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The Chemoselective and Regioselective Hydroxylation or Chlorination onto The Aryl Ring of N-(4-Substituted-Aryl) Nitrones. Preparation of 2-Aminophenols by Regiospecific Ortho-Hydroxylation

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This paper is dedicated to late Professor Henriette Riviere of French CNRS.

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Abstract

N-(substituted-aryl) Nitrones, in the reactions with a chlorinating reagent such as trichloroacetyl chloride, oxalyl chloride, or thionyl chloride, produce a hydroxylation or a chlorination onto the aryl ring of the aryl nitrones. The chemo-selectivity and the region selectivity (hydroxylation or chlorination) depend largely on the nature of chlorinating reagent and on that of the 4-substituent in the aryl ring of the aryl nitrones. This work provides a novel synthetic route to important intermediates: 2-aminophenols, 2-chloroanilines and 3-chloroanilines which are important industrial intermediates for pharmaceutical products (API), for azo-dye ingredients and for agricultural products.

Keywords: Chemoselectivity; Arylnitrones; Chemoselectivity; Meta-Chlorination; Ortho-Hydroxylation; Regioselectivity

Introduction

Nitrones are emerging chemicals belonging to an important class of synthetic intermediates. They are used in the reactions of 1, 3 dipolar cycloadditions. They are important synthons for the synthesis of 5-membered heterocyclic rings [1,2]. Nitrones possess high reactivity towards nucleophiles to form useful compounds of general importance [3-7]. In addition to the aforementioned ability of forming heterocyclic rings and the reactivity towards nucleophiles, aryl nitrones have another utility in that they can be served as a synthon for the introduction of ortho-hydroxylation, ortho-chlorination or meta-chlorination to the aryl ring by the action of an acid chloride or thionyl chloride. Arylnitrone compounds lend themselves to being very useful for that purpose. The final results of the ortho-hydroxylation, the ortho-chlorination or the meta-chlorination to the aromatic ring may be considered as

a nucleophilic aromatic substitution. In order to gain some insight of these substitution reactions, we embarked in an investigation of the reactions between N-(4-substituted-phenyl) Nitrones and different chlorinating reagents. For this work, we chose three chlorinating reagents: trichloroacetyl chloride, oxalyl chloride, and thionyl chloride, and selected N-(4-substituted-aryl) Nitrones with a variety of 4- substituents: activating group and deactivating group.

The rationale behind this investigation is the expectation that under the action of different chlorinating reagents to the different N-(4-substituted-aryl) nitrone compounds, the results of the reaction products would offer us the information about what products would form: hydroxylated or chlorinated anilines, and that about at what position of the aryl ring where the substitution would take place. The success of the accomplishment of this project would provide to us the information relating to the influence of (1) the nature of the 4-substituent in the aryl ring of the aryl nitrones: (activating or deactivating group), and (2) that of the chlorinating

reagents on the outcome of the final products (hydroxylated or chlorinated anilines) and the position of the substitution [8-13].

Results and Discussion

Our work began with the preparation of different N-(4-substituted-aryl) Nitrones as depicted in Figure 1 whereas R is chosen from activating groups (such as CH_3O , $\text{C}_2\text{H}_5\text{O}$, and CH_3) or deactivating groups (such as F, Cl, and Br).

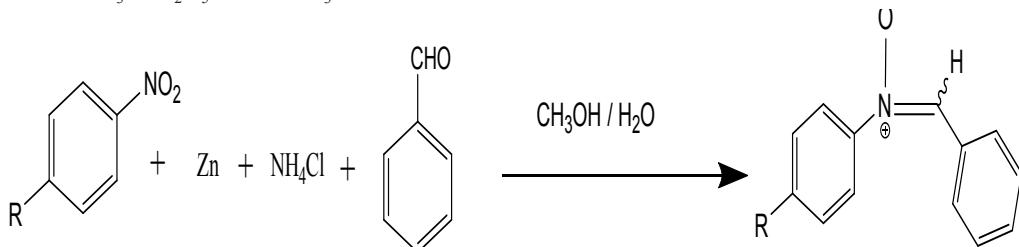


Figure 1: Preparation of N-(4-substituted-aryl) nitrone compounds.

