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Graphical Abstract

Nickel (II)-Catalyzed Efficient Aminocarbonylation of Unreactive Alkanes with Formanilides—Exploiting the Deformylation Behavior of Imides

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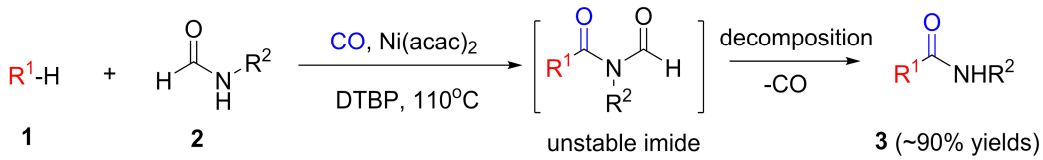

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ABSTRACT

Challenging functionalization of C(sp^3)-H has recently attracted much attention of organic chemists. In this paper, we developed a $Ni(acac)_2$-catalyzed activation of unreactive alkanes with formanilides in the presence of carbon monoxide to furnish moderate to excellent yields of amides. This is the first example of aminocarbonylation of inert alkanes using nickel-based catalyst, and formanilides is disclosed to be an interesting amine source owing to the peculiar deformylation nature of imide intermediates.

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1. Introduction

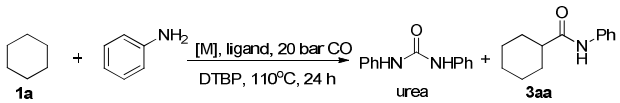
A tremendous growth in transition-metal-catalyzed C-H activation has been witnessed over recent decades.[1] Functionalization of C-H bonds represents a powerful, valuable, straightforward strategy for the construction of complex organic frameworks relative to pharmaceuticals and natural products, etc.[2] In comparison with the well-developed C(sp^2)-H activation, synthetically useful C(sp^3)-H activation started rather late because of the inert nature of alkanes and the selectivity issue in the reaction.[3] Group-assisting methodology has been exploited to improve the reactivity and selectivity of alkanes in order to achieve the controllable functionalization.[4] In spite of the most recent progress in straight-functionalization of directing-group-free alkanes, C(sp^3)-H activation has still been a challenging issue pursued by synthetic chemists.[5] On the other hand, the first-row transition metals have acted as positive alternatives to the second- and third-row metals in many organic reactions. In the case of VIII elements, different valence of Fe, Co, Ni, have presented comparable performance in some reactions[6] that catalyzed by Ru, Rh, Pd, Ir, and Pt.[7] And lately, nickel-based catalyst has been reported for the activation of some inert sp^3 carbon-hydrogen bonds.[8]

Promoted by those pioneering progress in sp^3 C-H activation, we have developed a Ni-catalyzed carbonylation of unreactive alkanes with formanilides in carbon monoxide to acquire high yields of amide products. Herein, we wish to describe the results of this study.

2. Results and discussion

We initiated the activation reaction with cyclohexane (**1a**, also as the solvent) and aniline as the model substrates for catalyst-screening (Table 1). Most reactions gave N, N′-diphenylurea as the main product, wherein, Cu-catalytic procedures just leaded to inseparable mixtures (Table 1, Entries 1-15). To our pleasure, $Co(acac)_2$ and $Ni(acac)_2$ also exhibited certain activation on the transformation even without assistance of auxiliary ligands (Table 1, Entries 11-15). Replacing aniline with its hydrochloride, urea formation was partly controlled, but the yield of **3aa** was still unsatisfactory (Table 1, Entry 16). Without the catalyst, the activation of cyclohexane didn't take place but urea was generated by the interaction between aniline and CO in the presence of DTBP (Table 1, Entry 17).

Table 1. The initial exploration into activation of cyclohexane with aniline for catalyst-screening[a]



Entry	Metal	Ligand	**3aa** Yield(%)[b]
1	$CoCl_2$	1,10-phen	trace
2	$CoCl_2$	PPh_3	trace
3	$NiCl_2$	1,10-phen	Trace
4	$NiCl_2$	PPh_3	Trace
5	$Co(OAc)_2$	1,10-phen	Trace

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6	CuCl	1,10-phen	Trace
7	CuI	1,10-phen	Trace
8	$Cu(OAc)_2$	1,10-phen	Trace
9	$FeCl_3$	1,10-phen	0
10	$Fe(acac)_2$	1,10-phen	13
11	$Co(acac)_2$	1,10-phen	31
12	$Co(acac)_2$	PPh_3	34
13	$Ni(acac)_2$	1,10-phen	39
14	$Ni(acac)_2$	PPh_3	40
15	$Ni(acac)_2$	–	42
16[c]	$Ni(acac)_2$	–	47
17	–	–	0

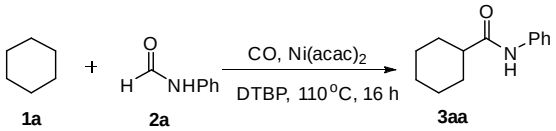
acac= acetylacetonate. DTBP= di-*tert*-butylperoxide. 1,10- phen= 1,10-phenanthroline.

[a] Reaction conditions unless otherwise stated: **1a** (20 mL), **2a** (10 mmol), metal (10% mol), ligand (20% mol), DTBP (12 mmol), CO (20 bar), time 24 h.

[b] Isolated yields, Urea was obtained as the main product.

[c] Aniline hydrochloride was utilized instead of **2a**.

