Chapter-4

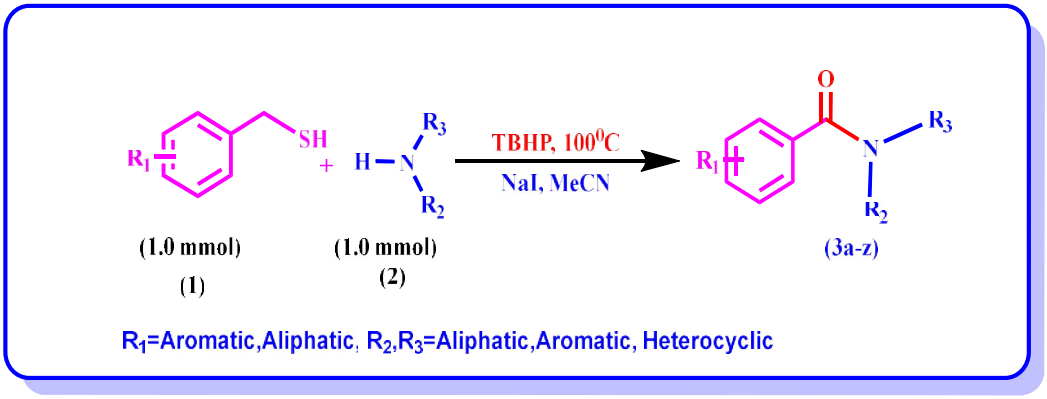
NaI/TBHP-Promoted C-N Bond Formation Via Oxidative Coupling of Benzyl Mercaptan with Amine: A Facile Approach for The Synthesis of Amides

4.1 Introduction

The amide bonds are not only significant chemical links of peptides [1], polypeptides, and proteins but are also used as intermediates in organic chemistry[2], pharmaceuticals, polymers[3][4][5], and agrochemicals. Additionally, the amide bond is the most liked dedicated functional group in organic chemistry due to its auspicious properties like stability, high polarity, and conformational diversity. In recent times, amides have also been engaged in several cross-coupling reactions via C–N bond cleavage[6][7][8]. Usually, various methods have been reported for the synthesis of amides, such as the reaction of the amine with carbonyl derivatives, hydration of nitriles [9][10][11][12][13], hydroamination of alkynes,[14][15][16][17] direct oxidation of benzylamines to benzamides, [18][19] and also oxidative decyanation of aryl-acetonitriles to primary benzamides[20][21][22][23]. Nonetheless, these methods endure several disadvantages, such as using stoichiometric amounts of toxic/hazardous reagents, forming large amounts of by-products, using costly metal complexes and ligands, etc. During the last decades, excessive hard work has been carried out by chemists to develop proper and green approaches to the synthesis of amides. In view of this, the development of a novel and more efficient approach for the synthesis of an amide has become a challenging task for chemists and industrialists. The use of metal

catalyst in amide bond formation allows the beginning from other substrates rather than carboxylic acids, which opens the new synthetic route to achieve the goal compounds.

As a result of our research on the development of a sustainable approach towards organic synthesis and amide bond formation [24] and based on the reported methods to avoid the use of transition metal catalyst by NaI in organic synthesis, we report an efficient and facile technique for the oxidative coupling of benzyl mercaptan with amine into the corresponding benzamides using NaI/TBHP. The present reaction proceeds through the C–H bond cleavage of benzylic carbon of benzyl mercaptan under mild reaction conditions. As far as we know, there is no report on the oxidative coupling of benzyl mercaptan with an amine to provide the corresponding amide, and this is the first report about this reaction under transition metal-free conditions (**Scheme 4.1**).



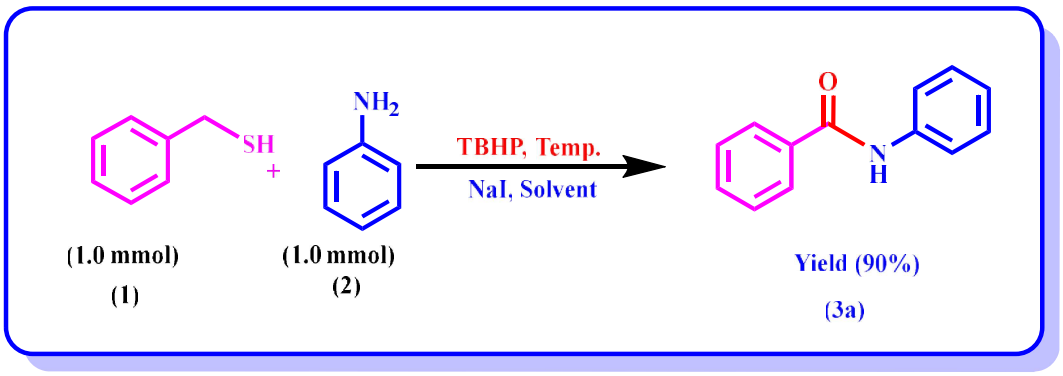
`**Scheme 4.1** NaI/TBHP-Promoted C-N bond formation via oxidative coupling of benzyl mercaptan with amine

4.2 Results and Discussion

Our study initiated with optimization using a model reaction of benzyl mercaptan (mmol) (**1**) and aniline (mmol) (**2**) in the presence of NaI and TBHP (**Table**

4.1) in acetonitrile solvent. While the reaction was carried out at 100^0 C with 50 mol% of catalyst NaI and 1equivalent of TBHP(aq), only 35% of the product was isolated (**Table 4.1, entry 1**). First of all, the amount of oxidant was screened. The % yield was increased with the increasing amount of oxidant (**Table 4.1, entries 2,3**). Even on increasing the amount of oxidant TBHP(aq) from 3 to 4 equivalent, there was a decrease in the product's yield (**Table 4.1**, **entry 4**). Therefore the amount of oxidant was fixed as 3 equivalent for further studies. Decreasing the amount of catalyst also significantly impacted the yields of product **2a** (**Table 4.1, entries 5-7**). Surprisingly, the maximum yield of the product was obtained with 30 mol% of catalyst NaI (**Table 4.1, entry 7**). The use of TBHP (decane) as a substitute for TBHP (aq) significantly reduced the reaction yield (**Table 4.1 entry 9**). Other catalysts KI, I_2, NH_4I, and TBAI, were also screened, but none of them would match the catalytic efficacy of NaI (**Table 4.1, entries 10-13**). Consequently, the effect of various solvents was screened, and the reaction was suppressed in both polar and non-polar solvents (**Table 4.1, entries 14-18**). Next, various oxidants H_2O_2, DTBP, $K_2S_2O_8$, MnO2, and DDQ were also examined, but the expected yield of the product was not obtained(**Table 4.1, entries 19-23**). In additional optimization, NaI without TBHP (**Table 4.1, entry 24**), TBHP without NaI (**Table 4.1, entry 25**), and reaction without NaI and TBHP (**Table 4.1, entry 26**) in the presence of MeCN have been carried out; still, they did not provide the desired product. Finally, the effect of temperature was examined, and it was found that 100^0C was the best condition (**Table 4.1, entries 27-29**).

Table 4.1 Optimized reaction condition for the model reaction (**3a**)



S.N.	Oxidant (Equiv.)	Catalyst (mol%)	Solvent	Temp(°C)	Yield[b] (%)
1	TBHP (1)(aq.)	NaI (50)	MeCN	100	35
2	TBHP (2)(aq.)	NaI (50)	MeCN	100	45
3	TBHP (3)(aq.)	NaI (50)	MeCN	100	60
4	TBHP (4)(aq.)	NaI (50)	MeCN	100	55
5	TBHP (3)(aq.)	NaI (40)	MeCN	100	72
6	TBHP (3)(aq.)	NaI (35)	MeCN	100	84
7	**TBHP (3)(aq.)**	**NaI (30)**	**MeCN**	**100**	**90**
8	TBHP (3)(aq.)	NaI (25)	MeCN	100	68
9	TBHP (3) (dec.)	NaI (30)	MeCN	100	35
10	TBHP (3) (aq.)	KI (30)	MeCN	100	45
11	TBHP (3) (aq.)	I_2 (30)	MeCN	100	48
12	TBHP (3) (aq.)	NH_4I (30)	MeCN	100	51
13	TBHP (3) (aq.)	TBAI (30)	MeCN	100	35
14	TBHP (3) (aq.)	NaI (30)	EtOAc	100	30
15	TBHP (3) (aq.)	NaI (30)	DMSO	100	66
16	TBHP (3) (aq.)	NaI (30)	DMF	100	58
17	TBHP (3) (aq.)	NaI (30)	THF	100	65
18	TBHP (3) (aq.)	NaI (30)	H_2O	100	43
19	H_2O_2	NaI (30)	MeCN	100	38

20	DTBP	NaI (30)	MeCN	100	30
21	$K_2S_2O_8$	NaI (30)	MeCN	100	44
22	MnO_2	NaI (30)	MeCN	100	36
23	DDQ	NaI (30)	MeCN	100	22
24	---	NaI (30)	MeCN	100	ND
25	TBHP(aq)	--	MeCN	100	ND
26	-	--	MeCN	100	ND
27	TBHP(aq)	NaI (30)	MeCN	80	70
28	TBHP(aq)	NaI (30)	MeCN	90	82
29	TBHP(aq)	NaI (30)	MeCN	110	87

The bold row represents optimized conditions.

