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Pd/C-Catalyzed Alkylation of Heterocyclic Nucleophiles with Alcohols through the "Borrowing Hydrogen" Process

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The alkylation of heterocyclic compounds is important for the synthesis of various biologically active compounds. In this paper, we present the development of a Pd/C-catalyzed alkylation of heterocyclic compounds using alcohols as the alkylating agents. This method gives the corresponding alkylated heterocyclic compounds in high yields (up to 99 %). The commercially available catalyst can be recovered and reused five times without significant loss of catalytic efficiency, and the turnover number (TON) was as high as 900. Moreover, the reaction could be scaled up.

Introduction

Heterocyclic compounds are an important class of organic substances due to their roles in biological processes. Heterocyclic motifs are very common in natural products, pharmaceuticals, and other biologically active synthetic compounds.[1] Therefore, the development of a new, green, and regioselective method for alkylating heterocyclic compounds is an important subject. For example, the regioselective alkylation of coumarins, barbiturates, oxindoles, and indoles is very important, because alkylated derivatives of these heterocyclic compounds are intermediates for the synthesis of various useful biologically active compounds, some of which are shown in Figure 1.[2]

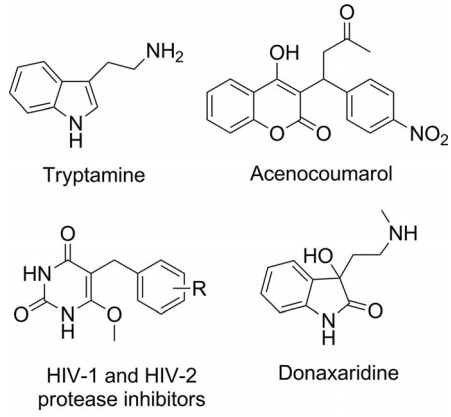
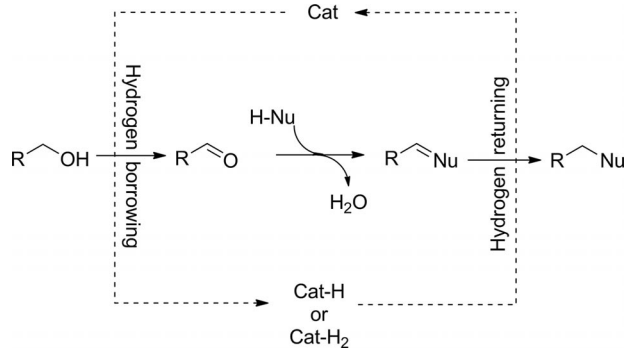


Figure 1. Examples of pharmacologically active simple heterocycles.

Recently, the use of alcohols as alkylating agents has received much attention from organic chemists. There are several advantages to this approach, such as the fact that water is the only expected byproduct. Therefore, this method is one of the most ideal alkylation methods from the perspective of green chemistry.[3] Although alcohols are rather unreactive as electrophiles, they can be activated through the "borrowing hydrogen" method, in which they are temporarily dehydrogenated to form aldehydes or ketones. After the "activated" species is formed, it undergoes nucleophilic addition with a nucleophile to form an unsaturated intermediate. Finally, the "borrowed hydrogen" on the catalyst is returned to give the corresponding alkylated product (Scheme 1).[3] Based on this approach, various types of C–N and C–C bond-forming reactions with both homogeneous and heterogeneous catalysts have been developed to date.[4] Although the use of heterogeneous catalysts is highly promising for industrial purposes due to the possibility of reusing the catalyst, to the best of our knowledge, the use



Scheme 1. General concept of alcohol activation through the "borrowing hydrogen" method.

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of commercially available heterogeneous catalysts like Pd/C in this method is rare.

Pd/C is one of the most well-known heterogeneous catalysts for various synthetic organic purposes, including hydrogenation,[5] dehydrogenation,[6] Suzuki–Miyaura coupling,[7] and others.[8] Since Pd/C is relatively inexpensive, commercially available, and in most cases reusable, it has been used for large-scale reactions in industry.[9] We recently reported that Pd/C effectively catalyzed the regioselective alkylation of indoles with alcohols via the "borrowing hydrogen" method to give the corresponding 3-alkylindoles.[10g] In this paper, we present the results of our work on the development of a Pd/C-catalyzed alkylation with alcohols through the "borrowing hydrogen" method for general heterocyclic compounds such as coumarins, quinolinones, barbituric acids, and oxindoles.[10,11]

