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Cascade Reactions

A Cascade C–H-Functionalization/Cyclization Reaction of Indoles with α-Halo or α-Sulfonyloxy Ketones for the Synthesis of Dihydropyrimidoindolone Derivatives

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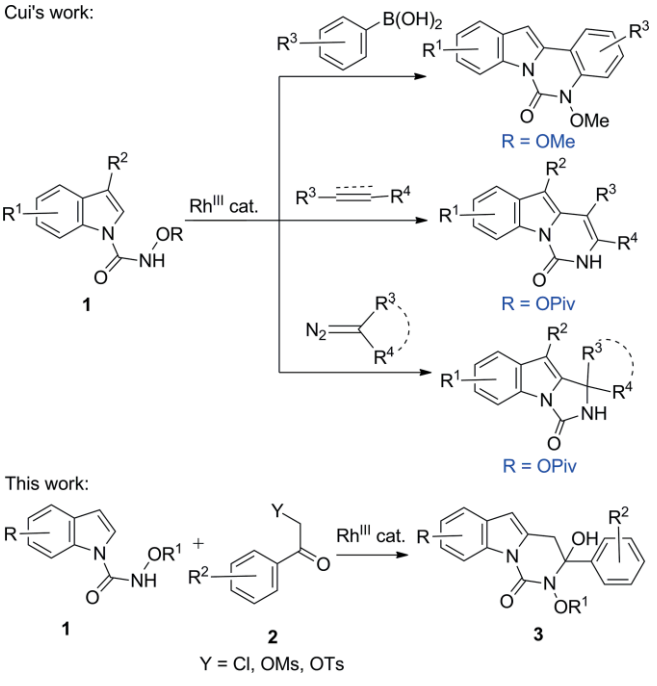
Abstract: A new cascade C–H-functionalization/cyclization reaction of *N*-carbamoylindoles **1** with α-halo, α-mesyloxy, or α-tosyloxy ketones **2** has been developed under rhodium(III) catalysis, leading to dihydropyrimido[1,6-*a*]indolone derivatives **3** in moderate to excellent yields.

Introduction

Recently, much attention has been given to the C–H functionalization of indoles.[1] Very recently, some work has been done on the α-C–H functionalization of indoles directed by an *N*-carbamoyl group under rhodium(III) catalysis.[2] In 2014, the Cui group developed cascade α-C–H-functionalization/cyclization reactions of *N*-carbamoylindoles **1** with arylboronic acids, alkynes, alkenes, or diazo carboxylate derivatives using rhodium catalysis (Scheme 1).[3] In 2015, Zeng and co-workers reported an α-C–H-functionalization reaction of *N*-carbamoylindoles with alkynes to give alkenylated indoles using rhodium catalysis.[4] However, to the best of our knowledge, the α-C–H functionalization of indoles with α-halo ketones still remains unknown. Chi et al. reported that free indoles underwent a coupling reaction with α-halo ketones to give β-C–H-functionalized indoles.[5] Considering that an *N*-carbamoyl group can direct and assist in the activation of an α-C–H bond,[3,4] we embarked on an investigation of the α-C–H functionalization of *N*-carbamoylindoles **1** with α-halo ketones **2**. In 2014, Glorius and co-workers reported a cascade C–H-functionalization/cyclization reaction of benzamides with α-mesyloxy, α-tosyloxy, or α-chloro ketones by α-C–H activation to give isoquinolones under rhodium catalysis.[6] Thus, we further envisioned that the α-C–H-functionalization products of *N*-carbamoylindoles with α-halo ketones, i.e., α-indolyl ketones, might subsequently undergo cyclization through intramolecular nucleophilic attack of the nitrogen atom in the *N*-carbamoyl group onto the carbonyl group in the ketone moiety. This would produce dihydropyrimido[1,6-*a*]indolone derivatives **3** (Scheme 1), which have important biological activities.[7] In this paper, we present our recent results on the cascade α-C–H-functionalization/cyclization reaction of *N*-carbamoylindoles **1** with α-halo or α-sulfonyloxy ketones **2** for the synthesis of dihydropyrimido[1,6-*a*]indolone derivatives **3**.



Scheme 1. Cascade C–H-functionalization/cyclization reactions of *N*-carbamoylindoles.

Results and Discussion

Initially, *N*-carbamoylindole **1a** and α-chloro ketone **2aC** (C represents chloro) were chosen as model substrates to explore and optimize the cascade C–H-functionalization/cyclization reaction. When $[Cp^*RhCl_2]_2$ (Cp^* = 1,2,3,4,5-pentamethylcyclopentadienyl) and CsOAc were used as a transition-metal catalyst and an additive, respectively, the expected cascade reaction took