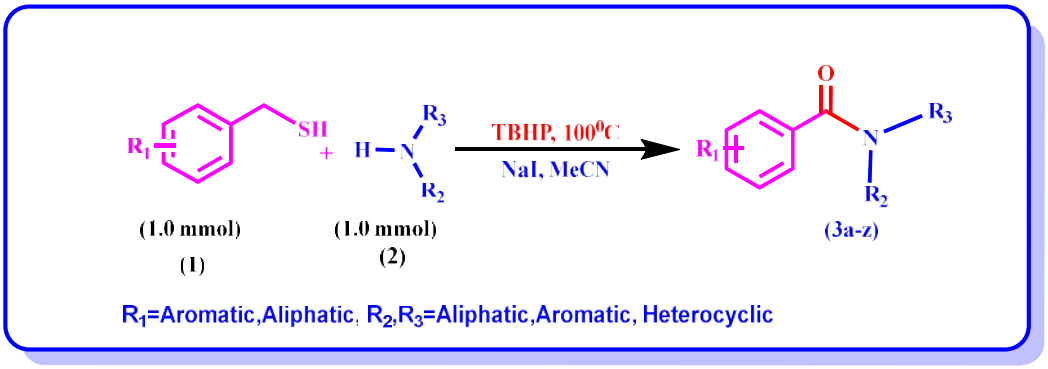
(a) All the reactions were performed with 1 mmol of benzyl mercaptan.

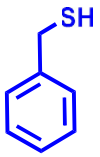
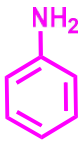
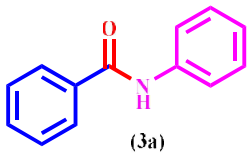
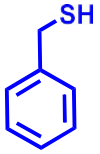
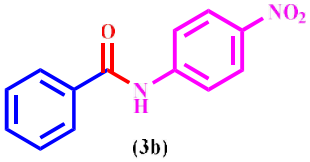
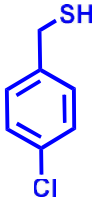
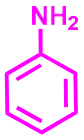
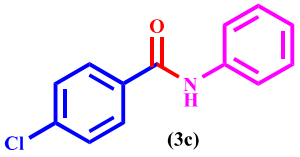
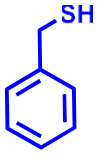
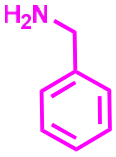
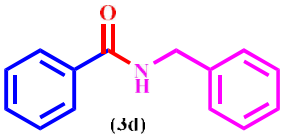
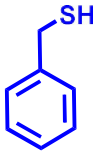
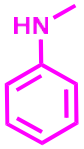
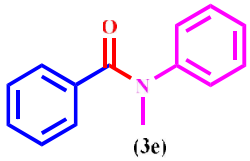
(b) The yields refer to the isolated pure products after 26 h of the reaction times

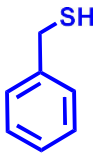
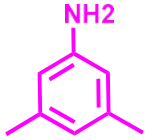
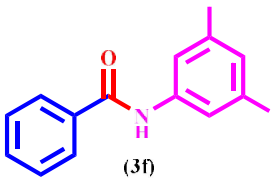
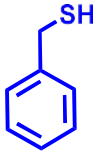
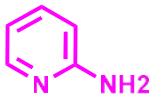
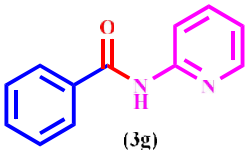
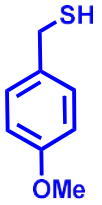
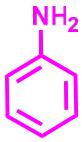
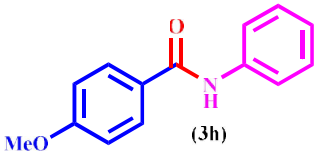
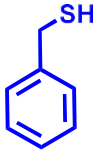
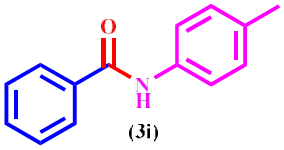
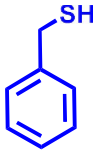
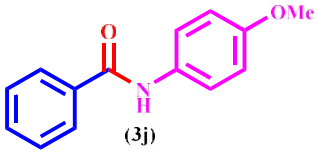
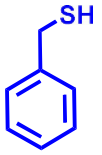
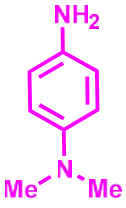
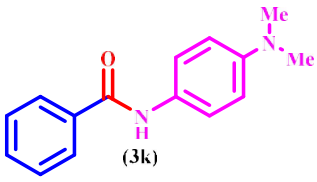
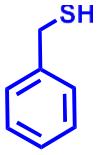
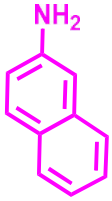
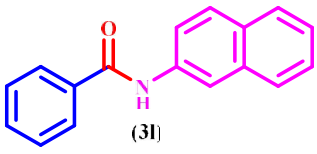
To increase the prospect of the substrate that is benzyl mercaptans (**1**) and different amines aniline **(2a**), 4-nitroaniline **(2b),** Benzyl amine **(2d),** n-methyl aniline (**2e**), 3,5-dimethylaniline **(2f),** 2-aminopyridine **(2g),** 4-methylaniline **(2i),** 4-methoxyaniline **(2j),** N,N-dimethylbenzene-1,4-diamine **(2k),** 2-napthylamine **(2l),** piperidine **(2m),** diphenylmethanamine **(2n),** cyclohexanamine **(2o),** diethylamine **(2r),** 3-nitroaniline **(2s)** having different substitution patterns were examined (**Table 4.2**). All the substrates were successfully converted to the corresponding amides in good to excellent yields. It was observed that the % yield of the product was increased slightly in the case of the electron-withdrawing group containing benzylamine due to the increase in the polarity of the carbonyl group. In contrast, the % yield was decreased in the case of the electron-donating group containing benzylamine due to the decrease in polarity of the carbonyl group. There is also the effect of aliphatic acyclic and cyclic amine on the yield of the products. The yield was somewhat lower in the case of aliphatic amine than cyclic amine as a result of the improved nucleophilicity of

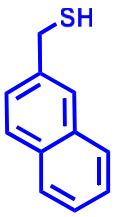
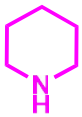
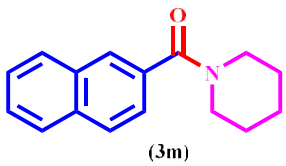
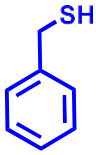
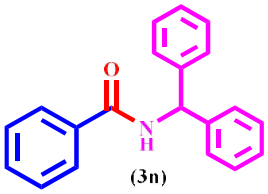
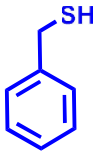
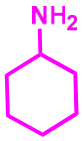
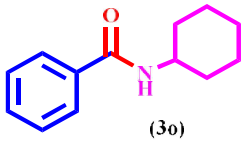
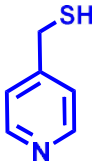
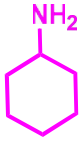
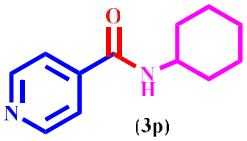
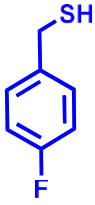
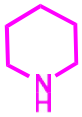
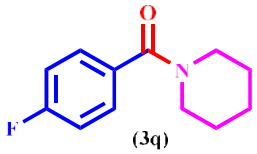
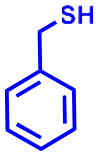
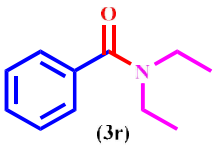
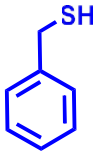
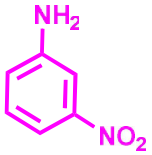
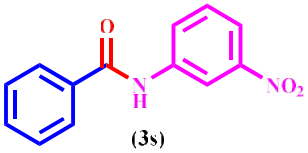
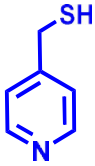
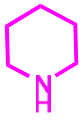
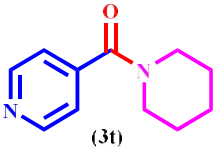
piperidine & pyrrolidine. It was also noted that there is a slight reduction in % yield of morpholine owing to the –I effect of oxygen.