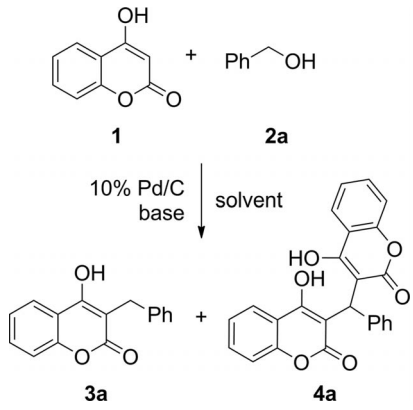
Results and Discussion

Our study started with the benzylation of 4-hydroxycoumarin (**1**). Coumarin **1** was treated with an excess of benzyl alcohol (**2a**; 5 equiv.) to avoid dimerization, which would lead to the formation of byproduct **4a**. By heating the reaction mixture at 140 °C in the presence of Pd/C (10 mol-%) and KOH (1 equiv.), the desired benzylated 4-hydroxycoumarin (i.e., **3a**) was obtained in 57% yield (Table 1, entry 1). No byproduct **4a** was observed under these solvent-free conditions. Referring to the reported mechanism, the reaction may involve a base-catalyzed Knoevenagel reaction between the "activated alcohol" (i.e., benzaldehyde) and 4-hydroxycoumarin to form an alkene intermediate.[10a,10b] Screening of several bases revealed that the addition of bases did not significantly affect the reaction (Table 1, entries 2–6 vs. entry 7). Therefore, the optimization was continued without the addition of bases. Although a 91% yield of the desired product (i.e., **3a**) was obtained under solvent-free conditions, this required a large excess of the alcohol and a high temperature (Table 1, entry 9). We believe that the alcohol acted not only as an alkylating agent, but also as a solvent under the reaction conditions. In order to decrease the amount of alcohol required, we next examined reaction solvents. Initially, the reaction was tested in xylenes with equimolar amounts of benzyl alcohol and **1** at 150 °C, and the corresponding alkylated 4-hydroxycoumarin (i.e., **3a**) was obtained in 58% yield, along with 24% of byproduct **4a** (Table 1, entry 10). Similar reaction efficiencies were observed when solvents with lower boiling points, such as toluene, *t*-amyl alcohol, and 1,4-dioxane, were used at 120 °C in sealed tubes (Table 1, entries 11–13). As 1,4-dioxane gave a slightly better yield and chemoselectivity than the other solvents (Table 1, entry 13), this solvent was chosen for further optimization. When 2 equiv. of benzyl alcohol (**2a**) was used to suppress the formation of **4a**, the desired product (i.e., **3a**) was obtained in an almost quantitative yield (Table 1, entry 14).

Having determined the optimized reaction conditions, we then tested the set of alcohols shown in Table 2. Benzylic alcohols with electron-donating methyl groups at the *para* and *meta* positions gave the corresponding products in excellent yields (Table 2, entries 2 and 3). In contrast, 4-chlorobenzyl alcohol (**2d**) had a negative effect on the reaction efficiency (Table 2, entry 4). The catalytic system also worked well with the heteroaromatic alcohol 2-pyridinemethanol (**2e**). The use of **2e** gave an 81% yield of alkylated coumarin **3e**. Interestingly, when the heterocyclic diol 2,6-bis(hydroxymethyl)pyridine (**2f**) was used as the alkylating agent, the reaction proceeded selectively to give monoalkylated product **3f** in 82% yield; no doubly alkylated product was detected by ^{1}H NMR spectroscopic analysis of the crude product. This method also gave the desired product (i.e., **3g**) in good yield when 2-naphthylmethanol (**2g**) was used (Table 2, entry 7). Unfortunately, the reaction failed to give a satisfactory result when the aliphatic alcohol cyclohexylmethanol (**2h**) was used (Table 2, entry 8). With some changes in the reaction conditions, the method also allowed the benzylation of 4-hydroxy-1-methylquinolinone (**5**), as shown in Scheme 2.

In 2001, Jursic and Neumann reported a one-pot, two-step C-5 alkylation of barbituric acids by treatment of barbituric acids **7** with aldehydes or ketones, followed by Pd/

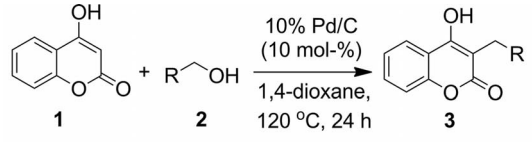
Table 1. Optimization of reaction conditions.[a]



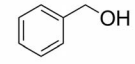
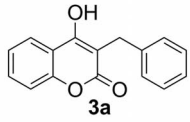
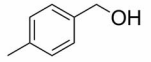
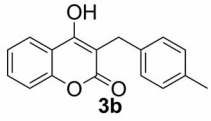
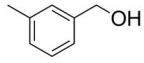
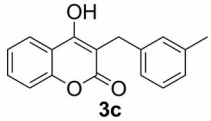
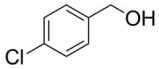
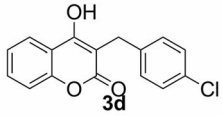
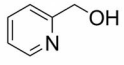
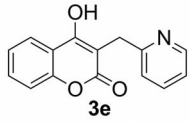
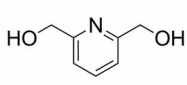
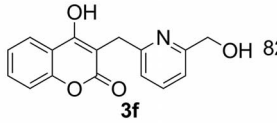
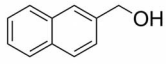
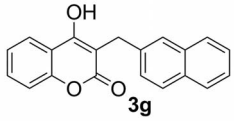
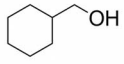
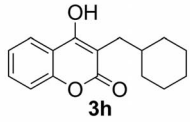
Entry	**2a** [equiv.]	Base	Solvent	Temp. [°C]	**3a**[b] [%]	**4a**[b] [%]
1	5	K_2CO_3	–	140	57	n.d.
2	5	K_2CO_3	–	150	77	n.d.
3	5	KOH	–	150	83	n.d.
4	5	NaOH	–	150	83	n.d.
5	5	Na_2CO_3	–	150	60	n.d.
6	5	Cs_2CO_3	–	150	50	n.d.
7	5	–	–	150	76	n.d.
8	6	–	–	150	80	n.d.
9	7	–	–	150	91	n.d.
10	1	–	xylenes	150	58	24
11	1	–	toluene	120	52	32
12	1	–	*tert*-amyl alcohol	120	56	20
13	1	–	1,4-dioxane	120	65	26
14	2	–	1,4-dioxane	120	99	n.d.

