CHAPTER-5

tert-Butyl Nitrite Promoted Transamidation of Secondary Amides under Metal and Catalyst FreeConditions

5.1 Introduction

Amides are key functional groups that exist in many biomolecules, natural products, drugs, etc. (Fig. 5.1) [1]. On the other hand, amides are also employed as valuable precursors in organic synthesis [2-5]. Transamidation is an important reaction that has received significant interest in recent years [6-18]. Owing to the high stability of amide bonds, transamidation of secondary amides was considered to be a more challenging task in organic synthesis [14-17]. In this context, Garg and coworkers developed a two-step process for the efficient transamidation of secondary amides under mild conditions [19-21]. In the Garg method, secondary amides are converted into non-planar *N*-Boc amides in the first step and subjected to transamidation with different amines in the presence of nickel catalysts. Later, Szostak *et al*. demonstrated the activation of *N*-Boc and *N*-tosyl protected secondary amides using palladium catalysts [22-23]. Moreover, recently the Szostak group has also successfully demonstrated the base promoted transamidation and esterification of *N*-Boc and *N*-tosyl amides under metal free conditions [24-25].

N-Nitrosamines are valuable precursors in organic synthesis [26-30]. In contrast, the applications of *N*-nitrosamides are less explored in synthetic organic chemistry [31-38]. In 1983, Garcia *et al*. reported that *N*-nitrosamides undergo transamidation efficiently with different amines in the absence of any catalysts or bases [35-36]. However, this transamidation approach remained unpopular in organic synthesis because the preparation, isolation and handling of *N*-nitrosamides are quite difficult.

In this context, our aim was to identify a suitable nitrosating reagent for the generation of *N*-nitrosamides in situ which can be directly subjected to the transamidation process without isolation of the *N*-nitrosamide intermediate. In fact, such protocols will reduce not only the number of steps but also tedious workup procedures. Moreover, it will be an alternative to *N*-Boc and *N*-tosyl amide mediated transamidation processes. In this context, here we report an efficient, metal and catalyst free method for the transamidation of secondary amides using *tert*-butyl nitrite at room temperature (Scheme 5.1).

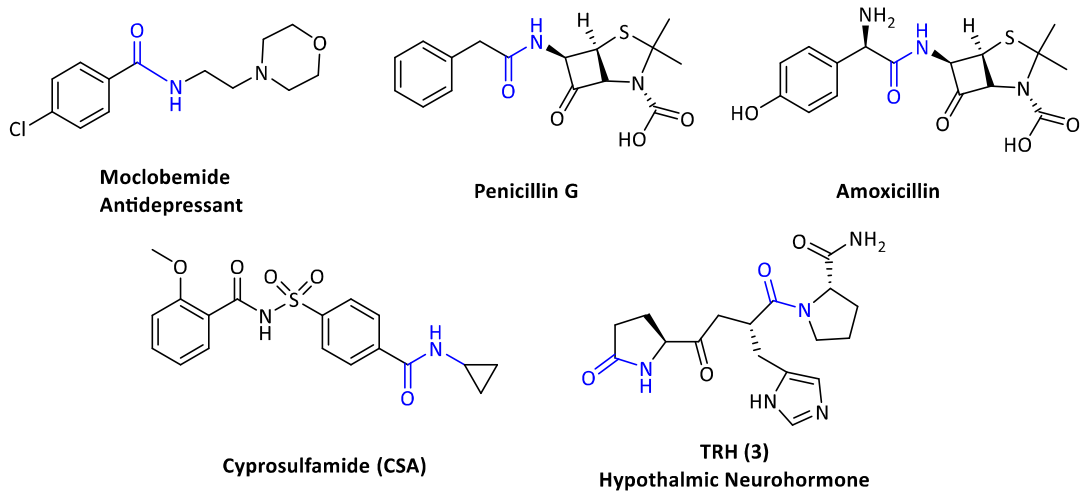
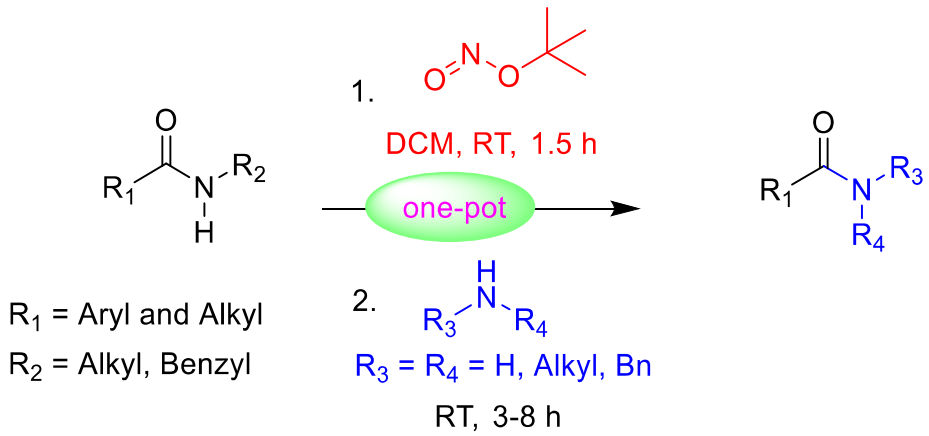


Figure 5.1 Some important natural products and drug molecules bearing amide bonds

The *N*-nitrosation of secondary amides has been achieved using different nitrosyl sources including $NaNO_2$-HCl [33], nitrogen oxide-NaOAc [35-36], nitrosyl chloride-KOAc [39], nitrosyl tetrafluoroborate-pyridine [40], and *tert*-butyl nitrite [41].



Scheme 5.1 Synthetic route for transamidation of *N*-alkylbenzamide *via N*-Nitrosamide

However, some of these reagents may not be suitable for the one-pot transamidation process. For example, the $NaNO_2$-HCl system requires aqueous acidic conditions which may lead to different side reactions. On the other hand, nitrogen oxide and nitrosyl chloride are gases that are difficult to prepare and handle. In this context, we have envisioned that nitrosyl tetrafluoroborate or *tert*-butyl nitrite might be more appropriate for one-pot transamidation reactions because these reagents are relatively milder and also commercially available.

5.2 Results and discussion

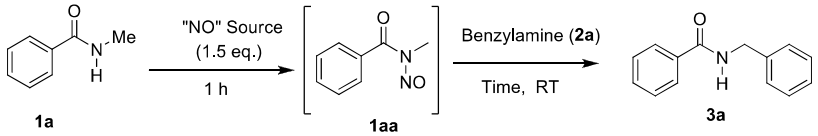
5.2.1 Optimization of transamidation of *N*-methylbenzamide

At the outset, transamidation of *N*-methylbenzamide (1a) was investigated with benzylamine (2a) in the presence of nitrosyl tetrafluoroborate (Table 5.1, entries 1–4). Initially, the formation of *N*-nitrosamide (1aa) was assessed with nitrosyl tetrafluoroborate using crude ^{1}H NMR. The reaction was performed in acetonitrile and

dichloromethane solvents in the presence and absence of pyridine. The maximum yield of *N*-nitrosamide 1aa (i.e. 92%) was obtained in acetonitrile in the presence of pyridine after 12 hours at room temperature (Table 5.1, entry 3). However, the other conditions gave relatively low yields of *N*-nitrosamide 1aa. Nevertheless, after 12 hours, benzylamine (the external nucleophile) was added to the reaction mixture containing *N*-nitrosamide and the reaction mixture was allowed to stir for an additional 12 hours at room temperature. The transamidation proceeded effciently in dichloromethane in the absence of pyridine and gave the desired product 3a in 54% yield (Table 5.1, entry 2). However, only 20% yield of 3a was obtained in acetonitrile (Table 5.1, entry 1). It is surprising to note that the transamidation process was significantly suppressed in the presence of pyridine in both acetonitrile and dichloromethane solvents (Table 5.1, entries 3 and 4).

tert-Butyl nitrite (TBN) is an acid free nitrating and nitrosating reagent used in many synthetic transformations [42-48]. Over the past few years, our research work has focused on the chemistry of *N*-nitrosamines [49-54] and we have reported solvent free synthesis of *N*-nitrosamines [49], radical dimerization of thiobenzamides [52] and triazole formation of *o*-phenylenediamine [54] using *tert*-butyl nitrite. Recently, *N*-nitrosation of secondary amides using *tert*-butyl nitrite has been demonstrated by Bhanage *et al* [41]. Therefore, the one-pot transamidation reaction was investigated with *tert*-butyl nitrite in different solvents.

Table 5.1 Optimization of transamidation of *N*-methylbenzamide



				Nitrosation		Transamidation	
S.No.	Nitroso source	Solvent	Bases	Time (h)	Yield **1aa** (%)[b]	Time (h)	Yield **3a** (%)[c]
1	$NOBF_4$	AcCN	-	12	65	12	20
2	$NOBF_4$	DCM	-	12	74	12	54
3	$NOBF_4$	AcCN	Py	12	92	12	30
4	$NOBF_4$	DCM	Py	12	74	12	15
5	***t*-BuONO**	**DCM**	**-**	**1**	**95**	**3**	**91**
6	*t*-BuONO	DCE	-	1	91	3	87
7	*t*-BuONO	THF	-	1	50	12	15
8	*t*-BuONO	Toluene	-	1	35	12	30
9	*t*-BuONO	Benzene	-	1	30	12	17
10	*t*-BuONO	AcCN	-	1	80	12	60
11	*t*-BuONO	1-4 dioxane	-	1	70	12	40
12	*t*-BuONO	MeOH	-	1	<5	12	nr
13	*t*-BuONO	EtOH	-	1	<5	12	nr
14	*t*-BuONO	H_2O	-	1	<5	12	nr
15	*t*-BuONO	Solvent-free	-	1	97	12	47
16	*t*-BuONO	DCM	Pyridine	1	75	3	48
17	*t*-BuONO	DCM	Et_3N	1	82	3	48
18	*t*-BuONO	DCM	$Et(i\text{-}Pr)_2N$	1	78	3	44
19	*t*-BuONO	DCM	DBU	1	68	3	45
20	*t*-BuONO	DCM	DABCO	1	67	3	42
21	*iso*-AmylONO	DCM	-	1	70	3	51
22	*n*-BuONO	DCM	-	1	83	3	64
23	*t*-BuONO	DCM	-	-	-	6	10[d]
24	*t*-BuONO	DCM	-	-	-	6	nr[e]

[a]Reaction conditions: Substrate (1 mmol) and TBN (1.5 equiv.) stirred in appropriate solvents (5 mL) for appropriate time after which benzyl amine (2.2 equiv.) was added. [b]Crude yield in ^{1}HNMR. [c]Isolated yield. [d]TBN was added to the pre-stirred solution of *N*-methylbenzamide and benzylamine. [e]*N*-methylbenzamide was added to the pre-stirred solution of benzyl amine and TBN.

