optimize the geometries of grand state molecules. The geometries of transition states have been confirmed by frequency analysis and IRC calculation.[18] The results are summarized in Table 1, Figure 5 and Figure S1

(see Supporting Information). Rate determining step is not elimination of *t*-BuOH but nucleophilic addition of anilinic nitrogen atom to carbonyl carbon atom (Figure 5). Interestingly, proton transfer with MeOH decreased activation Gibbs free energy of the addition step.

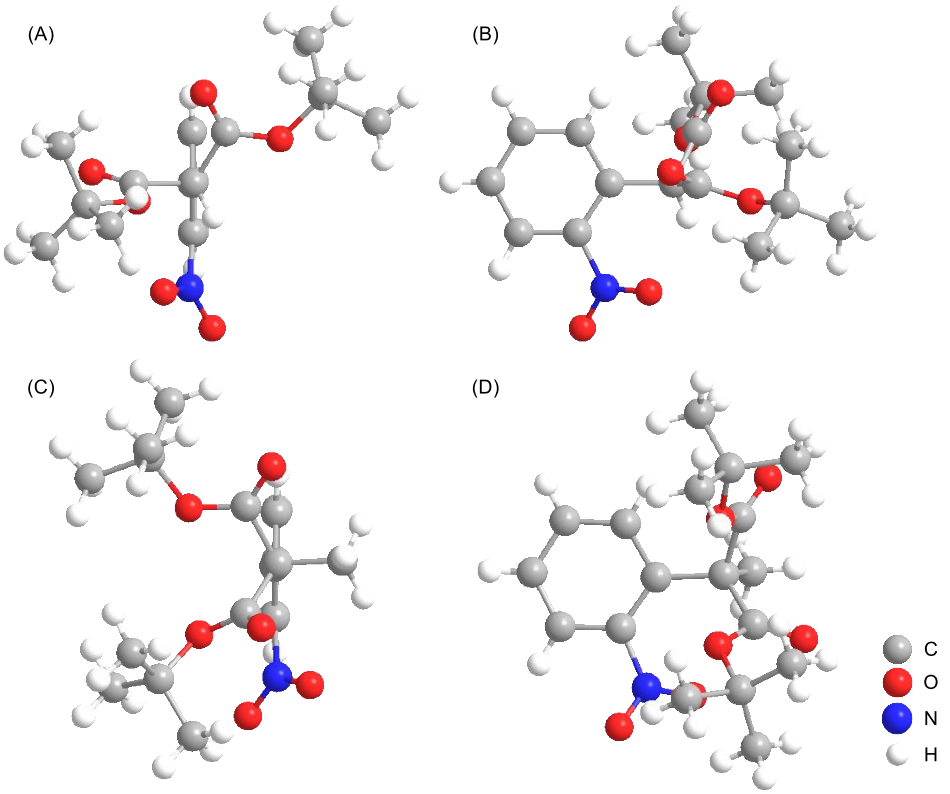


Figure 4. X-Ray analysis of compounds **7** (A, B) and **8** (C, D)

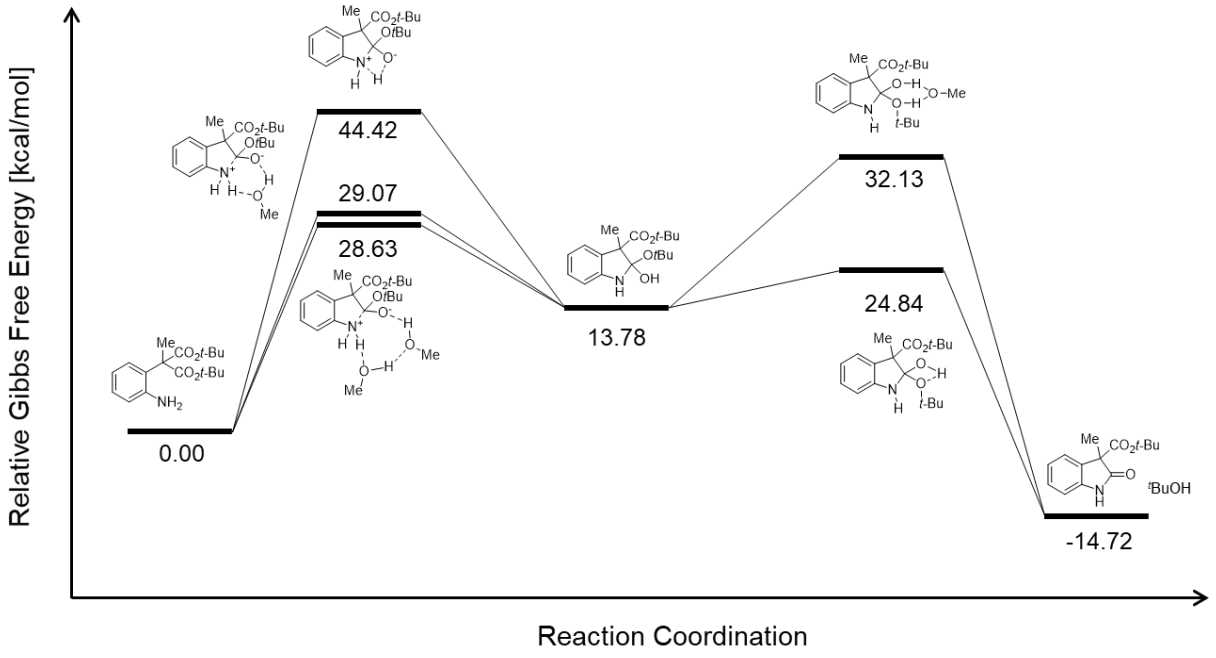


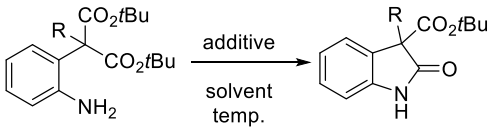
Figure 5. Transition states of cyclization reaction of compound **6** in MeOH

