

TBHP initiated C-N Bond Formation via Oxidative Coupling of Benzyl Bromides with Amine using TBAI as a Catalyst

3.1 Introduction

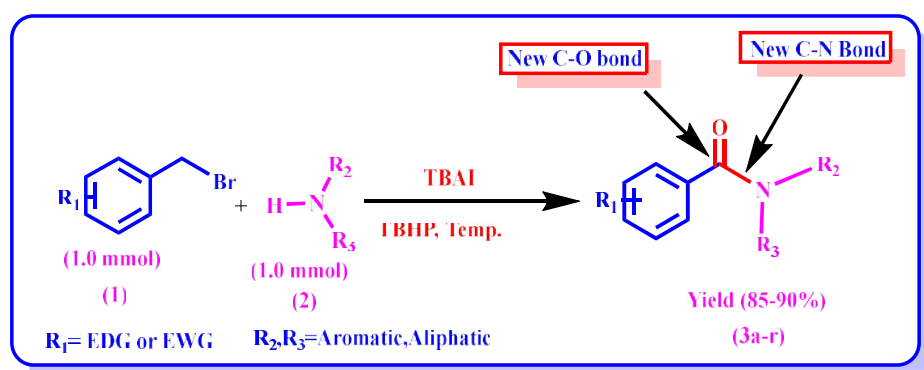
In heterocyclic, as well as in biologically active molecules, the most important structural component is the C-N bond [1][2][3][4][5]. Furthermore, such bonds extensively occur in natural products, pharmaceuticals, and functional constituents [6][7][8][9]. Presently, substantial development has been done, and various conventional methods have emerged in this field[10][11][12]. But these methods are associated with many drawbacks, such as harsh reaction conditions and the use of expensive and transition metal catalysts, etc. Even after considerable development in this field, the formation of the C-N bond is a challenging task for organic chemists. Thus, there is a need to develop an efficient, mild, inexpensive, and environmentally friendly, green approach to form a C-N bond[13] [14].

The most important C-N bond containing structural motif is an amide, which is the smallest unit of peptide and protein and also the main component of various drugs and polymeric ingredients [15][16]. The most conventional method for the synthesis of the amide is the coupling of an activated carboxylic acid with amine, acid, or base prompted rearrangement reaction [17][18][19][20][21][22][23][24][25]. Recently, various transition-metal-catalyzed [17] and transition metal-free reactions [26] have been developed to synthesize amide. Among them, amino carbonylation of aryl halide is one of the most important methods for the synthesis of an amide using

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palladium or palladium-based catalyst and use of carbon monoxide. Though, the use of expensive catalysts and toxic carbon monoxide are the drawbacks of these syntheses [17] [26][27]. Therefore, the direct amidation of benzylbromide without transition metal and toxic chemical waste under mild reaction conditions remains an exciting task for the organic chemist. The oxidation of benzyl halide and benzyl alcohol to carbonyl compound and then coupling with amine would be the most acceptable approach for the amidation of benzyl halide [17] [28][29]. This will become a new and more straightforward approach than all reported methods. However, to the best of our knowledge, the TBAI catalyzed oxidative coupling of benzyl halide with an amine in the presence of TBHP has not been reported earlier.

Because of the above and as a part of our studies[17][30][31], we have developed a new, metal-free, and TBAI catalyzed oxidative coupling of benzyl halide with various amines in the presence of TBHP. (**Scheme 3.1**).

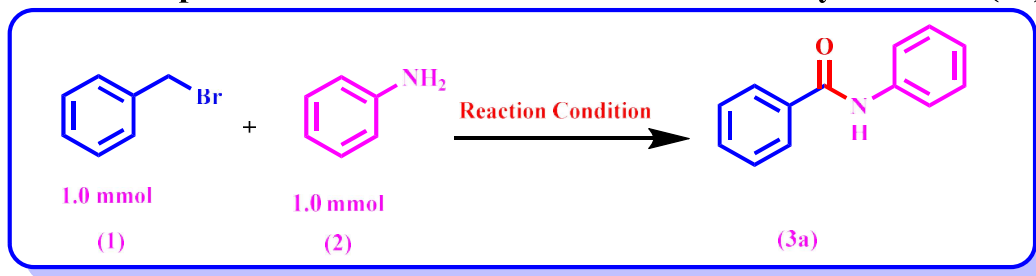


Scheme 3.1 Synthesis of an amide from benzyl bromide and amine

3.2 Results and Discussion

In order to increase the efficiency of the product, the optimization was carried out by taking the model reaction of benzylbromide (mmol) (**1**) and aniline (mmol) (**2**) in the presence of TBAI and TBHP. When the reaction was carried out at 80 °C with 5 mol% of catalyst and 1 equivalent of TBHP, only the trace amount of the product was isolated (**Table 3.1, entry 1**). 20% Yield was obtained as the temperature was increased to 100° C (**Table 3.1, entry 2**). First of all, the amount of catalyst was screened. The % yield was increased with the increasing amount of catalyst 10, 15 mol% (**Table 3.1, entries 3,4**). Even on increasing the amount of catalyst from 15 to 20 mol %, there was no increase in the yield of the product (**Table 3.1, entry 5**). Thus the amount of catalyst was fixed as 15 mol% for further studies. Increasing the amount of oxidant also significantly impacted the yields of product **2a** (**Table 3.1, entries 6-7**). Surprisingly, the higher yield was obtained with 3 equivalents of TBHP(aq). The use of TBHP (decane) as a substitute for TBHP (aq) significantly reduced the reaction yield (entry 9). Other oxidants were also screened, but no one could provide the expected yield of the product (**Table 3.1, entries 10-12**). Subsequently, the effect of various solvents was screened, and the reaction was suppressed in both polar and non-polar solvents (**Table 3.1, entries 13-20**). Various catalysts I₂, TBAB, NaI, AIBN, and KI were also screened, but none of them would match the catalytic efficacy of TBAI (**Table 3.1, entries 21–25**).