Table 4.2 Screening of substrates for the synthesis of amide



Entry	1	2	3[a]	Yield[b] (%)
1			 (3a)	90
2			 (3b)	84
3			 (3c)	89
4			 (3d)	87
5			 (3e)	89

6			 (3f)	86
7			 (3g)	86
8			 (3h)	89
9			 (3i)	87
10			 (3j)	88
11			 (3k)	84
12			 (3l)	89

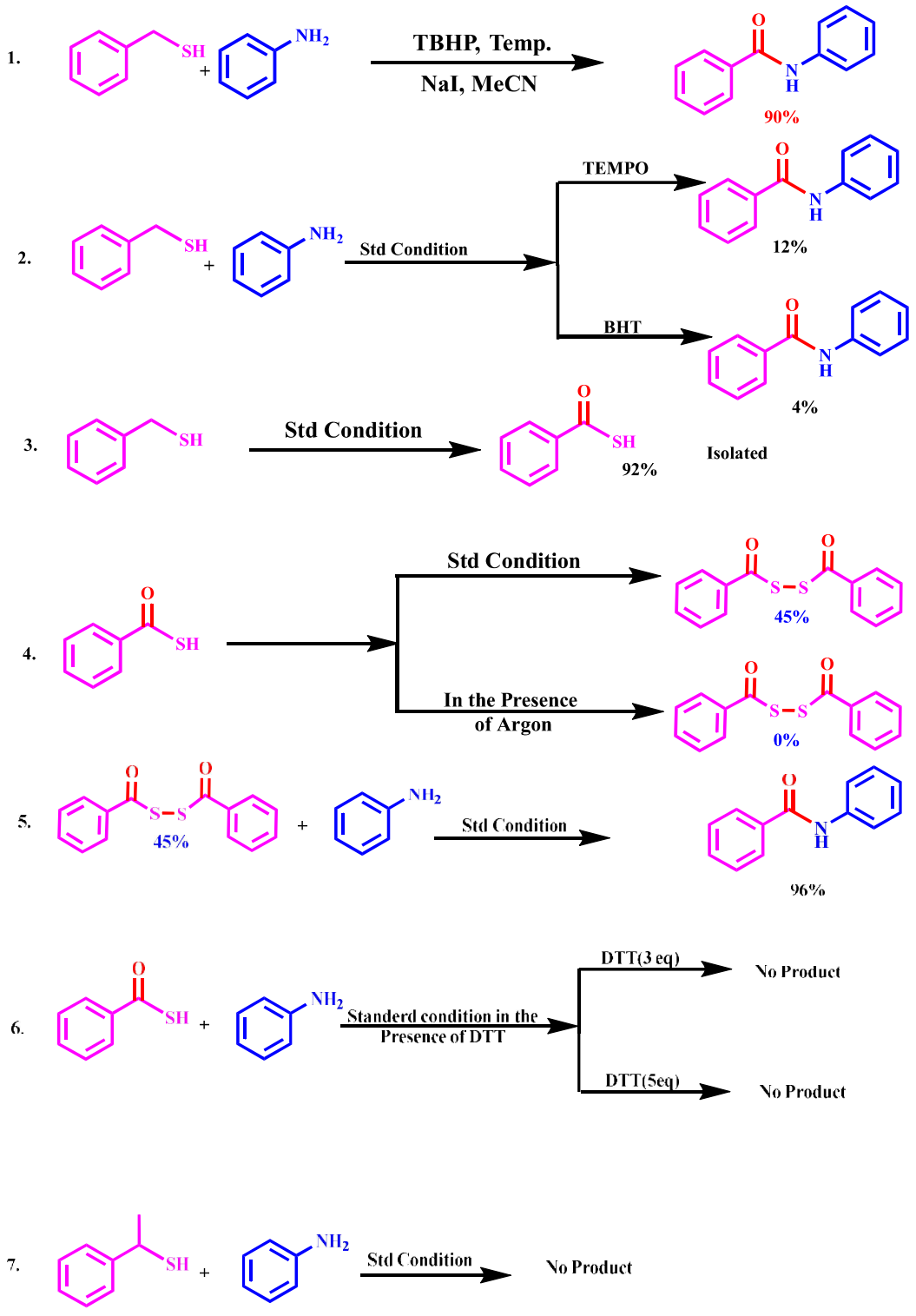
13			 (3m)	85
14			 (3n)	88
15			 (3o)	89
16			 (3p)	89
17			 (3q)	90
18			 (3r)	90
19			 (3s)	89
20			 (3t)	84

[a]Products were characterized by ^{1}H, ^{13}C NMR and IR analysis.

[b]Isolated yield.

4.3 Control experiments to establish the mechanism of the reaction

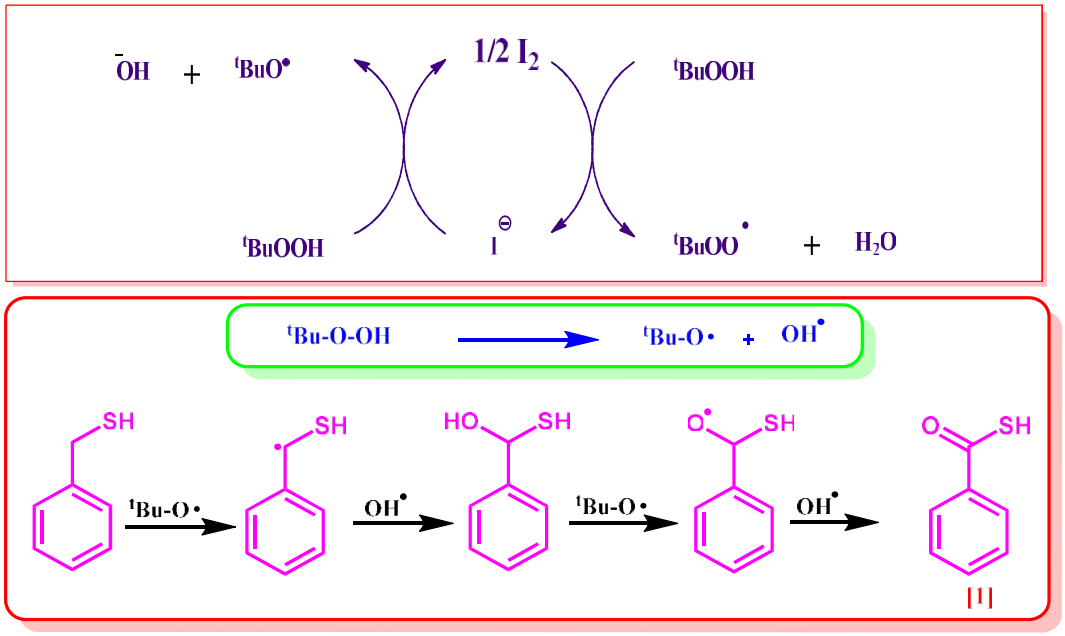
To understand the reaction mechanism, some control experiments were carried out using radical scavengers TEMPO and BHT (**Scheme 4.2**). The results of the control experiment recognized the involvement of radical intermediates in the course of the reaction. The blank experiments using benzyl mercaptan alone formed thiobenzoic acid (**Scheme 4.2,** reaction no 3). Therefore, we suspect the intermediacy of thiobenzoic acid, which is obtained from benzyl mercaptan under standard reaction, to confirm this already synthesized thiobenzoic acid was subjected to the standard reaction conditions, which provided the disulfide in 45% yield. Still, when the same reaction was carried out in the absence of TBHP, no product was formed (**Scheme 4.2,** reaction no 4). Now disulfide reacts with an amine to provide amide, i.e., the final product in more than 92% yield (**Scheme 4.2,** reaction no 5). These outcomes showed that first benzyl mercaptan converted to thiobenzoic acid that can be spontaneously converted to disulfide, and the disulfide can suddenly react with an amine to form an amide. To validate the intermediacy of disulfide, the reaction of thiobenzoic acid with aniline was carried out in the presence of disulfide reducing agent DL dithiothreitol (DTT) (3 equivalent and 5 equivalent) under standard conditions; no product was formed (**Scheme 4.2,** reaction no 6). The formation of disulfide was also identified from its ^{1}H NMR and ^{13}CNMR. In another control experiment i.e., in reaction 7, the product amide was not formed. These results supported our estimation that intermediate thiobenzoic acid is undoubtedly the main intermediate during the reaction path (**Scheme 4. 2,** reaction no 7).