Table 1. DFT calculation for the cyclization reaction in MeOH

entry	R^1	activation Gibbs free energy (kcal/mol)		
		without MeOH	one MeOH	two MeOH
1	H (**5**)	49.58	33.27	31.79
2	Me (**6**)	44.42	29.07	28.63

DFT calculation also supported the assumption that introduction of a methyl group would promote cyclization. As shown in entry 2, compound **6** activation Gibbs free energy was decreased in association with one MeOH (29.07 kcal/mol) or two MeOH (28.63 kcal/mol). These results indicate that cyclization of compound **6** can proceed in MeOH through proton transfer. Although compound **5** activation Gibbs free energy was also decreased in association with one MeOH (33.27 kcal/mol) or two MeOH (31.79 kcal/mol), both of these were more than 30 kcal/mol, which is not enough to cause cyclization. These results prompted us to optimize the reaction conditions for a prompt cyclization.

Table 2. Oxindole cyclization using compounds **5** and **6**



5: R = H
6: R = Me

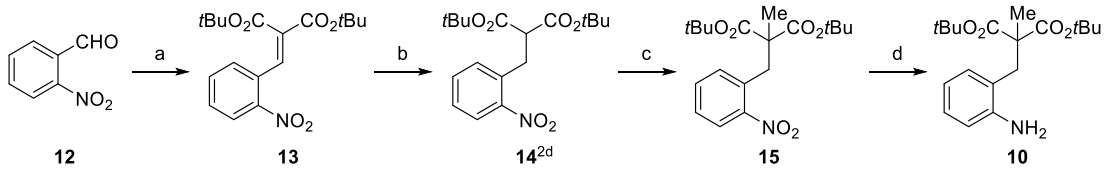
9: R = H
1: R = Me

entry	R	solvent	additive	temp. (°C)	time (h)	ratio[a]	isolated yield (%)
1	Me	MeOH	-	rt	165	**6** / **1** = 57 / 43	-
2	H	MeOH	-	rt	156	**5** / **9** = 100 / 0	-
3	Me	CH_2Cl_2	-	rt	74	**6** / **1** = 95 / 5	-
4	Me	MeOH	-	60	165	**6** / **1** = 48 / 52	-
5	H	MeOH	-	60	156	**5** / **9** = 100 / 0	-
6	Me	MeOH	AcOH	rt	24	**6** / **1** = 0 / 100	90 (**1**)
7	Me	MeOH	AcOH	60	4	**6** / **1** = 0 / 100	91 (**1**)
8	Me	CH_2Cl_2	AcOH	rt	24	**6** / **1** = 0 / 100	-
9	H	MeOH	AcOH	rt	156	-	92 (indoline-2-one)
10	H	MeOH	AcOH	60	48	-	100 (indoline-2-one)

[a] The ratio was determined by ^{1}H NMR analysis of the reaction mixture.

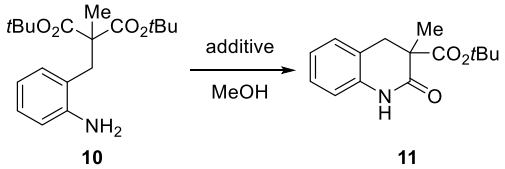
Second, we examined cyclization of compounds **5** and **6** in MeOH at room temperature. The results are summarized in Table 2. Stirring compound **6** in MeOH afforded the oxindole **1** in 43% yield (entry 1). On the other hand, stirring compound **5** in MeOH produced no oxindole at all (entry 2). As expected from calculation results, the reactivity of the cyclization was decreased in CH_2Cl_2 at room temperature (entry 3). Next, we examined the effects of a higher reaction temperature and addition of AcOH. Increase in the reaction temperature from room temperature to 60 °C slightly accelerated the cyclization of compound **6**, but did not improve the cyclization of compound **5** (entries 4 and 5). On the other hand, addition of AcOH resulted in prompt cyclization of compound **6** both at room temperature and at 60 °C (entries 6 and 7). Addition of AcOH also increased cyclized compound **1** in CH_2Cl_2 (entry 8). In spite of addition of AcOH, compound **9** was not obtained at any temperature, instead, the reaction afforded the indolin-2-one (entries 9 and 10). These results indicate that the methyl group at the α-position is essential for oxindole cyclization and that the use of AcOH enhances reactivity toward cyclization.

Contrary to the results reported by Bunce and co-workers,[2h] we hypothesized that our strategy for increasing compound **6** reactivity does not expand to the cyclization of compound **10** to form the dihydroquinolinone **11,** because the free rotation of Cα-Cβ keeps away the ester moiety from the anilinic nitrogen atom. To confirm this hypothesis, we synthesized compound **10** as a substrate of the cyclization reaction according to Scheme 2.



Scheme 2. Reagents and conditions: (a) di-*t*-butyl malonate, K_2CO_3, Ac_2O, 80 °C, 48%; (b) $NaBH_4$, MeOH, 0 °C, 99%; (c) NaH, MeI, THF, 0 °C, 58%; (d) Pd/C, H_2, MeOH, rt, 86%

Table 3. Cyclization of compound **10** to form compound **11**



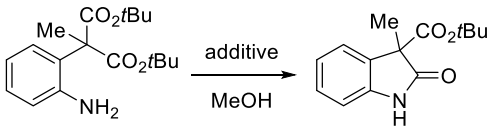
entry	additive	time (h)	ratio (SM / TM)[a]
1	-	24	100 / 0
2	AcOH	24	100 / 0

[a] The ratio was determined by ^{1}H NMR analysis of the reaction mixture.

As expected, cyclization of compound **10** did not proceed at room temperature (Table 3, entry 1). In addition, acetic acid did not increase reactivity of cyclization reaction of compound **10** (entry 2). Thus, cyclization of compound **6** is more readily achieved than that of compound **10**.

