Chapter 4

TBHP-Initiated Transamidation of Secondary Amides via C-N Bond Activation: A Metal-Free Approach

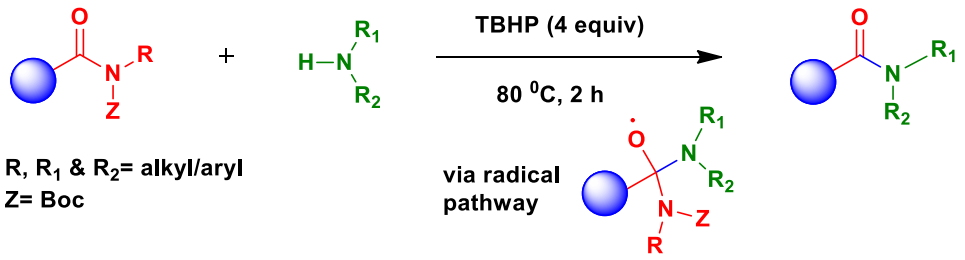
4.1 Introduction

American Chemical Society's Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) in 2007, voted 'amide formation avoiding poor atom economy reagents' as a top challenge for organic chemistry (Constable et al. 2007). Wide applicability and stability of amides make them special reagent and precursor in organic synthesis. Therefore, several strategies have been developed for the amide synthesis but among them transamidation provides a direct and rapid approach with good atom economy. However, unreactivity of amide C-N bond is due to resonance stabilization and it is relatively inert as compared to other acyl donors. Due to poor electrophilic character of amide carbonyl, it requires various homogeneous and heterogeneous catalysts and therefore, catalyst-free transamidation reaction requires strong forcing conditions.

The previously reported methods for secondary amide transamidation involves the metal catalysts (Ni and Pd) which twisted amide bond by metal insertion and restrict the resonance stabilization of amide bond (Meng et al. 2016, Liu et al. 2017). In case of Ce catalyst, Ce polarizes the amide bond and increases the electrophilicity of carbonyl for nucleophilic substitution. There is only one metal-free approach for secondary transamidation using Et_3N was reported by Szostak and co-workers in 2017 but this method

suffers the substrate scope (Liu et al. 2017) and later in 2018 they have observed that it is also applicable for the transamidation of *N*-acyl-glutarimides with amines (Liu et al. 2018).

In continuation of our earlier work of secondary amide transamidation (Mishra et al. 2018) herein, we plan to establish an efficient and environment friendly, metal and organic solvent-free procedure for the secondary amide transamidation using a radical initiator. In this chapter, we describe a green protocol using *tert*-butyl hydroperoxide (TBHP) for transamidation of secondary amides. TBHP has found extensive applications in variety of reactions as a radical initiator and also as a powerful green oxidant (Chen, Meng et al. 2016, Tan, Zheng et al. 2017). Commercial availability, inexpensiveness, odorless and nontoxic nature are the additional advantages of TBHP. To the best of our knowledge, TBHP radical initiated transamidation of secondary amide under metal-free condition has not been reported till date. Therefore, site selective N-functionalization and TBHP as a radical initiator promotes the secondary amide transamidation to give good to excellent yield (**Scheme 4.1**).



Scheme 4.1: TBHP initiated secondary amide transamidation.

4.2 Results and Discussion

In order to optimize the reaction conditions, a model reaction using *tert*-butyl benzoyl(phenyl)carbamate (**1a**) and morpholine (**2a**) was screened in detail and outcomes are summarized in **Table 4.1**. First of all, the model reaction was performed in acetonitrile under refluxed condition using conventional heating method without initiator for 24 h, no product was obtained. Therefore, the model reaction was performed by using 1 equiv. of TBHP under same reaction condition and it gave the 20% yield of transamidated product in 24 h. Further, to increase the reaction rate and yield, amount of TBHP was increased to 4 equiv. under similar reaction condition and it gave 52% yield of transamidated product in 6 h, any further increase in TBHP amount as well as reaction time had shown no improvement in yield. Further different radical initiators like hydrogen peroxide (H_2O_2), *tert*-butyl nitrite (TBN), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), oxone, ceric ammonium nitrate (CAN) and chloranil were tested over the model reaction in acetonitrile under reflux condition by conventional heating method. In case of H_2O_2 it gave 30% of product along with 70% of the deprotected amide and in other cases either deprotected amide or the mixture of deprotected amide with transamidated product were obtained (**Table 4.1, Entries 5-10**). The results show that among all the radical initiators tested to improve the yield TBHP gives the best result with 52% transamidated product and no deprotection was observed in compare to other existing protocols therefore, different polar and non-polar solvents were screened over the model reaction using TBHP (4 equiv.) as

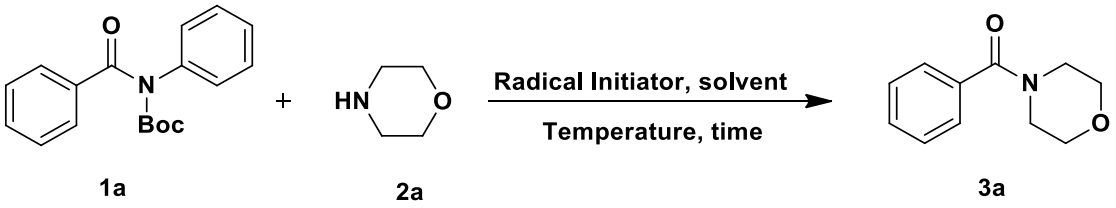
radical initiator. In case of non-polar solvents like toluene and xylene no desired product was obtained even after 6 h (**Table 4.1, Entries 16 & 17**) and with polar solvents like acetonitrile, ethanol and methanol reaction proceeded with low yields.

Since among all the solvents tested acetonitrile gave the best result with the yield of 52% with TBHP (4 equiv.) therefore to improve the yield it was decided to investigate the model reaction under solvent-free condition using TBHP (4 equiv.). At room temperature there is no formation of, therefore the temperature of the reaction was increases to 40, 60, 80 and 100 ^{0}C. At 80 ^{0}C temperature with 4 equiv. TBHP it showed a profound effect on the yield of 92% and considerably reduced reaction time (**Entry 20**).

Since at 40 ^{0}C and 60 ^{0}C poor yield of product was observed which shows that the temperature plays a crucial role in reaction and at higher temperature (80 ^{0}C) there is increases in the rate of radical generation which accelerated the rate of reaction as well as yield and any further increase in reaction temperature and TBHP amount does not shows any considerable change in product yield, it suggests that 4 equiv. of TBHP at 80 ^{0}C is optimal condition for this reaction. The formation of product (**3a**) was confirmed by ^{1}H and ^{13}C NMR spectroscopy.