[a] Reaction conditions: a mixture of 4-hydroxycoumarin (1 mmol), benzyl alcohol (prescribed amount), Pd/C (10%; 10 mol-%), base (1 equiv.), and solvent (1 mL) was heated for 24 h under an argon atmosphere. [b] Determined by ^{1}H NMR spectroscopy with triphenylmethane as an internal standard. n.d.: not detected.

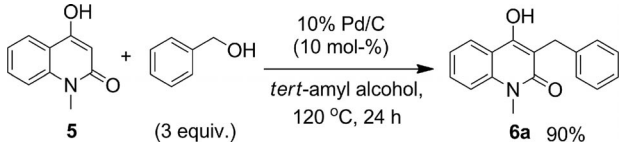
Table 2. Alkylation of 4-hydroxycoumarin with alcohols.[a]



1 2 3

Entry	Alcohol	Product	Yield[b]
1	 2a	 3a	99
2	 2b	 3b	96
3	 2c	 3c	83
4	 2d	 3d	5
5	 2e	 3e	81
6	 2f	 3f	82
7[c]	 2g	 3g	77
8	 2h	 3h	8

[a] Reaction conditions: a mixture of 4-hydroxycoumarin (1 mmol), alcohol (2 mmol), and Pd/C (10%; 10 mol-%) in 1,4-dioxane (1 mL) was heated at 120 °C for 24 h under an argon atmosphere. [b] Determined by ^{1}H NMR spectropscopy with triphenylmethane as the internal standard. [c] The amount of alcohol used was 3 mmol.



5 (3 equiv.) 6a 90%

Scheme 2. Pd/C-catalyzed benzylation of 4-hydroxy-1-methylquinolinone.

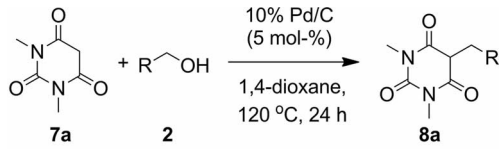
C-catalyzed hydrogenation of the resulting products with hydrogen gas as the hydrogen donor.[12] We were curious as to whether our method could be used for the one-step alkylation of barbituric acids without an additional hydrogen donor. To examine this possibility, 1,3-dimethylbarbituric acid (**7a**) was treated with benzyl alcohol (**2a**) under the optimized reaction conditions described above. We were pleased to find that a nearly quantitative yield of the corresponding benzylated barbituric acid (i.e., **8aa**) was obtained. Even with only 5 mol-% of Pd/C, the corresponding benzylated product (i.e., **8aa**) was obtained in 99% yield (Table 3, entry 1). On the basis of this result, we went on to test several alcohols in the reaction, and the results are outlined in Table 3. Generally, the the electronic properties of the alcohols determined their behavior in the reaction, and the effects seen here were similar to those observed in the alkylation of 4-hydroxycoumarin described above. The alcohols with electron-donating groups gave the corresponding products in high yields, while those with electron-withdrawing groups gave poor yields. Good results were obtained when the substituent was in either the *para* or the *ortho* position, while lower yields were obtained with benzylic alcohols with a substituent in the *meta* position. An excellent result was also observed when **7a** was alkylated using 2-naphthalenemethanol (**2g**; Table 3, entry 8). Moreover, this method was also found to be effective for the alkylation of unalkylated barbituric acid **7b** (Scheme 3). In this case, no *N*- or *O*-alkylated products were obtained.

We were also interested in the alkylation of oxindole, because of its biological activity and abundance in nature.[13] Therefore, we tested our catalytic system on the benzylation of oxindole (**9**). However, we found that only 15% of the oxindole was benzylated under the reaction conditions described above, presumably due to the fact that the methylene group of **9** is less reactive than those in 1,3-dicarbonyls **1** and **7**. The addition of K_2CO_3 (20 mol-%) to the reaction mixture greatly improved the efficiency of the reaction, and 3-benzyloxindole (**10a**) was formed in 94% yield. The use of a stronger base, KOH instead of K_2CO_3, further increased the product yield to 99% (Table 4, entry 1).