Next, we investigated various acids to optimize oxindole cyclization (Table 4). Based on Park's report indicating that silica gel increases reactivity of the carbonyl carbon atom of *t*-butyl ester,[9a] we tested some Brønsted acids and Lewis acids. Addition of AcOH increased oxindole cyclization (entries 1 and 2). On the other hand, NH_4Cl decreased this cyclization (entry 3). Citric acid, *p*-toluenesulfonic acid, PPTS and Lewis acids, including $BF_3 \cdot OEt_2$ and $AlCl_3$, accelerated oxindole cyclization. In general, oxindole cyclization was promoted with increasing acidity (entries 4-8).

Table 4. Cyclization of compound **6**



6 **1**

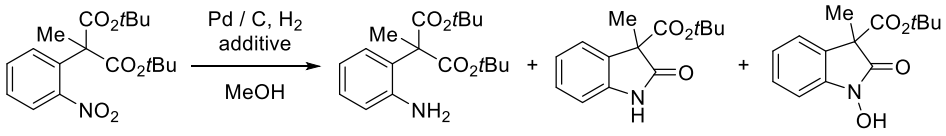
entry	additive	time (h)	ratio (SM / TM)[a]	isolated yield (%)
1	-	165	57 / 43	-
2	AcOH	24	0 / 100	90
3	NH_4Cl	156	30 / 70	-
4	citric acid	4	0 / 100	89
5	$TsOH \cdot H_2O$	0.25	0 / 100	86
6	PPTS	0.5	0 / 100	98
7	$BF_3 \cdot OEt_2$	0.25	0 / 100	90
8	$AlCl_3$	0.25	0 / 100	85

[a] The ratio was determined by ^1H NMR analysis of the reaction mixture.

Based on these findings, we optimized reaction conditions to achieve tandem reduction-cyclization reaction and produce the oxindole **1** using compound **8** as a substrate. As shown in Table 5, addition of a Brønsted or Lewis acid increased oxindole cyclization (entries 1–6). Especially, addition of AcOH or citric acid resulted in prompt cyclization (entries 1 and 2). On the other hand, addition of *p*-toluenesulfonic acid, $BF_3 \cdot OEt_2$ or $AlCl_3$ afforded the *N*-hydroxyoxindole **16** as a by-product (entries 3-5). Addition of PPTS increased the production of the *N*-hydroxyoxindole **16** to 55% yield. Comparing

these results with those in Table 4, it is considered that acids promote nucleophilic addition of *N*-hydroxyaniline, an intermediate of the reduction reaction of the nitro group. Especially, PPTS produced the *N*-hydroxyoxindole **16** in high yield, probably due to the effect of the pyridine moiety against on the Pd catalyst.

Table 5. Tandem reduction-cyclization reaction using Brønsted acids or Lewis acids



8 **6** **1** **16**

entry	additive	time (h)	**6** (%)	**1** (%)	**16** (%)
1	AcOH	53	N.D.[a]	quant.[b]	N.D.[a]
2	citric acid	4	N.D.[a]	quant.[b]	N.D.[a]
3	$BF_3 \cdot OEt_2$	1	N.D.[a]	80[b]	16[b]
4	$AlCl_3$	2	N.D.[a]	71[b]	26[b]
5	$TsOH \cdot H_2O$	1	N.D.[a]	64[b]	35[b]
6	PPTS	3	N.D.[a]	42[b]	55[b]

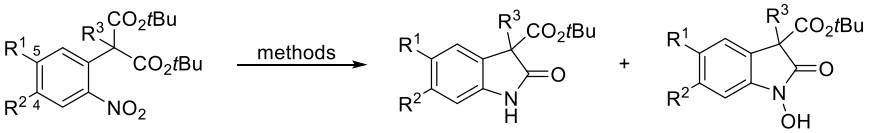
[a] Determined by ^1H NMR analysis of the reaction mixture.

[b] Isolated yield.

N.D.: not detected.

Third, we used the above findings to synthesize various substituted oxindoles (Table 6). The effects of substituents were dependent on the position of the benzene ring. Substitution of the fluoro or methoxy group at the 5-position of the benzene ring or replacement of the methyl group at the α-position by an ethyl group did not increase reactivity (entries 1, 2 and 7). On the other hand, substitution of the methyl group or trifluoromethyl group at the 4-position under normal conditions promoted cyclization to afford *N*-hydroxyoxindoles (method A, entries 3 and 5). The desired oxindoles were successfully obtained by delayed addition of citric acid (method B, entry 4) or its complete removal (method C, entry 6). The substituted malonates were prepared as described in Schemes 3 and 4.

Table 6. Synthesis of a variety of oxindoles



8a: R^1 = F, R^2 = H, R^3 = Me
8b: R^1 = OMe, R^2 = H, R^3 = Me
8c: R^1 = H, R^2 = Me, R^3 = Me
8d: R^1 = H, R^2 = CF_3, R^3 = Me
8e: R^1 = H, R^2 = H, R^3 = Et

entry	malonate	method	time (h)	product ratio[a]	
				oxindole	*N*-hydroxy oxindole
1	**8a**	A	4	100 (95)	0
2	**8b**	A	6	100 (91)	0
3	**8c**	A	4	70	30
4	**8c**	B	32	100 (81)	0
5	**8d**	A	4	0	100
6	**8d**	C	34	100 (93)	0
7	**8e**	A	6	100 (91)	0

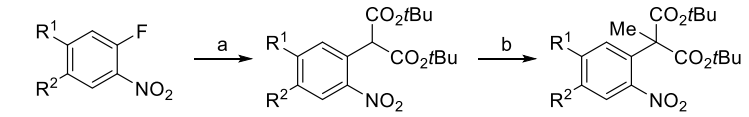
[a] The ratio was determined by ^{1}H NMR analysis of the reaction mixture.

The number in the parentheses is isolated yield (%).

Method A: Pd/C, citric acid, H_2, MeOH.

