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Graphical Abstract

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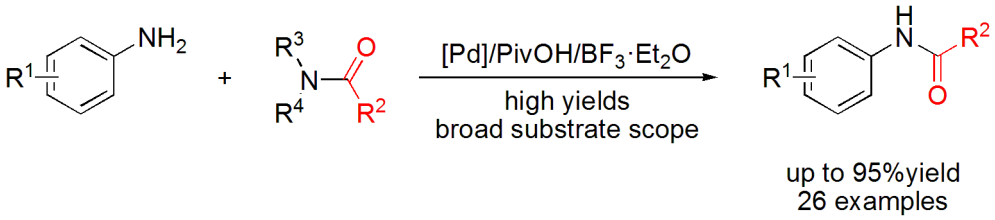

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ABSTRACT

A novel protocol for the transamidation of DMF and derivatives with weakly nucleophilic anilines has been developed, utilizing a catalytic amount of $Pd(OAc)_2$ and 2,2'-bipyridine, and with PivOH and $BF_3 \cdot Et_2O$ as additives. This methodology has a broad substrate scope, and various corresponding transamidation products were prepared in good to excellent yields from commercially available DMF derivatives and anilines. The synthetic utility of the reported protocol was further demonstrated with a gram-scale experiment. Control experiments suggested the efficient transformation of DMF and derivatives with anilines might owe to the synergistic effect of palladium complex, PivOH, and $BF_3 \cdot Et_2O$.

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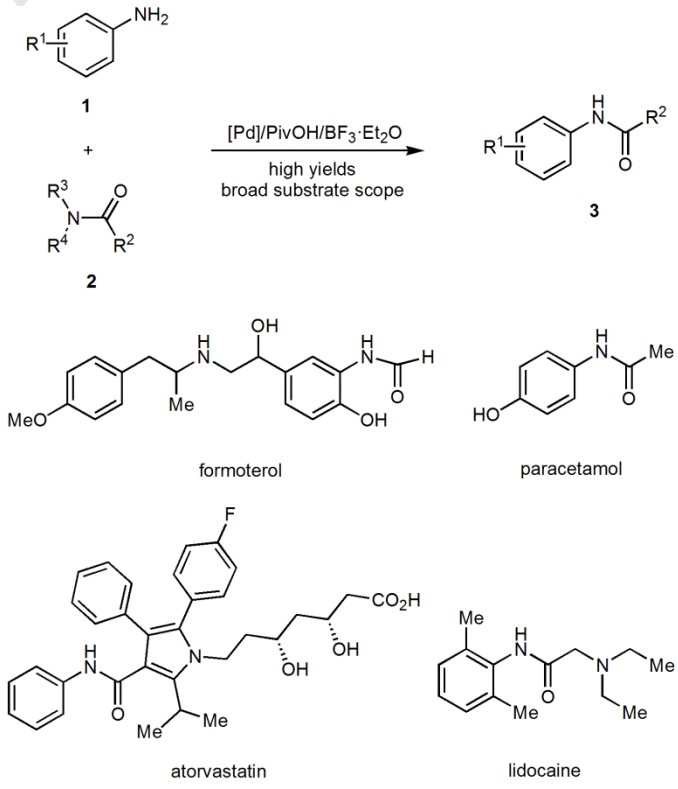
1. Introduction

Amides are extremely important compounds with extensive applications in both the industrial and academic communities.[1] As a class of important amides, *N*-arylcarboxamides are present in many pharmaceuticals. In 2009, more than 10 of the top 200 pharmaceutical products by worldwide sales were *N*-arylcarboxamides.[2] For example, formoterol is a long-acting β_2-agonist used in the treatment of asthma and chronic obstructive pulmonary disease.[3] Paracetamol is a widely used non-narcotic analgesic and antipyretic drug.[4] Atorvastatin is a cholesterol and triglyceride regulator marketed for the treatment of dyslipidemia and the prevention of cardiovascular disease.[5] Lidocaine is a common local anesthetic and class-1b antiarrhythmic drug (Scheme 1).[6]

As an efficient method for the construction of amides, transamidation reaction has attracted much attention.[7] Some novel protocols involving the use of boric acid,[8] benzoic acid,[9] L-proline,[10] hydroxylamine hydrochloride,[11] hypervalent iodine,[12] cerium oxide,[13] copper acetate,[14] other Lewis acids,[15] and even in the absence of a catalyst,[16] have been developed. Although the transamidation reactions proceed well, substrate scope is limited to active primary amides and aliphatic amines.

Although several synthetic protocols have been reported for the synthesis of *N*-arylcarboxamides, the reactions suffered from disadvantages of using hazardous and toxic reagents.[17] This led



Scheme 1. Transamidation of DMF with anilines, and selected important pharmaceuticals derived from *N*-arylcarboxamide.

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us to focus on the development of a new protocol for the preparation of *N*-arylcarboxamides. In order to effectively prepare *N*-arylcarboxamides, the direct transamidation of dimethylformamide (DMF) with anilines should be of special importance because DMF is inexpensive, commercially available, low toxic, and easily separated from the reaction mixture. However, due to the low reaction activity of DMF, successful examples concerning the transamidation of DMF have only been reported by using active benzylamines as the nucleophiles.[8,10,12,18] The direct transamidation of DMF with anilines, which are weakly nucleophilic agents, has thus far been unsuccessful. The reported transamidations gave poor yields[18c, 18e] or suffered the harsh reaction conditions[15c, 18a, 19] (≥150 °C, and use of cerium oxide or hydrous zirconium oxide or a strong acid as a mediator). Furthermore, DMF was used as not only a reagent but also a solvent in almost all the reactions, which resulted in low atom economy of the reactions.[20] Because of the low cost and easily availability of the starting materials, the development of a convenient and efficient protocol for the transamidation of DMF with anilines is highly desired.

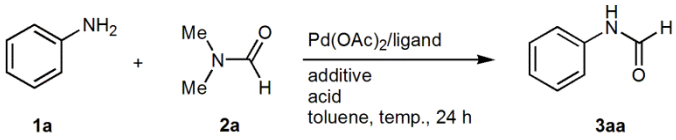
Herein, we report an efficient synthesis of *N*-arylcarboxamides via the transamidation of DMF derivatives with anilines. Under the optimized catalytic system, the transformation of DMF and its derivatives with anilines was realized giving the desired products in good to excellent yields. This protocol also has a broad substrate scope (Scheme 1).

2. Results and discussion

Initially, we selected aniline and DMF as the model starting materials to test the reaction. The reaction of aniline (**1a**) and DMF (**2a**) in the presence of 5 mol% of $Pd(OAc)_2$ with 2 equivalents of PivOH in toluene at 120 °C for 24 hours gave the desired product **3aa** in 21% yield (Table 1, entry 1). The addition of 5 mol% of PPh_3, 1,10-phenanthroline (phen), or 2,2'-bipyridine (bpy) as a ligand to the reaction improved the yield of **3aa** (Table1, entries 2-4). Bpy proved to be the best ligand, giving **3aa** in 59% yield (Table 1, entry 4). In order to further increase the yield of **3aa**, several Lewis acids were examined. Although both $ZnCl_2$ and $Zn(OTf)_2$ afforded lower yields of **3aa** (Table 1, entries 5-6), the addition of 1.5 equivalents of $BF_3{\cdot}Et_2O$ greatly improved the yield of **3aa** to 90% (Table 1, entry 7). We used $BF_3{\cdot}Et_2O$ to examine other reaction conditions. The addition of benzoic acid and TFA afforded **3aa** in lower yields, however PivOH proved to be the best acid in this reaction (Table 1, entries 7-9). We carried out the reaction in different solvents and found that toluene gave the highest yield of **3aa** (Table 1, entries 10-12 *vs* entry 7). Additionally, we altered the amount of additive, acid, and DMF, and found that this had no significant impact on the yields of **3aa** (Table 1, entries 13-16). The reaction proceeded in air although the yield of **3aa** was somewhat lower (Table 1, entry 17). We also investigated the effect of reaction temperature, and found that the best yield was obtained when the reaction was carried out at 120 °C (Table 1, entries 18-19 *vs* entry 7). To our delight, the reaction provided **3aa** in 93% yield when the catalyst loading was decreased to 3 mol% (Table 1, entry 20). However, the yield of **3aa** descreased to 83% when 1 mol% of catalyst loading was used in the reaction (Table 1, entry 21).

With the optimal reaction conditions in hand (Table 1, entry 20), we investigated the aniline scope, the results of which are summarized in Table 2. It was found the reaction conditions were suitable for a variety of substituted anilines, providing the corresponding transamidation products in good to excellent yields (Table 2, **3aa**−**ra**). For example, the reaction of aniline and

Table 1.
Optimization of the reaction conditions[a]



1a **2a** **3aa**

Entry	Ligand	Additive	Acid	Yield[b] (%)
1	--	--	PivOH	21
2	PPh_3	--	PivOH	41
3	Phen	--	PivOH	50
4	bpy	--	PivOH	59
5	bpy	$ZnCl_2$	PivOH	53
6	bpy	$Zn(OTf)_2$	PivOH	28
7	bpy	$BF_3{\cdot}Et_2O$	PivOH	90
8	bpy	$BF_3{\cdot}Et_2O$	$PhCO_2H$	69
9	bpy	$BF_3{\cdot}Et_2O$	TFA	34
10[c]	bpy	$BF_3{\cdot}Et_2O$	PivOH	45
11[d]	bpy	$BF_3{\cdot}Et_2O$	PivOH	71
12[e]	bpy	$BF_3{\cdot}Et_2O$	PivOH	74
13[f]	bpy	$BF_3{\cdot}Et_2O$	PivOH	73
14[g]	bpy	$BF_3{\cdot}Et_2O$	PivOH	77
15[h]	bpy	$BF_3{\cdot}Et_2O$	PivOH	69
16[i]	bpy	$BF_3{\cdot}Et_2O$	PivOH	42
17[j]	bpy	$BF_3{\cdot}Et_2O$	PivOH	61
18[k]	bpy	$BF_3{\cdot}Et_2O$	PivOH	64
19[l]	bpy	$BF_3{\cdot}Et_2O$	PivOH	83
20[m]	**bpy**	**$BF_3{\cdot}Et_2O$**	**PivOH**	**93**
21[n]	bpy	$BF_3{\cdot}Et_2O$	PivOH	83

[a] Unless otherwise noted, the reactions were performed in a sealed tube with **1a** (0.2 mmol), DMF (2.0 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.01 mmol), additive (0.3 mmol), and acid (0.4 mmol) in solvent (2.0 mL) at 120 °C for 24 h under O_2 (1 atm).
[b] Isolated yields.
[c] 1,4-Dioxane.
[d] DCE.
[e] ᵗamyl alcohol.
[f] Additive (0.2 mmol).
[g] Acid (0.2 mmol).
[h] DMF (1.0 mmol).
[i] DMF (0.4 mmol).
[j] In air.
[k] 110 °C.
[l] 130 °C.
[m] $Pd(OAc)_2$ (0.006 mmol), bpy (0.006 mmol).
[n] $Pd(OAc)_2$ (0.002 mmol), bpy (0.002 mmol).

DMF in the presence of 3 mol% of $Pd(OAc)_2$ and bpy, with 1.5 equivalents of $BF_3{\cdot}Et_2O$ and 2 equivalents of PivOH in toluene at 120 °C for 24 hours, afforded product **3aa** in 93% yield. A wide range of functional groups are tolerated in the present reaction, including halogens (**3ka**-**na**), ethers (**3ea**-**ia**), ester (**3oa**), and

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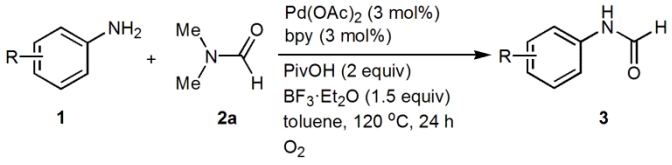
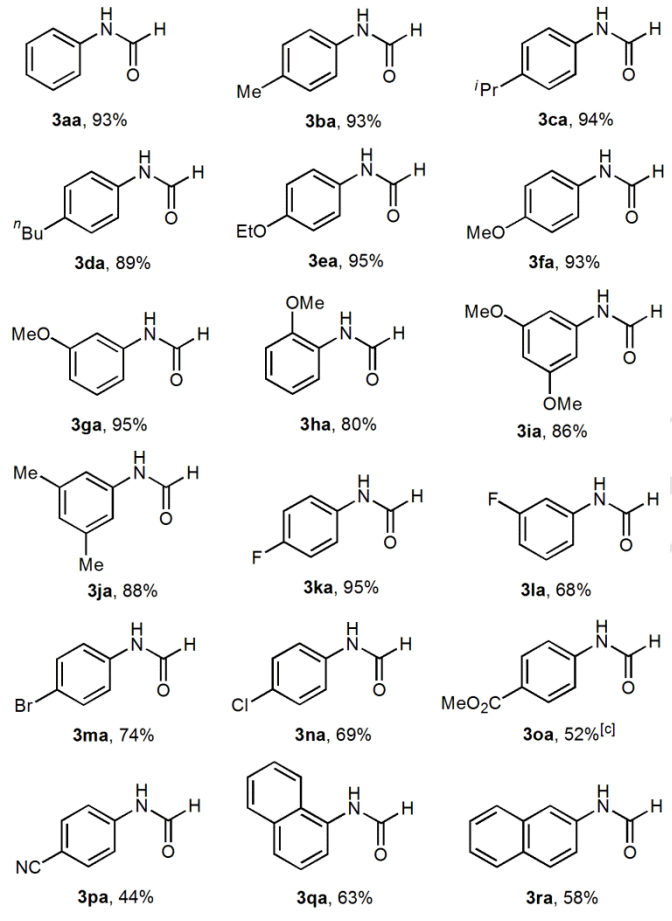
nitrile (**3pa**). Anilines bearing electron-donating and electron-withdrawing substituents are also tolerated. Generally speaking, anilines bearing electron-donating substituents gave higher yields than their electron-withdrawing substituted counterparts (Table 2, **3ba**-**ja** *vs* **3la**-**pa**). Treatment of di-substituted anilines with DMF afforded the corresponding transamidation products in good yields (Table 2, **3ia** and **3ja**). Furthermore, transamidation reactions with naphthyl substituted amines and DMF also proceeded smoothly giving the products **3qa** and **3ra** in good yields.

Table 2.
Transamidation of DMF with anilines[a, b]

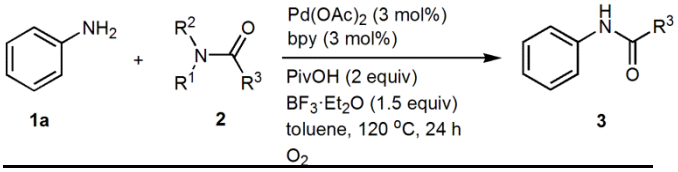


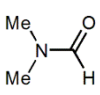
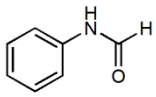
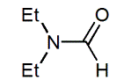
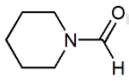
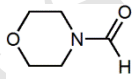
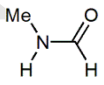
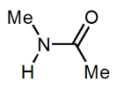
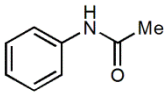
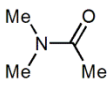
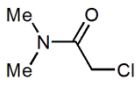
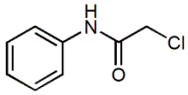


[a] Unless otherwise noted, the reactions were performed in a sealed tube with **1** (0.2 mmol), DMF (2.0 mmol), $Pd(OAc)_2$ (0.006 mmol), bpy (0.006 mmol), $BF_3{\cdot}Et_2O$ (0.3 mmol), and PivOH (0.4 mmol) in toluene (2.0 mL) at 120 °C for 24 h under O_2 (1 atm).
[b] Isolated yields.
[c] 130 °C.

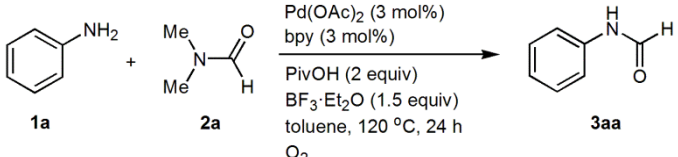
DMF substrate scope was also examined. As shown in Table 3, several DMF derivatives can be employed to this reaction giving the corresponding products in moderate to good yields (Table 3, entries 1−9). To our delight, DMF derivatives bearing formyl groups and ketone groups were suitable for the reaction conditions. For example, amides **2c**-**2f**, and **2i** provided their corresponding transamidation products in good yields (Table 3, entries 3−6 and entry 9). These results demonstrate the high efficiency of the present methodology, and also provide an alternative and efficient method for the protection of anilines.

Table 3.
Pd-catalyzed transamidation of DMF derivatives with aniline[a]



Entry	Amides	Products	Yield[b] (%)
1	 **2a**	 **3aa**	93
2[c]	 **2b**	**3aa**	57
3	 **2c**	**3aa**	81
4	 **2d**	**3aa**	80
5	 **2e**	**3aa**	80
6	 **2f**	**3aa**	91
7[d]	 **2g**	 **3ag**	48
8[d]	 **2h**	**3ag**	55
9	 **2i**	 **3ai**	81

[a] Reaction conditions: unless otherwise noted, the reactions were performed in a sealed tube with **1a** (0.2 mmol), **2** (2.0 mmol), $Pd(OAc)_2$ (0.006 mmol), bpy (0.006 mmol), $BF_3{\cdot}Et_2O$ (0.3 mmol), and PivOH (0.4 mmol) in toluene (2.0 mL) at 120 °C for 24 h under O_2 (1 atm).
[b] Isolated yields.
[c] $Pd(OAc)_2$ (0.01 mmol), bpy (0.01 mmol).
[d] 130 °C.