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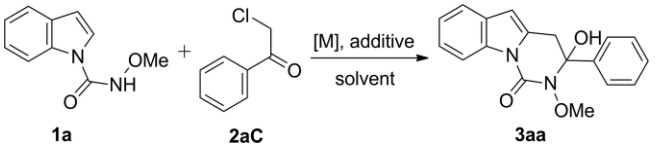
place in MeOH at 60 °C, and the desired dihydropyrimido[1,6-*a*]indolone derivative (i.e., **3aa**) was obtained, albeit in a low yield (Table 1, Entry 1). When $[Rh(COD)_2Cl]_2$ (COD = cyclooctadienyl) or $Pd(OAc)_2$ was used as catalyst, product **3aa** was not obtained (Table 1, Entries 2 and 3). When NaOAc was used as an additive instead of CsOAc, the yield of **3aa** increased from 35 to 95 % (Table 1, Entry 5).[3b] Optimization experiments with different solvents revealed that a solvent with a higher polarity is beneficial to the cascade reaction (Table 1, compare Entries 5 and 6 with Entries 7 and 8). The effect of temperature on the reaction was also studied, and lower yields of **3aa** were obtained when the temperature was either higher or lower than 60 °C (Table 1, Entries 9 and 10). When the cascade reaction was carried out under air instead of nitrogen, the yield of **3aa** decreased remarkably (Table 1, compare Entry 5 with Entry 11). In the absence of either $[RhCp^*Cl_2]_2$ or NaOAc, none of the dihydropyrimido[1,6-*a*]indolone derivative (i.e., **3aa**) was obtained (Table 1, Entries 12 and 13).

Table 1. Optimization of the cascade C–H-functionalization/cyclization reaction of *N*-carbamoylindole **1a** with α-chloro ketone **2aC**.[a]



1a **2aC** **3aa**

Entry	[M]	Additive (equiv.)	Solvent	Yield [%][b]
1	$[Cp^*RhCl_2]_2$	CsOAc (1.2)	MeOH	35
2	$Pd(OAc)_2$	CsOAc (1.2)	MeOH	0
3	$[Rh(COD)_2Cl]_2$	CsOAc (1.2)	MeOH	0
4	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$ (1.2)	MeOH	trace
5	***$[Cp^*RhCl_2]_2$***	***NaOAc (1.2)***	***MeOH***	***95***
6	$[Cp^*RhCl_2]_2$	NaOAc (1.2)	EtOH	90
7	$[Cp^*RhCl_2]_2$	NaOAc (1.2)	MeCN	9
8	$[Cp^*RhCl_2]_2$	NaOAc (1.2)	DCE	trace
9	$[Cp^*RhCl_2]_2$	NaOAc (1.2)	MeOH	73[c]
10	$[Cp^*RhCl_2]_2$	NaOAc (1.2)	MeOH	trace[d]
11	$[Cp^*RhCl_2]_2$	NaOAc(1.2)	MeOH	45[e]
12	–	NaOAc(1.2)	MeOH	0
13	$[Cp^*RhCl_2]_2$	–	MeOH	0

[a] Reaction conditions: **1a** (0.10 mmol), **2aC** (0.12 mmol), [M] (2 mmol-%), solvent (1 mL), N_2, 60 °C, 18 h. DCE = 1,2-dichloroethane. [b] Isolated yields. [c] At 90 °C. [d] At 25 °C. [e] Under air.

After screening the reaction conditions, we concluded that the optimized reaction should be carried out using $[Cp^*RhCl_2]_2$ as a catalyst and NaOAc as an additive at 60 °C in methanol under nitrogen. We investigated the substrate scope of the reaction under the optimized conditions, and found that various *N*-carbamoylindoles **1** were able to undergo the cascade C–H-functionalization/cyclization reaction smoothly with α-chloro phenyl ketone **2aC**, leading to dihydropyrimido[1,6-*a*]indolone derivatives **3aa**–**3ga** in moderate to excellent yields (Table 2). The structure of dihydropyrimido[1,6-*a*]indolone derivative **3da** was further determined by X-ray crystallography (Figure 1). α-Chloro aromatic ketones **2bC**–**2eC** bearing different substituents on the benzene rings led to dihydropyrimido[1,6-*a*]-indolone derivatives **3ad**–**3ef** in good yields. α-Chloro aliphatic ketones also underwent the cascade reaction with *N*-carbamoylindole **1a** expediently, producing dihydropyrimido-[1,6-*a*]indolone derivatives **3ag** and **3ah** in excellent yields. α-Mesyloxy and α-tosyloxy aromatic ketones **2aM** and **2aT** also readily underwent the cascade reaction with **1a** to give the desired dihydropyrimido[1,6-*a*]indolone derivative (i.e., **3aa**). α-Mesyloxy aromatic ketones **2hM** and **2iM**, bearing electron-withdrawing groups on the benzene rings, seem more liable to undergo the cascade reaction than those (**2eM** and **2jM**) bearing electron-donating groups. Switching the directing group from an *N*-methoxycarbamoyl group to an *N*-ethoxycarbamoyl group also led to dihydropyrimido[1,6-*a*]indolone derivative **3ha** in a satisfactory yield.