The aryl nitrones were prepared from 4-substituted-nitrobenzene, zinc powder, ammonium chloride and benzaldehyde in a mixture of solvents comprising methanol and water. The yields of the prepared Nitrones are, in general, good to excellent. We submitted each of the synthesized Nitrones to a chlorinating reagent (trichloroacetyl chloride, oxalyl chloride or thionyl chloride) in dichloromethane or in THF at room temperature for two hours. The resulting intermediate was hydrolyzed by concentrated hydrochloric acid. The amino-products resulted from these reactions of the N-(4-substituted-aryl) Nitrones with each of the three chlorinating agents were given in the (Table 1, 2).

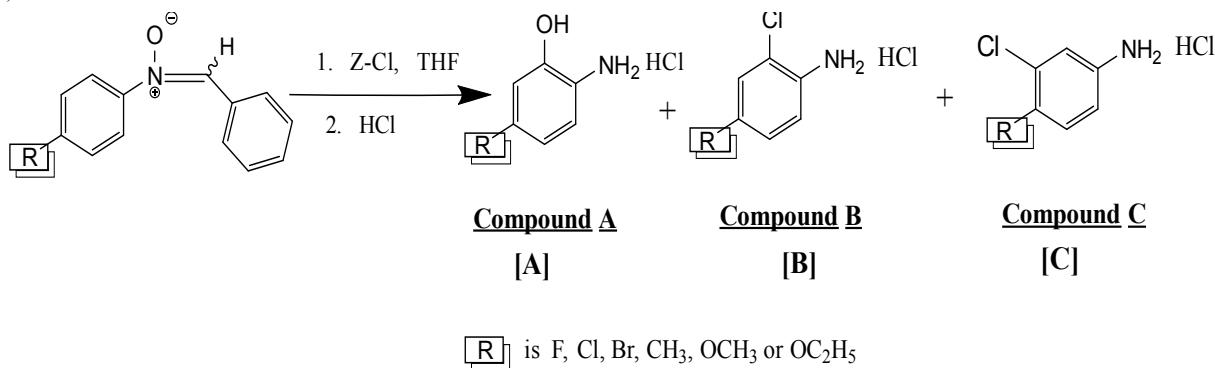


Figure 2: Action of CCl_3COCl , ClCOCOCl or ClSOCl upon an aryl nitrone.

Z-Cl	Trichloroacetyl chloride			Oxalyl chloride		Thionyl chloride	
	R	Entry	Yield [%] of Compound [A]1,2	Entry	Yield [%] of Compound [A]1,2,2	Entry	Yield [%] of Compound [B]3
F		1a	18.3	1b	19.2	1c	38.5
Cl		2a	25	2b	27.2	2c	40.3
Br		3a	29.7	3b	36.1	3c	41.2
CH_3		4a	50.9	4b	60.7	4c	56.7

1 Isolated yield, not optimized. No compounds [B] and [C] were found in HPLC. 2 Isolated yield, not optimized. No compounds [B] and [C] were found in HPLC. 3 Isolated yield, not optimized. No compounds [A] and [C] were found in HPLC.

Table 1: Amino-products produced by the reaction of different chlorinating reagents on N-(4-substituted-phenyl) Nitrones.

Z-Cl	Trichloroacetyl chloride			Oxalyl chloride			Thionyl chloride					
	% of [A], [B] and [C] in the mixture [§]			% of [A], [B] and [C] in the mixture [§]			% of [B] and [C] in the mixture [§] 1					
Entry	Cpd [A]	Cpd [B]	Cpd [C]	Entry	Cpd [A]	Cpd [B]	Cpd [C]	Entry	Cpd [A]	Cpd [B]	Cpd [C]	
CH ₃ O	5a	23.80%	30.70%	45.50%	5b	2.50%	7.80%	89.7%2	5c	0	65.80%	23%
C ₂ H ₅ O	6a	10.80%	44.60%	44.60%	6b	0	0	100% 3	6c	0	84.40%	15.60%

[§] Compounds found in the mixture, identified with purchased authentic samples. Percentages determined by HPLC and ¹H NMR. 1 This mixture contained 11% of 4-R-aniline; 2 isolated yield: 38.5%; 3 isolated yield: 38.5%.