The scope of alcohol substrates in the alkylation of **9** was similar to the other alkylation reactions discussed above. Benzyl alcohols with electron-donating groups successfully gave the desired alkylated oxindoles in high yields. In contrast, benzyl alcohols with electron-withdrawing groups did not give satisfactory results. A nearly quantitative yield of the desired alkylated product (i.e., **10e**) was obtained when 2-pyridinylmethanol was used (Table 4, entry 6). The use of 2,6-bis(hydroxymethyl)pyridine resulted in the formation of monoalkylated product **10f** in 81% yield (Table 4, entry 7). When the secondary alcohol 1-phenylethanol (**2l**) was used, the desired product was obtained in the form of two diastereomers in reasonable yield (Table 4, entry 9).

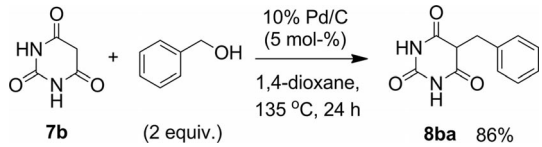
Finally, we investigated the scalability of the method and the reusability of the Pd/C catalyst. To test the scalability and turnover, we first carried out the reaction with 1,3-dimethylbarbituric acid (**7a**; 10 mmol) with benzyl alcohol (**2a**; 2 equiv.) in the presence of Pd/C (0.1 mol-%) in 1,4-

Table 3. Alkylation of 1,3-barbituric acids with alcohols.[a]



Entry	Alcohol	Product	Yield[b]
1	2a	8aa	99
2	2i	8ai	75
3	2j	8aj	95
4	2b	8ab	99
5	2c	8ac	94
6	2k	8ak	50
7[c]	2d	8ad	17
8	2g	8ag	99

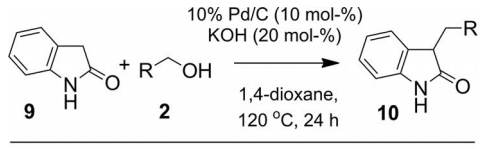
[a] Reaction conditions: a mixture of 1,3-dimethylbarbituric acid (1 mmol), alcohol (2 mmol), and Pd/C (10%; 5 mol-%) in 1,4-dioxane (1 mL) was heated for 120 °C for 24 h under an argon atmosphere. [b] Determined by ^{1}H NMR spectroscopy, using triphenylmethane as the internal standard. [c] 150 °C using xylenes as the solvent.



Scheme 3. Pd/C-catalyzed benzylation of barbituric acid.

dioxane (2 mL). After 98 h, the product yield reached 90% (turnover number, TON = 900). The Pd/C catalyst could also be reused, as illustrated in Figure 2. Thus, under the standard reaction conditions (5 mol-% of Pd/C, 1,4-dioxane, 120 °C, 24 h), an almost quantitative yield of product **8aa** was obtained, and the catalyst was recovered by simple filtration and reused. The catalyst could be reused for five cycles without significant loss of activity.

Table 4. Alkylation of oxindole with alcohols.[a]



Entry	Alcohol	Product	Yield[b]
1	2a	10a	99
2	2j	10j	92
3	2b	10b	80
4	2c	10c	81
5	2d	10d	trace
6	2e	10e	99
7	2f	10f	81
8	2g	10g	48
9	2l	10l	41 *dr* 1.4:1

[a] Reaction conditions: a mixture of oxindole (1 mmol), alcohol (2 mmol), Pd/C (10%; 10 mol-%), and KOH (20 mol-%) in 1,4-dioxane (1 mL) was heated at 120 °C for 24 h under an argon atmosphere. [b] Determined by ^{1}H NMR spectroscopy, using triphenylmethane as the internal standard.

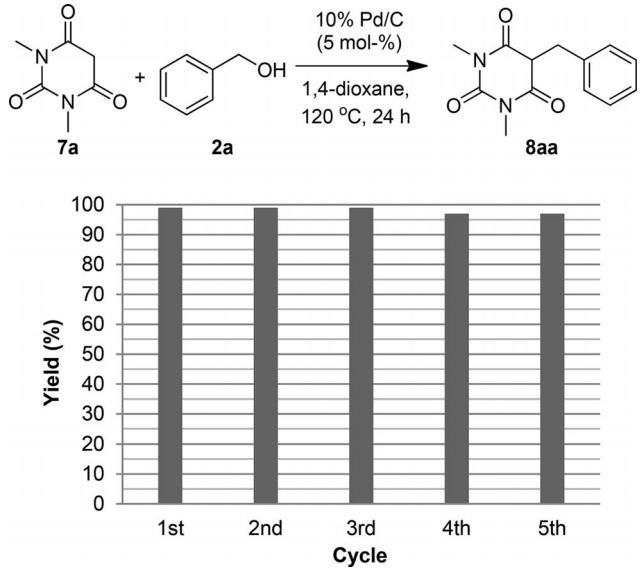


Figure 2. Recycling of the Pd/C catalyst. Reaction conditions: a mixture of 1,3-dimethylbarbituric acid (10 mmol), alcohol (20 mmol), and Pd/C (10%; 5 mol-%) in 1,4-dioxane (10 mL) was heated at 120 °C for 24 h under an argon atmosphere. The Pd/C was collected by filtration under argon, and washed with dry solvent before reuse, yields were determined by ^{1}H NMR spectroscopy, using triphenylmethane as the internal standard.