Table 2. Condition optimization for the Ni-catalyzed reaction of **1a** and **2a** in CO[a]



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

Entry	Catalyst loading	Auxiliary solvent	Pressure	**3aa** Yield(%)[b]
1	10 mol%	–	20 bar N_2	trace
2	10 mol%	–	20 bar CO	90
3	10 mol%	–	10 bar CO	85
4	5 mol%	–	20 bar CO	80
5	10 mol%	benzene[c]	20 bar CO	87
6	10 mol%	acetonitrile[c]	20 bar CO	44
7	–	–	20 bar CO	0
8[d]	–	$ClCH_2CH_2Cl$[c]	60 bar CO	<10%
9	10 mol%	$ClCH_2CH_2Cl$[c]	20 bar CO	88

[a] Reaction conditions (unless otherwise stated): **1a** (20 mL), **2a** (10 mmol), CO, catalyst (10 mol%,), DTBP (12 mmol), 110 °C, 16 h.

[b] Isolated yield.

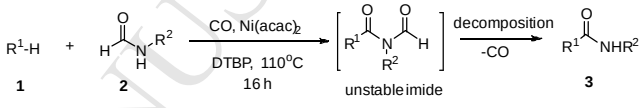
[c] solvent (20 mL), **1a** (10 mmol)

[d] The reaction was conducted under the conditions according to the literature.[9]

Hindered by the serious urea formation between aniline and CO, we had to turn to other amine sources to improve the selectivity. Formanilide, which can be looked as the integrity of CO and aniline, seemed a desirable substrate due to its weakened nucleophilicity. Hence a new round of probe into the reaction of formanilide (**2a**) was started using $Ni(acac)_2$ as the catalyst.

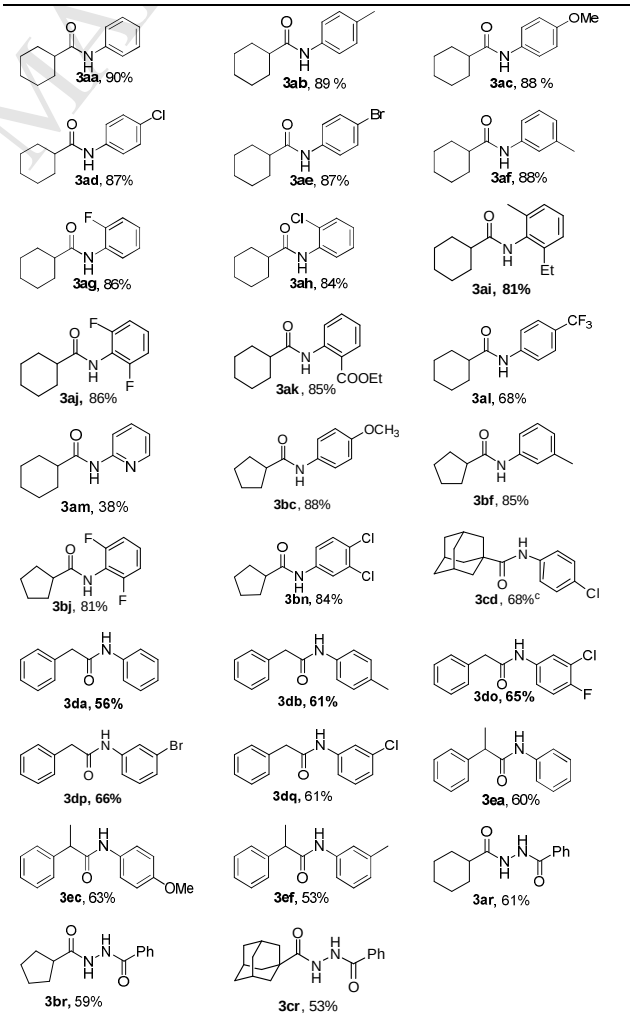
The first reaction between **1a** and **2a** was conducted under 20 bar nitrogen pressure at 110 °C only giving trace of **3aa** without urea generation (Table 2, Entry 1). Surprisingly, an excellent yield of **3aa** (90%) was obtained while the reaction underwent under 20 bar of carbon monoxide (Table 2, Entry 2). Noteworthy, the requirement of carbon monoxide disclosed clearly that a deformylation behavior should be involved in the process. Then, condition-optimization was performed concerning mainly the pressure and the charging amounts of catalyst but leading to no better results (Table 2, Entries 3 and 4). Benzene was checked as an auxiliary solvent giving a comparably satisfactory result (Table 2, Entry 5), from which it can also be seen that sp^2 C-H bond be steady enough to the catalytic conditions. Acetonitrile was an unfavorable solvent for this conversion (Table 2, Entry 6). To confirm the effect in this transformation, control experiments were carried out as shown in Entries 7-9 (Table 2). Without the catalyst and additional solvents, DTBP was also able to generate a little quantity of urea in no more than 10% yield but with no **3aa** observed (Table 2, Entry 7). Dichloroethane, which was reported by Lei and coworkers as a facilitating solvent for metal-free carbonylation of cyclohexane,[9] was confirmed to be some helpful to the reaction in the absence of metal catalyst, but the yield of **3aa** was very low and no imide was obtained (Table 2, Entry 8). Compared with cyclohexane and benzene, dichloroethane in the presence of $Ni(acac)_2$ cannot exerted distinct facilitation on the transformation under such conditions (Table 2, Entry 9).

Table 3. Ni-catalyzed carbonylation of alkanes with formanilides[a]



1 **2** **3**

3, yield[b]



[a] Reaction conditions (unless specially illustrated): **1** (20 mL), **2** (10 mmol), CO, $Ni(acac)_2$ (10 mol%), DTBP (12 mmol), 110 °C, 16 h.