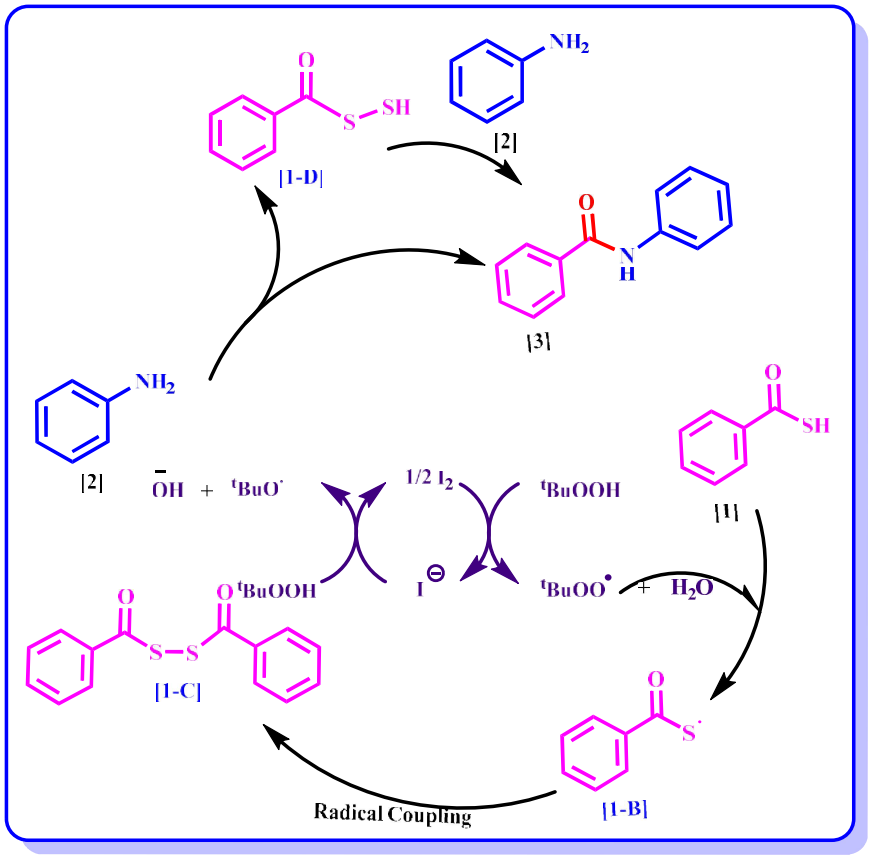


Scheme 4.2: Control experiments to establish mechanism of the reaction

4.4 Mechanism of C-N bond formation via oxidative coupling

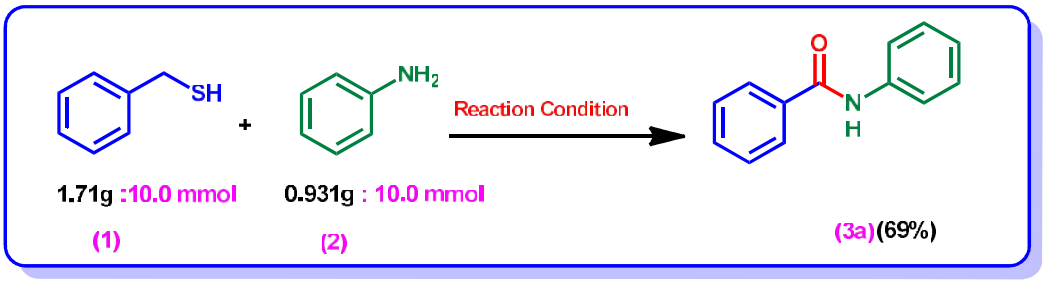
On the basis of the above outcomes and forgoing literature reports[25], a possible mechanism was proposed (**Scheme 4.3**). At the outset, *tert*-butoxyl and *tert*-butylperoxy radicals are generated by the reaction of TBHP with iodide anions. Now the benzyl mercaptan is converted to thiobenzoic(**1A**) acid with the help of TBHP. Then, thiobenzoic acid **1A** reacts with *tert*-butyl peroxy radicals to provide the free radical **1-B**, and **1-B** further undergoes a self-homocoupling process to provide disulphide**1-C**. Finally, disulfide **1-C** reacts with amine **2** to form the final product **3** and **1-D**, and thus **1-D** reacts spontaneously with an amine to give the final product.





Scheme 4.3: Plausible mechanism of amide bond formation

4.5 Gram-scale synthesis of benzamide with benzyl mercaptan & aniline



Scheme 4.4 Gram-scale synthesis of Benzamide (**3a**)

Moreover, the usefulness of the current plan was authenticated by undertaking the model reaction on a gram scale (**Scheme 4.4**). Benzylmercaptan **1**(10.0mmol) with

aniline **2** (10mmol) were stirred at 100°C for 24 h using 30 mol% NaI catalyst & 3.00 mol% TBHP in 100mL MeCN solvent. After completing the reaction (monitored by TLC), water was added to quench the reaction. The reaction mixture was extracted with ethyl acetate (10 mL x 3) followed by drying over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to provide the crude product which was purified by column chromatography on silica gel (100-200 mesh) to give the desired pure products **3** in good to excellent yields (69%).

4.6 Conclusions

In summary, a facile, novel method has been developed for the NaI catalyzed direct amidation of benzyl mercaptan through oxidative coupling with the amine using TBHP as an oxidant. All the reactions were accomplished without transition metal. The current procedure performed adequately for various substrates, together with electron releasing and an electron-withdrawing group containing benzyl mercaptan and various amines.

4.7 Experimental Section

4.7.1 General experimental procedure for the synthesis of compound 3

Benzyl mercaptan (1.0 mmol), *tert*-butyl hydroperoxide (TBHP) (70% aqueous solution,3.0 mmol),NaI (30 mol%) and MeCN(15mL)were added to a 50 ml round bottom (RB) flask. The reaction mixture was agitated at 100 °C with amine (1.0 mmol) for 24 hr. After completing the reaction (monitored by TLC), water was added to quench the reaction. The reaction mixture was extracted with ethyl acetate (10mL x3) followed by drying over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to provide the crude product, which was purified by column chromatography

on silica gel (100-200 mesh) to give the desired pure products **3** in good to excellent yields.

4.7.2 Characterization data of synthesized compounds and 3(a-t)

N-Phenylbenzamide (3a)

White solid, m.p.162-163 °C; 90% yield **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.94 – 7.83 (m, 3H), 7.71 – 7.64 (m, 2H), 7.61 – 7.56 (m, 1H), 7.54 – 7.49 (m, 2H), 7.44 – 7.36 (m, 2H), 7.22 – 7.15 (m, 1H).**^{13}C NMR (126 MHz, CDCl3)** δ 165.7, 137.9, 135.0, 131.9, 129.1, 128.8, 127.0, 124.6, 120.2.

N-(4-Nitrophenyl)benzamide(3b)

Light yellow solid, m.p.196-198 °C; 84% yield;**^{1}H NMR (500 MHz, $CDCl_3$)** δ: 8.28-8.25 (xm, 2H), 8.08 (s, 1H),7.93-7.89 (m, 2H), 7.87-7.84 (m, 2H), 7.62-7.57 (m, 1H), 7.54 (4.8 Hz, 2H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ: 171.5, 150.2, 147.6, 139.5, 136.3, 133.1, 132.6, 129.3, 124.4 ppm;

4-Chloro-N-phenylbenzamide(3c)

White solid, m.p.154-156 °C; 89% yield;**^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.90 – 7.84 (m, 2H), 7.77 (brs, 1H), 7.68 – 7.63 (m, 2H), 7.43 – 7.36 (m,2H), 7.21 – 7.13 (m, 1H), 7.04 – 6.97 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.2, 162.5, 138.1, 129.1, 128.9, 127.1, 124.4, 120.1, 114.0.