When the same model reaction was performed using additives such as I_2, KI and CuI together with the TBHP and it was observed that the use of additive causes deprotection of *tert*-butylbenzoyl(phenyl)carbamate (**1a**) and diminishes the product yield and gave a mixture of product and unprotected amide.

Table 4.1: Optimization of reaction conditions[a]



1a 2a 3a

Entry	Solvent	Initiator (equiv)	Condition	Time (h)	Yield (%)[b]
1	Acetonitrile	-	Reflux	24	NR
2	Acetonitrile	TBHP (1)	Reflux	24	20
3	Acetonitrile	TBHP (4)	Reflux	6	52
4	Acetonitrile	TBHP (6)	Reflux	6	53
5	Acetonitrile	H_2O_2 (4)	Reflux	12	30% Product + deprotected amide
6	Acetonitrile	TBN (4)	Reflux	6	Deprotected amide
7	Acetonitrile	DDQ (4)	Reflux	6	Deprotected amide
8	Acetonitrile	CAN (4)	Reflux	6	Deprotected amide
9	Acetonitrile	Oxone (4)	Reflux	6	Deprotected amide
10	Acetonitrile	Chloranil (4)	Reflux	6	Deprotected amide
11	Ethanol	TBHP (4)	Reflux	6	30
12	Methanol	TBHP (4)	Reflux	6	28
13	DMF	TBHP (4)	80	6	10
14	DMSO	TBHP (4)	80	6	12
15	Toluene	TBHP (4)	80	6	NR
16	Xylene	TBHP (4)	80	6	NR
17	Solvent-free[c]	TBHP (4)	40	6	15

18	Solvent-free	TBHP (4)	60	6	43
19	Solvent-free	TBHP (4)	80	6	93
20	**Solvent-free**	**TBHP (4)**	**80**	**2**	**92**
21	Solvent-free	TBHP (4)	100	2	92
22	Solvent-free	TBHP (6)	80	2	91

[a] **Reaction condition:** *tert*-butylbenzoyl(phenyl)carbamate (**1a**) (1.0 mmol, 1 equiv), morpholine (**2a**) (1.2 mmol, 1.2 equiv) under different conditions. [b] Isolated yield. [c] Without additional solvent.

Having optimized reaction conditions in hand, further the substrate scope and generality of the TBHP-initiated methodology for transamidation of secondary amide was examined over a variety of N-Boc activated aliphatic and aromatic amides with a series of unsubstituted, electron donating, electron withdrawing, di-*ortho*-sterically hindered aromatic amines as well as aliphatic amines. The results obtained are summarized in **Scheme 4.2** - **Scheme 4.4**. The amides and amines containing both electron donating and electron withdrawing groups underwent the conversion smoothly.

To explore the substrate scope we had started with aromatic amides *tert*-butyl benzoyl(phenyl)carbamate (**1a**), *tert*-butyl (2-chlorobenzoyl)(phenyl)carbamate (**1b**) and *tert*-butyl (3-nitrobenzoyl)(phenyl)carbamate (**1c**) with different amines like morpholine (**2a**), pipridine (**2b**), *N*-methylaniline (**2c**), 2,6-dimethylaniline (**2d**), adamantylamine (**2e**), *p*-methoxyaniline (**2f**), *p*-nitroaniline (**2g**) and benzylamine (**2h**) were heated at 80 ^{0}C under optimized reaction conditions. After completion of reaction the reaction mixture was diluted with ethyl acetate, washed with water and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by

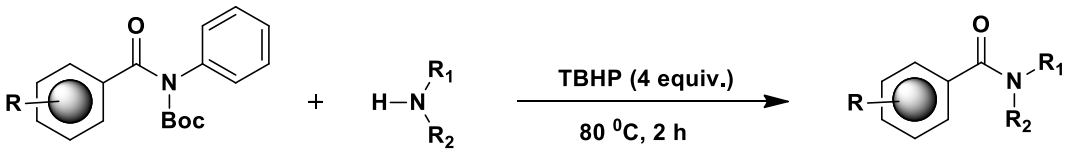
column chromatography over silica gel using *n*-hexane-ethyl acetate to obtain the pure products *viz.* morpholino(phenyl)methanone (**3a**), phenyl(piperidin-1-yl)methanone (**3b**), *N*-methyl -*N*-phenylbenzamide (**3c**), *N*-(2,6-dimethylphenyl)benzamide (**3d**), *N*-((3s,5s,7s)-adamantan-1-yl)benzamide (**3e**), *N*-(4-methoxyphenyl)benzamide (**3f**), *N*-(4-nitrophenyl) benzamide (**3g**), *N*-benzyl-2-chlorobenzamide (**3h**), (2-chlorophenyl)(morpholino) methanone (**3i**), *N*-methyl-3-nitro-*N*-phenylbenzamide (**3j**) and *N*-benzyl-3-nitrobenzamide (**3k**) in good to excellent yield.

Further, we have tried secondary amide transamidation with aliphatic substituents on the nitrogen of the amides *viz. tert*-butyl benzoyl(methyl)carbamate (**1d**), *tert*-butyl benzoyl(benzyl)carbamate (**1e**), *tert*-butyl benzyl(4-methoxybenzoyl) carbamate (**1f**) and *tert*-butyl benzyl(4-(trifluoromethyl)benzoyl)carbamate (**1g**) with different amines (**2**) *viz.* cyclopropylamine (**2i**), aniline (**2j**), 2-ethylaniline (**2k**), cyclohexylamine (**2l**), benzylamine (**2h**), *tert*-butylamine (**2m**) and *N*-methylaniline (**2c**) under optimized reaction conditions to give transamidated product *viz. N*-cyclopropylbenzamide (**3l**), *N*-phenylbenzamide (**3m**), *N*-(2-ethylphenyl)benzamide (**3n**), *N*-cyclohexylbenzamide (**3o**), *N*-benzylbenzamide (**3p**), *N*-(*tert*-butyl)benzamide (**3q**), *N*-cyclohexyl-4-methoxybenzamide (**3r**), 4-methoxy-*N*-methyl-*N*-phenylbenzamide (**3s**), *N*-cyclohexyl-4-(trifluoromethyl)benzamide (**3t**) and *N*-methyl-*N*-phenyl-4-(trifluoromethyl)benzamide (**3u**) in good to excellent yield.

At last, we have changed amide bearing aliphatic acyl and the N-Boc activated amides *viz.* *tert*-butyl acetyl(phenyl) carbamate (**1h**) and *tert*-butyl isobutyryl (phenyl)carbamate (**1i**)

were treated with benzyl amine (**2h**) and *o*-chloroaniline (**2n**) to furnish transamidated products *viz.* *N*-benzylacetamide (**3v**), *N*-(2-chlorophenyl)acetamide (**3w**), *N*-phenyl isobutyramide (**3x**) and *N*-(2-chlorophenyl) isobutyramide (**3y**) in good to excellent yield.

