Multicomponent reactions: development, scope, and applications

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Chapter 8

Direct Amination of α-Hydroxy Amides

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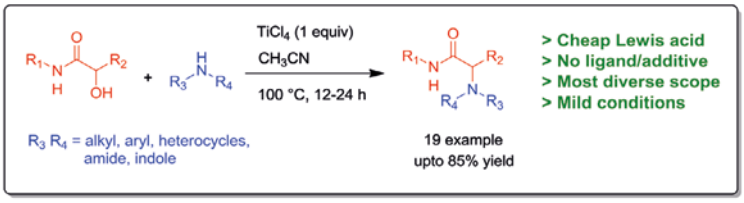


Abstract

The $TiCl_4$-mediated reaction for the direct amination of a-hydroxy amide has been developed. This simple, general, additive/base/ligand-free reaction is mediated by economical $TiCl_4$. The reaction runs under mild condition. This highly efficient C-N bond formation protocol is valid for diverse amines, including primary, secondary, heterocyclic and even primary amide and indole.

Introduction

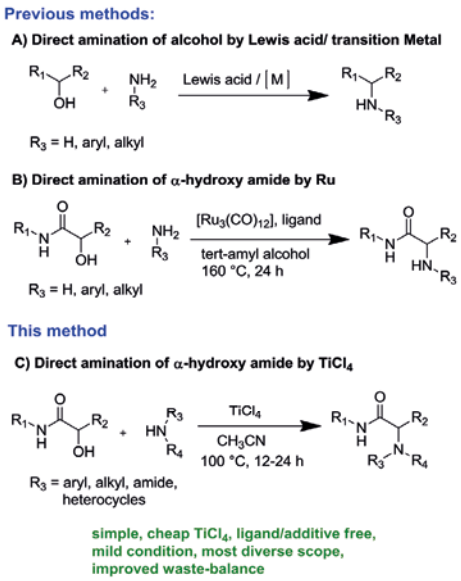
α-Amino amides are very important molecules, that are widely used in organic and medicinal chemistry. They are present in many drugs, such as Leukotriene D4, Safinamide, Lidoderm, Altace, Indinavir, Vyvanse, and in all aminopenicillins. They are also present in many natural products, such as canthiumine, coelichelin,[1] zorbamycin,[2] guadinomine B,[3] myrianthine B,[4] abyssenine,[5] paliurine E,[5] and mucronine J.[6] Moreover, a-amino amides are used as a building block to synthesize different molecules and scaffolds like hydantoins.[7] Recently, the use of α-amino amides as organocatalyst for various asymmetric reactions has proven to be an extremely valuable approach due to their easy structural modification and straight forward access.[8]

Tremendous progress has been achieved in the use of C-N bond formation for the direct amination reactions.[9] Recently more efforts have been focused on the direct amination of alcohol by using transition metals or Lewis acids (Scheme 1 Method **A**).[9,10] These protocols improved the waste balance and are a powerful tool for the C-N bond formation. This approach is also strongly preferred in industry and more research in this field is desirable.[11]

Despite good progress in this field, the scope of alcohol and amine is largely restricted. Moreover, these approaches are not valid for a more complex structure like α-hydroxy amide and also for inactivated amines where reaction typically proceeds with poor yield. Direct amination of the α-hydroxy amide is more challenging than the alcohol, as amide group could hinder the coordination sites on the catalyst to resist direct amination. So finding a new method for the direct amination of α-hydroxy amide to get access to highly important a-amino amide remains an important challenge.

Conversely, to the best of our knowledge, there is only one report by Beller and co-workers for the direct amination of α-hydroxy amide (Scheme 1 Method **B**).[12] They used the ruthenium-catalyzed "borrowing-hydrogen" process for the direct amination. This protocol is simple and green, but it involves the use of costly catalyst and ligands. Moreover, high reaction temperature with limited substrate scope were major disadvantages.

Here we are reporting the $TiCl_4$-assisted, general, economical, base/ligand-free, a relatively mild method for the direct amination of α-hydroxy amides (Scheme 1 Method **C**). The method is distinguished by its wide scope, which includes amines such as primary, secondary, heterocyclic, and even indole and primary amide.