Method B: Pd/C, H_2, MeOH. After the reduction reaction, citric acid was added.

Method C: Pd/C, H_2, MeOH.

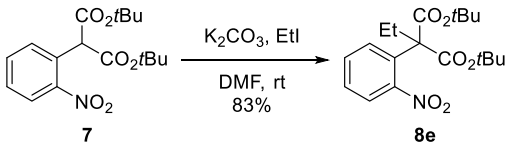


17a: R^1 = F, R^2 = H
17b[19]**:** R^1 = OMe, R^2 = H
17c: R^1 = H, R^2 = Me
17d: R^1 = H, R^2 = CF_3

7a, 50%
7b[20], 84%
7c, 78%
7d, quant.

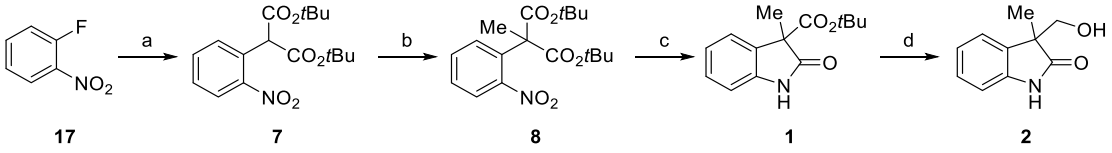
8a, 88%
8b, 70%
8c, 73%
8d, 90%

Scheme 3. Preparation of di-*t*-butyl 2-methyl-2-(2-nitrophenyl)malonate derivatives. Reagents and conditions: (a) di-*t*-butyl malonate, NaH, DMF, 0 °C to rt; (b) K_2CO_3, MeI, rt



Scheme 4. Preparation of di-*t*-butyl 2-ethyl-2-(2-nitrophenyl)malonate

Finally, we preceded to the preparation of the 3-(hydroxymethyl)-3-methylindolin-2-one **2**,[2f] a useful intermediate in the synthesis of bioactive compounds. Compounds **1**, **7** and **8** were successfully prepared using only crystallization, but no column chromatography (Scheme 5).



17 7 8 1 2

Scheme 5. Column-less synthesis of compounds **1** and **2**. Reagents and conditions: (a) di-*t*-butyl malonate, NaH, DMF, crystallization from *n*-hexane, 54%; (b) MeI, K_2CO_3, DMF, crystallization from *n*-hexane, 96%; (c) Pd/C, H_2, citric acid, MeOH, crystallization from *n*-hexane, 88%; (d) LAH, THF, crystallization from $CHCl_3$/*n*-hexane, 57%

In summary, we have found that introduction of an alkyl group at the α-position of compound **5** promotes cyclization reaction to afford the oxindole **1** via intramolecular nucleophilic addition of the anilinic nitrogen atom to the carbonyl carbon atom of the *t*-butyl ester. This report is the first to describe a direct attack of the anilinic nitrogen atom on the carbonyl carbon atom of *t*-butyl ester to afford substituted *t*-butyl 3-alkyl-oxindole-3-carboxylates.

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 silicagel 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-*t*-butyl 2-alkyl-2-(2-nitrophenyl)malonate derivatives (Schemes 1, 3 and 4). Di-*t*-butyl 2-(2-nitrophenyl)malonate derivative (1.00 g) was dissolved in DMF (0.7 M). K_2CO_3 (1.3 eq.) and alkyl 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).

Di-*t*-butyl 2-methyl-2-(2-nitrophenyl)malonate (8): Yield: 73%; as a colorless solid; mp 102–103 °C; IR ($CHCl_3$): 1726, 1533, 1164, 1121 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.98 (1H, d, *J* = 7.6 Hz), 7.55 (1H, t, *J* = 7.6 Hz), 7.43 (1H, t, *J* = 7.6 Hz), 7.30 (1H, d, *J* = 7.6 Hz), 1.94 (3H, s), 1.45 (18H, s); ^{13}C NMR ($CDCl_3$) δ: 168.6, 149.0, 135.5, 132.8, 129.3, 128.0, 125.7, 82.8, 61.0, 27.6, 23.7; HRMS (ESI): *m/z* calcd. for $C_{18}H_{25}NO_6Na$: 374.1574 $[M+Na]^+$; found: 374.1576.

Di-*t*-butyl 2-(5-fluoro-2-nitrophenyl)-2-methylmalonate (8a): Yield: 88%; as a colorless solid; mp 69–71 °C; IR (film): 1730, 1535, 1165, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.08 (1H, dd, *J* = 9.2, 5.6 Hz), 7.12 (1H, ddd, *J* = 9.2, 7.2, 2.4 Hz), 7.05 (1H, dd, *J* = 10.0, 2.4 Hz), 1.94 (3H, s), 1.45 (18H, s); ^{13}C NMR ($CDCl_3$) δ: 168.2, 164.4 (d, *J* = 255.2 Hz), 145.1 (d, *J* = 3.9 Hz), 138.9 (d, *J* = 8.7 Hz), 128.4 (d, *J* = 9.7 Hz), 116.6 (d, *J* = 25.1 Hz), 114.8 (d, *J* = 23.2 Hz), 83.1, 60.8, 27.6, 23.5; HRMS (ESI): *m/z* calcd. for $C_{18}H_{24}FNO_6Na$: 392.1480 $[M+Na]^+$; found: 392.1477.

Di-*t*-butyl 2-(5-methoxy-2-nitrophenyl)-2-methylmalonate (8b): Yield: 70%; as a colorless solid; mp 117–118 °C; IR (film): 1742, 1524, 1168, 1121 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.12 (1H, d, *J* = 9.2 Hz), 7.12 (1H, dd, *J* = 9.2, 2.4 Hz), 6.69 (1H, d, *J* = 2.4 Hz), 3.87 (3H, s), 1.80 (3H, s), 1.43 (18H, s); ^{13}C NMR (DMSO-d_6) δ: 167.8, 162.7, 141.4, 137.3, 128.6, 115.2, 112.3, 82.2, 60.6, 56.1, 27.2, 23.5; HRMS (ESI): *m/z* calcd. for $C_{19}H_{27}NO_7Na$: 404.1680 $[M+Na]^+$; found: 404.1676.