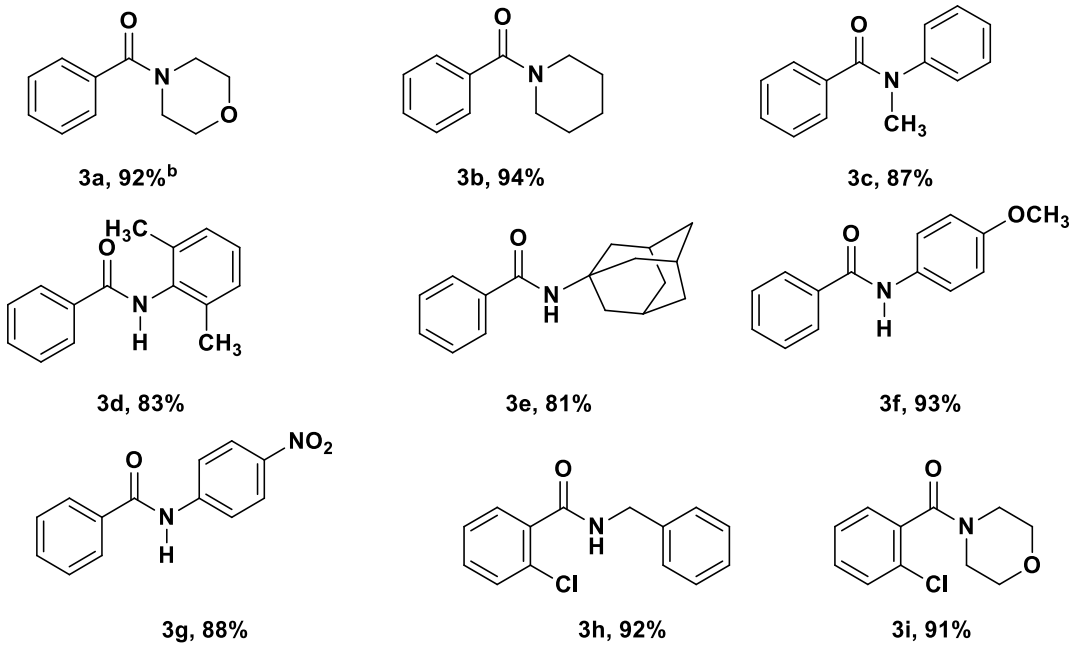
Scheme 4.2: TBHP initiated transamidation of N-Boc activated secondary aromatic amides[a]

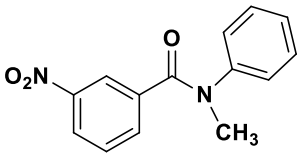


1a, R=H
1b, R=2-Cl
1c, R=3-NO_2

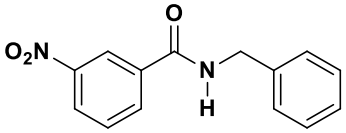
2

3a-k





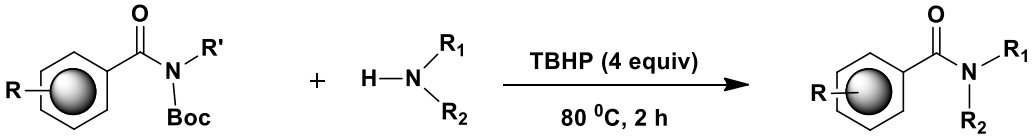
3j, 86%



3k, 90%

[a] **Reaction condition**: N-Boc activated amide (1.0 mmol, 1 equiv.), amine (1.2 mmol, 1.2 equiv.) in aqueous TBHP (4 equiv.) under solvent-free conditions at 80 ^{0}C for 2 h. [b] Isolated yield.

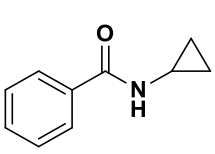
Scheme 4.3: TBHP-initiated transamidation of N-Boc activated secondary aliphatic amides[a]



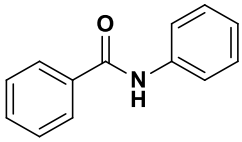
1d, R=H, R'=Me
1e, R=H, R'=Bn
1f, R=4 OCH_3, R'=Bn
1g, R=4 CF_3, R'=Bn

2

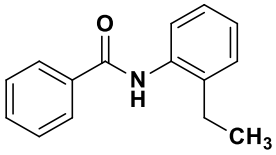
3l-u



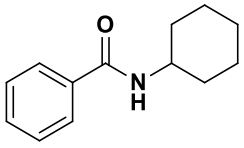
3l, 94%[b]



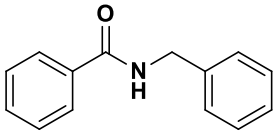
3m, 92%



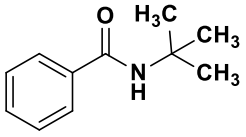
3n, 87%



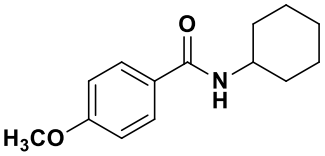
3o, 89%



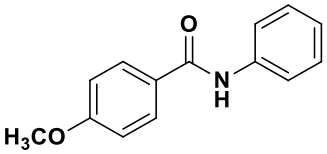
3p, 92%



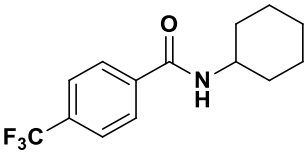
3q, 79%



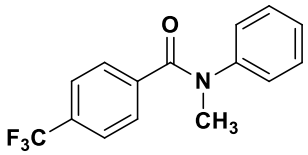
3r, 85%



3s, 83%



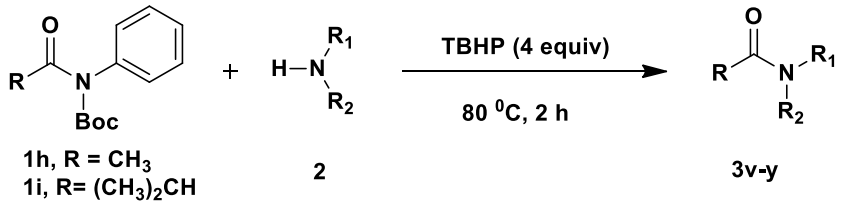
3t, 91%

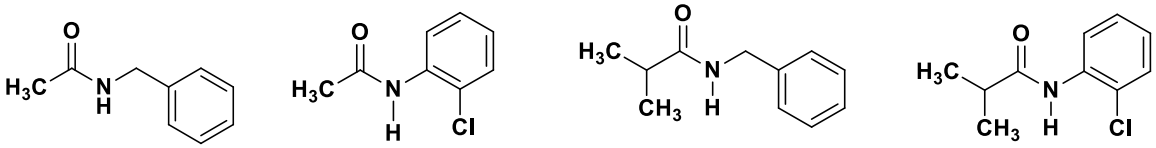


3u, 88%

[a] **Reaction condition**: N-Boc activated amide (1.0 mmol, 1 equiv.), amine (1.2 mmol, 1.2 equiv.) in aqueous TBHP (4 equiv.) under solvent-free conditions at 80 ^{0}C for 2 h. [b] Isolated yield.