***N*-Benzylbenzamide (3d)**

Yellow solid, m.p.120-122 °C; 87% yield; **^{1}H NMR (500 MHz, CDCl3)** δ 7.84 – 7.80 (m, 2H), 7.55 – 7.49 (m, 1H), 7.47 – 7.41 (m, 2H), 7.39 –7.36 (m, 4H), 7.35 – 7.30 (m, 1H), 6.59 (brs, 1H), 4.66 (d, J = 7.1, 2H). **^{13}C NMR (126 MHz, CDCl3)** δ 167.5, 138.2, 134.4, 131.6, 128.8, 128.6, 128.0, 127.7, 127.0, 44.2.

N-Methyl-N-phenylbenzamide(3e)

White solid, m.p. 125 -126 ^{o}C; 89% yield; **^{1}H NMR (500 MHz, CDCl3)** δ 7.34 – 7.29 (m, 2H), 7.27 – 7.21 (m, 3H), 7.21 – 7.15 (m, 3H), 7.08 –7.03 (m, 2H), 3.53 (s, 3H).**^{13}C NMR (126 MHz, CDCl3)** δ 170.9, 144.8, 135.8, 129.7, 129.2, 128.7, 127.8, 126.9, 126.6, 38.5.

N-(3,5-Dimethylphenyl)benzamide (3f)

White solid, m.p. 141 -143 ^{o}C; 86% yield;**^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.98 (brs, 1H), 7.91 – 7.83 (m, 2H), 7.59 – 7.52 (m, 1H), 7.52 – 7.43 (m,2H), 7.31 (s, 2H), 6.81 (s, 1H), 2.32 (s, 6H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.8, 138.8, 137.8, 135.1, 131.7, 128.7, 127.1, 126.3, 118.1, 21.4.

N-(Pyridin-2-yl)benzamide(3g)

White solid, m.p. 83 -84 ^{o}C; 86% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.38 (brs, 1H), 8.43 (d, J = 10.5, 1H), 8.10 (ddd, J = 6.25, 2.3, 1.12, 1H),7.97 – 7.90 (m, 2H), 7.76 (ddd, J = 10.5, 9.25, 2.3, 1H), 7.60 – 7.53 (m, 1H), 7.51 – 7.44 (m, 2H), 7.03(ddd, J = 9.25, 6.25, 1.3, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.1, 151.8, 147.8, 138.5, 134.4, 132.2, 128.8, 127.4, 119.9, 114.4.

4-Methoxy-N-phenylbenzamide(3h)

White sold, m.p. 156 -158 ^{o}C; 89% yield;**^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.90 – 7.84 (m, 2H), 7.77 (brs, 1H), 7.68 – 7.63 (m, 2H), 7.43 – 7.36 (m, 2H), 7.21 – 7.13 (m, 1H), 7.04 – 6.97 (m, 2H), 3.90 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.2, 162.5, 138.1, 129.1, 128.9, 127.1, 124.4, 120.1, 114.0, 55.5.

N-(*p*-Tolyl)benzamide (3i)

White solid, m.p.157-158 ^{o}C; 87% Yield: **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.95 (s, 1H), 7.86 – 7.79 (m, 2H), 7.50 (dd, J = 8.6, 3.5 Hz, 3H), 7.43 (t, J = 7.7Hz, 2H), 7.14 (d, J = 6.8 Hz, 2H), 2.32 (s, 3H**); ^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.7, 135.5, 135.1, 134.2,131.7, 129.5, 128.7, 127.1, 120.4, 20.9.

N-(4-Methoxyphenyl)benzamide(3j)

White solid, m.p.155-156 ^{o}C; 88% Yield: **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 6.1 Hz, 2H), 7.80 (s, 1H), 7.53 (t, *J* = 6.0 Hz, 3H), 7.46 (t, *J*= 6.3 Hz, 2H), 6.90 (d, *J* = 7.4 Hz, 2H), 3.81 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.6, 156.7, 135.1,131.7, 131.1, 128.7, 127.0, 122.2, 114.3, 55.5.

***N*-(4-(Dimethylamino)phenyl)benzamide (3k)**

White solid, m.p.161-163 ^{o}C; 84% Yield: **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 7.4 Hz,2H), 7.75 (s, 1H), 7.55-7.46 (m, 5H), 6.75 (d, *J* = 9.0 Hz, 2H), 2.95 (s, 6H); **^{13}C NMR (126MHz, $CDCl_3$)** δ 165.5, 148.2, 135.3, 131.5, 128.7, 127.7, 127.0, 122.1, 113.0, 40.9.

N-(Naphthalen-1-yl)benzamide (3l)

Yellowish solid, m.p.159-160 ^{o}C; 89% Yield: **^{1}H NMR (500 MHz, DMSO)** δ 10.44 (s, 1H), 8.11 (d, J = 7.5 Hz, 2H), 8.04 – 7.94 (m, 2H), 7.87 (d, J =8.1 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.60 – 7.47 (m, 5H); **^{13}C NMR (126 MHz, DMSO)** δ 166.7, 135.0,134.4, 134.3, 132.1, 129.7, 128.9, 128.5, 128.3, 126.8, 126.5, 126.4, 126.0, 124.4, 123.8.

1-(2-Naphthalenecarbonyl)piperidine (3m)

Pale Yellow solid, m.p.172-173 ^{o}C; 85% Yield: **^{1}H NMR (500 MHz, $CDCl_3$):** 7.91− 7.86 (m, 4H), 7.56 − 7.48 (m, 3H), 3.71 (br s, 4H), 1.70 − 1.53 (br s,6H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 170.5, 133.9, 133.6, 132.8, 128.4, 128.2, 127.8, 126.9, 126.6, 126.5, 124.3, 49.0, 46.3, 26.5, 26.2, 24.6.

N-Benzhydrylbenzamide (3n)

Yellow solid, m.p.193-195 ^{o}C; 88% Yield: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (d, J = 7.1 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H),7.40 (t, J = 7.5 Hz, 2H), 7.35-7.23 (m, 10H), 6.78 (d, J = 7.5 Hz, 1H), 6.44 (d, J = 7.9 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.5, 141.5, 134.3, 131.7, 128.8, 128.7, 127.6, 127.6, 127.1,57.5.

N-Cyclohexylbenzamide (3o)

Yellow solid, m.p.145-146 ^{o}C; 89% Yield: **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.80 – 7.73 (m, 2H), 7.51 – 7.47 (m, 1H), 7.45 – 7.39 (m, 2H), 6.10 (d, J= 5.5 Hz, 1H), 4.02 – 3.95 (m, 1H), 2.04 (dd, J = 12.8, 3.9 Hz, 2H), 1.79 – 1.73 (m, 2H), 1.69 – 1.63 (m, 1H), 1.47 – 1.38 (m, 2H), 1.23 (tdd, J = 12.2, 9.7, 3.4 Hz, 3H**); ^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.6, 135.1, 131.2, 128.5, 126.9, 48.7, 33.2, 25.6, 25.0.

1-(4-Pyridinecarbonyl)piperidine (3p)

Yellow solid, m.p.145-146 ^{o}C; 89% Yield: **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 8.70 (s, 4H), 3.75 (m, 2H), 3.32 (t, J=5.0 Hz, 2H), 1.71 (br s, 2H), 1.56 (brs, 6H); **^{13}C NMR ($CDCl_3$, 126 MHz):** δ 167.6, 150.2, 144.1, 121.1, 48.5, 43.0, 26.5, 25.5, 24.4ppm

1-(4-Fluorobenzoyl)piperidine (3q)

Yellow solid, m.p.60-61 ^{o}C; 90% Yield: **^{1}H NMR ($CDCl_3$,500 MHz):** δ 7.43 - 7.39 (m, 2H), 7.12 - 7.06 (m, 2H), 3.66 (s, 2H), 3.36 (br s, 2H), 1.61 (br s,6H); **^{13}C NMR ($CDCl_3$, 126 MHz)**: δ 169.4, 164.85, 161.6, 132.5, 129.1, 115.6, 115.3, 48.9, 43.3,26.4, 25.8, 24.6.