Table 3.1 Optimization of reaction conditions for the synthesis of (3a)



S.N.	Catalyst (Mol %)	Amount (Mol%)	Oxidant	Oxidant (Mol%)	Solvent	Temp (°C)	Time (hr)	Yield ^b (%)
1	TBAI	5	TBHP(aq.)	1	-	80	2	Traces
2	TBAI	5	TBHP(aq.)	1	-	100	2	20
3	TBAI	10	TBHP(aq.)	1	-	100	2	28
4	TBAI	15	TBHP(aq.)	1	-	100	2	35
5	TBAI	20	TBHP(aq.)	1	-	100	2	35
6	TBAI	15	TBHP(aq.)	2	-	100	2	66
7	TBAI	15	TBHP(aq.)	3	-	100	2	90
8	TBAI	15	TBHP(aq.)	4	-	100	2	88
9	TBAI	15	TBHP(decane)	3	-	100	2	50
10	TBAI	15	MnO ₂	3	-	100	2	52
11	TBAI	15	DDQ	3	-	100	2	48
12	TBAI	15	K ₂ S ₂ O ₈	3	-	100	2	35
13	TBAI	15	TBHP(aq.)	3	DMSO	100	2	45
14	TBAI	15	TBHP(aq.)	3	THF	100	2	48
15	TBAI	15	TBHP(aq.)	3	CH ₃ CN	100	2	51
16	TBAI	15	TBHP(aq.)	3	Benzene	100	2	35
17	TBAI	15	TBHP(aq.)	3	n-Hexane	100	2	30
18	TBAI	15	TBHP(aq.)	3	H ₂ O	100	2	66
19	TBAI	15	TBHP(aq.)	3	EtOH	100	2	58
20	TBAI	15	TBHP(aq.)	3	MeOH	100	2	65
21	I ₂	15	TBHP(aq.)	3	-	100	2	30
22	TBAB	15	TBHP(aq.)	3	-	100	2	n.d.
23	NaI	15	TBHP(aq.)	3	-	100	2	14
24	AIBN	15	TBHP(aq.)	3	-	100	2	18

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25	KI	15	TBHP(aq.)	3	-	100	2	10
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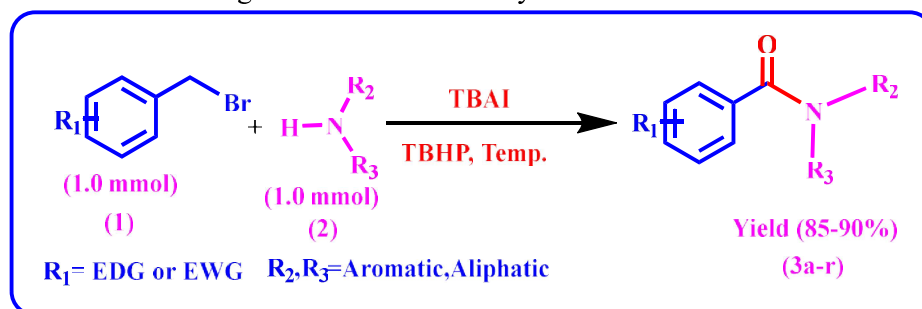
The bold row represents optimized conditions.

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

^(b) The yields refer to the isolated pure products after 2 h of the reaction times

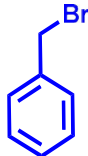
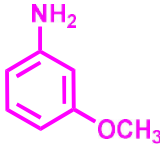
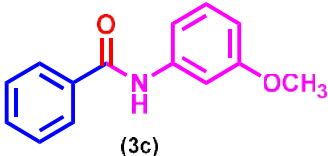
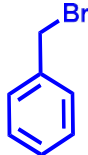

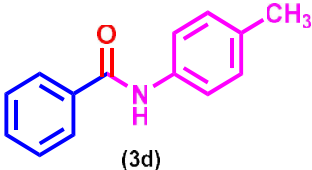
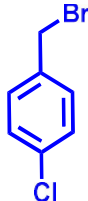
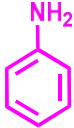
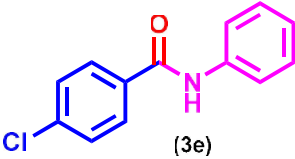
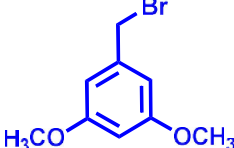

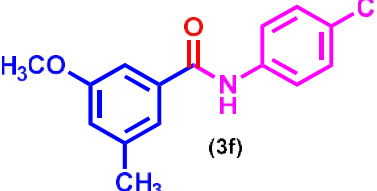

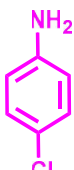
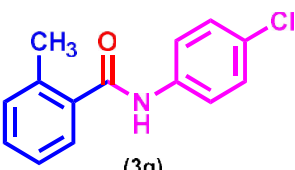
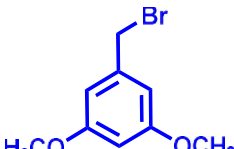

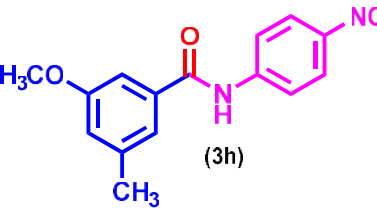
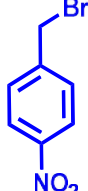
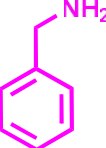
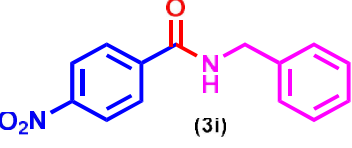
To further expand the opportunity of the substrates, benzyl bromide (**1**) and different amine (**2**) having different substitution patterns were screened (**Table 3.2**). All the substrates fruitfully transformed to the corresponding amides in good to excellent yields. It was found that the presence of an electron-withdrawing group at benzylamine increases % yield of the product slightly due to an increase in the polarity of the carbonyl group. While in the presence of electron-donating group, the % yield is decreased due to a decrease in polarity of the carbonyl group.

Table 3.2 Screening of substrates for the synthesis of amide

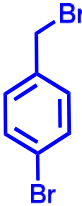
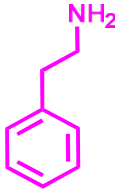
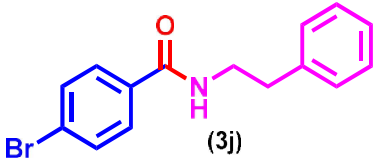
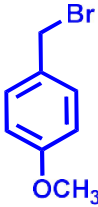
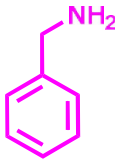
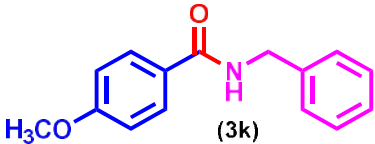
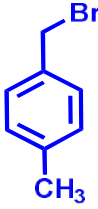
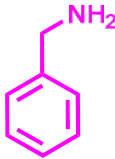
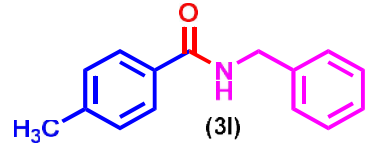
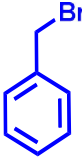
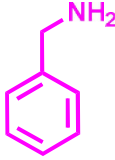
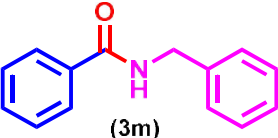
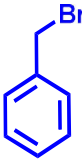