Initially, the conversion of *N*-methylbenzamide into the corresponding *N*-nitrosamide (1aa) was assessed in the presence of TBN in different solvents including dichloromethane, dichloroethane, THF, toluene, benzene, acetonitrile and dioxane using 1H NMR (Table 5.1, entries 5–11). Among them, dichloromethane was found to be the most efficient which provided the *N*-nitrosamide 1aa in 95% yield within 1 h (Table 5.1, entry 5). On the other hand, polar protic solvents such as methanol, ethanol and water failed to provide the *N*-nitrosamide 1aa (Table 5.1, entries 12–14). As reported by Bhanage *et al*. the *N*-nitrosamide 1aa was obtained in 97% yield under solvent free conditions (Table 5.1, entry 15). Nevertheless, after 1 hour, benzylamine (2.2 equiv.) was added to the reaction mixture containing *N*-nitrosamide and the reaction mixture was allowed to stir up to 12 h at room temperature. To our delight, the one-pot transamidation was successfully achieved with 91% yield in dichloromethane within 3 h while other conditions gave the desired product 3a in low yields. It is also worth mentioning that the transamidation product 3a was obtained only in 47% yield under solvent free conditions even after 12 h at room temperature (Table 5.1, entry 15).

Encouraged, we have studied the effect of the different bases including pyridine, Et_3N, $Et(i\text{-}Pr)_2N$, DBU and DABCO in the transamidation process in dichloromethane (Table 5.1, entries 16–20). It was observed that in the presence of a base, not only nitrosamide formation but also the transamidation process was significantly suppressed. Furthermore, the transamidation reaction was investigated with other alkyl nitrites such as *iso*-amyl nitrite and *n*-butyl nitrite in dichloromethane. These reagents gave the

desired product 3a in 70% and 83% yields, respectively (Table 5.1, entries 21 and 22). Furthermore, transamidation of *N*-methylbenzamide was executed in two other conditions in dichloromethane using *tert*-butyl nitrite (TBN), namely, (i) TBN was added to the pre-stirred solution of *N*-methylbenzamide and benzylamine (Table 5.1, entry 23) in dichloromethane and (ii) *N*-methylbenzamide was added to the pre-stirred solution of benzylamine and TBN (Table 5.1, entry 24) in dichloromethane. In the first case, the desired product 3a was obtained only in 10% yield while the latter conditions failed to yield the desired transamidation product.

5.3 Substrate Scope

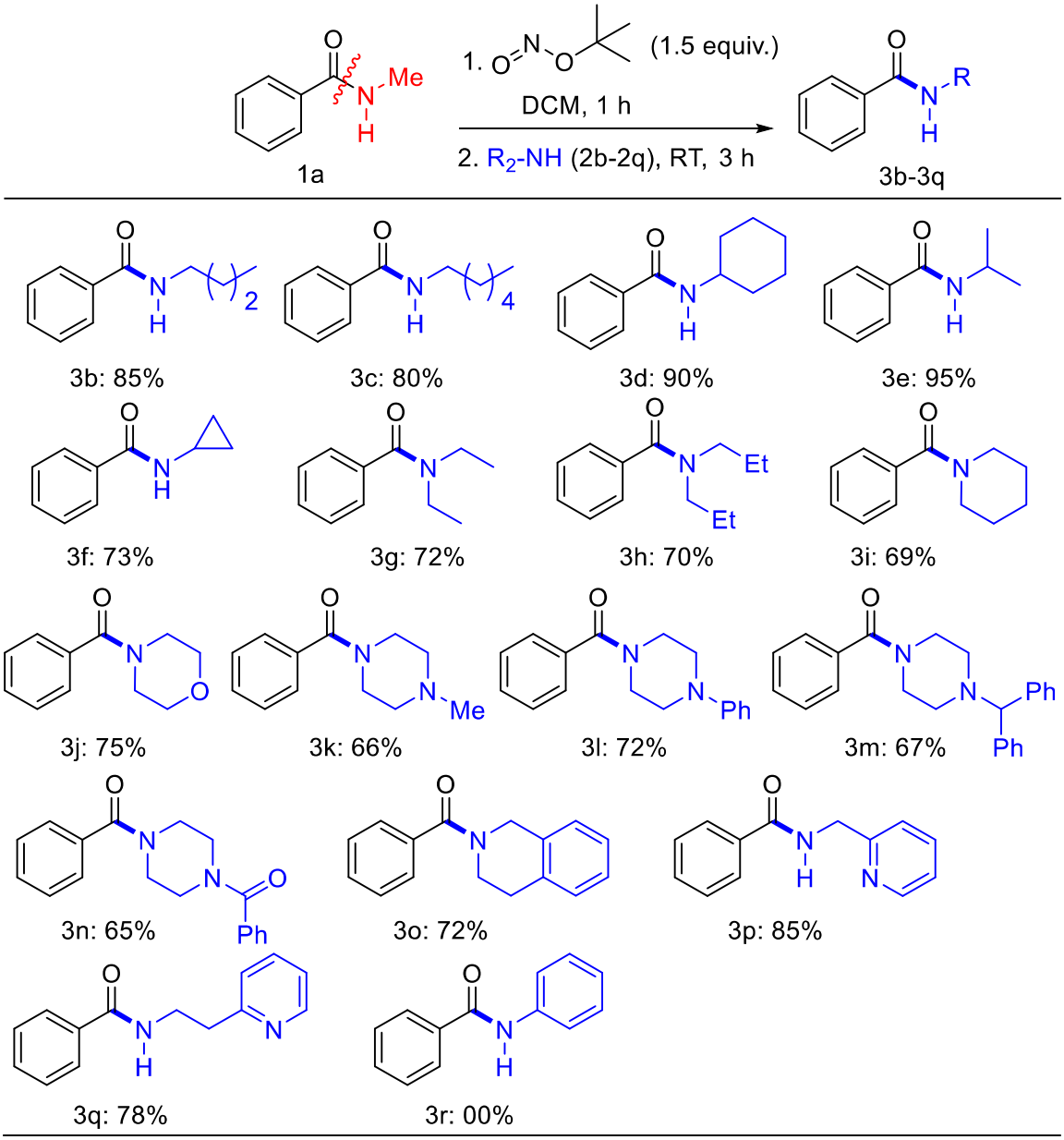
5.3.1 Transamidation of *N*-methylbenzamide with aliphatic amines

Having established the optimized conditions (Table 5.1, entry 5), transamidation of *N*-methylbenzamide was investigated with various amines in the presence of *tert*-butyl nitrite (Table 5.2). Initially, *N*-methylbenzamide was subjected to transamidation with different primary amines such as *n*-butyl, *n*-hexyl, cyclohexyl, *iso*-propyl and cyclopropyl-amines under optimized conditions. All these reactions proceeded smoothly at room temperature while the desired transamidation products were obtained in 73–95% yields (Table 5.2, 3b–3f).

Similarly, cyclic and acyclic secondary amines such as diethylamine, dipropylamine, piperidine, morpholine, *N*-methyl piperazine, *N*-phenyl piperazine, *N*-benzhydryl piperazine, *N*-benzoyl piperazine and 1,2,3,4-tetrahydroisoquinoline

participated in the transamidation process smoothly and gave the desired products in good to excellent yields (Table 5.2, 3g–3o).

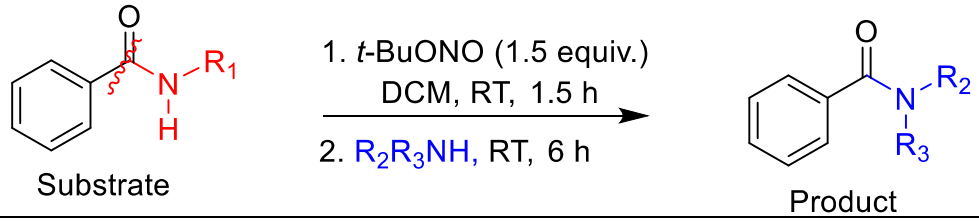
Table 5.2 One-pot transamidation of *N*-methylbenzamide with aliphatic amines

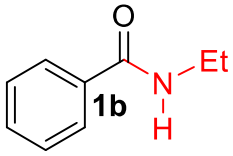
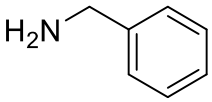
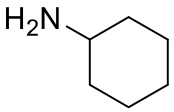
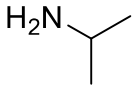
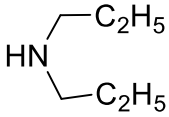
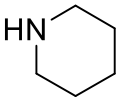
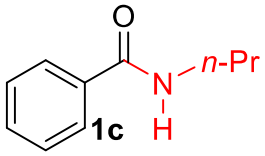


[a]Reaction conditions: Substrate (1 mmol), TBN (1.5 equiv.) and amine (2.2 equiv.) in DCM (5 mL) at room temperature. [b]Isolated yields.

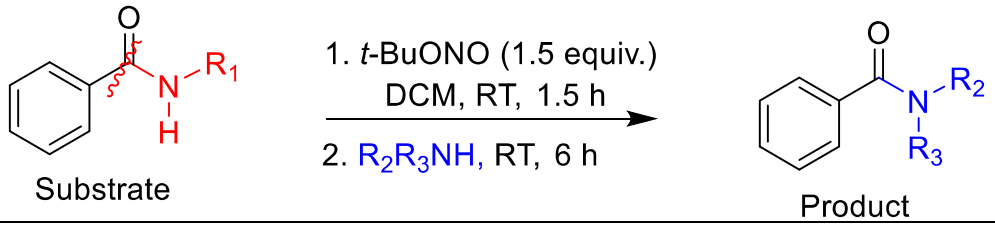
Interestingly, heteroaromatic amines such as 2-aminomethyl pyridine and 2-aminoethyl pyridine also acted as efficient nucleophiles in the transamidation process and provided the desired products 3p and 3q in 85% and 78% yields, respectively.