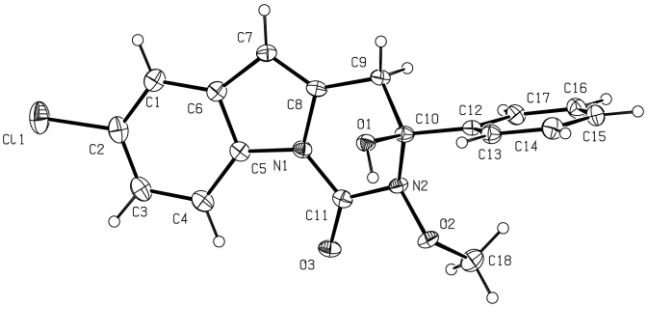
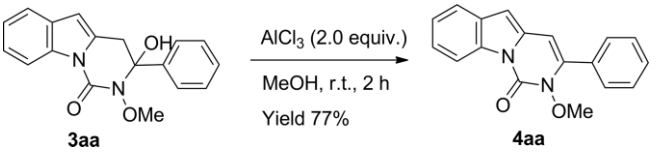


Figure 1. X-ray structure of dihydropyrimido[1,6-*a*]indolone derivative **3da**.

Further experiments indicated that in the presence of $AlCl_3$, dihydropyrimido[1,6-*a*]indolone derivative **3aa** was dehydrated in MeOH at room temperature to give pyrimido[1,6-*a*]indolone **4aa** in good yield (Scheme 2). However, pyrimido[1,6-*a*]indolone **4aa** is unstable at room temperature.

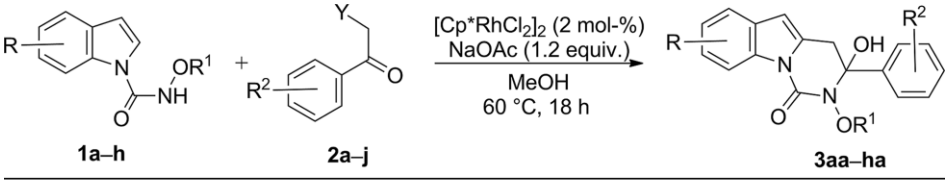


3aa **4aa**

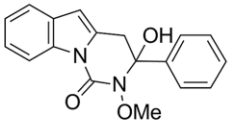
Scheme 2. Dehydration reaction of dihydropyrimido[1,6-*a*]indolone derivative **3aa** for the formation of pyrimido[1,6-*a*]indolone **4aa**.

A plausible mechanism for the cascade C–H-functionalization/cyclization reaction is proposed. $[Cp^*RhCl_2]_2$ is not a typical Lewis acid catalyst for Friedel–Crafts alkylation reactions. If it had functioned as a Lewis acid catalyst in the cascade reaction, β-alkylated products would have been observed instead of α-alkylated products **3**; β-alkylated indoles are formed more usually than α-alkylated indoles in Friedel–Crafts reactions of indoles with alkyl halides.[5,8] When *N*-methylindole was used instead of *N*-carbamoylindole **1a**, none of the α-C–H-coupling product was observed (Scheme 3). The result of this control experiment supports the idea that the *N*-carbamoyl group may direct and assist the α-C–H activation by rhodium catalysis in the cascade C–H-functionalization/cyclization reaction.[3] Thus, we tend towards a mechanism that proceeds through α-C–H activation by rhodium catalysis rather than via a carbocationic intermediate by Lewis acid catalysis. The plausible mechanism is as follows (Scheme 4). First, NaOAc reacts with $[Cp^*RhCl_2]_2$ to

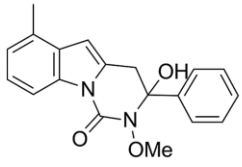
Table 2. Cascade C–H-functionalization/cyclization reactions of *N*-carbamoylindoles **1a**–**1h** with α-chloro, α-mesyloxy, or α-tosyloxy ketones **2a**–**2m**.[a,b]



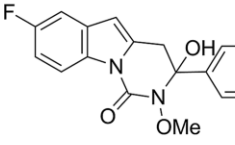
1a–h **2a–j** **3aa–ha**



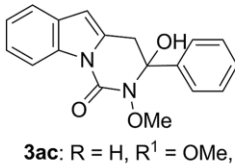
3aa: R = H, R^1 = OMe, 95%
R^2 = H, Y = Cl



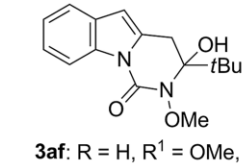
3ca: R = 4-CH_3, R^1 = OMe, 83%
R^2 = H, Y = Cl



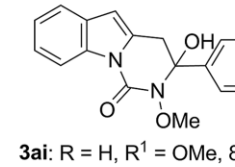
3fa: R = 5-F, R^1 = OMe, 76%
R^2 = H, Y = Cl



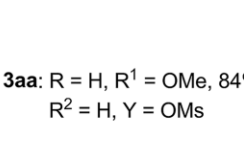
3ac: R = H, R^1 = OMe, 91%
R^2 = 4-Cl, Y = Cl



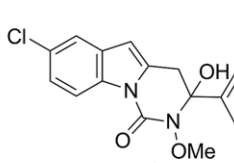
3af: R = H, R^1 = OMe, 63%
Y = Cl



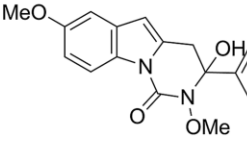
3ai: R = H, R^1 = OMe, 86%
R^2 = 4-Br, Y = OMs