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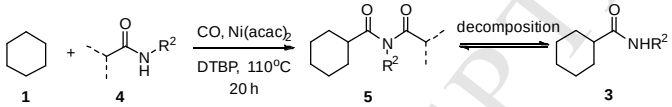
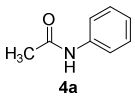
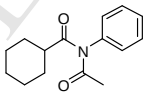
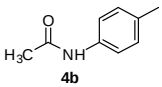
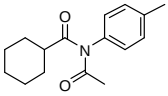
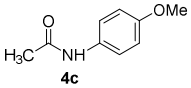
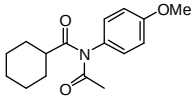
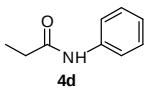
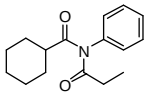
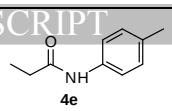
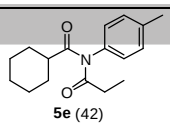
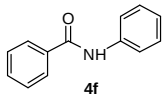
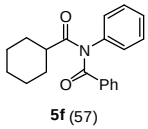
[b] Isolated yield.
[c] adamantane (**3c**, 10 mmol), dichloroethane solvent (20 mL).

With the optimized conditions, a range of formanilides were inspected, and all worked well with cyclohexane to give the corresponding amides with good yields (Table 3, **3aa**– **3al**). N-pyridylformamide was also tolerated in the reaction to furnish amide **3am**, though the yield was some lowered (Table 3, **3am**). Under the same conditions, Cylcopentane activations with several formanilides in the presence of carbon monoxide provided comparably high yields of carbonylation products (Table 3, **3bc**– **3bn**). It can be seen that substituents of formanilides (**2**) with different electronic effect were well tolerated with this transformation. When adamantane (**2c**) was tried using dichloroethane as the sole solvent, **3cd** were obtained in a lowered yield (68%). The reaction can be also applicable to toluene and ethylbenzene expressing an obvious benzylic selectivity, though the yields were just moderate (Table 3, **3da**–**3ef**). Utilizing *N'*-formylbenzohydrazide in the place of **2**, the reactions under the optimal conditions gave the corresponding diacylhydrazines in moderate yields (Table 3, **3ar**– **3cr**).

Then, attention of us was shifted to acetanilide substrates, since from which the formation of imides was expectable under similar conditions to ours except for using a Cu catalyst according to Wu's work.[5d] When **4a** was reacted with cyclohexane in CO for 20 h, both amide (**3aa**) and imide (**5a**) were obtained by flash chromatography (Table 4, Entry 1). Several other amides were then reacted with **1a** to afford imides and amides with different distribution, among of which benzanilide reaction gave the corresponding imide **5e** besides trace of **3aa** (Table 4, Entries 2-6). Different extent of decomposition of these imides was also observed even after several hours of storage at room temperature in line with the literature.[5d, 10]

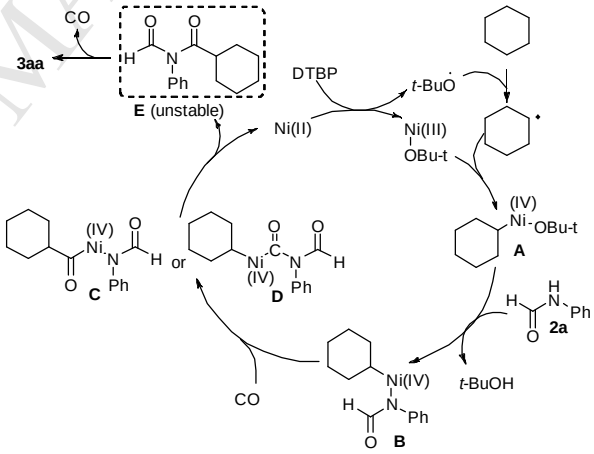
Table 4. Ni-catalyzed aminocarbonylation of alkanes with other amides[a]



Entry	**4**	**3** (yield%)[b]	**5** (yield%)[b]
1	 **4a**	**3aa** (50)	 **5a** (25)
2	 **4b**	**3ab**(48)	 **5b** (37)
3	 **4c**	**3ac**(45)	 **5c** (40)
4	 **4d**	**3aa**(32)	 **5d** (37)
5	 **4e**	**3ab**(28)	 **5e** (42)
6	 **4f**	**3aa**(trace)	 **5f** (57)

[a] Reaction conditions: **1a** (20 mL), **4** (10 mmol), CO, catalyst (10 mol%,), DTBP (12 mmol), 110 °C, 20 h.
[b] Isolated yield.

Based on the above experimental results and previous reports,[5d, 10] a plausible mechanism of this carbonylation was proposed as depicted in Scheme 1. Initially, homolytic cleavage of DTBP with the assistance of Ni(II) catalyst generates Ni(III) species and the *tert*-butyloxy radical, which subsequently abstracts hydrogen from **1a** to generate cyclohexyl radical and tert-butyl alcohol. Oxidative addition of Ni(III) species with cyclohexyl radical leads to Nickel (IV) species (**A**). The reaction between complex **A** with **2a** gives the intermediate **B** with releasing *tert*-butyl alcohol through an H-transfer process. Following CO insertion allows the generation of **C** or **D** species, which transforms to unstable **E** through reductive elimination and regenerates the Ni(II) catalyst. Finally, Thermal decomposition of **E** completes immediately under the reaction conditions leading to the formation of **3aa**.



Scheme 1. Proposed reaction mechanism

3. Conclusion

In conclusion, activation of alkanes bearing no assisting group were realized by using $Ni(acac)_2$ catalyst without auxiliary ligands. The inexpensive nickel-based catalyst and the high yields of the reaction enable this protocol synthetically useful for straight functionalization of alkanes to provide amides. Further efforts will be made to expand the applicable scope of nickel-based catalysts in the direction of C(sp^3)-H activation.