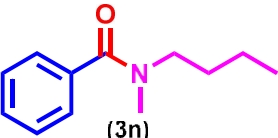
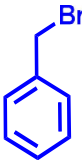
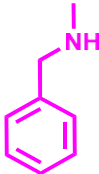
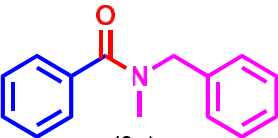
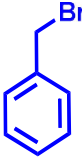
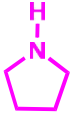



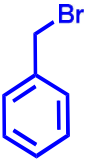
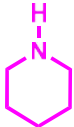
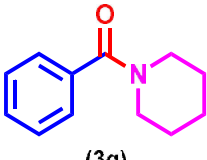
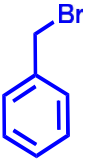
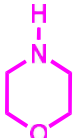
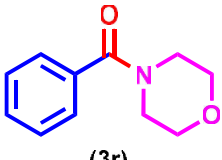
Entry	1	2	3 ^a	Yield ^b %
3a				90
3b				84

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3c			 (3c)	90
3d			 (3d)	87
3e			 (3e)	89
3f			 (3f)	81
3g			 (3g)	85
3h			 (3h)	90
3i			 (3i)	90

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3j			 (3j)	88
3k			 (3k)	81
3l			 (3l)	84
3m			 (3m)	85
3n			 (3n)	87
3o			 (3o)	88
3p			 (3p)	90

3q			 (3q)	89
3r			 (3r)	88

^la] Products were characterized by ¹H, ¹³C NMR and IR analysis.

^lb] Isolated yield.

3.3 Control Experiment

To understand the reaction mechanism, some control experiments were carried out using radical scavengers TEMPO and BHT (**Scheme 3.2**). The outcomes of the control experiment established the participation of radical intermediates during the reaction. The blank experiments using benzylbromide alone did not produce benzoyl bromide (as expected). Thus, we suspect the intermediacy of benzylic amines, which is obtained by the reaction of benzylbromide and amine in one hour (**Scheme 3.2**, reaction no 4), to confirm this already synthesized benzylic amine was subjected to the standard reaction conditions which delivered the yield of amide more than 90% (**Scheme 3.2**, reaction no 5). Further, to confirm the intermediacy of benzylic amine, the blank reaction of benzylbromide was carried out in the presence of 2,4 DNP, and no formation of an orange precipitate indicates the absence of carbonyl intermediate in this reaction (**Scheme 3.2**, reaction no 3b). In another control experiment, i.e., in reaction 3, the product amide was not formed. These outcomes underpinned our conjecture that intermediate benzylic amine is certainly the main intermediate during the course of the reaction. Actually, *in situ* formed benzylic amines should be the first

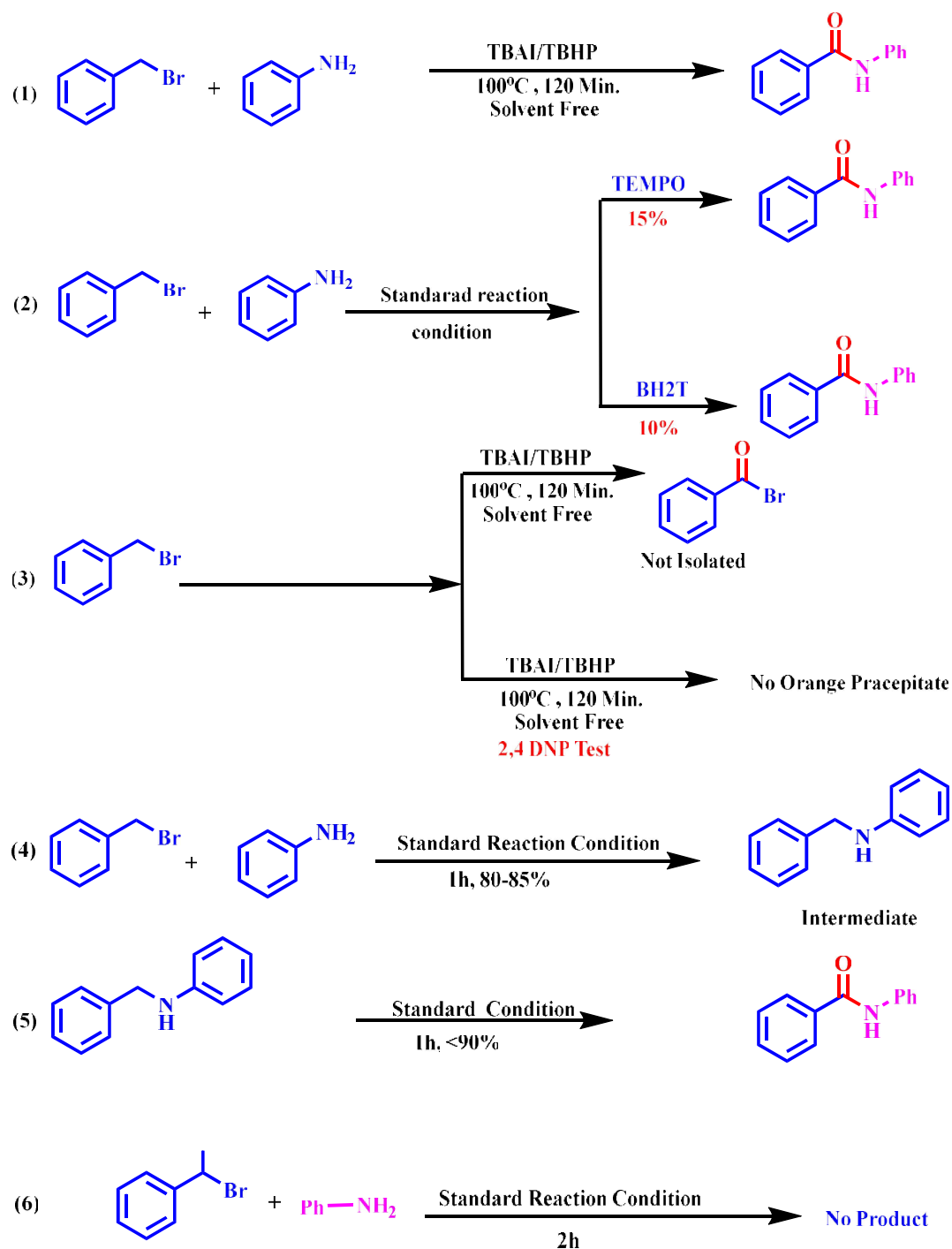
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intermediate, because the reaction of benzylic bromides and amines is exothermic, and the bond energy of the C-H bond of the formed benzylic amines is weaker than that of C-H bond of benzylic bromides toward t-BuO⁻K⁺.