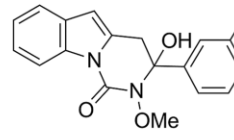
3aa: R = H, R^1 = OMe, 84%
R^2 = H, Y = OMs



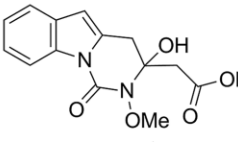
3aa: R = H, R^1 = OMe, 66%
R^2 = H, Y = OTs



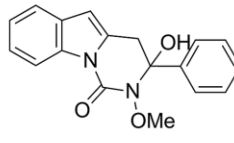
3da: R = 5-Cl, R^1 = OMe, 89%
R^2 = H, Y = Cl



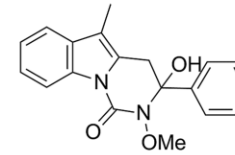
3ga: R = 5-OMe, R^1 = OMe, 66%
R^2 = H, Y = Cl



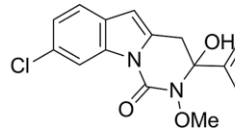
3ad: R = H, R^1 = OMe, 88%
R^2 = 3,4-2Cl, Y = Cl



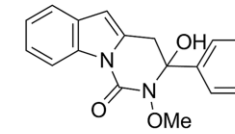
3aj: R = H, R^1 = OMe, 66%
R^2 = 4-OMe, Y = OMs



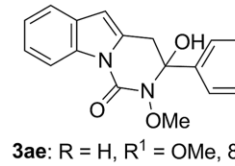
3ba: R = 3-CH_3, R^1 = OMe, 86%
R^2 = H, Y = Cl



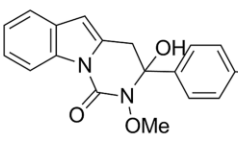
3ea: R = 6-Cl, R^1 = OMe, 90%
R^2 = H, Y = Cl



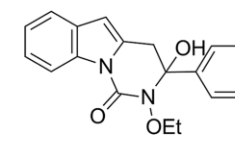
3ab: R = H, R^1 = OMe, 76%
R^2 = 4-F, Y = Cl



3ae: R = H, R^1 = OMe, 87%
R^2 = 4-Me, Y = Cl
3ae: R = H, R^1 = OMe, 75%
R^2 = 4-Me, Y = OMs



3ah: R = H, R^1 = OMe, 88%
R^2 = 4-NO_2, Y = OMs

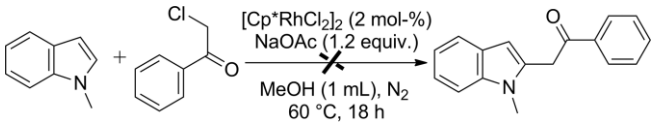


3ha: R = H, R^1 = OEt, 66%
R^2 = H, Y = Cl

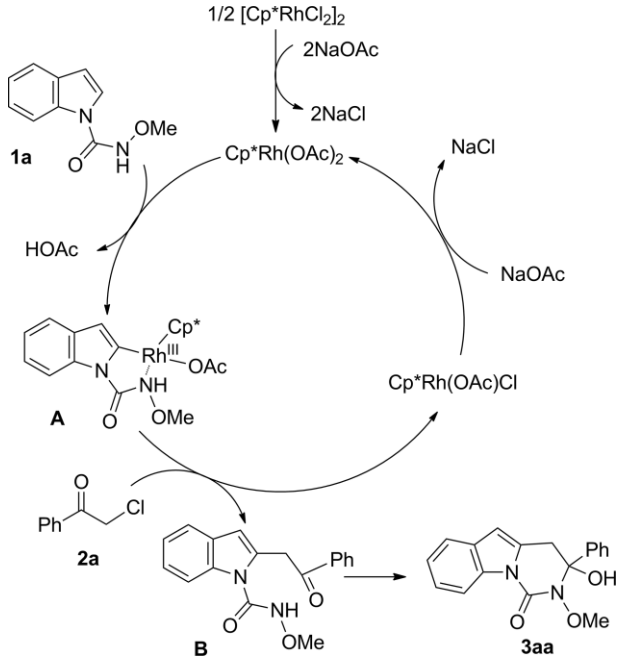
[a] Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), $[Cp^*RhCl_2]_2$ (2 mmol-%), NaOAc (0.12 mmol), MeOH (1 mL), N_2, 60 °C, 18 h. [b] Isolated yields.

generate $Cp^*Rh(OAc)_2$.[3b] The carbamoyl group in *N*-carbamoylindole **1a** directs and assists the α-C–H-bond activation to form rhodacycle **A**. The α-carbon atom in rhodacycle **A** attacks α-chloro ketone **2aC** nucleophilically to produce α-indolyl ketone intermediate **B**.[6] Finally, the nitrogen atom in the *N*-carbamoyl group carries out an intramolecular nucleophilic addi-

tion to the carbonyl group in intermediate **B** to give the desired dihydropyrimidoindolone derivative (i.e., **3aa**).



Scheme 3. Control experiment.



Scheme 4. Plausible mechanism for the cascade C–H-functionalization/cyclization reaction.