Scheme 1. Previous and New Methods for Amination.

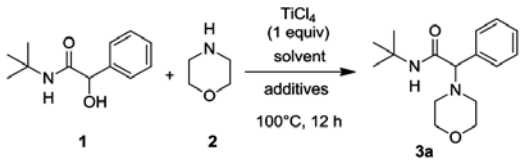
Results and Discussion

We started our optimization with screening different Lewis acids, as Lewis acid activated reactions are well developed for the direct amination of alcohol which is used in catalytic and stoichiometric amounts.[9,10] We sought to examine the possibility of these economical and non-toxic Lewis acids for direct amination of a-hydroxy amides. We evaluated different Lewis acids, such as $InCl_3$, $ZnCl_2$, $ZrCl_4$, $GdCl_2$, $Sc(OTf)_3$, $TiCl_4$, and $FeCl_3$ in a catalytic amount at room temperature in DCE solvent, however only with $TiCl_4$ the trace target product formation observed. Next, we increased the temperature and catalyst amount of $TiCl_4$. Ultimately, we found that increasing the temperature to 100 °C, and a stoichiometric amount of $TiCl_4$, product formation slightly improved. Then we screened different solvents with 1 equivalent of $TiCl_4$ at 100 °C (Table 1). In DCE, a low amount of desired amination product **3a** was observed together with a significant amount of starting material (Table 1, entry **1**). The reaction did not go to completion even after 3 days. With further solvent screening, the coupling product yield improved remarkably up to 62% in solvents, such as dioxane, toluene, and THF (Table 1, entries **2**–**4**). The reaction in methanol did not proceed at all. In DCM less product yield (53%) was observed. Further improvement was realized when acetonitrile was used as a solvent, which gave an excellent 85% yield (Table 1, entry **7**). The reaction did not go for completion with xylene and DMF even after 3 days.

Aiming to get a higher yield, we turned our attention toward the use of different additives,[9,10] such as bases, KOH and triethylamine or drying agents, molecular sieves and $MgSO_4$. With this additive, the rate of reaction became slow and did not finish even with longer reaction times and

starting materials remained in substantial amount ~50-60%. Next, we performed equivalence studies of the amine morpholine and we found that 1 and 2 equivalent amount of morpholine formed only 23% and 42% product respectively. When the $TiCl_4$ equivalent was reduced to 20 mol % it did not form any product. However, at 50 mol % product was formed, but the conversion remain incomplete even after 3 days and 130 °C temperature. In conclusion, optimal conditions for this reaction are 100 °C with 1 equivalent of $TiCl_4$ in acetonitrile as solvent.

Table 1. Optimization Conditions.[a]



Entry	Solvent	Additive / Equivalence	Yield (%)[b]
1	DCE		<5
2	dioxane		65
3	toluene		59
4	THF		62
5	MeOH		<5
6	DCM		53
7	CH_3CN		85
8	xylene		42
9	DMF		<5
10	CH_3CN	Et_3N	<5
11	CH_3CN	mol. sieve	30
12	CH_3CN	KOH	<5
13	CH_3CN	$MgSO_4$	<5
14	CH_3CN	(1 equiv) **2**	23
15	CH_3CN	(2 equiv) **2**	42
16	CH_3CN	(0.2 equiv) $TiCl_4$	nr
17	CH_3CN	(0.5 equiv) $TiCl_4$	39

[a]The reaction was carried out with a-hydroxy amide **1** (1.0 mmol), morpholine (4.0 mmol), $TiCl_4$ (1 mmol) and 4 mL CH_3CN solvent. [b]Yield of isolated product **3a**. nr = no reaction.

