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Iridium-Catalyzed Single-Step *N*-Substituted Lactam Synthesis from Lactones and Amines

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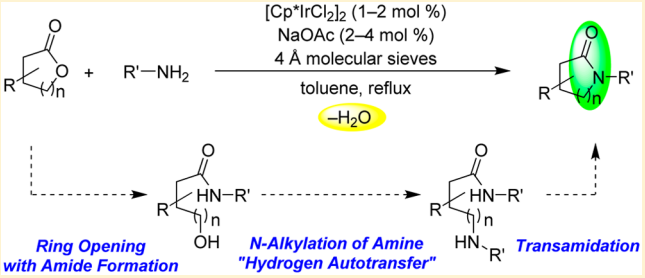
Supporting Information

ABSTRACT: Catalytic lactam synthesis was achieved directly from lactones and amines using an Ir catalyst. Three sequential transformations—aminolysis of lactone, *N*-alkylation of amine with hydroxyamide, and intramolecular transamidation of aminoamide—afforded the corresponding *N*-substituted lactams.



Lactams are one of the fundamental functional molecules in organic chemistry.[1] They serve as pharmacophores in antibiotics, antipsychotics, drug candidates, and intermediates in the synthesis of dopamine receptors.[2] Moreover, they can be used as the monomers of versatile synthetic polymers, such as poly(1-vinylpyrrolidin-2-one) derivatives.[3] Conventional synthetic methods for lactam include the intramolecular condensation of amino acid derivatives under extremely high temperature conditions and the use of activating reagents, such as Grignard reagents[4] and Brønsted acids.[5] Moreover, the intramolecular cyclization of haloamides with Brønsted bases affords lactams.[6] Among these methods, the lactamization of lactones with amines is a straightforward approach because the substrates are readily available without any prefunctionalization. However, the previous methods for this reaction suffer from harsh temperatures (220−270 °C) or high pressures[7] and require stoichiometric amounts of activating reagents[8] and multistep reactions.[9] Moreover, catalytic methods also suffer from the use of prefunctionalized substrates.[10] Herein, we report the first Ir-catalyzed *N*-substituted lactam synthesis from readily available lactones and amines. Mechanistic investigations indicated that three distinct C−N bond transformation reactions occurred sequentially.

Ir-catalyzed amination of alcohols using "hydrogen autotransfer" has been extensively explored over the past decade.[11] Our group recently reported the tandem synthesis of amides and secondary amines from linear esters and amines via hydrogen autotransfer using the [Cp*Ir] catalytic system.[12] Inspired by these results, we expected that aminoamides could be synthesized by the ring-opening reaction of lactones. The reaction of γ-butyrolactone (**1a**) with benzylamine (**2a**) using the reported Ir catalyst[12] afforded the corresponding lactam 1-benzyl-2-pyrrolidinone (**3aa**) in 39% yield instead of the aminoamide (entry 5, Table 1). Encouraged by the unexpected result, the reaction conditions were optimized for the selective lactamization with several Ru and Ir complexes, which are well-known for dehydrogenative C−N bond formation reactions (Table 1).[11h,13] A combination of $[Cp^*IrCl_2]_2$ and a base was identified as the best precatalyst with an additional amount of amine (1.5−2 equiv) to achieve good yields (entries 5−7). The use of molecular sieves as drying agents increased the efficiency of the reaction by removing H_2O byproducts (entry 8). The addition of X- or L-type ligands did not improve the yield (entries 9 and 10). Both $[Cp^*IrCl_2]_2$ and NaOAc were essential for efficient conversion (entries 11 and 12).