3.4 Mechanism of amide formation

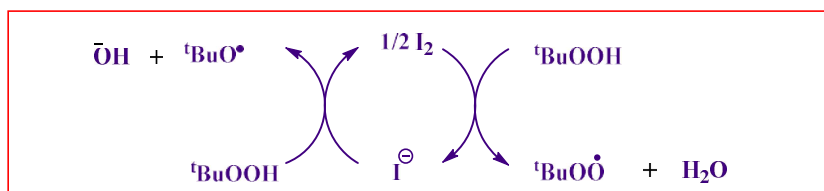
On the basis of isolation of the product, reported literature, and controlled experiments, the possible mechanism was proposed. (**Scheme 3.3**). First of all, the I⁻ anion provides an electron to TBHP to produce an I₂ molecule and a *tert*-butoxyl radical [32] [33][34][35] [36]. Now the generated molecule I₂ abstracts an electron from another molecule of TBHP and provides the original I⁻ anion species and a *tert*-butyl peroxy radical. First, benzylbromide reacts with the amine to form *in situ* benzylic amine, which oxidizes to amide with the help of *tert*-butyl peroxy radical[37][38].

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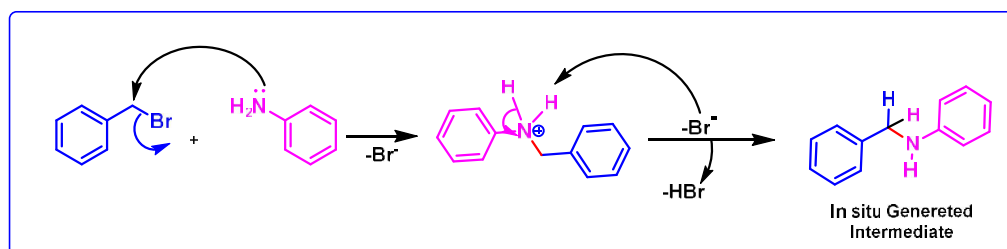


Scheme 3.2 Control experiments to establish the mechanism of the reaction

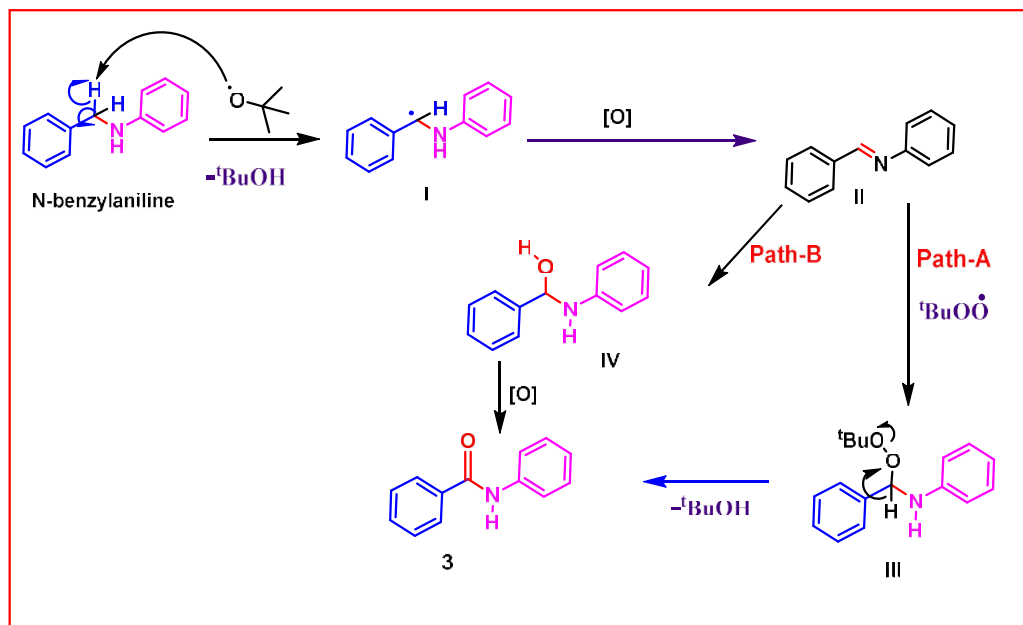
TBHP initiated C-N Bond Formation via Oxidative Coupling of Benzyl...



Preparation of N-benzylaniline Intermediate



Oxidation of C-H Bond of N-benzylaniline Intermediate



Scheme 3.3 Plausible reaction mechanism

3.5 Conclusions

In conclusion, a facile, new approach for the direct amidation of benzyl bromide through oxidative coupling with amine has been developed. All the reactions were carried out under transition metal-free conditions. The present technique works

well for an extensive range of substrates, including electron releasing as well as a withdrawing group containing benzyl bromide and many amines.

3.6 Experimental Section

3.6.1 General experimental procedure for the synthesis of the compound of 3

Benzyl bromide (1.0 mmol), *tert*-butyl hydroperoxide (TBHP) (70% aqueous solution, 3.0 mmol) and TBAI (15 mol%) were added to a 50 ml round bottom (RB) flask. The reaction mixture was stirred at 100 °C with amine (1.0 mmol) for 2 hr. Upon completion of the reaction (monitored by TLC), the reaction was quenched with water. Then the reaction mixture was extracted with ethyl acetate (10x3) followed by drying over anhydrous Na₂SO₄, and the solvent was evaporated under reduced pressure. The crude product obtained was purified by column chromatography on silica gel (100-200 mesh) to give the desired pure products **3** in good to excellent yields.

3.6.2 Characterization data of synthesized compounds 3(a-r):

N-Phenylbenzamide (3a)

White solid, m.p. 162-163 °C; 90% yield; ¹H NMR (500 MHz, CDCl₃) δ: 7.87-7.84 (m, 3 H), 7.63 (d, *J* = 7.9 Hz, 2 H), 7.55-7.43 (m, 3 H), 7.34 (t, *J* = 7.9 Hz, 2H), 7.14 (t, *J* = 7.2 Hz, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃); δ: 166.1, 138.2, 135.3, 131.8, 129.4, 128.7, 127.1, 124.5, 120.2 ppm.

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

Light yellow solid, m.p. 196-198 °C; 84% yield; ¹H NMR (500 MHz, CDCl₃) δ: 8.28-8.25 (m, 2H), 8.08 (s, 1H), 7.93-7.89 (m, 2H), 7.87-7.84 (m, 2H), 7.62-7.57

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(m, 1H), 7.54 (dd, $J = 10.4, 4.8$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, $\text{CDCl}_3 + \text{DMSO}$)
 δ : 171.5, 150.2, 147.6, 139.5, 136.3, 133.1, 132.6, 129.3, 124.4 ppm.