Conclusions

We have described an alkylation method for heterocycles that uses benzylic alcohols as the alkylating agents, and commercially available Pd/C as the catalyst. The method was demonstrated using 4-hydroxycoumarin, 4-hydroxy-1-methylquinolinone, barbituric acids, and oxindole. We successfully carried out a gram-scale reaction, and showed that the catalyst was reusable with negligible loss of efficiency, even after five cycles.

Experimental Section

General Information: Nuclear magnetic resonance (NMR) spectra were measured with a Bruker Ascend 400 spectrometer (400 MHz), using tetramethylsilane at δ = 0 ppm as the internal standard for ^{1}H NMR spectra (400 MHz), and $CDCl_3$ at δ = 77 ppm or [D_6]-DMSO at δ = 40 ppm for ^{13}C NMR spectra (100 MHz). Mass spectral (GC–MS) data were recorded with a Shimadzu QP5000 instrument. High-resolution mass spectra (HRMS) were recorded with a JEOL JMS-700 instrument, using *meta*-nitrobenzyl alcohol as the matrix, and PEG-200 as the calibration standard. Reagents and dry solvents obtained from commercial sources were used without further purification.

Procedure for the Alkylation of 4-Hydroxycoumarin with Alcohols: 4-Hydroxycoumarin (162 mg, 1 mmol), a representative alcohol (2 mmol), Pd/C (10%; 106 mg, 0.1 mmol), and dry 1,4-dioxane (1 mL) were added to an argon-purged 20 mL reaction tube equipped with a J-Young stop valve. The mixture was degassed using three or more freeze–pump–thaw cycles, and was then purged with argon gas. The reaction mixture was stirred at 120 °C for 24 h, then it was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography or recrystallized to give the 3-alkylated 4-hydroxycoumarins. A similar procedure was used for the alkylation of 1,3-barbituric acid and oxindole with the following exceptions: the amount of Pd/C was 5 mol-% (0.05 mmol) for 1,3-barbituric acid, and KOH (11.3 mg, 0.02 mmol) was added to the reaction mixture for the alkylation of oxindole.

3-Benzyl-4-hydroxycoumarin (3a): Isolated as a white solid. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 3.90 (s, 2 H), 7.16–7.17 (m, 1 H), 7.26 (d, J = 4.4 Hz, 4 H), 7.35–7.39 (m, 2 H), 7.59–7.63 (m, 1 H), 7.99 (dd, J = 1.6, 8.4 Hz, 1 H), 11.67 (br., 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 29.58, 104.69, 116.66, 116.69, 123.80, 124.36, 126.33, 128.57, 128.65, 132.32, 140.25, 152.47, 160.94, 163.29 ppm. MS (GC): m/z = 252 $[M]^+$. CAS registry number: 15074-18-7.

4-Hydroxy-3-(4-methylbenzyl)coumarin (3b): Isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 3.97 (s, 2 H), 7.10 (d, J = 8 Hz, 2 H), 7.21–7.06 (m, 4 H), 7.49–7.54 (m, 1 H), 7.77 (dd, J = 1.2, 8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.02, 29.70, 104.46, 115.78, 116.53, 122.85, 123.95, 128.35, 129.94, 131.88, 134.36, 136.97, 152.47, 160.58, 164.09 ppm. MS (GC): m/z = 266 $[M]^+$. CAS registry number: 6619-24-5.

4-Hydroxy-3-(3-methylbenzyl)coumarin (3c): Isolated as a white solid. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.25 (s, 3 H), 3.86 (s, 2 H), 6.97 (d, J = 7.2 Hz, 1 H), 7.02–7.06 (m, 2 H), 7.13 (t, J = 7.2 Hz, 1 H), 7.37 (d, J = 7.6 Hz, 2 H), 7.59–7.63 (m, 1 H), 7.99 (dd, J = 1.2, 8.2 Hz, 1 H), 11.63 (br., 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 21.50, 29.51, 104.76, 116.66, 116.71, 123.80, 124.35, 125.67, 126.99, 128.55, 129.17, 132.29, 137.62, 140.16, 152.46, 160.89, 163.30 ppm. MS (GC): m/z = 266 $[M]^+$. CAS registry number: 6432-71-9.

4-Hydroxy-3-(2-pyridinylmethyl)coumarin (3e): Isolated as a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22 (s, 2 H), 7.25–7.32 (m, 3 H), 7.47–7.51 (m, 2 H), 7.80 (td, J = 1.6, 8 Hz, 1 H), 7.96 (dd, J = 1.2, 8.2 Hz, 1 H), 8.47 (d, J = 4 Hz, 1 H), 11.55 (br., 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.72, 101.07, 116.17, 117.70, 122.43, 123.58, 123.60, 123.85, 131.60, 139.28, 146.33, 152.63, 159.92, 164.11, 165.34 ppm. MS (GC): m/z = 253 $[M]^+$. CAS registry number: 1261157-51-0.