Scheme 2. Gram-scale synthesis of **3aa**

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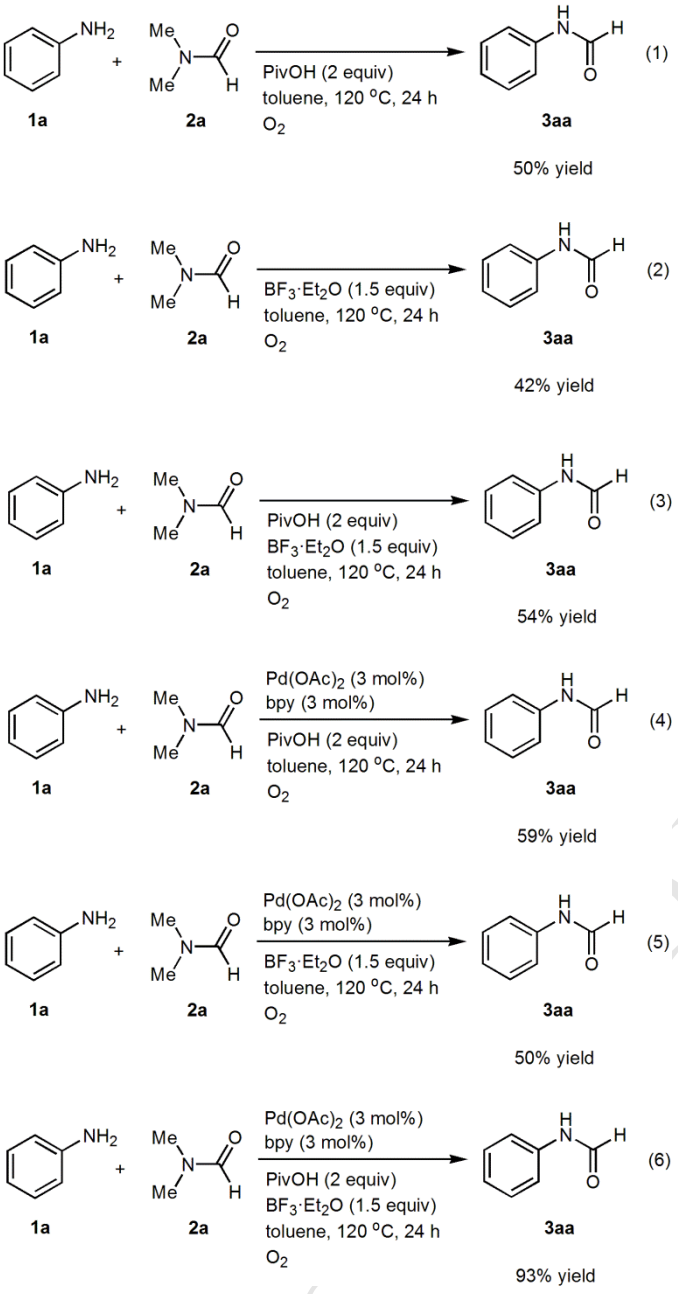
To further show the synthetic utility of the present protocol, we performed a gram-scale experiment using aniline **1a** with DMF under the optimal reaction conditions. As highlighted in Scheme 2, the reaction proceeded well to afford transamidation product **3aa** in 92% yield.



Scheme 3. Control experiments.

Although precise mechanistic details are not clear at this stage, a series of control experiments were carried out to detect the information on the reaction mechanism. The transamidation of DMF with aniline proceeded in the presence of either 2 equivents of PivOH or 1.5 equivents of $BF_3 \cdot Et_2O$ to give the corresponding transamidation product **3aa** in moderate yields (Scheme 3, eq 1 and 2). The use of 2 equivents of PivOH and 1.5 equivents of $BF_3 \cdot Et_2O$ slightly increased the yield of **3aa** (Scheme 3, eq 3). We also found that the use of 3 mol% of $Pd(OAc)_2$ and bpy with 2 equivents of PivOH or 1.5 equivents of $BF_3 \cdot Et_2O$ gave the desired transamidation product in moderate yields (Scheme 3, eq 4 and 5). However, the high yield of transamidation product was obtained in the presence of a combination of 3 mol% of $Pd(OAc)_2$ and bpy with 2 equivents of PivOH and 1.5 equivents of $BF_3 \cdot Et_2O$ (Scheme 3, eq 6). These results suggested that it might be the synergistic effect of palladium complex, PivOH, and $BF_3 \cdot Et_2O$ that promoted smoothly the present reaction. Further investigations are ongoing to determine a detailed mechanism.

3. Conclusion

In conclusion, we have developed an efficient method for the transamidation of DMF with weakly nucleophilic anilines. The transamidation products were obtained in good to excellent yields by using a catalytic amount of $Pd(OAc)_2$ and bpy with PivOH and $BF_3 \cdot Et_2O$ as the additives. A wide range of functional groups including halogens, ethers, ester, and nitrile are tolerated in the present reaction. The use of low cost and commercially available anilines and DMF derivatives as the starting materials provide great potential for future transamidation reactions.

4. Experimental section

4.1. General experimental methods

Toluene was distilled over benzophenone ketyl under N_2. DMF was distilled over CaH_2 under reduced pressure. All commercial reagents were used without further purification. NMR spectra were recorded on a 400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C) with deuterated chloroform ($CDCl_3$) or hexadeuteriodimethylsulfoxide (DMSO-d_6) as a solvent at 298K. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^1H NMR, $CDCl_3$ (δ 77.16) and DMSO-d_6 (δ 39.52) for ^{13}C NMR: the following abbreviations are used; s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet.

4.2. General procedure for the synthesis of product 3

Under molecular oxygen atmosphere, to a mixture of $Pd(OAc)_2$ (1.3 mg, 0.006 mmol) and bpy (0.9 mg, 0.006 mmol), toluene (2.0 mL) was added. Then aniline (0.2 mmol), amide (2.0 mmol), PivOH (40.9 mg, 0.4 mmol), and $BF_3 \cdot Et_2O$ (42.6 mg, 0.3 mmol) were added to the mixture. The mixture was heated to 120 °C and it stirred at 120 °C for 24 h. After completion, the mixture was cooled to room temperature and diluted with ethyl acetate. Washed with aq $NaHCO_3$, water, and aq NaCl. Dried over $MgSO_4$ and filtered. After evaporation of the solvent, the residue was purified by preparative thin-layer chromatography on silica gel with PE/EtOAc (1/1) as an eluent to give the product **3**.

4.2.1. N-Phenylcarboxamide (3aa).[21] Yellow solid; 22.5 mg (93% yield); mp 46-47 °C; ^1H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/0.9): δ 8.70 (d, J = 11.4 Hz, 1H), 8.39 (s, 0.9H), 8.07 (brs, 1H), 7.55 (d, J = 8.1 Hz, 1.8H), 7.39-7.32 (m, 4.2H), 7.20-7.09 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 118.95, 120.12, 124.96, 125.42, 129.24, 129.88, 136.83, 136.99, 159.19, 162.84.

4.2.2. N-(4-Methylphenyl)formamide (3ba).[22] White solid; 25.1 mg (93% yield); mp 48-49 °C; ^1H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/0.8): δ 8.62 (d, J = 11.5 Hz, 1H), 8.35 (d, J = 1.5 Hz, 0.8H), 7.98 (brs, 1H), 7.42 (d, J = 8.4 Hz, 1.6H), 7.26 (brs, 0.8H), 7.15 (t, J = 8.9 Hz, 4H), 6.98 (d, J = 8.3 Hz, 1.6H), 2.34 (s, 3H), 2.32 (s, 2.4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.93, 21.02, 119.35, 120.15, 129.72, 130.38, 134.15, 134.38, 134.67, 135.34, 158.99, 162.77.

4.2.3. N-Formyl-p-cumidin (3ca). Yellow liquid; 30.7 mg (94% yield); ^1H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/1): δ 9.00 (brs, 1H), 8.64 (d, J = 11.4 Hz, 1H), 8.31 (d, J = 1.4 Hz, 1H), 8.23 (brs, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.24-7.09 (m, 4H), 7.03 (d, J = 8.4 Hz, 2H), 2.91-2.82 (m, 2H), 1.33-1.09

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(m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.09, 33.68, 33.73, 119.34, 120.30, 127.08, 127.76, 134.48, 134.68, 145.69, 146.34, 159.19, 163.03.

4.2.4. p-Butyl-formanilide (3da). Yellow liquid; 31.5 mg (89% yield); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/0.8): δ 8.75 (brs, 1H), 8.64 (d, J = 11.4 Hz, 1H), 8.33 (s, 0.8H), 7.84 (brs, 0.8H), 7.45 (d, J = 8.2 Hz, 1.6H), 7.16-7.11 (m, 3.6H), 7.01 (d, J = 8.1 Hz, 2H), 2.60-2.54 (m, 3.6H), 1.61-1.52 (m, 3.6H), 1.39-1.28 (m, 3.6H), 0.94-0.89 (m, 5.4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.02, 22.34, 33.71, 35.04, 35.14, 119.15, 120.19, 129.01, 129.67, 134.43, 134.64, 139.61, 140.26, 159.33, 163.18

4.2.5. N-(4-Ethoxyphenyl)formamide (3ea).[17e] White solid; 31.4 mg (95% yield); mp 66-67 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 0.9/1): δ 8.52 (brs, 1.8H), 8.29 (s, 1H), 7.84 (brs, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.6 Hz, 1.8H), 6.88-6.82 (m, 3.8H), 4.03-3.97 (m, 3.8H), 1.42-1.37 (m, 5.7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.86, 14.88, 63.78, 63.89, 114.87, 115.53, 121.57, 121.91, 129.60, 130.02, 156.10, 157.01, 159.29, 163.42.

4.2.6. N-(4-Methoxyphenyl)formamide (3fa).[23] White solid; 28.1 mg (93% yield); mp 78-79 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/1.1): δ 8.65 (brs, 1H), 8.52 (d, J = 11.4 Hz, 1H), 8.28 (s, 1.1H), 8.01 (brs, 1.1H), 7.45 (d, J = 8.9 Hz, 2.2H), 7.04 (d, J = 8.8 Hz, 2H), 6.83-6.89 (m, 4.2H), 3.79 (s, 3H), 3.77 (s, 3.3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.52, 55.60, 114.24, 114.93, 121.53, 121.95, 129.76, 130.16, 156.71, 157.61, 159.38, 163.46.

4.2.7. N-(3-Methoxyphenyl)formamide (3ga). Yellow liquid; 28.7 mg (95% yield); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/0.9): δ 8.70 (d, J = 11.3 Hz, 1H), 8.37 (s, 0.9H), 8.28 (brs, 1H), 7.46 (brs, 0.9H), 7.30-7.20 (m, 3H), 7.01 (d, J = 8.0 Hz, 0.9H), 6.74-6.68 (m, 2.7H), 6.62 (s, 1H), 3.81 (s, 3H), 3.80 (s, 2.7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.46, 55.52, 105.05, 105.99, 110.53, 110.69, 111.04, 112.14, 129.94, 130.74, 138.06, 138.19, 159.16, 160.29, 160.82, 162.69.

4.2.8. N-(2-Methoxyphenyl)formamide (3ha).[23] White solid; 24.2 mg (80% yield); mp 81-82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/2.2): δ 8.74 (d, J = 11.6 Hz, 1H), 8.45 (d, J = 1.6 Hz, 2.2H), 8.36 (dd, J = 8.0, 1.5 Hz, 2.2H), 7.85 (brs, 2.2H), 7.73 (brs, 1H), 7.22-7.17 (d, J = 7.9 Hz, 1H), 7.16-7.04 (m, 3H), 7.00-6.87 (m, 6.6H), 3.88 (s, 6.6H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.83, 110.15, 111.39, 116.74, 120.56, 121.17, 121.21, 124.38, 125.32, 126.31, 126.86, 147.89, 148.84, 158.85, 161.57.

4.2.9. N-(3,5-Dimethoxyphenyl)formamide (3ia).[24] White solid; 31.2 mg (86% yield); mp 88-89 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/0.7): δ 8.70 (d, J = 11.3 Hz, 1H), 8.59 (brs, 1H), 8.34 (d, J = 1.9 Hz, 0.7H), 7.73 (brs, 0.8H), 6.79 (d, J = 2.2 Hz, 1.4H), 6.28 (t, J = 2.1 Hz, 1H), 6.25 (t, J = 2.2 Hz, 0.7H), 6.24 (d, J = 2.1 Hz, 2H), 3.78 (s, 6H), 3.77 (s, 4.2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.49, 55.56, 96.85, 97.06, 97.24, 98.40, 138.66, 138.76, 159.36, 161.13, 161.75, 162.77.

4.2.10. Formic acid-(3,5-dimethyl-anilide) (3ja). White solid; 26.3 mg (88% yield); mp 67-69 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/0.6): δ 8.68 (d, J = 11.4 Hz, 1H), 8.60 (brs, 1H), 8.33 (d, J = 1.8 Hz, 0.6H), 7.54 (brs, 0.6H), 7.17 (s, 1.2H), 6.82 (s, 1H), 6.77 (s, 0.6H), 6.71 (s, 2H), 2.30 (s, 6H), 2.29 (s, 3.6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.38, 21.43, 116.60, 117.85, 126.62, 127.03, 136.73, 136.87, 138.94, 139.70, 159.23, 163.01.

4.2.11. N-(4-Fluorophenyl)formamide (3ka).[25] White solid; 26.4 mg (95% yield); mp 63-64 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 0.7/1): δ 8.63 (brs, 1.4H), 8.35 (s, 1H), 7.76 (brs, 1H), 7.53-7.50 (m, 2H), 7.11-6.99 (m, 4.8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 115.88 (d, J = 22.0 Hz), 116.67 (d, J = 23.0 Hz), 121.27 (d, J = 8.0 Hz), 121.98 (d, J = 8.0 Hz), 132.87 (d, J = 3.0 Hz), 132.99 (d, J = 3.0 Hz), 159.28, 159.72 (d, J = 243.0 Hz), 160.56 (d, J = 243.0 Hz), 163.15.

4.2.12. N-(3-Fluorophenyl)formamide (3la). White solid; 18.9 mg (68% yield); mp 56-57 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/1.2): δ 8.73 (d, J = 11.1 Hz, 1H), 8.64 (brs, 1H), 8.38 (s, 1.2H), 7.71 (brs, 1.2H), 7.50 (d, J = 10.6 Hz, 1.2H), 7.38-7.23 (m, 2.4H), 7.20 (d, J = 8.1 Hz, 1.2H), 6.98-6.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 106.05 (d, J = 25.0 Hz), 107.74 (d, J = 26.0 Hz), 111.73 (d, J = 21.0 Hz), 112.16 (d, J = 21.0 Hz), 114.18 (d, J = 3.0 Hz), 115.30 (d, J = 3.0 Hz), 130.39 (d, J = 9.0 Hz), 131.29 (d, J = 10.0 Hz), 138.42 (d, J = 11.0 Hz), 138.52 (d, J = 10.0 Hz), 159.28, 162.60, 163.03 (d, J = 244.0 Hz), 163.49 (d, J = 245.0 Hz).

4.2.13. N-(4-Bromophenyl) formamide (3ma).[23] White solid; 29.6 mg (74% yield); mp 111-113 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 0.7/1): δ 8.67 (brs, 1.4H), 8.37 (s, 1H), 7.70 (brs, 1H), 7.52-7.39 (m, 5.4H), 6.99 (d, J = 8.4 Hz, 1.4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.62, 118.39, 120.44, 121.66, 132.22, 132.92, 135.94, 136.02, 159.14, 162.55.

4.2.14. N-(4-Chlorophenyl)formamide (3na).[23] White solid; 21.5 mg (69% yield); mp 98-99 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/1.4): δ 8.65 (d, J = 11.3 Hz, 1H), 8.38 (s, 1.4H), 8.06 (brs, 1H), 7.50 (d, J = 8.7 Hz, 2.8H), 7.35-7.29 (m, 5.8H), 7.04 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.24, 121.33, 129.29, 130.00, 130.92, 135.39, 135.51, 159.06, 162.54.

4.2.15. N-Formyl p-aminobenzoic acid methyl ester (3oa). White solid; 18.6 mg (52% yield); mp 121-122 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/1.3): δ 8.87 (d, J = 9.9 Hz, 1H), 8.66 (brs, 1H), 8.44 (s, 1.3H), 8.03 (t, J = 9.2 Hz, 4.6H), 7.83 (brs, 1.3H), 7.65 (d, J = 8.4 Hz, 2.6H), 7.15 (d, J = 8.3 Hz, 2H), 3.92 (s, 3H) , 3.91 (s, 3.9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.24, 52.33, 117.31, 119.25, 126.26, 126.73, 131.03, 131.68, 141.09, 141.18, 159.28, 162.17, 166.46, 166.67.

4.2.16. N-(4-Cyanophenyl)formamide (3pa).[17b] White solid; 12.9 mg (44% yield); mp 185-187 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6, mixture of two rotamers, ratio: 0.33/1): δ 10.64 (brs, 1H), 10.52 (d, J = 10.3 Hz, 0.33H), 8.99 (d, J = 10.6 Hz, 0.33H), 8.37 (d, J = 1.3 Hz, 1H), 7.92-7.65 (m, 4.62H), 7.38 (d, J = 8.5 Hz, 0.66H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 105.44, 117.06, 118.93, 119.30, 133.42, 133.80, 142.30, 160.42, 162.67.

4.2.17. N-(1-Naphthyl)formamide (3qa).[26] White solid; 21.6 mg (63% yield); mp 137-138 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/0.4): δ 8.64-8.62 (m, 1.4H), 8.45 (brs, 1H), 8.03-7.99 (m, 1.4H), 7.91-7.85 (m, 2H), 7.79 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 0.4H), 7.62-7.45 (m, 4.4H), 7.32 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.07, 120.59, 121.01, 121.53, 125.62, 125.80, 126.23, 126.30, 126.60, 126.78, 126.91, 127.09, 127.12, 127.88, 128.62, 128.92, 131.18, 132.37, 134.18, 134.39, 159.90, 164.45.

4.2.18. N-(2-Naphthyl)formamide (3ra). White solid; 19.9 mg (58% yield); mp 124-126 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two rotamers, ratio: 1/1): δ 8.85 (d, J = 10.5 Hz, 1H), 8.84 (brs, 1H), 8.43 (s, 1H), 8.22 (s, 1H), 7.83-7.75 (m, 7H), 7.51-7.38 (m,

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6H), 7.24 (d, J = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 115.25, 117.23, 118.85, 119.77, 125.40, 125.61, 126.77, 127.23, 127.36, 127.70, 127.79, 127.91, 129.03, 130.05, 130.93, 131.20, 133.82, 133.89, 134.36, 134.43, 159.45, 163.09.

4.2.19. N-Phenylacetamide (3ag).[27] White solid; 13.0 mg (48% yield); mp 113-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (brs, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.27 (t, J = 7.7 Hz, 2H), 7.08 (t, J = 7.2 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.41, 120.27, 124.33, 128.93, 138.14, 169.20.

4.2.20. 2-Chloro-N-phenylacetamide (3ai).[28] White solid; 27.5 mg (81% yield); mp 134-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (brs, 1H), 7.54 (d, J = 7.7 Hz, 2H), 7.35 (t, J = 7.9 Hz, 2H), 7.17 (t, J = 7.4 Hz, 1H), 4.18 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.01, 120.26, 125.39, 129.27, 136.79, 163.92.

4.3. Gram-Scale experiment for the synthesis of product 3aa

Under molecular oxygen atmosphere, to a mixture of $Pd(OAc)_2$ (67.3 mg, 0.3 mmol) and bpy (46.9 mg, 0.3 mmol), toluene (20.0 mL) was added. Then aniline (0.93 g, 10.0 mmol), DMF (7.31 g, 100.0 mmol), PivOH (2.04 g, 20.0 mmol), and $BF_3 \cdot Et_2O$ (2.13 g, 15.0 mmol) were added to the mixture. The mixture was heated to 120 °C and it stirred at 120 °C for 24 h. After completion, the mixture was cooled to room temperature and diluted with ethyl acetate. Washed with aq $NaHCO_3$, water, and aq NaCl. Dried over $MgSO_4$ and filtered. After evaporation of the solvent, the residue was purified by column with PE/EtOAc (2/1) as an eluent to give the product **3aa** (1.11 g, 92% yield).