Table 2: Amino-products produced by the reaction of different chlorinating reagents on N-(4-alkoxyphenyl) Nitrones.

A number of important generalizations emerge from the data in Tables 1,2. First, when the substituted group R in N-(4-substituted-aryl) Nitrones was a deactivating group such as F, Cl, Br or a moderate activating group such as CH₃, the reactions of arylnitrones with chlorinating reagents (trichloroacetyl chloride or oxalyl chloride) gave rise chemo specifically and region specifically to ortho-hydroxylated aniline products: 5-R-2-aminophenols (compounds A) [Entries 1a, 1b; 2a, 2b; 3a, 3b; and 4a, 4b]. It is well known that the direct nucleophilic aromatic substitution with (OH)⁻ to make phenol compounds was achieved under harsh conditions: high pressure and high temperature (ca 350°C) [14]. The formation of the phenol compounds, via the nitrone route, is accomplished under much milder conditions [room temperature,

no pressure, and short reaction time]. The ortho-hydroxylation via nitrone methodology could offer a novel route to important intermediates: ortho-amino-phenols [15] (Figure 3). It is also noteworthy that while with moderate activating group (CH₃), the isolated yield of ortho-hydroxylation products (compound [A]) is good (60.7%) [4b], the isolated yields of ortho-hydroxylation products (compound [A]) with the deactivating groups (such as F, Cl or Br) are low (less than 36.1%) [for example: 3b]. It is worth mentioning that the traditional method of making 2-aminophenols by the nitration of the starting phenol compounds, followed by the hydrogenation of the nitro group. However, the nitration always leads to a mixture of the ortho and para nitrophenos, and the separation of these two isomers are tedious [16].

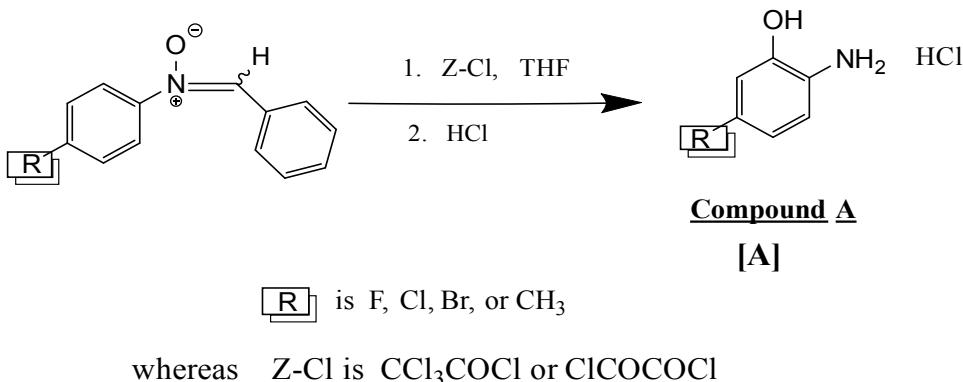


Figure 3: Regiospecific ortho-hydroxylation: Preparation of ortho-aminophenol compounds.

Second, when the substituted group R in N-(4-substituted-aryl) nitrone was a strong activating group such as OCH₃ or OC₂H₅, the reactions with chlorinating reagents: oxalyl chloride and trichloroacetyl chloride failed to produce chemo specifically ortho-hydroxylated products. Instead, a mixture of three products was produced: one major product: 3-chloro-4-alkoxyaniline (compound [C]), accompanied with two minor products: 2-chloro-4-alkoxyaniline (compound [B]) and 5-alkoxy-2-aminophenol (compound [A]). It is noteworthy that (1) based on the analysis by

