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Chemodivergent Synthesis of Aza-Heterocycles with a Quarternary Carbon Center via [4 + 1] Annulation between Azoalkenes and α-Bromo Carbonyl Compounds

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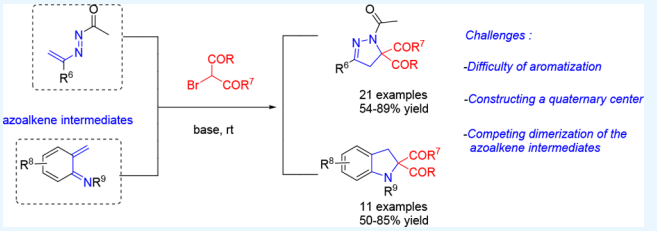
ABSTRACT: An efficient [4 + 1] annulation reaction between in situ generated azoalkene intermediates and α-bromocarbonyls has been established. A series of skeletally diverse aza-heterocycles with a functionalized quaternary center were obtained in up to 89% yield under mild conditions.



INTRODUCTION

Dihydropyrazole and indoline skeletons are privileged units and widely exist in a number of natural products with a broad spectrum of biological activities.[1] They have been employed as a receptor-interacting protein 1 kinase inhibitor, antibacterial agent, monoamine oxidase inhibitor, COX-2 inhibitor and acyl-CoA: cholesterol acyl-transferase (ACAT) inhibitor (Figure 1).[2] Thus, an array of methods for the construction of such compounds have been developed.[3] However, these protocols are often plagued by the need for metal catalysis and a high reactive partner to obtain an indoline-2-carboxylic acid skeleton and 4,5-dihydropyrazole-containing ester functional group. For instance, indoline-2-carboxylic acid skeletons were obtained through reduction of an indole derivative and cycloaddition reaction catalyzed by the metals Rh and Fe.[3h,i] Meanwhile, the Nicolini group and Liu group reported a copper-catalyzed process with the combination of 1,2-diaza-1,3-diene and diazo ester providing ester-substituted dihydropyrazole.[3l,m] Therefore, exploring a mild and metal-free method to achieve indoline-2-carboxylic acid and dihydropyrazole carboxylic acid skeletons is still desirable.

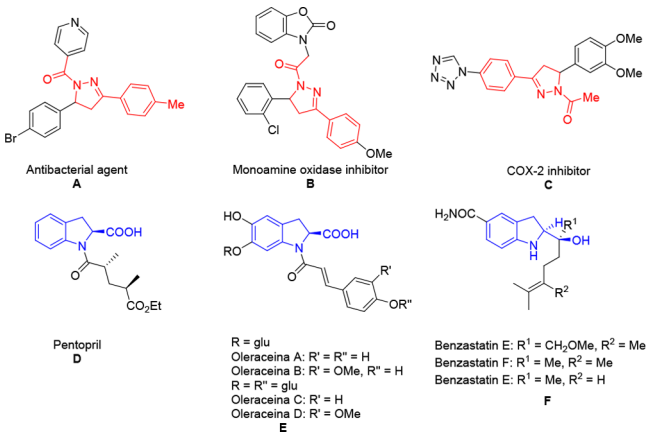


Figure 1. Biologically active molecules with a dihydropyrazole (A−C) and indoline skeleton (D−F).

The α-halo carbonyl compound has been proven as an attractive C1 partner for the construction of cyclopropane, oxirane, or other cyclic compounds.[4] An N-containing five-membered compound could be obtained with an α-halo carbonyl compound as the C2 partner via the annulation reaction.[5] Recently, the α-halo carbonyl was successfully used as the C3 partner to construct heterocyclic compounds with amine, an indole derivative, and alkene.[6] However, α-halo carbonyl compounds are rarely employed in the [4 + 1] annulation of azoalkene due to the presence of other side reactions. Indeed, in 2019, Chen and co-workers developed a unique [4 + 1 + 1] annulation between α-bromo carbonyls and benzofuran-derived azadiene which offered the fused benzo-aza-heterocycle (Scheme 1a).[7] Moreover, Zhao's group used indanone-derived or benzofuran-derived azadiene as the starting material to react with bromomalonate, providing the cyclopropane product (Scheme 1b).[8] A similar strategy was also used by Yang and co-workers to access spiro-cyclopropane indole derivatives (Scheme 1c).[9] In all of the results mentioned

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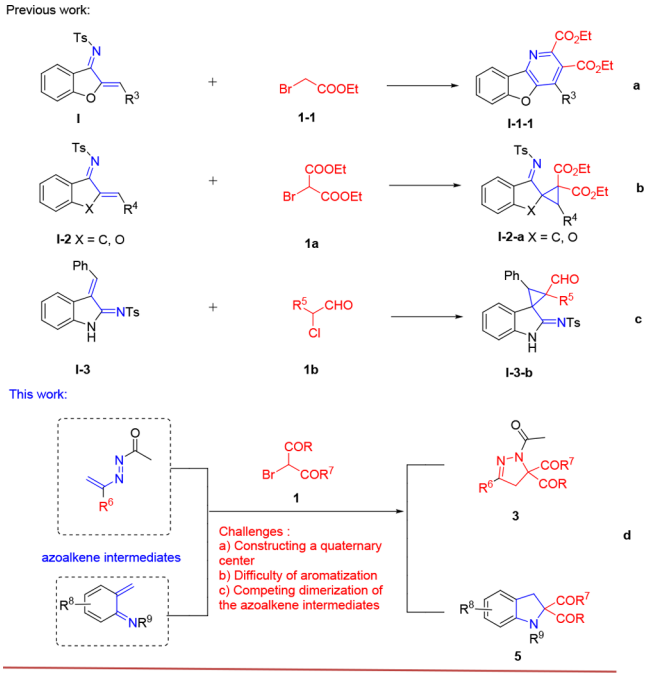
Scheme 1. Annulation Pathways between Azoalkenes and α-Halo Carbonyl Compounds

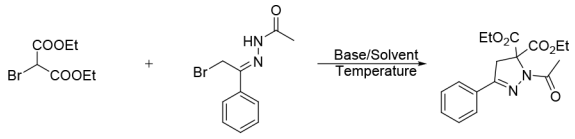


above, the [4 + 1] annulation product could not be detected, which demonstrated the challenge of [4 + 1] annulation between azoalkene and α-halo carbonyl compounds. Due to our previous successes in the exploration of the transformation of azoalkene intermediates,[10] we hypothesized that the [4 + 1] annulation would occur between the azoalkene intermediate and α-halo carbonyl compound, providing a metal- and organocatalysis-free protocol to obtain the functionalized dihydropyrazole and indoline derivative (Scheme 1d). Achievement of such a reaction is particularly challenging because: (1) the potential competing dimerization of the azoalkene intermediate leads to an eight-membered N-containing heterocycle;[10b,11] (2) the construction of the quaternary carbon center in the product is difficult;[12] and (3) the lower leaving ability of Br may suppress the occurrence of the [4 + 1] cycloaddition reaction.