N-(3-Methoxyphenyl)benzamide (3c)

White solid, m.p.126-127 °C; 90% yield; ^1H NMR (500 MHz, CDCl_3) δ : 8.21 (s, br, 1H), 7.83 (dd, $J = 7.3, 1.7$ Hz, 2H), 7.32-7.44 (m, 4H), 7.12-7.23 (m, 2H), 6.61-6.65 (m, 1H), 3.84 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 165.4, 161.3, 139.4, 135.2, 132.8, 129.9, 127.6, 127.3, 113.8, 110.7, 107.4, 55.6 ppm.

N-*p*-Tolylbenzamide (3d)

White solid, m.p.157-158 °C; 87% Yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.91-7.88 (m, 2H), 7.80 (br s, 1H), 7.58-7.48 (m, 5H), 7.21-7.19 (m, 2H), 2.36 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 164.6, 135.3, 137.0, 134.2, 133.8, 129.51, 128.6, 126.9, 120.2, 20.9 ppm.

4-Chloro-*N*-phenylbenzamide (3e)

White solid, m.p.154-156 °C; 89% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.82 (d, $J = 8.6$ Hz, 2H), 7.76 (s, 1H, NH), 7.62 (d, $J = 7.6$ Hz, 2H), 7.47 (d, $J = 8.6$ Hz, 2H), 7.38 (t, $J = 8.6$ Hz, 2H), 7.17 (t, $J = 7.4$ Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 169.7, 143.8, 141.9, 138.5, 134.3, 133.4, 133.2, 128.8, 125.7 ppm.

3,5-Dimethoxy-*N*-phenylbenzamide (3f)

White solid, m.p.125-127 °C; 81% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.80 (s, 1H), 7.63 (d, $J = 7.7$ Hz, 2H), 7.37 (t, $J = 7.9$ Hz, 2H), 7.22-7.09 (m, 1H), 6.98 (d,

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$J = 2.2$ Hz, 2H), 6.62 (s, 1H), 3.85 (s, 6H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 165.5, 161.1, 137.8, 137.2, 129.1, 124.6, 120.1, 105.0, 103.8, 55.6 ppm.

N-(4-Chlorophenyl)-2-methylbenzamide (3g)

White solid, m.p.132-134 °C;85% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.76 (s, 1H, NH), 7.44 (dd, $J = 17.2, 7.4$ Hz, 3H), 7.38 (td, $J = 7.6, 1.3$ Hz, 1H), 7.31-7.22 (m, 3H), 7.13 (ddd, $J = 8.0, 2.0, 0.9$ Hz, 1H), 2.51(s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 167.0, 139.2, 137.6, 134.9, 133.8, 131.4, 131.6,130.1, 125.5, 126.0, 124.5, 119.8, 116.8, 19.8 ppm.

3,5-Dimethoxy-N-(4-nitrophenyl)benzamide (3h)

Light yellow solid, m.p.147-148 °C;90% yield; ^1H NMR (500 MHz, CDCl_3) δ : 8.31(d, $J = 8.9$ Hz, 2H), 8.06 (s, 1H, NH), 7.88 (d, $J = 8.9$ Hz, 2H), 6.98 (s, 2H), 6.66 (s, 1H), 3.86 (s, 6H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 165.7, 161.2, 143.7, 136.2, 125.2, 119.5, 105.2, 104.3, 55.7 ppm.

N-Benzyl-4-nitrobenzamide (3i)

Yellow solid,m.p.115-117 °C; 90% yield; ^1H NMR (500 MHz, CDCl_3) δ : 8.23 (d, $J = 7.6$ Hz, 2H), 7.91 (d, $J = 7.6$ Hz, 2H), 7.33-7.25 (m, 5H), 6.79 (brs, 1H), 4.64 (d, $J = 4.8$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 164.7,148.9, 140.2, 137.9, 129.5, 128.5, 128.1, 123.1, 44.7ppm.

N-Phenethyl-4-bromobenzamide (3j)

Yellow solid, m.p.131-133 °C; 88% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.63-7.47 (m, 4H), 7.35-7.32 (m, 2H), 7.27-7.21 (m, 3H), 6.15 (brs, 1H), 3.72 (q, $J =$

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6.9 Hz, 2H), 2.93 (t, $J = 6.9$ Hz, 2H) ppm ; ^{13}C NMR (125 MHz, CDCl_3) δ : 165.8, 138.8, 132.6, 132.9, 129.4, 129.9, 129.5, 126.9, 127.1, 42.4, 35.7 ppm.

N-Benzyl-4-methoxybenzamide (3k)

White solid, 147-149 °C; 81% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.74 (d, $J = 7.7$ Hz, 2 H), 7.35-7.28 (m, 5H), 6.78 (d, $J = 7.6$ Hz, 2H), 6.42 (brs, 1H), 4.64 (d, $J = 5.5$ Hz, 2H), 3.85 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 168.1, 161.3, 137.5, 127.9, 127.8, 127.8, 127.5, 125.7, 114.8, 55.4, 44.1 ppm.

N-Phenethyl-4-methylbenzamide (3l)

Yellow solid, m.p. 123-124 °C; 84% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.56 (d, $J = 8.1$ Hz, 2H), 7.31-7.27 (m, 2H), 7.25-7.20 (m, 3H), 7.18 (d, $J = 8.1$ Hz, 2H), 6.24 (brs, 1H), 3.69 (q, $J = 6.4$ Hz, 2H), 2.92 (t, $J = 6.4$ Hz, 2H), 2.39 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 167.4, 142.7, 139.4, 131.4, 129.2, 127.7, 129.5, 126.8, 125.6, 42.1, 35.6, 21.2 ppm.

N-Benzylbenzamide (3m)

Yellow solid, m.p. 120-122 °C; 90% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.82-7.78 (m, 2H), 7.54-7.38 (m, 3H), 7.34-7.28 (m, 5H), 6.49 (brs, 1H), 4.63 (d, $J = 5.6$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 168.4, 137.2, 134.3, 131.5, 128.8, 128.5, 128.1, 126.6, 127.1, 44.1 ppm.

N-Butyl-N-methylbenzamide (3n)

Yellow oil, 90% yield; ^1H NMR (4500 MHz, CDCl_3) δ : 7.45-7.42 (m, 3H), 7.35-7.30 (m, 2H), 3.32 (s, 2H), 2.91 (s, 3H), 1.44 (m, 2H), 1.25 (s, 2H), 0.96 (s, 3H)

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ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 172.2, 136.3, 129.7, 128.6, 127.3, 52.2, 36.6, 30.4, 20.1, 14.1 ppm.

N-Benzyl-N-methylbenzamide (3o)

Pale yellow oil, 90% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.46-7.28 (m, 10H), 4.62 (s, 2H), 2.87 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 170.5, 136.8, 135.4, 128.8, 128.5, 126.9, 127.2, 55.2, 33.3 ppm.