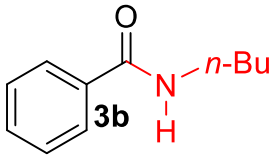
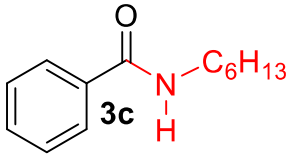
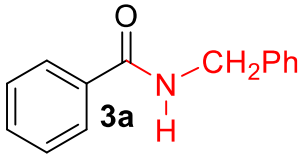
Table 5.3 Trasamidation of *N*-substituted benzamide with aliphatic amines



Entry	Amide	Nucleophile	Product	Yield (%)
1	 **1b**	 **(2a)**	**3a**	83
2	**1b**	 **(2d)**	**3d**	79
3	**1b**	 **(2e)**	**3e**	76
4	**1b**	 **(2h)**	**3h**	58
5	**1b**	 **(2i)**	**3i**	62
6	 **1c**	**2a**	**3a**	85
7	**1c**	**2d**	**3d**	81
8	**1c**	**2e**	**3e**	80
9	**1c**	**2h**	**3h**	57
10	**1c**	**2i**	**3i**	63

[a]Reaction conditions: Substrate (1 mmol), TBN (1.5 equiv.) Amine (2.2 equiv.) in DCM (5 mL) at RT. [b]Isolated yields.



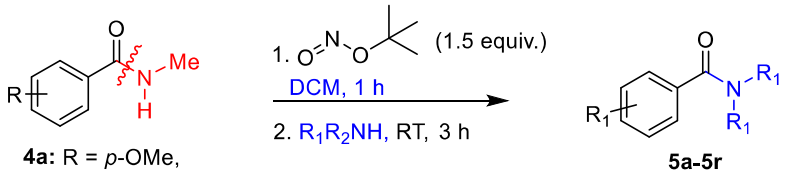
Entry	Amide	Nucleophile	Product	Yield (%)
11		**2a**	**3a**	86
12	**3b**	**2d**	**3d**	82
13	**3b**	**2e**	**3e**	74
14	**3b**	**2h**	**3h**	56
15	**3b**	**2i**	**3i**	60
16		**2a**	**3a**	88
17	**3c**	**2d**	**3d**	85
18	**3c**	**2e**	**3e**	78
19	**3c**	**2h**	**3h**	56
20	**3c**	**2i**	**3i**	60
21		**2d**	**3d**	54
22	**3a**	**2e**	**3e**	72
23	**3a**	**2i**	**3i**	63

[a]Reaction conditions: Substrate (1 mmol), TBN (1.5 equiv.) Amine (2.2 equiv.) in DCM (5 mL) at RT. [b]Isolated yields.

However, transamidation was not successful when aniline was used as a nucleophile, perhaps due to less nucleophilicity of the amine (Table 5.2, 3r).

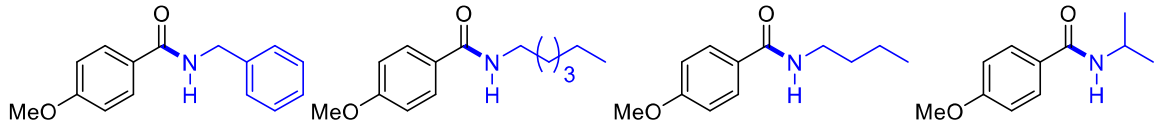
The scope of the developed methodology was further examined with different *N*-alkyl benzamides under optimized conditions (Table 5.3). Similar to *N*-methylbenzamides, *N*-ethyl (1b), *N*-propyl (1c), *N*-butyl (3b), *N*-hexyl (3c) and *N*-benzylbenzamides (3a) also underwent nitrosation followed by transamidation very efficiently with different primary and secondary amines (cyclic and acyclic) under optimized conditions (Table 5.3). These reactions provided the desired transamidation products in 54–88% yields. Moreover, irrespective of the substitutes present on the aryl ring (i.e. electron donating or withdrawing), nitrosation followed by transamidation occurred smoothly to provide the desired products in good to excellent yields (Table 5.4, 5a–5r).

Table 5.4 Trasamidation of *N*-methylbenzamide with aliphatic amines



4a: R = *p*-OMe,
4b: R = *p*-NO_2,
4c: R = *o*-F

5a-5r

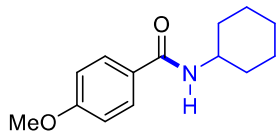


5a: 98%

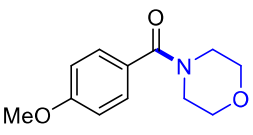
5b: 95%

5c: 95%

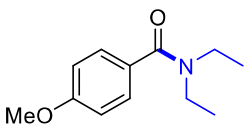
5d: 88%



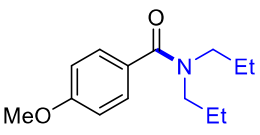
5e: 86%



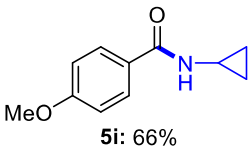
5f: 68%



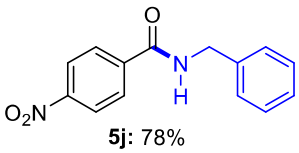
5g: 82%



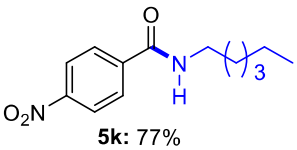
5h: 67%



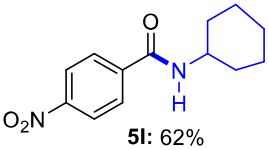
5i: 66%



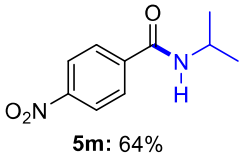
5j: 78%



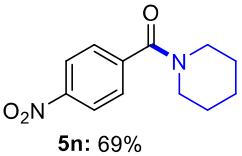
5k: 77%



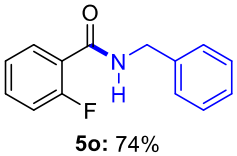
5l: 62%



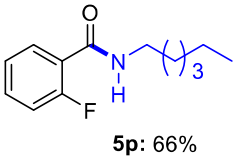
5m: 64%



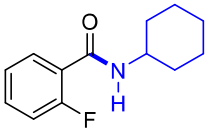
5n: 69%



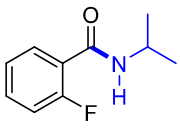
5o: 74%



5p: 66%



5q: 68%



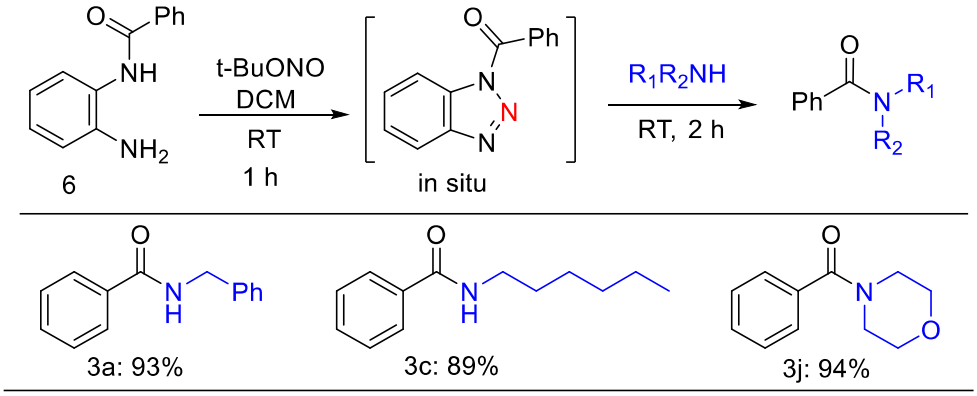
5r: 60%

[a]Reaction conditions: Substrate (1 mmol), TBN (1.5 equiv.) amine (2.2 equiv.) in DCM (5 mL) at RT. [b]Isolated yields.

5.3.2 Transamidation of *N*-benzoyl *o*-phenylenediamine

It is also interesting to note that the transamidation of *N*-benzoyl *o*-phenylenediamine (6) with different amines was achieved with excellent yields (Scheme 5.2). The reaction proceeds through the *N*-acyl benzimidazole intermediate under optimized conditions.

Scheme 5.2 Transamidation of *N*-benzoyl *o*-phenylenediamine *via* *N*-acyl benzimidazole

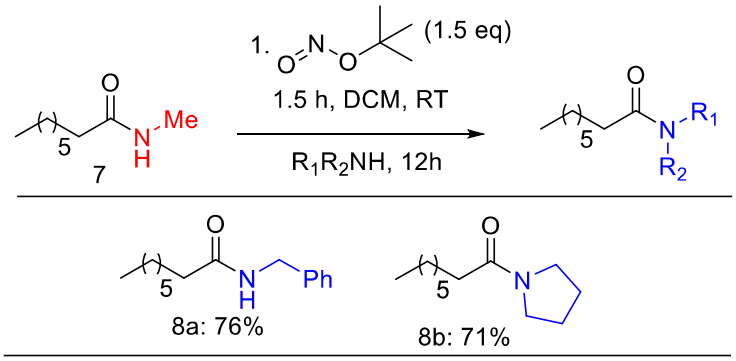


[a]Reaction conditions: Substrate (1 mmol), TBN (1.5 equiv.) amine (2.2 equiv.) in DCM (5 mL) at RT. [b]Isolated yields.

5.3.3 Transamidation of various *N*-alkyl secondary amide

Having explored the transamidation of various *N*-substituted benzamides, an alkyl secondary amide, *i.e.* *N*-methyloctanamide (7), was subjected to transamidation with benzylamine and pyrrolidine under optimized conditions. To our delight, the one-pot transamidation proceeded smoothly in the presence of *tert*-butyl nitrite to provide the desired products 8a and 8b in high yields (Scheme 5.3).