4. Experimental section

4.1. General Information

Commercially available materials were used as received. Carbon monoxide (99.99%) was used as the carbon source. Solvents were not further purified unless stated. Melting points

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were measured with an Electrothermal-9200 melting points apparatus. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ = 0.00 ppm). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400 MHz) (101 MHz) spectrometer. Thin-layer chromatography (TLC) was carried out on WFH-203 F254 silica gel plate. High-resolution mass spectra (HRMS) were reported on a Bruker APEX IV 7T FT-ICR instrument. YT-r50 autoclave was used as the reactor (Nanjing Yantu Experimental Instrument co. LTD, China).

4.2. Experimental procedures

*(1) Typical procedure for the reaction of alkanes (**1**) and formanilides (**2**) without auxiliary solvent*

To a 50 mL of autoclave, was added cyclohexane (**1a**, 20 mL), formanilide (**2a**, 10 mmol), Ni(acac)$_2$ (1 mmol, 0.26 g) and DTBP (12 mmol, 1.76 g). After replaced with argon twice, the autoclave was rinsed three times with CO and then heated to 110 °C under 20 bar CO for 16 h. The autoclave is then cooled to room temperature and carefully relieved of pressure. The solid catalyst was filtered off. The excess alkane was removed under reduced pressure and the residue was separated by silica gel column chromatography (Petroleum ether/ ethyl acetate) to give the product **3aa**.

*(2) Special procedure for the reaction of alkanes (**1c**) and formanilide (**2d**) using benzene as the solvent*

Following the above described procedure, adamantine (**1c**, 10 mmol) was used in the place of **1a** with dichloroethane (20 mL) as the solvent to perform the reaction to furnish **3cd** product.

*(3) Typical procedure for the reaction of alkanes (**1a**) with amides (**4a**)*

According to the above procedure, acetanilide (**4a**, 10 mmol) was used in the place of **2a** to react with **1a** (20 mL) in the atmosphere of 20 bar CO for 20 h. After removing the excess **1a**, product **3aa** and **5a** were obtained by flash chromatography (Petroleum ether/ ethyl acetate).

4.3. Product characterization

*N-Phenyl-cyclohexanecarboxamide **3aa***

White solid, 90% yield, mp 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J*= 7.8 Hz, 2H), 7.24 (t, *J*= 7.9 Hz, 2H), 7.14 (br, 1H NH), 7.02 (t, *J*= 7.4 Hz, 1H), 2.16 (tt, *J*= 11.8, 3.4 Hz, 1H), 1.89 (d, *J*= 13.2 Hz, 2H), 1.77 (d, *J*= 12.2 Hz, 2H), 1.66– 1.41 (m, 4H), 1.24– 1.18 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.40, 138.07, 128.99, 124.10, 119.73, 46.60, 29.67, 25.68; HRMS (ESI): calcd for $C_{13}H_{17}NO$ $[M+H]^+$ 204.1310, found 204.1308.

*N-(4-Methylphenyl)-cyclohexanecarboxamide **3ab***

White solid, 89% yield, mp 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J*= 8.4 Hz, 2H), 7.13 (br, 1H NH), 7.03 (d, *J*= 8.2 Hz, 2H), 2.23 (s, 3H), 2.14 (t, *J*= 11.6 Hz , 1H), 1.87 (d, *J*= 12.8 Hz, 2H), 1.76 (d, *J*= 12.0 Hz, 2H), 1.62 (d, *J*= 6.6 Hz, 2H), 1.54– 1.40 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.36, 135.58, 133.64, 129.42, 119.89, 46.48, 29.68, 25.69, 20.85; HRMS (ESI): calcd for $C_{14}H_{19}NO$ $[M+H]^+$ 218.1467, found 218.1470.

*N-(4-Methoxyphenyl)-cyclohexanecarboxamide **3ac***

White solid, 88% yield, mp 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J*= 8.5 Hz, 2H), 7.21 (br, 1H NH), 6.86 (d, *J*= 8.5 Hz, 2H), 3.80 (s, 3H), 2.22 (t, *J*= 11.6 Hz, 1H), 1.97 (d, *J*= 12.3 Hz, 2H), 1.85 (d, *J*= 9.6 Hz, 2H), 1.71 (s, 2H), 1.55 (d, *J*= 10.8 Hz, 2H), 1.29 (d, *J*= 8.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.01, 157.63, 121.61, 114.10, 77.35, 77.04, 76.72, 55.50, 46.43, 29.72, 25.71; HRMS (ESI): calcd for $C_{14}H_{19}NO_2$ $[M+H]^+$ 234.1416, found 234.1417.

*N-(4-Chlorophenyl)-cyclohexanecarboxamide **3ad***

White solid, 87% yield, mp 182-186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J*= 8.6 Hz, 2H), 7.30 (br, 1H NH), 7.26 (d, *J*= 8.6 Hz, 2H), 2.23 (t, *J*= 12.8 Hz, 1H), 1.94 (d, *J*= 12.6 Hz, 2H), 1.83 (d, *J*= 11.4 Hz, 2H), 1.71 (s, 1H), 1.61– 1.45 (m, 2H), 1.37– 1.17 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.46, 136.66, 129.12, 128.95, 121.02, 46.50, 29.62, 25.63; HRMS (ESI): calcd for $C_{13}H_{17}ClNO$ $[M+H]^+$ 238.0920, found 238.0922.

*N-(4-Bromophenyl)-cyclohexanecarboxamide **3ae***

White solid, 87% yield, mp 188-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 4H), 7.26 (br, 1H NH), 2.22 (t, *J*= 12.8 Hz, 1H), 1.94 (d, *J*= 10.8 Hz, 2H), 1.82 (s, 2H), 1.71 (s, 1H), 1.53 (d, *J*= 11.1 Hz, 2H), 1.27 (d, *J*= 8.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.48, 136.94, 128.91, 121.32, 46.54, 29.62, 25.63; HRMS (ESI): calcd for $C_{13}H_{16}BrNO$ $[M+H]^+$ 282.0415, found 282.0410.