With the reaction conditions optimized, our method was attempted for the synthesis of diverse *N*-substituted lactams (Table 2). The reactions of **1a** with a variety of benzylamines and 3-phenylpropylamine **2h** afforded the corresponding lactams in fair-to-excellent yields (entries 1−6). Electron-deficient benzylamines resulted in slightly higher conversion than electron-rich benzylamines (entries 4 and 5). The reactions of α-branched primary amines such (*S*)-(−)-α-methylbenzylamine with **1a** did not give the corresponding lactams but only produced the corresponding hydroxyamides and/or aminoamides. The α-methyl substituent on butyrolactone did not interfere with the reaction (entry 7). The reactions of 3-isochromanone **1c** with benzylamines and aliphatic amines proceeded smoothly to afford the corresponding lactams in fair-to-excellent yields (entries 8−14). In the lactamization of **1c**, both electron-rich and electron-deficient benzylamines participated in the reaction efficiently. The catalytic system tolerated various functional groups, including ether, alkyl, chloro, and trifluoromethyl groups. Trifluoromethylated lactams **3ae** and **3ce**, potential building blocks for pharmaceutical compounds,[14,15] were synthesized efficiently (entries 5 and 12). Linear aliphatic amine **2g** was lactamized with **1c** in 71% yield (entry 14). To gain further insight into the effect of lactone ring size, we conducted the reactions of δ-

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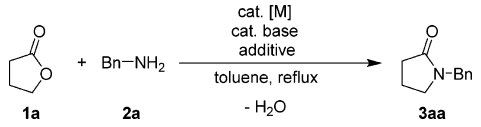
Table 1. Optimization of Reaction Conditions[a]

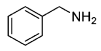
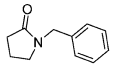
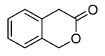
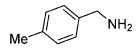
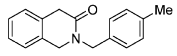
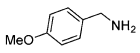
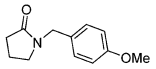
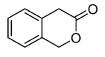
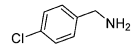
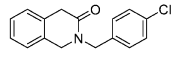
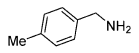
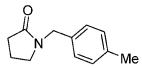
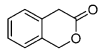
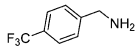
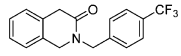
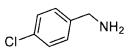
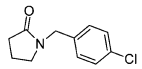
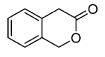
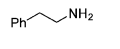
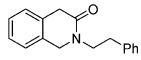
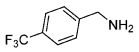
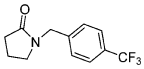
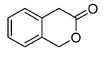
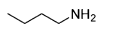
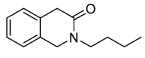
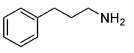
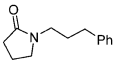
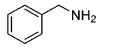
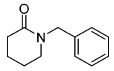
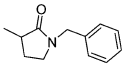


1a 2a 3aa

entry	2a/1a	[M] (mol %)	base (mol %)	additives	yield (%)[b]
1	2.0	$[RuH_2(PPh_3)_4]$ (5)	NaH (20)	**4**, CH_3CN[c]	0
2	2.0	$[Cp^*IrCl_2]_2$ (1)	$NaHCO_3$ (2)		16
3	2.0	$[Ru(p\text{-cymene})Cl_2]_2$ (5)		dppf[d]	1
4	2.0	$[Sc(OTf)_3]$ (5)			1
5	1.0	$[Cp^*IrCl_2]_2$ (1)	NaOAc (2)		39
6	1.5	$[Cp^*IrCl_2]_2$ (1)	NaOAc (2)		59
7	2.0	$[Cp^*IrCl_2]_2$ (1)	NaOAc (2)		63
8	2.0	$[Cp^*IrCl_2]_2$ (1)	NaOAc (2)	4 Å MS[e]	77
9	2.0	$[Cp^*IrCl_2]_2$ (1)	NaOAc (2)	**5**[f]	8
10	2.0	$[Cp^*IrCl_2]_2$ (1)	NaOAc (2)	**4**, CH_3CN[g]	53
11	2.0		NaOAc (2)	4 Å MS[e]	0
12	2.0	$[Cp^*IrCl_2]_2$ (1)		4 Å MS[e]	26

[a]Standard reaction conditions: **1a** (0.25 mmol, 1.0 equiv), **2a** (0.5 mmol, 2.0 equiv), [M] (1 mol %), toluene (0.6 mL), reflux, 36 h. [b]Determined by GC using dodecane as the internal standard. [c]1,3-diisopropylimidazoluim bromide (**4**, 5 mol %), CH_3CN (5 mol %). [d]Dppf = 1,1′-bis(diphenylphosphino)ferrocene (10 mol %) [e]4 Å MS = 4 Å molecular sieves (~20 mg). [f]Tri(*p*-tolyl)phosphine (**5**, 2 mol %). [g]Both at **4** and CH_3CN at 2 mol %.