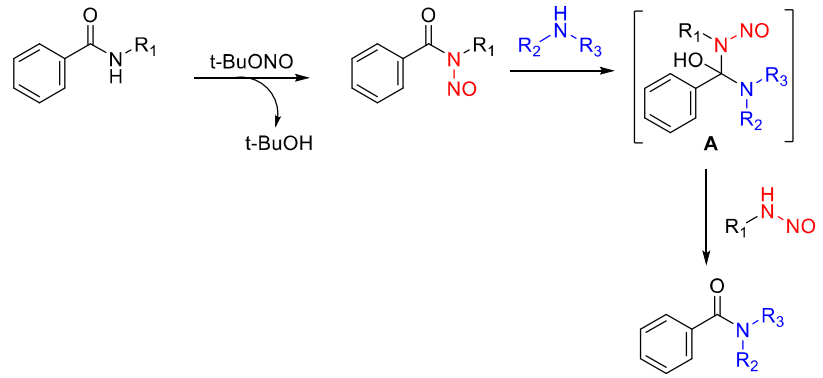
Scheme 5.3 Transamidation of *N*-methyl-octanamide



[a]Reaction conditions: Substrate (1 mmol), TBN (1.5 equiv.) amine (2.2 equiv.) in DCM (5 mL) at RT. [b]Isolated yields.

5.4 Plausible mechanism

A proposed mechanism for the transamidation process is shown in Scheme 5.4. In the first step, the secondary amide undergoes *N*-nitrosation to form *N*-nitrosamide in the presence of *tert*-butyl nitrite. In the second step, *N*-nitrosamide undergoes nucleophilic addition with an external amine to form the intermediate **A**. This unstable intermediate undergoes elimination to provide the desired product and alkyl *N*-nitrosamine.



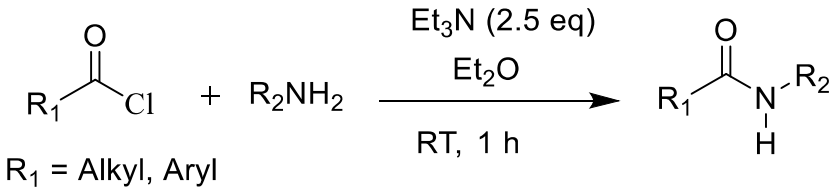
Scheme 5.4 Proposed mechanism for the transamidation reaction

5.5 Conclusion

In conclusion, a mild and practical method for the one-pot transamidation of various secondary amides was demonstrated with different amines in the presence of *tert*-butyl nitrite. The reaction proceeds through the *N*-nitrosamide intermediate. All the reactions were carried out at room temperature to obtain the desired products in good to excellent yields. Moreover, the developed methodology does not require any catalyst, acidic medium or high temperature which demonstrates the broad scope of the methodology.

5.6 Experimental section

5.6.1 Synthesis of amides from acid chloride



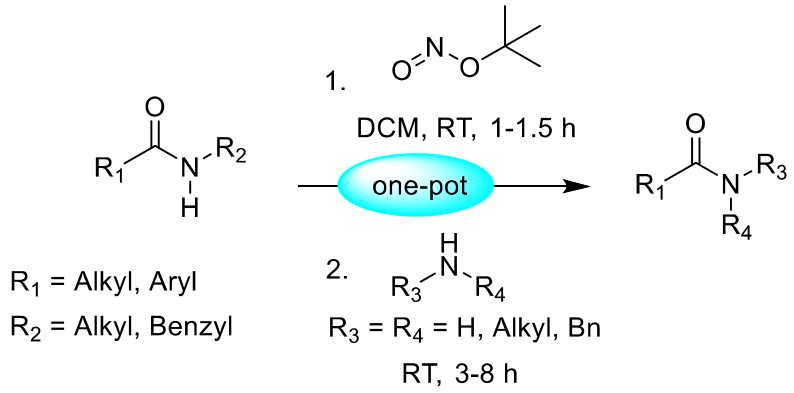
Methyl amine (40% aqueous solution) (5 equiv.), Et_3N (2.5 equiv.) and Et_2O (0.5 M) were added into a round bottom flask and acid chloride (1.0 equiv.) was slowly added at 0 °C. The mixture was stirred at room temperature for 1 h. The crude reaction mixture was washed with water and extracted with Et_2O, The organic layer dried over Na_2SO_4 and the solvent was removed in vacuo to obtain a white solid (70-95% yield) (*J. Am. Chem. Soc*., 2013, **135**, 4628−4631).

N-Methylbenzamide **(1a),** *N*-Ethylbenzamide **(1b),** *N*-propylbenzamide **(1c),** 4-Methoxy-*N*-Methylbenzamide**(4a),** 4-Nitro-*N*-methylbenzamide**(4b),** 2-Fluoro-*N*-methylbenzamide **(4c),** *N*-Methyloctanamide **(7).**

5.6.2 Synthesis of *N*-(2-aminophenyl)benzamide (6)

Et_3N (0.695 mL, 5 mmol, 0.5 eq.) was added drop wise to a stirred solution of *o*-phenylenediamine (1.08 g, 10 mmol, 1 eq.) in DCM (20 mL) at room temperature. The solution was heated to reflux and benzoyl chloride (0.578 mL, 5 mmol, 0.5 eq.) in DCM (10 mL) was added drop wise through a dropping funnel over 30 min. The solution was heated to reflux for 2 h and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 1:1) to afford amide 6a (1.46 g, 69 %) as a white solid. (*Chem. Eur. J.,* 2015, **21**, 9493–9504.)

5.6.3 Procedure for the transamidation of amides

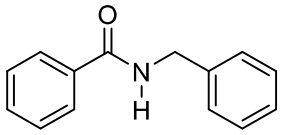


Amide (*N*-methylbenzamide **1a**) (1 mmol, 135 mg) was stirred in dichloromethane (5 mL) approximately for 2 min at room temperature to which *tert*-butyl nitrite (1.5 mmol, 0.179 mL) was added *via* syringe and allowed to stir for 1–1.5 h at room temperature.

After conversion of *N*-nirtosation, benzyl amine **2a** (2.2 mmol, 0.240 mL) was added to the reaction mixture and allowed to stir at room temperature for a 3 h. The progress of the reaction was monitored by TLC. After completion, dichloromethane was evaporated and then, subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: ethyl acetate/hexane) to obtain the corresponding *N*-benzylbenzamide (**3a**). Similar procedure was used for the transamidation with other *N*-alkylbenzamides, substituted *N*-methylbenzamides and *N*-methyloctanamide .

5.7 Analytical data of the products

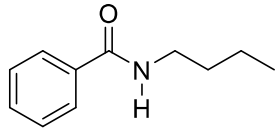
[5.7.1] *N*-Benzylbenzamide (3a)



3a

The title compound was obtained as a white solid. M.p. 99 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (85:15), R_f = 0.55; Yield 91% (192 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.79 (d, J = 7.3 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.3 Hz, 2H), 7.33 (s, 4H), 7.29 (s, 1H), 6.69 (s, 1H), 4.62 (d, J = 5.2 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 167.3, 138.1, 134.3, 131.4, 128.6, 128.4, 127.8, 127.4, 126.9, 44.0. **HRMS**: Calc. for $C_{14}H_{14}NO$ $[M+H]^+$: 212.1075, Obser.: 212.1064.

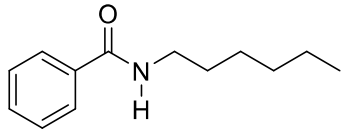
[5.7.2] *N*-Butylbenzamide (3b)



3b

The title compound was obtained as a colourless liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (85:15), R_f = 0.54; Yield 85% (150 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.75 (dd, J = 8.2, 1.1 Hz, 2H), 7.41–7.39 (m, 1H), 7.35–7.31 (m, 2H), 6.75 (s, 1H), 3.39–3.35 (m, 2H), 1.57–1.51 (m, 2H), 1.36–1.31 (m, 2H), 0.89 (dd, J = 8.8, 6.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 167.5, 134.7, 131.0, 128.2, 126.8, 39.6, 31.5, 20.0, 13.6. **HRMS**: Calc. for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1232, Obser.:178.1224.

[5.7.3] *N*-Hexylbenzamide (3c)

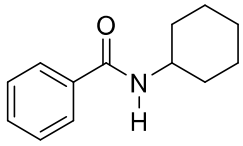


3c

The title compound was obtained as a pale yellow liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (85:15), R_f = 0.56; Yield 80% (164 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.76 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 6.78 (s, 1H), 3.37 (q, J = 6.5 Hz, 2H), 1.58–1.52 (m, 2H), 1.32–1.26 (m, 6H), 0.85 (t, J = 6.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 167.5, 134.7, 131.0, 128.2, 126.8, 40.0, 31.3, 29.4, 26.5, 22.4, 13.8. **HRMS**: Calc. for

$C_{13}H_{20}NO$ $[M+H]^+$: 206.1545, Obser.:206.1537.

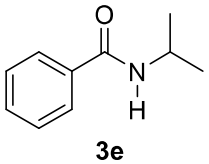
[5.7.4] *N*-Cyclohexylbenzamide (3d)



3d

The title compound was obtained as a white solid. M.p. 154-156 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (85:15), R_f = 0.60; Yield 90% (182 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.74 (d, J = 7.7 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.4 Hz, 2H), 6.11 (s, 1H), 3.99–3.93 (m, 1H), 2.01 (d, J = 11.3 Hz, 2H), 1.74 (d, J = 13.4 Hz, 2H), 1.64 (d, J = 12.9 Hz, 1H), 1.44–1.36 (m, 2H), 1.27–1.14 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.5, 135.0, 131.1, 128.4, 126.7, 48.6, 33.1, 25.50, 24.8. **HRMS**: Calc. for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1388, Obser.:204.1377.