Di-*t*-butyl 2-methyl-2-(4-methyl-2-nitrophenyl)malonate (8c): Yield: 73%; as a yellow oil; IR (film): 1715, 1541, 1161, 1052 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.81 (1H, s), 7.54 (1H, d, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 8.0 Hz), 2.37 (3H, s), 1.76 (3H, s), 1.35 (18H, s); ^{13}C NMR (DMSO-d_6) δ: 167.9, 148.2, 138.8, 134.1, 131.6, 129.0, 125.7, 82.2, 60.2, 27.1, 23.8, 19.9; HRMS (ESI): *m/z* calcd. for $C_{19}H_{27}NO_6Na$: 388.1731 $[M+Na]^+$; found: 388.1728.

Di-*t*-butyl 2-methyl-2-(2-nitro-4-(trifluoromethyl)phenyl)malonate (8d): Yield: 90%; as a yellow oil; IR (film): 1733, 1539, 1143, 1053 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.34 (1H, d, *J* = 1.8 Hz), 8.14 (1H, dd, *J* = 7.9, 1.8 Hz), 7.55 (1H, d, *J* = 7.9 Hz), 1.82 (3H, s), 1.36 (18H, s); ^{13}C NMR (DMSO-d_6) δ: 167.3, 148.7, 138.6, 131.0, 130.1 (q, *J* = 3.8 Hz), 129.2 (q, *J* = 33.6 Hz), 122.8 (q, *J* = 272.6 Hz), 122.8 (q, *J* = 3.8 Hz), 82.8, 60.5, 27.1, 23.5; HRMS (ESI): *m/z* calcd. for $C_{19}H_{24}F_3NO_6Na$: 442.1448 $[M+Na]^+$; found: 442.1450.

Di-*t*-butyl 2-ethyl-2-(2-nitrophenyl)malonate (8e): Yield: 83%; as a pale yellow solid; mp 39–40 °C; IR (film): 1733, 1538, 1168, 1117 cm^{-1}; ^1H-NMR (DMSO-d_6) δ: 8.01 (1H, dd, *J* = 7.6, 1.6 Hz), 7.75 (1H, td, *J* = 7.6, 1.6 Hz), 7.59 (1H, td, *J* = 7.6, 1.6 Hz), 7.33 (1H, dd, *J* = 7.6, 1.6 Hz), 2.40 (2H, q, *J* = 7.6 Hz),

1.36 (18H, s), 0.77 (3H, t, J = 7.6 Hz); ^{13}C NMR (DMSO-d_6) δ: 167.6, 149.4, 132.8, 131.7, 131.0, 128.7, 125.4, 82.1, 64.1, 28.1, 27.2, 10.1; HRMS (ESI): *m/z* calcd. for $C_{19}H_{27}NO_6Na$: 388.1731 $[M+Na]^+$; found: 388.1733.

Reduction reaction of di-*t*-butyl 2-(2-nitrophenyl)malonate (7) (Scheme 1). Di-*t*-butyl 2-(2-nitrophenyl)malonate **7** (520 mg, 1.54 mmol) was dissolved in MeOH (5.1 mL, 0.3 M). 10% Pd/C (52.0 mg, w/w = 1/10) was added to the reaction mixture. The resultant mixture was stirred at room temperature under H_2 atmosphere. The reaction was followed by ^{1}H NMR. After 2 h, the mixture was passed through a pad of Celite with MeOH and the solvent was removed *in vacuo*. Purification using silica gel column chromatography (*n*-hexane/EtOAc = 100/0 – 70/30) afforded di-*t*-butyl 2-(2-aminophenyl)malonate **5** (467 mg, 98%).

Reduction reaction of di-*t*-butyl 2-methyl-2-(2-nitrophenyl)malonate (8) (Scheme 1). Di-*t*-butyl 2-methyl-2-(2-nitrophenyl)malonate **8** (1.01 g, 2.88 mmol) was dissolved in MeOH (3.4 mL, 0.3 M). 10% Pd/C (101 mg, w/w = 1/10) was added to the reaction mixture. The resultant mixture was stirred at room temperature under H_2 atmosphere. The reaction was followed by ^{1}H NMR. After 2 h, the mixture was passed through a pad of Celite with MeOH and the solvent was removed *in vacuo*. Purification using silica gel column chromatography (*n*-hexane/EtOAc = 100/0 – 70/30) afforded di-*t*-butyl 2-(2-aminophenyl)-2-methylmalonate **6** (0.75 g, 81%) as a brown oil; IR ($CHCl_3$): 3439, 1736, 1620, 1255, 1163, 1119 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.14 (1H, dd, J = 8.0, 1.2 Hz), 7.09 (1H, td, J = 8.0, 1.2 Hz), 6.76 (1H, td, J = 8.0, 1.2 Hz), 6.70 (1H, dd, J = 8.0, 1.2 Hz), 4.19 (2H, br s), 1.81 (3H, s), 1.47 (18H, s); ^{13}C NMR ($CDCl_3$) δ: 171.1, 145.8, 128.2, 127.1, 125.6, 118.5, 118.4, 81.8, 58.9, 27.7, 22.1; HRMS (ESI): *m/z* calcd. for $C_{18}H_{28}NO_4$: 322.2013 $[M+H]^+$; found: 322.2013.