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Supplementary data

Supplementary data related to this article can be found at http://

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Supporting Information

Synthesis of N-arylcarboxamides by the Efficient Transamidation of DMF and Derivatives with Anilines

Da-Wei Gu, and Xun-Xiang Guo*

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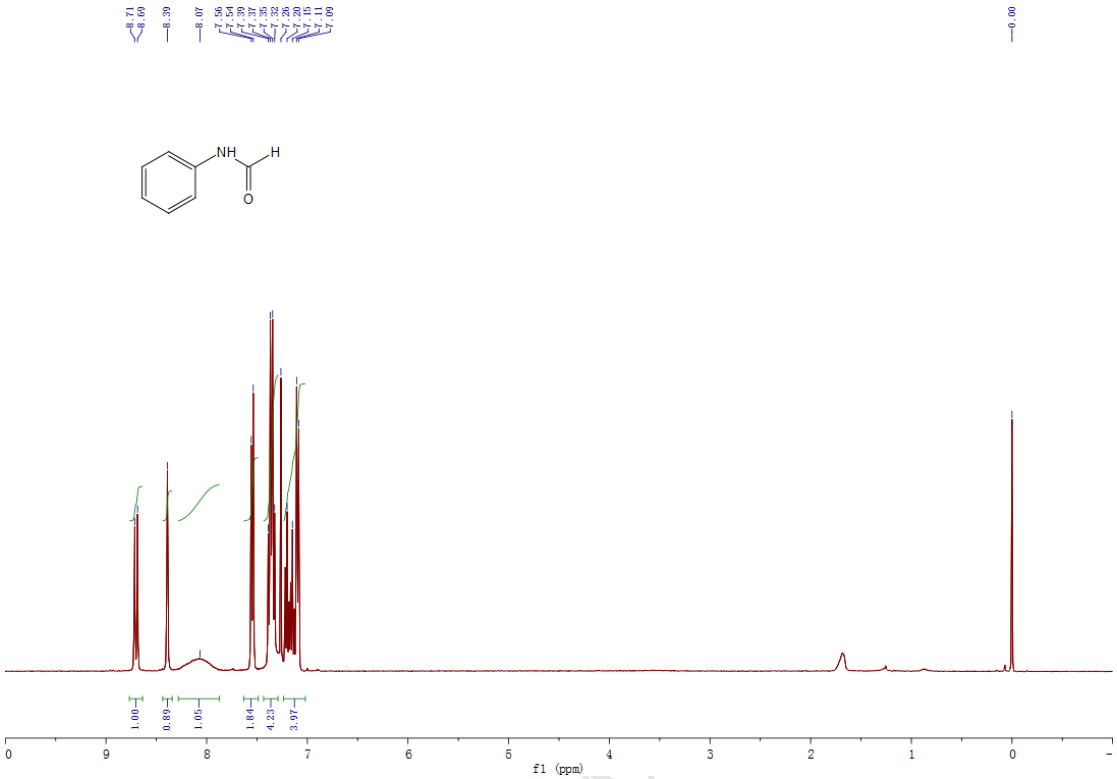
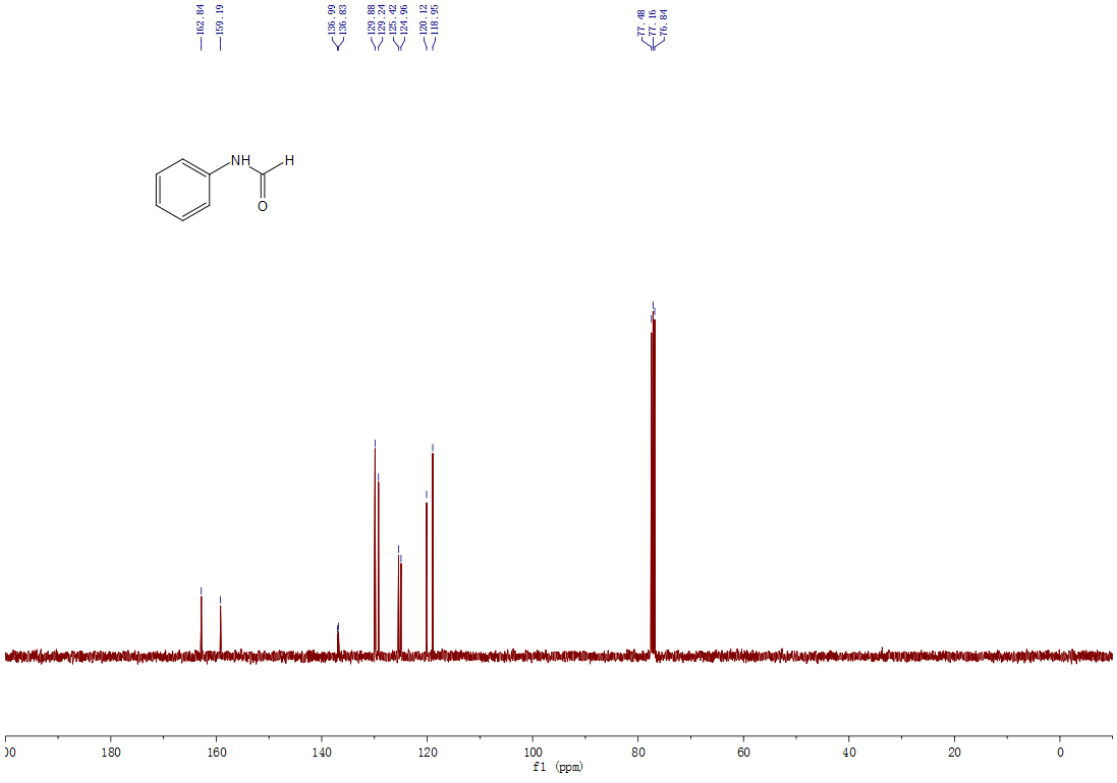
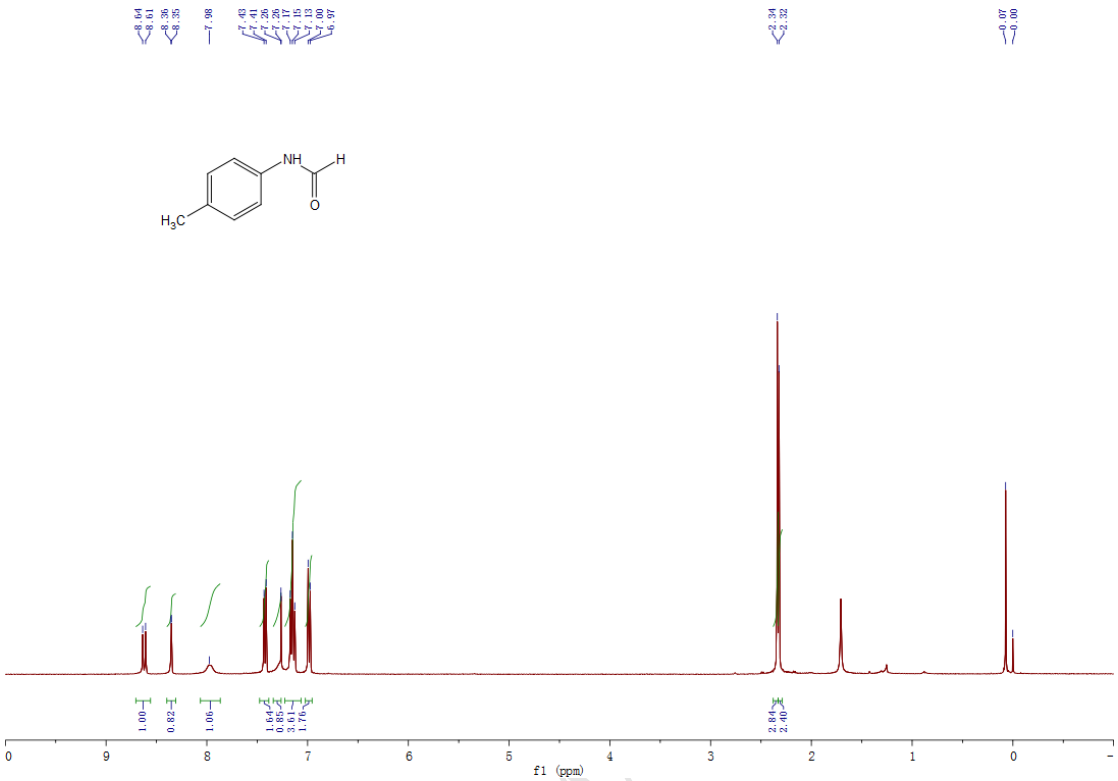
4. ^{1}H and ^{13}C NMR Spectra