N,N-Diethylbenzamide (3r)

White solid, m.p.39-40 ^{o}C; 90% Yield: **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.41 – 7.33 (m, 5H), 3.55 (q, J = 7.2, 2H), 3.24 (q, J = 7.2, 2H), 1.25 (t, J = 6.5, 3H), 1.10 (t, J = 6.5, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.4, 137.2, 129.1, 128.4, 126.2, 43.3, 39.3, 14.2, 12.9.

N-(3-Nitrophenyl)benzamide (3s)

White solid, m.p.39-40 ^{o}C; 90% Yield: **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.53 (t, J = 2.2, 1H), 8.13 (ddd, J = 8.2, 2.2, 1.0, 1H), 8.09 – 8.02 (m, 2H), 7.96 – 7.89 (m, 2H), 7.66 – 7.59 (m, 1H), 7.59 – 7.53 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.9, 148.7, 139.0, 134.0, 132.5, 130.0, 129.0, 127.1, 125.8, 119.2, 114.9.

1-(4-Pyridinecarbonyl)piperidine(3t)

White solid, m.p.139-140 ^{o}C; 84% Yield:**^{1}H NMR($CDCl_3$, 500 MHz**): δ 8.70 (s, 4H), 3.75 (m, 2H), 3.32 (t, J=8.33 Hz, 2H), 1.71 (br s, 2H), 1.56 (brs, 6H); **^{13}C NMR ($CDCl_3$, 126 MHz):** δ 167.6, 150.2, 144.1, 121.1, 48.5, 43.0, 26.5, 25.5, 24.4;

4.7.3 Spectral Data of Product N-Phenylbenzamide (3a)

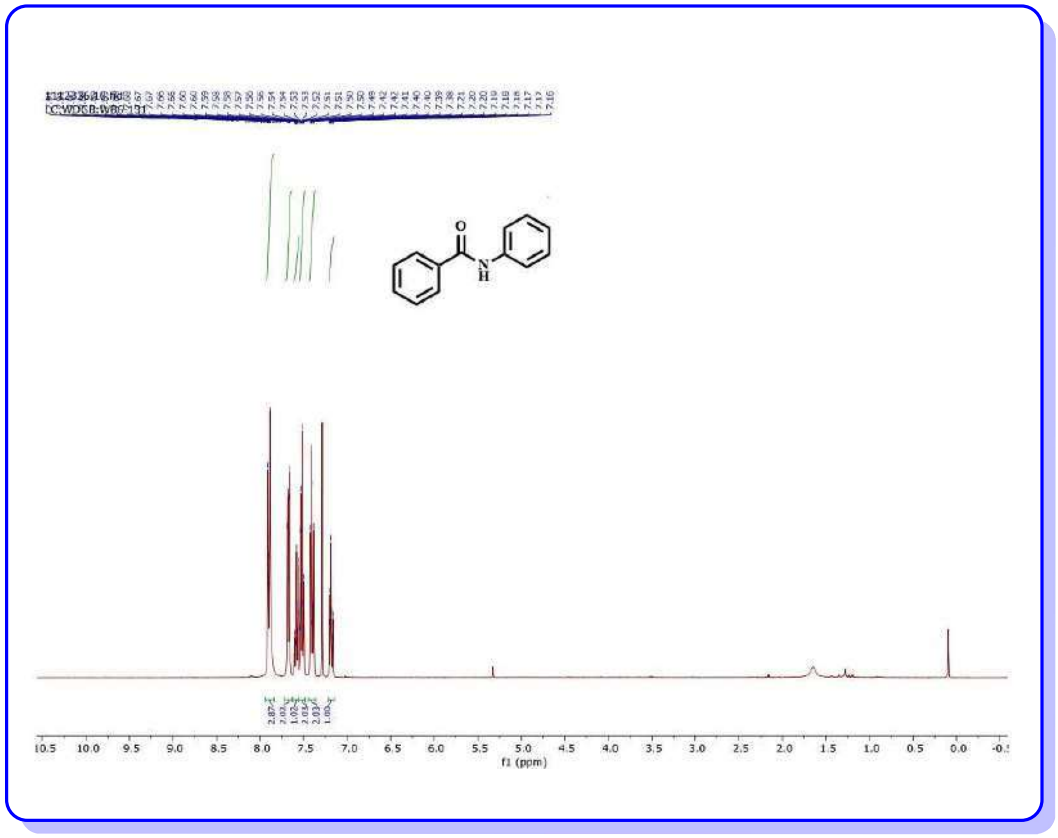


Figure 4.1 ^{1}H NMR of N-Phenylbenzamide(3a)