Scheme 4.4: TBHP initiated transamidation of N-Boc activated secondary aliphatic amides[a]



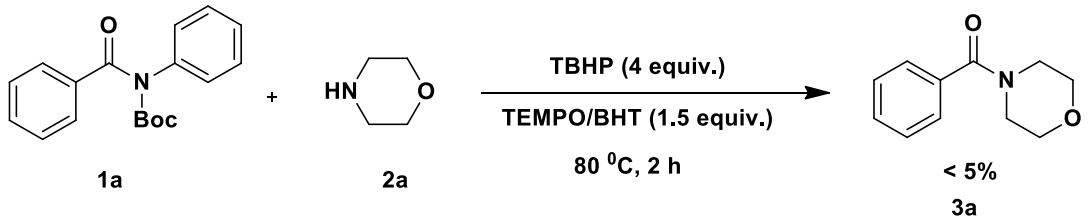


3v, 95% 3w, 92% 3x, 94% 3y, 90%

[a]**Reaction condition**: N-Boc activated amide (1.0 mmol, 1 equiv.), amine (1.2 mmol, 1.2 equiv.) in aqueous TBHP (4 equiv.) under solvent-free conditions at 80 ^{0}C for 2 h. [b] Isolated yield.

4.3 Mechanistic studies and control experiment

On the basis of our observations and the literature precedents, a tentative mechanistic pathway for the TBHP initiated transamidation of secondary amides is delineated in **Figure 4.1**. To support the mechanistic information of the TBHP-initiated secondary amide transamidation, control experiment was carried out on model reaction with 1.5 equiv. radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxydanyl) and BHT (butylated hydroxytoluene) under optimized reaction conditions. The reaction was suppressed by both TEMPO/BHT and less than 5% of desired product was obtained. The result shows the transformation was proceeds with radical pathways as expected **Figure 4.1**.



Scheme 4.5: Control experiment with TEMPO/BHT.

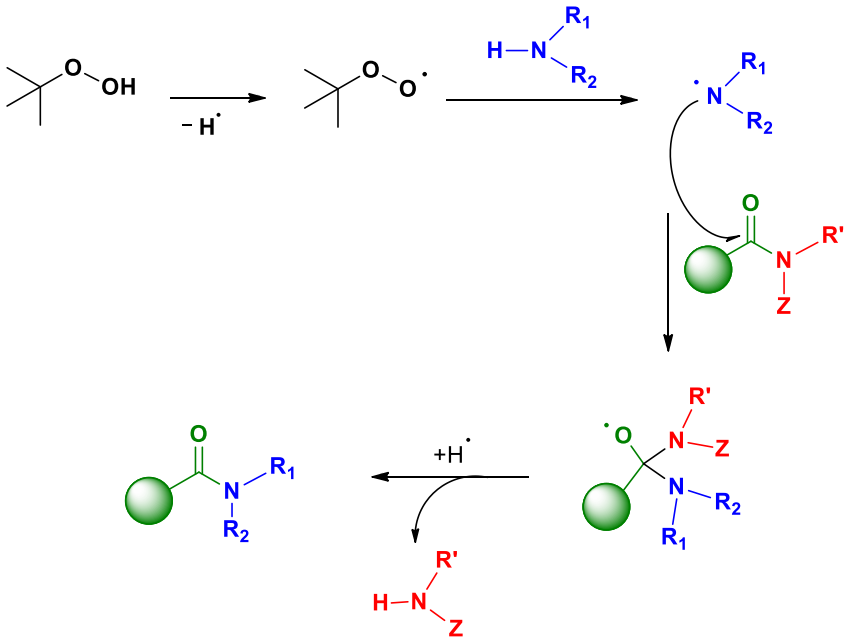
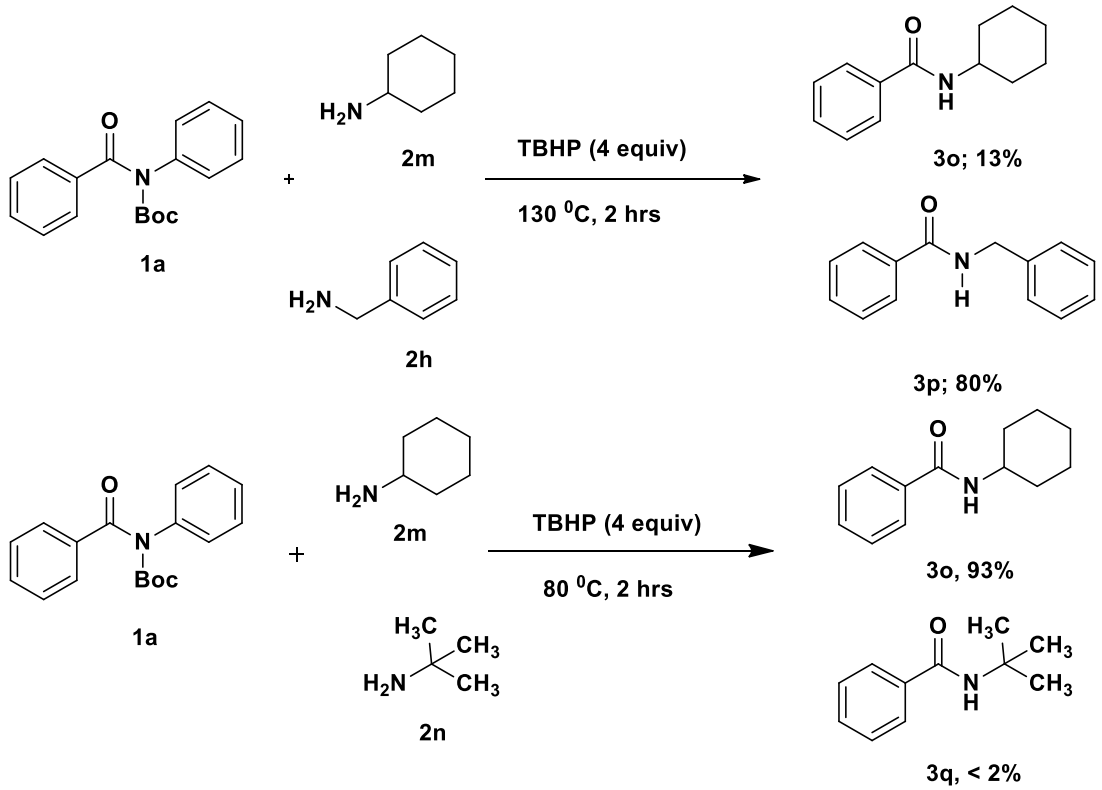