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7.15
7.13
7.00
6.97
2.34
2.32
0.07
0.00
NH
H
O
H3C
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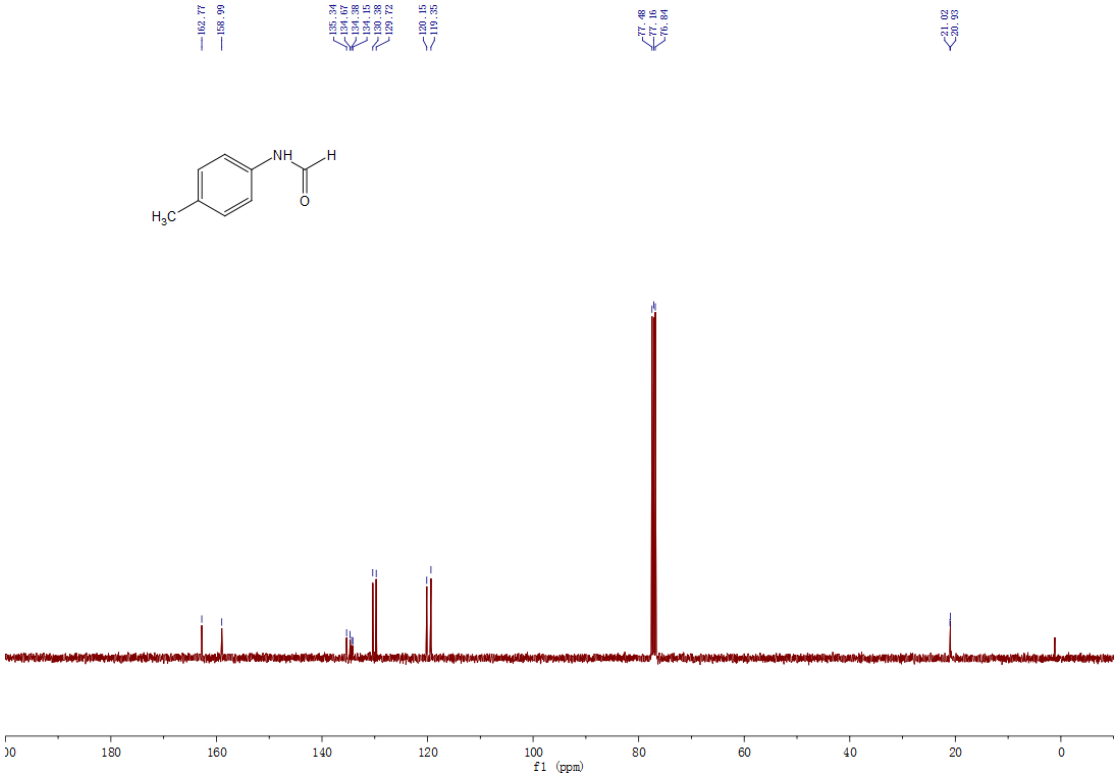
1.06
1.64
0.85
3.61
1.76
2.84
2.40
f1 (ppm)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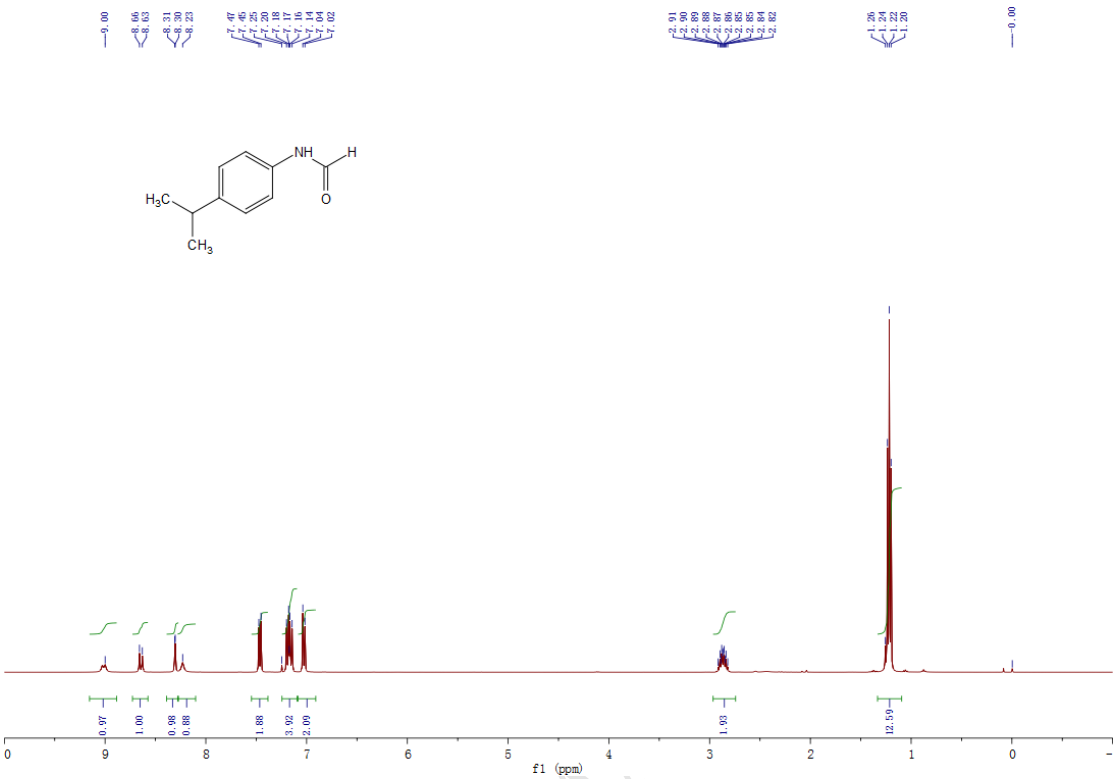
77.16
76.84
21.02
20.93
NH
H
O
H3C
f1 (ppm)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7.17
7.16
7.14
7.04
7.02
2.91
2.90
2.89
2.88
2.87
2.86
2.85
2.84
2.82
1.26
1.24
1.22
1.20
0.00
NH
H
O
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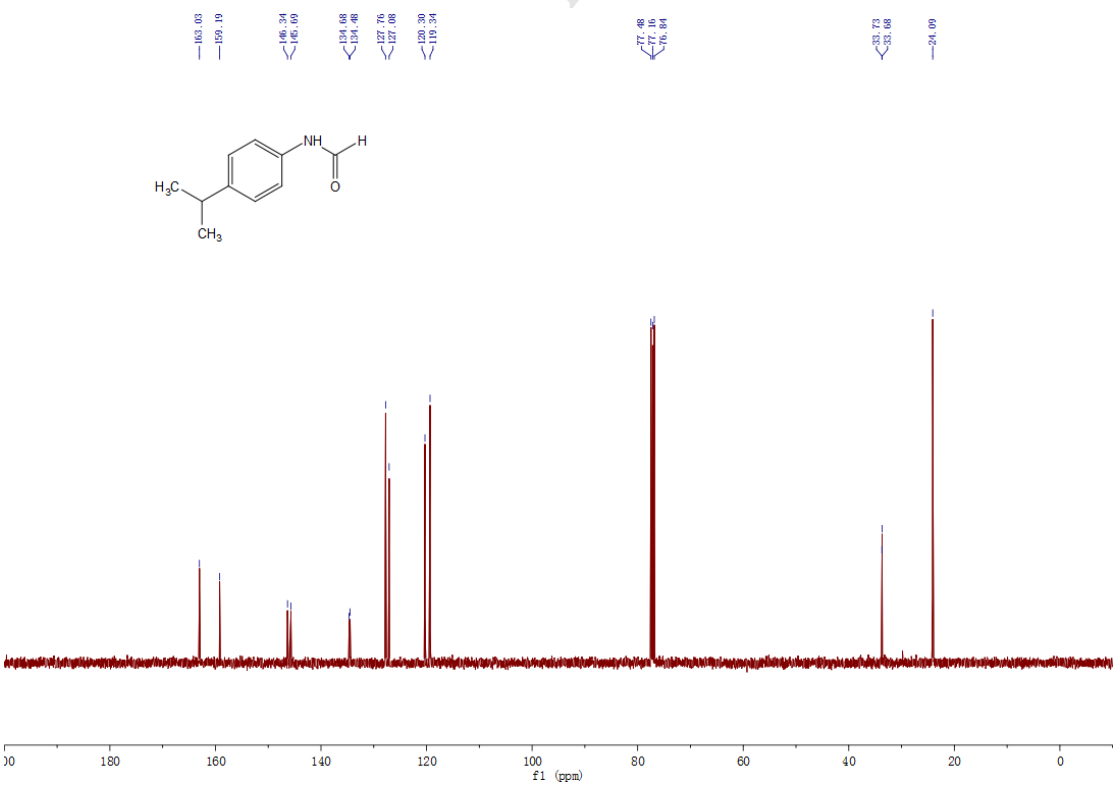
1.88
3.92
2.09
1.93
12.59
f1 (ppm)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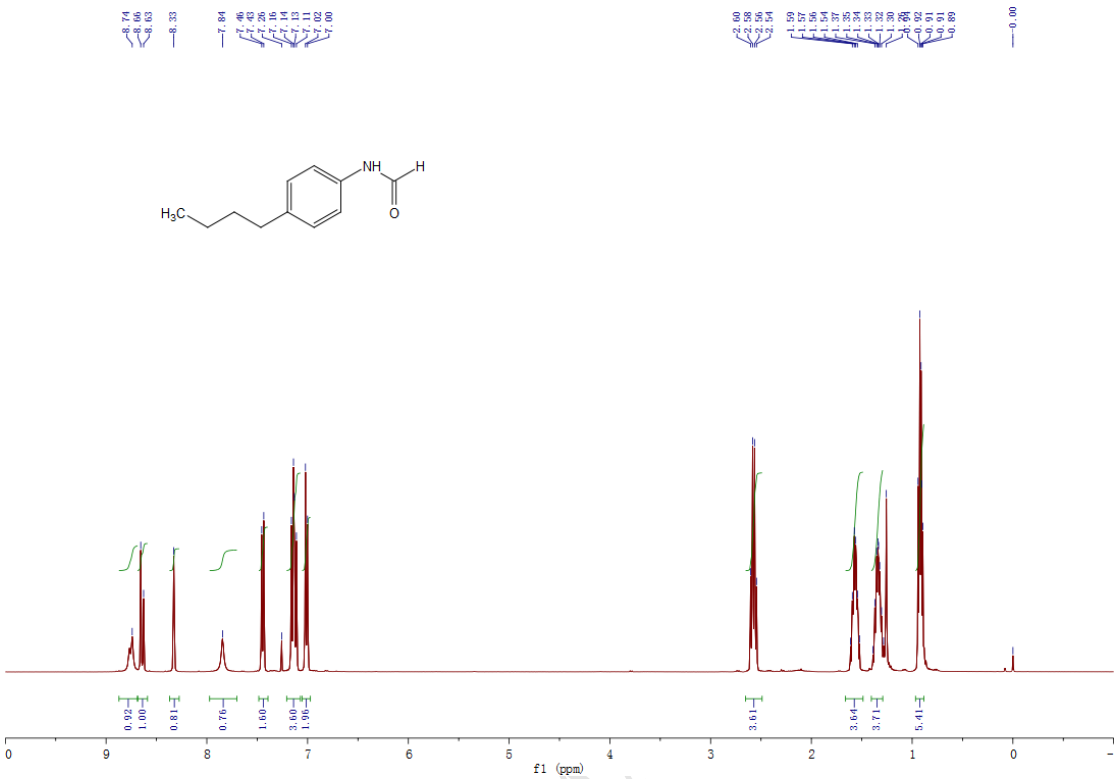
33.68
24.09
NH
H
O
H3C
CH3
f1 (ppm)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7.26
7.16
7.14
7.13
7.11
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7.00
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2.54
1.59
1.57
1.56
1.54
1.37
1.35
1.34
1.33
1.32
1.30
0.92
0.91
0.89
0.00
NH
H
O
H3C
0.92
1.00
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0.76
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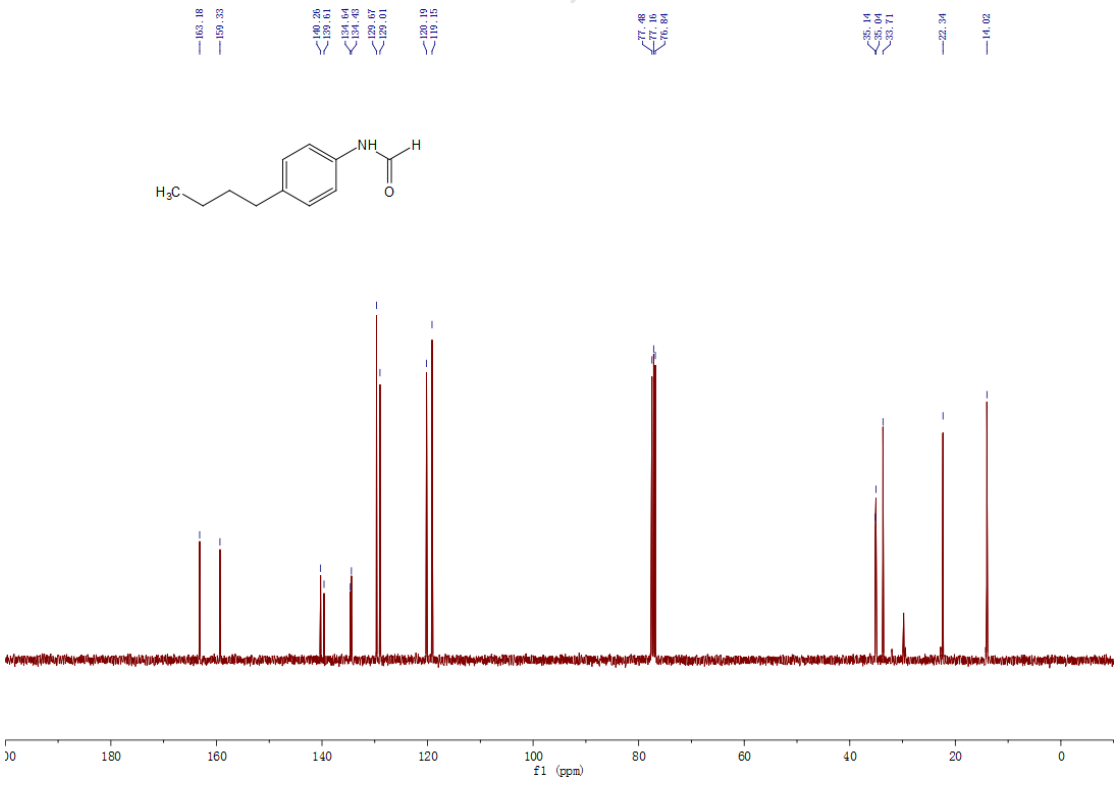
3.60
1.96
3.61
3.64
3.71
5.41
f1 (ppm)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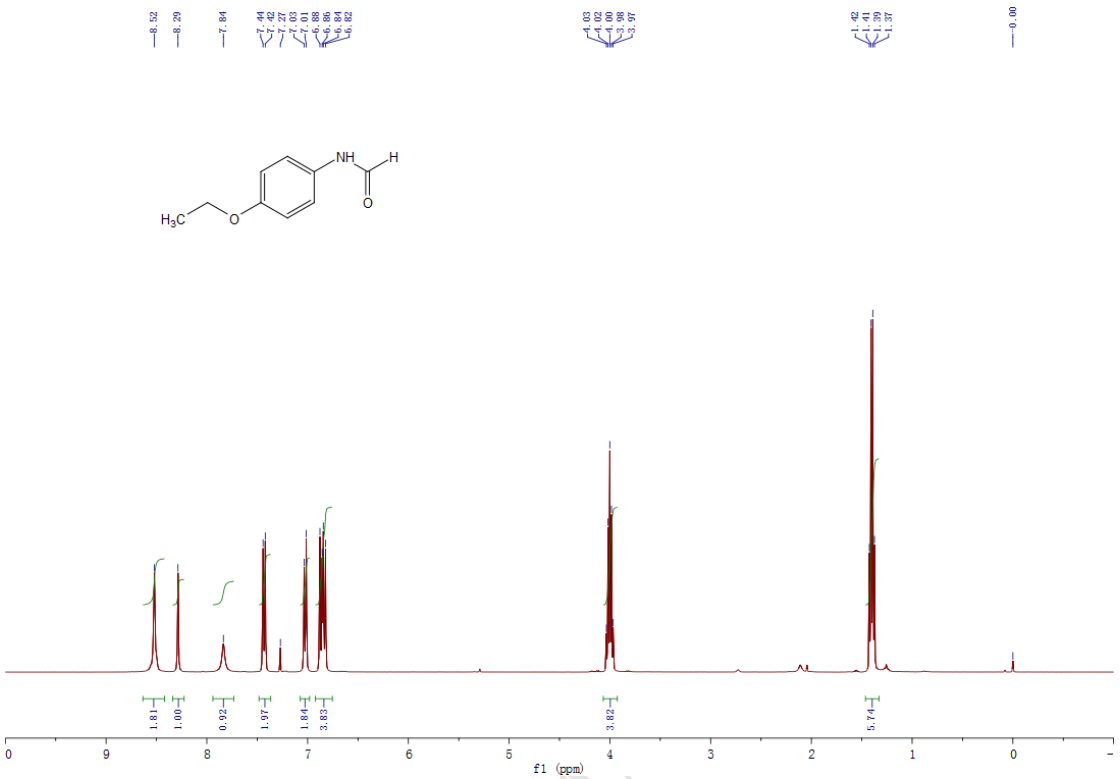
14.02
NH
H
O
H3C
f1 (ppm)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7.01
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6.86
6.84
6.82
4.03
4.02
4.00
3.98
3.97
1.42
1.41
1.39
1.37
0.00
NH
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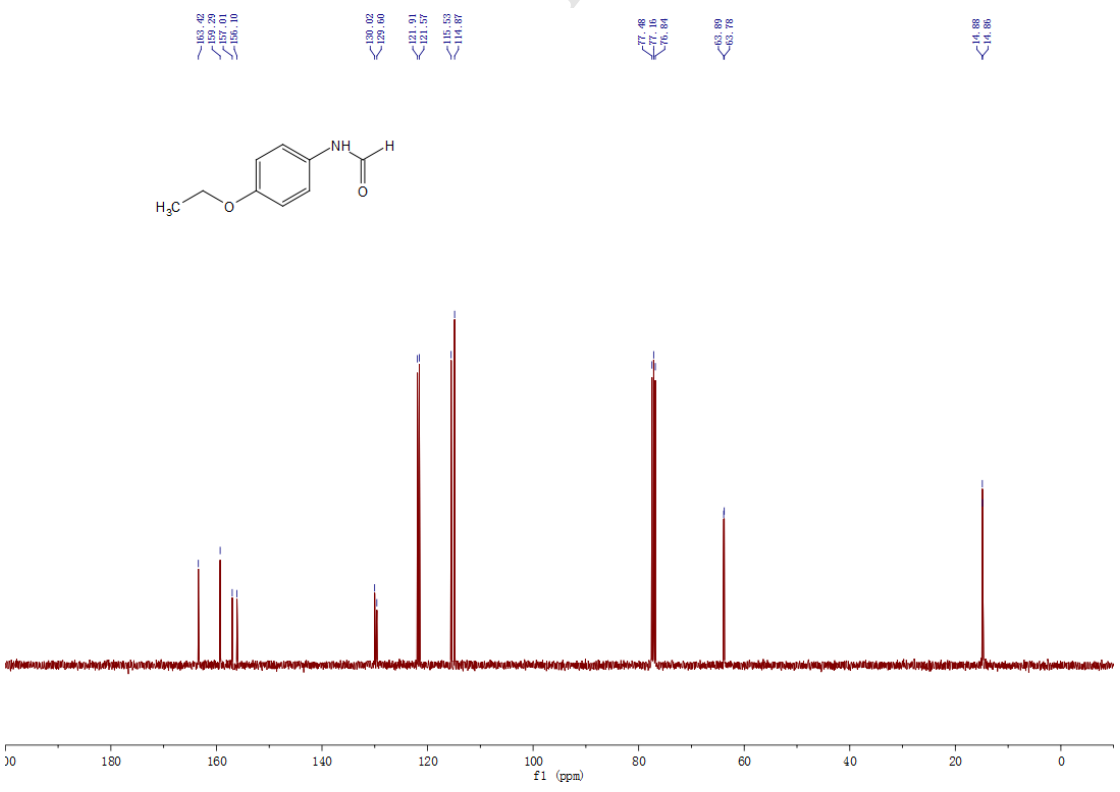
O
1.81
1.00
0.92
1.97
1.84
3.83
3.82
5.74
f1 (ppm)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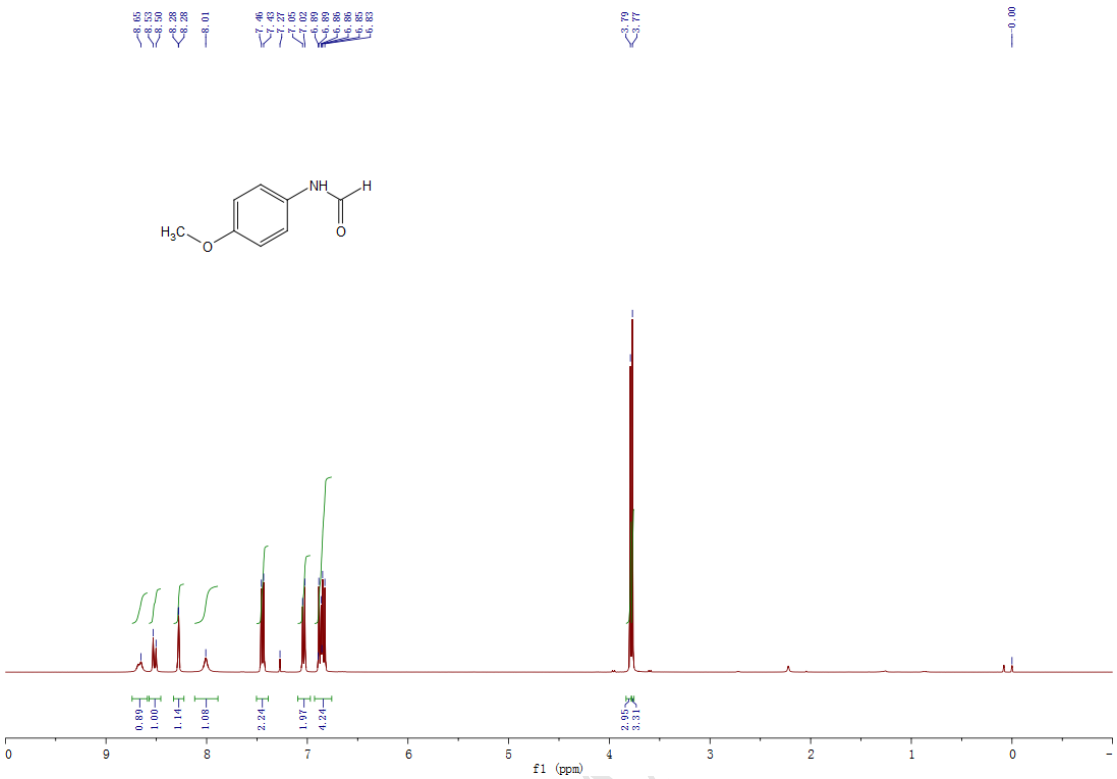
63.78
14.88
14.86
NH
H
O
H3C
O