RESULTS AND DISCUSSION

We initially treated α-halo hydrazone (**2a**) with KOH in the presence of diethyl 2-bromomalonate (**1a**) in CH_2Cl_2 at room temperature. To our delight, the [4 + 1] cycloaddition product dihydropyrazole **3a** was isolated in 58% yield, which was identified through NMR data and confirmed by the X-ray crystallographic analysis of **3e**.[13] Then, several other bases were screened with the aim to improve the yield of cycloaddition product **3a**. These results indicated that (1) all other screened bases were better than KOH except triethylamine (TEA) and triethylenediamine (TEDA) (Table 1, entries 1−8); (2) among the different bases, K_2CO_3 was proven to be the best one for this transformation (Table 1, entry 3); and (3) the type of base had an unignorable influence comparing the promotion effect of inorganic base and organic base on this reaction (Table 1, entries 7−8). Using K_2CO_3 as the base, various solvents have been evaluated. We found that this reaction in THF afforded **3a** in 89% yield (Table 1, entry 9), while other solvents including $CHCl_3$, MeCN, DMF, Et_2O,

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	base	solvent	yield (%)[b]
1	KOH	CH_2Cl_2	58
2	Cs_2CO_3	CH_2Cl_2	62
3	K_2CO_3	CH_2Cl_2	81
4	Na_2CO_3	CH_2Cl_2	72
5	$NaHCO_3$	CH_2Cl_2	75
6	KO^tBu	CH_2Cl_2	68
7	TEDA	CH_2Cl_2	trace
8	TEA	CH_2Cl_2	trace
9	**K_2CO_3**	**THF**	**89**
10	K_2CO_3	$CHCl_3$	76
11	K_2CO_3	MeCN	77
12	K_2CO_3	DMF	63
13	K_2CO_3	Et_2O	86
14	K_2CO_3	EtOAc	43
15[c]	K_2CO_3	THF	56
16[d]	K_2CO_3	THF	86

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), and base (0.2 mmol) were reacted at room temperature. [b]Isolated yield based on **2a** [c]Reaction was performed at 0 °C. [d]Reaction was performed at 70 °C.

and EtOAc were not as good as THF (Table 1, entries 10−14). Subsequent research showed that the temperature had little influence on the efficiency of this transformation (Table 1, entries 15−16). For example, elevated temperature to 70 °C led to the formation of **3a** in 86% yield, while decreasing the temperature to 0 °C generated the product in 56% yield. Based on the above screening results, we thus obtained these optimal reaction conditions for this transformation: using K_2CO_3 as the base and THF as the solvent while stirring the reaction mixture at room temperature.

With the optimized conditions in hand, the reaction compatibility was then explored, and these results were summarized in Table 2. The variation of α-halo hydrazone was tested first. When the azoalkene precursor bearing an electron-withdrawing group at the 4-position of the benzene ring was examined, each of the transformations underwent smooth, leading to the formation of the expected product in good yield (**3b**−**3e**). However, the fluorine group at the 4-position furnished the product **3f** in lower yield. The possible reason is that the strong electron-withdrawing force affects the reactivity of the azoalkene intermediate. As anticipated, α-halo hydrazone having a 3-chlorophenyl group and a 3-bromophenyl group could also provide a similar cyclization process toward dihydropyrazole **3g** and **3h** in 81% and 85% yields, respectively. Delightedly, the 3,4-disubstituted azoalkene precursor was compatible in this annulation. Moreover, substrates containing an electron-donating (e.g., methyl) group at the *para*-position proved to be effective as well, which provided the corresponding dihydropyrazole **3j** with comparable efficiency. In addition, the ether functional group was well-tolerated with this annulation system (**3k**). However, the *tert*-butyl-substituted azoalkene precursor seemed to be less reactive and achieved **3l** in relatively lower yield. To our delight, a sterically encumbered naphthalen-2-yl counterpart

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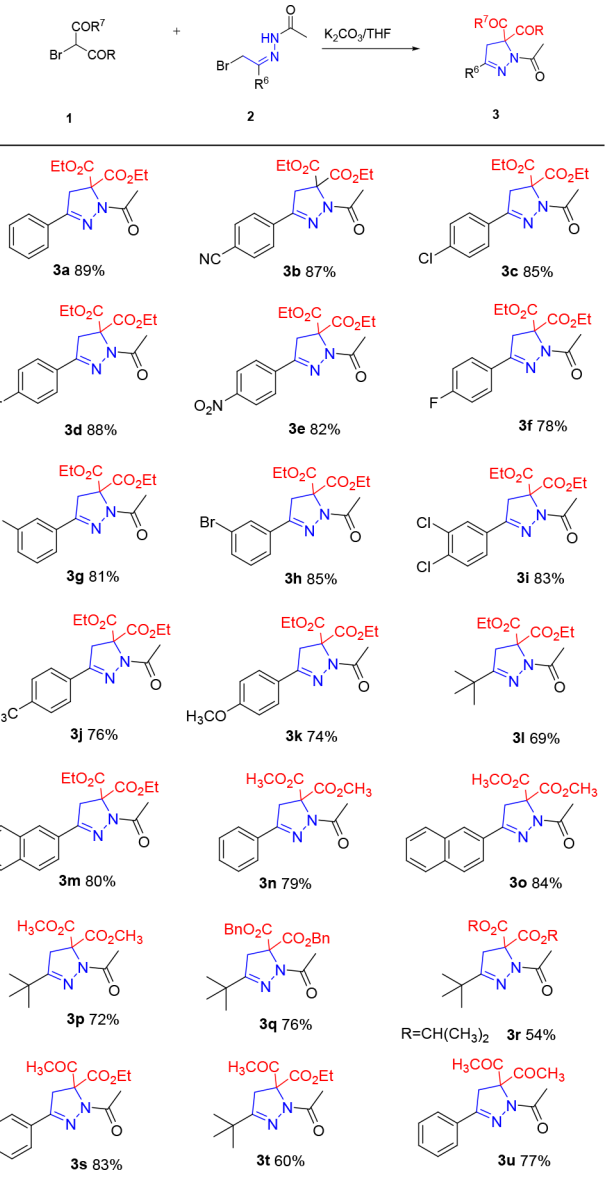
Table 2. Scope with Various α-Halogeno Hydrazone and α-Bromocarbonyl[a]

