CHAPTER-2

Diversification of α–Ketoamides *via* Transamidation Reactions with Alkyl and Benzyl Amines at Room Temperature

2.1 Introduction

Amides represent one of the key functional groups in both chemistry and biology [1]. Exchange of amine group in amides via selective C(O)-N cleavage known as transamidation reactions. Transamidation is one of the important routes for the diversification of amides [2]. However, direct transamidation usually requires harsh reaction conditions due to the inherent stability of C(O)-N bond in planar amides [3]. In this context, recently a promising two-step strategy, i.e. transformation of planner amides into twisted amides (also known as activated amides) followed by nucleophilic displacement with external amines, has been developed for the facile transamidation process [4]. Using this approach, Garg [5], Szostak [6] and others [7] have explored various metal and metal-free transamidation reactions in a wide range of simple amides with different amines under mild conditions.

α-Ketoamides are prevalent structural motifs present in drugs [8] (e.g. narlaprevir-antiviral; biricodar-anticancer), drug candidates [9] (e.g. inhibitors of SARS-CoV-2 main protease, proteasome and epoxy hydrolase inhibitors) and bioactive natural products [10] (e.g. complestatin, rapamycin) (**Figure 2.1**, **I-III**). In addition, α-ketoamides have also been explored as H_2O_2-activated prodrugs [11], photo-affinity labelling (PAL) probes [12], etc., (**Figure 2.1**, **IV-V**). On the other hand, α-ketoamides are valuable synthetic intermediates and synthons that have been exploited in the preparation of various cyclic and acyclic molecules [13], heterocyclic compounds [14], etc. [15].

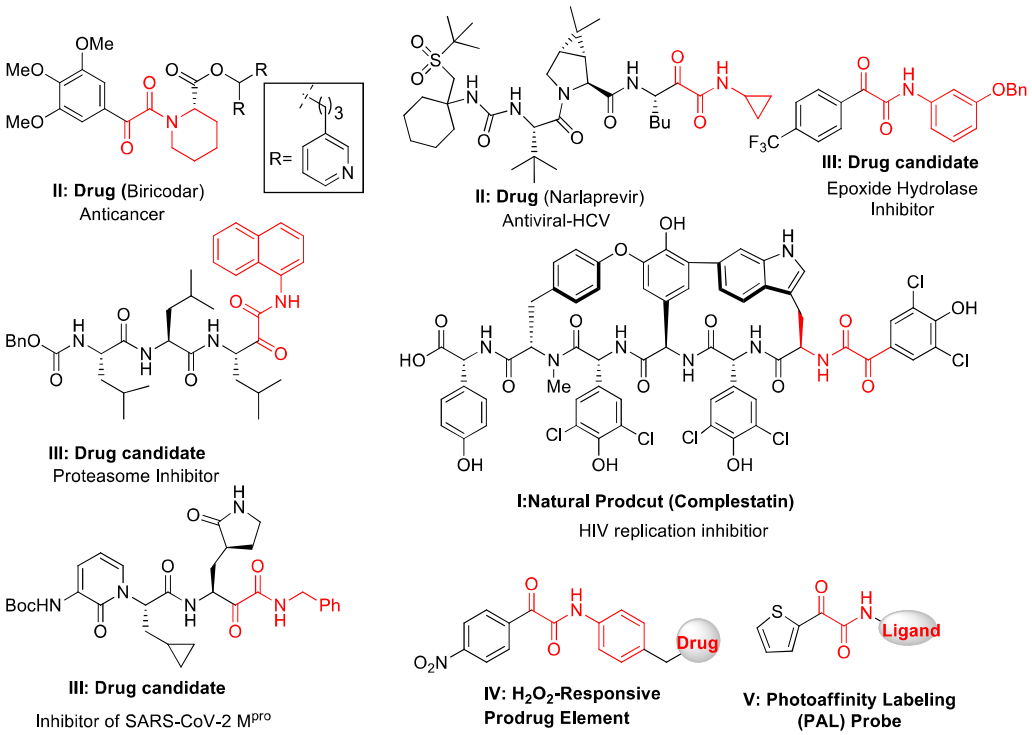
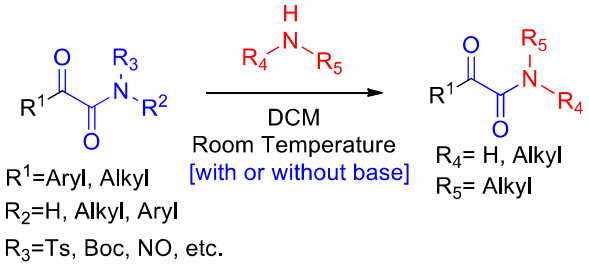


Figure 2.1 Structures of some bioactive α-ketoamides.



Scheme 2.1 Transamidation of α-ketoamides with alkyl amines.

Considering the biological and synthetic importance, different approaches have been developed for the preparation of α-ketoamides [16]. In particular, i) oxidation of α-hydroxyamides [16c, d] and α-arylacetamides [16e], ii) oxidative amidation of aryl methyl ketones [16f, g], aryl glyoxals [16h, i], ethylarenes [16j, k] and terminal-alkynes [16l, m], iii) direct amidation of α-ketoacids with amines using amide coupling agents [16n, o] and

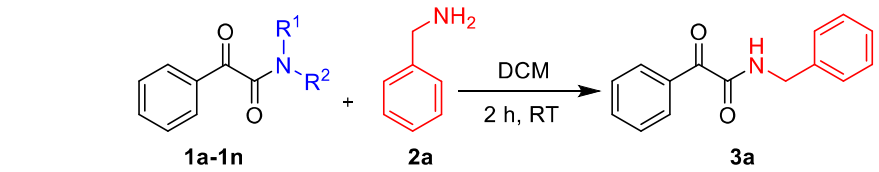
iv) palladium-catalyzed double carbonylative amination of aryl halides [16p], have been well explored. However, most of the above methods suffer from some disadvantages including use of harsh reaction conditions, low yields, longer reaction time, etc. [16a, b]. To the best of our knowledge, transamidation approach in *α*–ketoamides has not been explored in the literature. Nevertheless, transamidation approach will be highly useful for generating a library of *α*–ketoamides of biological importance without using amide-coupling agents, oxidants, etc. Moreover, *α*–ketoamides are very interesting substrates for the transamidation reactions because *α*–ketoamides are known as "activated amides" due to adjacent keto-group and easier rotation of the *C(O)–N* bond [13d, 16a-b, 17]. The last couple of years, our research group is focused on the chemistry of *N*-nitrosamines [18], and we have reported *tert*-butyl nitrite promoted transamidation of secondary amides with various amines at room temperature [19]. In addition, recently, we have also explored the transformation of *N*-Boc-amides into aryl ketones with Grignard reagents [20]. In continuation of these works, here we disclose the transamidation reactions in *α*-ketoamides with alkyl amines under different conditions at room temperature (**Scheme 2.1**).

2.2 Results and discussion

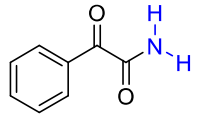
At the outset, to understand the reactivity of simple *α*-ketoamides in transamidation, primary amide such as 2-oxo-2-phenylacetamide (**1a**), secondary amides such as *N*-methyl and *N*-phenyl 2-oxo-2-phenyl acetamides (**1b** and **1c**) and *tert*-amides such as *N*-ethyl *N*-phenyl and *N*-benzyl *N*-phenyl 2-oxo-2-phenylacetamides (**1d** and **1e**) were subjected to the transamidation reactions with benzylamine (**Table 2.1**). The reactions were performed in dichloromethane (AR grade) for 2 hours at room temperature in the absence of catalyst,

base and additives. However, no reactions were observed with all these amides (i.e. **1a-1e**), while starting materials were recovered. It is also worth noting that these amides were also found to be unreactive with benzylamine even at 80 °C (the reaction were carried in DCE), which indicates their high stability.

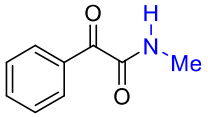
Table 2.1 Transamidation of various α-ketoamides with benzylamine.[a,b]



1a-1n **2a** **3a**



(**1a**)
00% (00%)[c]



(**1b**)
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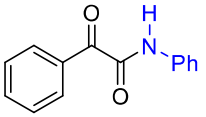

(**1c**)
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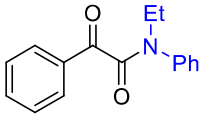

(**1d**)
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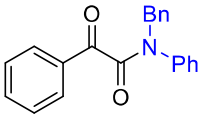

(**1e**)
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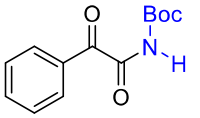
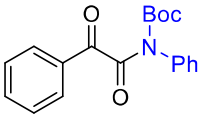
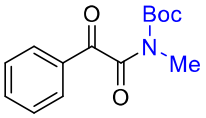


(**1f**)
00%



(**1g**)
<5%



(**1h**)
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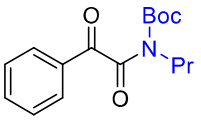

(**1i**)
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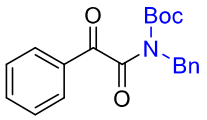

(**1j**)
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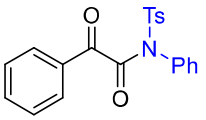
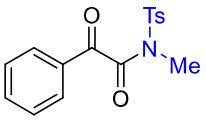
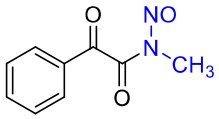


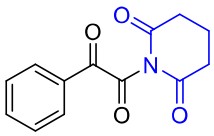
(**1k**)
97%



(**1l**)
87%



(**1m**)
92%

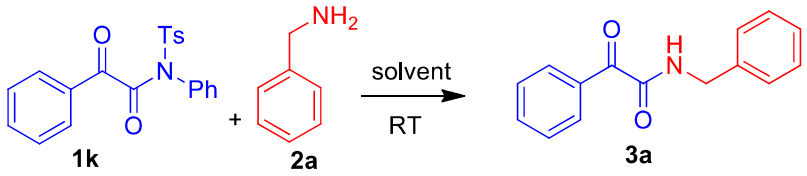


(**1n**)
95%

[a]Reaction conditions: Amide **1a-1n** (1 mmol) and benzylamine (120 µL, 1.1 equiv.) was stirred in DCM (3 mL) at room temperature. [b]Isolated yields. [c]Yield of the reaction at 80 °C in DCE.

Therefore, activated amides such as *N*-Boc, *N*-tosyl and *N*-nitroso amides (**1f-1m**) as well as *N*-acyl glutarimide (**1n**) were prepared and subjected to transamidation reactions in dichloromethane at room temperature. Surprisingly, *N*-Boc-protected primary and secondary amides (**1f-1j**) failed to undergo transamidation, while starting materials were recovered. However, to our delight, 2-oxo-*N*-tosyl (**1k** and **1l**) and *N*-nitroso (**1m**) phenylacetamides as well as 2-oxo *N*-acyl glutarimide (**1n**) underwent transamidation very efficiently and gave the desired product **3a** in good to excellent yields in the absence of base or catalyst. In particular, 2-oxo-*N*-tosyl *N*-phenyl 2-phenylacetamide (**1k**) gave **3a** in quantitative yield.

Table 2.2 Screening of solvent and base.[a]



S. No.	Solvent	Base	Time (min)	Yield (**3a**) (%)[b]
1	Acetonitrile		15	71
2	Dichloromethane		15	80
3	Dioxane		15	68
4	Tetrahydrofuran		15	70
5	Methanol		15	64
6	Dichloromethane	Cs_2CO_3	15	85
7	Dichloromethane	Et_3N	15	81
8	Dichloromethane	DBU	15	82
9	Dichloromethane		30	97

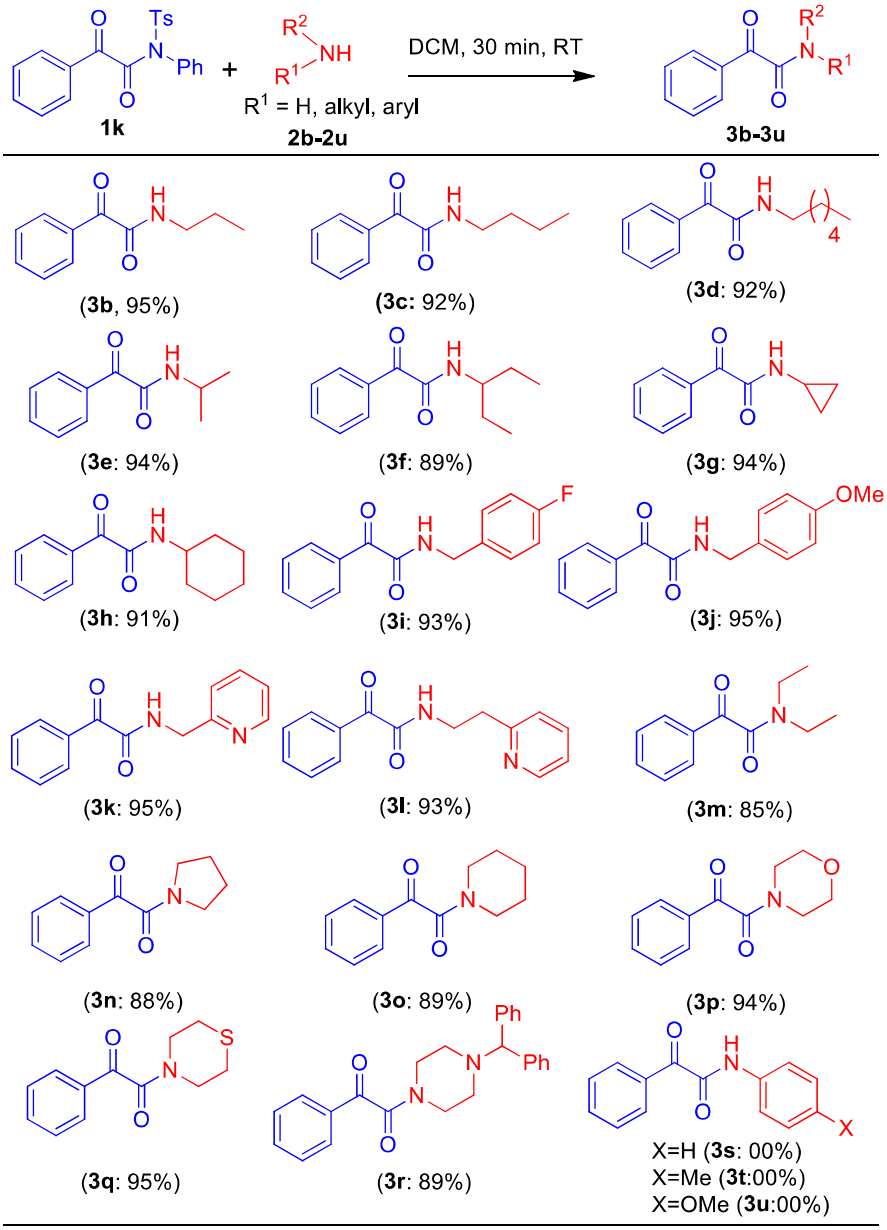
[a]Reaction conditions: Amide **1k** (0.379 gm, 1 mmol) and benzylamine (120 µL, 1.1 equiv.) was stirred in solvent (3 mL) at room temperature without or with base (1.1 equiv.). [b]Isolated yields.