HPLC and ¹H NMR, the order of the magnitude of the percentage of three compounds in the mixture is [C] ≥ [B] > [A] for the reaction of N-(4-alkoxy-aryl)nitrone with chlorinating reagents: trichloroacetyl chloride and oxalyl chloride (entries 5a, 5b, 6a and 6b); and (2) the reaction with oxalyl chloride offered higher percentage of [C] than that with trichloroacetyl chloride (entries 5b versus 5a, and 6b versus 6a); and (3) in the case with a stronger activating group (example: R group is C₂H₅O), the reaction with oxalyl chloride offered chemo specifically and region specifically 3-chloro-4-

ethoxy-aniline (Entry 6b, Compound [C]), and no minor products: [A] and [B] were detected. From the commercial standpoint, 3-chloro-4-ethoxyaniline and 3-chloro-4-methoxyaniline are expensive chemicals. They are valuable intermediates, especially for the dye industry [17-19]. It is remarkable that in any event there is no hydroxylation substitution taken place at the 3-position on the phenyl ring. Third, when the substituted group R in the N-(substituted-aryl) Nitrones is a deactivating group such as F, Cl, Br or moderate activating group such as CH_3 , the reactions with thionyl chloride gave rise exclusively to ortho-chlorinated products: 2-chloro-4-halo-anilines [B] (entries 1c, 2c, and 3c) or 2-chloro-4-methyl-anilines [B] (entry 4c). Finally, when the substituted group R in the N-(4-alkoxy-aryl) nitrone is a strong activating group such as OCH_3 or OC_2H_5 , the reactions with thionyl chloride gave rise to a mixture of two products: a major product: 2-chloro-4-alkoxyanilines, (compound [B]) [entries 5c and 6c] which were accompanied by a minor product 3-chloro-4-alkoxy-aniline (compounds [C]) [entries 5c and 6c]. There is no compound [A] produced in the reaction with thionyl chloride. It is worth mentioning that the ratio of the percentage of two isomers: [B] and [C] depended largely on the electronic donating strength of the activating group on the aryl ring. The stronger the activating group was, the higher the ratio [B] over [C] (entries 6c versus 5c) resulted. The compounds produced by these reactions are Important Industrial Intermediates for Pharmaceutical products (API), for azo-dye ingredients and for agricultural products.

In terms of plausible mechanism, we postulate that the first step would be the nucleophilic attack of the negatively charged oxygen atom of the nitrone compound to the acid chloride (trichloroacetyl chloride, oxalyl chloride or thionyl chloride) giving rise to the intermediate I (Figure 4,5). The formation of intermediate I was followed by a possible cyclic six-membered transition state, and a nucleophilic aromatic substitution by oxygen atom leading to the intermediate II (oxygenation in the aromatic ring, as shown in Figure 4) or by chlorine atom leading to the intermediate II-a (chlorination in the aromatic ring, as shown in Figure 5). The following step was the hydrogen transfer step with the re-aromatization leading to the ortho-substituted intermediate III or III-a. The subsequent hydrolysis of the intermediate III offers the final product: ortho-aminophenol (Figure 4), and that of the intermediate III-a offers the final product: 2-chloroaniline (Figure 5).

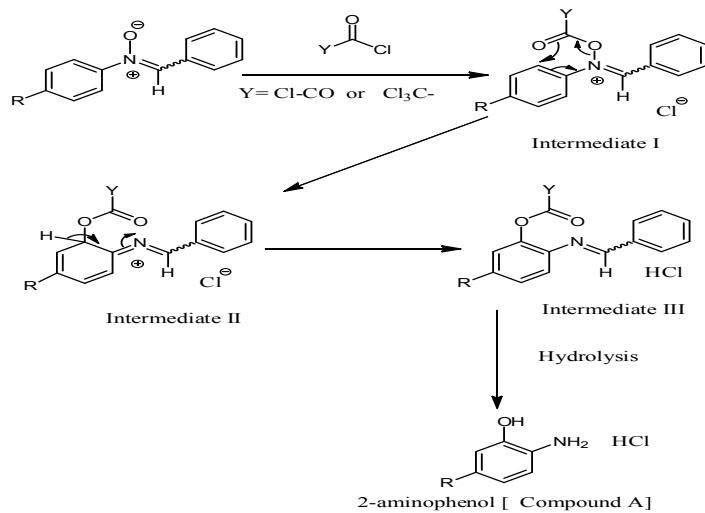


Figure 4: Reaction of carboxylic acid chloride with aryl nitrone.