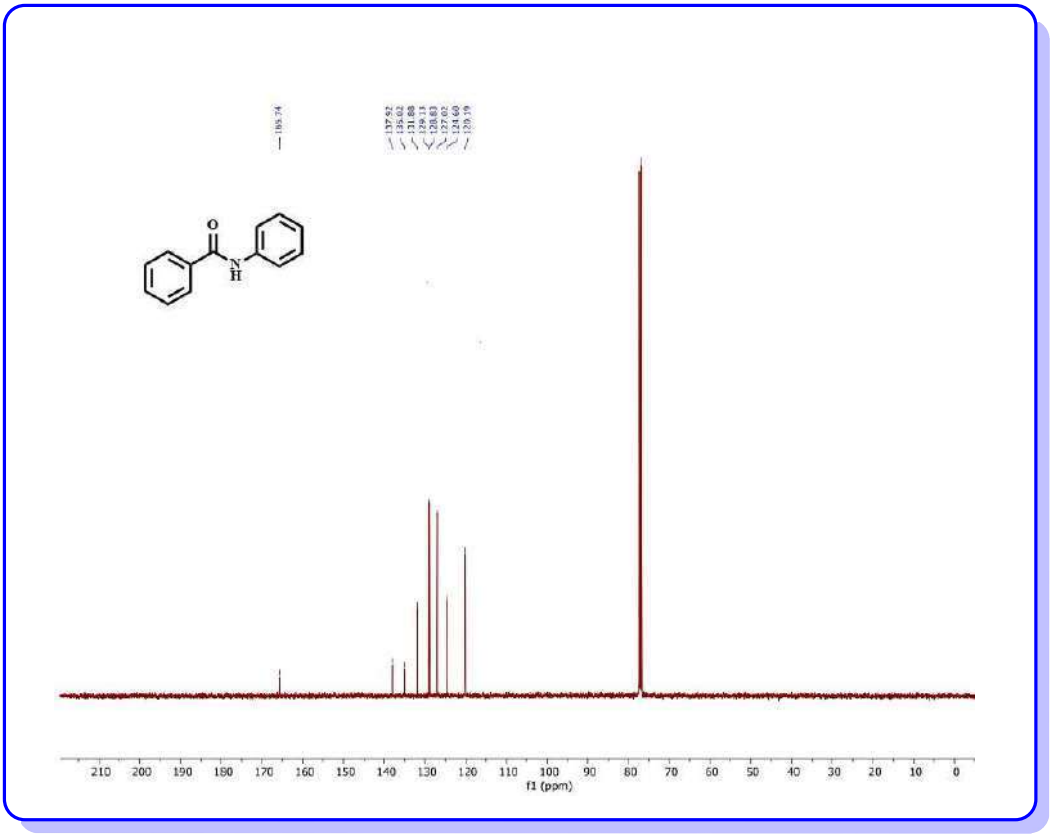


Figure 4.2 ^{13}C NMR of N-Phenylbenzamide

4.7.4 Spectral Data of Product 1-(2-Naphthalenecarbonyl)piperidine(3m)

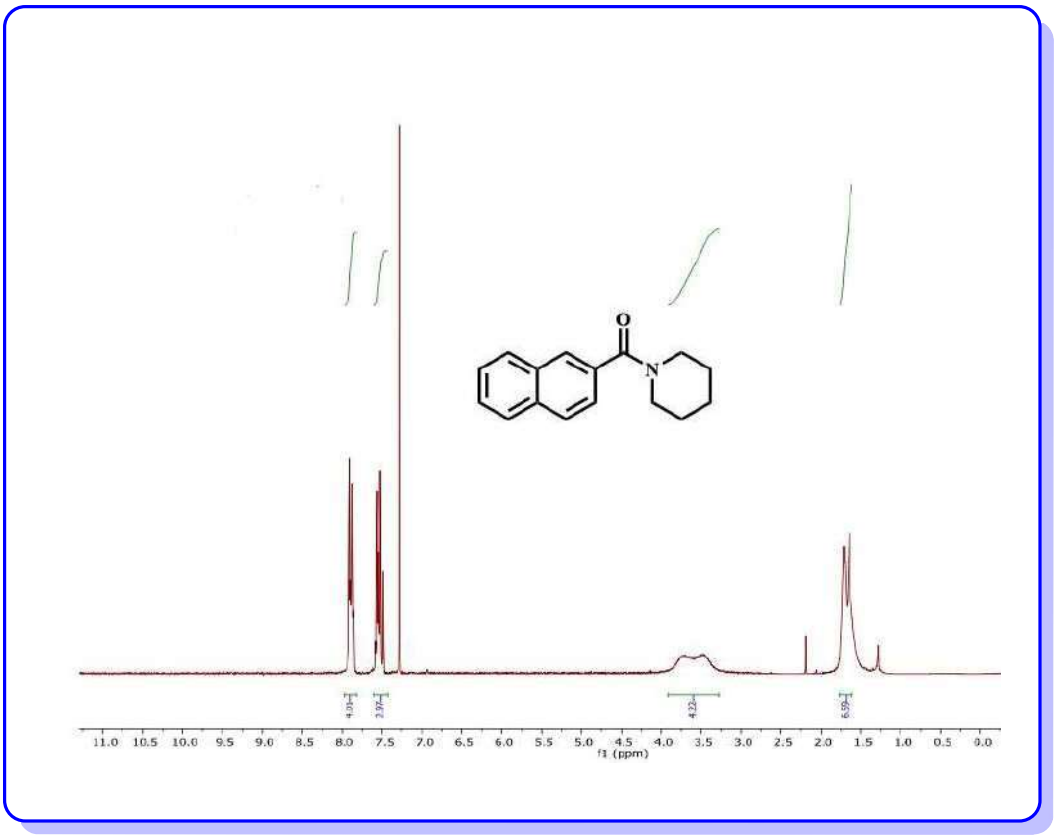


Figure 4.3 ^{1}H NMR of 1-(2-Naphthalenecarbonyl)piperidine(3m)

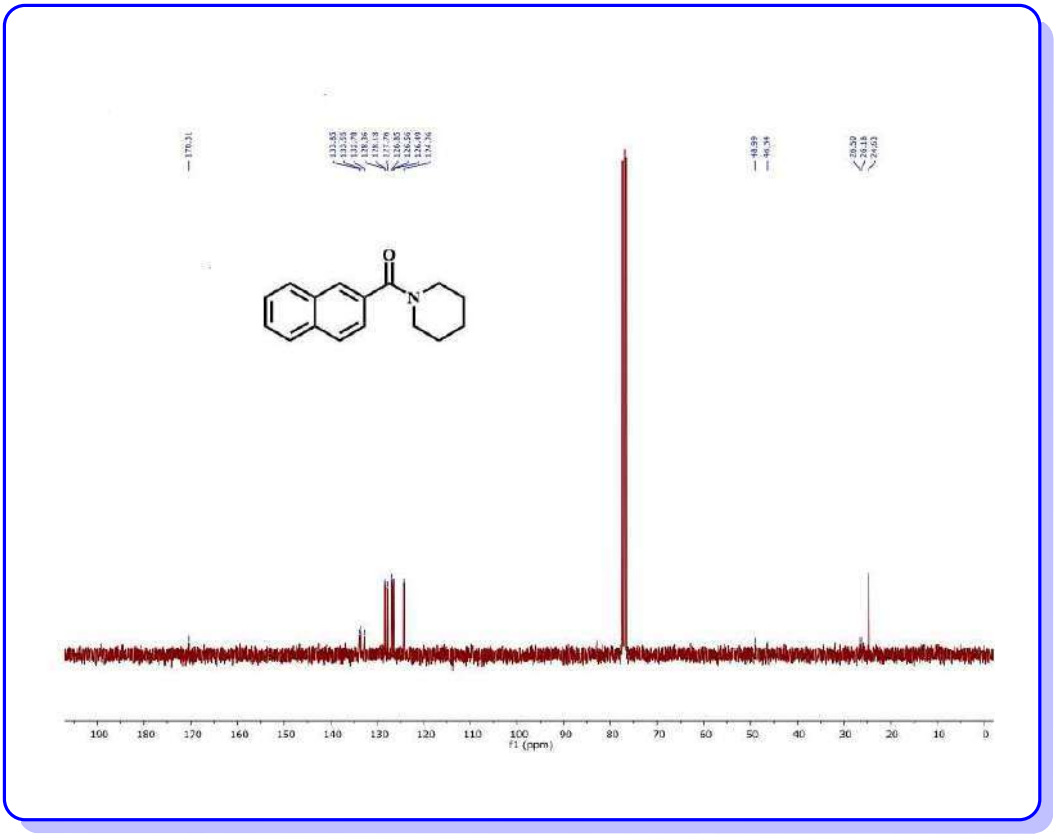


Figure 4.4 ^{1}H NMR of 1-(2-Naphthalenecarbonyl)piperidine(3m)

4.7.5 Spectral Data of Product piperidin-1-yl(pyridin-4-yl)methanone(3t)

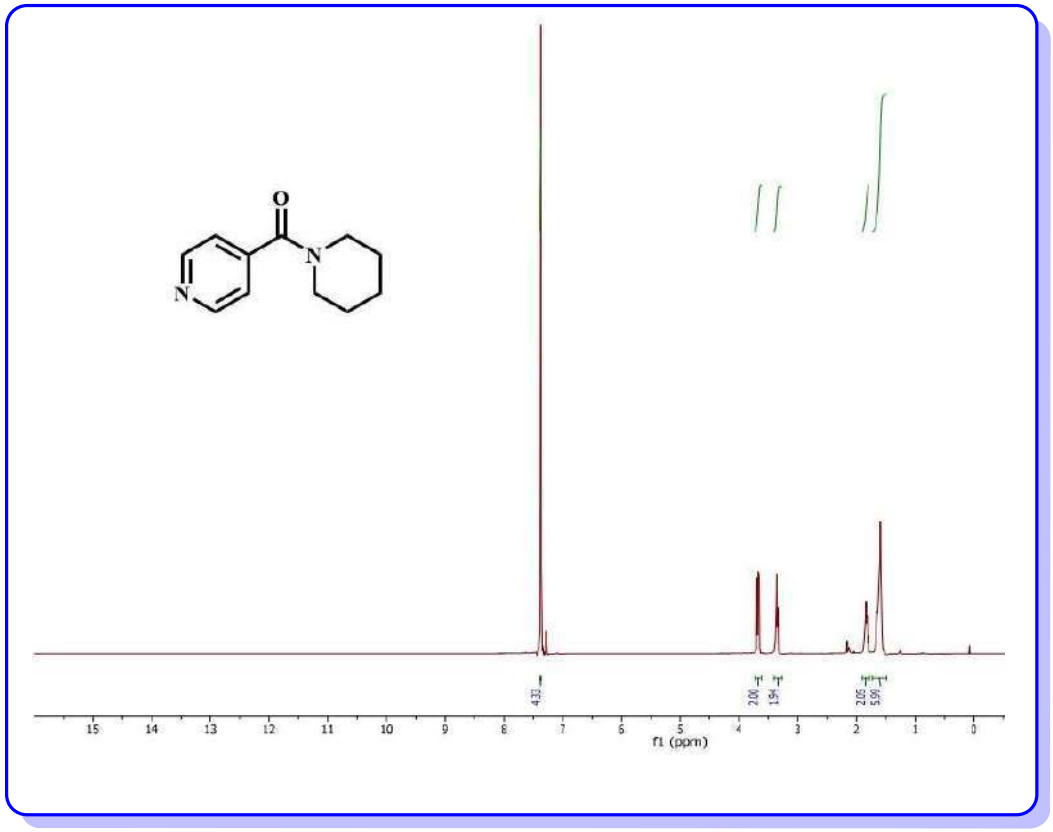


Figure 4.5 ^{1}H NMR of piperidin-1-yl(pyridin-4-yl)methanone(3t)