Conclusions

We have developed a new cascade C–H-functionalization/cyclization reaction of *N*-carbamoyl indoles **1** with α-halo or α-sulfonyloxy ketones **2**. We found that under rhodium(III) catalysis, various *N*-carbamoylindoles **1a**–**1h** were able to undergo the cascade C–H-functionalization/cyclization reaction smoothly with α-chloro, α-mesyloxy, or α-tosyloxy ketones **2** to give the desired dihydropyrimido[1,6-*a*]indolone derivatives (i.e., **3aa**–**3hj**) in moderate to excellent yields. A plausible mechanism proceeding through α-C–H functionalization directed by the *N*-carbamoyl group in substrate **1** is postulated for the cascade reaction. The cascade C–H-functionalization/cyclization reaction may have applications in the synthesis of related pharmaceuticals in the future.

Experimental Section

General Procedure for the Cascade C–H-Functionalization/Cyclization Reaction of *N*-Carbamoyl Indoles 1 with α-Chloro or α-Sulfonyloxy Ketones 2 for the Synthesis of Dihydropyrimidoindolone Derivatives 3: A mixture of *N*-carbamoylindole **1a**–**1h** (0.10 mmol), α-chloro or α-sulfonyloxy ketone **2** (0.12 mmol), $[Cp^*RhCl_2]_2$ (1.2 mg, 2 mol-%), and NaOAc (9.8 mg, 1.2 equiv) was stirred under nitrogen at 60 °C for 18 h. After this time, the mixture was cooled to room temperature, and then concentrated under vacuum. The residue was purified by column chromatography (silica gel; petroleum ether/ethyl acetate) to give dihydropyrimidoindolone derivative **3aa**–**3hj**.

3-Hydroxy-2-methoxy-3-phenyl-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3aa): Yellow solid (95 %); m.p. 165–167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 7.2 Hz, 2 H), 7.47–7.37 (m, 4 H), 7.30–7.21 (m, 2 H), 6.30 (s, 1 H), 4.13 (br., 1 H), 3.69 (s, 3 H), 3.60 (d, J = 16.4 Hz, 1 H), 3.45 (d, J = 16.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 140.9, 135.6, 131.2, 130.2, 128.8, 128.6, 125.9, 124.2, 123.5, 120.3, 115.6, 105.4, 91.9, 64.7, 38.0 ppm. HRMS (ESI): calcd. for $[C_{18}H_{15}N_2O_3]^-$ 307.1088; found 307.1095.

3-Hydroxy-2-methoxy-5-methyl-3-phenyl-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3ba): Pale yellow solid (86 %); m.p. 200–202 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27 (d, J = 7.6 Hz, 1 H), 7.66 (d, J = 7.2 Hz, 2 H), 7.50 (d, J = 7.2 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.38–7.35 (m, 2 H), 7.32–7.24 (m, 2 H), 3.62 (s, 3 H), 3.61 (d, J = 16.0 Hz, 1 H), 3.33 (d, J = 16.4 Hz, 1 H), 2.09 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.7, 141.5, 134.3, 130.9, 128.2, 128.0, 126.2, 123.8, 122.9, 118.5, 114.5, 111.5, 91.0, 63.6, 36.7, 7.9 ppm. HRMS (ESI): calcd. for $[C_{19}H_{18}N_2O_3 + Na]^+$ 345.1210; found 345.1194.

3-Hydroxy-2-methoxy-6-methyl-3-phenyl-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3ca): White solid (83 %); m.p. 192–193 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.10 (d, J = 8.0 Hz, 1 H), 7.62 (d, J = 7.2 Hz, 2 H), 7.43–7.33 (m, 4 H), 7.17 (t, J = 7.8 Hz, 1 H), 7.03 (d, J = 7.2 Hz, 1 H), 6.46 (s, 1 H), 3.74 (d, J = 16.0 Hz, 1 H), 3.64 (s, 3 H), 3.38 (d, J = 16.0 Hz, 1 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.4, 141.2, 134.5, 131.8, 129.4, 129.1, 128.1, 128.0, 126.1, 123.6, 123.4, 112.2, 102.9, 91.1, 63.6, 38.3, 18.1 ppm. HRMS (ESI): calcd. for $[C_{19}H_{18}N_2O_3 + Na]^+$ 345.1210; found 345.1193.

7-Chloro-3-hydroxy-2-methoxy-3-phenyl-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3da): White solid (89 %); m.p. 205–208 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.25 (d, J = 8.8 Hz, 1 H), 7.64–7.62 (m, 3 H), 7.44–7.34 (m, 4 H), 7.31 (dd, J = 8.8, J = 2.0 Hz, 1 H), 6.44 (s, 1 H), 3.78 (d, J = 16.4 Hz, 1 H), 3.62 (s, 3 H), 3.39 (d, J = 16.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.1, 140.9, 134.3, 133.2, 131.4, 128.2, 128.0, 127.4, 126.1, 123.3, 119.7, 115.8, 103.8, 91.1, 63.6, 38.1 ppm. HRMS (ESI): calcd. for $[C_{18}H_{15}ClN_2O_3 + Na]^+$ 365.0663; found 365.0652.