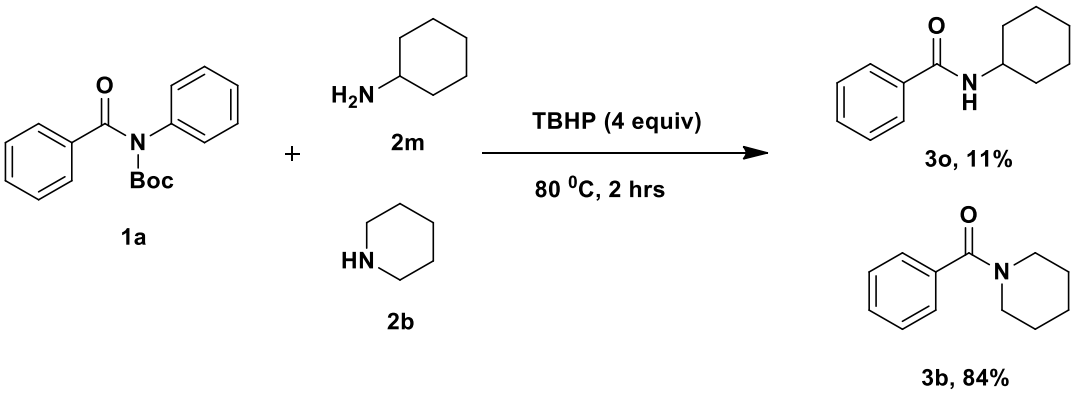
Figure 4.1: Plausible mechanism of TBHP initiated secondary amide transamidation.

4.4 Selectivity of amines in transamidation

In order to take a close look at reaction rate, selectivity pattern, steric and electronic influences, three additional competitive experiment were carried out. Started our study with *tert*-butyl benzoyl(phenyl)carbamate (**1a**) and different amines. First of all, we compared

between benzyl amine (**2h**) and cyclohexyl amine (**2m**), *N*-benzylbenzamide (**3p**) was obtained as the major product (80%) under same optimal reaction condition which shows less hindered amine undergoes reaction easily than the α-disubstituted hindered amine. A competition reaction of benzoyl(phenyl) carbamate (**1a**) with cyclohexyl amine (**2m**) and *tert*-butyl amine (**2n**) gives *N*-cyclohexylbenzamide (**3o**) as a result of stearic factor. The competition reaction of benzoyl(phenyl)carbamate (**1a**) with cyclohexyl amine (**2m**) and piperidine (**2b**) gives phenyl(piperidin-1-yl)methanone (**3b**) as major product since the secondary amine is more nucleophilic (**Scheme 4.6**).





Scheme 4.6: Selectivity of amines in transamidation under optimized reaction condition.

4.5 Experimental section

4.5.1 General procedure for synthesis of amides: All amide used in study were synthesized by using pervious reported methods. (Phukan et al. 2009, de Figueiredo et al. 2016, Mishra et al. 2018).

4.5.2 General procedure for Synthesis of *N*-Boc activated amides from secondary amides: N-Boc activated amides were synthesized according to the previously reported method (QináZhou 2015, Liu, Shi et al. 2017). To an oven dried round bottom flask, amide (1 equiv.), DMAP (0.1 equiv.) in dichloromethane (25 mL) was added, the reaction temperature was maintained to 0 ^{0}C and then dropwise Boc anhydride (1.5 equiv.) was added. After complete addition of Boc anhydride the reaction mixture was brought to the room temperature and allowed to stir at room temperature for 15-24 h. The progress of reaction was monitored by TLC. After complete conversion of amide to N-Boc amide the

reaction mixture was concentrated under reduced pressure and directly loaded over column chromatography and the product was obtained in more than 95% yield. The column chromatography was performed over neutral silica or neutral alumina due to deprotection of the product in case of acidic silica.

4.5.3 General Procedure for the TBHP radical initiated transamidation: To a round bottom flask N-Boc activated amide (1.0 mmol, 1 equiv.), amine (1.2 mmol, 1.2 equiv.) and TBHP (70% aq., 4 equiv.) were mixed. The reaction mixture was heated at 80 ^{0}C in an oil bath while stirring for appropriate time. After completion of reaction monitored by TLC the reaction mixture was cooled to the room temperature. The reaction mixture was extracted with ethyl acetate, washed with water and the organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography over silica gel using *n*-hexane-ethyl acetate as an eluent.

4.6 Analytical data

4.6.1 Analytical data of N-Boc activated amides

***tert*-Butyl benzoyl(phenyl)carbamate (1a)** (Liu et al. 2017, Meng et al. 2017). White solid; yield 94%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.74 (d, 2 H), 7.53 (t, 1 H), 7.44 (q, 4 H), 7.35 (t, 1 H), 7.28 (d, 2 H), 1.24 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 172.91, 153.42, 139.21, 137.09, 131.83, 129.33, 128.40, 128.25, 128.07, 127.92, 83.62, 27.59.

***tert*-Butyl (2-chlorobenzoyl)(phenyl)carbamate (1b).** White solid; yield 95%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.51 – 7.46 (m, 3 H), 7.44 – 7.30 (m, 6 H), 1.21 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 169.69, 152.15, 138.40, 137.75, 130.83, 130.21, 129.51, 129.35, 128.80, 128.42, 128.38, 127.11, 84.04, 27.51.

***tert*-Butyl (3-nitrobenzoyl)(phenyl)carbamate (1c).** White solid; yield 94%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.47 – 8.43 (m, 1 H), 8.29 (d, 1 H), 7.95 (d, 1 H), 7.57 (t, 1 H), 7.38 (t, 2 H), 7.31 (t, 1 H), 7.21 – 7.17 (m, 2 H), 1.20 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 170.31, 152.92, 148.01, 138.45, 138.44, 133.79, 129.62, 129.47, 128.44, 128.12, 126.00, 123.03, 84.49, 29.81, 27.68.

***tert*-Butyl benzoyl(methyl)carbamate (1d)** (Liu et al. 2017, Meng et al. 2017)**.** Yellow oil; yield 96%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.47 – 7.38 (m, 2 H), 7.38 – 7.31 (m, 1 H), 7.31 – 7.21 (m, 2 H), 3.21 (s, 3 H), 1.05 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 173.34, 153.34, 137.81, 130.71, 127.85, 127.31, 127.27, 127.24, 82.75, 32.40, 27.15.