Table 2. Direct Lactam Synthesis from Lactones and Amines[a]

entry	lactone	amine	product	yield (%)[b]	entry	lactone	amine	product	yield (%)[b]
1	 **1a**	 **2a**	 **3aa**	65	10	 **1c**	 **2c**	 **3cc**	95
2[c]	 **1a**	 **2b**	 **3ab**	62	11	 **1c**	 **2d**	 **3cd**	>97
3[c]	 **1a**	 **2c**	 **3ac**	65	12	 **1c**	 **2e**	 **3ce**	70
4[c]	 **1a**	 **2d**	 **3ad**	80	13	 **1c**	 **2f**	 **3cf**	53
5[c]	 **1a**	 **2e**	 **3ae**	86	14[c]	 **1c**	 **2g**	 **3cg**	71
6[c]	 **1a**	 **2h**	 **3ah**	>97	15	 **1d**	 **2a**	 **3da**	56
7[c]	 **1b**	 **2a**	 **3ba**	72	16[c]	**1d**	**2d**	**3dd**	48
8	**1c**	**2a**	**3ca**	92	17[c]	**1d**	**2h**	**3dh**	49
9	**1c**	**2b**	**3cb**	85	18[c]	**1e**	**2a**	**6ea**	88

[a]Reaction conditions: lactone (0.5 mmol, 1.0 equiv), amine (1.0 mmol, 2.0 equiv), $[Cp^*IrCl_2]_2$ (1 mol %), NaOAc (2 mol %), 4 Å molecular sieves, toluene (1.2 mL), reflux, 36 h in a 5 mL Schlenk tube. [b]Isolated yield. [c]$[Cp^*IrCl_2]_2$ (2 mol %) and NaOAc (4 mol %) were used.

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valerolactone (**1d**) and ε-caprolactone (**1e**) with **2a**. The reaction of six-membered lactone **1d** resulted in a reduced yield (56%) with dibenzylamine as the byproduct (entry 15). Inefficient reactions were caused by the homocoupling reaction of amines, producing secondary amines.[16] The reaction of ε-caprolactone (**1e**) afforded only the corresponding aminoamide **6ea** in 88% yield, indicating that an aminoamide may be the intermediate before intramolecular transamidation to furnish the corresponding lactam (entry 18).

To understand the reaction mechanism, we monitored the reactions of **1a** with **2a** by ^{1}H NMR spectroscopy (Figure 1).

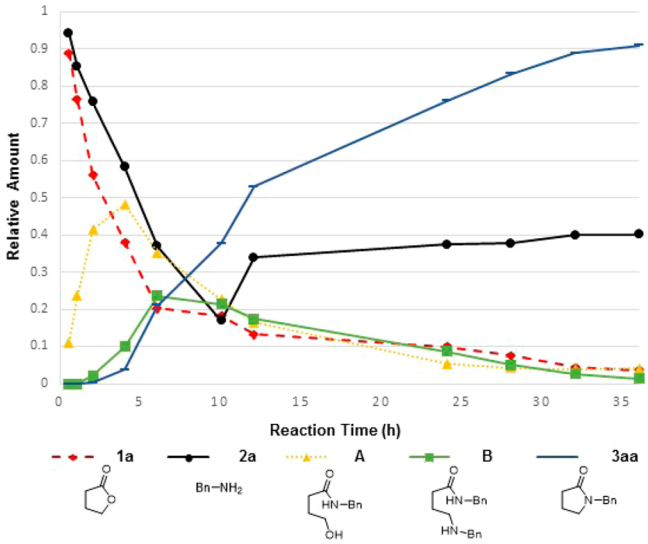
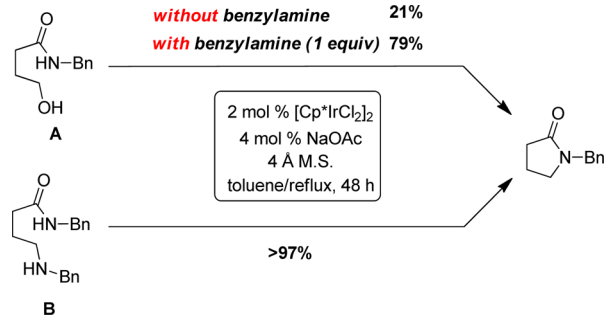