With these optimized conditions in hand, we examined scope and limitations of this $TiCl_4$-mediated amination reaction (Table 2). Alkylamines like allylamine, cyclohexylamine, and benzylamine were effectively worked in this method to form a product in good yield 68%, 76% and 83% respectively. Arylamines worked well (**3e** and **3f**). Electron-donating and electron-withdrawing substituents on the arylamines are compatible with the reaction, leading to the desired products in good to moderate yield (**3g** and **3h**). Further, we expanded the scope of the reaction to the heterocyclic

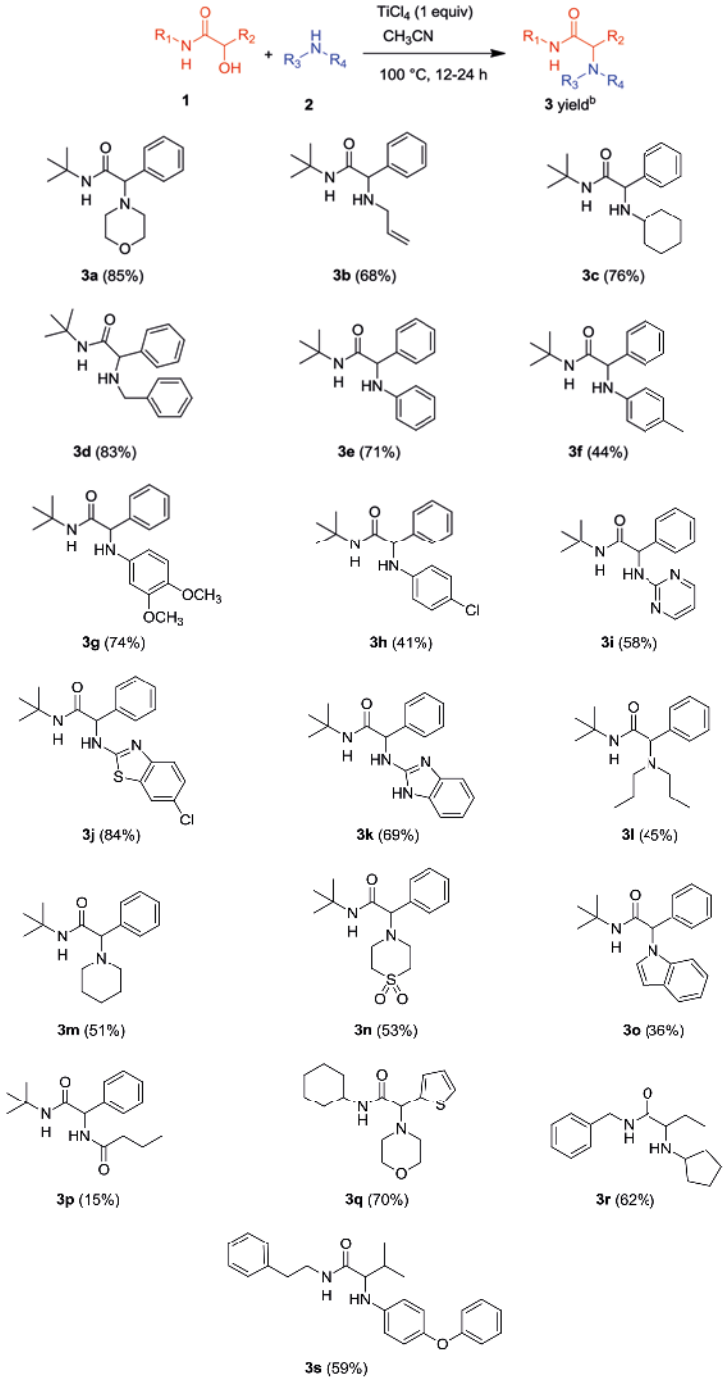
amine. Heteroaryl molecules are very important in drugs, as these molecules are present in almost half of the top 200 drugs.[13] Heterocyclic amine like pyrimidine, benzothiazole and benzimidazoles are known to be inactivated amines, however, can be used in this protocol providing good yields of 58%, 84% and 69% (**3i**–**3k**).