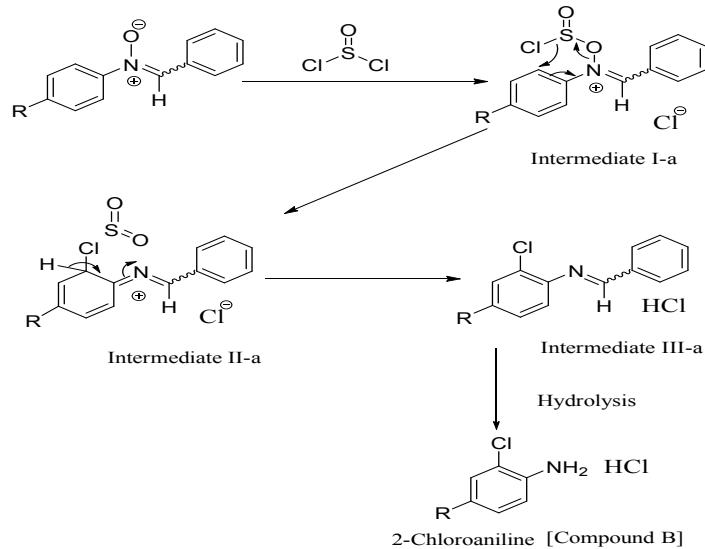


Figure 5: Reaction of thionyl chloride with aryl nitrone.

When the substituted group R in N-(4-substituted-aryl) nitrones is a deactivating group such as F, Cl, Br or a moderate activating group such as CH_3 , the reaction of Nitrones with an acid chloride (trichloroacetyl chloride or oxalyl chloride) gave rise

chemo specifically and region specifically to the ortho-hydroxylated amino-products: 5-R-2-aminophenols (Compound [A]). Likewise, the action of thionyl chloride offered chemo specifically and region specifically 5-R-2-chloroanilines (Compound [B]). Nonetheless, when the substituted group R in N-(4-substituted-aryl) nitrone is a strong activating group such as OCH_3 or OC_2H_5 , the reaction of nitrones with acid chlorides (trichloroacetyl chloride or oxalyl chloride) gave a mixture of three compounds in which the major product is [C] and the minor products are [A] and [B]. Likewise, with thionyl chloride, the reaction offered a mixture of two chlorinated anilines. The formation of this unexpected 3-chloro-4-alkoxyanilines from these reaction, has not been previously reported in the literature. While the six-membered ring mechanism explains well the formation of the ortho-substituted products, it could not, however, account for the formation of 3-chlorinated product: 3-chloro-4-alkoxyaniline (compound C). Other pathways leading to these two compounds could be account for their formation.

Conclusion

The reaction of N-(4-substituted-aryl) Nitrones with chlorinating reagents such as trichloroacetyl chloride, oxalyl chloride, or thionyl chloride produced a hydroxylation or a chlorination to the aryl ring of the nitrone compounds. The chemoselective and the regioselective hydroxylation or chlorination to the ring depend largely on the nature of chlorinating reagents and on that of the 4-substituent in the aryl ring. When the substituted group R in the aryl ring is a deactivating group such as F, Cl, Br or a moderate activating group such as CH_3 , the reactions of Nitrones with trichloroacetyl chloride or oxalyl chloride gave rise chemo selectively and region specifically to ortho-hydroxylated amino-products: 5-R-2 amino-phenols (compound [A]). The reported methodology, via nitrone intermediate, provides a novel synthetic route to the preparation of the valuable ortho-aminophenol compounds. Ortho-aminophenol compounds are important industrial intermediates for pharmaceutical products (API), for azo-dye industrial ingredients and for agricultural products. Likewise, the same reactions with thionyl chloride offered chemo specifically and region specifically 5-R-2-chloroanilines (compound [B]). Nonetheless, when the substituted group R in N-(4-substituted-aryl) nitrone is a strong activating group such as OCH_3 or OC_2H_5 groups, the aforementioned chemo specificity and region specificity did not occur in the reactions of arylnitrones with chlorinating reagents (trichloroacetyl chloride, oxalyl chloride or thionyl chloride).