Figure 1. Reaction profiles monitored by ^{1}H NMR spectroscopy. Relative amount is the ratio of the observed integration value to its original 1 equiv value. Lactone (**1a**, 0.25 mmol, 1.0 equiv), amine (**2a**, 2.0 equiv), $[Cp^*IrCl_2]_2$ (1 mol %), NaOAc (2 mol %), toluene-d_8 (0.6 mL), reflux in a screw-capped NMR tube.

At the initial stage, hydroxyamide **A** was generated along with the consumption of **1a** and **2a**. Subsequently, the amounts of aminoamide **B** and lactam **3aa** increased with the decrease in the amounts of **1a**, **2a**, and **A**. After ∼5 h, both the amounts of **A** and **B** gradually decreased, whereas the amount of **3aa** continuously increased. The concentration of **2a** started to increase after ∼10 h and finally remained mostly constant at ∼40% of the initial concentration.

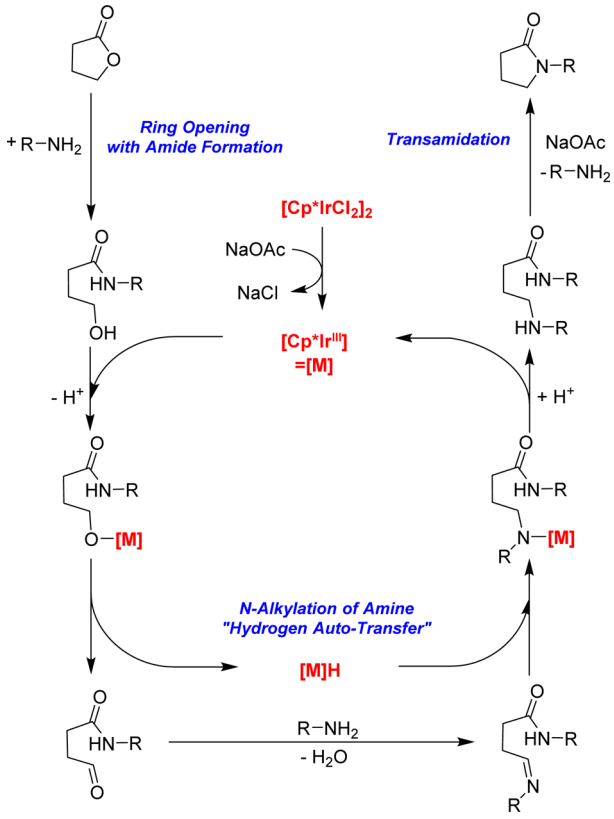
To confirm the intermediacy of hydroxyamide and aminoamide in the mechanism of the reaction, independent reactions with **A** and **B** were performed under catalytic conditions. Hydroxyamide **A** may be formed by the nucleophilic addition of amine to the carbonyl carbon of lactone and the ring-opening process. When **A** alone was subjected to these reaction conditions, a small amount (21%) of **3aa** was obtained (Scheme 1). This result indicates that the direct intramolecular cyclization of hydroxyamides to lactams via the *N*-alkylation of amides is unlikely in our case. In the catalytic *N*-alkylation of amides with alcohols, only primary amides were generally applicable even under harsh reaction conditions.[17] Considering that an amine is needed for the *N*-alkylation of amine with **A** to afford the second intermediate candidate **B**, 1 equiv of **2a** was added to the reaction of **A**. The reaction smoothly afforded **3aa** in 79% yield. Aminoamide **B** was efficiently transformed to **3aa** in quantitative yield under the reaction conditions. The intramolecular transamidation reaction even occurred quantitatively with only a catalytic amount of NaOAc (4 mol %) and 4 Å molecular sieves without using $[Cp^*IrCl_2]_2$. These results, including the reaction profiles, indicate that the last step in the reaction pathway is the intramolecular transamidation of aminoamide.