Next, we screened different secondary amines, including cyclic amines like piperidine and thiomorpholine 1,1-dioxide. They also proved to be good substrates in this reaction. The reaction with indole also works with 36% isolated product. The low yield was due incomplete conversion, even though the reaction continued for 3 days and increase in temperature to 130 °C and increased the $TiCl_4$ quantity to 1.5 or 3 equivalent. The method also worked for a primary amide, butyramide, to form bis-amide product (**3p**), however, in low 15% yield, while recovering mostly starting material.

Finally, we extended the scope of reaction with differentially substituted a-hydroxy amides. As expected, other α-hydroxy amides derivatives also show similar results. Aliphatic, aromatic and the heterocycle thiophene also worked well. The product of thiophene substituted α-hydroxy amide with morpholine **3q** was produced in 70% yield. Aliphatic derivatives (**3r** and **3s**) formed moderate yields of 62% and 59% as the reaction remained incomplete.

Previously $TiCl_4$-assisted substitution reactions were reported to proceed through a carbocation mechanism.[14] Others described $TiCl_4$ catalyzed nucleophilic substitutions of alcohol which proceed via carbon cation formation followed by nucleophile attack.[14a,15] Studies on detail mechanism of direct amination of a-hydroxy amides are now going on.

Table 2. Scope of Direct Amination of a-hydroxy amides with Amines.[a]



[a]The reaction was carried out with a-hydroxy amide (1.0 mmol), amine (4.0 mmol) and $TiCl_4$ (1 mmol) in 4 mL CH_3CN. [b]Yield of isolated product **3**.

Conclusions

In summary, we developed a $TiCl_4$-facilitated, ligand/additive-free, a relatively mild reaction for the direct amination of α-hydroxy amides. Under the optimized reaction conditions, a broad range of amines including primary, secondary, heterocycles, and even primary amides and indoles were found to participate in this transformation, providing moderate to high yields. Different derivatives on a-hydroxy amides like aliphatic, aromatic or heterocycle like thiophene also worked well.

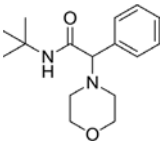
Experimental Procedures and Spectral Data

General procedure for the synthesis of α-amino amides

In a glass pressure tube (10 mL), morpholine (4 mmol, 351 ml) and N-(tert-butyl)-2-hydroxy-2-phenylacetamide (1 mmol, 207 mg) was added in acetonitrile (4 ml). Then $TiCl_4$ [1 M in DCM] (1 mmol, 1 ml) was added under nitrogen and the resulting mixture was stirred at 100 °C till completion of the reaction (monitored by TLC). After cooling down to room temperature, the reaction mixture was poured into the saturated solution of a $NaHCO_3$. The aqueous layer was extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography using EtOAc-hexane as eluent.

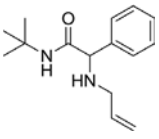
Spectral Data

N-(*tert*-butyl)-2-morpholino-2-phenylacetamide (**3a**)



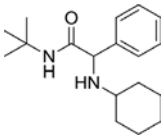
Obtained from 1 mmol reaction as a white solid, mp 140–142 °C; yield: 234 mg (85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 5H), 6.97 (s, 1H), 3.74 – 3.66 (m, 5H), 2.48 – 2.35 (m, 4H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 135.8, 128.7, 128.6, 128.2, 77.0, 67.1, 52.2, 50.7, 28.7. HRMS (ESI) m/z calculated $[M+H]^+$: 277.19105; found $[M+H]^+$: 277.19089.

2-(allylamino)-*N*-(tert-butyl)-2-phenylacetamide (**3b**)



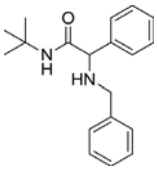
Obtained from 1 mmol reaction as a colorless liquid, yield: 167 mg (68%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 4H), 7.30 – 7.27 (m, 1H), 7.13 (s, 1H), 5.94 – 5.80 (m, 1H), 5.25 – 5.16 (m, 1H), 5.13 (dd, J = 10.3, 1.2, 1H), 4.05 (s, 1H), 3.25 – 3.18 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 139.8, 135.9, 128.8, 128.0, 127.2, 116.5, 74.2, 67.5, 50.9, 28.7. HRMS (ESI) m/z calculated $[M+H]^+$: 247.18049; found $[M+H]^+$: 247.18031.