4-Hydroxy-3-(6-hydroxymethyl-2-pyridinylmethyl)coumarin (3f): This compound is unknown. Isolated as a white solid. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 4.09 (s, 2 H), 4.62 (s, 2 H), 7.30–7.37 (m, 3 H), 7.44 (d, J = 8 Hz, 1 H), 7.58–7.62 (m, 1 H), 7.87–7.95 (m, 2 H), 9.57 (br., 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 32.36, 63.61, 101.21, 116.50, 117.66, 119.59, 121.62, 123.94, 124.27, 132.38, 139.99, 152.64, 158.61, 160.61, 163.32, 164.33 ppm. HRMS: calcd. for $C_{16}H_{13}NO_4$ $[M + H]^+$ 283.0845; found 284.0923.

4-Hydroxy-3-(2-naphthalenylmethyl)coumarin (3g): Isolated as a white solid. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 4.08 (s, 2 H), 7.36–7.47 (m, 5 H), 7.62 (td, J = 1.6, 8 Hz, 1 H), 7.71 (s, 1 H), 7.81–7.85 (m, 3 H), 8.02 (dd, J = 1.2, 7.6 Hz, 1 H), 11.76 (br., 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 29.86, 104.46, 116.73, 116.75, 123.89, 124.40, 125.72, 126.23, 126.44, 127.71, 127.81, 127.87, 128.14, 132.11, 132.39, 133.53, 137.89, 152.56, 161.19, 163.37 ppm. MS (GC): m/z = 266 $[M]^+$. CAS registry number: 166281-56-7.

3-Benzyl-4-hydroxy-1-methylquinolinone (6a): Isolated as a white solid. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 3.58 (s, 3 H), 3.99 (s, 2 H), 7.10–7.14 (m, 1 H), 7.19–7.28 (m, 5 H), 7.48 (d, J = 8 Hz, 1 H), 7.60 (t, J = 8 Hz, 1 H), 8.03 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 29.69, 29.84, 110.88, 114.85, 116.62, 121.76, 123.64, 126.01, 128.47, 128.74, 130.99, 138.99, 141.22,

156.98, 163.14 ppm. MS (GC): *m*/*z* = 265 $[M]^+$. CAS registry number: 72587-96-3.

5-Benzyl-1,3-dimethylbarbituric Acid (8aa): Isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.12 (s, 6 H), 3.47 (d, *J* = 4.8 Hz, 2 H), 3.78 (t, *J* = 4.8 Hz, 1 H), 7.02–7.04 (m, 2 H), 2.23–7.25 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.18, 37.89, 50.69, 127.83, 128.60, 128.84, 135.09, 150.98, 168.28 ppm. MS (GC): *m*/*z* = 246 $[M]^+$. CAS registry number: 15018-52-7.

1,3-Dimethyl-5-(4-methylbenzyl)barbituric Acid (8ab): Isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 3.13 (s, 6 H), 3.42 (d, *J* = 4.8 Hz, 2 H), 3.75 (t, *J* = 4.8 Hz, 1 H), 6.90 (d, *J* = 8 Hz, 2 H), 7.03 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.08, 28.18, 37.60, 50.78, 128.73, 129.28, 131.94, 137.47, 151.07, 168.39 ppm. MS (GC): *m*/*z* = 260 $[M]^+$. CAS registry number: 361446-71-1.

1,3-Dimethyl-5-(3-methylbenzyl)barbituric Acid (8ac): This compound is unknown. Isolated as white needles. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 3.12 (s, 6 H), 3.41 (d, *J* = 4.4 Hz, 2 H), 3.76 (t, *J* = 4.8 Hz, 1 H), 6.81 (d, *J* = 7.6 Hz, 1 H), 6.84 (s, 1 H), 7.04 (d, *J* = 7.6 Hz, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.19, 28.07, 38.08, 50.72, 125.76, 128.41, 128.51, 129.47, 134.89, 138.29, 150.98, 168.37 ppm. HRMS: calcd. for $C_{14}H_{16}N_2O_3$ $[M + H]^+$ 260.1161; found 261.1238.

1,3-Dimethyl-5-(2-naphthylmethyl)barbituric Acid (8ag): Isolated as a white solid. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.01 (s, 6 H), 3.44 (d, *J* = 4.8 Hz, 2 H), 4.14 (t, *J* = 5.2 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 7.47 (t, *J* = 3.6 Hz, 2 H), 7.58 (s, 1 H), 7.79–7.86 (m, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 28.40, 35.89, 50.80, 126.19, 126.64, 127.59, 127.92, 128.21, 132.33, 133.36, 135.30 ppm. MS (GC): *m*/*z* = 296 $[M]^+$. CAS registry number: 590372-34-2.