Scheme 1. Catalytic Reactions of Observed Intermediates in the Presence or Absence of Amines



On the basis of these results, a mechanism that involves three sequential chemical transformations is proposed (Scheme 2).

Scheme 2. Proposed Catalytic Cycle



At the initial stage, the carbonyl group of lactone is aminolyzed by an amine, generating the corresponding hydroxyamide. Then, the Ir-catalyzed *N*-alkylation of an amine with the hydroxyamide via "hydrogen autotransfer" affords the corresponding aminoamide.[11g,18] Finally, the aminoamide undergoes intramolecular transamidation to afford the corresponding lactam. Ir catalysis is necessary for *N*-alkylation of an amine with the hydroxyamide, whereas the aminolysis of lactone with amine and transamidation of aminoamide occurred without the Ir complex.

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In conclusion, a catalytic lactam synthesis was developed from lactones and amines using the readily available Ir complex $[Cp^*IrCl_2]_2$ and sodium acetate. The mechanistic studies revealed an interesting domino reaction involving the following sequential reactions: aminolysis of lactone, *N*-alkylation of amine with hydroxyamide, and intramolecular transamidation of aminoamide.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, all reactions were carried out using standard Schlenk techniques or in an Ar-filled glovebox. NMR spectra were recorded in $CDCl_3$ or toluene-d_8, and residual solvent signals were used as the reference. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Multiplicity is indicated by one or more of the following: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sext), and multiplet (m). High resolution mass spectrometry (HRMS) was performed using the fast atom bombardment (FAB) ionization mode, electrospray ionization (ESI) Q-TOF mode, and electron ionization (EI) mode. GC analysis was carried out using a GC system equipped with an HP-5 column and FID detector. NHC precursor (1,3-diisopropylimidazolium bromide),[19] *N*-benzyl-4-hydroxybutanamide (**A**),[7a] and *N*-benzyl-4-(benzylamino)butanamide (**B**)[7a] were prepared based on literature procedures. Other chemicals were purchased from commercial suppliers and used as received without further purification.

General Procedure for Lactam Synthesis from Lactones and Amines. Inside an Ar-filled glovebox, 1 mol % of $[Cp^*IrCl_2]_2$ (3.98 mg, 0.005 mmol), 2 mol % NaOAc (0.82 mg, 0.010 mmol), 4 Å molecular sieves (ca. 35 mg), and toluene (1.2 mL) were added to an oven-dried 5 mL Schlenk tube equipped with a magnetic spin bar and septum. After the tube with the catalytic system was removed from the box, 0.50 mmol lactone and 1.00 mmol amine were added to the tube under an Ar flow using the Schlenk technique. Then, the reaction mixture was stirred at 110 °C for 36 h before cooling to room temperature. All of the volatiles were removed in vacuo, and the resulting residue was purified by flash column chromatography (hexane/EtOAc = 4:1 v/v or DCM/MeOH = 30:1 v/v) to afford the corresponding lactam.