8-Chloro-3-hydroxy-2-methoxy-3-phenyl-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3ea): Yellow solid (90 %); m.p. 203–205 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.28 (d, J = 2.0 Hz, 1 H), 7.63 (d, J = 7.6 Hz, 2 H), 7.57 (d, J = 8.4 Hz, 1 H), 7.44–7.35 (m, 4 H), 7.28 (dd, J = 8.4, J = 2.0 Hz, 1 H), 6.48 (s, 1 H), 3.73 (d, J = 16.4 Hz, 1 H), 3.63 (s, 3 H), 3.38 (d, J = 15.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.1, 140.9, 135.0, 133.6, 128.7, 128.2, 128.0, 127.9, 126.1, 123.3, 121.6, 114.2, 104.2, 91.1, 63.7, 38.2 ppm. HRMS (ESI): calcd. for $[C_{18}H_{15}ClN_2O_3 + Na]^+$ 365.0663; found 365.0646.

7-Fluoro-3-hydroxy-2-methoxy-3-phenyl-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3fa): Pale yellow solid (76 %); m.p. 198–200 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27 (dd, J = 8.8, J = 4.8 Hz, 1 H), 7.65 (d, J = 7.2 Hz, 2 H), 7.45–7.35 (m, 5 H), 7.16–7.11 (m, 1 H), 6.45 (s, 1 H), 3.77 (d, J = 16.4 Hz, 1 H), 3.64 (s, 3 H), 3.39 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 158.8 (d, J = 235.2 Hz), 152.2, 141.0, 134.5, 131.3, 131.1 (d, J = 10.3 Hz),

128.2, 128.0, 126.2, 115.6 (d, J = 9.3 Hz), 110.9 (d, J = 24.9 Hz), 105.9 (d, J = 23.9 Hz), 104.2 (d, J = 3.8 Hz), 91.2, 63.6, 38.2 ppm. ^{19}F NMR (376 MHz, [D$_6$]DMSO): δ = –119.99 ppm. HRMS (ESI): calcd. for [$C_{18}H_{15}FN_2O_3$ + Na]$^+$ 349.0959; found 349.0939.

3-Hydroxy-2,7-dimethoxy-3-phenyl-3,4-dihydropyrimido-[1,6-*a*]indol-1(2*H*)-one (3ga): White solid (66 %); m.p. 206–209 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.13 (d, J = 8.8 Hz, 1 H), 7.62 (d, J = 7.6 Hz, 2 H), 7.43–7.31 (m, 4 H), 7.06 (d, J = 2.4 Hz, 1 H), 6.88 (dd, J = 9.0, J = 2.6 Hz, 1 H), 6.35 (s, 1 H), 3.78 (s, 3 H), 3.72 (d, J = 16.4 Hz, 1 H), 3.61 (s, 3 H), 3.34 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 155.8, 152.3, 141.2, 133.1, 130.9, 129.3, 128.1, 127.9, 126.1, 115.1, 111.8, 104.2, 103.2, 91.1, 63.6, 55.3, 38.2 ppm. HRMS (ESI): calcd. for [$C_{19}H_{18}N_2O_4$ + Na]$^+$ 361.1159; found 361.1142.

3-(4-Fluorophenyl)-3-hydroxy-2-methoxy-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3ab): Yellow solid (76 %); m.p. 184–186 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.31 (d, J = 8.0 Hz, 1 H), 7.72 (dd, J = 8.2, J = 5.4 Hz, 2 H), 7.58 (d, J = 7.2 Hz, 1 H), 7.44 (s, 1 H), 7.34–7.25 (m, 4 H), 6.49 (s, 1 H), 3.81 (d, J = 16.0 Hz, 1 H), 3.66 (s, 3 H), 3.41 (d, J = 15.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.8 (d, J = 242.9 Hz), 152.3, 137.4 (d, J = 2.9 Hz), 134.8, 132.4, 129.9, 128.5 (d, J = 8.3 Hz), 123.5, 123.1, 120.3, 114.8, 114.6 (d, J = 4.8 Hz), 104.4, 90.6, 63.6, 38.1 ppm. ^{19}F NMR (376 MHz, [D$_6$]DMSO): δ = –114.50 ppm. HRMS (ESI): calcd. for [$C_{18}H_{15}FN_2O_3$ + Na]$^+$ 349.0959; found 349.0944.

3-(4-Chlorophenyl)-3-hydroxy-2-methoxy-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3ac): White solid (91 %); m.p. 197–200 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.28 (d, J = 8.0 Hz, 1 H), 7.67 (d, J = 7.6 Hz, 2 H), 7.56–7.44 (m, 4 H), 7.31–7.24 (m, 2 H), 6.46 (s, 1 H), 3.77 (d, J = 16.0 Hz, 1 H), 3.63 (s, 3 H), 3.37 (d, J = 16.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.2, 140.2, 134.7, 132.8, 132.3, 129.9, 128.2, 128.0, 123.5, 123.1, 120.3, 114.6, 104.4, 90.6, 63.6, 37.9 ppm. HRMS (ESI): calcd. for [$C_{18}H_{15}ClN_2O_3$ + Na]$^+$ 365.0663; found 365.0646.