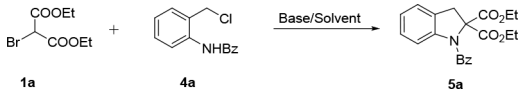


[a]Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), and K_2CO_3 (0.2 mmol) were reacted at room temperature. [b]Isolated yield based on **2**.

was found to be a suitable partner, giving the product **3m** in 80% yield. Next, we investigated the transformation of *N*-acetyl hydrazone with dimethyl malonate. These results indicated that aromatic-substituted, fused-ring-substituted, and alkyl-substituted hydrazones could be smoothly converted into their dihydropyrazole derivatives in 72−84% yields (**3n**, **3o**, and **3p**). Besides, other malonates such as dibenzyl 2-bromomalonate and diisopropyl 2-bromomalonate were all successfully tolerated and offered the expected products **3q** and **3r**. However, the yield was decreased to 54% when diisopropyl 2-bromomalonate was used as the starting material. We reasoned that the steric hindrance has a significant impact on this transformation. Notably, the C1 synthon is not restricted only to the malonate compound, but instead, the bromide of ethyl acetoacetate was also a suitable substrate for this transformation, and the corresponding annulation products (**3s**, **3t**) were isolated in 83% and 60% yields, respectively. When 3-bromopentane-2,4-dione was used as the starting material, **3u** was obtained in moderate yield.

To further demonstrate the effectiveness of this method, we turned our attention to checking other azoalkene precursors such as **4a** which was used as the four-unit intermediate. Thus, **4a** was reacted with diethyl 2-bromomalonate **1a** under the standard conditions. Delightedly, the desired annulation product **5a** was observed in 26% yield. Next, we optimized the reaction conditions. A higher yield (65%) was obtained after the base screening (Table 3, entries 1−4). Subsequent

Table 3. Optimization of Reaction Conditions for Indoline 5a[a]



entry	base	solvent	yield (%)[b]
1	K_2CO_3	THF	26
2	Cs_2CO_3	THF	65
3	KO^{t}Bu	THF	31
4	Na_2CO_3	THF	52
5	**Cs_2CO_3**	**CH_2Cl_2**	**77**
6	Cs_2CO_3	CH_3CN	74
7	Cs_2CO_3	Et_2O	48

[a]Reaction conditions: **1a** (0.15 mmol), **4a** (0.1 mmol), and base (0.2 mmol) were reacted at room temperature. [b]Isolated yield based on **4a**.

solvent screening indicated it was more efficient when CH_2Cl_2 was used as the solvent, which delivered product **5a** in 77% yield (entries 5−7). Finally, it was decided to carry out the cyclization process by using Cs_2CO_3 as the base and CH_2Cl_2 as the solvent.

Next, the substrate scope of azoalkene precursor **4** was carefully studied under the optimized conditions. Some salient results were summarized in Table 4. Initially, we focused on the scope of the benzene ring. These results showed that the azoalkene precursor with electron-withdrawing property seemed to be more reactive. *N*-(2-(Chloromethyl) phenyl) benzamide **4** having F and CF_3 substitutes at the 3-position were converted to the corresponding azoalkene intermediates which then underwent [4 + 1] annulation, affording the desired products in better yield (Table 4, **5b** and **5c**). Moreover, the electron-withdrawing groups at the 2-position and 4-position of the benzene ring were tolerated well and provided indoline derivatives **5d** and **5e** in moderate to good yield. The use of an electron-donating substituted azoalkene precursor offered the expected product **5f** in good yield (63%) as well. Furthermore, a functionalized azoalkene intermediate with ether could also be used as the reaction partner to access the corresponding product **5g** in 71% yield. The *tert*-butoxycarbonyl-protected azoalkene precursor was also used in this reaction, and the product **5a** was obtained in 50% yield. In addition, the protecting group was not only limited to benzoyl (Bz) and *tert*-butoxycarbonyl (Boc). The annulation of *N*-benzyloxyformyl (Cbz) azoalkene precursors with C1 synthon **1a** under the optimized conditions also furnished the corresponding products **5i**−**5k** in 68−85% yields.

The synthetic utility of the annulation protocol was then demonstrated by performing these reactions on a gram scale, and these corresponding products **3a** and **5a** were isolated in 86% and 74% yield on a 4 mmol scale, respectively (Scheme

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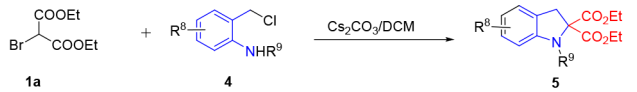
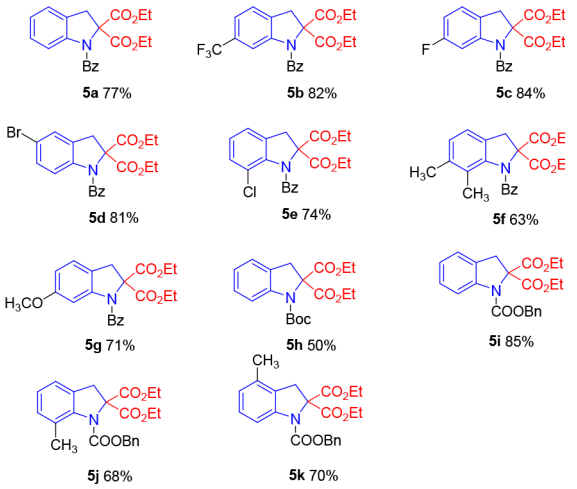
Table 4. Scope with the Azoalkene Precursor 4[a,b]

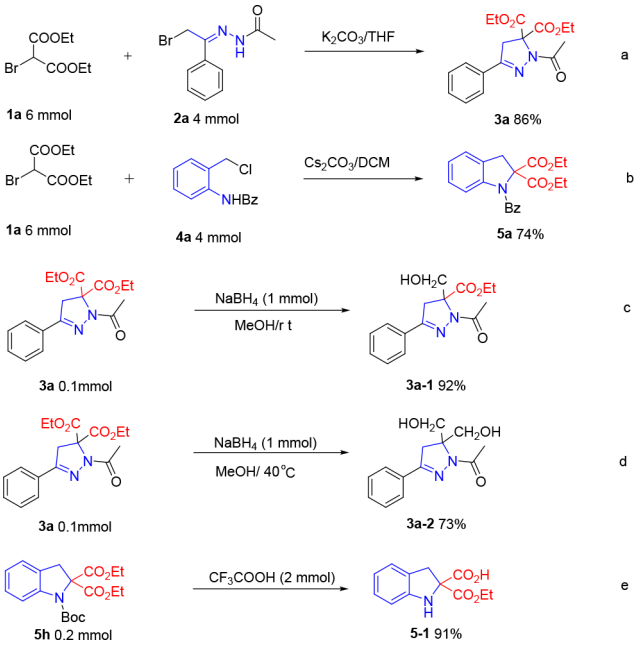




[a]Reaction conditions: **1** (0.15 mmol), **4** (0.1 mmol), and Cs_2CO_3 (0.2 mmol) were reacted at room temperature. [b]Isolated yield based on **4**.