*1-(Phenylmethyl)-2-pyrrolidinone (**3aa**).* Yellow liquid (57 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29−7.15 (m, 5H), 4.38 (s, 2H), 3.20 (t, J = 7.5 Hz, 2H), 2.39 (t, J = 8.3 Hz, 2H), 1.92 (quin, J = 7.9 Hz, 2H). The spectral data were consistent with those reported in the literature.[20]

*1-[(4-Methoxyphenyl)methyl]-2-pyrrolidinone (**3ab**).* Brown liquid (64 mg, 62%). ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.18 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.39 (s, 2H), 3.81 (s, 2H), 3.25 (t, J = 7.1 Hz, 2H), 2.43(t, J = 8.1 Hz, 2H), 1.98 (quin, J = 7.7 Hz, 2H). The spectral data were consistent with those reported in the literature.[21]

*1-[(4-Methylphenyl)methyl]-2-pyrrolidinone (**3ac**).* Brown liquid (62 mg, 65%). IR (neat): 1679, 1514, 1461, 1423, 1285, 1261, 806, 754, 662 cm^{-1}. ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.14 (s, 4H), 4.42 (s, 2H), 3.25 (t, J = 7.1 Hz, 2H), 2.46 (t, J = 8.1 Hz, 2H), 2.34 (s, 3H), 1.98 (quin, J = 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ174.8, 137.2, 133.5, 129.3, 128.1, 46.5, 46.2, 30.9, 21.0, 17.6. HRMS−EI (m/z): $[M]^+$ calcd for $C_{12}H_{15}NO$, 189.1154; found: 189.1153.

*1-[(4-Chlorophenyl)methyl]-2-pyrrolidinone (**3ad**).* Brown liquid (84 mg, 80%). ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.31 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 4.43 (s, 2H), 3.26 (t, J = 7.2 Hz, 2H), 2.45 (t, J = 8.3 Hz, 2H), 2.01 (quin, J = 7.6 Hz, 2H). The spectral data were consistent with those reported in the literature.[22]

*1-[(4-Trifluoromethylphenyl)methyl]-2-pyrrolidinone (**3ae**).* Yellow liquid (105 mg, 86%). IR (neat): 1683, 1417, 1323, 1291, 1161, 1110, 1065, 1018, 819 cm^{-1}. ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.60 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 4.51 (s, 2H), 3.29 (t, J = 7.3 Hz, 2H), 2.47 (t, J = 8.3 Hz, 2H), 2.04 (quin, J = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.7, 140.5, 129.2 (q, J = 32.0 Hz), 127.8, 125.1 (q, J = 3.8 Hz), 124.5 (q, J = 271.6 Hz), 46.3, 45.6, 30.3, 17.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.67. HRMS−ESI (m/z): $[M + Na]^+$ calcd for $C_{12}H_{12}F_3NNaO$, 266.0763; found: 266.0764.

*1-(3-Phenylpropyl)-2-pyrrolidinone (**3ah**).* Yellow liquid (101 mg, >97%). ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.31−7.27 (m, 2H), 7.22−7.17 (m, 3H), 3.35 (t, J = 7.8 Hz, 4H), 2.64 (t, J = 7.8 Hz, 2H), 2.37 (t, J = 8.3 Hz, 2H), 1.98 (quin, J = 7.3 Hz, 2H), 1.86 (quin, J = 7.7 Hz, 2H). The spectral data were consistent with those reported in the literature.[23]

*3-Methyl-1-(phenylmethyl)-2-pyrrolidinone (**3ba**).* Brown liquid (68 mg, 72%). ^{1}H NMR (499 MHz, $CDCl_3$) 7.36−7.23 (m, 5H), 4.50−4.42 (m, 2H), 3.21−3.13 (m, 2H), 2.52 (sext, J = 7.8 Hz, 1 H), 2.26−2.16 (m, 1H), 1.65−1.55 (m, 1H), 1.25 (d, J = 7.3 Hz, 3H). HRMS−EI (m/z): $[M]^+$ calcd for $C_{12}H_{15}NO$, 189.1154; found, 189.1153. The spectral data were consistent with those reported in the literature.[24]

*1,4-Dihydro-2-(phenylmethyl)-3(2H)-isoquinolinone (**3ca**).* Brown liquid (109 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.09 (m, 9H), 4.79 (s, 2H), 4.41 (s, 2H), 3.74 (s, 2H). The spectral data were consistent with those reported in the literature.[25]