5-(3,4-Dimethoxybenzyl)-1,3-dimethylbarbituric Acid (8ai): Isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.15 (s, 6 H), 3.42 (d, *J* = 4.8 Hz, 2 H), 3.75 (t, *J* = 4.4 Hz, 1 H), 3.80 (s, 3 H), 3.83 (s, 2 H), 6.55–6.59 (m, 2 H), 6.71 (d, *J* = 8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.18, 37.26, 50.69, 55.71, 55.75, 110.93, 111.83, 121.07, 127.46, 148.42, 148.78, 150.90, 168.31 ppm. MS (GC): *m*/*z* = 206 $[M]^+$. CAS registry number: 321657-26-5.

1,3-Dimethyl-5-(4-methoxybenzyl)barbituric Acid (8aj): Isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.13 (s, 6 H), 3.41 (d, *J* = 4.8 Hz, 2 H), 3.73 (t, *J* = 4.8 Hz, 1 H), 3.76 (s, 3 H), 6.75 (d, *J* = 8.8 Hz, 2 H), 6.94 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.15, 39.10, 50.80, 55.12, 113.89, 126.93, 129.93, 150.98, 159.05, 168.36 ppm. MS (GC): *m*/*z* = 276 $[M]^+$. CAS registry number: 114656-99-4.

1,3-Dimethyl-5-(2-methylbenzyl)barbituric Acid (8ak): This compound is unknown. Isolated as white needles. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 3.16 (s, 6 H), 3.46 (d, *J* = 5.2 Hz, 2 H), 3.75 (t, *J* = 5.6 Hz, 1 H), 6.93 (d, *J* = 7.2 Hz, 1 H), 7.05–7.09 (m, 1 H), 7.11–7.13 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.20, 28.29, 34.44, 50.34, 125.83, 127.60, 129.17, 130.70, 133.71, 136.44, 151.17, 168.45 ppm. MS (GC): *m*/*z* = 260 $[M]^+$ HRMS: calcd. for $C_{14}H_{16}N_2O_3$ $[M + H]^+$ 260.1161; found 261.1238.

5-Benzylbarbituric Acid (8ba): Isolated as a white solid. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.25 (d, *J* = 4.8 Hz, 2 H), 3.90 (t, *J* = 5.2 Hz, 1 H), 7.05 (d, *J* = 6.8 Hz, 2 H), 7.20–7.27 (m, 3 H), 11.17 (s, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 33.80, 49.91, 127.08, 128.81, 129.29, 137.90, 151.09, 170.52 ppm. MS (GC): *m*/*z* = 218 $[M]^+$. CAS registry number: 5909-45-5.

3-Benzyloxindole (10a): Isolated as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.92 (dd, *J* = 9.2, 13.6 Hz, 1 H), 3.48 (dd, *J* = 4.4, 13.6 Hz, 1 H), 3.74 (dd, *J* = 4.8, 9.2 Hz, 1 H), 6.72 (d, *J* = 7.2 Hz, 1 H), 6.84–6.90 (m, 2 H), 7.15–7.26 (m, 6 H), 9.2 (br., 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.61, 47.59, 109.82, 121.98, 124.79, 126.65, 127.95, 128.32, 128.98, 129.41, 137.81, 141.55, 180.01 ppm. MS (GC): *m*/*z* = 223 $[M]^+$. CAS registry number: 7511-08-2.

3-(4-Methylbenzyl)oxindole (10b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.89 (dd, *J* = 9.2, 13.8 Hz, 1 H), 3.45 (dd, *J* = 4.4, 13.6 Hz, 1 H), 3.72 (dd, *J* = 4.4, 8.6 Hz, 1 H), 6.76 (d, *J* = 7.2 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.87–6.91 (m, 1 H), 7.03–7.07 (m, 4 H), 7.13–7.17 (m, 1 H), 8.79 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.05, 36.21, 47.61, 109.69, 121.97, 124.85, 127.89, 129.02, 129.13, 129.27, 134.68, 136.14, 141.45, 179.76 ppm. MS (GC): *m*/*z* = 237 $[M]^+$. CAS registry number: 170956-94-2. Isolated as yellow solid.

3-(3-Methylbenzyl)oxindole (10c): Isolated as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.85 (dd, *J* = 9.6, 15.6 Hz, 1 H), 3.47 (dd, *J* = 4.0, 13.6 Hz, 1 H), 3.73 (dd, *J* = 4.4, 9.4 Hz, 1 H), 6.71 (d, *J* = 7.6 Hz, 1 H), 6.85–6.90 (m, 2 H), 6.97–7.03 (m, 3 H), 7.12–7.17 (m, 2 H), 9.04 (br., 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.36, 36.62, 47.55, 109.75, 121.96, 124.89, 126.41, 127.39, 127.91, 128.21, 129.13, 130.18, 137.83, 137.93, 141.49, 179.93 ppm. MS (GC): *m*/*z* = 237 $[M]^+$. CAS registry number: 931696-20-7.