***tert*-Butyl benzoyl(benzyl)carbamate (1e)** (Meng et al. 2017)**.** White solid; yield 94%; m.p. 62-63 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.51 (d, 2 H), 7.47 – 7.42 (m, 3 H), 7.38 (t, 2 H), 7.33 (t, 2 H), 7.29 – 7.25 (m, 1 H), 4.99 (s, 2 H), 1.12 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 173.24, 153.61, 138.01, 137.88, 131.17, 128.59, 128.30, 128.20, 127.60, 127.54, 83.32, 49.01, 27.48.

***tert*-Butyl benzyl(4-methoxybenzoyl)carbamate (1f).** Yellow oil; yield 95%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.57 (d, 2 H), 7.45 (d, 2 H), 7.34 (t, 2 H), 7.27 (t, 1 H), 6.90 (d, 2 H), 4.99 (s, 2 H), 3.83 (s, 3 H), 1.21 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 172.64, 162.27, 153.74, 138.11, 130.01, 129.61, 128.43, 128.06, 127.32, 113.32, 82.83, 55.40, 49.14, 27.49.

***tert*-Butyl benzyl(4-(trifluoromethyl)benzoyl)carbamate (1g).** White solid; yield 94%; m.p. 78-79 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.67 (d, 2 H), 7.61 (d, 2 H), 7.43 (d, 2 H), 7.36 (t, 2 H), 7.32 – 7.27 (m, 1 H), 5.01 (s, 2 H), 1.16 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 171.86, 153.09, 141.25, 137.62, 128.68, 128.29, 127.75, 127.67, 125.28, 125.25, 84.02, 48.93, 27.51; **^{19}F NMR** (471 MHz, $CDCl_3$) δ –62.89.

***tert*-Butyl acetyl(phenyl)carbamate (1h)** (Grehn et al. 1986, Raju et al. 2009). White solid; yield 98%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.28 (m, 3 H), 7.15 – 7.03 (m, 2 H), 2.48 (s, 3 H), 1.33 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 171.60, 151.92, 138.60, 128.48, 128.20, 127.23, 82.40, 27.36, 26.15.

***tert*-Butyl isobutyryl(phenyl)carbamate (1i).** Yellow oil; yield 96%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.29 (t, 2 H), 7.22 (d, 1 H), 7.02 – 6.95 (m, 2 H), 3.62 – 3.47 (m, 1 H), 1.30 (s, 9 H), 1.14 (d, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 180.44, 152.73, 139.43, 128.92, 128.13, 128.12, 127.61, 82.96, 34.75, 34.63, 27.72, 19.53.

4.6.2 Analytical data of transamidation products

Morpholino(phenyl)methanone (3a) (Ohshima, Iwasaki et al. 2008)**.** Yellow solid; yield 92%; m.p. 73-74 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.57 – 7.30 (m, 5 H), 4.09 – 3.19 (m, 8 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 170.61, 135.45, 130.03, 128.71, 127.23, 67.05.

Phenyl(piperidin-1-yl)methanone (3b) (Ohshima, Iwasaki et al. 2008)**.** Yellow oil; yield 94%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.43 – 7.37 (s, 5 H), 3.72 (s, 2H), 3.34 (s, 2 H), 1.68 (s, 4 H), 1.52 (s, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 170.46, 136.64, 129.48, 128.53, 126.91, 48.90, 43.24, 26.68, 25.75, 24.73.

***N*-Methyl-*N*-phenylbenzamide (3c)** (Racine, Monnier et al. 2011)**.** Yellow oil; yield 87%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.29 (d, 2 H), 7.25 – 7.18 (m, 3 H), 7.17 – 7.09 (m, 3 H), 7.03 (d, 2 H), 3.49 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 170.69, 144.91, 135.94, 129.60, 129.16, 128.71, 127.74, 126.92, 126.51, 38.42.

***N*-(2,6-Dimethylphenyl)benzamide (3d)** (Mishra et al. 2018)**.** White solid; yield 83%; m.p. 168-69 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.94 (d, 2 H), 7.58 (t, 1 H), 7.51 (t, 2 H), 7.42 (s, 1 H), 7.18 – 7.13 (m, 3 H), 2.30 (s, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.06, 135.72, 134.66, 133.98, 131.97, 128.93, 128.45, 127.61, 127.35, 18.64.

***N*-((3s,5s,7s)-Adamantan-1-yl)benzamide (3e)** (Faler et al. 2006)**.** White solid; yield 81%; m.p. 144-45 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.76 – 7.66 (m, 2 H), 7.48 – 7.44 (m, 1 H), 7.40 (t, 2 H), 5.80 (bs, 1 H), 2.13 (s, 9 H), 1.74 (d, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.80, 136.18, 134.69, 131.17, 130.72, 129.02, 128.59, 126.83, 52.42, 41.81, 36.52, 29.63.

***N*-(4-Methoxyphenyl)benzamide (3f)** (Faler et al. 2006)**.** Green solid; yield 93%; m.p. 155-56 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.85 (d, 3 H), 7.54 (d, 3 H), 7.46 (t, 2 H), 6.89 (d, 2 H), 3.81 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.82, 156.76, 135.15, 131.82, 131.13, 128.86, 127.12, 122.28, 114.36, 55.63.

***N*-(4-Nitrophenyl)benzamide (3g)** (Faler and Joullié 2006)**.** White solid; yield 88%; m.p. 197-98 ^{0}C; **^{1}H NMR** (500 MHz, DMSO–d_6) δ (ppm): 10.82 (s, 1 H), 8.27 (d, 2 H), 8.06 (d, 2 H), 7.97 (d, 2 H), 7.64 (t, 1 H), 7.56 (t, 2 H); **^{13}C NMR** (126 MHz, DMSO–d_6) δ (ppm): 166.39, 145.45, 142.60, 134.24, 132.35, 128.67, 128.01, 124.92, 120.00, 119.92.

***N*-Benzyl-2-chlorobenzamide (3h)** (Thansandote et al. 2009)**.** White solid; yield 92%; m.p. 104-05 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.68 (d, 1 H), 7.48 – 7.24 (m, 8 H), 6.55 (s, 1 H), 4.67 (s, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.55, 137.79, 135.06, 131.48, 130.79, 130.36, 130.33, 128.90, 128.01, 127.78, 127.23, 44.35.

(2-Chlorophenyl)(morpholino)methanone (3i) (Lysén et al. 2005)**.** Yellow solid; yield 91%; m.p. 72-73 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.37 – 7.31 (m, 1 H), 7.30 – 7.19 (m, 3 H), 3.86 – 3.77 (m, 1 H), 3.75 – 3.66 (m, 3 H), 3.66 – 3.59 (m, 1 H), 3.55 – 3.49 (m, 1 H), 3.26 – 3.19 (m, 1 H), 3.18 – 3.09 (m, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 167.06, 135.48, 130.47, 130.42, 129.78, 127.94, 127.39, 66.89, 66.80, 47.21, 42.16.