2a,b). Next, these late-stage transformations of product **3a** were conducted. As shown in Scheme 2c,d, the selective

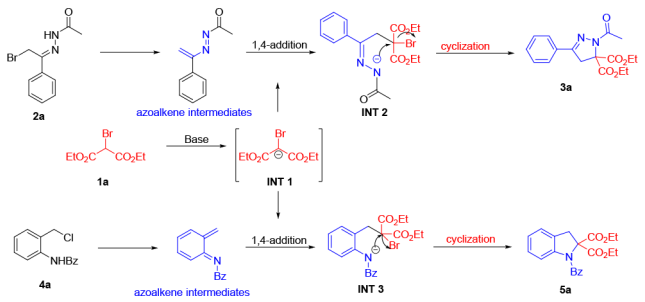
Scheme 2. Gram-Scale Reactions and the Transformation of 3a and 5h



reduction of dihydropyrazole **3a** was realized with $NaBH_4$ in CH_3OH by controlling the temperature. **3a-1** was afforded in 92% yield at room temperature. While the reaction was run at 40 °C, the double reduction product with two hydroxyl groups **3a-2** was delivered in 73% yield (Scheme 2d). Besides, the protected indoline compound could offer the 2-carboxylate indoline derivative **5-1** under the catalysis of trifluoroacetic acid.

According to our previous studies and the literature,[10] we proposed the following annulation mechanism (Scheme 3).

Scheme 3. Proposed [4 + 1] Annulation Mechanism



These azoalkene intermediates were generated in situ via precursors **2a** and **4a** under the base conditions. Meanwhile, deprotonation of **1** formed the nucleophilic intermediate **INT 1**. Then, the 1,4-conjugate addition occurred between the **INT 1** and azoalkene intermediates, offering **INT 2** and **INT 3**. Subsequently, intramolecular cyclization through the simultaneous C−N and C−C bond formations offered [4 + 1] annulation products **3a** and **5a**.

CONCLUSIONS

In summary, we have successfully developed a metal-free annulation protocol between α-bromocarbonyl compound **1** and α-halo hydrazone **2** or azoalkene precursor **4** to construct the skeletally diverse aza-heterocycle with a quaternary carbon center under mild conditions. Moreover, this approach has a general substrate scope for both the α-bromocarbonyl reagent and α-halo hydrazone or azoalkene precursor **4** with an electron-donating and electron-withdrawing group on the aromatic ring. Furthermore, this transformation developed a method for selective construction of a hydroxyl functional group in the dihydropyrazole compound.

EXPERIMENTAL SECTION

General Information. The ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with chloroform-*d* and dimethyl sulfoxide-d_6 as the solvent. High-resolution mass spectra (HRMS) were recorded on an FT-ICR MS spectrometer. Melting points are uncorrected. Column chromatography was performed on silica gel (200−300 mesh). α-Bromocarbonyl compound **1** and azoalkene precursors **2** and **4** were synthesized according to literature methods.[14]

General Procedure for the Preparation of Dihydropyrazole 3. To a stirred solution of these α-bromocarbonyl compounds **1** (0.15 mmol) and K_2CO_3 (0.2 mmol) in THF (2 mL) at room temperature was added azoalkene precursor **2** (0.1 mmol). After the reaction was completed, as indicated by TLC, the mixture was concentrated in vacuo, and the crude product was purified by flash chromatography, eluting with ethyl acetate/petroleum ether = 1:20 to afford the product **3**.

*Diethyl 2-Acetyl-5-phenyl-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3a**).* Ethyl acetate/petroleum ether = 1:20 was used as an eluent. White solid (30 mg, 89%). MP: 56.3−58.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74−7.66 (m, 2H), 7.45−7.37 (m, 3H), 4.32−4.25 (m, 4H), 3.83 (s, 2H), 2.43 (s,

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3H), 1.30 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.06, 167.66, 151.94, 130.74, 130.47, 128.90, 126.70, 72.07, 62.95, 44.29, 21.92, 14.02. HRMS (ESI): m/z calcd for $C_{17}H_{21}N_2O_5$ $[M + H]^+$: 333.1445, found 333.1449.

*Diethyl 2-Acetyl-5-(4-cyanophenyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3b**).* Ethyl acetate/petroleum ether = 1:15 was used as an eluent. White solid (31 mg, 87%). MP: 54.7−55.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 4.29 (qd, J = 7.2, 2.8 Hz, 4H), 3.81 (s, 2H), 2.43 (s, 3H), 1.30 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.14, 167.34, 149.91, 134.69, 132.63, 127.12, 118.33, 113.84, 72.41, 63.16, 43.86, 21.92, 14.00. HRMS (ESI): m/z calcd for $C_{18}H_{19}N_3NaO_5$ $[M + Na]^+$: 380.1217, found 380.1218.

*Diethyl 2-Acetyl-5-(4-chlorophenyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3c**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (31 mg, 85%). MP: 53.9−55.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 4.30 (dq, J = 7.1, 4.2 Hz, 4H), 3.80 (s, 2H), 2.42 (s, 3H), 1.31 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.94, 167.48, 150.72, 136.65, 129.10, 128.90, 127.84, 72.10, 62.94, 44.05, 21.82, 13.92. HRMS (ESI): m/z calcd for $C_{17}H_{19}ClN_2NaO_5$ $[M + Na]^+$: 389.0875, found 389.0871.

*Diethyl 2-Acetyl-5-(4-bromophenyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3d**).* Ethyl acetate/petroleum ether = 1:20 was used as an eluent. White solid (36 mg, 88%). MP: 61.2−63.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 4H), 4.30 (qd, J = 7.1, 2.7 Hz, 4H), 3.79 (s, 2H), 2.42 (s, 3H), 1.31 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.06, 167.59, 150.91, 132.18, 129.48, 128.16, 125.14, 72.24, 63.07, 44.13, 21.95, 14.05. HRMS (ESI): m/z calcd for $C_{17}H_{19}BrN_2NaO_5$ $[M + Na]^+$: 433.0370, found 433.0378.