Phenyl(pyrrolidin-1-yl)methanone (3p)

Colorless oil, 90% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.42-7.33 (m, 2H), 7.41-7.33 (m, 3H), 3.53 (t, $J = 6.8$ Hz, 2H), 3.43 (t, $J = 6.4$ Hz, 2H), 1.98-1.88 (m, 2H), 1.83-1.77 (m, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 169.4, 136.8, 128.4, 126.9, 125.8, 49.1, 44.8, 26.1, 24.1 ppm.

Phenyl(piperidin-1-yl)methanone (3q)

Pale yellow oil, 90% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.38 (m, 5H), 3.71 (s, 2H), 3.34 (s, 2H), 1.69 (s, 4H), 1.53 (s, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 170.3, 135.7, 128.4, 127.7, 126.9, 47.8, 43.4, 26.4, 25.4, 24.7 ppm.

N-Benzoylmorpholine (3r)

Colourless oil, 90% yield; ^1H NMR (500 MHz, CDCl_3) δ : 7.41-7.28 (m, 5H), 3.78 (s, 4H), 3.64 (t, $J = 4.7$ Hz, 2H), 3.33 (t, $J = 4.7$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ : 170.5, 134.5, 131.9, 128.8, 129.1, 66.7, 46.4, 41.7 ppm.

3.6.3.1 Spectral Data of Product N-phenylbenzamide (3a)

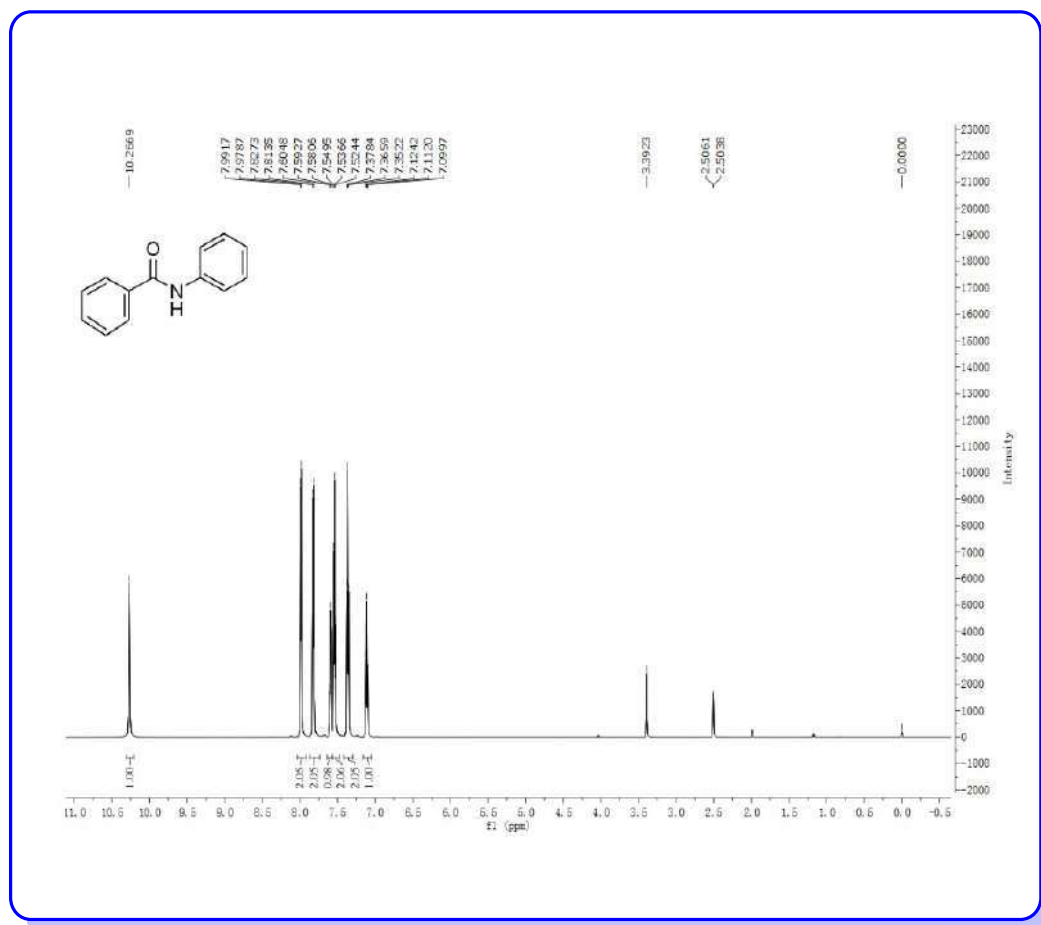


Figure 3.1 ¹H NMR of N-phenylbenzamide(3a)

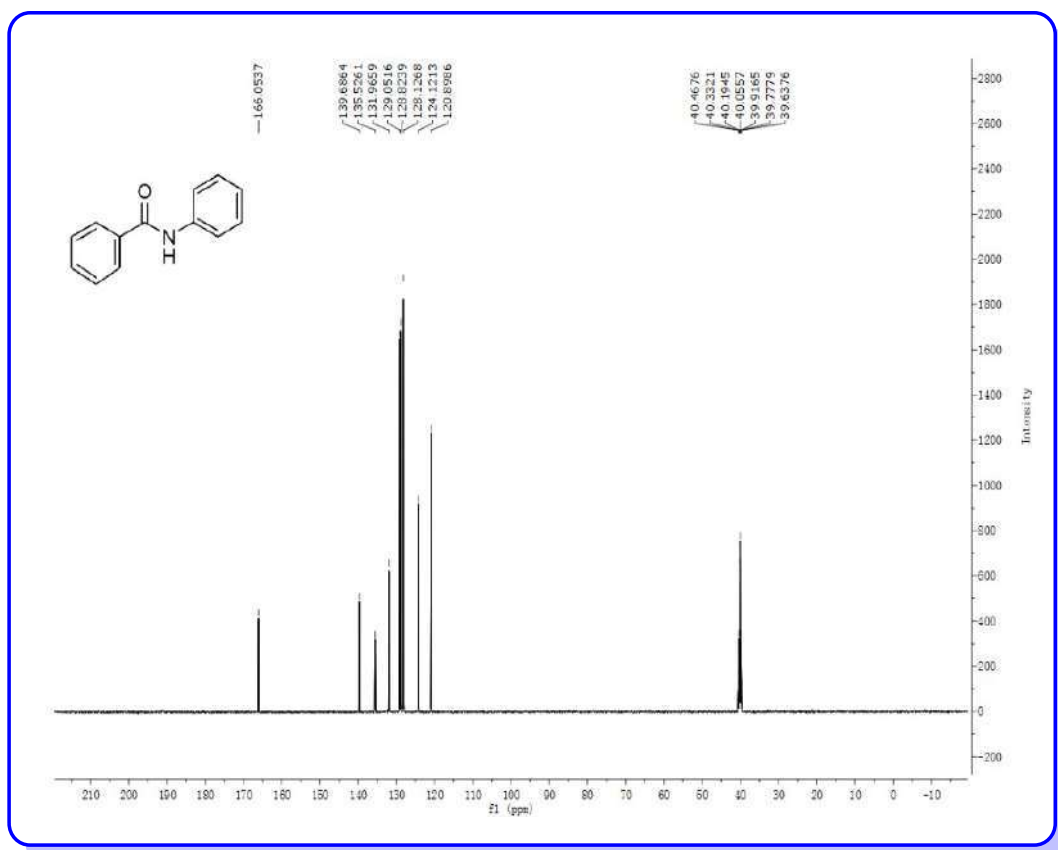


Figure 3.2 ¹³C NMR of N-phenylbenzamide(3a)