Seeking further optimization, transamidation of *N*-tosyl *N*-phenyl 2-oxo-2-phenylacetamide (**1k**) with benzylamine was screened in different solvents (AR grade), including acetonitrile, dichloromethane, dioxane, tetrahydrofuran and methanol (**Table 2.2**).

These reactions were carried out at room temperature only for 15 minutes. Among these solvents, dichloromethane was found to be superior to provide the desired product in 80% yield, while other solvents gave relatively low yields (**Table 2.2, entries 1-5**). Further, the effect of a base in transamidation was investigated in the presence of Cs_2CO_3, Et_3N and DBU **(Table 2.2, entries 6-8**). However, the influence of base with respect to yield was found to be negligible. Nevertheless, in the absence of a base, the reaction was completed within 30 minutes to provide the desired product **3a** in 97% yield (**Table 2.2, entry 9**).

Having realized the optimized condition, the scope of different amines in transamidation reaction was investigated with *N*-tosyl *N*-phenyl 2-oxo-2-phenylacetamide (**1k**) (**Table 2.3**). Initially, linear and branched primary alkyl amines such as *n*-propyl, *n*-butyl, *n*-hexyl, *iso*-propyl, *iso*-pentyl, cyclopropyl and cyclohexyl-amines were subjected to the transamidation at room temperature. To our delight, all these reactions proceeded very smoothly and provided a library of *α*–ketoamides **3b-3h** in 89-95% yields. Likewise, electron donating and withdrawing groups functionalized benzyl amines also participated in the transamidation reaction and provided the desired products **3i** and **3j** in 93-95% yields. Interestingly, heteroaromatic amines such as 2-aminomethyl pyridine and 2-aminoethyl pyridine also acted as efficient nucleophiles in the transamidation process and provided the desired products **3k** and **3l** in 95% and 93% yields, respectively.

Table 2.3 Transamidation of *N*-tosyl *α*–ketoamide (**1k**) with different amines.[a,b]



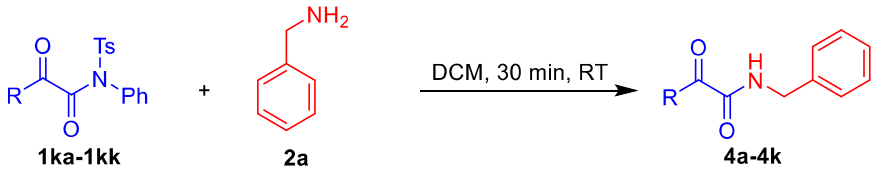
[a]Reaction conditions: Amide **1k** (0.379 gm, 1 mmol) and amine (1.1 equiv.) were stirred in DCM (3 mL) at room temperature. [b]Isolated yields.

Similarly, acyclic, and cyclic secondary amines such as diethylamine, pyrrolidine, piperidine, morpholine and *N*-benzhydryl piperazine participated in transamidation process

efficiently and gave the desired products **3m-3r** in good to excellent yields. Further, the transamidation of **1k** was investigated with arylamines such as aniline, 4-methoxy and 4-methyl anilines under optimized conditions. However, no reaction was observed with anilines suggesting that the nucleophilicity of amines play important role in transamidation reactions (**Table 2.3, 3s-3u**).

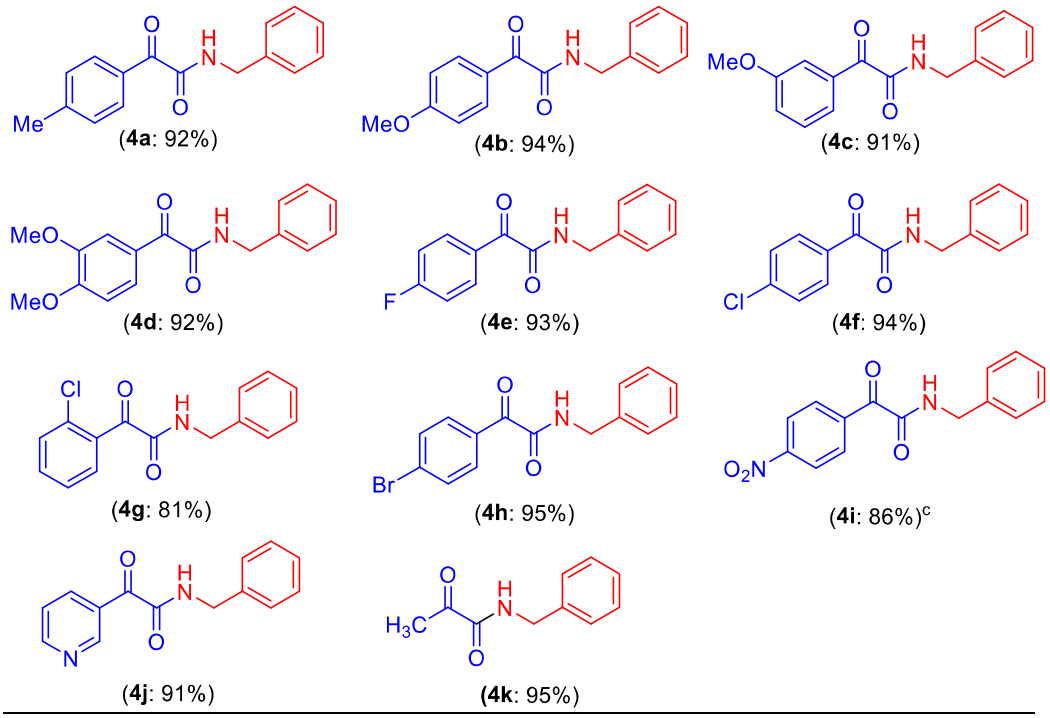
Having explored the scope of amines, different *N*-tosyl protected aryl *α*–ketoamides (**1ka-1ki**) were examined in transamidation reaction with benzylamine to attest broad scope of the developed methodology (**Table 2.4**). It was pleasant to observe that electron donating (e.g. Me and OMe) as well as withdrawing groups (e.g. F, Cl, and Br) functionalized (i.e. on aryl ring) *N*-tosyl *N*-phenyl *α*–ketoamides **1ka-1kh** readily underwent transamidation within 30 minutes to provide the desired products **4a-4h** in 81-95% yields. However, strong electron withdrawing group such as 4-NO_2 functionalized substrate **1ki** took three hours to provide the desired product **4i** in 86% yield. Furthermore, heteroaryl *α*–ketoamide **1kj** also efficiently participated in the transamidation reaction and provided the desired product **4j** in 91% yield. Having examined the transamidation of various aryl *α*–ketoamides, an alkyl *α*–ketoamide i.e. 2-oxo-*N*-phenyl-*N*-tosylpropanamide (**1kk**) was subjected to the transamidation with benzylamine under optimized conditions. It was pleasant to observe that the transamidation proceeded smoothly at room temperature and provided the desired product **4k** in 95% yield, witnessing a broad scope of the developed methodology.

Table 2.4 Transamidation of different *N*-tosyl *α*–ketoamides with benzylamine.[a,b,c]



1ka-1kk + **2a** → **4a-4k**

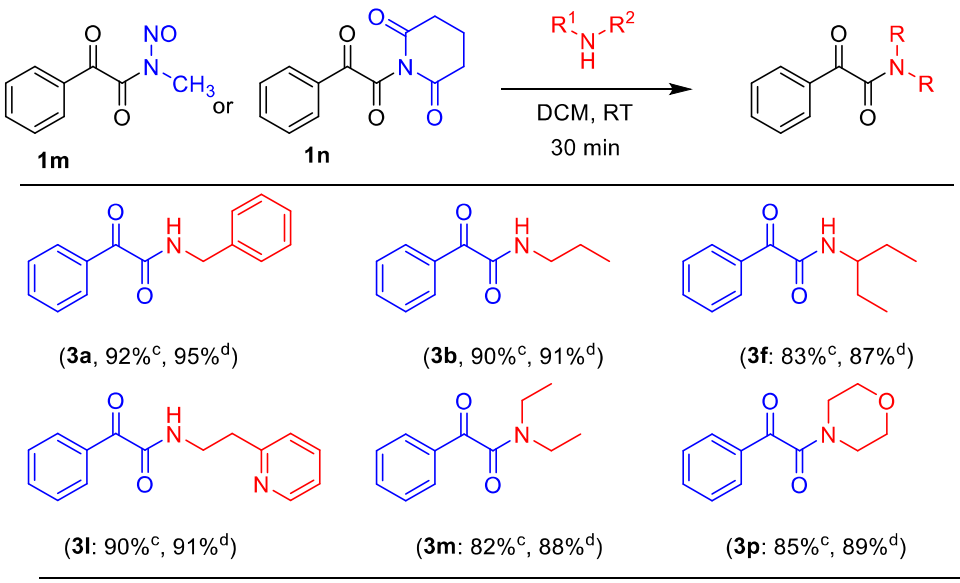
1ka:R=4-MePh; **1kb:**R=4-OMePh;**1kc:**R=3-OMePh
1kd:R=3,4-di-OMePh; **1ke:**R=4-FPh; **1kf:**R=4-ClPh;**1kg:**R=2-ClPh
1kh:R=4-BrPh;**1ki:**R=4-NO_2Ph; **1kj:**R=3-Pyridyl; **1kk**:R=Me



[a]Reaction conditions: Amide **1ka-1kk** (1 mmol) and benzylamine (120 µL, 1.1 equiv.) were stirred in DCM (3 mL) at room temperature. [b]Isolated yields. [c]The reaction was carried out for 3 hours.

Furthermore, the scope of transamidation in other activated amides, such as *N*-nitroso *α*-ketoamide (**1m**) and 2-oxo-*N*-acyl glutarimide (**1n**) was investigated with selected amines under the optimized condition developed for *N*-tosyl-amides (**Table 2.5**). To our delight, various primary and secondary *α*-ketoamides were achieved in 82-95% yields from **1m** and **1n** *via* transamidation within 30 minutes at room temperature.

Table 2.5 Transamidation of *N*-nitroso *α*–ketoamide (**1m**) and *N*-acyl glutarimide (**1n**) with amines.[a,b]



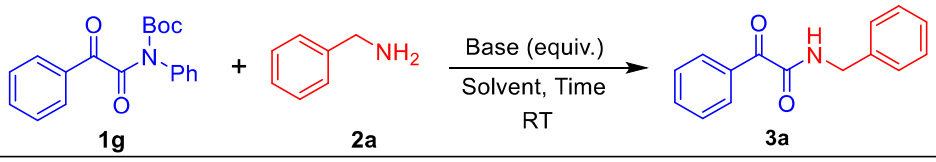
[a]Reaction conditions: Amide **1m** or **1n** (1 mmol) and amine (1.1 equiv.) were stirred in DCM (3 mL) at room temperature. [b]Isolated yields. [c]Yields from **1m**. [d]Yields from **1n**.

Among the different activated amides used in transamidation reactions, *N*-Boc-amides received special attention [4-7]. Because, *N*-Boc-amides can be easily generated from existing primary and secondary amides under mild conditions. As indicated in the introduction, simple *N*-Boc amides are well investigated in transamidation reactions under different reaction conditions, including under nickel [4a] and palladium [4b] catalysis, base [6a, b] or solvent [6e] promoted conditions, etc. [4]. Considering these reports, *N*-Boc *N*-phenyl *α*–ketoamide (**1g**) was subjected to transamidation with benzylamine in different solvents without and with bases.

The optimization of reaction condition was investigated using *N*-Boc *N*-phenyl *α*-ketoamide (**1g**, 1 mmol) and benzylamine (**2a**, 1.5 mmol) as model substrates (**Table 2.6**).

Initially, the reaction was tested in different solvents (AR grade) including THF, acetonitrile, dichloromethane, toluene and DMSO in the absence of base or additives.

Table 2.6 Optimization of transamidation of *N*-Boc *N*-phenyl *α*-ketoamide (**1g**) with benzylamine (**2a**).[a,b]



1g **2a** **3a**

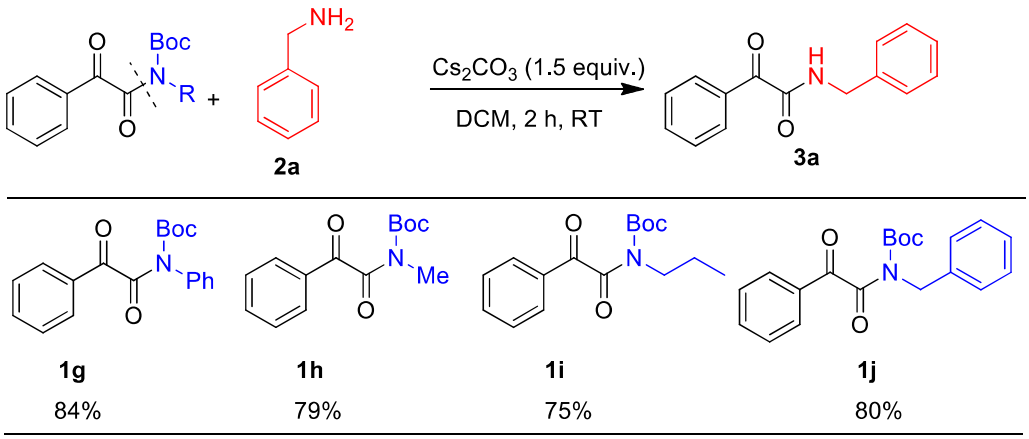
Entry	Base	Equiv.	Solvent	Time	Yield(%)[b]
1.	-	-	THF	6 h	nr
2.	-	-	CH_3CN	6 h	nr
3.	-	-	DCM	6 h	nr
4.	-	-	Toluene	6 h	nr
5.	-	-	DMSO	6 h	nr
6.	Cs_2CO_3	1.0	DCM	6 h	68
7.	K_2CO_3	1.0	DCM	6 h	20
8.	CsF	1.0	DCM	6 h	34
9.	Et_3N	1.0	DCM	6 h	21
10.	DBU	1.0	DCM	6 h	66
11.	DABCO	1.0	DCM	6 h	47
12.	Pyridine	1.0	DCM	6 h	nr
13.	**Cs_2CO_3**	**1.5**	**DCM**	**2 h**	**84**
14.	Cs_2CO_3	2.0	DCM	2 h	80[c]
15.	Cs_2CO_3	3.0	DCM	2 h	70[c]
16.	Cs_2CO_3	1.5	THF	2 h	70
17.	Cs_2CO_3	1.5	CH_3CN	2 h	77

[a]Reaction conditions: Substrate (**1g,** 1 mmol, 325 mg), benzylamine (**2a**, 1.5 mmol, 0.164 mL) and base were stirred in solvents (AR grade) (3 mL) for an appropriate time. [b]Isolated yield.[c]5-10% of Boc-deprotected parent amide was observed.