N-(tert-butyl)-2-(cyclohexylamino)-2-phenylacetamide (**3c**)



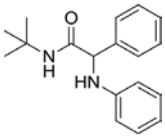
Obtained from 1 mmol reaction as a white solid, mp 68–70 °C; yield: 219 mg (76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.38 – 7.30 (m, 4H), 7.30 – 7.23 (m, 1H), 4.15 (s, 1H), 2.50 – 2.37 (m, 1H), 1.99 – 1.84 (m, 2H), 1.79 – 1.68 (m, 2H), 1.67 – 1.58 (m, 1H), 1.57 – 1.45 (m, 1H), 1.38 (s, 9H), 1.28 – 1.21 (m, 2H), 1.20 – 1.00 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 140.9, 128.8, 127.7, 127.1, 66.0, 56.5, 50.5, 34.3, 33.7, 28.7, 25.9, 25.1, 25.0. HRMS (ESI) m/z calculated $[M+H]^+$: 289.22744; found $[M+H]^+$: 289.22729.

2-(benzylamino)-*N*-(*tert*-butyl)-2-phenylacetamide (**3d**)



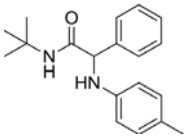
Obtained from 1 mmol reaction as a white solid, mp 90–92 °C; yield: 246 mg (83%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 9H), 7.16 (s, 1H), 4.09 (s, 1H), 3.75 (d, *J* = 2.6, 2H), 1.99 (s, 1H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 139.8, 139.5, 128.8, 128.6, 128.2, 128.0, 127.4, 127.3, 67.8, 52.7, 50.7, 28.8, 28.7, 28.7. HRMS (ESI) m/z calculated $[M+H]^+$: 297.19614; found $[M+H]^+$: 297.19598.

N-(*tert*-butyl)-2-phenyl-2-(phenylamino)acetamide (**3e**)



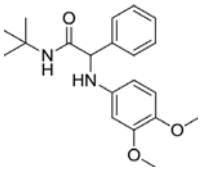
Obtained from 0.5 mmol reaction as a white solid, mp 102–104 °C; yield: 100 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 4H), 7.35 – 7.29 (m, 1H), 7.18 (t, *J* = 7.9, 2H), 6.80 (t, *J* = 7.3, 1H), 6.63 (d, *J* = 7.7, 2H), 6.52 (s, 1H), 4.60 (d, *J* = 1.7, 1H), 4.50 (s, 1H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 146.8, 139.3, 129.3, 129.2, 128.5, 127.3, 119.1, 113.9, 64.9, 51.2, 28.6. HRMS (ESI) m/z calculated $[M+H]^+$: 283.18049; found $[M+H]^+$: 283.1803.

N-(*tert*-butyl)-2-phenyl-2-(*p*-tolylamino)acetamide (**3f**)



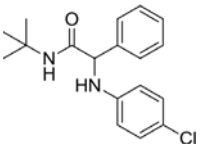
Obtained from 1 mmol reaction as a white solid, mp 158–160 °C; yield: 130 mg (44%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.39 – 7.34 (m, 2H), 7.34 – 7.29 (m, 1H), 6.99 (d, *J* = 8.2, 2H), 6.68 (s, 1H), 6.55 (d, *J* = 8.4, 2H), 4.55 (d, *J* = 1.5, 1H), 4.30 (s, 1H), 2.24 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 144.6, 139.4, 129.8, 129.2, 128.4, 127.4, 114.0, 65.4, 51.1, 28.6, 20.5. HRMS (ESI) m/z calculated $[M+H]^+$: 297.19614; found $[M+H]^+$: 297.19598.