f1 (ppm)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8.28
8.01
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7.43
7.27
7.05
7.02
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6.86
6.86
6.85
6.83
3.79
3.77
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H
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H3C
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1.08
2.24
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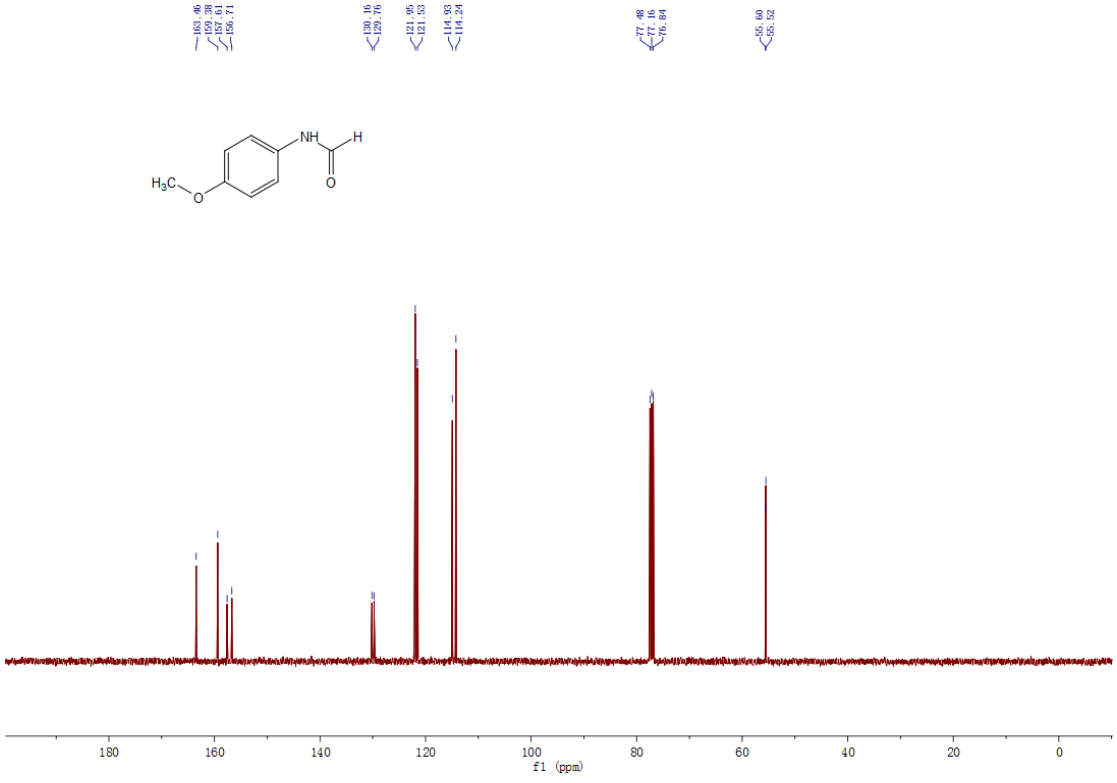
4.24
2.95
3.31
f1 (ppm)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77.16
76.84
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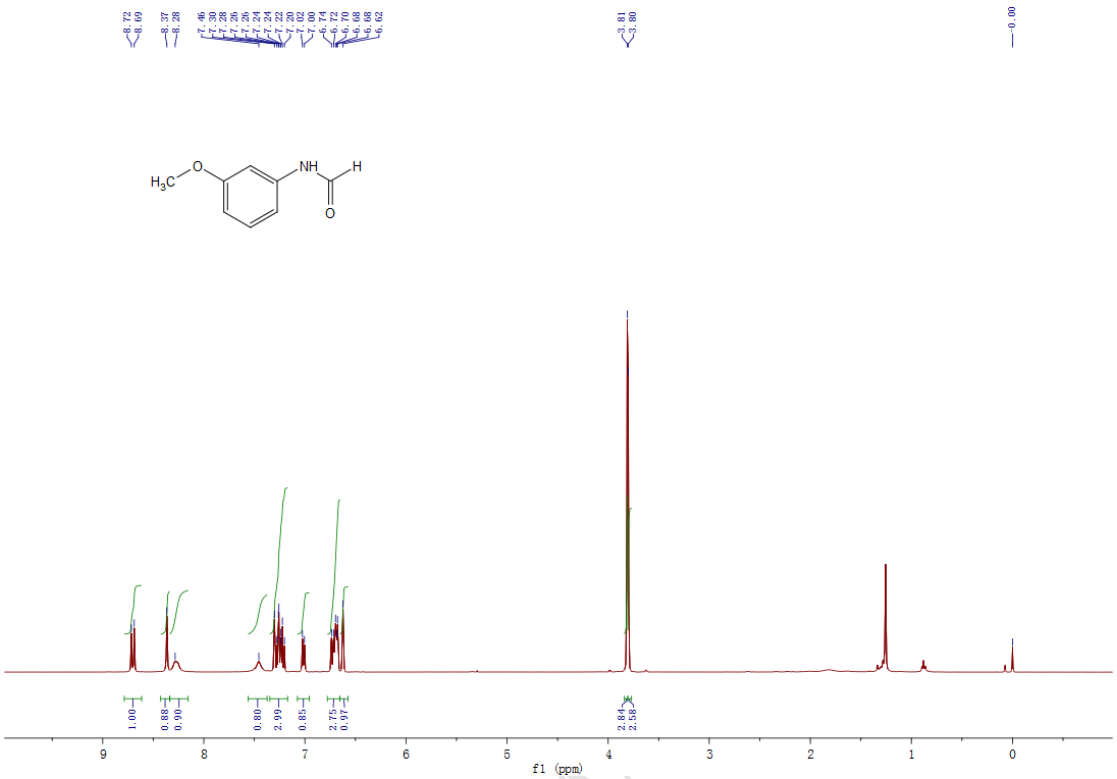
55.52
NH
H
O
H3C
O
f1 (ppm)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7.24
7.22
7.20
7.02
7.00
6.74
6.72
6.70
6.68
6.68
6.62
3.81
3.80
0.00
O
NH
H
H3C
1.00
0.88
0.90
0.80
2.99
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2.84
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9
8
7
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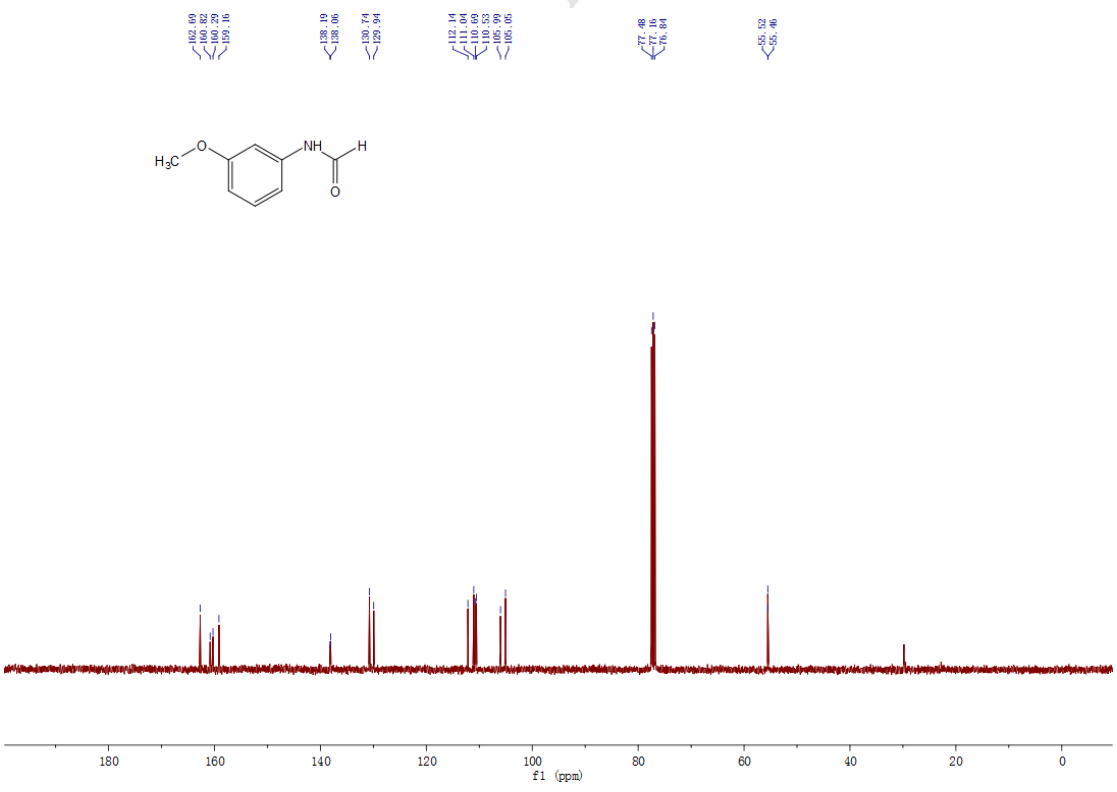
5
4
3
2
1
0
f1 (ppm)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110.53
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105.05
77.48
77.16
76.84
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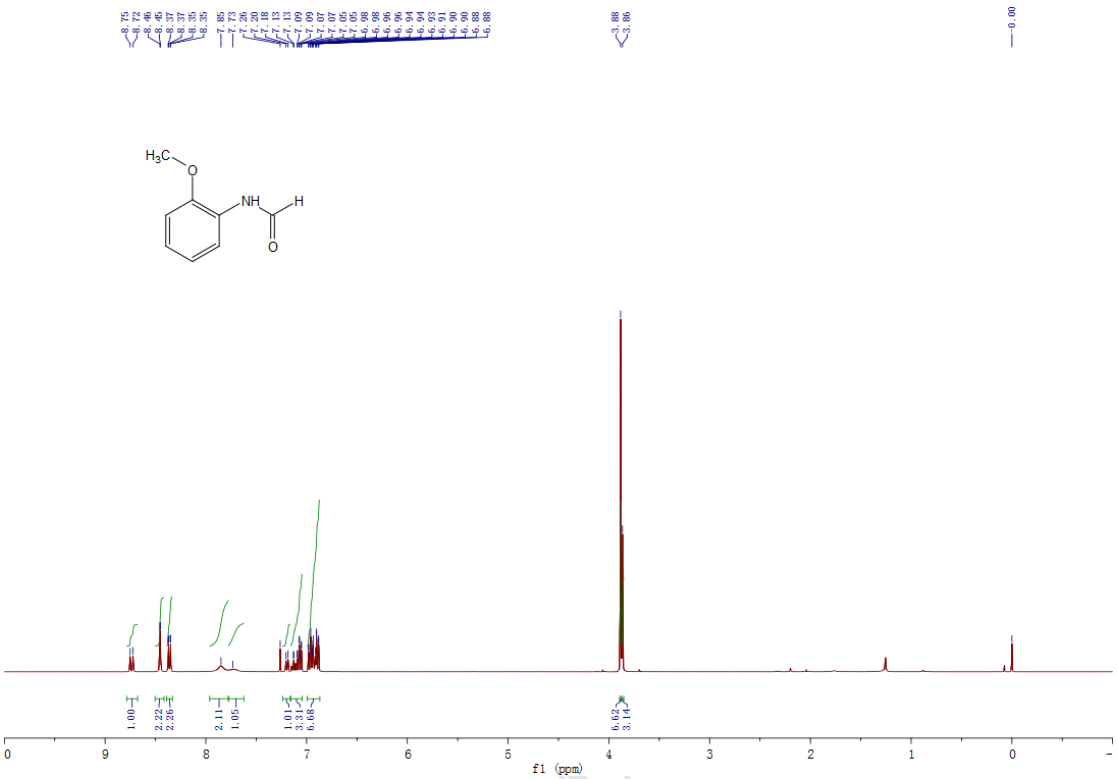
O
NH
H
H3C
180
160
140
120
100
80
60
40
20
0
f1 (ppm)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7.13
7.13
7.09
7.09
7.07
7.07
7.05
7.05
6.98
6.98
6.96
6.96
6.94
6.94
6.93
6.91
6.90
6.90
6.88
6.88
3.88
3.86
0.00
H3C
O
NH
H
O
1.00
2.22
2.20
2.11
1.05
1.01
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6.62
3.14
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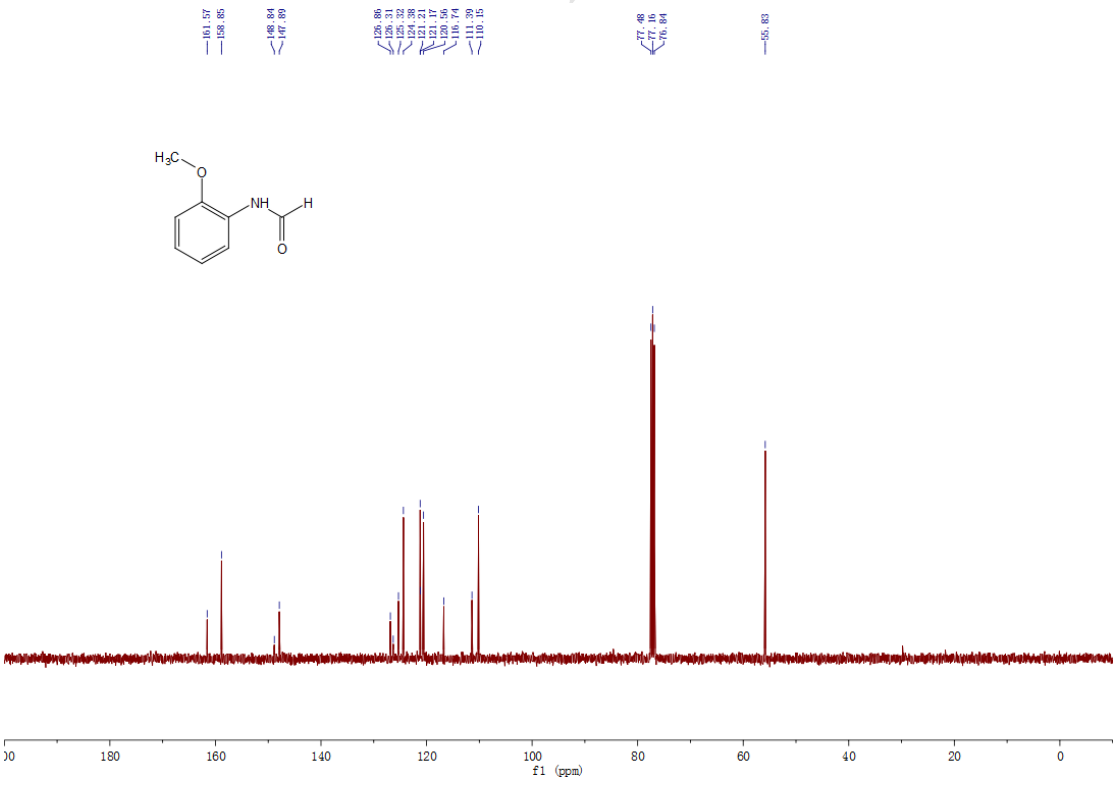
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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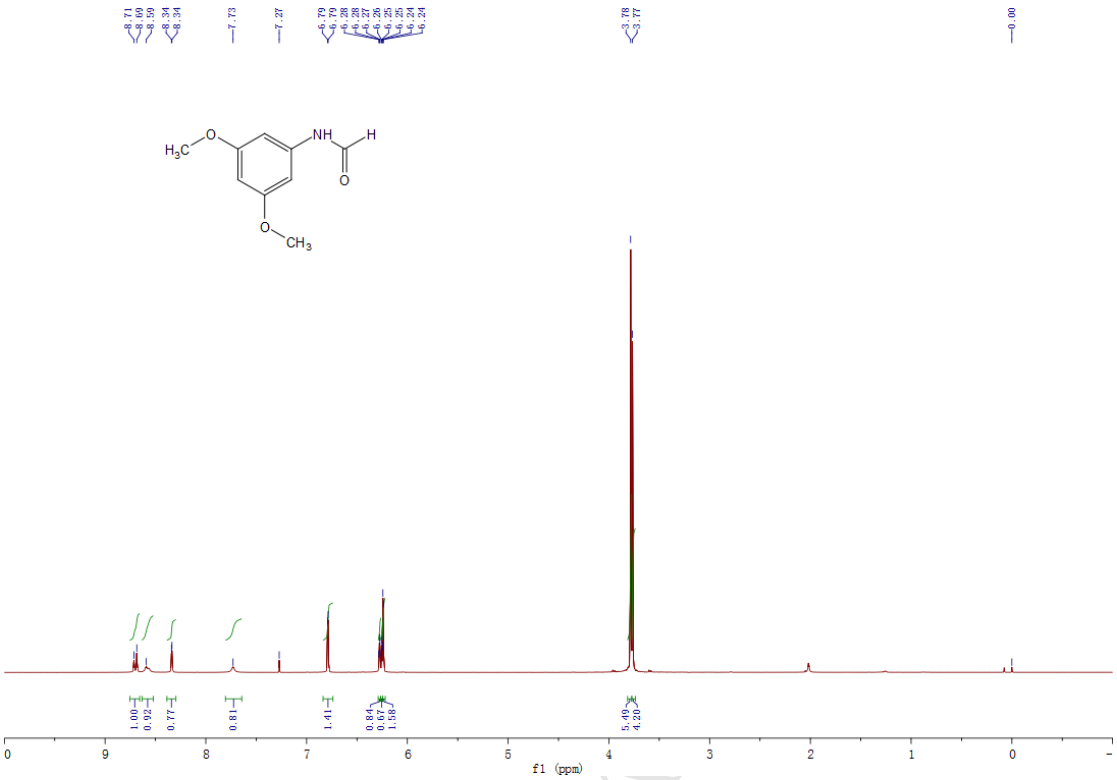