However, the desired product **3a** was not observed even after 6 h at room temperature (**Table 2.6, entries 1-5**). Therefore, the reaction was further investigated in the presence of different organic and inorganic bases (1.0 equiv.) in dichloromethane (**Table 2.6, entries 6-12**). Among them, Cs_2CO_3 gave the desired product **3a** relatively in high yield, i.e. 68% (**Table 2.6, entry 6**). The optimization of the reaction was further continued by increasing the equivalence of Cs_2CO_3. To our delight, **3a** was achieved in 84% yield in the presence of 1.5 equiv. of Cs_2CO_3 within 2 h at room temperature (**Table 2.6, entry 13**).

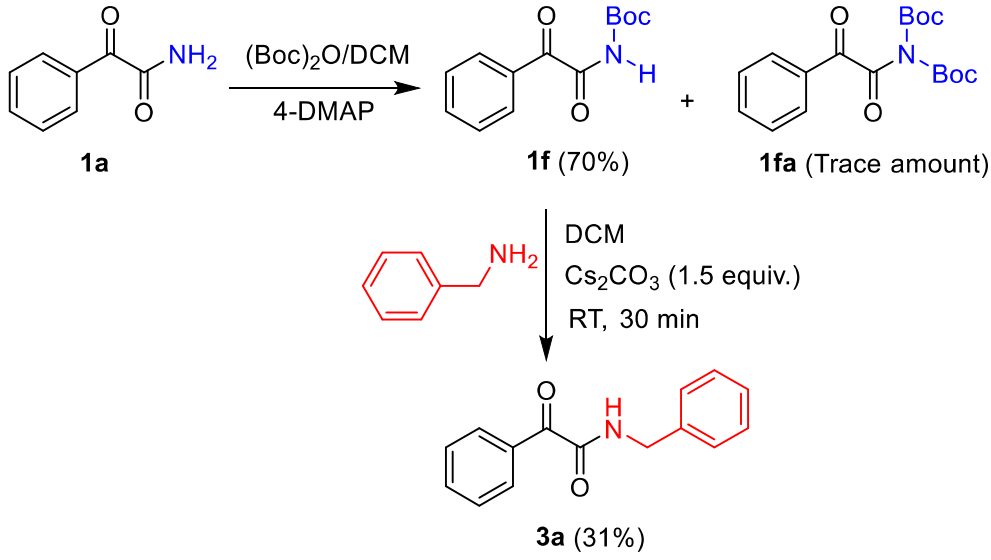
In fact, a decrease in yield was observed with 2.0 and 3.0 equiv. of Cs_2CO_3 (**Table 2.6, entries 14-15**). In these cases, considerable amount (~ 5-10%) of deprotection of Boc group in **1g** was observed indicating that *N*-Boc amides are not stable under strong basic conditions. Moreover, the transamidation reactions in THF and acetonitrile in the presence of Cs_2CO_3 also gave the desired product **3a**, however in low yields (**Table 2.6, entries 16** and **17**).

This optimization study reveals that transamidation in *N*-Boc *α*–ketoamides can be achieved efficiently in dichloromethane in the presence of Cs_2CO_3 (1.5 equiv.) at room temperature. Under this condition, *N*-Boc *N*-phenyl *α*–ketoamide (**1g**), *N*-Boc *N*-methyl *α*–ketoamide (**1h**), *N*-Boc *N*-propyl *α*–ketoamide (**1i**) and *N*-Boc *N*-benzyl *α*–ketoamide (**1j**) were participated in transamidation with benzylamine and provided **3a** in 75-84% yields within two hours (**Scheme 2.2**).



Scheme 2.2 Transamidation of different *N*-Boc *α*-ketoamides with benzylamine.

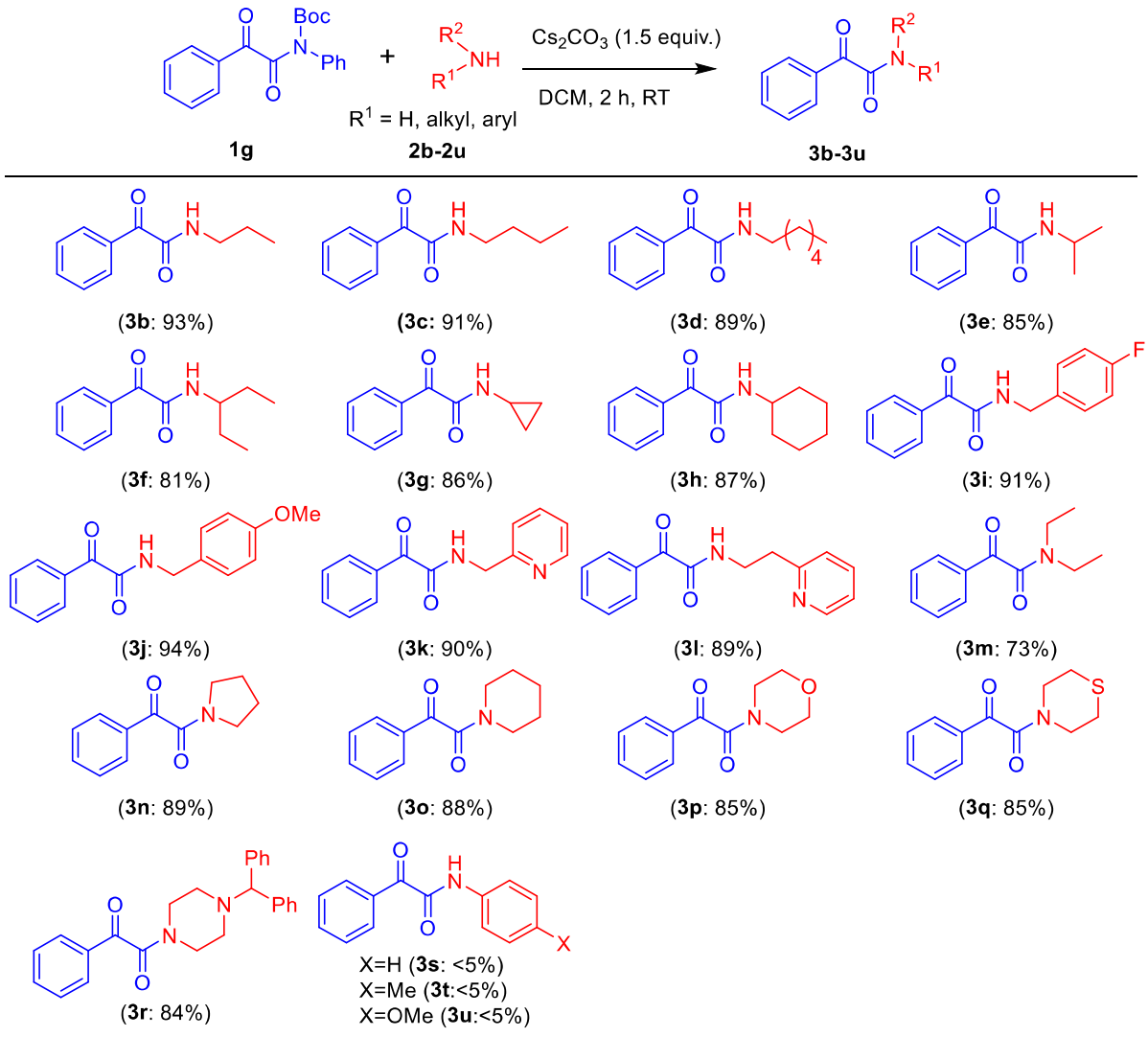
It is also worth mentioning that the mono-*N*-Boc amide **1f** was obtained as the major product while attempting the preparation of *N,N*-di-Boc-2-oxo 2-phenyl acetamide (**1fa**) from the primary amide **1a** (**Scheme 2.3**). Moreover, the transamidation of *N*-Boc 2-oxo 2-phenyl acetamide (**1f**) with benzylamine gave the desired product **3a** only in 31% yield.



Scheme 2.3 Preparation of *N*-Boc *α*-ketoamide **1f** and transamidation with benzylamine.

Further, the scope of different amines in transamidation was investigated with *N*-Boc *N*-phenyl *α*–ketoamide (**1g**) in the presence of Cs_2CO_3 (**Table 2.7**). Initially, the amide **1g** was subjected to transamidation with different primary alkyl and benzyl amines under optimized conditions.

Table 2.7 Transamidation of *N*-Boc *α*-ketoamide (**1g**) with different amines.[a,b]

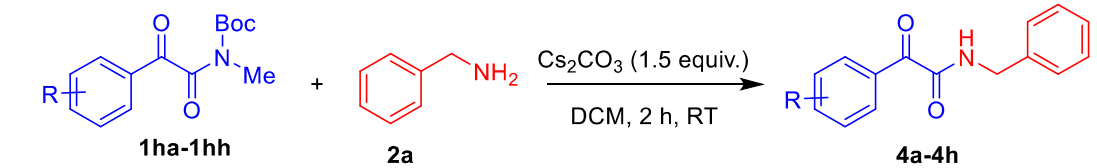


[a]Reaction conditions: Amide **1g** (325 mg, 1 mmol), Cs_2CO_3 (489 mg, 1.5 equiv.), and amine (1.5 equiv.) were stirred in DCM (3 mL) at room temperature. [b]Isolated yields.

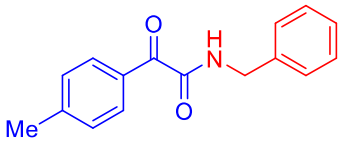
These reactions proceeded smoothly and provided the desired products **3b-3l** in comparable yields (i.e. 81-94%) to that of *N*-tosyl amides. Further, various secondary amines were subjected to transamidation with amide **1g**. It was pleasant to observe that all these secondary amides participated in the transamidation reaction and provided the desired products **3m-3r** in 73-89% yields. It is worth noting that the deprotection of Boc-group in amide **1g** was observed in ~5-10% during the transamidation reaction with secondary amines. Moreover, as shown in the **Table 2.6**, more amount of Boc-deprotection was observed with the increased amount of base Cs_2CO_3. These data indicate that a strong basic condition (i.e. reactions with secondary amines or in the presence of more amount of base) can lead to deprotection of Boc group in the *N*-Boc amides. However, *N*-tosyl amides were found to be stable in which no deprotection of tosyl groups was observed with secondary amines during the transamidation reactions. Nevertheless, like *N*-tosyl amide, *N*-Boc amide also failed to react with anilines in the presence of Cs_2CO_3 (**Table 2.7**, **3s-3u**).

Having explored the scope of different amines, the transamidation of a wide range of functionalized *N*-Boc *α*–ketoamides withbenzylamine was investigated under optimized conditions (**Table 2.8**). To our delight, *N*-Boc *α*-ketoamides bearing electron donating and withdrawing groups (i.e. on aryl ring) such as methyl, methoxy, fluoro, chloro and bromo underwent transamidation smoothly and provided the corresponding *α*–ketoamides **4a-4h** in 72-90% yields. The effect of substitution on the aryl ring was found to be negligible with respect yields.

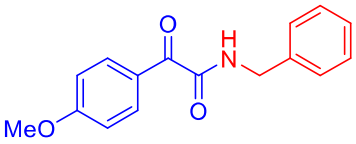
Table 2.8 Transamidation of different *N*-Boc *N*-methyl *α*-ketoamides with benzylamine.[a,b]



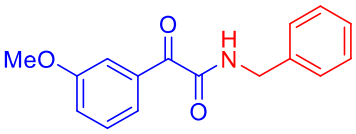
1ha:R=4-Me; **1hb:**R= 4-OMe; **1hc:**R=3-OMe
1hd:R= 3,4-di-OMe; **1he:**R=4-F; **1hf:**R=4-Cl
1hg:R=2-Cl;**1hh:**R=4-Br



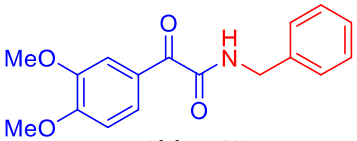
(**4a**: 89%)



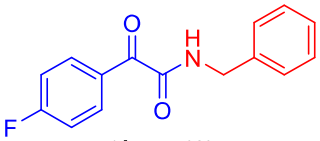
(**4b**: 90%)



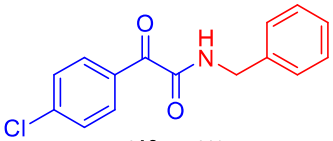
(**4c**: 87%)



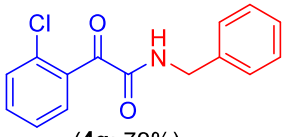
(**4d**: 87%)



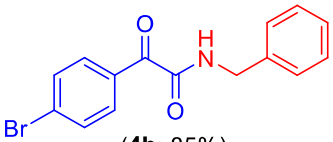
(**4e**: 82%)



(**4f**: 83%)



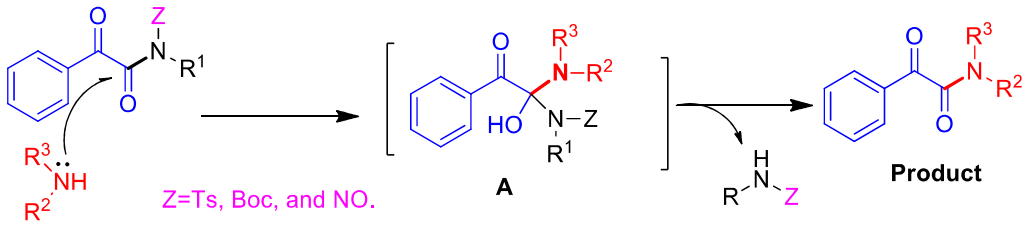
(**4g**: 72%)



(**4h**: 85%)

[a]Reaction conditions: Amide **1ha-1hh** (1 mmol), Cs_2CO_3 (489 mg, 1.5 equiv.), benzylamine (0.164 mL, 1.5 equiv.) in DCM (3 mL) at room temperature. [b]Isolated yields.