*Diethyl 2-Acetyl-5-(4-nitrophenyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3e**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (31 mg, 82%). MP: 62.7−64.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8.9 Hz, 2H), 7.85 (d, J = 8.9 Hz, 2H), 4.31 (qd, J = 7.2, 2.7 Hz, 4H), 3.85 (s, 2H), 2.45 (s, 3H), 1.32 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.20, 167.33, 149.58, 148.78, 136.48, 127.43, 124.19, 72.54, 63.23, 43.97, 21.96, 14.03. HRMS (ESI): m/z calcd for $C_{17}H_{19}N_3NaO_7$ $[M + Na]^+$: 400.1115, found 400.1114.

*Diethyl 2-Acetyl-5-(4-fluorophenyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3f**).* Ethyl acetate/petroleum ether = 1:15 was used as an eluent. White solid (27 mg, 78%). MP: 48.9−51.7 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75−7.64 (m, 2H), 7.15−7.08 (m, 2H), 4.34−4.26 (m, 4H), 3.80 (s, 2H), 2.42 (s, 3H), 1.31 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.04, 167.67, 150.95, 128.78 (d, J = 8.0 Hz), 126.84, 116.16 (d, J = 21.0 Hz), 72.21, 63.05, 44.34, 21.95, 14.06. HRMS (ESI): m/z calcd for $C_{17}H_{19}FN_2NaO_5$ $[M + Na]^+$: 373.1170, found 373.1172.

*Diethyl 2-Acetyl-5-(3-chlorophenyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3g**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (30 mg, 81%). MP: 71.3−72.9 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (t, J = 1.8 Hz, 1H), 7.54 (dt, J = 7.5, 1.5 Hz, 1H), 7.42−7.32 (m, 2H), 4.29 (qd, J = 7.2, 3.0 Hz, 4H), 3.79 (s, 2H), 2.43 (s, 3H), 1.31 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.11, 167.50, 150.57, 135.02, 132.26, 130.64, 130.19, 126.66, 124.82, 72.18, 63.06, 44.11, 21.95, 14.03. HRMS (ESI): m/z calcd for $C_{17}H_{19}ClN_2NaO_5$ $[M + Na]^+$: 389.0875, found 389.0871.

*Diethyl 2-Acetyl-5-(3-bromophenyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3h**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (35 mg, 85%). MP: 51.9−54.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (t, J = 1.8 Hz, 1H), 7.62−7.54 (m, 2H), 7.29 (t, J = 7.9 Hz, 1H), 4.30 (qd, J = 7.1, 2.7 Hz, 4H), 3.79 (s, 2H), 2.43 (s, 3H), 1.31 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.14, 167.52, 150.46, 133.57, 132.56, 130.44, 129.61, 125.28, 123.10, 72.22, 63.08, 44.12, 21.97, 14.05. HRMS (ESI): m/z calcd for $C_{17}H_{19}BrN_2NaO_5$ $[M + Na]^+$: 433.0370, found 433.0378.

*Diethyl 2-Acetyl-5-(3,4-dichlorophenyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3i**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent, White solid (33 mg, 83%). MP: 56.5−57.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 1.8 Hz, 1H), 7.54−7.47 (m, 2H), 4.30 (qd, J = 7.2, 2.9 Hz, 4H), 3.78 (s, 2H), 2.43 (s, 3H), 1.31 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.09, 167.44, 149.70, 134.82, 133.41, 130.96, 130.53, 128.42, 125.75, 72.33, 63.13, 44.01, 21.95, 14.04. HRMS (ESI): m/z calcd for $C_{17}H_{18}Cl_2N_2NaO_5$ $[M + Na]^+$: 423.0485, found 423.0481.

*Diethyl 2-Acetyl-5-(p-tolyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3j**).* Ethyl acetate/petroleum ether = 1:15 was used as an eluent. White solid (26 mg, 76%). MP: 61.3−64.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 4.29 (qd, J = 7.2, 3.0 Hz, 4H), 3.81 (s, 2H), 2.43 (s, 3H), 2.39 (s, 3H), 1.30 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.02, 167.76, 152.06, 141.16, 129.61, 127.71, 126.68, 72.02, 62.94, 44.37, 21.95, 21.66, 14.05. HRMS (ESI): m/z calcd for $C_{18}H_{22}N_2NaO_5$ $[M + Na]^+$: 369.1421, found 369.1423.

*Diethyl 2-Acetyl-5-(4-methoxyphenyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3k**).* Ethyl acetate/petroleum ether = 1:15 was used as an eluent, White solid (27 mg, 74%). MP: 57.4−58.8 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.67−7.61 (m, 2H), 6.96−6.91 (m, 2H), 4.29 (qd, J = 7.2, 2.9 Hz, 4H), 3.85 (s, 3H), 3.80 (s, 2H), 2.42 (s, 3H), 1.30 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.93, 167.83, 161.67, 151.77, 128.38, 123.13, 114.34, 72.04, 62.94, 55.56, 44.41, 21.95, 14.06. HRMS (ESI): m/z calcd for $C_{18}H_{22}N_2NaO_6$ $[M + Na]^+$: 385.1370, found 385.1366.

*Diethyl 2-Acetyl-5-(tert-butyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3l**).* Ethyl acetate/petroleum ether = 1:20 was used as an eluent. White solid (22 mg, 69%). MP: 59.6−61.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.28 (ddt, J = 10.1, 7.1, 3.2 Hz, 4H), 3.41 (s, 2H), 2.31 (s, 3H), 1.29 (t, J = 7.1 Hz, 6H), 1.18 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.08, 167.94, 163.49, 72.13, 62.78, 43.65, 34.08, 27.99, 21.80, 14.07. HRMS (ESI): m/z calcd for $C_{15}H_{24}N_2NaO_5$ $[M + Na]^+$: 335.1577, found 335.1576.

*Diethyl 2-Acetyl-5-(naphthalen-2-yl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3m**).* Ethyl acetate/petroleum ether = 1:20 was used as an eluent. White solid (31 mg, 80%). MP: 55.8−58.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (dd, J = 8.7, 1.7 Hz, 1H), 7.92 (s, 1H), 7.88−7.82 (m, 3H), 7.58−7.50 (m, 2H), 4.35−4.24 (m, 4H), 3.96 (s, 2H), 2.49 (s, 3H), 1.32 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.10, 167.72, 152.00, 134.36, 133.02, 128.77, 128.56, 128.10, 128.02, 127.58, 127.36, 127.00, 123.26, 72.20, 63.01, 44.29, 22.01, 14.07. HRMS (ESI): m/z calcd for $C_{21}H_{22}N_2NaO_5$ $[M + Na]^+$: 405.1421, found 405.1422.