3-Hydroxy-2-methoxy-6-methyl-3-phenyl-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3ad): White solid (88 %); m.p. 204–205 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26 (d, J = 8.0 Hz, 1 H), 7.91 (d, J = 1.6 Hz, 1 H), 7.72–7.64 (m, 2 H), 7.55–7.54 (m, 2 H), 7.31–7.22 (m, 2 H), 6.47 (s, 1 H), 3.83 (d, J = 16.4 Hz, 1 H), 3.63 (s, 3 H), 3.37 (d, J = 16.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.1, 142.3, 134.7, 132.2, 130.9, 130.8, 130.3, 129.9, 128.6, 126.7, 123.6, 123.1, 120.3, 114.6, 104.6, 90.2, 63.7, 37.6 ppm. HRMS (ESI): calcd. for [$C_{18}H_{14}Cl_2N_2O_3$ + Na]$^+$ 399.0274; found 399.0258.

3-Hydroxy-2-methoxy-3-(*p*-tolyl)-3,4-dihydropyrimido[1,6-*a*]-indol-1(2*H*)-one (3ae): White solid (87 %); m.p. 198–201 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27 (d, J = 8.0 Hz, 1 H), 7.53–7.49 (m, 3 H), 7.29–7.19 (m, 5 H), 6.42 (s, 1 H), 3.72 (d, J = 16.0 Hz, 1 H), 3.63 (s, 3 H), 3.34 (d, J = 16.0 Hz, 1 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.4, 138.3, 137.3, 134.8, 132.5, 129.9, 128.5, 126.1, 123.4, 123.0, 120.2, 114.5, 104.2, 91.0, 63.6, 38.2, 20.6 ppm. HRMS (ESI): calcd. for [$C_{19}H_{18}N_2O_3$ + Na]$^+$ 345.1210; found 345.1215.

3-(*tert*-Butyl)-3-hydroxy-2-methoxy-3,4-dihydropyrimido-[1,6-*a*]indol-1(2*H*)-one (3af): White solid (63 %); m.p. 151–153 °C. ^{1}H NMR (400 MHz,[D$_6$]DMSO): δ = 8.20 (d, J = 7.6 Hz, 1 H), 7.51 (d, J = 6.8 Hz, 1 H), 7.22–7.18 (m, 2 H), 6.43 (s, 1 H), 6.39 (s, 1 H), 3.86 (s, 3 H), 3.63 (d, J = 16.4 Hz, 1 H), 3.28 (d, J = 17.2 Hz, 1 H), 0.92 (s, 9 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 149.5, 134.6, 132.6, 129.6, 123.2, 122.7, 120.1, 114.2, 102.7, 93.6, 64.3, 40.6, 33.2, 26.0 ppm. HRMS (ESI): calcd. for [$C_{16}H_{20}N_2O_3$ + Na]$^+$ 311.1366; found 311.1344.

Methyl 2-(3-Hydroxy-2-methoxy-1-oxo-1,2,3,4-tetrahydro-pyrimido[1,6-*a*]indol-3-yl)acetate (3ag): White solid (90 %); m.p. 168–170 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.21 (d, J = 7.6 Hz, 1 H), 7.53 (d, J = 7.2 Hz, 1 H), 7.27–7.20 (m, 2 H), 7.00 (s, 1 H), 6.50 (s, 1 H), 3.83 (s, 3 H), 3.66 (d, J = 16.8 Hz, 1 H), 3.62 (s, 3 H), 3.47 (d, J = 16.4 Hz, 1 H), 3.06 (s, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 169.3, 151.3, 134.6, 132.1, 129.8, 123.4, 123.0, 120.1, 114.5, 104.5, 87.9, 64.1, 51.6, 41.1, 34.0 ppm. HRMS (ESI): calcd. for [$C_{15}H_{16}N_2O_5$ + Na]$^+$ 327.0951; found 327.0935.

3-Hydroxy-2-methoxy-3-(4-nitrophenyl)-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3ah): Yellow solid (88 %); m.p. 201–203 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.31–8.26 (m, 3 H), 7.95 (d, J = 8.8 Hz, 2 H), 7.68 (s, 1 H), 7.56 (d, J = 7.2 Hz, 1 H), 7.32–7.22 (m, 2 H), 6.48 (s, 1 H), 3.82 (d, J = 16.0 Hz, 1 H), 3.36 (s, 3 H), 3.40 (d, J = 16.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.1, 148.3, 147.3, 134.8, 132.1, 129.9, 127.8, 123.7, 123.23, 123.17, 120.3, 114.6, 104.7, 90.6, 63.7, 37.7 ppm. HRMS (ESI): calcd. for [$C_{18}H_{15}N_3O_5$ + Na]$^+$ 376.0904; found 376.0892.