Overall, these studies indicate that *N*-tosyl *α*–ketoamides are providing better results than *N*-Boc *α*–ketoamides in terms of yields and reaction conditions. Moreover, the reactivity of *α*–ketoamides is comparable or better than simple amides. A plausible mechanism for the transamidation reaction is shown in **Scheme 2.4** [6]. The reaction of activated *α*–ketoamide with amines generates the tetrahedral intermediate **A**. This unstable intermediate undergoes C-N bond cleavage to provide the desired transamidation product.



Scheme 2.4 Proposed mechanism for transamidation of *α*–keto amides with amines.

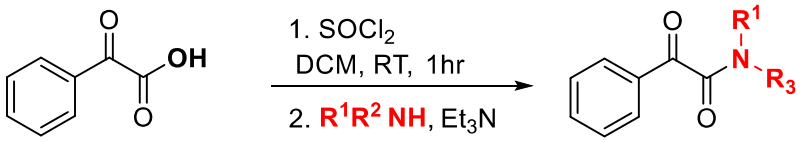
2.3 Conclusion

In conclusion, transamidation reaction in *α*–ketoamides was demonstrated with a wide range of *N*-tosyl and *N*-Boc *α*–ketoamides at room temperature. Transamidation of *N*-tosyl *α*–ketoamides with alkyl amines carried out in the absence of catalyst, base or additives, while $Cs_2CO_3$was used in the case of *N*-Boc *α*–ketoamides. Broad substrate scope and excellent functional group tolerance are the merits of the developed methodology. We believe that this methodology will be highly useful for combinatorial synthesis *α*–ketoamides in a short span of time.

2.4 Experimental section

2.4.1. General procedure for the synthesis of *α*-Ketoamides (1a-1c, 1d, 1e and 1n)

The *α*-ketoamides **1a-1c** were prepared using the literature reports [21]. The amides **1d**, **1e**, and **1n** were synthesized using following procedure-

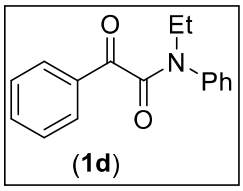


2-Oxo-2-phenylacetic acid (1 mmol, 0.150 gm) was taken in a round bottom flask under N_2 atomosphere in DCM and cooled to 0 °C to which thionyl chloride (2 mmol, 0.145 mL)

was added. The reaction mixture was allowed to stir for 1 hour after which a mixture of amine (1.5 mmol) and triethylamine (2 mmol, 0.264 mL) was added at 0 °C and stirred till the completion of reaction at room temperature. Reaction was monitored by thin layer chromatography. After that, the reaction mixture was diluted with ethyl acetate, and washed with brine and H_2O. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give crude product, which was purified by column chromatography on silica gel to afford the title compounds **1d**, **1e**, and **1n**.

2.5 Analytical Data of 1d, 1e and 1n

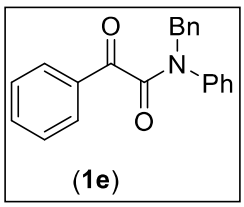
2.5.1. *N*-ethyl-2-oxo-*N*-2-diphenylacetamide (1d) [22]



(**1d**)

The title compound was obtained as a pale-yellow solid. M.p. 92–94 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.62; Yield 76% (191 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.83 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.4 Hz, 2H), 7.42 (t, J = 7.7 Hz, 2H), 7.23 (d, J = 6.9 Hz, 2H), 7.12 (dd, J = 7.3, 1.7 Hz, 2H), 3.97 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 190.8, 166.6, 139.3, 134.1, 133.6, 129.4, 129.3, 128.7, 128.6, 128.3, 43.5, 12.9.

2.5.2. *N*-benzyl-2-oxo-*N*,2-diphenylacetamide (1e) [23a]

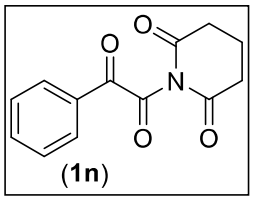


(**1e**)

The title compound was obtained sticky solid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.60; Yield 95% (235 mg). ^{1}H NMR (500 MHz,

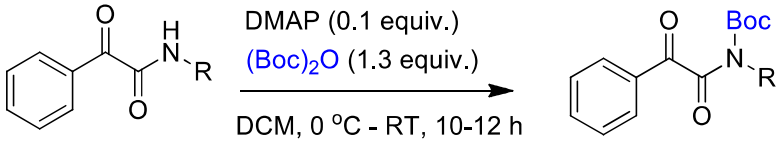
$CDCl_3$) δ = 7.88–7.82 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.33–7.28 (m, 5H), 7.17–7.11 (m, 3H), 6.95 (dd, J = 7.8, 1.5 Hz, 2H), 5.09 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 190.5, 166.9, 139.3, 136.2, 134.2, 133.5, 129.3, 129.2, 128.8, 128.7, 128.6, 128.3, 128.2, 127.8, 52.3.

2.5.3. 1-(2-oxo-2-phenylacetyl)piperidine-2,6-dione (1n)



The title compound was obtained as a dirty white wax. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.55; Yield 80% (195 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.01–8.03 (m, 2H), 7.65 (td, J = 7.6, 1.1 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 2.75 (td, J = 6.6, 1.5 Hz, 4H), 2.06 (dt, J = 6.3, 5.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 183.8, 171.8, 166.5, 134.7, 131.4, 130.5, 128.7, 32.6, 16.6. HRMS: Calc. for $C_{13}H_{12}NO_4$ $[M+H]^+$: 246.0766, Obser.: 246.0766.

2.6 General procedure for the synthesis of *N*-Boc *α*-ketoamides (1f-1j, 1ha-1hh)



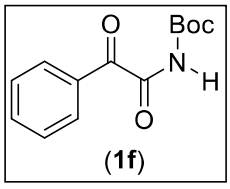
R= Alkyl or aryl

To a stirred solution of amide (1.0 mmol, 1.0 equiv.) and DMAP (0.1 equiv., 12 mg) in dichloromethane (5 mL) was added di-*tert*-butyl dicarbonate (Boc_2O) (1.3 equiv., 0.3 mL) or (2.6 equiv., 0.6 mL for **1f**) at room temperature. The resulting reaction mixture was

allowed to stir for 10-12 h at room temperature. After completion, the reaction mixture was quenched with saturated solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (1 × 20 mL) and brine (1 × 20 mL), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_2: ethyl acetate/hexane) to obtain the *N*-Boc-*α*-keto-amides **1f-1j, 1ha-1hh**.

2.7 Analytical data

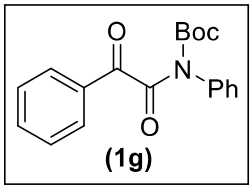
2.7.1. *tert*-Butyl (2-oxo-2-phenylacetyl)carbamate (1f)



(1f)

The title compound was obtained as a colorless liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (70:30), R_f = 0.35; Yield 70% (174 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.46 (s, 1H), 8.16 (s, 2H), 7.67 (d, J = 0.7 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.4, 149.3, 134.8, 132.3, 130.5, 128.8, 84.2, 27.8. HRMS: Calc. for $C_{13}H_{16}NO_4$ $[M+H]^+$: 250.1079, Obser.: 250.1079.

2.7.2. *tert*-Butyl (2-oxo-2-phenylacetyl)(phenyl)carbamate (1g)

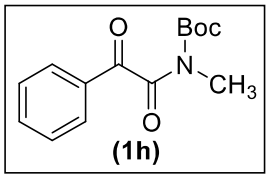


(1g)

The title compound was obtained as a white solid. M.p.116–118°C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:05), R_f = 0.32. Yield = 85% (276 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.99

(dd, J = 8.3, 1.2 Hz, 2H), 7.64 (dd, J = 11.3, 3.9 Hz, 1H), 7.55–7.45 (m, 4H), 7.43 (dd, J = 8.4, 6.3 Hz, 1H), 7.33–7.31 (m, 2H), 1.27 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.4, 169.4, 151.6, 135.7, 134.2, 132.9, 129.5, 129.3, 128.8, 128.8, 128.2, 86.1, 27.5. HRMS: Calc. for $C_{19}H_{19}NNaO_4$ $[M+Na]^+$: 348.1212, Obser.: 348.1229.

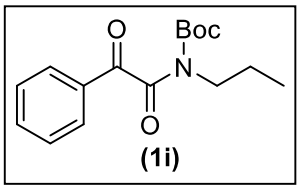
2.7.3. *tert*-Butylmethyl(2-oxo-2-phenylacetyl)carbamate (1h) [23b]



(1h)

The title compound was obtained as a white solid. M.p. 72–74°C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:05), R_f = 0.62. Yield = 83% (218 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.86–7.84 (m, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 3.29 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.7, 169.9, 151.7, 134.1, 132.9, 129.4, 128.7, 86.0, 29.8, 27.5.

2.7.4. *tert*-Butyl (2-oxo-2-phenylacetyl)(propyl)carbamate (1i)

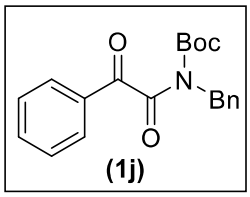


(1i)

The title compound was obtained as a colorless sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:05), R_f = 0.56. Yield = 81% (236 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.83 (d, J = 8.1 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H),

3.79– 3.74 (m, 2H), 1.71 (dt, *J* = 8.9, 6.7 Hz, 2H), 1.26 (s, 9H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.6, 169.6, 151.7, 133.9, 132.9, 129.3, 128.6, 85.6, 44.7, 27.4, 21.5, 11.1. HRMS: Calc. for $C_{14}H_{17}NNaO_4$ $[M+Na]^+$: 286.1055, Obser.: 286.1062.

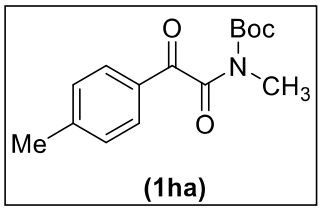
2.7.5. *tert*-Butyl benzyl(2-oxo-2-phenylacetyl)carbamate (1j)



(1j)

The title compound was obtained as a white solid. M.p. 51-52 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:05), R_f = 0.35. Yield = 86% (292 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.83–7.84 (m, 2H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 1H), 4.99 (s, 2H), 1.25 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.5, 169.7, 151.7, 136.7, 134.0, 132.9, 129.4, 128.8, 128.6, 128.0, 127.7, 86.0, 46.4, 27.5. HRMS: Calc. for $C_{14}H_{17}NNaO_4$ $[M+Na]^+$: 362.1368, Obser: 362.1352.

2.7.6. *tert*-Butyl methyl(2-oxo-2-(*p*-tolyl)acetyl)carbamate (1ha)

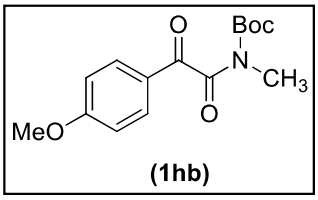


(1ha)

The title compound was obtained as a colorless sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.58. Yield = 80% (222 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.74 (d, *J* =

8.2 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 3.29 (s, 3H), 2.43 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 187.6, 170.0, 151.7, 145.2, 130.4, 129.5, 129.5, 85.9, 29.8, 27.5, 21.8. HRMS: Calc. for $C_{15}H_{19}NNaO_4$ $[M+Na]^+$: 300.1212, Obser.: 300.1213.

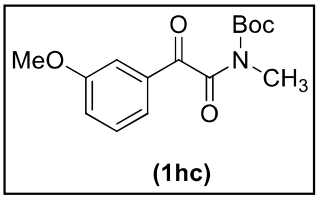
2.7.7. *tert*-Butyl(2-(4-methoxyphenyl)-2-oxoacetyl)(methyl)carbamate (1hb)



(1hb)

The title compound was obtained as a colorless sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:05), R_f = 0.58. Yield = 81% (237 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 8.9 Hz, 2H), 6.95 (d, 2H), 3.86 (s, 3H), 3.27 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.7, 170.0, 164.2, 151.7, 131.7, 125.8, 114.0, 85.7, 55.5, 29.7, 27.5. HRMS: Calc. for $C_{15}H_{19}NNaO_5$ $[M+Na]^+$: 316.1161, Obser.: 316.1161.

2.7.8. *tert*-Butyl(2-(3-methoxyphenyl)-2-oxoacetyl)(methyl)carbamate (1hc)

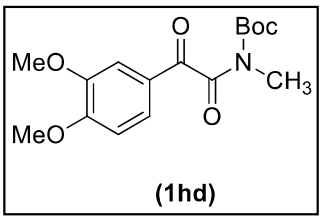


(1hc)

The title compound was obtained as a colorless sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.53. Yield = 78% (229 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42–7.33 (m, 3H), 7.13–7.15 (m, 1H), 3.84 (s, 3H), 3.28 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.5, 169.7, 159.9,

151.7, 134.2, 129.7, 122.4, 120.8, 112.9, 85.9, 55.5, 29.7, 27.5. HRMS: Calc. for $C_{15}H_{19}NNaO_5$ $[M+Na]^+$: 316.1161, Obser.: 316.1159.

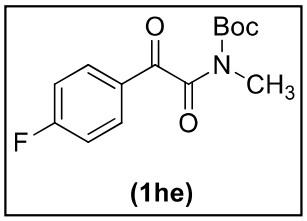
2.7.9. *tert*-Butyl(2-(3,4-dimethoxyphenyl)-2-oxoacetyl)(methyl)carbamate (1hd)



(1hd)

The title compound was obtained as a colorless sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:05), R_f = 0.56. Yield = 76% (245 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47 (d, J = 1.7 Hz, 1H), 7.31 (dd, J = 8.3, 1.8 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 3.92 (d, J = 9.5 Hz, 6H), 3.27 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.8, 169.8, 154.1, 151.7, 149.3, 126.0, 125.1, 110.3, 110.2, 85.6, 56.1, 56.0, 29.8, 27.5. HRMS: Calc. for $C_{14}H_{17}NNaO_4$ $[M+Na]^+$: 286.1055, Obser.: 286.1062.

2.7.10. *tert*-Butyl (2-(4-fluorophenyl)-2-oxoacetyl)(methyl)carbamate (1he)

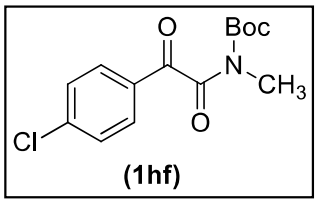


(1he)

The title compound was obtained as a colorless sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:05), R_f = 0.55. Yield = 79% (222 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.89–7.86 (m, 2H), 7.17 (t, J = 8.6 Hz, 2H), 3.28 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 186.2, 169.6, 166.2 (d, J = 256.8)J, 151.8, 132.0 (d, J = 9.6 Hz), 129.4 (d, J = 2.9 Hz),

116.1 (d, *J*=22.3 Hz, 86.0, 29.8, 27.6. HRMS: Calc. for $C_{14}H_{16}FNNaO_4$ $[M+Na]^+$: 304.0961, Obser.: 304.0958.