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*Dimethyl 2-Acetyl-5-phenyl-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3n**).* Ethyl acetate/petroleum ether = 1:20 was used as an eluent. White solid (24 mg, 79%). MP: 50.8−51.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73−7.64 (m, 2H), 7.45−7.37 (m, 3H), 3.84 (s, 2H), 3.83 (s, 6H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.14, 168.19, 152.14, 130.82, 130.23, 128.89, 126.69, 71.75, 53.80, 44.43, 21.91. HRMS (ESI): m/z calcd for $C_{15}H_{16}N_2NaO_5$ $[M + Na]^+$: 327.0951, found 327.0952.

*Dimethyl 2-Acetyl-5-(naphthalen-2-yl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3o**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (29 mg, 84%). MP: 51.2−53.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (dd, J = 8.7, 1.7 Hz, 1H), 7.92 (s, 1H), 7.89−7.83 (m, 3H), 7.58−7.50 (m, 2H), 3.99 (s, 2H), 3.86 (s, 6H), 2.49 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.27, 168.26, 152.26, 134.36, 132.96, 128.79, 128.56, 128.00, 127.86, 127.63, 127.45, 127.01, 123.18, 71.89, 53.89, 44.44, 22.01. HRMS (ESI): m/z calcd for $C_{19}H_{18}N_2NaO_5$ $[M + Na]^+$: 377.1108, found 377.1106.

*Dimethyl 2-Acetyl-5-(tert-butyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3p**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (21 mg, 72%). MP: 50.6−52.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 6H), 3.42 (s, 2H), 2.30 (s, 3H), 1.17 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.07, 168.50, 163.74, 71.75, 53.72, 43.73, 34.07, 27.95, 21.78. HRMS (ESI): m/z calcd for $C_{13}H_{20}N_2NaO_5$ $[M + Na]^+$: 307.1264, found 307.1260.

*Dibenzyl 2-Acetyl-5-(tert-butyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3q**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (33 mg, 76%). MP: 49.6−51.2 °C. ^{1}H N MR (400 MHz, $CDCl_3$): δ 7.31−7.21 (m, 10H), 5.19 (dd, J = 12, 2.3 Hz, 4H), 3.35 (s, 2H), 2.30 (s, 3H), 1.09 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.14, 167.51, 163.41, 135.05, 128.56, 128.39, 128.12, 72.00, 68.22, 43.58, 33.96, 27.81, 21.68. HRMS (ESI): m/z calcd for $C_{25}H_{28}N_2NaO_5$ $[M + Na]^+$: 459.1890, found 459.1897.

*Diisopropyl 2-Acetyl-5-(tert-butyl)-2,4-dihydro-3H-pyrazole-3,3-dicarboxylate (**3r**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (19 mg, 54%). MP: 56.4−58.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07−5.01 (m, 2H), 3.32 (s, 2H), 2.24 (s, 3H), 1.21 (dd, J = 13.2, 6.3 Hz, 12H), 1.11 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.88, 167.11, 163.16, 72.26, 70.38, 43.34, 33.83, 27.71, 21.59, 21.51, 21.33. HRMS (ESI): m/z calcd for $C_{17}H_{28}N_2NaO_5$ $[M + Na]^+$: 363.1890, found 363.1892.

*Ethyl 1,5-Diacetyl-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3s**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (25 mg, 83%). MP: 64.2−65.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72−7.69 (m, 2H), 7.49−7.26 (m, 3H), 4.26 (qd, J = 7.2, 3.0 Hz, 2H), 3.91 (d, J = 17.6 Hz, 1H), 3.59 (d, J = 17.7 Hz, 1H), 2.46 (s, 3H), 2.45 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 130.92, 128.94, 126.82, 62.87, 43.17, 27.78, 22.04, 14.08. HRMS (ESI): m/z calcd for $C_{16}H_{18}N_2NaO_4$ $[M + Na]^+$: 325.1159, found 325.1153.

*Ethyl 1,5-Diacetyl-3-(tert-butyl)-4,5-dihydro-1H-pyrazole-5-carboxylate (**3t**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (17 mg, 60%). MP: 62.5−63.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (qd, J = 10.7, 7.1 Hz, 2H), 3.52 (d, J = 17.7 Hz, 1H), 3.15 (d, J = 17.7 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.18 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 201.24, 169.34, 168.69, 164.90, 76.07, 62.63, 42.25, 34.13, 27.92, 27.67, 21.86, 14.03. HRMS (ESI): m/z calcd for $C_{14}H_{23}N_2O_4$ $[M + H]^+$: 283.1652, found 283.1659.

*1,1′,1″-(3-Phenyl-4,5-dihydro-1H-pyrazole-1,5,5-triyl)tris-(ethan-1-one) (**3u**).* Ethyl acetate/petroleum ether = 1:15 was used as an eluent. White solid (21 mg, 77%). MP: 56.7−59.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70−7.64 (m, 2H), 7.44−7.36 (m, 3H), 3.60 (s, 2H), 2.44 (s, 3H), 2.27 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 202.14, 169.87, 153.82, 131.06, 129.95, 128.88, 126.78, 81.06, 77.48, 77.16, 76.84, 41.64, 26.90, 22.00. HRMS (ESI): m/z calcd for $C_{15}H_{17}N_2O_3$ $[M + H]^+$: 273.1234, found 273.1238.

General Procedure for the Preparation of Indoline 5. To a stirred solution of the α-bromocarbonyl compound **1** (0.15 mmol) and Cs_2CO_3 (0.2 mmol) in dichloromethane (DCM) (2 mL) at room temperature, azoalkene precursor **4** (0.1 mmol) was added. After the reaction was completed, as indicated by TLC, the mixture was concentrated in vacuo, and the crude product was purified by flash chromatography by eluting with ethyl acetate/petroleum ether = 1:10 to afford the product **5**.