[5.7.5] *N*-Isopropylbenzamide (3e)

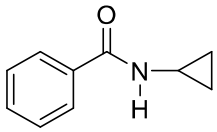


3e

The title compound was obtained as a white solid. M.p. 84 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (85:15), R_f = 0.60; Yield 95% (155 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.74 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 7.0 Hz, 1H), 7.38 (t, J = 7.3 Hz, 2H), 6.15 (s, 1H), 4.29–4.23 (m, 1H), 1.24 (d, J = 6.5 Hz, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.6, 134.9, 131.1, 128.3, 126.7, 41.7, 22.7.

HRMS: Calc. for $C_{10}H_{14}NO$ $[M+H]^+$: 164.1075, Obser.: 164.1068.

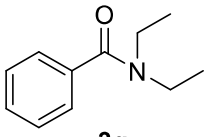
[5.7.6] *N*-Cyclopropylbenzamide (3f)



3f

The title compound was obtained as a white solid. M.p. 54-56 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.66; Yield 73% (117 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.73 (d, J = 7.6 Hz, 2H), 7.43 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 6.73 (s, 1H), 2.88–2.83 (m, 1H), 0.81–0.77 (m, 2H), 0.62–0.58 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 168.9, 134.3, 131.2, 128.3, 126.8, 23.0, 6.5. **HRMS**: Calc. for $C_{14}H_{14}NO$ $[M+H]^+$: 162.0919, Obser.: 162.0912.

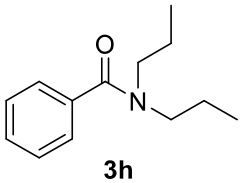
[5.7.7] *N,N*-Diethylbenzamide (3g)



3g

The title compound was obtained as a colourless liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.62; Yield 72% (127 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.40–7.33 (m, 5H), 3.52 (s, 2H), 3.22 (s, 2H), 1.23 (s, 3H), 1.08 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 171.2, 137.1, 129.0, 128.2, 126.1, 43.2, 39.1, 14.0, 12.7. **HRMS**: Calc. for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1232, Obser.:178.1223.

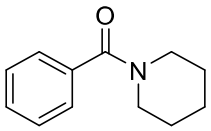
[5.7.8] *N,N*-Dipropylbenzamide (3h)



3h

The title compound was obtained as a pale yellow liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.60; Yield 70% (143 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.32 (d, J = 6.8 Hz, 5H), 3.41 (s, 2H), 3.11 (s, 2H), 1.64 (s, 2H), 1.48 (s, 2H), 0.93 (s, 3H), 0.69 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 171.5, 137.2, 128.7, 128.1, 126.2, 50.4, 46.0, 21.7, 20.5, 11.2, 10.8. **HRMS**: Calc. for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1545, Obser.: 206.1537.

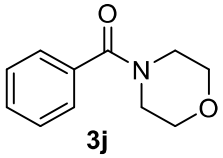
[5.7.9] Phenyl(piperidin-1-yl)methanone (3i)



3i

The title compound was obtained as a white solid. M.p. 48 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (85:15), R_f = 0.45; Yield 69% (130 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.37 (s, 5H), 3.69 (s, 2H), 3.32 (s, 2H), 1.66 (s, 4H), 1.49 (s, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 170.2, 136.4, 129.2, 128.3, 126.6, 48.6, 43.0, 26.4, 25.5, 24.5. **HRMS**: Calc. for $C_{12}H_{16}NO$ $[M+H]^+$: 190.1232, Obser.: 190.1229.

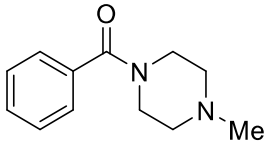
[5.7.10] Morpholino(phenyl)methanone (3j)



3j

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 (85:15), R_f = 0.46; Yield 75% (143 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.39 (s, 5H), 3.76 (s, 4H), 3.61 (s, 2H), 3.43 (s, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 170.3, 135.2, 129.8, 128.4, 127.0, 66.8. 48.1, 42.5. **HRMS**: Calc. for $C_{11}H_{14}NO_2$ $[M+H]^+$: 192.1025, Obser.: 192.1017.

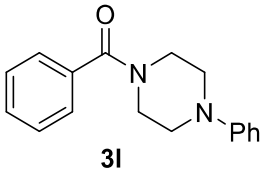
[5.7.11] (4-Methylpiperazin-1-yl)(phenyl)methanone (3k)



3k

The title compound was obtained as oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (70:30), R_f = 0.36; Yield 66% (135 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.54–7.35 (m, 5H), 3.76 (s, 2H), 3.40 (s, 2H), 2.44 (s, 3H), 2.27 (s, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 170.1, 135.6, 129.5, 128.3, 126.8, 55.1, 54.5, 47.4, 45.8, 41.8. **HRMS**: Calc. for $C_{12}H_{17}N_2O$ $[M+H]^+$: 205.1341, Obser.: 205.1337.

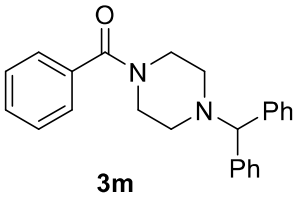
[5.7.12] Phenyl(4-phenylpiperazin-1-yl)methanone (3l)



3l

The title compound was obtained as a brown solid. M.p. 94 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (70:30), R_f = 0.66; Yield 72% (191 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.45–7.41 (m, 5H), 7.29 (dd, J = 8.7, 7.3 Hz, 2H), 6.92 (dd, J = 15.3, 7.7 Hz, 3H), 3.94 (s, 2H), 3.60 (s, 2H), 3.19 (d, J = 61.2 Hz, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 170.3, 150.8, 135.5, 129.7, 129.2, 128.4, 127.0, 120.6, 120.5, 116.7, 116.6, 49.7, 42.0. **HRMS**: Calc. for $C_{17}H_{19}N_2O$ $[M+H]^+$: 267.1497, Obser.: 267.1489.

[5.7.13] (4-benzhydrylpiperazin-1-yl)(phenyl)methanone (3m)

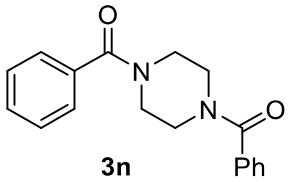


3m

The title compound was obtained as a white solid. M.p. 145–146 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (70:30), R_f = 0.60; Yield 67% (238 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ = 7.43–7.39 (m, 7H), 7.36–7.34 (m, 2H), 7.29 (t, J = 7.6 Hz, 4H), 7.19 (t, J = 7.3 Hz, 2H), 4.34 (s, 1H), 3.40 (s, 8H).**^{13}C NMR** (125 MHz, DMSO-d_6) δ = 168.8, 142.4, 135.7, 129.4, 128.5, 128.3, 127.6,

126.9, 126.9, 74.7, 51.6, 51.2, 47.1, 41.5. **HRMS**: Calc. for $C_{24}H_{25}N_2O$ $[M+H]^+$: 357.1967, Obser.: 357.1961.

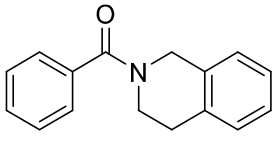
[5.7.14] Piperazine-1,4-diylbis(phenylmethanone) (3n)



3n

The title compound was obtained as a white solid. M.p. 193–195 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (70:30), R_f = 0.55; Yield 65% (191 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.40 (s, 10H), 3.62 (d, J = 111.1 Hz, 8H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 170.5, 135.0, 130.0, 128.5, 126.9, 47.6, 42.1. **HRMS**: Calc. for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1447, Obser.: 295.0939.

[5.7.15] (3,4-Dihydro*iso*quinolin-2(1H)-yl)(phenyl)methanone (3o)

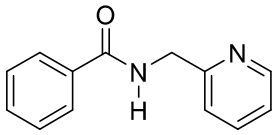


3o

The title compound was obtained as a light yellow solid. M.p. 127–129 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (70:30), R_f = 0.70; Yield 72% (170 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.44 (d, J = 4.2 Hz, 5H), 7.26-6.91(m, 4H), 4.90 (s, 1H), 4.59 (s, 1H), 4.00 (s, 1H), 3.64 (s, 1H), 2.93 (d, J = 56.5 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 170.9, 136.0, 133.7, 132.8, 130.3, 129.7, 128.4, 126.7, 126.5, 125.8, 49.7, 45.2, 44.7, 40.4, 29.5, 28.1. **HRMS**:

Calc. for $C_{16}H_{16}NO$ $[M+H]^+$: 238.1232, Obser.: 238.1229.

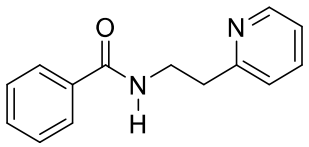
[5.7.16] *N*-(Pyridine-2-ylmethyl)benzamide (3p)



3p

The title compound was obtained as a yellow solid. M.p. 68 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (85:15), R_f = 0.60; Yield 85% (180 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.52 (d, J = 4.7 Hz, 1H), 7.87–7.83 (m, 2H), 7.68 (td, J = 7.7, 1.7 Hz, 1H), 7.49–7.46 (m, 1H), 7.40 (t, J = 7.5 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 7.20 (dd, J = 7.1, 5.2 Hz, 1H), 4.74 (d, J = 5.0 Hz, 2H). 3.45 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 167.3, 156.1, 148.5, 137.1, 134.1, 131.4, 128.8, 127.0, 122.4, 122.3, 44.5. **HRMS**: Calc. for $C_{13}H_{13}N_2O$ $[M+H]^+$: 235.0847, Obser.: 235.0839.

[5.7.17] *N*-(2-(Pyridin-2-yl)ethyl)benzamide(3q)

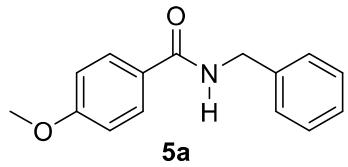


3q

The title compound was obtained as a pale yellow solid. M.p. 68–70 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (85:15), R_f = 0.60; Yield 78% (176 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.56 (d, J = 4.7 Hz, 1H), 7.79–7.77 (m, 2H), 7.74 (td, J = 7.7, 1.5 Hz, 1H), 7.46 (t, J = 7.3 Hz,

1H), 7.40 (t, J = 7.5 Hz, 2H), 7.31 (d, J = 7.8 Hz, 1H), 7.26–7.24 (m, 1H), 3.88 (dd, J = 12.2, 5.8 Hz, 2H), 3.66 (s, 1H), 3.18 (t, J = 6.3 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 167.3, 159.1, 147.6, 138.2, 134.4, 131.2, 128.4, 126.9, 124.4, 122.1, 39.0, 36.0. **HRMS**: Calc. for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1184, Obser.: 227.1176.