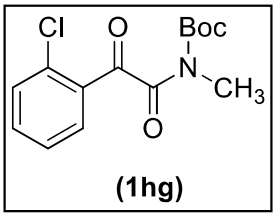
2.7.11. *tert*-Butyl (2-(4-chlorophenyl)-2-oxoacetyl)(methyl)carbamate (1hf)



(1hf)

The title compound was obtained as pale-yellow sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:05), R_f = 0.53. Yield = 78% (232 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 6.7, 2H), 7.47 (d, 2H), 3.28 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*= 186.5, 169.4, 151.8, 140.6, 131.3, 130.7, 129.2, 86.1, 29.9, 27.6. HRMS: Calc. for $C_{14}H_{16}NNaO_4$ $[M+Na]^+$: 320.0666, Obser.: 320.0664.

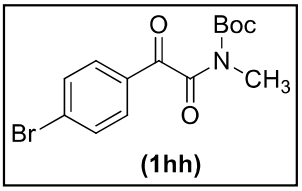
2.7.12. *tert*-Butyl (2-(2-chlorophenyl)-2-oxoacetyl)(methyl)carbamate (1hg)



(1hg)

The title compound was obtained as a pale sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:05), R_f = 0.51. Yield = 73% (217 mg). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*= 8.13 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.54–7.51 (m, 1H), 7.45–7.41 (m, 2H), 3.27 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* = 185.1, 169.7, 152.1, 135.0, 134.7, 132.5, 131.2, 131.0, 127.2, 85.7, 29.8, 27.6. HRMS: Calc. for $C_{14}H_{16}ClNNaO_4$ $[M+Na]^+$: 320.0666, Obser.: 320.0662.

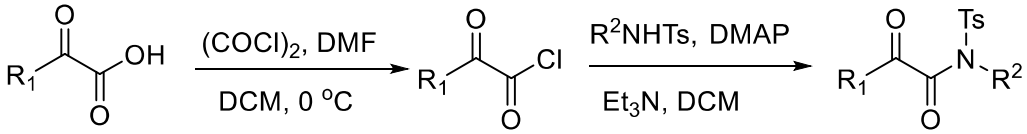
2.7.13. *tert*-Butyl (2-(4-bromophenyl)-2-oxoacetyl)(methyl)carbamate (1hh)



(1hh)

The title compound was obtained as colorless sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:05), R_f = 0.51. Yield = 75% (256 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.70 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 3.27 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.6, 169.4, 151.7, 132.1, 131.7, 130.7, 129.3, 86.0, 29.8, 27.6. HRMS: Calc. for $C_{14}H_{17}BrNNaO_4$ $[M+Na]^+$: 364.0160, Obser.: 364.0162.

2.8 General procedure for the synthesis of *N*-tosyl *α*-ketoamides (1k, 1l and 1ka-1kk) [24]

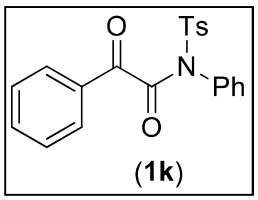


To a solution of 2-oxo-aryl/alkyl acetic acid (1 mmol) in CH_2Cl_2 (2 mL) were added oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv.) and DMF (two drops) at 0 °C. The mixture was stirred until gas evolution stopped. Then, the reaction mixture was concentrated under reduced pressure and was used directly in the next step. To a mixture of the *N*-phenyl sulfonamide (1 mmol), DMAP (0.5 mmol%) and Et_3N (0.155 mL, 2 mmol) in CH_2Cl_2 (10 mL) was added slowly the acyl chloride made above in CH_2Cl_2 (2 ml) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was washed with 5% HCl, brine and H_2O. The organic layer was dried over Na_2SO_4, filtered, and

evaporated under reduced pressure to give crude product, which was purified by column chromatography on silica gel to afford *N*-tosyl *α*-ketoamides **1k, 1l** and **1ka-1kk**.

2.9 Analytical data

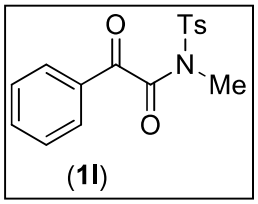
2.9.1. 2-Oxo-*N*,2-diphenyl-*N*-tosylacetamide (1k) [25]



(**1k**)

The title compound was obtained as a colorless oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.52; Yield 93% (351 mg). IR: 3061, 2921, 1700, 1377, 1229, 1173. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.94 (d, J = 7.4 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.63–7.62 (m, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.45–7.32 (m, 5H), 7.13 (d, J = 7.3 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.6, 166.7, 145.9, 134.6, 134.0, 133.4, 132.7, 130.5, 130.2, 129.7, 129.6, 129.4, 129.0, 128.9, 21.8.

2.9.2. *N*-Methyl-2-oxo-2-phenyl-*N*-tosylacetamide (1l) [25]

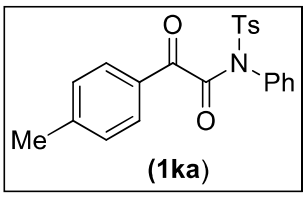


(**1l**)

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (70:30), R_f = 0.60; Yield 78% (137 mg). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* = 7.95–7.93 (m, 2H), 7.93–7.89 (m, 2H), 7.66–7.62 (m, 1H), 7.52 (dd, *J* = 10.6, 4.6 Hz, 2H), 7.39 (d, *J* = 6.7 Hz, 2H), 3.24 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* = 188.0, 167.2, 145.9, 134.4,

133.4, 132.7, 130.1, 129.6, 128.8, 128.3, 30.7, 21.7. HRMS: Calc. for $C_{16}H_{16}NO_4S$ $[M+H]^+$: 318.0800, Obser.: 318.0807.

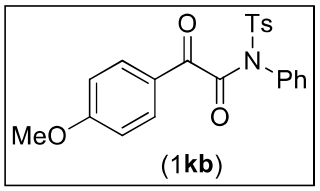
2.9.3. 2-Oxo-*N*-phenyl-2-(*p*-tolyl)-*N*-tosylacetamide (1ka) [25]



(1ka)

The title compound was obtained as pale-yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.48; Yield 82% (321 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.80 (dd, J = 25.8, 6.6 Hz, 4H), 7.44-7.31 (m, 8H), 7.14 (s, 2H), 2.47 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.2, 166.7, 145.9, 145.8, 134.1, 133.5, 130.5, 130.2, 130.1, 129.7, 129.7, 129.4, 129.0, 21.9, 21.7.

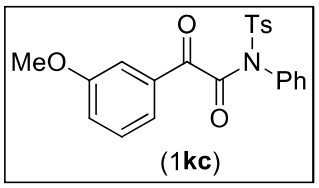
2.9.4. 2-(4-methoxyphenyl)-2-Oxo-*N*-phenyl-*N*-tosylacetamide (1kb) [25]



(1kb)

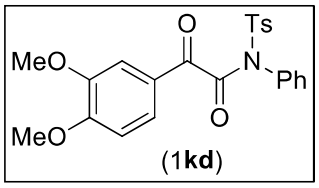
The title compound was obtained as pale-yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.52; Yield 83% (338 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.88 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H), 7.42–7.33 (m, 4H), 7.14 (d, J = 7.3 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.2, 166.9, 164.8, 145.7, 134.2, 133.6, 132.0, 130.6, 130.1, 129.7, 129.4, 129.0, 125.6, 114.3, 55.6, 21.7.

2.9.5. 2-(3-methoxyphenyl)-2-Oxo-*N*-phenyl-*N*-tosylacetamide (1kc)



The title compound was obtained as pale-yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.55; Yield 81% (330 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.75 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.5 Hz, 1H), 7.45–7.41 (m, 3H), 7.41–7.33 (m, 4H), 7.20–7.17 (m, 1H), 7.13 (d, J = 7.3 Hz, 2H), 3.85 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.3, 166.5, 159.9, 145.8, 133.3, 130.5, 130.2, 129.9, 129.7, 129.4, 129.0, 122.7, 121.5, 112.7, 55.4, 21.7. HRMS: Calc. for $C_{22}H_{20}NO_5S$ $[M+H]^+$: 410.1062, Obser.: 410.1069.

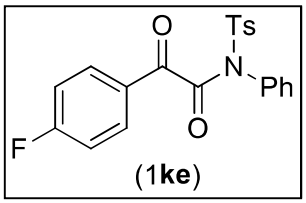
2.9.6. 2-(3,4-dimethoxyphenyl)-2-Oxo-*N*-phenyl-*N*-tosylacetamide (1kd)



The title compound was obtained as a pale-yellow sticky solid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.54; Yield 80% (350 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.79 (d, J = 8.1 Hz, 2H), 7.51 (dd, J = 8.3, 1.8 Hz, 1H), 7.42 (dd, J = 8.7, 6.1 Hz, 2H), 7.36 (dd, J = 14.2, 7.9 Hz, 4H), 7.13 (d, J= 7.3 Hz, 2H), 6.94 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.3, 166.6, 154.7, 149.4, 145.8, 134.2, 133.6, 130.6, 130.1, 129.7, 129.4, 129.1, 125.8, 125.8, 110.4, 110.1, 56.2, 56.0, 21.7.

HRMS: Calc. for $C_{23}H_{22}NO_6S$ $[M+H]^+$: 440.1168, Obser.: 440.1172.

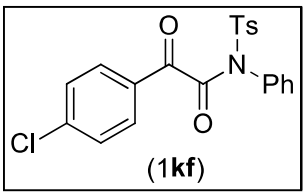
2.9.7. 2-(4-fluorophenyl)-2-Oxo-*N*-phenyl-*N*-tosylacetamide (1ke) [25]



(1**ke**)

The title compound was obtained as a pale-yellow solid. M.p. 159–161 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.52; Yield 75% (297 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.98 (dd, J = 8.7, 5.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.39 (ddd, J = 24.7, 16.3, 7.8 Hz, 5H), 7.23–7.17 (m, 2H), 7.13 (d, J = 7.4 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 185.9, 167.5, 166.4(d, J =256 Hz), 166.4, 145.9, 133.8, 133.3(d, J =9.8 Hz), 132.2, 130.4, 130.2, 129.7, 129.4, 129.1(d, J =23.2 Hz), 128.9, 116.3, 116.2, 21.7.

2.9.8. 3, 2-(4-chlorophenyl)-2-Oxo-*N*-phenyl-*N*-tosylacetamide (1kf) [25]

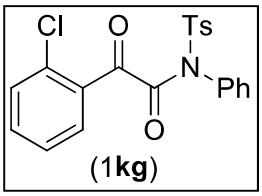


(1**kf**)

The title compound was obtained as a pale-yellow solid. M.p. 157–159 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.55; Yield 78% (322 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.89 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.46-7.34 (m, 5H), 7.12 (d, J = 7.4 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.3, 166.4, 146.0, 141.2, 133.8, 133.3, 131.1, 130.9, 130.4, 130.3,

129.5, 129.4, 129.0, 128.9, 21.8.

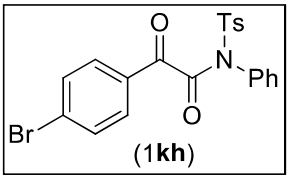
2.9.9. 2-(2-chlorophenyl)-2-Oxo-*N*-phenyl-*N*-tosylacetamide(1kg)



(1**kg**)

The title compound was obtained as a pale-yellow solid. M.p.158–151 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.50; Yield 74% (306 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.08 (s, 1H), 7.76 (d, J = 7.2 Hz, 2H), 7.52 (dt, J = 23.6, 7.7 Hz, 2H), 7.46–7.31 (m, 6H), 7.14 (d, J = 5.7 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 185.4, 166.1, 145.7, 135.1, 135.0, 134.0, 133.4, 132.4, 131.2, 131.0, 130.2, 130.1, 129.6, 129.4, 129.0, 127.1, 21.7. HRMS: Calc. for $C_{21}H_{18}NClO_4S$ $[M+H]^+$: 414.0567, Obser.: 414.0566.

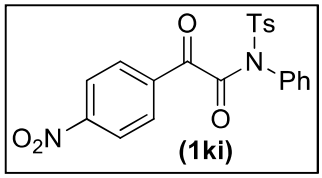
2.9.10. 2-(4-bromophenyl)-2-Oxo-*N*-phenyl-*N*-tosylacetamide (1kh) [25]



(1**kh**)

The title compound was obtained as pale-yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.50; Yield 78% (356 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.81 (d, J = 8.4 Hz, 2H), 7.73–7.67 (m, 4H), 7.46–7.34 (m, 5H), 7.12 (d, J = 7.4 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.5, 166.3, 146.0, 133.8, 133.3, 132.4, 131.5, 130.9, 130.4, 130.3, 130.1, 129.8, 129.5, 129.0, 21.8.

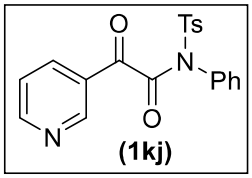
2.9.11. 2-(4-nitrophenyl)-2-Oxo-*N*-phenyl-*N*-tosylacetamide (1ki)



(1ki)

The title compound was obtained as a colorless sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.30; Yield 76% (321 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.39 (d, J = 8.8 Hz, 2H), 8.15 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.49–7.44 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 7.3 Hz, 2H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 185.7, 166.0, 151.0, 146.3, 137.3, 133.4, 133.0, 130.6, 130.5, 130.3, 129.9, 129.6, 129.0, 124.1, 21.8. HRMS: Calc. for $C_{21}H_{17}N_2O_6S$ $[M+H]^+$: 425.0807, Obser.: 425.0805.

2.9.12. 2-Oxo-*N*-phenyl-2-(pyridin-4-yl)-*N*-tosylacetamide (1kj)

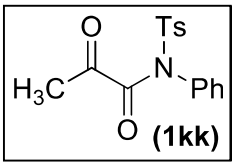


(1kj)

The title compound was obtained as a white solid. M.p. 114–116 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (70:30), R_f = 0.35; Yield 76% (288 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.15 (d, *J* = 1.5 Hz, 1H), 8.86 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.25–8.24 (m, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.51–7.44 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.37–7.33 (m, 2H), 7.12 (d, *J* = 7.4 Hz, 2H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.3, 166.0, 154.5, 150.9, 146.2, 136.6, 133.6, 133.2, 130.3, 129.8, 129.6,

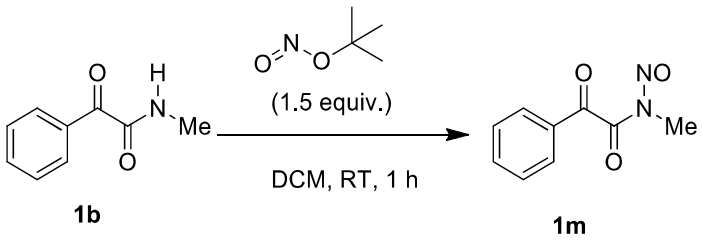
129.0, 128.5, 123.8, 21.8. HRMS: Calc. for $C_{20}H_{16}N_2NaO_4S$ $[M+Na]^+$: 403.0728, Obser.: 403.0728.