*Diethyl 1-Benzoylindoline-2,2-dicarboxylate (**5a**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (29 mg, 77%). MP: 123.1−125.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60−7.52 (m, 2H), 7.52−7.46 (m, 1H), 7.45−7.37 (m, 2H), 7.12 (d, J = 7.4 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.84−6.77 (m, 1H), 5.92 (d, J = 8.2 Hz, 1H), 4.26 (qd, J = 7.1, 2.7 Hz, 4H), 3.70 (s, 2H), 1.26 (t, J = 7.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.24, 167.85, 141.05, 135.40, 130.91, 128.66, 128.36, 127.34, 127.19, 124.84, 123.52, 114.68, 74.93, 62.30, 38.73, 13.84. HRMS (ESI): m/z calcd for $C_{21}H_{21}NNaO_5$ $[M + Na]^+$: 390.1312, found 390.1315.

*Diethyl 1-Benzoyl-6-(trifluoromethyl) Indoline-2,2-dicarboxylate (**5b**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (36 mg, 82%). MP: 127.9−129.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61−7.52 (m, 3H), 7.52−7.46 (m, 2H), 7.26 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.09 (s, 1H), 4.36−4.28 (m, 4H), 3.77 (s, 2H), 1.32 (td, J = 7.1, 1.0 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.58, 167.79, 141.84, 134.81, 132.49 (d, J = 1.3 Hz), 131.61, 129.98 (d, J = 32.3 Hz), 129.14, 127.41, 125.32, 123.56 (d, J = 272.4 Hz), 120.67 (q, J = 3.9 Hz), 111.78 (q, J = 4.2 Hz), 75.21, 62.86, 38.76, 14.05. HRMS (ESI): m/z calcd for $C_{22}H_{20}F_3NNaO_5$ $[M + Na]^+$: 458.1186, found 458.1181.

*Diethyl 1-Benzoyl-6-fluoroindoline-2,2-dicarboxylate (**5c**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (33 mg, 84%). MP: 125.6−127.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60−7.52 (m, 3H), 7.49−7.44 (m, 2H), 7.08−7.04 (m, 1H), 6.61 (td, J = 8.5, 2.3 Hz, 1H), 5.62 (dd, J = 10.4, 2.2 Hz, 1H), 4.30 (qd, J = 7.1, 2.9 Hz, 4H), 3.66 (s, 2H), 1.29 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.54, 167.88, 162.03 (d, J = 243.7 Hz), 142.61 (d, J = 11.6 Hz), 135.01, 131.52, 129.07, 127.51, 125.64 (d, J = 9.9 Hz), 123.90 (d, J = 2.6 Hz), 110.34 (d, J = 23.0 Hz), 103.26 (d, J = 29.5 Hz), 75.89, 62.71, 38.27, 14.06. HRMS (ESI): m/z calcd for $C_{21}H_{20}FNNaO_5$ $[M + Na]^+$: 408.1218, found 408.1214.

*Diethyl 1-Benzoyl-5-bromoindoline-2,2-dicarboxylate (**5d**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent, White solid (36 mg, 81%). MP: 123.4−125.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59−7.51 (m, 3H), 7.47−7.42 (m, 2H), 7.29−7.27 (m, 1H), 6.97 (dd, J = 8.7, 2.1 Hz, 1H),

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5.81 (d, J = 8.6 Hz, 1H), 4.31 (qd, J = 7.1, 3.4 Hz, 4H), 3.71 (s, 2H), 1.31 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.39, 167.80, 140.58, 135.11, 131.41, 130.86, 130.37, 129.02, 128.07, 127.62, 116.27, 116.25, 75.31, 62.79, 38.60, 14.08. HRMS (ESI): m/z calcd for $C_{21}H_{20}BrNNaO_5$ $[M + Na]^+$: 468.0417, found 468.0411.

*Diethyl 1-Benzoyl-7-chloroindoline-2,2-dicarboxylate (**5e**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (30 mg, 74%). MP: 126.5−128.7 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.59−7.51 (m, 3H), 7.46 (dd, J = 8.7, 6.6 Hz, 2H), 7.04 (d, J = 8.0 Hz, 1H), 6.87 (dd, J = 8.0, 1.8 Hz, 1H), 5.85 (d, J = 1.8 Hz, 1H), 4.28 (qd, J = 7.1, 2.0 Hz, 4H), 3.65 (s, 2H), 1.28 (t, J = 7.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.45, 167.76, 142.39, 134.85, 133.02, 131.51, 129.01, 127.43, 126.99, 125.70, 123.65, 115.31, 75.47, 62.69, 38.39, 13.99. HRMS (ESI): m/z calcd for $C_{21}H_{20}ClNNaO_5$ $[M + Na]^+$: 424.0922, found 424.0926.

*Diethyl 1-Benzoyl-6,7-dimethylindoline-2,2-dicarboxylate (**5f**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (25 mg, 63%). MP: 121.7−123.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64−7.51 (m, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.33−7.26 (m, 2H), 6.97 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 4.29−4.15 (m, 4H), 3.81 (s, 2H), 2.04 (s, 3H), 1.40 (s, 3H), 1.24 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.39, 141.43, 137.23, 135.93, 131.37, 128.78, 128.21, 127.62, 126.53, 125.20, 121.53, 78.64, 62.56, 40.21, 20.00, 16.57, 13.96. HRMS (ESI): m/z calcd for $C_{23}H_{25}NNaO_5$ $[M + Na]^+$: 418.1625, found 418.1624.

*Diethyl 1-Benzoyl-6-methoxyindoline-2,2-dicarboxylate (**5g**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (28 mg, 71%). MP: 120.9−123.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.62−7.56 (m, 2H), 7.56−7.43 (m, 3H), 7.01 (dd, J = 8.3, 1.0 Hz, 1H), 6.46 (dd, J = 8.3, 2.3 Hz, 1H), 5.49 (d, J = 2.2 Hz, 1H), 4.30 (qd, J = 7.2, 2.4 Hz, 4H), 3.64 (s, 2H), 3.38 (s, 3H), 1.30 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.71, 152.51, 141.61, 135.49, 133.64, 128.61, 128.50, 128.36, 125.02, 124.54, 112.72, 67.73, 62.50, 39.38, 18.49, 13.89. HRMS (ESI): m/z calcd for $C_{22}H_{23}NNaO_6$ $[M+ Na]^+$: 420.1418, found 420.1422.

*1-(tert-Butyl) 2,2-Diethyl Indoline-1,2,2-tricarboxylate (**5h**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (18 mg, 50%). MP: 128.7−129.9 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.80 (s, 1H), 7.26−7.15 (m, 2H), 6.99 (t, J = 7.4 Hz, 1H), 4.19 (q, J = 7.2 Hz, 4H), 3.62 (s, 2H), 1.40 (s, 9H), 1.20 (t, J = 7.3 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 168.39, 128.34, 124.93, 123.35, 114.48, 81.98, 73.39, 62.46, 27.96, 14.26. HRMS (ESI): m/z calcd for $C_{19}H_{25}NNaO_6$ $[M + Na]^+$: 386.1574, found 386.1569.