N-(*tert*-butyl)-2-((3,4-dimethoxyphenyl)amino)-2-phenylacetamide (**3g**)



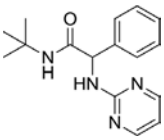
Obtained from 0.5 mmol reaction as a brown solid, mp 110–111 °C; yield: 126 mg (74%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H), 7.39 – 7.35 (m, 2H), 7.35 – 7.29 (m, 1H), 6.72 (d, *J* = 8.6, 1H), 6.66 (s, 1H), 6.26 (d, *J* = 2.6, 1H), 6.14 (dd, *J* = 8.5, 2.6, 1H), 4.55 (s, 1H), 4.27 (s, 1H), 3.80 (s, 6H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 149.8, 142.5, 141.5, 139.4, 129.2, 128.4, 127.3, 112.8, 104.7, 99.6, 65.6, 56.5, 55.7, 51.1, 28.6. HRMS (ESI) m/z calculated $[M+H]^+$: 343.20162; found $[M+H]^+$: 343.20105.

N-(*tert*-butyl)-2-((4-chlorophenyl)amino)-2-phenylacetamide (**3h**)



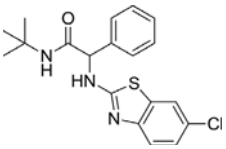
Obtained from 1 mmol reaction as a brown solid, mp 184–186 °C; yield: 129 mg (41%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.33 (m, 5H), 7.13 (d, *J* = 8.8, 2H), 6.55 (d, *J* = 8.8, 2H), 6.32 (s, 1H), 4.74 (s, 1H), 4.60 (s, 1H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 145.2, 138.9, 129.3, 129.1, 128.6, 127.2, 123.5, 114.9, 64.4, 51.4, 28.5. HRMS (ESI) m/z calculated $[M+H]^+$: 317.14152; found $[M+H]^+$: 317.14148.

N-(*tert*-butyl)-2-phenyl-2-(pyrimidin-2-ylamino)acetamide (**3i**)



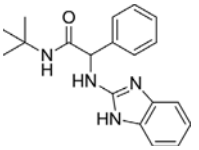
Obtained from 1 mmol reaction as a white solid, mp 160–162 °C; yield: 165 mg (58%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 4.8, 2H), 7.52 – 7.42 (m, 2H), 7.38 – 7.24 (m, 3H), 6.65 (d, *J* = 6.1, 1H), 6.53 (t, *J* = 4.8, 1H), 5.93 (s, 1H), 5.39 (d, *J* = 6.3, 1H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 161.5, 158.0, 138.9, 128.9, 128.1, 127.5, 111.6, 60.3, 51.4, 28.6. HRMS (ESI) m/z calculated $[M+H]^+$: 285.17099; found $[M+H]^+$: 285.17081.

N-(*tert*-butyl)-2-((6-chlorobenzo[*d*]thiazol-2-yl)amino)-2-phenylacetamide (**3j**)



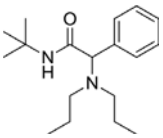
Obtained from 0.5 mmol reaction as a brown viscous liquid, yield: 156 mg (84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 1H), 7.44 (d, *J* = 2.1, 1H), 7.38 – 7.27 (m, 3H), 7.27 – 7.20 (m, 2H), 7.16 (dd, *J* = 8.6, 2.1, 1H), 5.85 (s, 1H), 5.44 (s, 1H), 1.27 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 165.8, 150.7, 137.9, 132.2, 129.1, 128.6, 127.5, 126.9, 126.2, 120.4, 119.6, 62.1, 51.9, 28.5. HRMS (ESI) m/z calculated $[M+H]^+$: 374.10884; found $[M+H]^+$: 374.10873.

((1H-benzo[d]imidazol-2-yl)amino)-N-(tert-butyl)-2-phenylacetamide (**3k**)



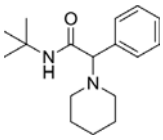
Obtained from 0.5 mmol reaction as a white solid, mp >200 °C; yield: 111 mg (69%); ^{1}H NMR (500 MHz, DMSO) δ 10.42 (s, 1H), 8.10 (s, 1H), 7.49 (d, J = 7.5, 2H), 7.32 (t, J = 7.6, 2H), 7.24 (t, J = 7.3, 1H), 7.13 (d, J = 8.9, 3H), 6.85 (br s, 2H), 5.62 (d, J = 8.9, 1H), 1.23 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 170.3, 154.7, 140.9, 134.0, 128.6, 127.6, 127.1, 120.4, 119.0, 115.2, 109.4, 59.4, 50.8, 28.9. HRMS (ESI) m/z calculated $[M+H]^+$: 323.18664; found $[M+H]^+$: 323.18658.