2.9.13. 2-Oxo-*N*-phenyl-*N*-tosylpropanamide (1kk)



The title compound was obtained as colorless oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.65; Yield 85% (268 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.66 (d, J = 8.4 Hz, 2H), 7.47–7.38 (m, 3H), 7.32 (d, J = 8.0 Hz, 2H), 7.07–7.05 (m, 2H), 2.52 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 194.6, 167.5, 145.9, 134.8, 133.4, 130.2, 130.1, 129.7, 129.4, 128.9, 26.8, 21.7. HRMS: Calc. for $C_{16}H_{16}NO_4S$ $[M+H]^+$: 318.0800, Obser.: 318.0798.

2.10 Synthesis of *N*-methyl-*N*-nitroso-2-oxo-2-phenylacetamide (1m)

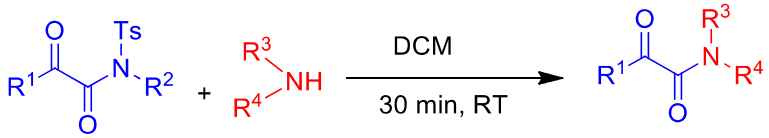


N-Methyl-2-oxo-2-phenylacetamide **1b** (163 mg, 1 mmol) was stirred in dichloromethane (3 mL) for approximately 2 min at room temperature to which *tert*-butyl nitrite (0.176 mL, 1.5 mmol) was added *via* a syringe and allowed to stir for 1 h. After completion, dichloromethane was evaporated and then subjected to silica gel (60−120 mesh) column chromatography purification (SiO_2: ethyl acetate/hexane) to obtain the title compound (**1m**)

obtained as yellow oil as non-separable isomers (1.0:0.5). Column chromatography was performed with hexane: EtOAc (90:10), R_f = 0.75; Yield 60% (115 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.02 (dd, J = 8.3, 1.0 Hz, 2H), 7.92 (dd, J = 8.3, 1.0 Hz, 4H), 7.71–7.64 (m, 3H), 7.56–7.49 (m, 6H), 3.98 (s, 3H), 3.28 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 188.5, 186.0, 172.4, 164.0, 135.3, 135.0, 132.5, 130.1, 129.5, 129.2, 128.9, 52.8, 25.5. This compound was found unstable during the mass spectrum analysis. Hence, HRMS could not be obtained.

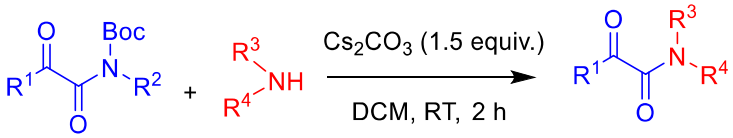
2.11 Procedures for the transamidation reactions

2.11.1. General procedure for the transamidation of *N*-tosyl amides with alkyl amines



To a stirred solution of alkyl amine (1.1 mmol) in DCM (3 mL) was added *N*-tosyl α-ketoamide **1k, 1l, 1ka-1kk** (1 mmol) at room temperature. The resulting mixture was allowed to stir for 30 min. After completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel (gradient eluent of EtOAc in hexane) to give the desired products **3a-3o** and **4a-4k**.

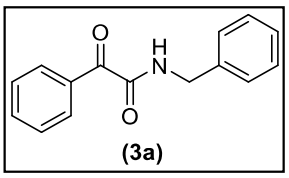
2.11.2. General procedure for the transamidation reaction of *N*-Boc amides with alkyl amines



To a stirred solution of alkyl amine (1.5 mmol) and cesium carbonate (1.5 mmol, 489 mg) in DCM (3 mL) was added *N*-Boc α-ketoamide **1f-1j**, **1ha-1hh** (1 mmol) at room temperature. The resulting mixture was allowed to stir for 2 hours. After completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel (gradient eluent of EtOAc in hexane) to give the desired products **3a-3o** and **4a-4h**.

2.12 Analytical data

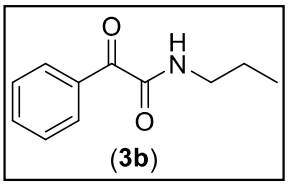
2.12.1. *N*-Benzyl-2-oxo-2-phenylacetamide (3a) [26a]



(3a)

The title compound was obtained as yellow gum. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.39. Yield = 96% (229 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.38–8.36 (m, 2H), 7.65–7.62 (m, 1H), 7.51–7.47 (m, 2H), 7.41 (s, 1H), 7.37–7.29 (m, 5H), 4.58 (d, J = 6.1 Hz, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.5, 161.5, 137.1, 134.5, 133.3, 131.2, 128.9, 128.5, 127.9, 127.9, 43.5. The title compound **3a** was also obtained from **1h** 31% (74 mg); from **1i** 84% (201 mg); from**1j** in 79% (189 mg); from **1k** in 75% (179 mg); from **1l** in 80% (191 mg); from **1m** 94% (225 mg); and from **1n** 96% (229 mg).

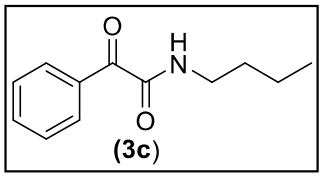
2.12.2. 2-Oxo-2-phenyl-*N*-propylacetamide (3b) [26a]



(**3b**)

The title compound was obtained as colorless oil. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.35. Yield = 95% (181 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.28–8.27 (m, 2H), 7.59–7.57 (m, 1H), 7.44–7.43 (t, J = 8.1 Hz, 2H), 7.23 (s, 1H), 3.34-3.39 (m, 2H), 1.63–1.55 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 188.0, 161.9, 134.2, 133.3, 131.0, 128.3, 41.0, 22.4, 11.2. The title compound **3b** was also obtained from *N*-Boc *N*-phenyl α-ketoamide **1g** in 93% (178 mg); from **1m** 90% (171 mg) from **1n** 91% (173 mg).

2.12.3. *N*-Butyl-2-oxo-2-phenylacetamide (3c) [26a]

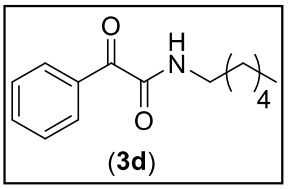


(**3c**)

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.48. Yield = 92% (188 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.34–8.32 (m, 2H), 7.63–7.60 (m, 1H), 7.48–7.45 (m 2H), 7.11 (s, 1H), 3.41–3.37 (m, 2H), 1.60–1.56 (m, 2H), 1.42–1.38 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.9, 161.7, 134.3, 133.4, 131.2, 128.4, 39.1, 31.3, 20.0, 13.7. The title compound **3c** was also obtained

from *N*-Boc *N*-phenyl *α*-ketoamide **1g** in 91% (187 mg).

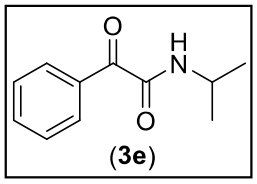
2.12.4. 2-Oxo-2-phenyl-*N*-propylacetamide (3d) [26a]



(**3d**)

The title compound was obtained as pale-yellow viscous oil. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.25. Yield = 92% (214 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.34–8.33 (m, 2H), 7.65–7.59 (m, 1H), 7.51–7.44 (m, 2H), 7.10 (s, 1H), 3.39 (dd, *J* = 13.4, 7.1 Hz, 2H), 1.60 (dd, *J* = 14.7, 7.5 Hz, 2H), 1.43–1.26 (m, 7H), 0.91-0.88 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.9, 161.7, 134.3, 133.4, 131.2, 128.4, 39.5, 31.4, 29.2, 26.5, 22.5, 14.0. The title compound **3d** was also obtained from *N*-Boc *N*-phenyl *α*-ketoamide **1g** in 89% (220 mg).

2.12.5. *N*-Isopropyl-2-oxo-2-phenylacetamide (3e) [27]

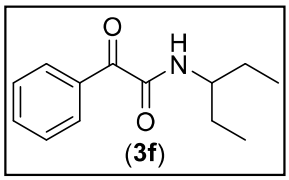


(**3e**)

The title compound was obtained as off white solid. M.p. 77–78°C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.42. Yield = 94% (179 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.34–8.32 (m, 2H), 7.63–7.60 (m, 1H), 7.49–7.46 (m, 2H), 6.92 (s, 1H), 4.18–4.12 (m, 1H), 1.26 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 188.0, 160.9, 134.3, 133.4, 131.2, 128.4, 41.7, 22.4. The

title compound **3e** was also obtained from *N*-Boc *N*-phenyl α-ketoamide **1g** in 85% (162 mg).

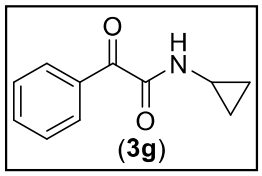
2.12.6. 2-Oxo-*N*-(pentan-3-yl)-2-phenylacetamide (3f)



(**3f**)

The title compound was obtained as sticky liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.35. Yield = 89%(194 mg). IR: 3000, 2953, 1708, 1672, 1480, 1235^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.34-8.32 (m, 2H), 7.62-7.59 m, 1H), 7.49-7.45 (m, 2H), 6.83 (s, 1H), 3.89–3.82 (m, 1H), 1.69–1.61 (m, 2H), 1.53-1.44 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 188.10, 161.6, 134.3, 133.4, 131.2, 128.4, 52.5, 27.3, 10.2. HRMS: Calc. for $C_{13}H_{18}NO_2$ $[M+Na]^+$: 220.1338, Obser.: 220.1344. The title compound **3f** was also obtained from *N*-Boc *N*-phenyl α-ketoamide **1g** in 83% (181 mg); from **1m** 83% (181 mg) from **1n** 81% (177 mg).

2.12.7. *N*-Cyclopropyl-2-oxo-2-phenylacetamide (3g) [28]

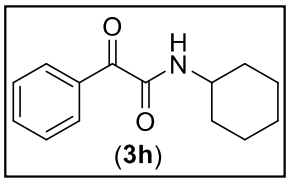


(**3g**)

The title compound was obtained as colorless oil. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.32. Yield = 94% (177 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.32–8.31 (m, 2H), 7.62-7.58 (m, 1H), 7.47-7.44 (m, 2H), 7.22

(s, 1H), 2.87–2.83 (m, 1H), 0.89–0.85 (m, 2H), 0.66–0.62 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 187.5, 163.1, 134.4, 133.2, 131.2, 128.4, 22.5, 6.4. The title compound **3g** was also obtained from *N*-Bo c*N*-phenyl α-ketoamide **1g** in 86% (163 mg).

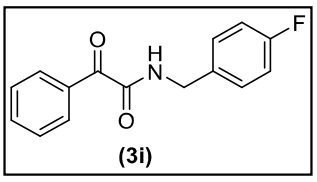
2.12.8. *N*-Cyclohexyl-2-oxo-2-phenylacetamide (3h) [21]



(**3h**)

The title compound was obtained as colorless gum. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.20. Yield = 91% (210 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.34–8.32 (m, 2H), 7.63–7.60 (m, 1H), 7.49–7.46 (dd, J = 11.1, 4.6 Hz, 2H), 6.95 (s, 1H), 3.89–3.83 (m, 1H), 2.0–1.97 (m, 2H), 1.78–1.75 (m, 2H), 1.65–1.64 (m, 1H), 1.44–1.38 (m, 2H), 1.32–1.21 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 188.1, 160.8, 134.3, 133.5, 131.2, 128.4, 48.5, 32.7, 25.4, 24.7. The title compound **3h** was also obtained from *N*-Boc *N*-phenyl α-ketoamide **1g** in 87% (201 mg).

2.12.9. *N*-(4-fluorobenzyl)-2-oxo-2-phenylacetamide (3i) [26a]

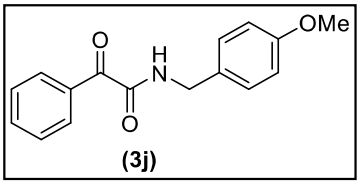


(**3i**)

The title compound was obtained as white solid. M.p. 84-86 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc

(90:10), R_f = 0.39. Yield = 93% (238 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.3 –8.28 (m, 2H), 7.6–7.60 (m, 1H), 7.53–7.43 (m, 3H), 7.33–7.27 (m, 2H), 7.02 (td, *J* = 8.7, 2.8 Hz, 2H), 4.53 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.4, 163.2, 161.5, 161.3, 134.4, 133.2, 132.9, 131.1, 129.6, 129.5, 128.4, 115.7, 115.5, 42.7. The title compound **3i** was also obtained from **1g** 91% (233 mg).

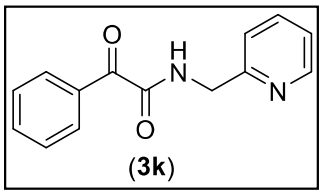
2.12.10. *N*-(4-methoxybenzyl)-2-oxo-2-phenylacetamide (3j) [26c]



(3j)

The title compound was obtained as yellow solid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:10), R_f = 0.39. Yield = 95% (255 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.36 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.67–7.61 (m, 1H), 7.50 (dd, *J* = 11.0, 4.7 Hz, 2H), 7.43 (s, 1H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.95–6.85 (m, 2H), 4.52 (d, *J* = 6.0 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.6, 161.5, 159.1, 134.3, 133.2, 131.1, 129.2, 129.1, 128.4, 114.1, 55.2, 42.9. The title compound **3j** was also obtained **1g** 94% (252 mg).

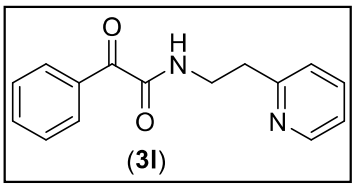
2.12.11. 2-Oxo-2-phenyl-*N*-(pyridin-2-ylmethyl)acetamide (3k) [29]



(**3k**)

The title compound was obtained as orange viscous liquid. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (90:20), R_f = 0.21. Yield = 95% (227 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.60 (d, J = 4.4 Hz, 1H), 8.36 (d, J = 7.6 Hz, 2H), 8.21 (s, 1H), 7.72–7.62 (m, 2H), 7.51 (t, J = 7.8 Hz, 2H), 7.32 (s, 1H), 7.24 (dd, J = 7.1, 5.3 Hz, 1H), 4.72 (d, J = 5.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.6, 162.0, 155.5, 149.3, 136.9, 134.3, 133.3, 131.1, 128.5, 122.6, 122.0, 44.3. The title compound **3k** was also obtained from *N*-Boc-*N*-phenyl α-ketoamide **1g** in 90% (216 mg).