***N*-Methyl-3-nitro-*N*-phenylbenzamide (3j).** Yellow solid; yield 86%; m.p. 115-16 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.16 (s, 1 H), 8.09 (s, 1 H), 7.62 (s, 1 H), 7.36 (s, 1 H), 7.27 (s, 2 H), 7.19 (s, 1 H), 7.07 (d, 2 H), 3.54 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 168.05, 147.60, 144.03, 137.67, 134.55, 129.71, 128.99, 127.47, 127.09, 124.41, 123.97, 38.55.

***N*-Benzyl-3-nitrobenzamide (3k)** (Agwada 1982)**.** White solid; yield 90%; m.p. 95-96 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.61 (s, 1 H), 8.35 (d, 1 H), 8.18 (d, 1 H), 7.64 (t, 1 H), 7.34 (d, 4 H), 6.74 (s, 1 H), 4.67 (d, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.08, 148.31, 137.61, 136.08, 133.43, 130.02, 129.04, 128.16, 128.04, 126.27, 121.93, 44.59.

***N*-Cyclopropylbenzamide (3l)** (Tsuritani et al. 2008)**.** White solid; yield 94%; m.p. 100-01 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.74 (d, 2 H), 7.55 – 7.33 (m, 3 H), 6.46 (s, 1 H), 3.10 – 2.72 (m, 1 H), 0.85 (s, 2 H), 0.63 (s, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 169.07, 134.54, 131.56, 128.62, 126.98, 23.25, 6.85.

***N*-phenylbenzamide (3m)** (Mishra et al. 2018)**.** White solid; yield 92%; m.p. 163-64 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.88 (d, 3 H), 7.66 (d, 2 H), 7.56 (t, 1 H), 7.49 (t, 2 H), 7.38 (t, 2 H), 7.17 (t, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.90, 138.06, 135.16, 131.99, 129.25, 128.94, 127.16, 124.73, 120.35.

***N*-(2-Ethylphenyl)benzamide (3n)** (Mishra et al. 2018)**.** White solid; yield 87%; m.p. 159-60 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.94 (d, 1 H), 7.88 (d, 2 H), 7.74 (s, 1 H), 7.57 (t, 1 H), 7.50 (t, 2 H), 7.27 (t, 2 H), 7.17 (t, 1 H), 2.69 (q, J = 7.6 Hz, 2 H), 1.28 (t, J = 7.6 Hz, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.96, 135.51, 135.19, 135.10, 131.91, 128.93, 128.71, 127.15, 126.88, 125.85, 124.02, 24.50, 14.05.

***N*-Cyclohexylbenzamide (3o)** (Mishra et al. 2018)**.** White solid; yield 89%; m.p. 196-97 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.75 (d, 2 H), 7.48 (t, 1 H), 7.42 (t, 2 H), 6.00 (s, 1 H), 4.07 – 3.91 (m, 1 H), 2.03 (d, 2 H), 1.76 (d, 2 H), 1.66 (d, 1 H), 1.43 (q, 2 H), 1.24 (dd, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.78, 135.24, 131.37, 128.65, 126.95, 48.80, 33.37, 25.71, 25.04.

***N*-Benzylbenzamide (3p)** (Mishra et al. 2018)**.** White solid; yield 92%; m.p. 104-05 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.79 (d, 2 H), 7.50 (t, 1 H), 7.43 (t, 2 H), 7.36 (d, 4 H), 7.33 – 7.28 (m, 1 H), 6.40 (s, 1 H), 4.66 (d, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 167.49, 138.31, 134.56, 131.71, 128.96, 128.76, 128.09, 127.81, 127.09, 44.32.

***N*-(*tert*-Butyl)benzamide (3q)** (Mishra et al. 2018)**.** White solid; yield 79%; m.p. 135-36 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.72 (dd, 2 H), 7.50 – 7.45 (m, 1 H), 7.41 (t, 2 H), 5.94 (s, 1 H), 1.48 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 167.06, 136.07, 131.23, 128.63, 126.83, 51.75, 29.02.

***N*-Cyclohexyl-4-methoxybenzamide(3r)** (Mishra et al. 2018)**.** White solid; yield 85%; m.p. 159-60 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.72 (d, 2 H), 6.91 (d, 2 H), 5.89 (s, 1 H), 4.06 – 3.90 (m, 1 H), 3.84 (s, 3 H), 2.07 – 1.99 (m, 2 H), 1.81 – 1.71 (m, 2 H), 1.68 – 1.61 (m, 1 H), 1.49 – 1.37 (m, 2 H), 1.23 (dt, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.24, 162.12, 128.72, 127.53, 113.80, 96.26, 88.58, 55.53, 48.70, 33.46, 25.75, 25.08.

4-Methoxy-*N*-methyl-*N*-phenylbenzamide (3s) (Mishra et al. 2018)**.** Yellow solid; yield 83%; m.p. 74-75 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$ + DMSO–d_6) δ (ppm): 7.95 – 7.84 (m, 2 H), 7.65 – 7.54 (m, 2 H), 6.93 – 6.85 (m, 2 H), 6.83 – 6.76 (m, 2 H), 3.80 (d, 3 H), 3.73 (d, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$ + DMSO–d_6) δ (ppm): 164.88, 161.48, 155.39, 131.70, 128.96, 126.94, 121.84, 113.22, 112.90, 112.87, 54.83.

***N*-Cyclohexyl-4-(trifluoromethyl)benzamide (3t)** (Prosser et al. 2010)**.** White solid; yield 91%; m.p. 182-83 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.85 (d, 2 H), 7.68 (d, 2 H), 6.06 (s, 1 H), 4.28 – 3.78 (m, 1 H), 2.04 (d, 2 H), 1.77 (dd, 2 H), 1.43 (dd, 2 H), 1.32 – 1.15 (m, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.50, 138.54, 127.47, 125.70 (q, J_{CF} = 3.6 Hz), 49.15, 33.30, 25.65, 25.02; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm): –65.7.

***N*-Methyl-*N*-phenyl-4-(trifluoromethyl)benzamide (3u)** (Mishra et al. 2018)**.** Yellow solid; yield 88%; m.p. 70-71 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.34 (q, 4 H), 7.25 – 7.05 (m, 3 H), 6.95 (d, 2 H), 3.43 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 169.28, 144.32, 139.55, 129.53, 129.10, 127.15, 127.02, 124.89 (q, J_{CF} = 3.6 Hz), 38.49.