3-(4-Bromophenyl)-3-hydroxy-2-methoxy-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3ai): White solid (86 %); m.p. 206–207 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26 (d, J = 8.0 Hz, 1 H), 7.64–7.58 (m, 4 H), 7.54 (d, J = 7.6 Hz, 1 H), 7.43 (s, 1 H), 7.30–7.21 (m, 2 H), 6.45 (s, 1 H), 3.75 (d, J = 16.4 Hz, 1 H), 3.63 (s, 3 H), 3.36 (d, J = 16.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.2, 140.6, 134.7, 132.3, 130.9, 129.9, 128.5, 123.5, 123.1, 121.5, 120.3, 114.6, 104.4, 90.7, 63.6, 37.9 ppm. HRMS (ESI): calcd. for [$C_{18}H_{14}BrN_2O_3$]$^-$ 385.0193; found 385.0200.

3-Hydroxy-2-methoxy-3-(4-methoxyphenyl)-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3aj): White solid (66 %); m.p. 188–189 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26 (d, J = 8.0 Hz, 1 H), 7.53 (d, J = 7.6 Hz, 3 H), 7.28–7.20 (m, 3 H), 6.95 (d, J = 8.8 Hz, 2 H), 6.42 (s, 1 H), 3.76 (s, 3 H), 3.74 (d, J = 14.4 Hz, 1 H), 3.62 (s, 3 H), 3.35 (d, J = 16.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 158.9, 152.3, 134.7, 133.1, 132.6, 129.9, 127.5, 123.4, 123.0, 120.2, 114.5, 113.2, 104.2, 90.8, 63.6, 55.1, 38.2 ppm. HRMS (ESI): calcd. for [$C_{19}H_{18}N_2O_4$ + Na]$^+$ 361.1159; found 361.1142.

2-Ethoxy-3-hydroxy-3-phenyl-3,4-dihydropyrimido[1,6-*a*]indol-1(2*H*)-one (3ha): White solid (66 %); m.p. 200–203 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.41 (d, J = 8.4 Hz, 1 H), 7.65 (d, J = 7.6 Hz, 2 H), 7.47–7.35 (m, 4 H), 7.32–7.28 (m, 1 H), 7.25–7.21 (m, 1 H), 6.32 (s, 1 H), 4.25–4.17 (m, 2 H), 3.75 (br., 1 H), 3.65 (d, J = 16.4 Hz, 1 H), 3.47 (d, J = 16.4 Hz, 1 H), 0.83 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.4, 141.1, 134.8, 132.6, 129.9, 128.1, 127.9, 126.2, 123.4, 123.0, 120.2, 114.5, 104.2, 90.8, 71.7, 37.9, 13.3 ppm. HRMS (ESI): calcd. for [$C_{19}H_{18}N_2O_3$ + Na]$^+$ 345.1210; found 345.1192.

Dehydration Reaction of Dihydropyrimido[1,6-*a*]indolone Derivatives 3aa for the Synthesis of Pyrimido[1,6-*a*]indolone 4aa: A mixture of *N*-carbamoylindole **3aa** (0.10 mmol) and anhydrous $AlCl_3$ (0.20 mmol) in MeOH (1 mL) was stirred at room temperature for 2 h. Then, the mixture was concentrated. The residue was subjected to flash column chromatography [silica gel; ethyl acetate/petroleum ether (1:10, v/v)] to give pyrimido[1,6-*a*]indolone **4aa**.

2-Methoxy-3-phenylpyrimido[1,6-*a*]indol-1(2*H*)-one (4aa): Yellow solid (77 %); a melting point could not be obtained due to the thermal instability of the compound. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.69–8.65 (m, 1 H), 7.66–7.62 (m, 3 H), 7.48–7.46 (m, 3 H), 7.40–7.36 (m, 2 H), 6.57 (s, 1 H), 6.38 (s, 1 H), 3.70 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 146.5, 139.0, 133.8, 133.7, 132.0, 130.9, 129.5, 129.1, 128.5, 124.2, 123.1, 120.1, 116.1, 99.2, 99.1, 63.9 ppm. HRMS (EI-TOF): calcd. for $C_{18}H_{14}N_2O_2$ [M]$^+$ 290.1055; found 290.1057.

CCDC 1503140 (for **3da**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Keywords: Cascade reactions · C-H functionalization · Cyclization · Nitrogen heterocycles · Rhodium · Homogeneous catalysis

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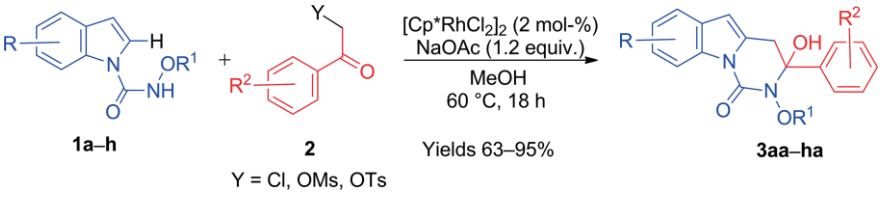

A rhodium(III)-catalyzed cascade C–H functionalization/cyclization reaction of *N*-carbamoylindoles **1** with α-halo, α-mesyloxy or α-tosyloxy ketones **2** has been developed, affording a novel synthesis of dihydropyrimido[1,6-*a*]-indolone derivatives **3**.

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