2.12.12. 2-Oxo-2-phenyl-N-(2-(pyridin-2-yl)ethyl)acetamide (3l)

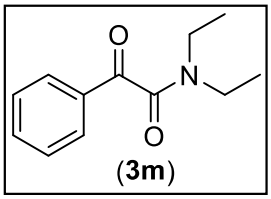


(**3l**)

The title compound was obtained as a white solid. M.p. 46–48 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (95:20), R_f = 0.15; Yield = 93% (236 mg). IR: 2966, 2871, 1710, 1677, 1544, 1287. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.56 (d, J = 4.7 Hz, 1H), 8.30–8.28 (m, 2H), 7.92 (s, 1H), 7.64–7.58 (m, 2H), 7.47–7.44 (m, 2H), 7.19–7.15 (m, 2H), 3.84–3.81 (m, 2H), 3.09 (t, J = 6.4 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.9, 162.0, 158.9, 149.3, 136.7, 134.2, 133.4, 131.1, 128.4, 123.4, 121.7, 38.5, 36.6. HRMS: Calc. for $C_{15}H_{15}N_2O_2$ $[M+Na]^+$: 255.1134, Obser.: 255.1147. The title compound **3l** was also obtained from *N*-Boc *N*-phenyl α-ketoamide 1g in 89% (226 mg); from **1m** 90% (227 mg) from **1n** 91% (229 mg).

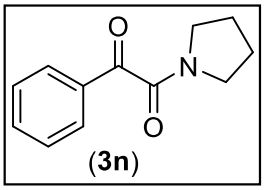
2.12.13. *N,N*-Diethyl-2-oxo-2-phenylacetamide (3m) [26a]



(**3m**)

The title compound was obtained as a colorless oil. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.25. Yield = 85% (174 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.91 (d, J = 8.4 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 3.54 (q, J = 7.2 Hz, 2H), 3.22 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = ^{13}C NMR (125 MHz, $CDCl_3$) δ = 191.5, 166.6, 134.4, 133.1, 129.5, 128.8, 77.2, 77.0, 76.7, 42.0, 38.7, 14.0, 12.7. The title compound **3m** was also obtained from *N*-Boc *N*-phenyl α-ketoamide **1g** in 73% (150 mg); from **1m** 82% (170 mg) from **1n** 88% (180 mg).

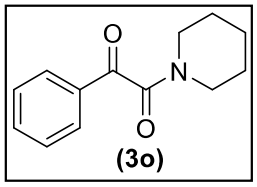
2.12.14. 2-Phenyl-1-(pyrrolidin-1-yl)ethan-1-one (3n) [27]



(**3n**)

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.26. Yield = 88% (168 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.02–7.98 (m, 2H), 7.65–7.62 (m, 1H), 7.52-7.49 (m, 2H), 3.66 (t, J = 6.8 Hz, 2H), 3.43 (t, J = 6.4 Hz, 2H), 1.95–1.94 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 191.6, 164.9, 134.6, 132.9, 129.9, 128.9, 46.7, 45.2, 25.9, 24.0. The title compound **3n** was also obtained from *N N*-Boc *N*-phenyl α-ketoamide **1g** in 89% (181 mg).

2.12.15. 1-Phenyl-2-(piperidin-1-yl)ethane-1,2-dione (3o) [26a]

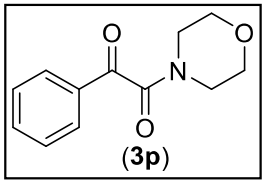


(**3o**)

The title compound was obtained as a white solid. M.p. 94–95 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.20. Yield = 89% (193 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.98 – 7.92 (m, 2H), 7.67 – 7.61 (m, 1H), 7.51 (t, J = 7.7 Hz, 2H), 3.70 (s, 2H), 3.30–3.27 (m, 2H), 1.71–1.68 (m, 4H), 1.55 (d, J = 5.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 191.9, 165.4, 134.6, 133.2, 129.6, 129.0, 47.0, 42.1, 26.2, 25.4, 24.4. The title compound **3o** was also obtained from *N*-Boc *N*-phenyl α-

ketoamide **1g** in 88% (191 mg).

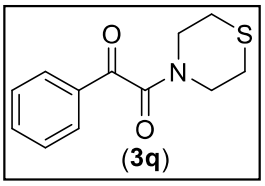
2.12.16. 1-Morpholino-2-phenylethane-1,2-dione (3p) [26a]



(**3p**)

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.21. Yield = 94% (205 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.97–7.95 (m, 2H), 7.67–7.64 (m, 1H), 7.54–7.51 (t, J = 7.8 Hz, 2H), 3.82–3.77 (m, 4H), 3.66–3.64 (m, 2H), 3.39–3.37 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 191.1, 165.4, 134.9, 133.0, 129.7, 129.1, 66.7, 66.7, 46.3, 41.6. The title compound **3p** was also obtained from *N*-Boc *N*-phenyl α-ketoamide **1g** in 85% (186 mg); from **1m** 85% (186 mg) from **1n** 89% (196 mg).

2.12.17. 1-Morpholino-2-phenylethane-1,2-dione (3q) [26b]

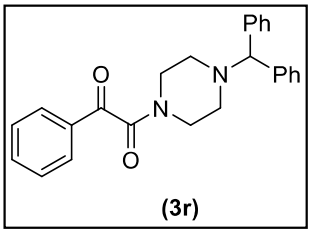


(**3q**)

The title compound was obtained as yellow solid. M.p. 82-84 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.45. Yield = 95% (223 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.92 (d, J = 8.1 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 4.04–3.98 (m, 2H), 3.62–3.57 (m, 2H), 2.76–2.71 (m, 2H), 2.63–2.58 (m, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ = 191.2, 165.6, 134.8,

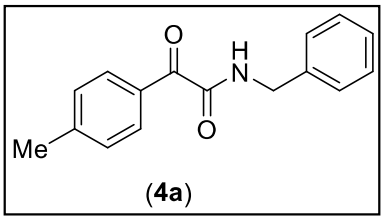
132.9, 129.5, 129.0, 48.6, 43.6, 27.7, 27.2. The title compound **3q** was also obtained from *N*-Boc *N*-phenyl *α*-ketoamide **1g** in 85% (200 mg).

2.12.18. 1-(4-Benzhydrylpiperazin-1-yl)-2-phenylethane-1,2-dione (3r) [30]



The title compound was obtained as brown viscous oil. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.10. Yield = 89% (341 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.96–7.91 (m, 2H), 7.62 (d, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.41-7.39 (d, J = 7.3 Hz, 4H), 7.28 (d, J = 7.4 Hz, 3H), 7.21-7.17 (m, 2H), 4.28 (s, 1H), 3.80–3.78 (m, 2H), 3.38–3.36 (m, 2H), 2.54–2.52 (m, 2H), 2.37–2.36 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 191.5, 165.3, 141.8, 134.7, 133.1, 129.6, 129.0, 128.7, 127.8, 127.3, 75.8, 51.9, 51.4, 46.1, 41.4. The title compound **3r** was also obtained from *N*-Boc *N*-phenyl *α*-ketoamide **1g** in 84% (323 mg).

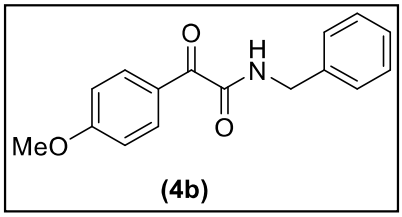
2.12.19. *N*-Benzyl-2-oxo-2-(*p*-tolyl)acetamide (4a) [28]



The title compound was obtained as a white solid. M.p. 81.1–81.5 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.62. Yield = 92% (232 mg). ^{1}H NMR (500

MHz, $CDCl_3$) δ = 8.29 (d, J = 8.2 Hz, 2H), 7.44 (s, 1H), 7.36-7.30 (m, 5H), 7.28 (d, J = 8.0 Hz, 2H), 4.57 (d, J = 6.1 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 187.0, 161.8, 145.7, 137.2, 131.4, 130.8, 129.2, 128.8, 127.9, 127.8, 43.4, 21.9. The title compound **4a** was also obtained from *N*-Boc *N*-methyl α-ketoamide **1ja** in 89% (225 mg).

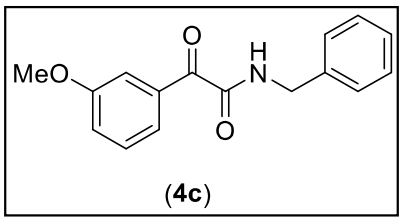
2.12.20. *N*-Benzyl-2-(4-methoxyphenyl)-2-oxoacetamide (4b) [28]



(4b)

The title compound was obtained as a white solid. M.p. 95.3–95.7 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.65. Yield = 94% (22 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.44–8.42 (m, 2H), 7.51 (s, 1H), 7.37–7.29 (m, 5H), 6.96–6.93 (m, 2H), 4.56 (d, J = 6.1 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 185.5, 164.7, 162.1, 137.2, 133.9, 128.8, 127.8, 127.7, 126.3, 113.8, 55.5, 43.4. The title compound **4b** was also obtained from *N*-Boc *N*-methyl α-ketoamide **1jb** in 90% (242 mg).

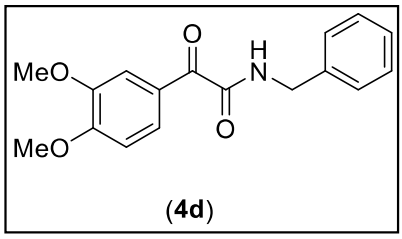
2.12.21. *N*-Benzyl-2-(3-methoxyphenyl)-2-oxoacetamide (4c) [28]



(**4c**)

The title compound was obtained as colorless oil. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.55. Yield = 91% (235 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.00 (d, *J*= 7.6 Hz, 1H), 7.84 (d, *J* = 1.3 Hz, 1H), 7.47 (s, 1H), 7.40–7.30 (m, 5H), 7.19–7.16 (m, 1H), 4.56 (d, *J* = 6.1 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.3, 161.6, 159.5, 137.1, 134.4, 129.5, 128.9, 127.8, 127.7, 124.1, 121.4, 114.6, 55.4, 43.4. The title compound **4c** was also obtained from *N*-Boc *N*-methyl *α*-ketoamide **1jc** in 87% (234 mg).

2.12.22. *N*-Benzyl-2-(3,4-dimethoxyphenyl)-2-oxoacetamide (4d) [31]

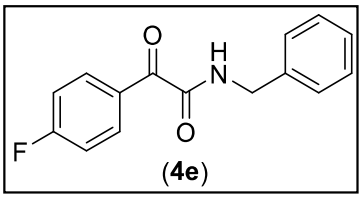


(**4d**)

The title compound was obtained as a white solid. M.p. 119–121 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.59. Yield = 92% (275 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.26 (d, *J* = 3.6 Hz, 1H), 7.88 (dd, *J* = 4.5, 2.3 Hz, 1H), 7.51 (s, 1H), 7.33–7.28 (m, 5H), 6.92 (dd, *J* = 9.6, 6.5 Hz, 1H), 4.55 (s, 2H), 3.95 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 185.3, 162.1, 154.7, 148.8, 137.2, 128.8, 127.8, 127.7, 127.4, 126.4, 112.6, 110.2, 56.1, 55.9, 43.4. The title compound **4d** was

also obtained from *N*-Boc *N*-methyl *α*-ketoamide **1jd** in 87% (260 mg).

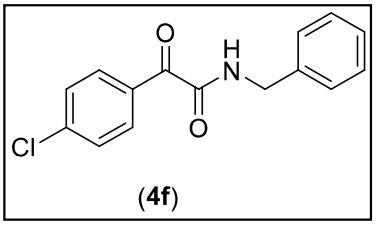
2.12.23. *N*-Benzyl-2-(4-fluorophenyl)-2-oxoacetamide (4e) [28]



(**4e**)

The title compound was obtained as a white solid. M.p. 66–67 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.60. Yield = 93% (239 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.48–8.46 (m, 2H), 7.47 (s, 1H), 7.38–7.30 (m, 5H), 7.17–7.13 (dd, *J* = 12.8, 4.5 Hz, 2H), 4.56 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 185.6, 166.6 (d, *J* = 256.25 Hz), 161.3, 137.0, 134.3 (d, *J* = 10.0 Hz), 129.8 (d, *J* = 2.5 Hz), 128.8, 127.8, 115.8, 115.6, 43.5. The title compound **4e** was also obtained from *N*-Boc *N*-methyl *α*-ketoamide **1je** in 82% (211mg).

2.12.24. *N*-Benzyl-2-(4-chlorophenyl)-2-oxoacetamide (4f) [28]

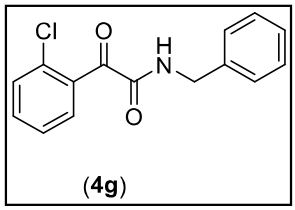


(**4f**)

The title compound was obtained as a white solid. M.p. 111.9–112.3 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.63. Yield = 94% (256 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.36 (d, *J* = 8.6 Hz, 2H), 7.47–7.45 (m, 2H), 7.38–7.31 (m, 5H), 4.57 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.1, 161.1, 141.3, 136.9,

132.7, 131.7, 129.0, 128.9, 127.90, 127.9, 43.5. The title compound **4f** was also obtained from *N*-Boc *N*-methyl α-ketoamide **1jf** in 83% (227 mg).

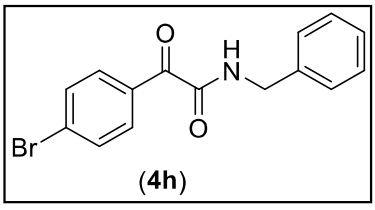
2.12.25. *N*-Benzyl-2-(2-chlorophenyl)-2-oxoacetamide (4g) [32]



(**4g**)

The title compound was obtained as a white solid. M.p. 91–92 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.63. Yield = 81% (221 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.71–7.69 (m, 2H), 7.50–7.44 (m, 4H), 7.40–7.32 (m, 2H), 7.29 (s, 1H), 4.58 (d, J = 6.1 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 190.0, 160.6, 136.9, 134.0, 133.1, 131.3, 130.4, 128.9, 128.0, 127.9, 126.6, 43.7. The title compound **4g** was also obtained from *N*-Boc *N*-methyl α-ketoamide **1jg** in 72% (197 mg).