*N-(3-Methylphenyl)-cyclohexanecarboxamide **3af***

White solid, 88% yield, mp 130-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.42 (br, 1H NH), 7.35– 7.28 (m, 1H), 7.20 (dd, *J*= 9.4, 6.2 Hz, 1H), 6.92 (d, *J*= 7.5 Hz, 1H), 2.34 (d, *J*= 4.9 Hz, 3H), 2.25 (tt, *J*= 11.7, 3.4 Hz, 1H), 1.96 (d, *J*= 13.3 Hz, 2H), 1.89– 1.76 (m, 2H), 1.71 (d, *J*= 8.2 Hz, 1H), 1.56 (qd, *J*= 12.3, 2.9 Hz, 2H), 1.36– 1.23 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.61, 138.86, 138.10, 128.75, 124.85, 120.51, 116.87, 46.51, 29.67, 25.67, 21.48. HRMS (ESI): calcd for $C_{14}H_{19}NO$ $[M+H]^+$ 218.1467, found 218.1464.

*N-(2-Fluorophenyl)-cyclohexanecarboxamide **3ag***

White solid, 86% yield, mp 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (br, 1H NH), 8.36 (t, *J*= 7.8 Hz, 1H), 7.43– 6.98 (m, 3H), 2.29 (t, *J*= 12.8 Hz, 1H), 1.98 (d, *J*= 13.2 Hz, 2H), 1.90– 1.80 (m, 2H), 1.73 (t, *J*= 10.8 Hz, 1H), 1.54-1.29 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.36, 161.44, 126.69, 124.61, 123.92, 121.63, 114.74, 46.51, 29.67, 25.68; HRMS (ESI): calcd for $C_{13}H_{16}FNO$ $[M+H]^+$ 222.1216, found 222.1216.

*N-(2-Chlorophenyl)-cyclohexanecarboxamide **3ah***

White solid, 84% yield, mp 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J*= 7.8 Hz, 1H), 7.65 (s, 1H NH), 7.28 (dd, *J*= 8.0, 1.4 Hz, 1H), 7.23– 7.14 (m, 1H), 6.95 (td, *J*= 7.8, 1.5 Hz, 1H), 2.24 (tt, *J*= 11.7, 3.5 Hz, 1H), 1.94 (dd, *J*= 13.3, 1.9 Hz, 2H), 1.84– 1.73 (m, 2H), 1.65 (dd, *J*= 10.0, 4.0 Hz, 1H), 1.47 (qd, *J*= 12.2, 3.0 Hz, 2H), 1.29– 1.17 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.30, 134.72, 128.91, 127.74, 124.38, 122.65, 121.55, 46.66, 29.67, 25.66; HRMS (ESI): calcd for $C_{13}H_{17}ClNO$ $[M+H]^+$ 238.0920, found 238.0925.

*N-(2-Ethyl-6-methylphenyl)-cyclohexanecarboxamide **3ai***

White solid, 81% yield, mp 160-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H NH), 7.24 (t, *J*= 7.6 Hz, 1H), 7.12 (dd, *J*= 17.1, 7.5 Hz, 2H), 2.36 (q, *J*= 7.6 Hz, 3H), 2.06 (m, 3H), 1.81– 1.59 (m, 7H), 1.46– 1.15 (m, 3H), 1.09 (t, *J*= 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.76, 141.13, 136.00, 133.49, 127.39, 126.70, 126.18, 45.95, 30.91, 25.92, 24.77, 18.42, 14.43;

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HRMS (ESI): calcd for $C_{16}H_{23}NO$ [M+H[$^+$ 246.1780, found 246.1776.

N-(2,6-Difluorophenyl)-cyclohexanecarboxamide ***3aj***

White solid, 86% yield, mp 112-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.35 (t, *J*= 8.5 Hz, 1H), 6.97 (d, *J*= 8.5 Hz, 2H), 2.78– 2.54 (m, 1H), 1.93– 1.71 (m, 3H), 1.72– 1.53 (m, 4H), 1.53– 1.07 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.22, 161.30, 159.72, 157.21, 131.3, 112.10, 111.59, 43.19, 28.75, 25.32, 25.22; HRMS (ESI): calcd for $C_{13}H_{15}F_2NO$ $[M+H]^+$ 240.1122, found 240.1120.

Ethyl 2-(Cyclohexanecarboxamido)benzoate ***3ak***

White solid, 85% yield, mp 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.68 (d, *J*= 8.5 Hz, 1H), 7.97 (d, *J*= 8.0 Hz, 1H), 7.45 (d, *J*= 8.7 Hz, 1H), 7.04– 6.86 (m, 1H), 4.31 (q, *J*= 7.1 Hz, 2H), 2.25 (t, *J*= 11.8 Hz, 1H), 1.95 (d, *J*= 13.4 Hz, 2H), 1.82– 1.72 (m, 2H), 1.68– 1.41 (m, 2H), 1.35 (t, *J*= 7.1 Hz, 3H), 1.29– 1.16 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.38, 168.40, 141.90, 134.56, 130.81, 122.17, 120.39, 115.07, 77.38, 77.06, 76.75, 61.36, 47.28, 29.61, 25.75, 14.22; HRMS (ESI): calcd for $C_{16}H_{21}NO_3$ [M+H[$^+$ 276.1521, found 276.1522.