123.21
121.17
120.56
116.74
111.39
110.15
77.48
77.16
76.84
55.83
H3C
O
NH
H
O
180
160
140
120
100
80
60
40
20
0
f1 (ppm)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6.79
6.28
6.27
6.26
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6.24
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3.77
0.00
H3C
O
NH
H
O
O
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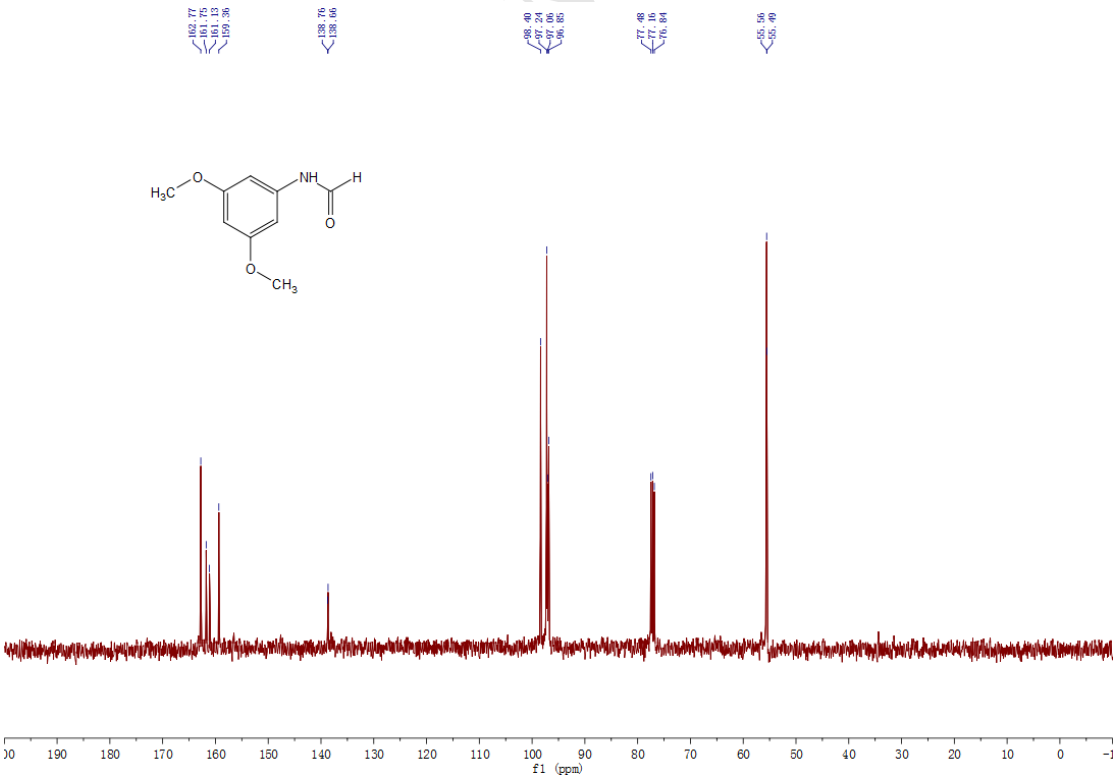
4.20
f1 (ppm)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97.24
97.06
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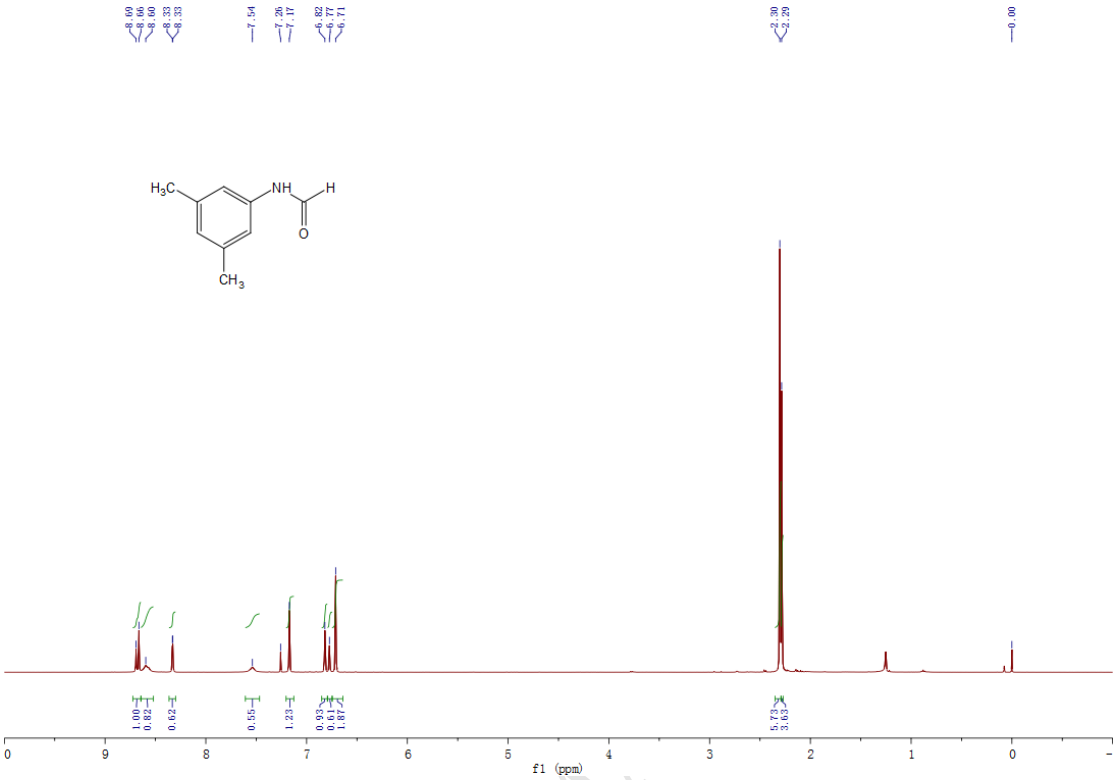
77.48
77.16
76.84
55.56
55.49
H3C
O
NH
H
O
O
CH3
f1 (ppm)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6.71
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2.29
0.00
H3C
NH
H
O
CH3
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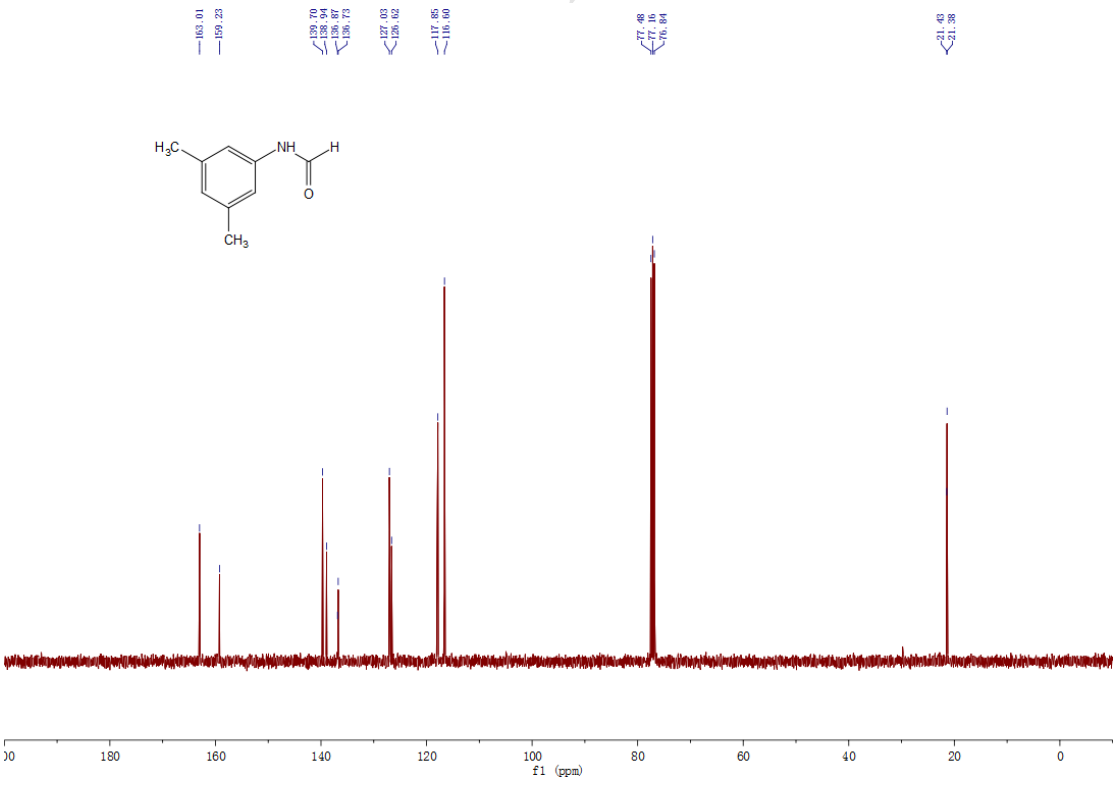
0.62
0.55
1.23
0.93
0.61
1.87
5.73
3.63
f1 (ppm)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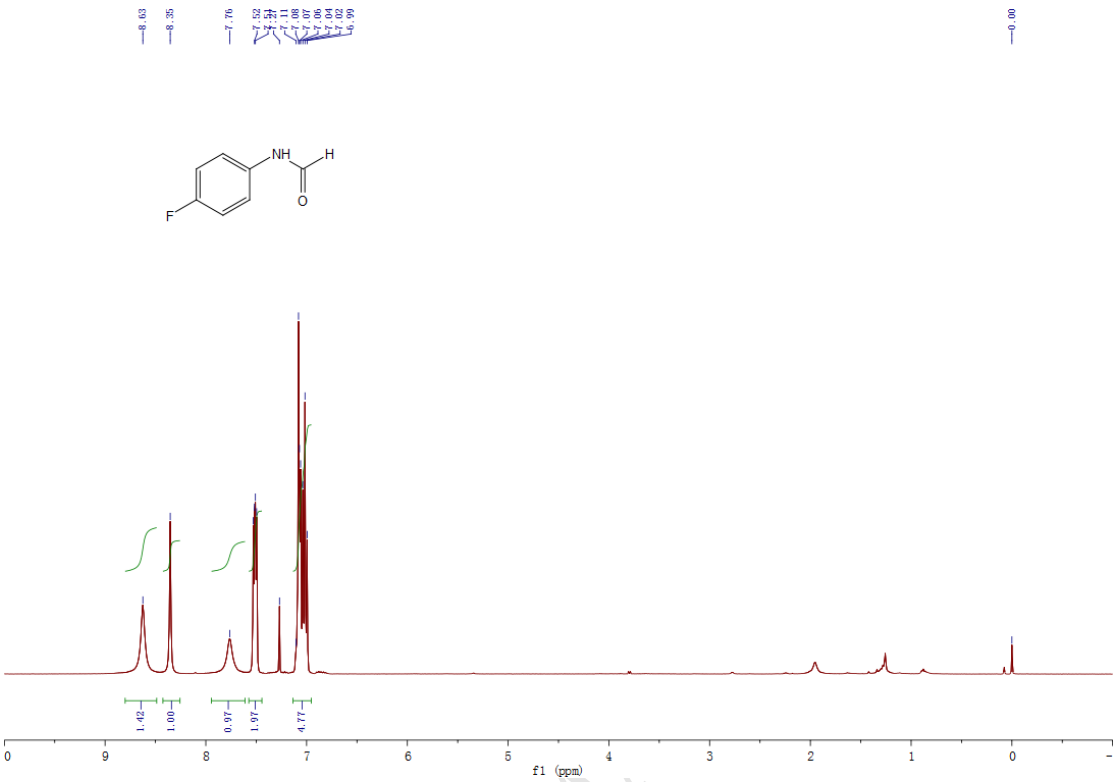
77.48
77.16
76.84
21.43
21.38
H3C
NH
H
O
CH3
f1 (ppm)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7.11
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7.07
7.06
7.04
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NH
H
O
F
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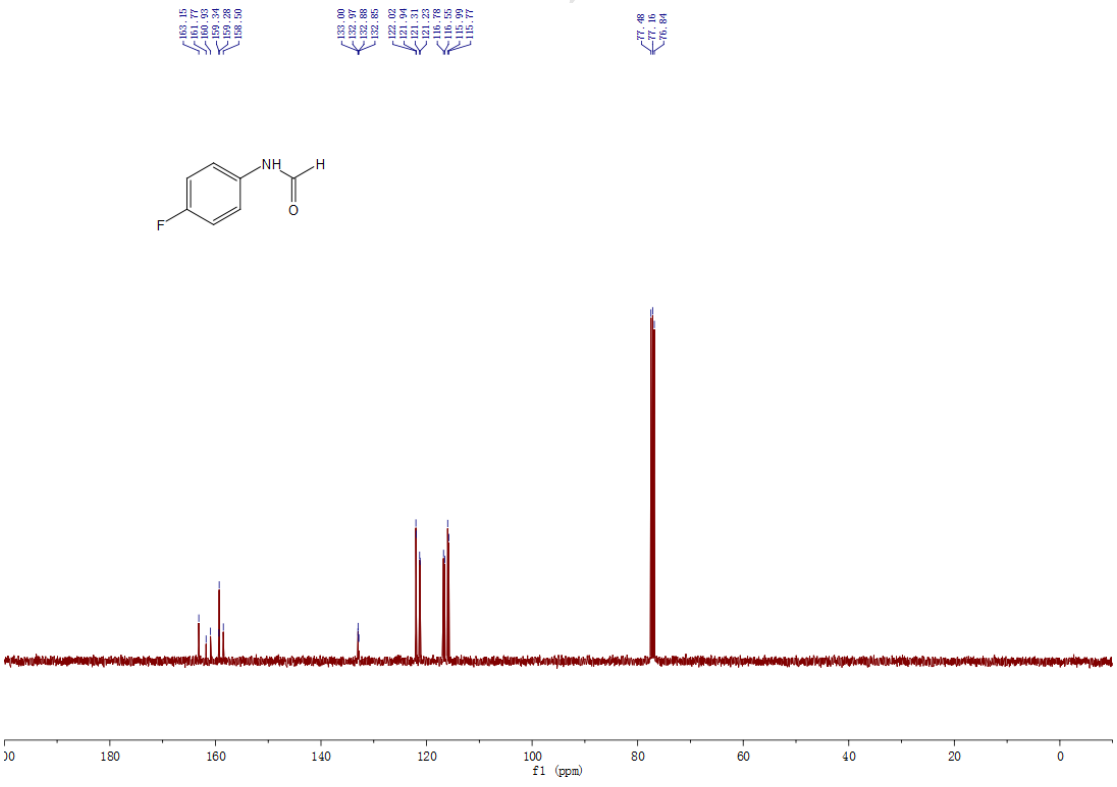
1.97
4.77
f1 (ppm)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122.02
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121.31
121.23
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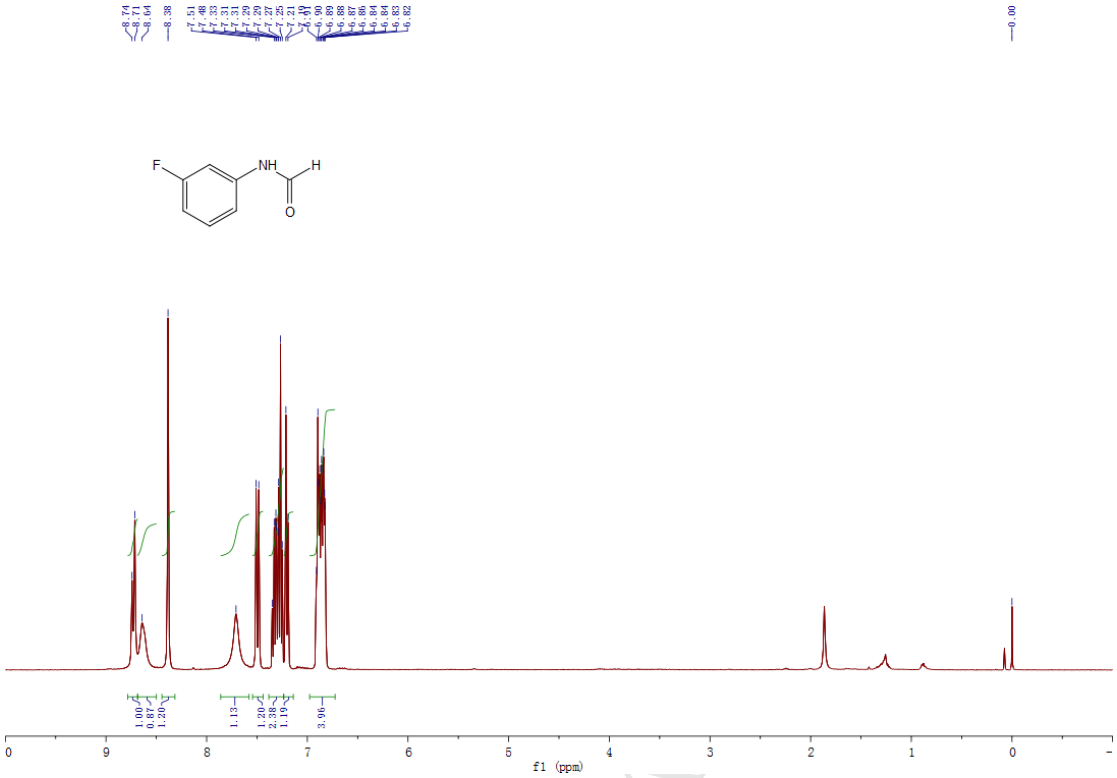
116.55
115.99
115.77
77.48
77.16
76.84
NH
H
O
F
f1 (ppm)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NH
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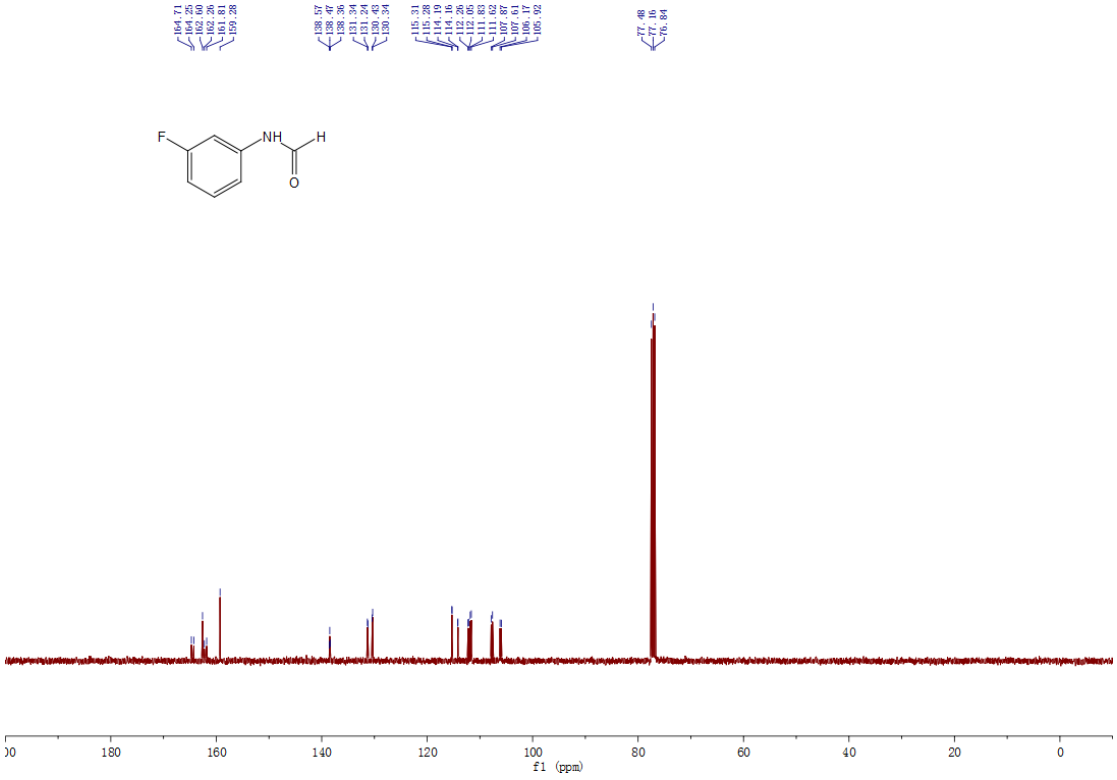
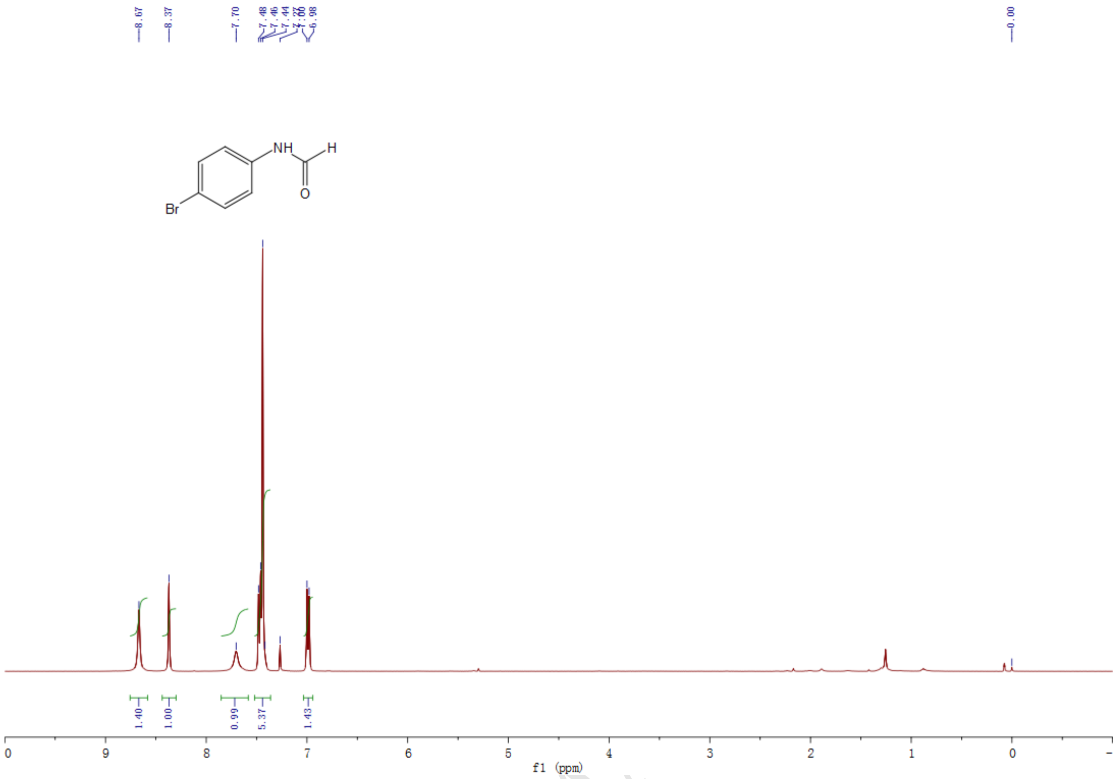
O
f1 (ppm)