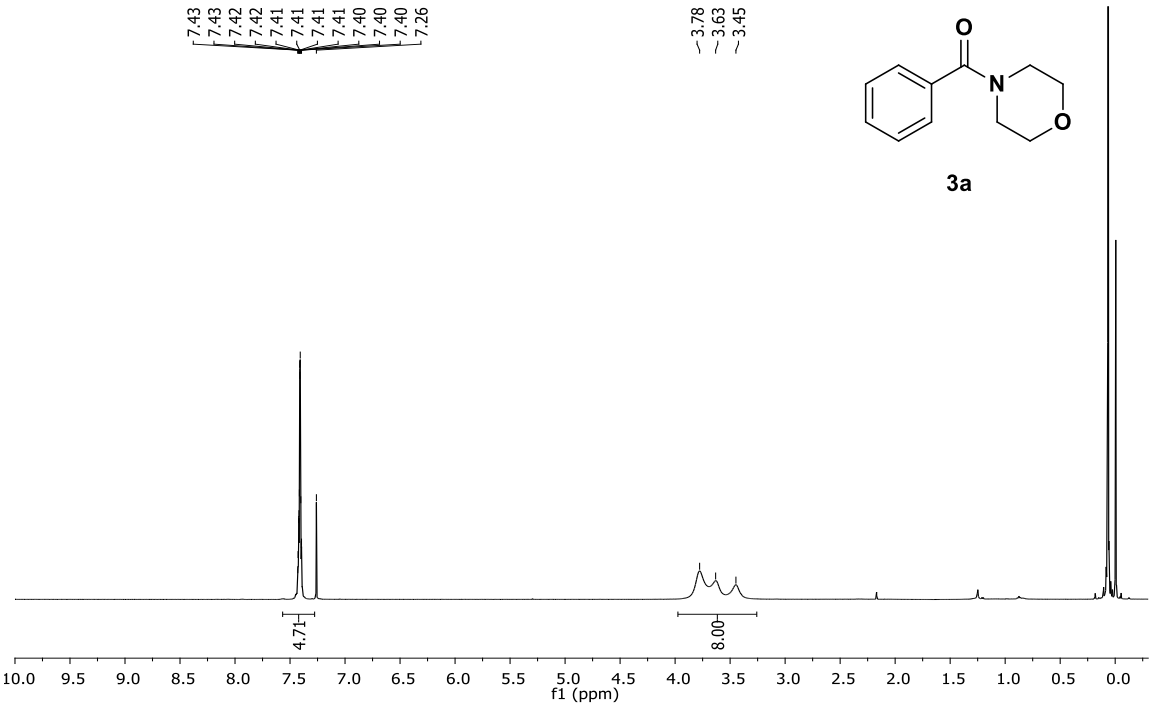
***N*-benzylacetamide (3v)** (Bi et al. 2010)**.** White solid; yield 95%; m.p. 60-61 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.11 (m, 5 H), 6.24 (s, 1 H), 4.29 (d, 2 H), 1.88 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 170.20, 138.38, 128.69, 127.82, 127.48, 43.70, 23.16.

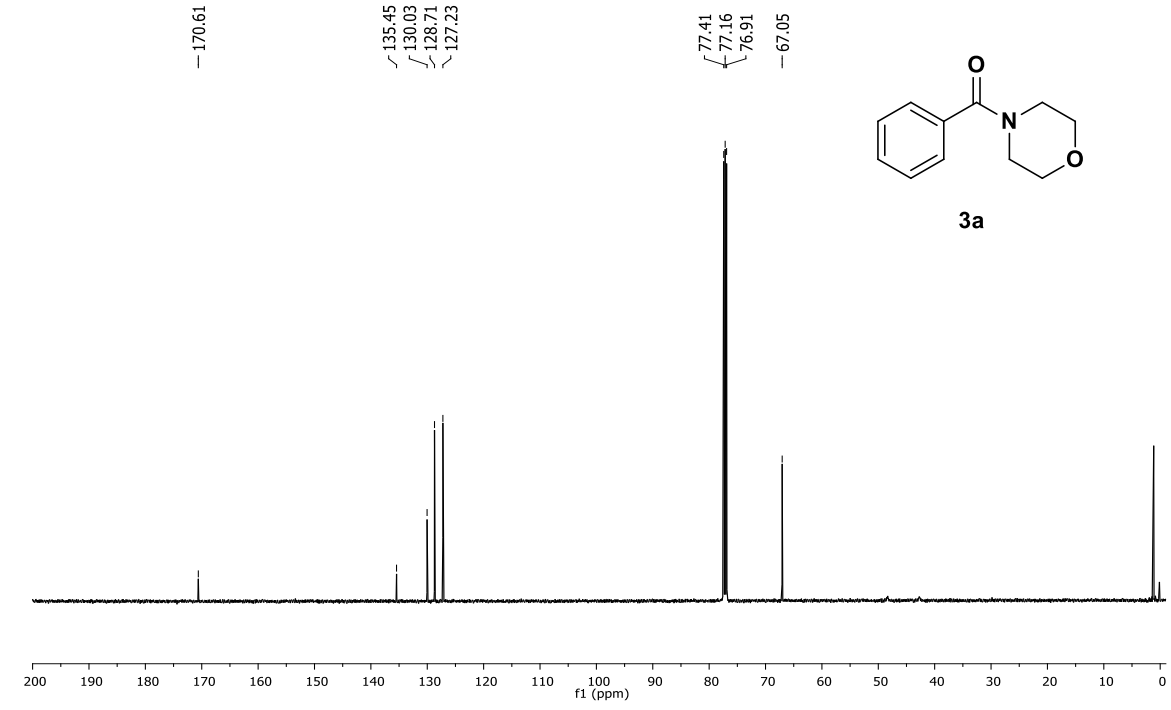
***N*-(2-Chlorophenyl)acetamide (3w)** (Wan et al. 2006)**.** White solid; yield 92%; m.p. 87-88 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.28 (d, 1 H), 7.56 (s, 1 H, NH), 7.29 (d, 1 H), 7.20 (dd, 1 H), 6.97 (t, 1 H), 2.17 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 168.41, 134.72, 129.10, 127.87, 124.75, 122.66, 121.77, 25.00.

***N*-Phenylisobutyramide (3x)** (Maran et al. 1987)**.** White solid; yield 94%; m.p. 90-91 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.54 (d, 2 H), 7.41 – 7.20 (m, 3 H), 7.10 (t, 1 H), 2.63 – 2.36 (m, 1 H), 1.26 (d, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 175.47, 138.17, 137.94, 129.09, 124.27, 121.78, 119.94, 36.81, 19.75.

***N*-(2-Chlorophenyl)isobutyramide (3y)** (Gowda et al. 2004)**.** White solid; yield 90%; m.p. 93-94 ^{0}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.33 (d, 1 H), 7.64 (s, 1 H, NH), 7.29 (d, 1 H), 7.20 (t, 1 H), 6.96 (t, 1 H), 2.66 – 2.35 (m, 1 H), 1.22 (d, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 175.29, 134.80, 129.04, 127.88, 124.56, 122.77, 121.66, 37.11, 19.69.

4.7 Spectral data of product (3a)





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