Cyclization reaction of di-*t*-butyl 2-(2-aminophenyl)malonate (5) and di-*t*-butyl 2-(2-aminophenyl)-2-methylmalonate (6) (Table 2 and 4). Di-*t*-butyl 2-(2-aminophenyl)malonate **5** or di-*t*-butyl 2-(2-aminophenyl)-2-methylmalonate **6** (100 mg) was dissolved in MeOH (0.3 M). Acid additive (1.0 eq.) was added to the reaction mixture. The resultant mixture was stirred at room temperature or 60 °C. The reaction was followed by ^{1}H NMR. After confirming the completion of the cyclization reaction by ^{1}H NMR, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 80/20 – 20/80).

***t*-Butyl 3-methyl-2-oxoindoline-3-carboxylate (1):** a colorless solid; mp 115–116 °C; IR ($CHCl_3$): 3439, 1736, 1618, 1163, 1124 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 10.56 (1H, br s), 7.22 (1H, t, J = 7.6 Hz), 7.17 (1H, d, J = 7.6 Hz), 6.97 (1H, t, J = 7.6 Hz), 6.86 (1H, d, J = 7.6 Hz), 1.43 (3H, s), 1.27 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 177.7, 168.5, 140.8, 131.2, 128.7, 123.0, 122.7, 110.0, 82.3, 56.4, 27.7, 19.8; HRMS (ESI): *m/z* calcd. for $C_{14}H_{17}NO_3Na$: 270.1101 $[M+Na]^+$; found: 270.1101.

Preparation of di-*t*-butyl 2-(2-aminobenzyl)-2-methylmalonate (10) (Scheme 2). Di-*t*-butyl 2-(2-nitrobenzylidene)malonate (13). 2-Nitrobenzaldehyde **12** (3.32 g, 22.0 mmol) was dissolved in Ac_2O (7.9 mL). Di-*t*-butyl malonate (8.24 mL, 44.0 mmol, 2.0 eq.) and K_2CO_3 (4.56 g, 33.0 mmol, 1.5 eq.) were added to the reaction mixture. The resultant mixture was stirred at 80 °C. After 4 h, the mixture was poured into water and the resulting aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography (*n*-hexane/EtOAc = 70/30) and crystallization from *n*-hexane afforded di-*t*-butyl 2-(2-nitrobenzylidene)malonate **13** (3.69 g, 48%) as a colorless solid; mp 93–95 °C; IR ($CHCl_3$): 1720, 1528, 1159 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.21 (1H, d, J = 7.6 Hz), 7.92 (1H, s), 7.81 (1H, t, J = 7.6 Hz), 7.69 (1H, t, J = 7.6 Hz), 7.47 (1H, d, J = 7.6 Hz), 1.48 (9H, s), 1.25 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 164.1, 162.6, 147.1, 138.3, 133.5, 132.2, 130.9, 130.5, 129.7, 124.8, 82.5, 82.3, 28.0, 27.6; HRMS (ESI): *m/z* calcd. for $C_{18}H_{23}NO_6Na$: 372.1418 $[M+Na]^+$; found: 372.1420.

Di-*t*-butyl 2-methyl-2-(2-nitrobenzyl)malonate (15). To a cooled (0 °C) solution of di-*t*-butyl 2-(2-nitrobenzyl)malonate **14** (3.01 g, 8.57 mmol) in THF (29 mL) was slowly added NaH (55% in mineral oil, 488 mg, 11.1 mmol, 1.3 eq.). After 5 min, MeI (800 μL, 12.9 mmol, 1.5 eq.) was added to the reaction mixture at 0 °C. The resultant mixture was stirred at room temperature overnight. The mixture was diluted with water and the resulting aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography (*n*-hexane/EtOAc = 80/20) afforded di-*t*-butyl 2-methyl-2-(2-nitrobenzyl)malonate **15** (1.86 g, 58%) as a pale yellow oil; IR ($CHCl_3$): 1720, 1529, 1163, 1117 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.83 (1H, dd, J = 7.6, 1.2 Hz), 7.48 (1H, td, J = 7.6, 1.2 Hz), 7.43 (1H, dd, J = 7.6, 1.6 Hz), 7.37 (1H, td, J = 7.6, 1.6 Hz), 3.59 (2H, s), 1.43 (18H, s), 1.22 (3H, s); ^{13}C NMR ($CDCl_3$) δ: 170.7, 150.9, 133.0, 132.1, 132.0, 127.7, 124.6, 81.7, 56.0, 35.6, 27.8, 19.9; HRMS (ESI): *m/z* calcd. for $C_{19}H_{27}NO_6Na$: 388.1731 $[M+Na]^+$; found: 388.1732.

Di-*t*-butyl 2-(2-aminobenzyl)-2-methylmalonate (10). Di-*t*-butyl 2-methyl-2-(2-nitrobenzyl)malonate **15** (1.81 g, 4.95 mmol) was dissolved in MeOH (17 mL). 10% Pd/C (w/w = 1/10, 180 mg) was added to the reaction mixture. The resultant mixture was stirred at room temperature under H_2 atmosphere overnight. 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 ($CHCl_3$/MeOH = 90/10) to afford di-*t*-butyl 2-(2-aminobenzyl)-2-methylmalonate **10** (1.43 g, 86%) as a brown solid; mp 68–70 °C; IR ($CHCl_3$): 3392, 1719, 1624, 1223, 1157, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.02 (1H, t, J = 7.6 Hz), 7.00 (1H, d, J = 7.6 Hz), 6.66 (1H, t, J = 7.6 Hz), 6.63 (1H, d, J = 7.6 Hz), 4.01 (2H, br s), 3.09 (2H, s), 1.43 (18H, s), 1.36 (3H, s); ^{13}C NMR ($CDCl_3$) δ: 172.0, 145.7, 132.3, 127.8, 121.4, 118.1, 116.1, 81.5, 55.9, 35.6, 27.8, 20.7; HRMS (ESI): *m/z* calcd. for $C_{19}H_{30}NO_4$: 336.2169 $[M+H]^+$; found: 336.2169.