F
NH
H
O
f1 (ppm)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O
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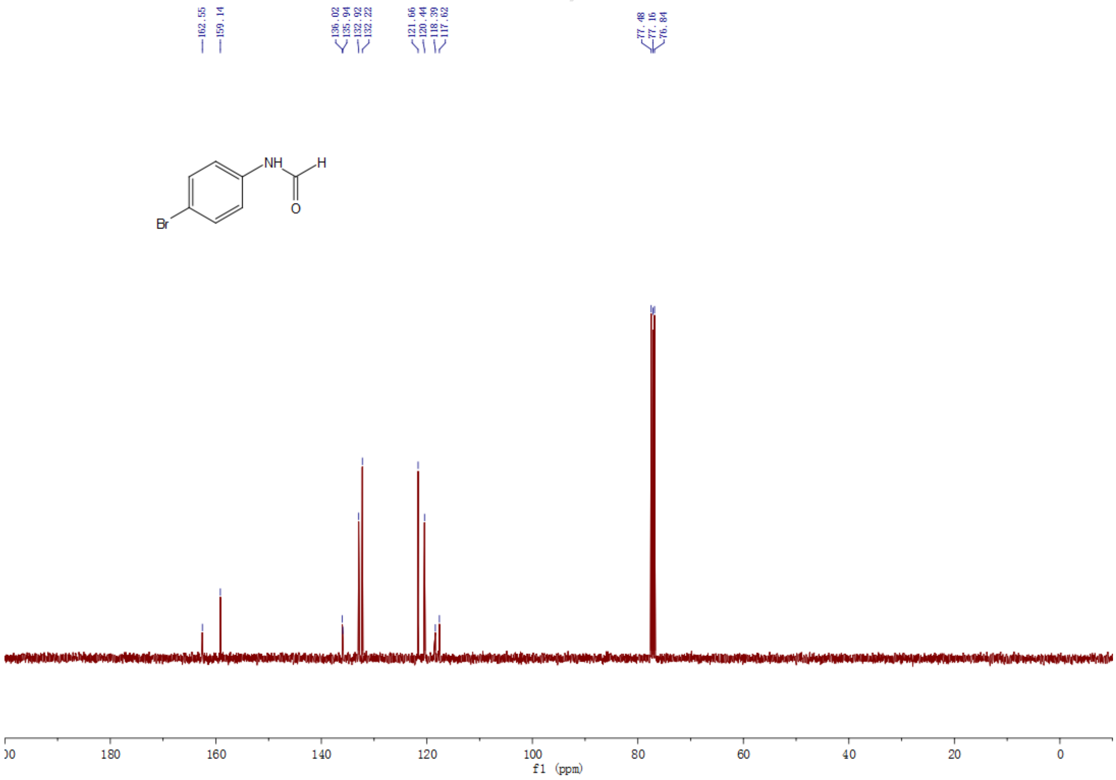
1.43
f1 (ppm)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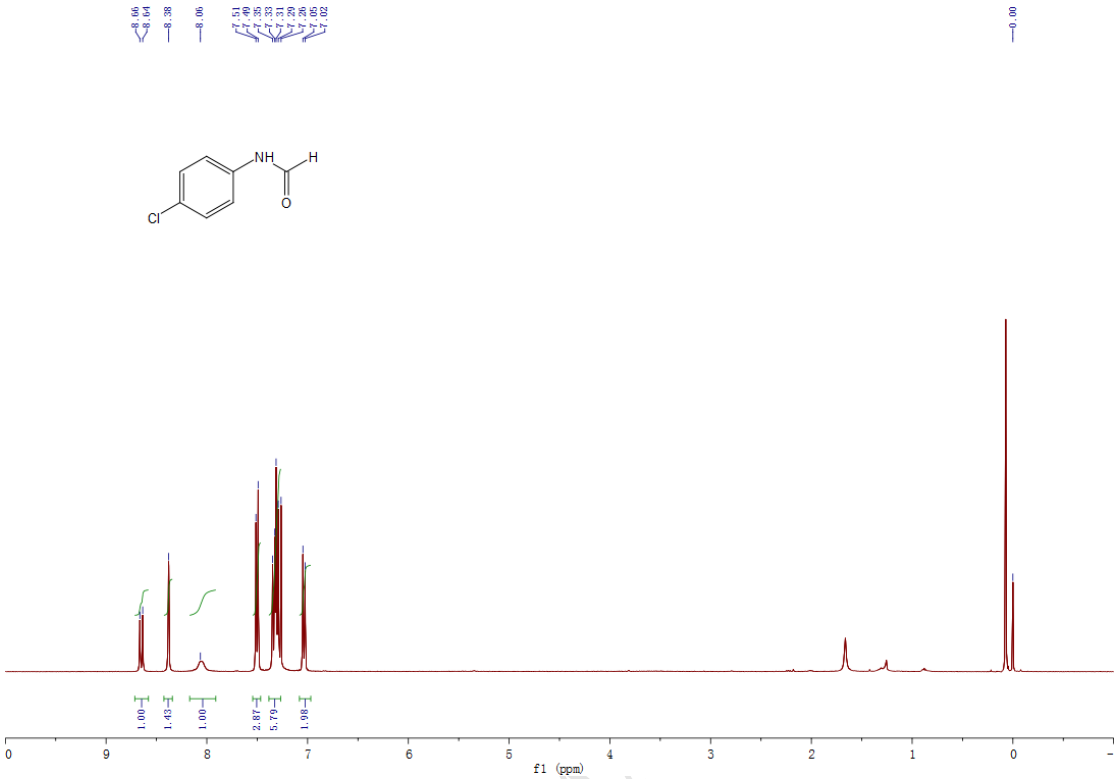
76.84
NH
H
O
Br
f1 (ppm)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7.29
7.26
7.05
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O
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2.87
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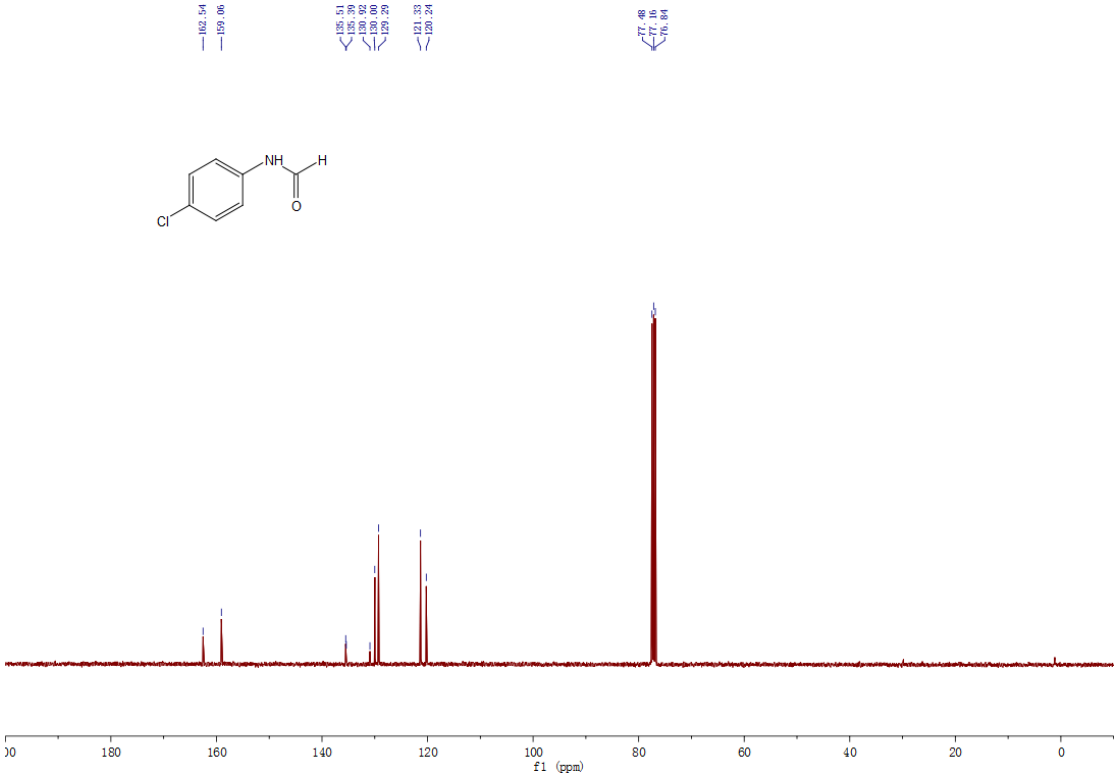
f1 (ppm)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76.84
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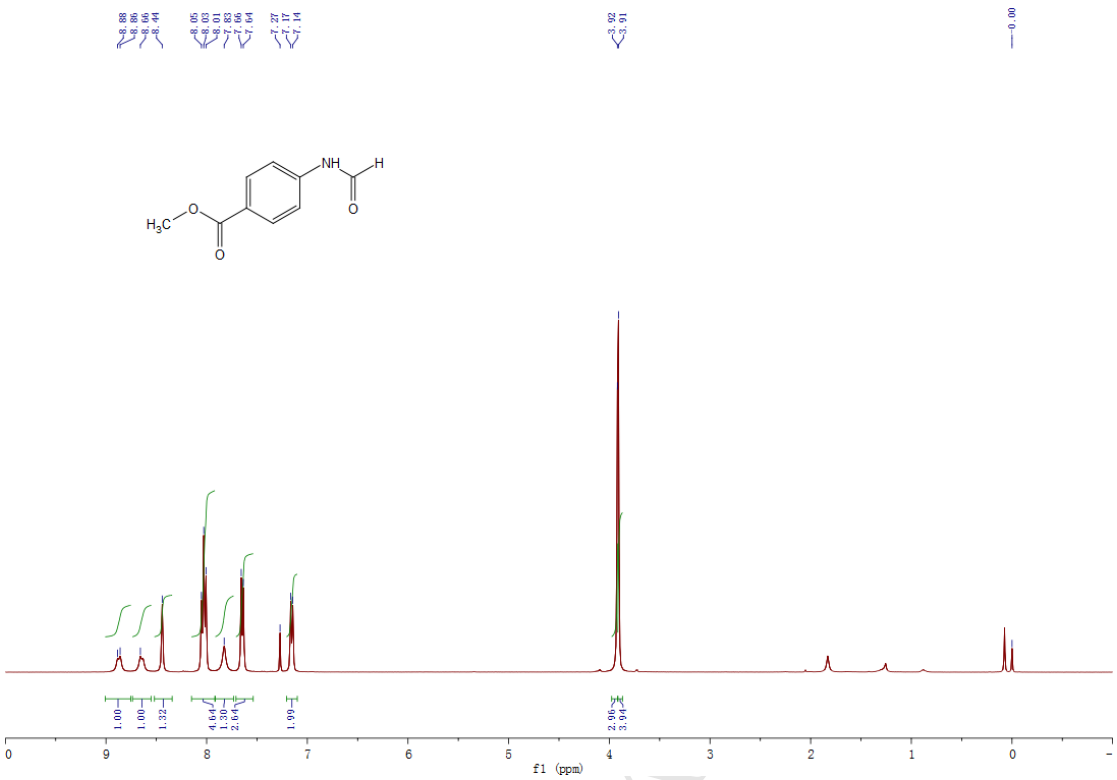
H
O
Cl
f1 (ppm)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8.03
8.01
7.83
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7.64
7.27
7.17
7.14
3.92
3.91
0.00
NH
H
O
H3C
O
O
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1.00
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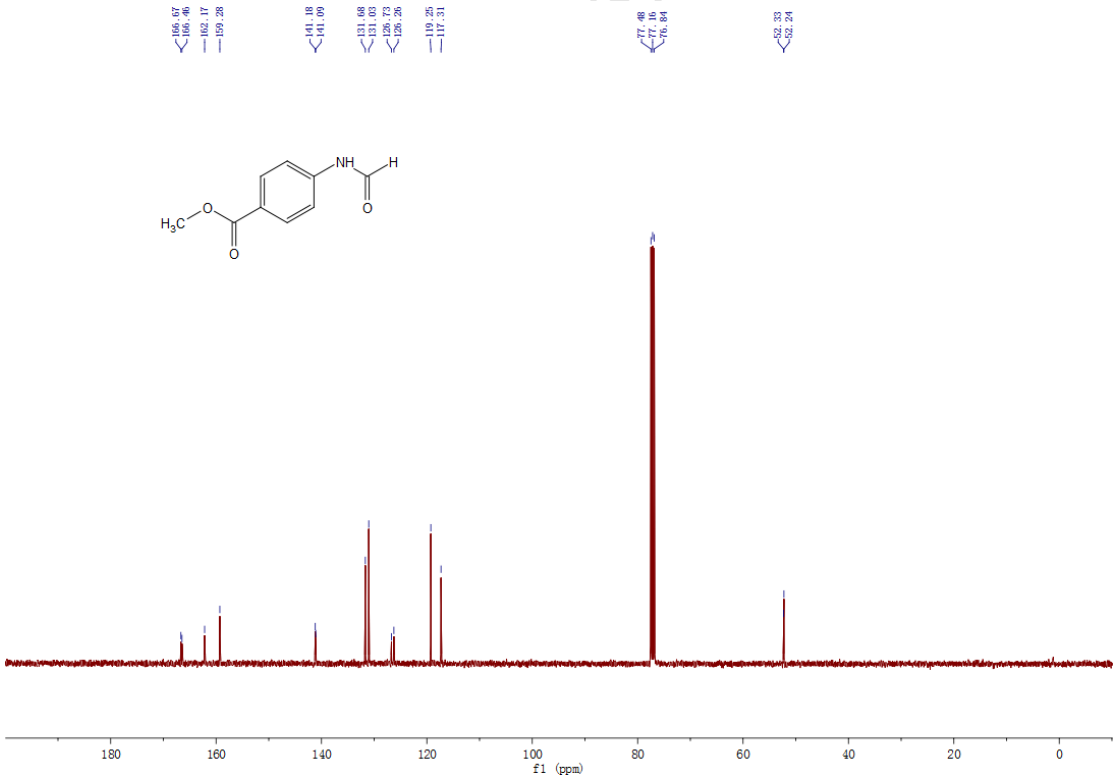
1.99
2.96
3.94
f1 (ppm)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126.26
119.25
117.31
77.48
77.16
76.84
52.33
52.24
NH
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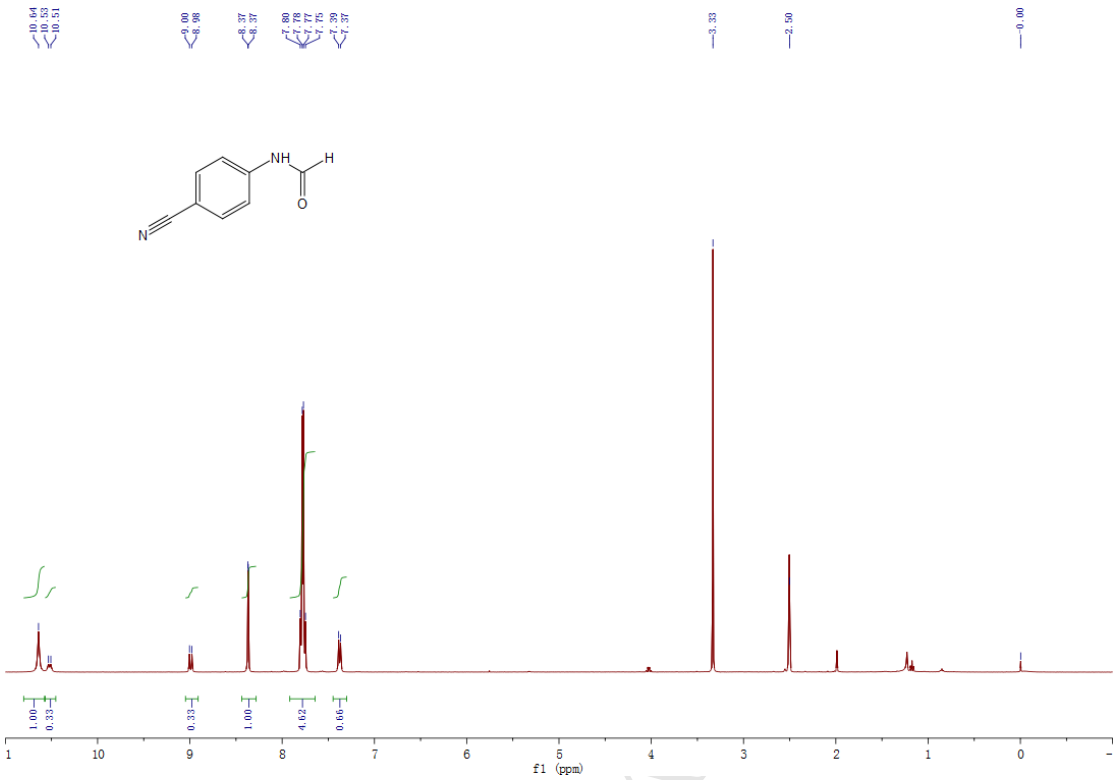
O
H3C
O
O
180
160
140
120
100
80
60
40
20
0
f1 (ppm)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7.75
7.39
7.37
3.33
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H
O
N
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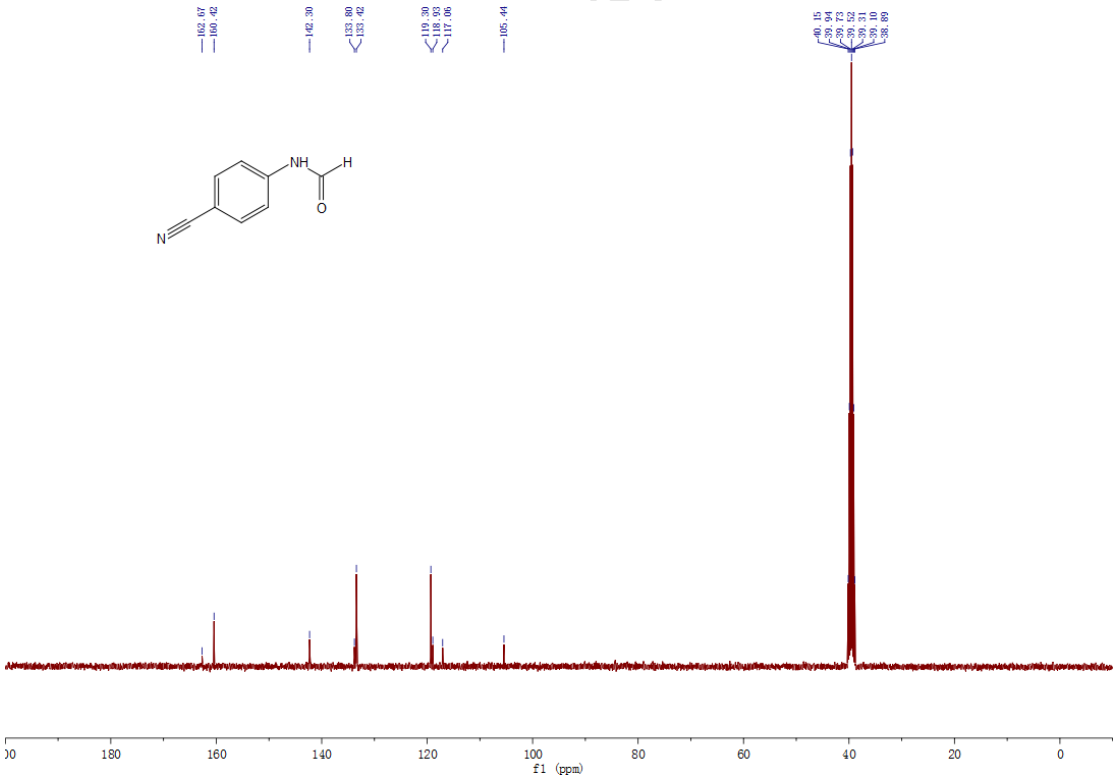
1.00
4.62
0.66
f1 (ppm)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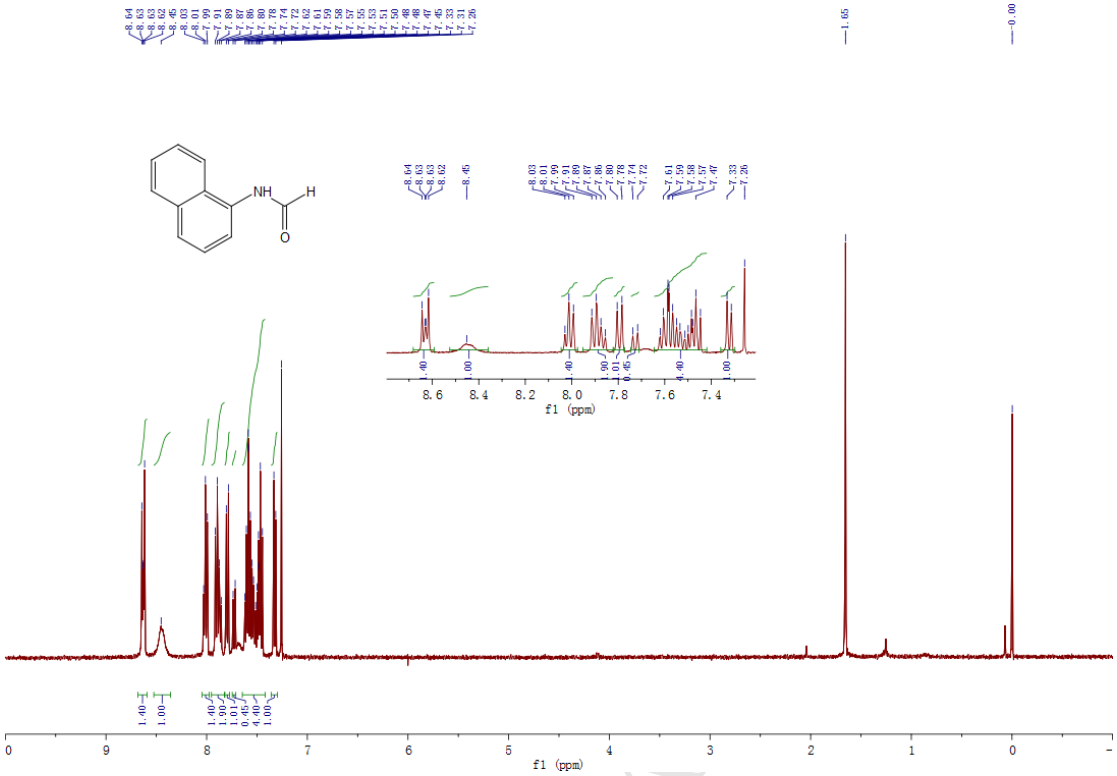
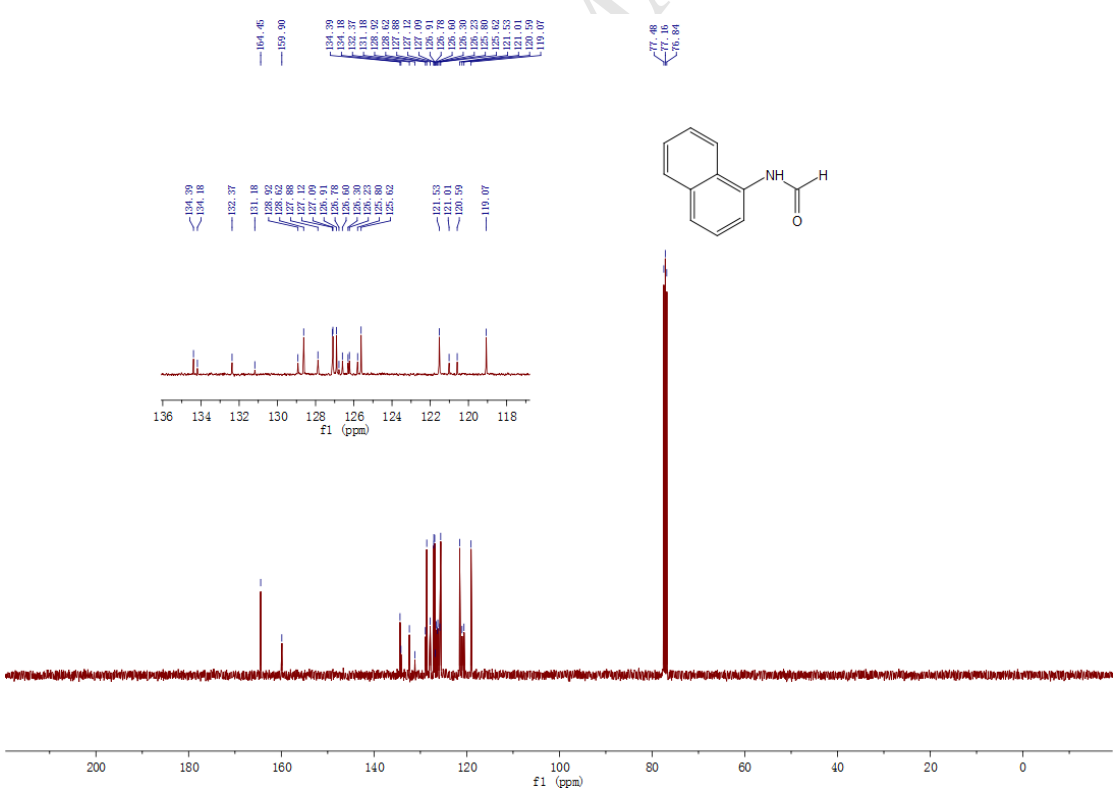
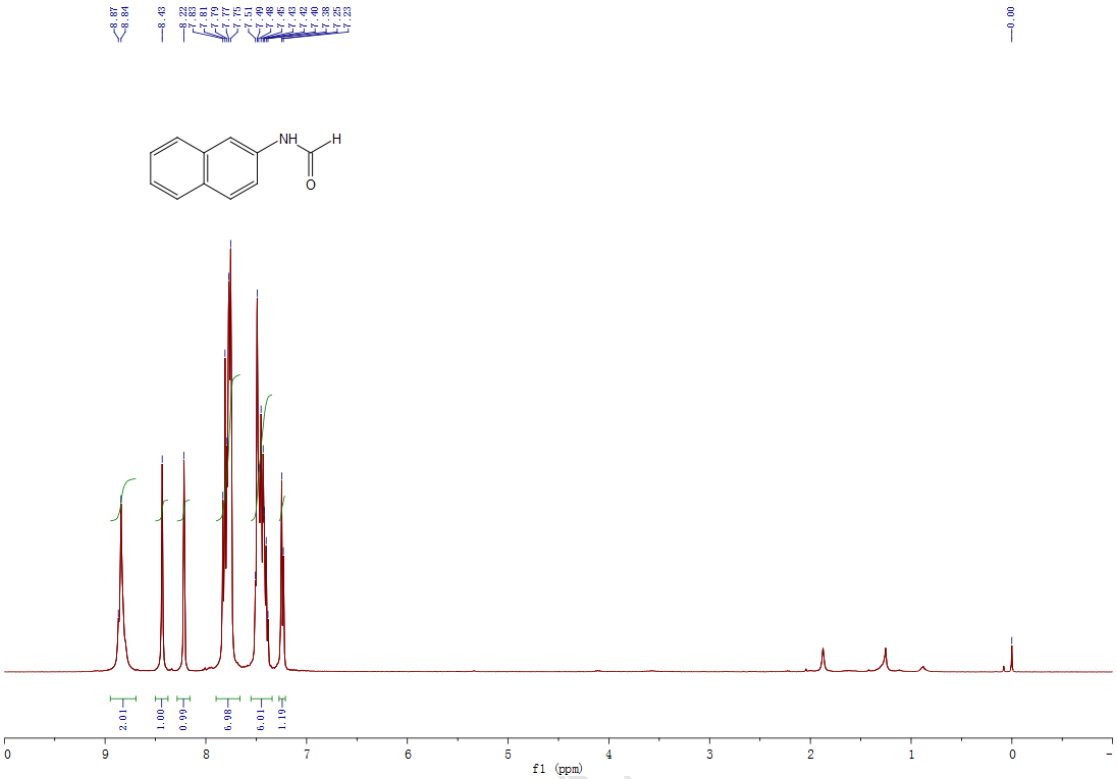
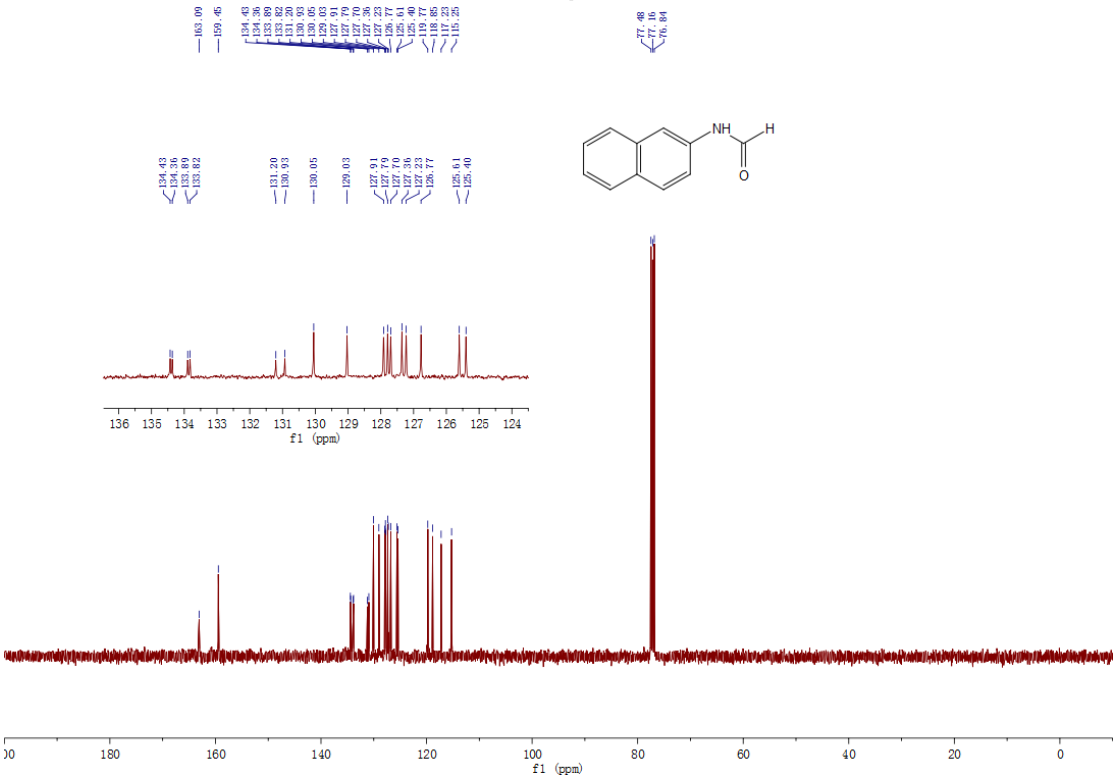
39.31
39.10
38.89
NH
H
O
N
f1 (ppm)