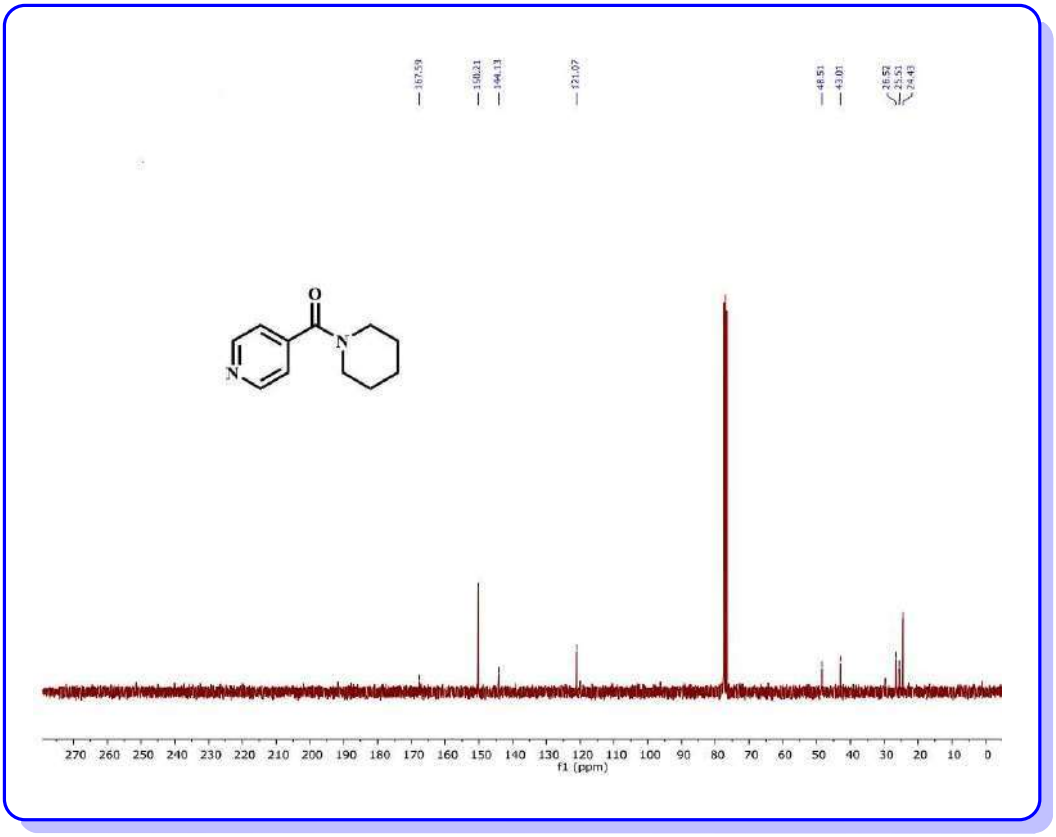


Figure 4.6 ^{13}C NMR of piperidin-1-yl(pyridin-4-yl)methanone(3t)

4.8 References

[1] A. Greenberg, C. M. Breneman, and J. F. Liebman, (eds). "The amide linkage: Structural significance in chemistry, biochemistry, and materials science". John Wiley & Sons, 2000.

[2] E. Valeur, M. Bradley, "Amide bond formation: beyond the myth of coupling reagents" Chemical Society Reviews, **38**(2009) 606-31.

[3] T. Wieland and M. Bodanszky, "The World of Peptides: A Brief History of Peptide Chemistry . T. Wieland, M. Bodanszky," *Isis*, **84** (1993) 174–175.

[4] J. I. Kroschwitz, M.Howe-Grant, R. E. Kirk, & D. F. Othmer. Encyclopedia of chemical technology. John Wiley & Sons. 1996

[5] S.Y Huang, D. W. Lipp, and R. S. Farinato. "Acrylamide polymers." Kirk-Othmer Encyclopedia of Chemical Technology 2000.

[6] X. Liu, C. C Hsiao, L. Guo, & M. Rueping. "Cross-Coupling of Amides with Alkylboranes via Nickel-Catalyzed C–N Bond Cleavage". *Organic letters*, **20** (2018), 2976-2979.

[7] D. Y. Wang *et al.*, "Stille coupling via C–N bond cleavage," *Nat. Commun. 2016 71*, **7** (2016) 1–9.

[8] G. Meng, and M. Szostak, "Palladium/NHC (NHC= N-heterocyclic carbene)-catalyzed B-alkyl suzuki cross-coupling of amides by selective N–C bond cleavage". *Organic letters*, **20**(2018.) 6789-6793.

[9] C. L. Allen, A. R. Chhatwal, and J. M. J. Williams, "Direct amide formation

from unactivated carboxylic acids and aminesw ChemComm," *This J. is Cite this Chem. Commun*, **48** (2012) 666–668.

[10] K. Ishihara, and T.Yano. "Synthesis of Carboxamides by LDA-Catalyzed Haller– Bauer and Cannizzaro Reactions". *Organic Letter*s, **6** (2004) 1983-1986.

[11] S. Chandra Ghosh, J. S. Y Ngiam, A. M. Seayad, D. Thanh Tuan, C. L. L Chai, and A. Chen, "Copper-Catalyzed Oxidative Amidation of Aldehydes with Amine Salts: Synthesis of Primary, Secondary, and Tertiary Amides," *The Journal of organic chemistry*, **77** (2012) 8007-8015.

[12] H. Morimoto, R. Fujiwara, Y. Shimizu, K. Morisaki, and T. Ohshima, "Lanthanum(III) Triflate Catalyzed Direct Amidation of Esters," *Organic letters,* **16** (2014) 2018-2021.

[13] S. Shi, S. P. Nolan and M. Szostak, Acc. Chem. Res., *Accounts of Chemical Research,* **51**, (2018): 2589-2599.

[14] K. Yamaguchi, M. Matsushita, and N. Mizuno, "Efficient Hydration of Nitriles to Amides in Water, Catalyzed by Ruthenium Hydroxide Supported on Alumina" Angewandte Chemie International Edition, 43 (2004) 1576-1580.

[15] A. Goto, K. Endo, S. Saito, A. Goto, K. Endo, and S. Saito, "Nitrile Hydration Rh I-Catalyzed Hydration of Organonitriles under Ambient Conditions," Angew. Chem. Int. Ed, vol. 47, (2008) pp. 3607–3609.

[16] R. S. Ramón, N. Marion, and S. P. Nolan, "Gold Activation of Nitriles: Catalytic Hydration to Amides." Chemistry–A European Journal 15, 35 (2009) 8695-8697.

[17] A. Joshi, R. Kumar, R. Semwal, D. Rawat, and S. Adimurthy, "Ionic liquid catalysed aerobic oxidative amidation and thioamidation of benzylic amines under neat conditions," *Green Chemistry 21*, 5 (2019): 962-967..

[18] S. H. Cho, E. J. Yoo, I. Bae, and S. Chang, "Copper-Catalyzed Hydrative Amide Synthesis with Terminal Alkyne, Sulfonyl Azide, and Water," *Journal of the American Chemical Society* 127, **46** (2005) 16046-16047.

[19] Z. W. Chen, H. F. Jiang, X. Y. Pan, and Z. J. He, "Practical synthesis of amides from alkynyl bromides, amines, and water," *Tetrahedron*, **67** (2011) 5920–5927.

[20] J. W. Kim, K. Yamaguchi, and N. Mizuno, "Heterogeneously Catalyzed Efficient Oxygenation of Primary Amines to Amides by a Supported Ruthenium Hydroxide Catalyst" *Angewandte Chemie International Edition* 47, **48** (2008) 9249-9251.

[21] X.-F. Wu, C. Beromeo Bheeter, H. Neumann, P. H. Dixneuf, and M. Beller, "12237 Cite this," *Chem. Commun*, **48**, (2012) 12237–12239.

[22] A. Poeschl and D. M. Mountford, "A facile manganese dioxide mediated oxidation of primary benzylamines to benzamides," *Organic & Biomolecular Chemistry* 12, **36** (2014) 7150-7158.

[23] S. N. Rao, N. Naresh, K. Reddy, S. Samanta, and S. Adimurthy, "I2-Catalyzed Oxidative Amidation of Benzylamines and Benzyl Cyanides under Mild Conditions," *The Journal of Organic Chemistry 82*, 24 (2017) 13632-13642

[24] X .Chen, Y. Peng, Y. Li, M. Wu. H. Guo, J. Wang, and S. Sun. "Cu-catalyzed aerobic oxidative C–CN bond cleavage of benzyl cyanide for the synthesis of primary amides". *RSC advances*, *7* (2017) 18588-18591.