3.6.3.2 Spectral Data of Product N-Butyl-N-methylbenzamide (3n)

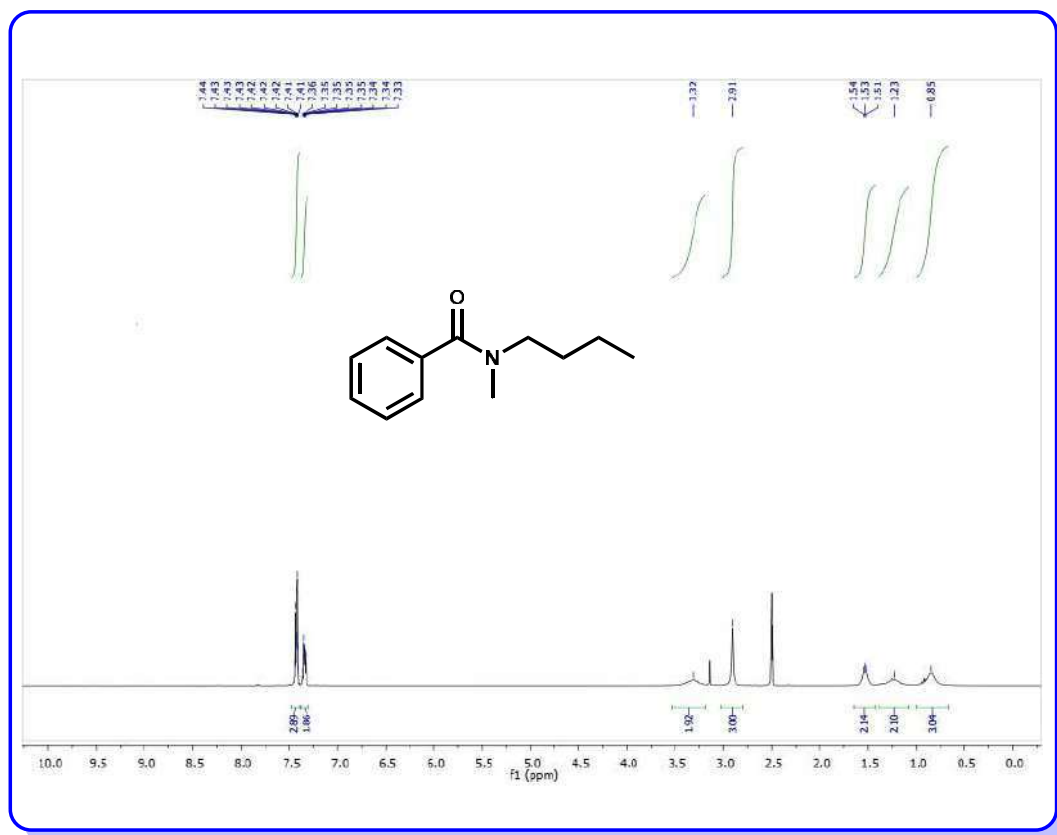


Figure 3.3 ¹H NMR of N-Butyl-N-methylbenzamide(3n)

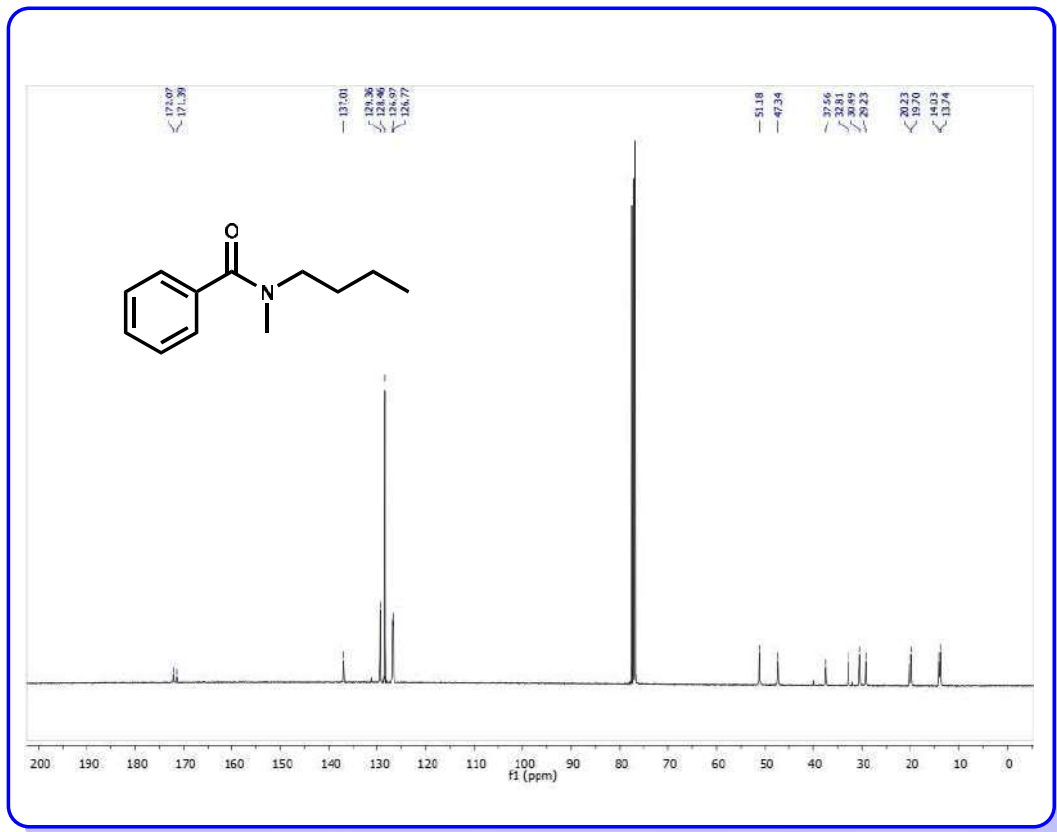


Figure 3.4 ^{13}C NMR of N-Butyl-N-methylbenzamide(3n)