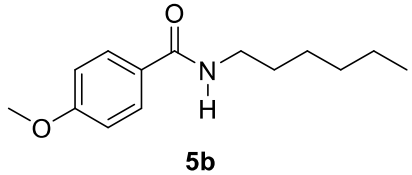
[5.7.18] *N*-Benzyl-4-methoxybenzamide(5a)



5a

The title compound was obtained as a white solid. M.p. 122 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.66; Yield 98% (236 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.79 (d, J = 7.9 Hz, 2H), 7.34–7.29 (m, 4H), 6.90 (d, J = 7.9 Hz, 2H), 6.67 (s, 1H), 4.61 (d, J = 3.8 Hz, 2H), 3.84 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.8, 162.1, 138.4, 128.7, 128.8, 127.7, 127.3, 126.5, 113.6, 55.3, 43.9. **HRMS**: Calc. for $C_{15}H_{16}NO_2$ $[M+H]^+$: 242.1181, Obser.: 242.1177.

[5.7.19] *N*-Hexyl-4-methoxybenzamide(5b)

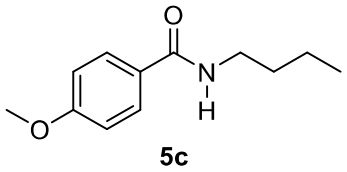


5b

The title compound was obtained as a white solid. M.p. 92 °C. The residue was purified by column chromatography in silica gel eluting with hexane:

EtOAc (80:20), R_f = 0.64; Yield 95% (223 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.73 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.28 (s, 1H), 3.82 (s, 3H), 3.40 (dd, J = 13.3, 6.7 Hz, 2H), 1.60–1.54 (m, 2H), 1.36–1.24 (m, 6H), 0.87 (t, J = 6.2 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.9, 161.9, 128.5, 127.1, 113.5, 55.2, 40.0, 31.4, 29.6, 26.6, 22.5, 13.95. **HRMS**: Calc. for $C_{14}H_{22}NO_2$ $[M+H]^+$: 236.1651, Obser.: 236.1644.

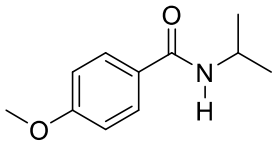
[5.7.20] *N*-Butyl-4-methoxybenzamide(5c)



5c

The title compound was obtained as a colourless liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.62; Yield 95% (196 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.72 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.44 (s, 1H), 3.79 (s, 3H), 3.38 (dd, J = 13.1, 7.1 Hz, 2H), 1.57–1.51 (m, 2H), 1.35 (dd, J = 15.1, 7.5 Hz, 2H), 0.90 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 167.0, 161.8, 128.5, 127.0, 113.5, 55.2, 39.6, 31.6, 20.0, 13.6. **HRMS**: Calc. for $C_{12}H_{18}NO_2$ $[M+H]^+$: 208.1338, Obser.: 208.1332.

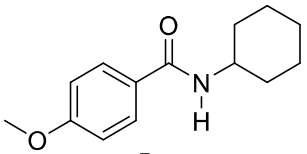
[5.7.21] *N*-Isopropyl-4-methoxybenzamide (5d)



5d

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 = 0.60; Yield 88% (170 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.71 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 6.03 (s, 1H), 4.26–4.21 (m, 1H), 3.81 (s, 3H), 1.22 (d, J = 6.3 Hz, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.1, 161.8, 128.5, 127.1, 113.5, 55.2, 41.6, 22.7. **HRMS**: Calc. for $C_{11}H_{16}NO_2$ $[M+H]^+$: 194.1181, Obser.:194.1178.

[5.7.22] *N*-Cyclohexyl-4-methoxybenzamide (5e)

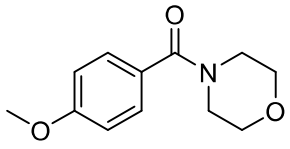


5e

The title compound was obtained as a white solid. M.p. 154 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.60; Yield 86% (200 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.71 (d, J = 7.7 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 6.04 (s, 1H), 3.93 (d, J = 7.6 Hz, 1H), 3.81 (s, 3H), 1.99 (d, J = 10.5 Hz, 2H), 1.72 (d, J = 12.7 Hz, 2H), 1.62 (d, J = 12.2 Hz, 1H), 1.40–1.35 (m, 2H), 1.24–1.15 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.0,

161.8, 128.5, 127.2, 113.5, 55.3, 48.5, 33.2, 25.5, 24.8. **HRMS**: Calc. for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1494, Obser.: 234.1487.

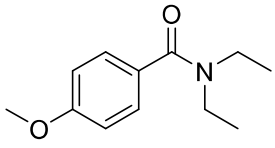
[5.7.23] (4-Methoxyphenyl)(morpholino)methanone(5f)



5f

The title compound was obtained as a colourless liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.45; Yield 68% (150 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.36 (d, J = 7.9 Hz, 2H), 6.89 (d, J = 7.9 Hz, 2H), 3.80 (s, 3H), 3.66 (s, 8H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 170.2, 160.7, 129.0, 127.2, 113.6, 66.7, 55.2. **HRMS**: Calc. for $C_{12}H_{16}NO_3$ $[M+H]^+$: 222.1130, Obser.: 222.1121.

[5.7.24] *N,N*-Diethyl-4-methoxybenzamide (5g)

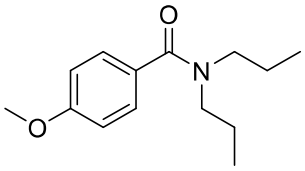


5g

The title compound was obtained as a colourless liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.60; Yield 82% (169 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.31 (d, J = 7.9 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 3.78 (s, 3H), 3.37 (d, J = 74.8 Hz, 4H), 1.14 (b, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 171.1, 160.1, 129.3, 128.0, 113.4,

55.1, 43.1, 39.2, 22.5, 13.9. **HRMS**: Calc. for $C_{12}H_{18}NO_2$ $[M+H]^+$: 208.1338, Obser.: 208.1329.

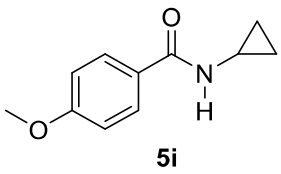
[5.7.25] 4-Methoxy-*N*,*N*-dipropylbenzamide (5h)



5h

The title compound was obtained as a colourless liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.60; Yield 67% (157 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.30 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 3.79 (s, 3H), 3.30 (d, J = 102.4 Hz, 4H), 1.58 (d, J = 42.9 Hz, 4H), 0.93–0.75 (m, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 171.5, 160.0, 129.4, 128.1, 113.4, 55.1, 50.7, 46.3, 21.7, 20.6, 11.0. **HRMS**: Calc. for $C_{14}H_{22}NO_2$ $[M+H]^+$: 236.1651, Obser.:236.1649.

[5.7.26] *N*-Cyclopropyl-4-methoxybenzamide (5i)

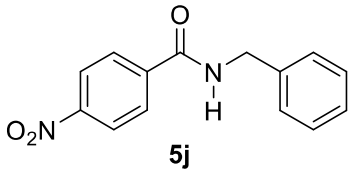


5i

The title compound was obtained as viscous liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.70; Yield 66% (126 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.70 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.32 (s, 1H), 3.82 (s, 3H), 2.87 (dt, J = 10.4, 3.3 Hz, 1H), 0.83 (q, J = 6.7 Hz, 2H), 0.61–0.57 (m, 2H). **^{13}C NMR** (125 MHz,

$CDCl_3$) δ = 168.4, 162.1, 128.5, 126.6, 113.6, 55.4 55.2, 23.1, 22.9, 6.7. **HRMS**: Calc. for $C_{11}H_{14}NO_2$ $[M+H]^+$: 192.1025, Obser.:192.1021.

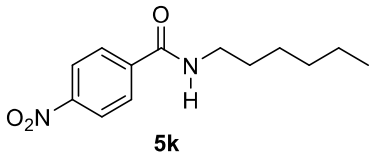
[5.7.27] *N*-Benzyl-4-nitrobenzamide (5j)



5j

The title compound was obtained as a white solid. M.p. 113 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.50; Yield 78% (199 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.22 (d, J = 7.8 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.2 Hz, 5H), 6.85 (s, 1H), 4.62 (d, J = 5.1 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 165.3, 149.5, 139.8, 137.4, 128.8, 128.8, 128.1, 127.8, 123.7, 44.35. **HRMS**: Calc. for $C_{11}H_{14}NO_2$ $[M+H]^+$: 192.1025, Obser.:192.1021.

[5.7.28] *N*-Hexyl-4-nitrobenzamide (5k)

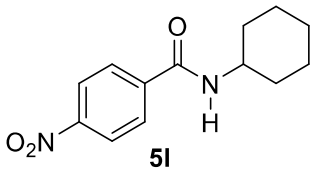


5k

The title compound was obtained as a white solid. M.p. 83 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.66; Yield 77% (192 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.19 (d, J = 8.1 Hz, 2H), 7.91 (d, J = 8.1 Hz, 2H), 6.89 (s, 1H), 3.40 (dd, J = 12.8, 6.3 Hz, 2H), 1.60–1.55 (m,

2H), 1.32–1.25 (m, 6H), 0.83 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 165.5, 149.2, 140.3, 128.0, 123.5, 40.3, 31.3, 29.3, 26.5, 22.4, 13.8. **HRMS:** Calc. for $C_{13}H_{19}N_2O_3$ $[M+H]^+$: 251.1396, Obser.: 251.1387.