N-(*tert*-butyl)-2-(dipropylamino)-2-phenylacetamide (**3l**)



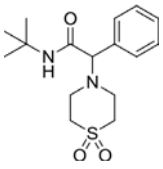
Obtained from 1 mmol reaction as a gray solid, mp 64–66 °C; yield: 131 mg (45%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.33 – 7.26 (m, 3H), 7.26 – 7.22 (m, 2H), 4.15 (s, 1H), 2.51 – 2.38 (m, 2H), 2.30 – 2.15 (m, 2H), 1.55 – 1.40 (m, 4H), 1.37 (s, 9H), 0.84 (t, *J* = 7.4, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 135.8, 129.8, 128.0, 127.6, 71.9, 52.4, 50.5, 28.7, 20.2, 11.8. HRMS (ESI) m/z calculated $[M+H]^+$: 291.24309; found $[M+H]^+$: 291.24295.

N-(*tert*-butyl)-2-phenyl-2-(piperidin-1-yl)acetamide (**3m**)



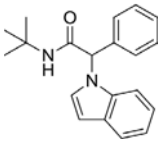
Obtained from 0.5 mmol reaction as a brown solid, mp 78–80 °C; yield: 70 mg (51%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 2H), 7.30 – 7.25 (m, 4H), 3.73 (s, 1H), 2.34 (br s, 4H), 1.64 – 1.53 (m, 4H), 1.48 – 1.41 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 136.4, 129.0, 128.3, 127.7, 52.7, 50.5, 44.9, 28.7, 26.4, 24.3. HRMS (ESI) m/z calculated $[M+H]^+$: 275.21179; found $[M+H]^+$: 275.21164.

N-(*tert*-butyl)-2-(1,1-dioxidothiomorpholino)-2-phenylacetamide (**3n**)



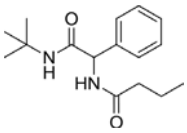
Obtained from 0.5 mmol reaction as a white solid, mp >200 °C; yield: 86 mg (53%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 3H), 7.33 – 7.29 (m, 2H), 6.48 (s, 1H), 4.00 (s, 1H), 3.15 – 2.86 (m, 8H), 1.34 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 135.4, 129.0, 128.7, 128.5, 74.1, 51.5, 51.2, 49.0, 28.7. HRMS (ESI) m/z calculated $[M+H]^+$: 325.15804; found $[M+H]^+$: 325.15796.

N-(*tert*-butyl)-2-(1H-indol-1-yl)-2-phenylacetamide (**3o**)



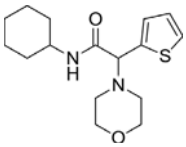
Obtained from 0.5 mmol reaction as a gray solid, mp >200 °C; yield: 55 mg (36%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.44 (d, J = 8.0, 1H), 7.36 – 7.27 (m, 5H), 7.25 – 7.21 (m, 1H), 7.20 – 7.14 (m, 1H), 7.07 (t, J = 7.2, 1H), 6.85 (d, J = 2.2, 1H), 5.68 (s, 1H), 5.00 (s, 1H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 139.9, 136.5, 128.6, 128.5, 127.0, 126.6, 123.8, 122.4, 119.8, 119.1, 115.1, 111.4, 52.0, 51.4, 28.6. HRMS (ESI) m/z calculated $[M+H]^+$: 307.18049; found $[M+H]^+$: 307.18045.