3-(2-Pyridinylmethyl)oxindole (10e): Isolated as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.14 (dd, *J* = 9.2, 14.4 Hz, 1 H), 3.62 (dd, *J* = 4.8, 14.2 Hz, 1 H), 4.15 (dd, *J* = 5.2, 9.2 Hz, 1 H), 6.69 (d, *J* = 7.6 Hz, 1 H), 6.82–6.87 (m, 2 H), 7.10–7.17 (m, 3 H), 7.56–7.60 (m, 1 H), 8.56–8.58 (m, 1 H), 9.5 (br., 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.70, 45.67, 109.79, 121.74, 121.95, 123.88, 124.49, 127.84, 129.41, 136.29, 141.68, 149.35, 158.21, 180.39 ppm. MS (GC): *m*/*z* = 224 $[M]^+$. CAS registry number: 3367-84-8.

3-(6-Hydroxymethyl-2-pyridinylmethyl)oxindole (10f): This compound is unknown. Isolated as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (dd, *J* = 8.0, 14.8 Hz, 1 H), 3.51 (dd, *J* = 4.8, 14.8 Hz, 1 H), 3.96 (dd, *J* = 4.8, 7.8 Hz, 1 H), 4.08 (br., 1 H), 4.57 (s, 2 H), 6.67 (d, *J* = 7.6 Hz, 1 H), 6.74–6.77 (m, 2 H), 6.95 (d, *J* = 7.6 Hz, 2 H), 7.02 (t, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 9.40 (br., 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.62, 45.41, 63.81, 109.88, 118.36, 121.97, 122.29, 124.15, 127.87, 129.40, 137.01, 141.78, 156.89, 158.41, 180.42 ppm. HRMS: calcd. for $C_{15}H_{14}N_2O_2$ $[M + H]^+$ 254.1055; found 255.1134.

3-(2-Naphthylmethyl)oxindole (10g): Isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.06 (dd, *J* = 9.6, 7 Hz, 1 H), 3.63 (dd, *J* = 4.4, 6.8 Hz, 1 H), 3.83 (dd, *J* = 4.4, 4.6 Hz, 1 H), 6.70 (d, *J* = 7.6 Hz, 1 H), 6.82–6.85 (m, 2 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.33 (dd, *J* = 1.6, 4.2 Hz, 1 H), 7.41–7.43 (m, 2 H), 7.60 (s, 1 H), 7.69–7.79 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.76, 47.42, 109.82, 121.98, 124.77, 125.50, 125.94, 127.49, 127.56, 127.59, 127.94, 127.96, 128.01, 128.94, 132.25, 133.28, 135.34, 141.48, 179.90 ppm. MS (GC): *m*/*z* = 273 $[M]^+$. CAS registry number: 1202521-48-9.

3-(4-Methoxybenzyl)oxindole (10j): Isolated as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.92 (dd, *J* = 9.2, 13.8 Hz, 1 H), 3.41 (dd, *J* = 4.8, 13.8 Hz, 1 H), 3.70 (dd, *J* = 4.4, 8.8 Hz, 1 H), 3.76 (s, 3 H), 6.76–6.83 (m, 4 H), 6.90 (t, *J* = 7.6 Hz, 1 H), 7.06 (d, *J* = 9.2 Hz, 2 H), 7.16 (t, *J* = 7.6 Hz, 3 H), 8.45 (br., 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.75, 47.69, 55.17, 109.59, 113.69, 122.01, 124.86, 127.90, 129.06, 129.70, 130.41, 141.37, 158.34, 179.40 ppm. MS (GC): *m*/*z* = 253 $[M]^+$. CAS registry number: 170956-93-1.

3-(1-Phenylethyl)oxindole (10l): Isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, J = 6.8 Hz, 3 H, major), 1.63 (d, J = 7.2 Hz, 3 H, minor), 3.47–3.54 (m, 1 H, minor), 3.65 (d, J = 5.6 Hz, 1 H, minor), 3.78 (d, J = 4 Hz, 1 H, major), 3.80–3.83 (m, 1 H, major), 6.50 (d, J = 7.6 Hz, 2 H, major), 6.75 (d, J = 7.6 Hz, 2 H, major), 6.82–7.26 (m, 8 H), 8.46 (s, 1 H, minor), 8.83 (s, 1 H, major) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.43, 19.20, 39.43, 41.79, 52.37, 52.96, 109.53, 121.82, 121.84, 125.08, 126.64, 126.69, 126.90, 127.82, 127.93, 127.94, 127.97, 128.06, 128.32, 141.65, 141.93, 142.05, 142.72, 179.04, 179.45 ppm. CAS registry number: 140701-16-2.

Procedure for Recycling Pd/C: 1,3-Dimethylbarbituric acid (1.56 g, 10 mmol), benzyl alcohol (20 mmol), Pd/C (10%; 1.06 g, 1 mmol), and dry 1,4-dioxane (10 mL) were added to an argon-purged 100 mL reaction tube equipped with a J-Young stopcock. The mixture was degassed using three or more freeze–pump–thaw cycles, and was then purged with argon gas. The reaction mixture was stirred at 120 °C for 24 h, then the Pd/C was collected by filtration under an Ar atmosphere, washed with dry 1,4-dioxane, and dried under vacuum before use in the next cycle. The yield of benzylated product **8aa** was determined by ^{1}H NMR spectroscopy, using triphenylmethane as the internal standard.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of all new compounds.

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