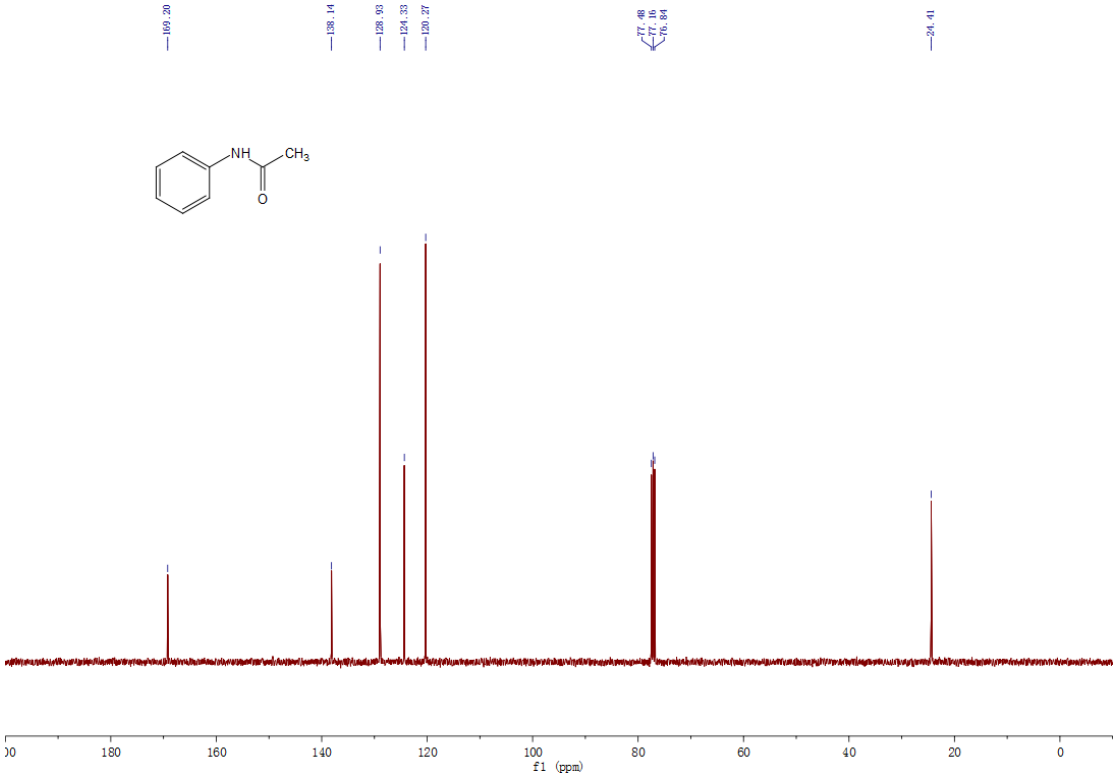

NH
H
O
f1 (ppm)

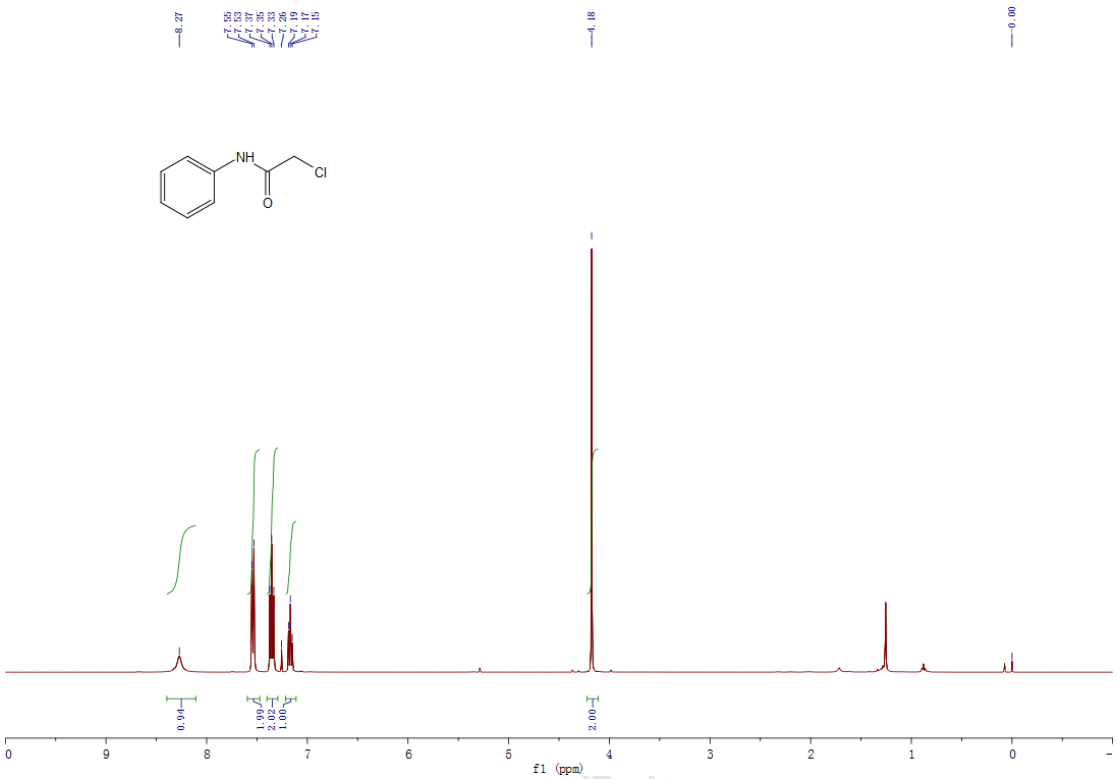

NH
H
O
f1 (ppm)

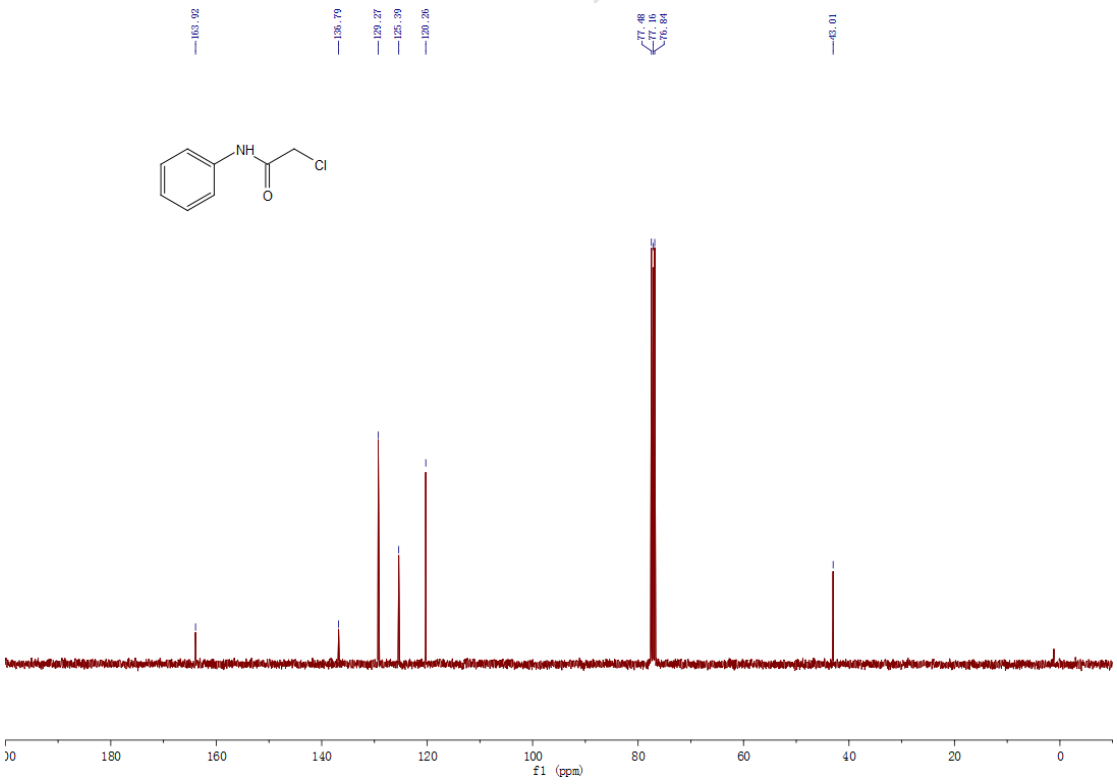

8.87
8.84
8.43
8.22
8.03
7.81
7.79
7.77
7.75
7.51
7.49
7.48
7.46
7.43
7.42
7.40
7.38
7.35
7.23
0.00
NH
H
O
2.01
1.00
0.99
6.98
6.01
1.19
f1 (ppm)


163.09
159.45
134.43
134.36
133.89
133.82
131.20
130.93
130.05
129.03
127.91
127.79
127.70
127.36
127.23
126.77
125.61
125.40
119.77
118.85
117.23
115.25
77.48
77.16
76.84
NH
H
O
136 135 134 133 132 131 130 129 128 127 126 125 124
f1 (ppm)
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


8.34
7.52
7.50
7.29
7.27
7.26
7.10
7.08
7.06
2.13
0.00
NH
CH3
O
0.99
1.97
2.01
1.02
3.00
f1 (ppm)


169.20
138.14
128.93
124.33
120.27
77.48
77.16
76.84
24.41
NH
CH3
O
f1 (ppm)


8.27
7.55
7.53
7.37
7.35
7.33
7.26
7.19
7.17
7.15
4.18
0.00
NH
Cl
O
0.94
1.99
2.02
1.00
2.00
f1 (ppm)


163.92
136.79
129.27
125.39
120.26
77.48
77.16
76.84
43.01
NH
Cl
O
f1 (ppm)