Cyclization reaction of di-*t*-butyl 2-(2-aminobenzyl)-2-methylmalonate (10) (Table 3). Di-*t*-butyl 2-(2-aminobenzyl)-2-methylmalonate **10** (101 mg, 301 μmol) was dissolved in MeOH (1.0 mL). AcOH (67.0 μL, 301 μmol, 1.0 eq.) was added to the reaction mixture. The resultant mixture was stirred at room temperature. The reaction was followed by ^{1}H NMR. After 24 h, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 100/0 – 40/60). *t*-Butyl 3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate **11** (15.2 mg, 19%) was obtained during purification of the compound **10** through column chromatography (SiO_2) as a brown oil; IR ($CHCl_3$): 3437, 1732, 1618, 1161, 1124 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.50 (1H, br s), 7.18 (1H, t, *J* = 7.6 Hz), 7.15 (1H, d, *J* = 7.6 Hz), 6.99 (1H, t, *J* = 7.6 Hz), 6.73 (1H, d, *J* = 7.6 Hz), 3.27 (1H, d, *J* = 15.6 Hz), 2.89 (1H, d, *J* = 15.6 Hz), 1.51 (3H, s), 1.23 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 171.4, 171.1, 137.0, 128.0, 127.7, 123.0, 122.6, 114.9, 82.0, 50.0, 37.5, 27.5, 19.9; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}NO_3Na$: 284.1257 $[M+Na]^+$; found: 284.1255.

General procedure for tandem reduction-lactamization reaction of di-*t*-butyl 2-methyl-2-(2-nitrophenyl)malonate (8) (Table 5 and Table 6 method A). Di-*t*-butyl 2-methyl-2-(2-nitrophenyl)malonate derivative (100 mg) was dissolved in MeOH (0.3 M). 10% Pd/C (w/w = 1/10) and acid additive (1.0 eq.) were added to the reaction mixture. The resultant mixture was stirred at room temperature under H_2 atmosphere. The reaction was followed by ^{1}H NMR. After confirming the completion of the cyclization 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 = 100/0 – 40/60).

***t*-Butyl 1-hydroxy-3-methyl-2-oxoindoline-3-carboxylate (16):** a brown solid; mp 124–125 °C; IR ($CHCl_3$): 3153, 1734, 1614, 1220, 1155 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 10.96 (1H, br s), 7.33 (1H, t, *J* = 7.6 Hz), 7.24 (1H, d, *J* = 7.6 Hz), 7.05 (1H, t, *J* = 7.6 Hz), 6.97 (1H, d, *J* = 7.6 Hz), 1.47 (3H, s), 1.28 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 171.8, 167.7, 141.1, 129.0, 127.0, 123.7, 122.4, 108.8, 82.8, 55.0, 27.6, 19.3; HRMS (ESI): *m/z* calcd. for $C_{14}H_{17}NO_4Na$: 286.1050 $[M+Na]^+$; found: 286.1049.

***t*-Butyl 5-fluoro-3-methyl-2-oxoindoline-3-carboxylate (1a):** Yield: 95%; as a colorless solid; mp 148–150 °C; IR (film): 3230, 1735, 1628, 1159, 1124 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.63 (1H, br s), 6.98 (1H, dd, *J* = 8.4, 2.8 Hz), 6.96 (1H, td, *J* = 8.4, 2.8 Hz), 6.83 (1H, dd, *J* = 8.4, 4.0 Hz), 1.63 (3H, s), 1.38 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 177.9, 167.9, 159.1 (d, *J* = 240.8 Hz), 136.8 (d, *J* = 1.9 Hz), 132.6 (d, *J* = 8.7 Hz), 115.1 (d, *J* = 24.1 Hz), 111.1 (d, *J* = 24.1 Hz), 110.7 (d, *J* = 8.7 Hz), 82.8, 57.0, 27.7, 19.9; HRMS (ESI): *m/z* calcd. for $C_{14}H_{16}FNO_3Na$: 288.1006 $[M+Na]^+$; found: 288.1005.

***t*-Butyl 5-methoxy-3-methyl-2-oxoindoline-3-carboxylate (1b):** Yield: 91%; as a colorless solid; mp 109–111 °C; IR ($CHCl_3$): 3439, 1736, 1605, 1161, 1123 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 10.39 (1H, br s), 6.82–6.77 (3H, m), 3.70 (3H, s), 1.44 (3H, s), 1.30 (9H, s); ^{13}C NMR (DMSO-d_6) δ: 176.0, 168.4, 154.9,

135.3, 132.4, 113.3, 110.1, 109.6, 81.3, 56.1, 55.5, 27.3, 19.6; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}NO_4Na$: 300.1206 $[M+Na]^+$; found: 300.1206.

***t*-Butyl 3-ethyl-2-oxoindoline-3-carboxylate (1e):** Yield: 91%; as a pale yellow solid; mp 113–117 °C; IR ($CHCl_3$): 3437, 1736, 1620, 1157 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 10.57 (1H, s), 7.22 (1H, t, J = 7.6 Hz), 7.15 (1H, d, J = 7.6 Hz), 6.98 (1H, t, J = 7.6 Hz), 6.86 (1H, d, J = 7.6 Hz), 2.03 (2H, q, J = 7.6 Hz), 1.28 (9H, s), 0.56 (3H, t, J = 7.6 Hz); ^{13}C NMR (DMSO-d_6) δ: 175.2, 168.2, 142.8, 128.7, 122.9, 121.8, 109.5, 81.3, 60.7, 27.4, 26.3, 7.9; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}NO_3Na$: 284.1257 $[M+Na]^+$; found: 284.1257.