3.6.3.3 Spectral Data of Product phenyl(pyrrolidin-1-yl)methanone (3p)

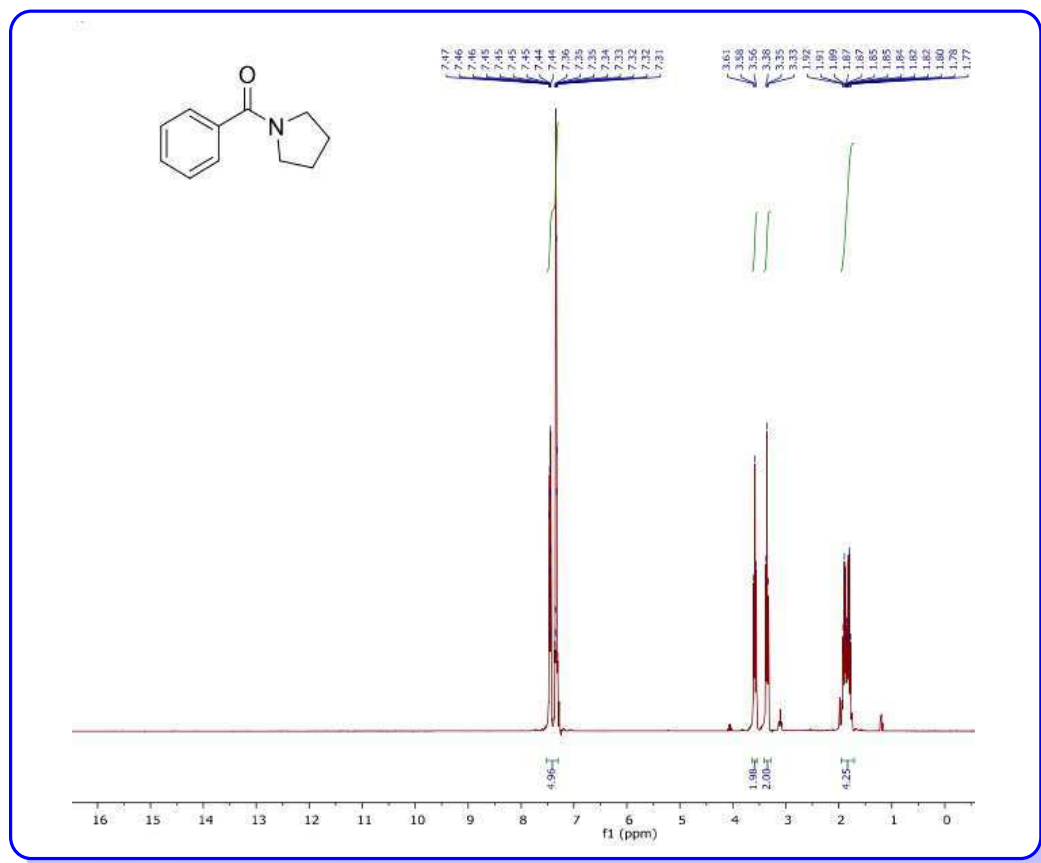


Figure 3.5 ¹H NMR of phenyl(pyrrolidin-1-yl)methanone(3p)

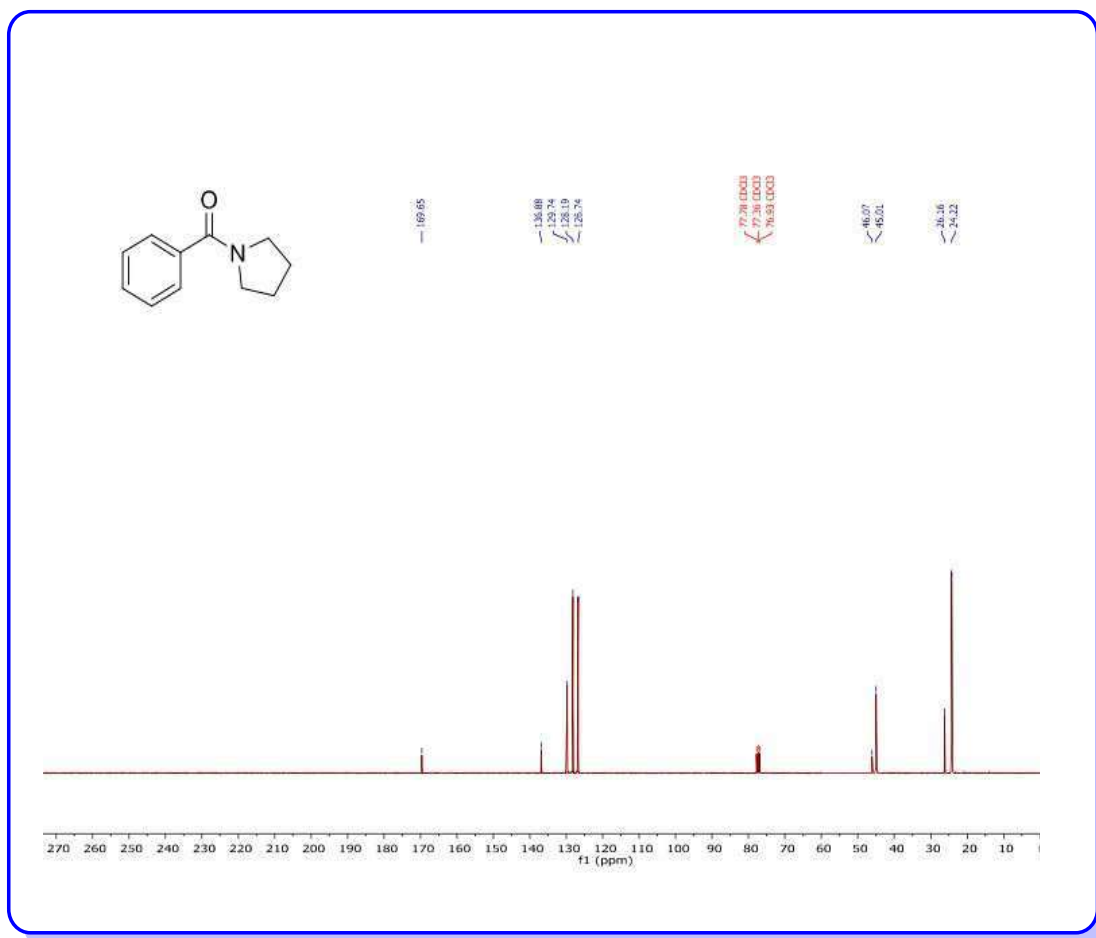


Figure 3.6 ^{13}C NMR of phenyl(pyrrolidin-1-yl)methanone

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