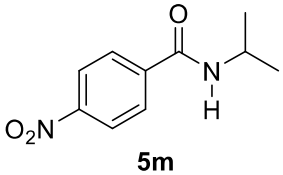
[5.7.29] *N*-Cyclohexyl-4-nitrobenzamide(5l)



5l

The title compound was obtained as a white solid. M.p. 178–179 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.50; Yield 62% (154 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.25 (d, J = 7.7 Hz, 2H), 7.90 (d, J = 7.7 Hz, 2H), 6.16 (d, J = 5.3 Hz, 1H), 4.00–3.94 (m, 1H), 2.03 (d, J = 11.2 Hz, 2H), 1.76 (d, J = 12.1 Hz, 2H), 1.66 (d, J = 12.9 Hz, 1H), 1.41 (q, J = 12.3 Hz, 2H), 1.29–1.18 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 164.5, 149.3, 140.6, 128.0, 123.7, 49.2, 33.0, 25.4, 24.8. **HRMS**: Calc. for $C_{13}H_{17}N_2O_3$ $[M+H]^+$: 249.1239, Obser.: 249.1231.

[5.7.30] *N*-Isopropyl-4-nitrobenzamide (5m)

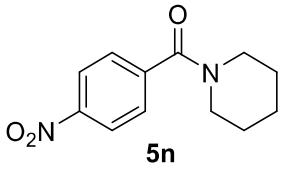


5m

The title compound was obtained as a white solid. M.p. 88 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.50; Yield 64% (133 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ

= 8.21 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 8.0 Hz, 2H), 6.36 (s, 1H), 4.25 (dq, *J* = 13.1, 6.5 Hz, 1H), 1.25 (d, *J* = 6.5 Hz, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 164.6, 149.3, 140.5, 128.0, 123.6, 42.3, 22.5. **HRMS**: Calc. for $C_{10}H_{13}N_2O_3$ $[M+H]^+$: 209.0926, Obser.: 209.0918.

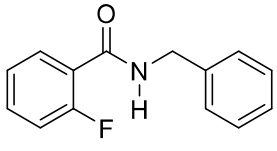
[5.7.31] (4-Nitrophenyl)(piperidin-1-yl)methanone (5n)



5n

The title compound was obtained as a white solid. M.p. 118 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.40; Yield 69% (162 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.25 (d, *J* = 7.8 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 3.70 (s, 2H), 3.26 (s, 2H), 1.68 (s, 4H), 1.51 (s, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 167.8, 148.0, 142.6, 127.7, 123.7, 48.5, 43.1, 26.4, 25.4, 24.3. **HRMS**: Calc. for $C_{12}H_{15}N_2O_3$ $[M+H]^+$: 235.1083, Obser.: 235.1079.

[5.7.32] *N*-Benzyl-2-fluorobenzamide (5o)

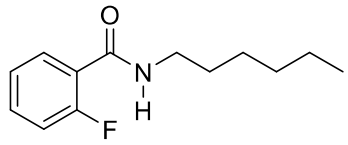


5o

The title compound was obtained as a white solid. M.p. 42 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.66; Yield 74% (170 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.16

(t, J = 7.7 Hz, 1H), 7.49 (td, J = 7.3, 1.7 Hz, 1H), 7.39–7.36 (m, 4H), 7.33–7.28 (m, 2H), 7.13 (dd, J = 11.8, 8.5 Hz, 2H), 4.71 (d, J = 5.6 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.2 (d, J = 3.7 Hz), 160.5 (d, J = 245 Hz), 137.9, 133.2, 132.0 (d, J = 15.0 Hz), 128.7, 127.6, 127.5, 124.7 (d, J = 3.7 Hz), 120.9 (d, J = 11.2 Hz), 115.9 (d, J = 23.7 Hz), 44.0. **HRMS**: Calc. for $C_{14}H_{13}FNO$ $[M+H]^+$: 230.0981, Obser.: 230.0977.

[5.7.33] 2-Fluoro-*N*-hexylbenzamide (5p)

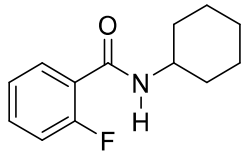


5p

The title compound was obtained as a colourless liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.60; Yield 66% (147 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.04–8.01 (m, 1H), 7.40–7.39 (m, 1H), 7.19 (dd, J = 10.8, 4.1 Hz, 1H), 7.05 (dd, J = 15.6, 4.6 Hz, 1H), 6.76 (s, 1H), 3.42 (d, J = 6.8 Hz, 2H), 1.57 (d, J = 7.2 Hz, 2H), 1.34–1.27 (m, 6H), 0.85 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 163.1 (d, J = 3.7 Hz), 160.4 (d, J = 245 Hz), 132.9 (d, J = 8.7 Hz), 131.9 (d, J = 2.5 Hz), 124.6 (d, J = 3.7 Hz), 121.2 (d, J = 12.5 Hz), 115.8 (d, J = 23.7 Hz), 40.0, 31.3, 29.3, 26.5, 22.4, 13.9. **HRMS**: Calc. for $C_{13}H_{19}FNO$

$[M+H]^+$: 224.1451, Obser.: 224.1446.

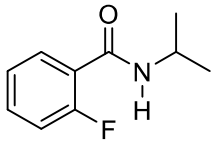
[5.7.34] *N*-Cyclohexyl-2-fluorobenzamide (5q)



5q

The title compound was obtained as a white solid. M.p. 132–134 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.60; Yield 68% (150 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.07 (td, J = 7.9, 1.5 Hz, 1H), 7.43 (td, J = 7.3, 1.7 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 7.08 (dd, J = 11.8, 8.5 Hz, 1H), 6.61 (s, 1H), 4.04–3.98 (m, 1H), 2.01 (dd, J = 12.3, 3.1 Hz, 2H), 1.75–1.71 (m, 2H), 1.65–1.61 (m, 1H), 1.47–1.38 (m, 2H), 1.31–1.21 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.1 (d, J = 2.5 Hz), 160.4 (d, J = 245 Hz), 132.8 (d, J = 10.0 Hz), 131.9, 124.6 (d, J = 2.5 Hz), 121.4 (d, J = 11.2 Hz), 115.8 (d, J = 25.0 Hz), 48.5, 32.8, 25.4, 24.6. **HRMS**: Calc. for $C_{13}H_{17}FNO$ $[M+H]^+$: 222.1294, Obser.: 222.1288.

[5.7.35] 2-Fluoro-*N*-*iso*propylbenzamide (5r)

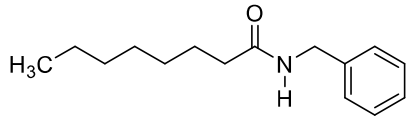


5r

The title compound was obtained as a colourless liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.62; Yield 60% (108 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ =

8.09–8.06 (m, 1H), 7.46–7.41 (m, 1H), 7.26–7.22 (m, 1H), 7.11–7.07 (m, 1H), 6.54 (s, 1H), 4.34–4.27 (m, 1H), 1.26 (d, J = 6.6 Hz, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 162.3 (d, J = 3.7 Hz), 160.5 (d, J = 245 Hz), 132.9 (d, J = 10.0 Hz), 131.9 (d, J = 2.5 Hz), 124.7 (d, J = 2.5 Hz), 121.3 (d, J = 11.2 Hz), 115.8 (d, J = 25.0 Hz), 41.9, 22.7. **HRMS**: Calc. for $C_{10}H_{13}FNO$ $[M+H]^+$: 182.0981, Obser.: 182.0974.

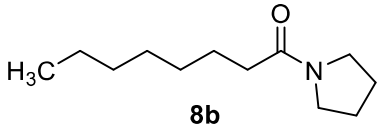
[5.7.36] *N*-Benzyloctanamide (8a)



8a

The title compound was obtained as a white solid. M.p. 64 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.32; Yield 76% (177 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.35–7.29 (m, 2H), 7.26 (dd, J = 6.9, 4.7 Hz, 3H), 5.93 (s, 1H), 4.42 (d, J = 5.7 Hz, 2H), 2.19 (t, J = 7.6 Hz, 2H), 1.65–1.63 (m, 2H), 1.30–1.27 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 173.0, 138.4, 128.6, 127.7, 127.3, 43.4, 36.7, 31.6, 29.2, 28.9, 25.7, 22.5, 14.0. **HRMS**: Calc. for $C_{15}H_{24}NO$ $[M+H]^+$: 234.1858, Obser.: 234.1852.

[5.7.37] 1-(Pyrrolidin-1-yl)octan-1-one (8b)



8b

The title compound was obtained as a yellow liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc (80:20), R_f = 0.30; Yield 71% (140 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 3.46 (t, J = 6.9 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 2.27–2.24 (m, 2H), 1.95 (p, J = 6.7 Hz, 2H), 1.85 (p, J = 6.8 Hz, 2H), 1.68–1.62 (m, 2H), 1.35–1.28 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 171.7, 46.4, 45.4, 34.7, 31.5, 29.3, 28.9, 26.0, 24.8, 24.2, 22.4, 13.9. **HRMS**: Calc. for $C_{12}H_{24}NO$ $[M+H]^+$: 198.1858, Obser.: 198.1856.