N-(2-(*tert*-butylamino)-2-oxo-1-phenylethyl)butyramide (**3p**)



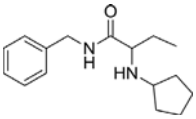
Obtained from 1 mmol reaction as a white solid, mp 188–190 °C; yield: 42 mg (15%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.35 – 7.31 (m, 1H), 7.30 – 7.26 (m, 1H), 6.97 (d, J = 7.1, 1H), 5.94 (s, 1H), 5.48 (d, J = 7.2, 1H), 2.20 (td, J = 7.4, 2.3, 2H), 1.68 – 1.61 (m, 2H), 1.28 (s, 10H), 0.90 (t, J = 7.4, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 169.3, 138.8, 128.9, 128.0, 127.1, 56.9, 51.7, 38.4, 28.5, 19.0, 13.7. HRMS (ESI) m/z calculated $[M+H]^+$: 277.19105; found $[M+H]^+$: 277.19095.

N-cyclohexyl-2-morpholino-2-(thiophen-2-yl)acetamide (**3q**)



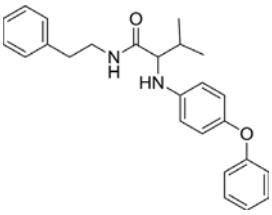
Obtained from 0.5 mmol reaction as a brown solid, mp 154–156 °C; yield: 108 mg (70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 6.4, 1H), 7.03 (d, J = 3.4, 1H), 6.95 (dd, J = 5.1, 3.5, 2H), 4.08 (s, 1H), 3.87 – 3.76 (m, 1H), 3.71 (t, J = 4.5, 4H), 2.55 – 2.36 (m, 4H), 1.96 – 1.86 (m, 2H), 1.75 – 1.68 (m, 2H), 1.66 – 1.56 (m, 1H), 1.47 – 1.32 (m, 2H), 1.28 – 1.19 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 138.2, 128.3, 126.6, 126.1, 71.2, 67.0, 51.9, 47.6, 33.1, 32.8, 25.5, 24.7, 24.7. HRMS (ESI) m/z calculated $[M+H]^+$: 309.16313; found $[M+H]^+$: 309.16296.

N-benzyl-2-(cyclopentylamino)butanamide (**3r**)



Obtained from 0.5 mmol reaction as a yellow solid, mp 80–82 °C; yield: 81 mg (62%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.35 – 7.31 (m, 2H), 7.30 – 7.23 (m, 3H), 4.51 – 4.41 (m, 2H), 3.09 (dd, *J* = 7.7, 4.6, 1H), 3.02 (p, *J* = 6.5, 1H), 1.88 – 1.78 (m, 2H), 1.76 – 1.67 (m, 1H), 1.66 – 1.55 (m, 3H), 1.55 – 1.43 (m, 2H), 1.32 – 1.20 (m, 3H), 0.96 (t, *J* = 7.5, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 138.7, 128.6, 127.6, 127.3, 63.0, 59.5, 43.0, 33.2, 33.1, 27.0, 23.6, 23.6, 10.4. HRMS (ESI) m/z calculated $[M+H]^+$: 261.19614; found $[M+H]^+$: 261.19595.

3-methyl-*N*-phenethyl-2-((4-phenoxyphenyl)amino)butanamide (**3s**)



Obtained from 0.5 mmol reaction as a dark brown solid, mp >200 °C; yield: 115 mg (59%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.25 – 7.15 (m, 3H), 7.09 – 7.00 (m, 3H), 6.96 – 6.88 (m, 4H), 6.82 (t, *J* = 5.8, 1H), 6.60 – 6.51 (m, 2H), 3.74 (d, *J* = 3.0, 1H), 3.68 – 3.59 (m, 1H), 3.55 – 3.37 (m, 2H), 2.85 – 2.64 (m, 2H), 2.43 – 2.27 (m, 1H), 1.03 (d, *J* = 7.0, 3H), 0.94 (d, *J* = 6.9, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 158.6, 149.1, 143.8, 138.7, 129.6, 128.7, 128.6, 126.4, 122.3, 121.1, 117.4, 114.7, 65.5, 40.2, 35.9, 31.1, 19.8, 17.6. HRMS (ESI) m/z calculated $[M+H]^+$: 389.22235; found $[M+H]^+$: 389.22229.

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