2.12.26. *N*-Benzyl-2-(4-bromophenyl)-2-oxoacetamide (4h) [28]

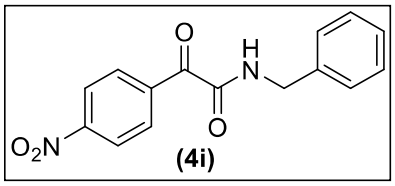


(**4h**)

The title compound was obtained as a white solid. M.p. 113–114 °C. The residue was purified by column chromatography in silica gel eluting with hexane/EtOAc (80:20), R_f = 0.58. Yield = 95% (301 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.27 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 7.43 (s, 1H), 7.37–7.32 (m, 5H), 4.56 (d, J = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.3,

161.1, 136.9, 132.8, 132.1, 131.98, 130.2, 128.9, 127.9, 129.9, 43.5. The title compound **4h** was also obtained from *N*-Boc *N*-methyl *α*-ketoamide **1jh** in 85% (270 mg).

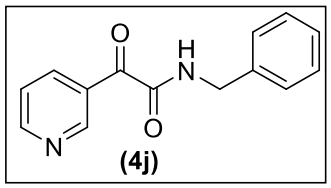
2.12.27. *N*-Benzyl-2-(4-nitrophenyl)-2-oxoacetamide (4i)



(4i)

The title compound was obtained as a pale-yellow solid. M.p. 91–92 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.38. Yield 86% (244 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.55 (d, J = 8.8 Hz, 2H), 8.31 (d, J = 8.8 Hz, 2H), 7.47 (s, 1H), 7.39–7.35 (m, 5H), 4.59 (d, J = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 185.9, 160.3, 150.8, 137.9, 136.6, 132.4, 128.9, 128.1, 127.9, 123.5, 43.7. HRMS: Calc. for $C_{15}H_{13}N_2O_4$ $[M+H]^+$: 285.0875, Obser.: 285.0875.

2.12.28. *N*-Benzyl-2-oxo-2-(pyridin-3-yl)acetamide (4j)

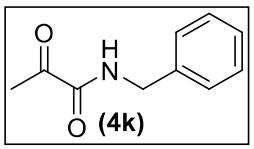


(4j)

The title compound was obtained as a white solid. M.p. 120 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.25. Yield = 91% (218 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.53 (d, J = 1.6 Hz, 1H), 8.82 (dd, J = 4.8, 1.5 Hz, 1H), 8.68 (dt, J = 8.0, 1.8 Hz, 1H), 7.54 (s, 1H), 7.44–7.42 (m, 1H), 7.38–7.30 (m, 5H), 4.57 (d, J =

6.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.4, 160.5, 154.3, 152.2, 138.6, 136.8, 129.1, 128.9, 128.0, 127.9, 123.3, 43.6. HRMS: Calc. for $C_{14}H_{12}N_2NaO_2$ $[M+Na]^+$: 263.0796, Obser.: 263.0792.

2.12.29. *N*-Benzyl-2-oxopropanamide (4k) [33]



The title compound was obtained as a colorless liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.30. Yield = 95% (168 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36–7.28 (m, 5H), 7.27 (s, 1H), 4.47 (d, J = 6.1 Hz, 2H), 2.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 197.0, 159.9, 136.9, 128.8, 127.9, 43.5, 24.5. HRMS: Calc. for $C_{10}H_{12}NO_2$ $[M+H]^+$: 178.0868, Obser.: 178.0861.

2.13 Few spectra of the products

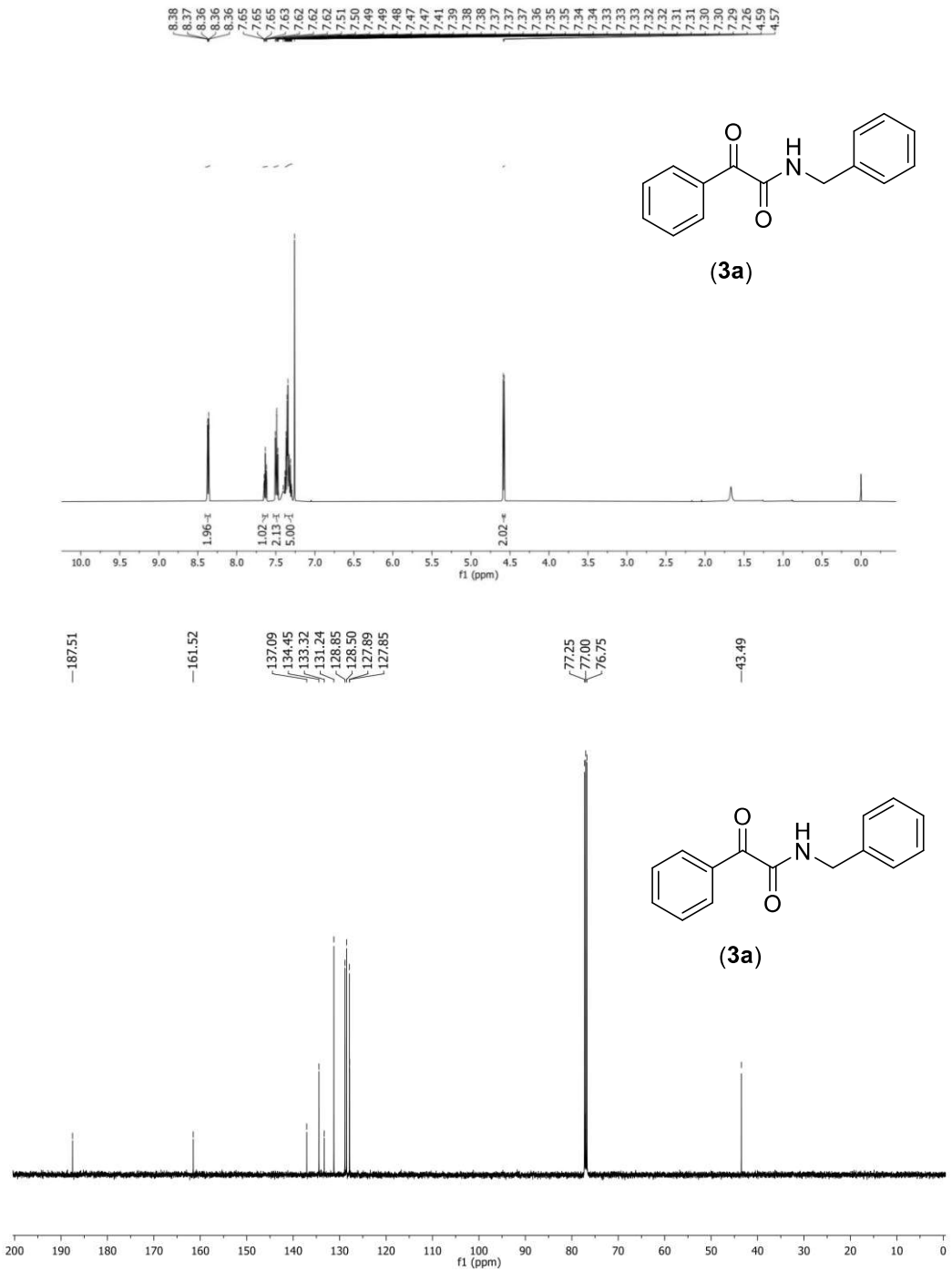


Figure 2.2 ^{1}H and ^{13}C NMR of product 3a in $CDCl_3$

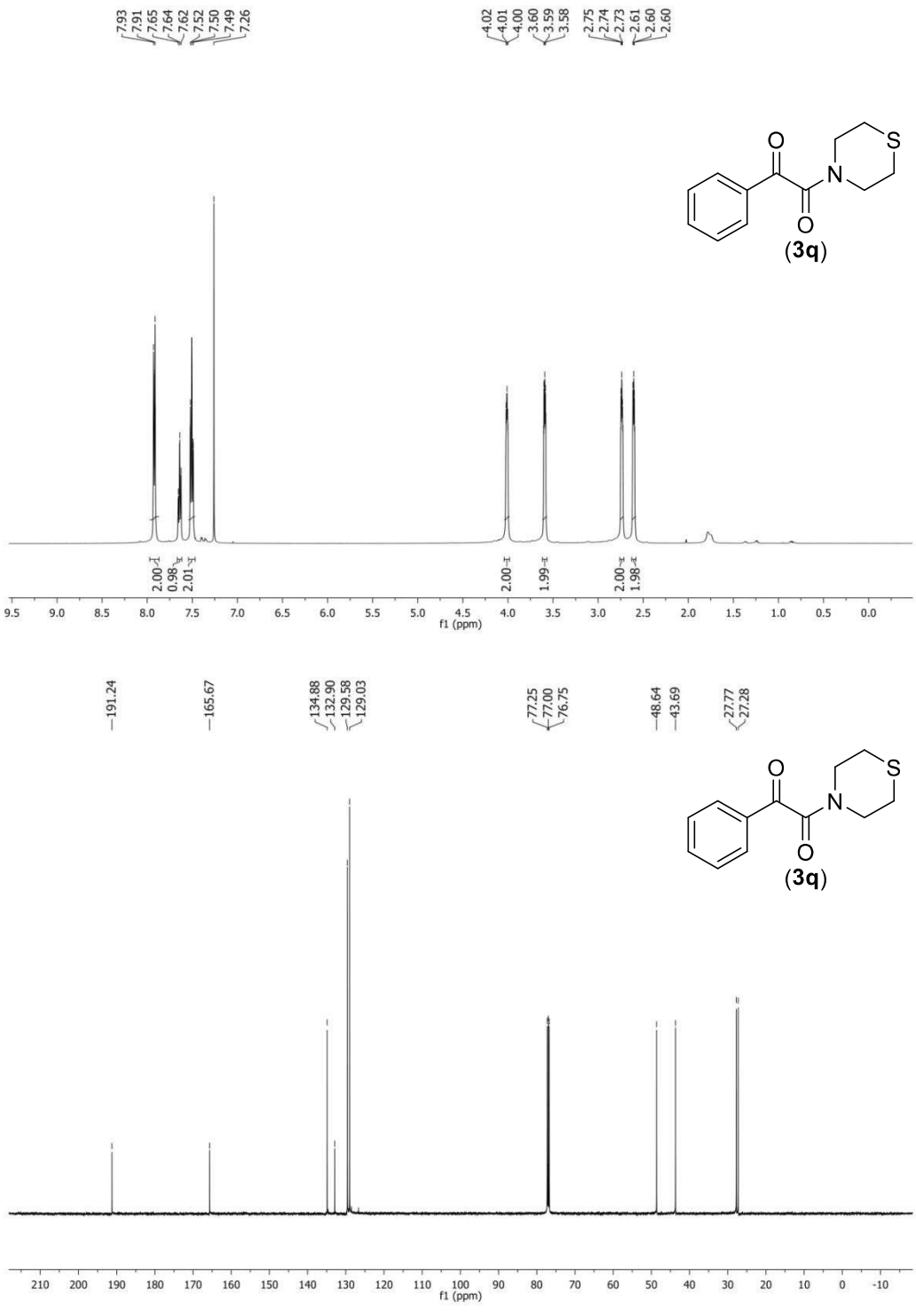


Figure 2.3 ^{1}H and ^{13}C NMR of product 3q in $CDCl_3$

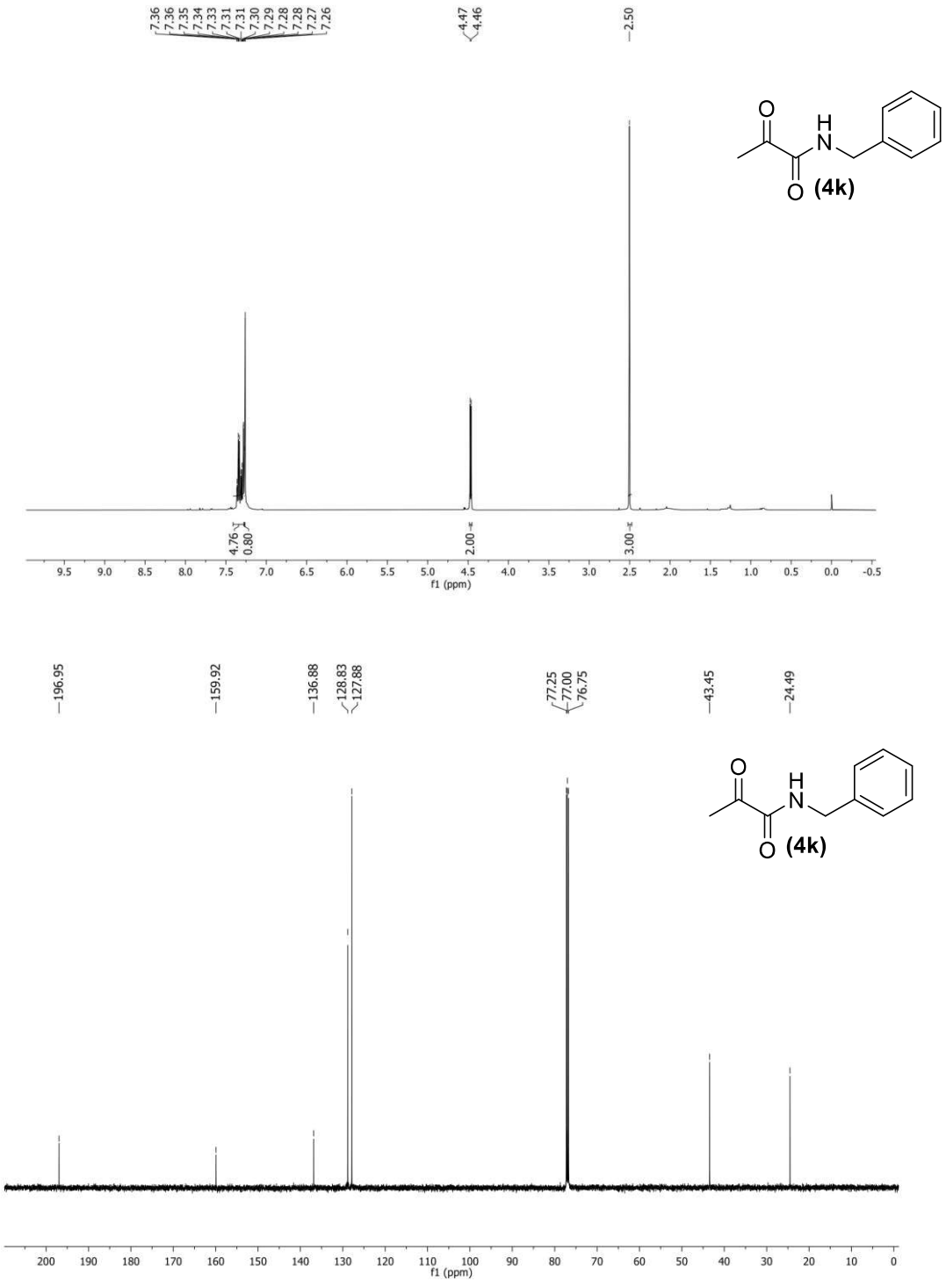


Figure 2.4 ^{1}H and ^{3}C of product 4k in $CDCl_3$

2.14 References

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