Supporting Information

Detailed description of the full experiments including ^1H & ^{13}C NMR and HRMS were given in the supporting information section

Part One: Experimental details for the preparation of Compounds

a. General

^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker AV III 400 spectrometer (400MHz). The chemical shifts were reported in ppm relative to Me_4Si as internal standard. Mass spectra were obtained with a Waters Xevo G2 QT of mass spectrometer. Thin Layer Chromatography (TLC) on pre-coated plates with silica gel F254, purchased from Qingdao Haiyang Chemical Co. Ltd., was employed to monitor the progress of the reaction. Dichloromethane was purchased from Beijing Chemical Works and dried over molecular sieves 4 \AA before use. Ethanol was purchased from Beijing Chemical Works and dried over molecular sieves 4 \AA before use. All reagents of analytical grade were purchased from Sigma-Aldrich, Beijing Inno-Chem Co. Ltd., Alfa Aesar, Beijing Chemical Works, and other commercial sources. They were used without further purification. All reactions were carried out in oven-dried glassware. Dried nitrogen was used to purge the reactor and all the glass apparatus before the reaction and to protect the reaction during the entire operation

b. General method of preparation of arylnitrone compounds

➤ N-(4-Ethoxyphenyl)-1-Phenylethan-1-Imine Oxide

To an oven dried 100-mL, three-necked, round-bottomed flask equipped with a thermometer, a reflux condenser fitted with a T-joint inlet, glass stoppers and a Teflon coated magnetic stirring bar were charged with 4-ethoxynitrobenzene (8.36g, 0.05mol, 1equiv.), 50mL of methanol, and benzaldehyde (5.84g, 0.055 mol, 1.1 equiv.) dissolved in 30mL of methanol. The mixture was stirred until a completed solution was obtained. Zinc powder (6.54g, 0.10mol) was added, followed by 20 mL of methanol. The reaction mixture was cooled to 0°C. A solution of NH_4Cl (10.7g, 0.2mol) dissolved in 40 mL of water was added dropwise into the reaction mixture. During the addition, the reaction temperature was kept between 0°C to 5°C. After the addition, has been completed, the reaction was stirred for 0.5 h between 0°C to 5°C. Then the reaction was allowed to warm up to room temperature. The stirring was continued for 1.5h. The thin layer chromatograph (eluent: ether: petroleum ether = 1:4, v/v) indicated the complete disappearance of nitrobenzene. The reaction was filtered through a sintered glass funnel and the solid in the funnel was thoroughly washed with dichloromethane (2x75mL). The mother filtrate and the washing liquid were combined. The resulting mixture was stirred for 30min and the aqueous phase was separated. After the organic phase, has been washed with water (3x50mL), it was separated from the aqueous phase and dried over anhydrous MgSO_4 . The organic phase was concentrated in vacuo. Petroleum ether was added (50mL) leading to a solid. The solid was collected and washed with

petroleum ether (2x25mL) and dried in vacuo first with a water aspirator and with an oil pump for 12h to yield an off-white solid: 6.17g (51.1%). Mp:139.2-140°C. ¹H NMR (400MHz, CD₃OD): δ =8.50(2H, m), 8.32(1H, s), 7.80(2H, d, J =8.94Hz), 7.54(3H, m), 7.08(2H, d, J =8.94Hz), 4.14(2H, m), 1.44(3H, m). ¹³C NMR (100MHz, CD₃OD): δ =161.90, 142.66, 138.18, 132.72, 131.88, 131.07, 129.71, 124.20, 115.79, 65.12, 15.01 ppm. HRMS (ESI): m/z (M+1)⁺ Calc'd for C₁₅H₁₅NO₂: 242.1182. Found: 242.1182.