N-(4-(trifluoromethyl)phenyl)cyclohexanecarboxamide ***3al***

White solid, 68% yield, mp 166-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 3H), 2.26 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.95 (d, *J* = 13.5 Hz, 2H), 1.88 – 1.80 (m, 2H), 1.73 – 1.69 (m, 1H), 1.55 (qd, *J* = 12.1, 2.9 Hz, 2H), 1.33 – 1.23 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.83, 141.16, 126.22 (q, *J* = 3.7 Hz, 4H), 125.99, 125.67, 125.45, 122.75, 119.33, 46.57, 29.59, 25.58; HRMS (ESI): calcd for $C_{14}H_{16}F_3NO$ $[M+H]^+$ 272.1184, found 272.1185.

N-(pyridin-2-yl)cyclohexanecarboxamide ***3am***

White solid, 38% yield, mp 180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.31 – 8.21 (m, 2H), 7.75 – 7.67 (m, 1H), 7.07 – 7.00 (m, 1H), 2.26 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.98 – 1.90 (m, 2H), 1.82 (dd, *J* = 9.7, 3.1 Hz, 2H), 1.69 (d, *J* = 5.5 Hz, 1H), 1.60 – 1.48 (m, 2H), 1.31 – 1.20 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.08, 151.86, 147.52, 138.49, 119.58, 114.34, 46.37, 29.46, 25.60, 25.58; HRMS (ESI): calcd for $C_{12}H_{16}N_2O$ $[M+H]^+$ 205.1263, found 205.1260.

N-(4-Methoxyphenyl)-cyclopentanecarboxamide ***3bc***

White solid, 88% yield, mp 149-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39– 7.32 (m, 2H), 7.16 (br, 1H), 6.81– 6.71 (m, 2H), 3.71 (s, 3H), 2.58 (t, *J*= 8.1 Hz, 1H), 1.87– 1.66 (m, 6H), 1.57– 1.48 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.55, 156.19, 131.33, 121.62, 114.06, 55.49, 46.68, 30.58, 26.03; HRMS (ESI): calcd for $C_{13}H_{17}NO_2$ $[M+H]^+$ 220.1259, found 220.1258.

N-(3-Methylphenyl)-cyclopentanecarboxamide ***3bf***

White solid, 85% yield, mp 143-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.30 (d, *J*= 9.7 Hz, 2H), 7.20 (t, *J*= 7.8 Hz, 1H), 6.93 (d, *J*= 7.4 Hz, 1H), 2.69 (p, *J*= 8.1 Hz, 1H), 2.34 (s, 3H), 1.92 (dd, *J*= 13.5, 5.8 Hz, 3H), 1.84– 1.75 (m, 2H), 1.64 (dt, *J*= 7.8, 5.7 Hz, 2H), 1.27 (d, *J*= 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.69, 138.91, 138.09, 128.77, 124.84, 120.37, 116.71, 46.89, 30.56, 26.03, 21.50; HRMS (ESI): calcd for $C_{13}H_{17}NO$ $[M+H]^+$ 204.1310, found 204.1305.

N-(2,6-Difluorophenyl)-cyclopentanecarboxamide ***3bj***

White solid, 81% yield, mp 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.33 (t, *J*= 6.3 Hz, 1H), 6.96 (d, *J*= 7.4 Hz, 2H), 2.22 (dd, *J*= 11.3, 7.0 Hz, 1H), 1.67 (dd, *J*= 11.9, 9.2 Hz, 4H), 1.48– 1.36 (m, 2H), 1.09– 0.98 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.69, 161.44, 159.86, 157.34, 131.39, 112.33, 112.13, 43.44, 29.93, 26.08; HRMS (ESI): calcd for $C_{12}H_{13}F_2NO$ $[M+H]^+$ 226.0965, found 226.0966.

N-(3,4-Dichlorophenyl)-cyclopentanecarboxamide ***3bn***

White solid, 84% yield, mp 157-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.30– 7.23 (m, 2H), 7.19 (br, 1H), 2.60 (t, *J*= 8.0 Hz, 1H), 1.82 (d, *J*= 12.1, Hz, 4H), 1.75– 1.66 (m, 2H), 1.59– 1.50 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.87, 137.58, 132.73, 130.44, 127.15, 121.41, 118.89, 46.78, 30.52, 26.02; HRMS (ESI): calcd for $C_{12}H_{13}Cl_2NO$ $[M+H]^+$ 258.0374, found 258.0371.

N-(4-Chlorophenyl)-adamantane-1-carboxamide ***3cd***

White solid, 68% yield, mp 160-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J*= 5.8 Hz, 2H), 7.25– 7.17 (m, 3H), 2.29 (br, 3H), 2.00– 1.78 (m, 6H), 1.78– 1.56 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.61, 138.33, 128.21, 126.65, 121.66, 40.91, 38.22, 36.09, 27.65; HRMS (ESI): calcd for $C_{17}H_{26}ClNO$ $[M+H]^+$ 290.1233, found 290.1234.

N-Phenyl-benzeneacetamide ***3da***

White solid, 56% yield, mp 117-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J*= 6.7 Hz, 4H), 7.27 (dd, *J*= 6.7, 4.0 Hz, 3H), 7.23– 7.18 (m, 2H), 7.06 (br, 1H NH), 7.01 (t, *J*= 7.4 Hz, 1H), 3.67 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.10, 137.59, 134.42, 130.54, 129.42, 128.18, 127.72, 124.50, 119.84, 44.83; HRMS (ESI): calcd for $C_{14}H_{13}NO$ $[M+H]^+$ 212.0997, found 212.1000.

N-(4-Methylphenyl)-benzeneacetamide ***3db***

White solid, 61% yield, mp 140-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 1H), 7.26 (dt, *J* = 14.7, 7.8 Hz, 4H), 7.26 – 7.19 (m, 3H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.62 (s, 2H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.21, 135.11, 134.62, 134.12, 129.57, 129.43, 129.18, 127.60, 120.05, 44.74, 20.89; HRMS (ESI): calcd for $C_{15}H_{15}NO$ $[M+H]^+$ 226.1154, found 226.1151.