5.8 Spectral data of few products

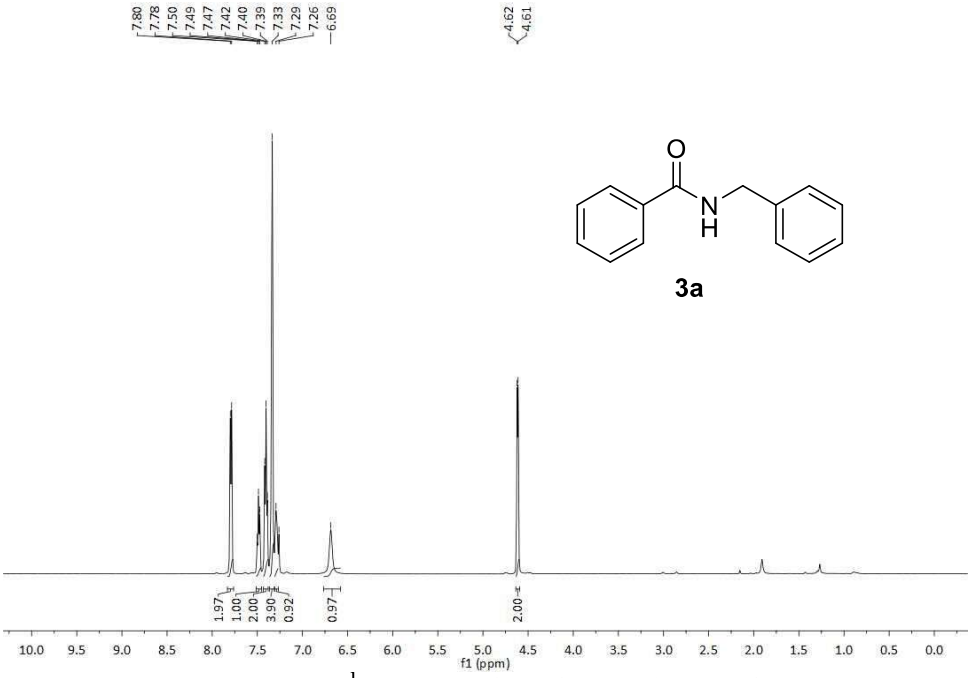


Figure 5.2 ^{1}H NMR of product **3a** in $CDCl_3$

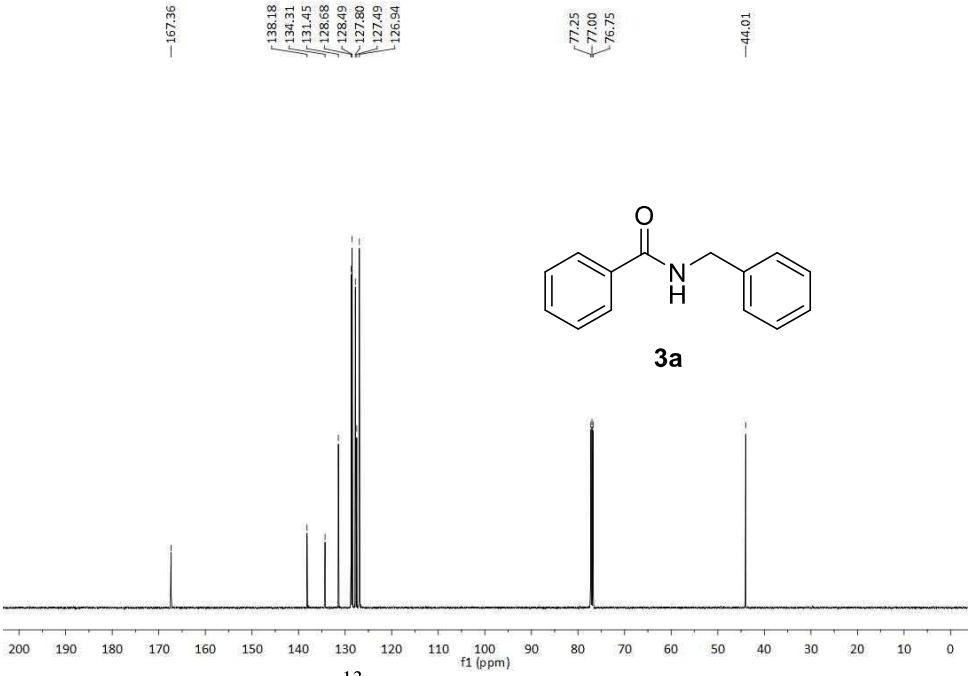


Figure 5.3 ^{13}C NMR of product **3a** in **$CDCl_3$**

Figure 5.4 ^{1}H NMR of product **3p** in $CDCl_3$

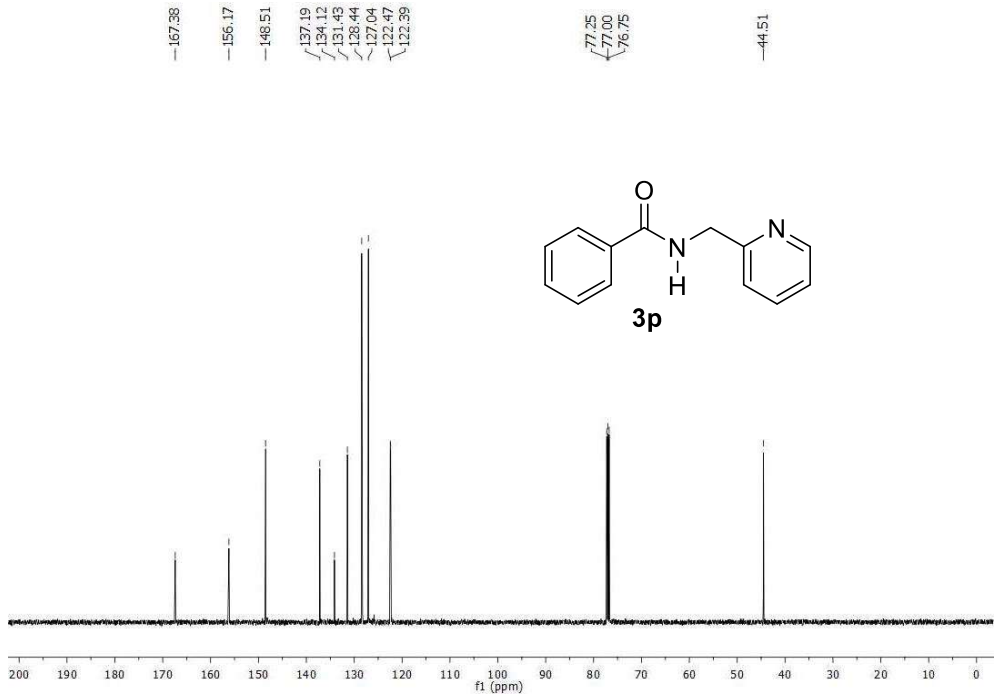


Figure 5.5 ^{13}C NMR of product **3p** in **$CDCl_3$**

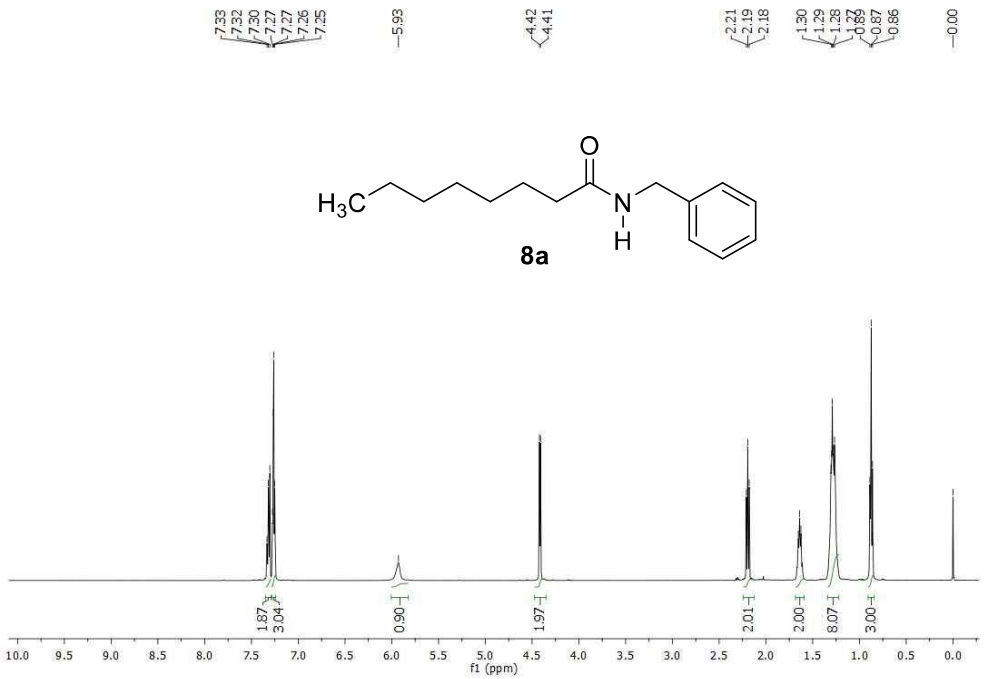


Figure 5.6 ^{1}H NMR of product 8**a** in $CDCl_3$

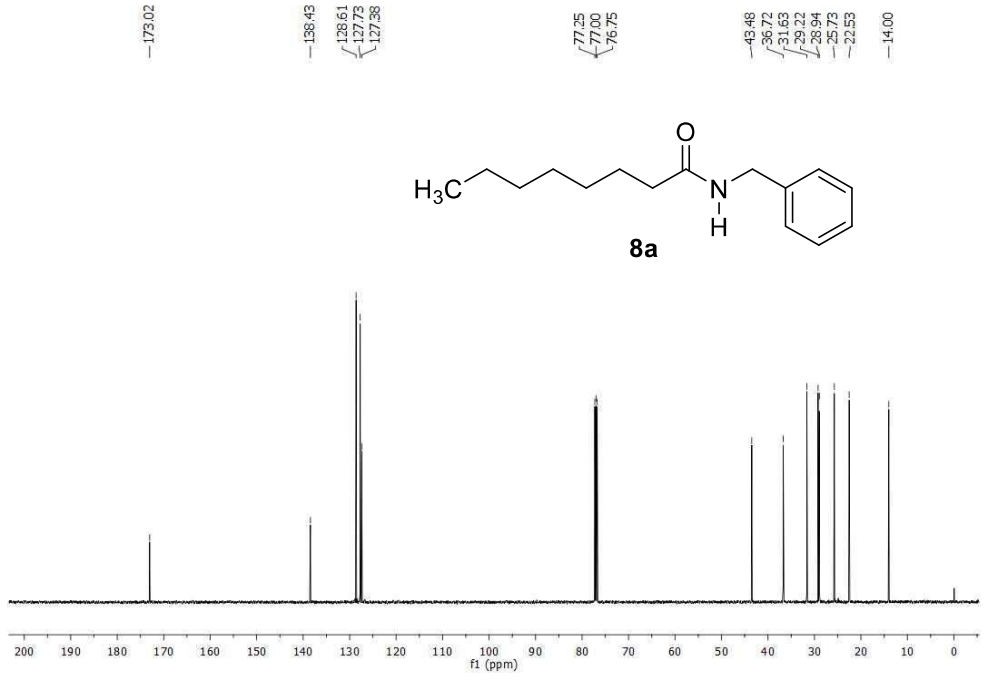


Figure 5.7 ^{13}C NMR of product **8a** in **$CDCl_3$**

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