➤ **2-Amino-5-Fluorophenol Hydrochloride (Compound 1a [A])**

To an oven dried 50-mL, three-necked, round-bottomed flask equipped with a thermometer, a reflux condenser fitted with a T-joint inlet, glass toppers and a Teflon coated magnetic stirring bar was charged with N-(4-fluoro phenyl)-1-phenylethan-1-imine oxide ((0.43g, 2 mmol, 1 equiv.) and 4 mL of THF. The mixture was stirred for 20 min at room temperature, then cooled to 0°C. Trichloroacetyl chloride (0.40g, 2.2 mmol, 1.1 equiv.) was added dropwise during which the reaction was maintained less than 30°C. After the addition, the reaction was stirred at about 30°C for 30 min. The reaction was allowed to warm up to room temperature, and stirred at room temperature for 2h. TLC analysis (eluent: butyl acetate/ toluene / DCM: 1/2/6 v/v) indicated that the disappearance of nitrone. Concentrated hydrochloric acid (0.5mL, 6mmol, 3 equiv.) was added to the reaction mixture, and the resulting mixture was heated for 4h at ca 72°C. Upon cooling, the reaction was poured with stirring into a mixture of ether (35mL) and petroleum ether (5mL) leading to a dark grey solid which was collected and washed with petroleum ether (2x25mL) and dried in vacuo first with a water aspirator and with an oil pump for 12 h to yield a dark grey solid 0.06g (18.33%). The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample [VWR]. ¹H NMR (400MHz, CD₃OD): δ =7.34(1H, dd, J ₁=8.65Hz, J ₂=5.73Hz), 6.78 (1H, dd, J ₁=9.82Hz, J ₂=2.33Hz), 6.73 (1H, m). ¹³C NMR (100MHz, CD₃OD): δ =165.83, 163.38, 153.85, 126.17, 107.74, 104.65ppm. HRMS (ESI) m/z (M+1)⁺ Calc'd for free amine C₆H₆FNO: 128.0512. Found: 128.0505.

➤ **2-Amino-5-Fluorophenol Hydrochloride (Compound 1b [A])**

Following the general procedure described as above, the title compound was prepared using 4-fluoroarylnitrone (0.43g, 2 mmol), oxalyl chloride (0.30g, 2.2 mmol) and THF (4ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.5mL, 6mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, the reaction was poured with stirring into a mixture of ether (30ml) and dichloromethane (60mL) leading to a dark grey solid. The title compound was obtained as a dark grey solid (0.063g, 19.2%). The obtained product was identified using HPLC analysis by comparison with a purchased authentic purchased sample and with the compound 1a [A].

➤ **2-chloro-4-fluoroaniline hydrochloride (Compound 1c [B])**

The title compound was prepared using 4-fluoroarylnitrone (0.43g, 2 mmol), thionyl chloride (0.29g, 2.4 mmol) and THF (4ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.5mL, 6mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, the reaction was poured with stirring into dichloromethane (50mL) leading to a solid. The title compound was obtained as a green solid (0.14g, 38.5%). The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample. ¹H NMR (400MHz, CD₃OD): δ =7.60(1H, dd, J ₁=9.01Hz, J ₂=3.88Hz), 7.55(1H, dd, J ₁=8.23Hz, J ₂=5.44Hz), 7.31 (1H, m). ¹³C NMR (100MHz, CD₃OD): δ =164.69, 162.20, 130.30, 127.20, 119.36, 117.03ppm. HRMS (ESI) m/z (M+1)⁺ Calc'd for free amine C₆H₅CIFN: 146.0174. Found: 146.0165.

➤ **2-Amino-5-Chlorophenol Hydrochloride (Compound 2a [A])**

The title compound was prepared using 4-chlorophenylnitrone (0.46g, 2 mmol), trichloroacetyl chloride (0.40g, 2.2 mmol) and THF (4ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.5mL, 6mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, the reaction was poured with stirring into dichloromethane (40 ml) leading to a dark grey solid. The title compound was obtained as a light purple solid: (0.09g, 25.0%). The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample. ¹H NMR (400MHz, CD₃OD): δ =7.31(1H, d, J =8.36Hz), 7.05 (1H, d, J =2.14Hz), 6.99(1H, dd, J ₁=8.46Hz, J ₂=2.14Hz). ¹³C NMR (100MHz, CD₃OD): δ =153.24, 136.47, 126.08, 121.06, 117.28 ppm. HRMS (ESI) m/z (M+1)⁺ Calc'd for free amine C₆H₆CINO: 144.0217. Found: 144.0213.

➤ **2-Amino-5-Chlorophenol Hydrochloride (Compound 2b [A])**

The title compound was prepared using 4-chlorophenylnitrone (0.46g, 2 mmol), oxalyl chloride (0.28g, 2.2 mmol) and THF (4ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.5mL, 6mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, the reaction was poured with stirring into dichloromethane (40 ml) leading to a dark grey solid. The title compound was obtained as a light purple solid (0.098g, 27.2%). The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample and with a sample of the compound 2a [A].