N-(3-Chloro-4-fluorophenyl)-benzeneacetamide ***3do***

White solid, 65% yield, mp 132-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J*= 6.5, 2.6 Hz, 1H), 7.40– 7.21 (m, 5H), 7.18– 7.12 (m, 1H), 6.97 (t, *J*= 8.8 Hz, 2H), 3.67 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.99, 156.07, 153.62, 129.45, 129.20, 127.73, 122.47, 120.95, 120.01, 116.63, 116.52, 116.41, 44.45; HRMS (ESI): calcd for $C_{14}H_{11}FNO$ $[M+H]^+$ 264.0513, found 264.0511.

N-(3-Bromophenyl)-benzeneacetamide ***3dp***

White solid, 66% yield, mp 179-181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 10.7 Hz, 2H), 7.32 – 7.17 (m, 6H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 3.58 (d, *J* = 12.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.78, 138.96, 134.18, 130.25, 129.50, 129.23, 127.73, 127.4, 122.94, 122.52, 118.56, 44.63; HRMS (ESI): calcd for $C_{14}H_{12}BrNO$ $[M+H]^+$ 290.0102, found 290.0106.

N-(2-Chlorophenyl)-benzeneacetamide ***3dq***

White solid, 61% yield, mp 129-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br, 1H), 7.51 – 7.40 (m, 1H), 7.32 – 7.13 (m, 6H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 3.58 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.82, 138.89, 134.52, 134.25, 129.94, 129.48, 129.19, 127.69, 124.50, 120.15, 118.09, 44.62;

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HRMS (ESI): calcd for $C_{14}H_{12}ClNO$ $[M+H]^+$ 246.0607, found 246.0611.

N-Phenyl-α-methyl-benzeneacetamide ***3ea***

White solid, 60% yield, mp 160-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J*= 8.1 Hz, 2H), 7.29– 7.13 (m, 7H), 7.00 (dd, *J*= 15.6, 8.2 Hz, 2H), 3.64 (q, *J*= 7.1 Hz, 1H), 1.52 (d, *J*= 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.46, 140.93, 137.84, 129.19, 128.93, 127.67, 124.26, 119.66, 48.15, 18.57; HRMS (ESI): calcd for $C_{15}H_{15}NO$ $[M+H]^+$ 226.1154, found 226.1150.

N-(4-Methoxyphenyl)-α-methyl-benzeneacetamide ***3ec***

White solid, 63% yield, mp 160-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 4H), 7.33 – 7.27 (m, 3H), 7.07 (br, 1H), 6.83 – 6.76 (m, 2H), 3.75 (s, 3H), 3.70 (q, *J* = 7.1 Hz, 1H), 1.59 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.24, 156.38, 141.08, 130.95, 129.13, 127.73, 127.53, 121.66, 114.03, 55.48, 47.90, 18.62; HRMS (ESI): calcd for $C_{16}H_{17}NO_2$ $[M+H]^+$ 256.1259, found 256.1263.

N-(3-Methylphenyl)-α-methyl-benzeneacetamide ***3ef***

White solid, 53% yield, mp 99-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J*= 14.1 Hz, 5H), 7.19– 7.15 (m, 3H), 6.98 (br, 1H NH), 6.91 (d, *J*= 6.7 Hz, 1H), 3.73 (q, *J*= 7.2 Hz, 1H, 2.32 (s, 3H), 1.62 (d, *J*= 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.36, 140.93, 137.84, 133.91, 129.41, 128.93, 127.73, 127.61, 124.26, 119.66, 48.15, 20.70, 18.57; HRMS (ESI): calcd for $C_{16}H_{17}NO$ $[M+H]^+$ 240.1310, found 240.1306.

N'-(Cyclohexanecarbonyl)benzohydrazide ***3ar***

White solid, 61% yield, mp 200-202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (d, *J*= 5.5 Hz, 1H), 9.48 (d, *J*= 5.5 Hz, 1H), 7.84 (d, *J*= 7.3 Hz, 2H), 7.51 (t, *J*= 7.4 Hz, 1H), 7.40 (t, *J*= 7.7 Hz, 2H), 2.35 (tt, *J*= 11.8, 3.4 Hz, 1H), 1.93– 1.73 (m, 5H), 1.68 (d, *J*= 5.6 Hz, 1H), 1.57– 1.46 (m, 2H), 1.37– 1.25 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.69, 164.07, 132.29, 131.40, 128.67, 127.28, 43.22, 29.30, 25.61, 25.54; HRMS (ESI): calcd for $C_{14}H_{18}N_2O_2$ $[M+H]^+$ 247.1368, found 247.1364.

N'-(Cyclopentanecarbonyl)benzohydrazide ***3br***

White solid, 59% yield, mp 210-212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, *J*= 5.3 Hz, 1H), 8.88 (d, *J*= 5.3 Hz, 1H), 7.84 (d, *J*= 7.4 Hz, 2H), 7.56 (t, *J*= 7.4 Hz, 1H), 7.46 (t, *J*= 7.6 Hz, 2H), 2.72 (dd, *J*= 16.2, 8.0 Hz, 1H), 1.96– 1.77 (m, 6H), 1.67 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.26, 164.07, 131.40, 128.67, 127.2, 43.22, 29.30, 25.70, 25.50; HRMS (ESI): calcd for $C_{13}H_{16}N_2O_2$ $[M+H]^+$ 233.1212, found 233.1217.