*1,4-Dihydro-2-(4-methoxyphenylmethyl)-3(2H)-isoquinolinone (**3cb**).* Yellow liquid (114 mg, 85%). IR (neat): 1711, 1667, 1611, 1512, 1460, 1334, 1285, 1246, 1176, 1032, 820, 741 cm^{-1}. ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.32 (m, 5H), 7.12 (d, J = 7.8 Hz, 1H), 6.90 (d, J = 8.3 Hz, 2H), 4.73 (s, 2H), 4.40 (s, 2H), 3.82 (s, 3H), 3.72 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 159.1, 132.0, 131.1, 129.4, 128.6, 127.5, 127.2, 126.6, 125.1, 114.1, 55.3, 50.0, 49.4, 37.3. HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{17}H_{18}NO_2$, 268.1338; found, 268.1338.

*1,4-Dihydro-2-(4-methylphenylmethyl)-3(2H)-isoquinolinone (**3cc**).* Yellow liquid (119 mg, 95%). IR (neat): 1711, 1669, 1430, 1380, 1349, 1309, 1284, 1248, 1047, 741, 697 cm^{-1}. ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.28−7.08 (m, 8H), 4.73 (s, 2H), 4.38 (s, 2H), 3.71 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 137.2, 133.5, 132.1, 131.2, 129.3, 128.0, 127.5, 127.2, 126.5, 125.1, 50.1, 49.7, 37.3, 21.1. HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{17}H_{18}NO$, 252.1388; found, 252.1386.

*1,4-Dihydro-2-(4-chlorophenylmethyl)-3(2H)-isoquinolinone (**3cd**).* Yellow liquid (135 mg, >97%). IR (neat): 1639, 1491, 1408, 1348, 1284, 1090, 1048, 1015, 881, 740, 698 cm^{-1}. ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.32−7.20 (m, 7H), 7.10 (d, 1H), 4.74 (s, 2H), 4.40 (s, 2H), 3.72 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 135.2, 133.4, 132.0, 131.0, 129.3, 128.9, 127.6, 127.3, 126.6, 125.1, 50.2, 49.3, 37.3. HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{16}H_{15}ClNO$, 272.0842; found, 272.0848.

*1,4-Dihydro-2-(4-trifluoromethylphenylmethyl)-3(2H)-isoquinolinone (**3ce**).* Dark yellow liquid (107 mg, 70%). IR (neat): 1670, 1326, 1286, 1162, 1112, 1067, 1048, 745 cm^{-1}. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 2H), 7.53(t, J = 7.8 Hz, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.25−7.18 (m, 2H), 7.10 (d, J = 7.3 Hz, 1H), 4.82 (s, 2H) 4.41 (s, 2H), 3.73(s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3, 140.7, 131.9, 130.8, 128.1, 127.7, 127.3, 126.7, 125.7, 125.7, 125.6, 125.1, 50.5, 49.7, 37.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.58. HRMS−CI (m/z): $[M + H]^+$ calcd for $C_{17}H_{15}F_3NO$, 306.1106; found, 306.1109.

*1,4-Dihydro-2-(2-phenylethyl)-3(2H)-isoquinolinone (**3cf**).* Orange liquid (53 mg, 53%). IR (neat): 1712, 1664, 1455, 1390, 1352, 1287, 1269, 1146, 1048, 751, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32−7.17 (m, 8H), 7.07 (d, J = 7.0 Hz, 1H), 4.32 (s, 2H) 3.78 (t, J = 7.4 Hz, 2H), 3.62 (s, 2H), 2.95 (t, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 139.0, 132.4, 131.5, 128.8, 128.5, 127.5, 127.1, 126.4, 126.4, 125.0, 51.8, 49.1, 37.7, 33.9. HRMS−EI (m/z): $[M]^+$ calcd for $C_{17}H_{17}NO$, 251.1310; found, 251.1310.