*1-Benzyl 2,2-Diethyl Indoline-1,2,2-tricarboxylate (**5i**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (34 mg, 85%). MP: 106.3−107.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.2 Hz, 1H), 7.52−7.09 (m, 7H), 6.98 (d, J = 7.8 Hz, 1H), 5.28 (d, J = 60.2 Hz, 2H), 4.28−3.96 (m, 4H), 3.69 (s, 2H), 1.26−1.02 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.49, 162.31, 152.43, 141.80, 135.40, 128.44, 128.30, 128.18, 126.15, 124.01, 123.35, 115.17, 73.81, 67.70, 62.41, 40.16, 13.79. HRMS (ESI): m/z calcd for $C_{22}H_{23}NNaO_6$ $[M + H]^+$: 398.1598, found 398.1591.

*1-Benzyl 2,2-Diethyl 7-Methylindoline-1,2,2-tricarboxylate (**5j**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (25 mg, 60%). MP: 99.7−102.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.31 (m, 5H), 7.05−6.96 (m, 3H), 5.24 (s, 2H), 4.11 (qq, J = 7.3, 3.6 Hz, 4H), 3.77 (s, 2H), 2.27 (s, 3H), 1.18 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.63, 152.26, 139.69, 135.53, 131.01, 129.22, 128.46, 128.24, 128.18, 126.90, 124.62, 121.46, 75.95, 67.79, 62.48, 40.30, 20.76, 13.86. HRMS (ESI): m/z calcd for $C_{23}H_{25}NNaO_6$ $[M + Na]^+$: 434.1574, found 434.1578.

*1-Benzyl 2,2-Diethyl 4-Methylindoline-1,2,2-tricarboxylate (**5k**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (29 mg, 70%). MP: 97.3−98.8 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.1 Hz, 1H), 7.50−7.31 (m, 5H), 7.21−7.08 (m, 1H), 6.85 (d, J = 7.8 Hz, 1H), 5.41−5.18 (m, 2H), 4.30−3.98 (m, 4H), 3.63 (s, 2H), 2.21 (s, 3H), 1.30−1.08 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.48, 168.15, 159.18, 142.38, 135.68, 131.12, 128.94, 127.69, 125.29, 120.45, 109.82, 101.51, 75.88, 62.62, 55.10, 38.34, 29.82, 14.12. HRMS (ESI): m/z calcd for $C_{23}H_{25}NNaO_6$ $[M + Na]^+$: 434.1574, found 434.1577.

General Procedure for the Preparation of 3a-1. To a stirred solution of the compound **3a** (0.1 mmol) in MeOH (2 mL) at room temperature was added $NaBH_4$ (1 mmol). After the reaction was completed as indicated by the TLC, the mixture was concentrated in vacuo, and the crude product was purified by flash chromatography eluting with ethyl acetate/petroleum ether = 1:10 to afford the products **3a-1** in 92% yield.

*Ethyl 1-Acetyl-5-(hydroxymethyl)-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3a-1**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. White solid (27 mg, 92%). MP: 93.4−96.5 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.78−7.71 (m, 2H), 7.50−7.43 (m, 3H), 5.12 (t, J = 7.8 Hz, 1H), 4.18 (dd, J = 11.5, 5.7 Hz, 1H), 4.14−4.05 (m, 2H), 3.69 (dd, J = 11.5, 6.8 Hz, 1H), 3.63−3.48 (m, 2H), 2.27 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 170.32, 168.24, 152.77, 131.05, 130.75, 129.23, 126.90, 70.19, 61.33, 61.05, 41.86, 22.23, 14.33. HRMS (ESI): m/z calcd for $C_{15}H_{18}N_2NaO_4$ $[M + Na]^+$: 313.1159, found 313.1158.

General Procedure for the Preparation of 3a-2. To a stirred solution of the compound **3a** (0.1 mmol) in MeOH (2 mL) at room temperature was added $NaBH_4$ (1 mmol). Then, the mixture was heated to 40 °C. After the reaction was completed an indicated by TLC, the mixture was concentrated in vacuo, and the crude product was purified by flash chromatography eluting with ethyl acetate/petroleum ether = 1:4 to afford the product **3a-2** in 73% yield.

*1-(5,5-Bis(hydroxymethyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (**3a-2**).* Ethyl acetate/petroleum ether = 1:4 was used as an eluent. White solid (18 mg, 73%). MP: 112.4−114.6 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.74−7.70 (m, 2H), 7.48−7.42 (m, 3H), 4.99 (s, 2H), 3.98 (d, J = 11.0 Hz, 2H), 3.52 (d, J = 11.0 Hz, 2H), 3.34 (s, 2H), 2.25 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 168.87, 152.87, 131.55, 129.96, 128.76, 126.27, 72.80, 61.04, 23.16. HRMS (ESI): m/z calcd for $C_{13}H_{16}N_2NaO_3$ $[M + Na]^+$: 271.1053, found 271.1055.

General Procedure for the Preparation of 5-1. To a stirred solution of compound **5h** (0.2 mmol) in dichloromethane (2 mL) at 0 °C was added trifluoroacetic acid (TFA) (2 mmol). Then, the mixture was heated to 30 °C. After the reaction was completed, as indicated by TLC, the mixture was concentrated in vacuo, and the crude product was purified by flash chromatography eluting with ethyl acetate/petroleum ether = 1:10 to afford the product **5-1** in 91% yield.

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*2-(Ethoxycarbonyl) Indoline-2-carboxylic Acid (**5-1**).* Ethyl acetate/petroleum ether = 1:10 was used as an eluent. Colorless oil liquid (43 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 7.26 (td, J = 7.7, 1.4 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.08 (td, J = 7.5, 1.1 Hz, 1H), 6.92 (dd, J = 7.9, 1.2 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.97 (d, J = 16.6 Hz, 1H), 3.40 (d, J = 16.6 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.56, 165.13, 135.92, 128.50, 128.29, 124.19, 120.88, 115.95, 63.80, 58.50, 39.90, 14.05. HRMS (ESI): m/z calcd for $C_{12}H_{13}NNaO_4$ $[M + Na]^+$: 258.0737, found 258.0739.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04127.

^{1}H and ^{13}C{^{1}H} NMR spectra for all of the products (PDF)

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Notes

The authors declare no competing financial interest.

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