N'-Benzoyladamantane-1-carbohydrazide ***3cr***

White solid, 53% yield, mp 230-232 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J*= 6.0 Hz, 1H), 8.72 (d, *J*= 5.7 Hz, 1H), 7.82– 7.72 (m, 2H), 7.46 (dd, *J*= 8.3, 6.4 Hz, 1H), 7.37 (td, *J*= 7.6, 3.0 Hz, 2H), 2.63– 1.99 (m, 3H), 1.90– 1.74 (m, 6H), 1.71– 1.61 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.50, 164.52, 132.24, 131.45, 128.64, 127.28, 48.67, 38.75, 38.72, 36.36; HRMS (ESI): calcd for $C_{13}H_{16}N_2O_2$ $[M+H]^+$ 299.1681, found 299.1676.

N-Acetyl-N-phenylcyclohexanecarboxamide ***5a***

Colorless solution, 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 3H), 7.08 – 6.98 (m, 2H), 2.67 – 2.56 (m, 1H), 2.24 (s, 3H), 1.79 – 1.73 (m, 2H), 1.68 – 1.62 (m, 2H), 1.53 (dd, *J* = 7.0, 5.3 Hz, 1H), 1.44 – 1.20 (m, 3H), 1.09 – 1.01 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.57, 173.37, 139.24, 129.72, 128.68, 119.72, 44.93, 29.35, 26.92, 25.65, 25.43; HRMS (ESI): calcd for $C_{15}H_{19}NO_2$ $[M+H]^+$ 246.1416, found 246.1410.

N-Acetyl-N-(p-tolyl)cyclohexanecarboxamide ***5b***

Colorless solution, 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 2H), 7.00 (d, *J* = 8.2 Hz, 2H), 2.68 (ddd, *J* = 11.5, 7.4, 3.3 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 1.82 (d, *J* = 11.7 Hz, 2H), 1.75 – 1.68 (m, 2H), 1.61 (d, *J* = 11.2 Hz, 1H), 1.52 – 1.41 (m, 2H), 1.15 (tdd, *J* = 25.3, 17.3, 7.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.68, 173.54, 138.67, 136.53, 130.39, 128.34, 44.82, 29.35, 26.92, 25.66, 25.42, 21.21; HRMS (ESI): calcd for $C_{16}H_{21}NO_2$ $[M+H]^+$ 260.1572, found 260.1569.

N-Acetyl-N-(4-methoxyphenyl)cyclohexanecarboxamide ***5c***

Colorless solution, 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 – 6.91 (m, 2H), 6.90 – 6.82 (m, 2H), 3.74 (s, 3H), 2.67 – 2.57 (m, 1H), 2.22 (s, 3H), 1.74 (dd, *J* = 13.3, 1.7 Hz, 2H), 1.69 – 1.59 (m, 2H), 1.58 – 1.49 (m, 1H), 1.44 – 1.30 (m, 2H), 1.17 – 0.96 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.71, 173.57, 159.49, 131.72, 129.62, 114.86, 55.42, 44.78, 29.33, 28.87, 26.81; HRMS (ESI): calcd for $C_{16}H_{21}NO_3$ $[M+H]^+$ 276.1521, found 276.1526.

N-Phenyl-N-propionylcyclohexanecarboxamide ***5d***

Colorless solution, 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.36 (m, 3H), 7.14 – 7.08 (m, 2H), 2.85 (tt, *J* = 11.4, 3.3 Hz, 1H), 2.51 (q, *J* = 7.3 Hz, 2H), 1.92 – 1.82 (m, 2H), 1.78 – 1.69 (m, 2H), 1.63 (dd, *J* = 5.1, 3.9 Hz, 1H), 1.54 – 1.41 (m, 2H), 1.28 – 1.13 (m, 3H), 1.10 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.63, 176.85, 139.23, 129.63, 128.83, 128.57, 45.15, 31.93, 29.43, 25.72, 25.50, 9.08; HRMS (ESI): calcd for $C_{16}H_{21}NO_2$ $[M+H]^+$ 260.1572, found 260.1573.

N-(p-Tolyl)-N-propionylcyclohexanecarboxamide ***5e***

Colorless solution, 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 2.79 (tt, *J* = 11.4, 3.2 Hz, 1H), 2.44 (q, *J* = 7.3 Hz, 2H), 2.31 (s, 3H), 1.78 (d, *J* = 12.4 Hz, 2H), 1.65 (dd, *J* = 8.8, 2.6 Hz, 2H), 1.58 – 1.51 (m, 1H), 1.45 – 1.32 (m, 2H), 1.20 – 1.05 (m, 3H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.77, 177.01, 138.53, 136.52, 130.32, 128.49, 45.09, 31.93, 29.43, 25.74, 25.50, 21.19, 9.11; HRMS (ESI): calcd for $C_{17}H_{23}NO_2$ $[M+H]^+$ 274.1729, found 274.1733.

N-(Cyclohexanecarbonyl)-N-phenylbenzamide ***5f***

Colorless solution, 57% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.33 – 7.25 (m, 4H), 7.25 – 7.18 (m, 1H), 7.15 – 7.06 (m, 2H), 2.81 (tt, *J* = 11.5, 3.4 Hz, 1H), 1.99 (dd, *J* = 11.3, 8.7 Hz, 2H), 1.75 (dd, *J* = 9.9, 2.7 Hz, 2H), 1.66 – 1.51 (m, 3H), 1.25 – 1.12 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.50, 173.29, 139.49, 135.17, 132.04, 129.45, 129.09, 128.49, 128.42, 127.98, 44.82, 29.66, 25.74, 25.55; HRMS (ESI): calcd for $C_{20}H_{21}NO_2$ $[M+H]^+$ 308.1572, found 308.1569.

Supplementary data

Supplementary data related to this article can be found in the supporting information.

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