*1,4-Dihydro-2-butyl-3(2H)-isoquinolinone (**3cg**).* Brown liquid (72 mg, 71%). IR (neat): 1711, 1665, 1602, 1353, 1247, 1223, 740, 685 cm^{-1}. ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.29−7.15 (m, 4H), 4.46 (s, 2H), 3.61 (s, 2H), 3.52 (t, J = 7.3 Hz, 2H), 1.58 (quin, J = 7.3 Hz, 2H), 1.35 (sext, J = 7.3 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 132.6, 131.6, 127.5, 127.2, 126.5, 125.0, 50.9, 46.7, 37.6, 29.5, 20.1, 13.9. HRMS−EI (m/z): $[M]^+$ calcd for $C_{13}H_{17}NO$, 203.1310; found, 203.1311.

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*1-(Phenylmethyl)-2-piperidinone (**3da**).* Orange liquid (53 mg, 56%). ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.33−7.23 (m, 5H), 4.55 (s, 2H), 3.18 (t, J = 5.9 Hz, 2H), 2.46 (t, J = 6.4 Hz 2H), 1.77(m, 4H). The spectral data were consistent with those reported in the literature.[26]

*1-[(4-Chlorophenyl)methyl]-2-piperidinone (**3dd**).* Brown liquid (54 mg, 48%). IR (neat): 1630, 1492, 1465, 1447, 1409, 1284, 1252, 1175, 1089, 1015, 829, 800, 655 cm^{-1}. ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.29 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 4.59 (s, 2H), 3.19 (t, J = 5.4 Hz, 2H), 2.45 (t, J = 6.1 Hz, 2H), 1.77 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.8, 135.7, 129.6, 128.9, 128.1, 49.3, 47.2, 32.2, 23.0, 21.2. HRMS−FAB (m/z): [M + H]$^+$ calcd for $C_{12}H_{15}ClNO$, 224.0842; found, 224.0843.

*1-[3-Phenylpropyl]-2-piperidinone (**3dh**).* Yellow liquid (54 mg, 49%). IR (neat): 2942, 1635, 1494, 1451, 1353, 1171, 731, 699 cm^{-1}. ^{1}H NMR (499 MHz, $CDCl_3$): δ 7.31−7.26 (m, 2H), 7.23−7.17 (m, 3H), 3.43 (t, J = 7.3 Hz, 2H), 3.24 (t, J = 5.9 Hz, 2H), 2.64 (t, J = 7.8 Hz, 2H), 2.36 (t, J = 5.8 Hz, 2H), 1.89 (q, J = 7.8 Hz, 2H), 1.76 (q, J = 3.0 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 141.6, 128.2, 128.2, 125.7, 47.7, 46.8, 33.1, 32.2, 28.4, 23.1, 21.2. HRMS−EI (m/z): [M]$^+$ calcd for $C_{14}H_{19}NO$, 217.1467; found, 217.1469

*N-(Phenylmethyl)-6-[(phenylmethyl)amino]-hexanamide (**6ea**).* Yellowish solid (137 mg, 88%). IR (neat): 1632, 1548, 1452, 727, 693 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.21 (m, 10H), 6.05 (br s, amide proton, 1H), 4.41 (d, J = 5.7 Hz, 2H), 3.79 (s, 2H), 3.22 (br s, amine proton, 1H), 2.64 (t, J = 7.2 Hz, 2H), 2.20 (s, J = 7.5 Hz, 2H), 1.66 (quin, J = 7.5 Hz, 2H), 1.57 (quin, J = 7.2 Hz, 2H), 1.36 (quin, J = 7.9 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 138.8, 138.4, 128.6, 128.4, 128.4, 127.8, 127.4, 127.2, 53.5, 48.6, 43.5, 36.4, 28.9, 26.7, 25.3. HRMS−EI (m/z): [M]$^+$ calcd for $C_{20}H_{26}N_2O$, 310.2045; found, 310.2043.

■ ASSOCIATED CONTENT

Supporting Information

NMR and IR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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