***t*-Butyl 3,6-dimethyl-2-oxoindoline-3-carboxylate (1c) (Table 6 method B).** Di-*t*-butyl 2-methyl-2-(4-methyl-2-nitrophenyl)malonate **8c** (100 mg, 275 μmol) was dissolved in MeOH (0.92 mL, 0.3 M). 10% Pd/C (10.0 mg, w/w = 1/10) was added to the reaction mixture. 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 reduction reaction by ^1H NMR (30 h), citric acid (52.8 mg, 275 μmol, 1.0 eq.) was 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 cyclization reaction by ^1H NMR (2 h), 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 = 100/0 – 40/60) to afford *t*-butyl 3,6-dimethyl-2-oxoindoline-3-carboxylate **1c** (57.9 mg, 81%) as a colorless sold; mp 159–161 °C; IR ($CHCl_3$): 3439, 1734, 1630, 1163, 1124 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 10.50 (1H, s), 7.03 (1H, d, J = 7.3 Hz), 6.77 (1H, d, J = 7.3 Hz), 6.68 (1H, s), 2.27 (3H, s), 1.40 (3H, s), 1.27 (9H, s); ^{13}C NMR (DMSO-d_6) δ: 176.5, 168.7, 142.2, 138.3, 128.3, 122.3, 110.4, 81.2, 55.4, 27.3, 21.3, 19.6; HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}NO_3Na$: 284.1257 $[M+Na]^+$; found: 284.1258.

***t*-Butyl 3-methyl-2-oxo-6-(trifluoromethyl)indoline-3-carboxylate (1d) (Table 6 method C).** Di-*t*-butyl 2-methyl-2-(2-nitro-4-(trifluoromethyl)phenyl)malonate **8d** (104 mg, 248 μmol) was dissolved in MeOH (0.82 mL, 0.3 M). 10% Pd/C (10.4 mg, w/w = 1/10) was added to the reaction mixture. 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 (40 h), 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 = 100/0 – 40/60) to afford *t*-butyl 3-methyl-2-oxo-6-(trifluoromethyl)indoline-3-carboxylate **1d** (73.0 mg, 93%) as a yellow oil; IR ($CHCl_3$): 3146, 1738, 1630, 1171, 1134 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.50 (1H, d, J = 7.9 Hz), 7.42 (1H, d, J = 7.9 Hz), 7.17 (1H, s), 1.50 (3H, s), 1.29 (9H, s); ^{13}C NMR (DMSO-d_6) δ: 169.2, 167.1, 143.2, 131.0, 129.7 (q, J = 31.8 Hz), 123.9 (q, J = 272.6 Hz), 123.5, 119.7, 103.5, 82.3, 54.1, 27.2, 19.0; HRMS (ESI): *m/z* calcd. for $C_{15}H_{16}F_3NO_3Na$: 338.0974 $[M+Na]^+$; found: 338.0972.

General procedure for di-*t*-butyl 2-(2-nitrophenyl)malonate derivatives (Scheme 3). To a cooled (0 °C) solution of NaH (60% in mineral oil, 2.2 eq.) in DMF (1.0 M) was slowly added di-*t*-butyl malonate (1.1 eq.). After 15 min, 2-fluoronitrobenzene derivative (5.00 g) was added to the reaction mixture dropwise at 0 °C. The resultant mixture was stirred at room temperature overnight and quenched with 0.1 N HCl aq. The resultant aqueous phase was extracted with EtOAc/*n*-hexane = 1/1. The combined organic phases were washed with brine. The resultant organic phase was 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 – 30/70).

Di-*t*-butyl 2-(5-fluoro-2-nitrophenyl)malonate (7a): Yield: 50%; as a colorless solid; mp 87–89 °C; IR (film): 1722, 1531, 1162 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.24 (1H, dd, J = 9.2, 5.2 Hz), 7.52 (1H, ddd, J = 9.2, 8.0, 2.8 Hz), 7.33 (1H, dd, J = 10.0, 2.8 Hz), 5.20 (1H, s), 1.43 (18H, s); ^{13}C NMR ($CDCl_3$) δ: 166.0, 164.7 (d, J = 257.2 Hz), 145.1 (d, J = 3.9 Hz), 132.5 (d, J = 9.7 Hz), 127.9 (d, J = 10.7 Hz), 118.1 (d, J = 25.1 Hz), 115.8 (d, J = 23.1 Hz), 83.3, 56.4 27.9; HRMS (ESI): *m/z* calcd. for $C_{17}H_{22}FNO_6Na$: 378.1323 $[M+Na]^+$; found: 378.1320.

Di-*t*-butyl 2-(4-methyl-2-nitrophenyl)malonate (7c): Yield: 78%; as a colorless solid; mp 49–52 °C; IR (film): 1728, 1538, 1135 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.90 (1H, s), 7.59 (1H, d, J = 7.9 Hz), 7.36 (1H, d, J = 7.9 Hz), 5.01 (1H, s), 2.40 (3H, s), 1.41 (18H, s); ^{13}C NMR (DMSO-d_6) δ: 166.0, 148.3, 140.0, 134.4, 130.9, 125.5, 125.1, 82.1, 56.0, 27.4, 20.2; HRMS (ESI): *m/z* calcd. for $C_{18}H_{25}NO_6Na$: 374.1574 $[M+Na]^+$; found: 374.1578.

Di-*t*-butyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate (7d): Yield: quant.; as a yellow oil; IR (film): 1733, 1538, 1136 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 8.41 (1H, s), 8.20 (1H, d, J = 7.9 Hz), 7.77 (1H, d, J = 7.9 Hz), 5.25 (1H, s), 1.42 (18H, s); ^{13}C NMR (DMSO-d_6) δ: 165.3, 148.8, 133.2, 132.9, 130.2 (q, J = 3.8 Hz), 129.7 (q, J = 33.7 Hz), 122.8 (q, J = 272.6 Hz), 122.2 (q, J = 3.8 Hz), 82.6, 56.1, 27.4; HRMS (ESI): *m/z* calcd. for $C_{18}H_{22}F_3NO_6Na$: 428.1291 $[M+Na]^+$; found: 428.1294.

SUPPLEMENTARY DATA

Deposition number CCDC-1584394 and CCDC-1584395 for compound No. 7 and 8 respectively. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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