➤ **2,4-Dichloroaniline Hydrochloride (Compound 2c [B])**

The title compound was prepared using 4-chlorophenylnitrone (0.43g, 2 mmol), thionyl chloride (0.29g, 2.4 mmol) and THF (4ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.5mL, 6mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, the reaction was poured with stirring into dichloromethane

(100mL) leading to a solid. The title compound was obtained as a pink solid (0.16g, 40.3%). The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample. ^1H NMR (400MHz, CD_3OD): δ =7.66(1H, d, J =2.25Hz), 7.45 (1H, dd, J_1 =8.54Hz, J_2 =2.25Hz), 7.38 (1H, d, J =8.62Hz). ^{13}C NMR (100MHz, CD_3OD): δ =131.20, 129.77, 125.92, 124.96 ppm. HRMS (ESI) m/z (M+1) $^+$ Calc'd for free amine $\text{C}_6\text{H}_5\text{Cl}_2\text{N}$: 161.9878 and 163.9849. Found: 161.9874 and 163.9845.

➤ **2-Amino-5-Bromophenol Hydrochloride (Compound 3a [A])**

The title compound was prepared using N-(4-bromophenyl)-1-phenylethan-1-imine oxide (15g, 54mmol, 1 equiv.), trichloroacetyl chloride (10.91g, 60mmol, 1.1 equiv.) and 50 mL of THF. Acid hydrolysis was conducted with hydrochloric acid (13.5mL, 162mmol, 3 equiv.) at reflux for 4h. Yield: 3.6g (29.7%) of 2-amino-5-bromophenol hydrochloride as a white solid. The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample. ^1H NMR (400MHz, CD_3OD): δ =7.24(1H, d, J =8.45Hz), 7.20 (1H, d, J =1.75Hz), 7.13(1H, dd, J_1 =8.36Hz, J_2 =1.85 Hz). ^{13}C NMR (100MHz, CD_3OD): δ =153.29, 126.28, 124.08, 123.91, 120.25, 119.13 ppm. HRMS (ESI) m/z (M+1) $^+$ Calc'd for free amine $\text{C}_6\text{H}_6\text{BrNO}$: 187.9712. Found: 187.9710.

➤ **2-Amino-5-Bromophenol Hydrochloride (Compound 3b [A])**

The title compound was prepared using N-(4-bromophenyl)-1-phenylethan-1-imine oxide (1.5g, 5.4 mmol, 1 equiv.), Oxalyl chloride 0.72g, 5.7mmol, 1.04 equiv.) and 10 mL of THF. Acid hydrolysis was conducted with hydrochloric acid (1.41mL, 17mmol, 3 equiv.) at reflux for 4h. Yield: 0.44g (36.1%) of 2-amino-5-bromophenol hydrochloride as a white solid. The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample and with a sample of the compound 3a [A].

➤ **4-Bromo-2-Chloroaniline Hydrochloride (Compound 3c [B])**

The title compound was prepared using 4-bromophenylnitrone (0.55g, 2 mmol), thionyl chloride (0.29g, 2.4 mmol) and THF (4ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.5mL, 6mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, the reaction was poured with stirring into dichloromethane (100mL) leading to a solid. The title compound was obtained as a light purple solid (0.2g, 41.2%). The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample. ^1H NMR (400MHz, CD_3OD): δ =7.79(1H, d, J =2.18Hz), 7.59(1H, dd, J_1 =8.54Hz, J_2 =6.37Hz), 7.34(1H, d, J =8.54Hz). ^{13}C NMR (100MHz, CD_3OD): δ =134.46, 134.01, 132.77, 131.41, 125.35, 120.85 ppm. HRMS (ESI) m/z (M+1) $^+$

Calc'd for free amine $\text{C}_6\text{H}_5\text{BrClN}$: 205.9373 and 207.9352. Found: 205.9369 and 207.9346.

➤ **2-Amino-5-Methylphenol Hydrochloride (Compound 4a [A])**

The title compound was prepared using 4-methylphenylnitrone (0.13g, 0.63 mmol, 1.0 equiv.), trichloroacetyl chloride (0.13g, 0.69 mmol, 1.1 equiv.) and THF (4ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.8mL, 9.6mmol, 15 equiv.) for 4h at ca 72°C. Upon cooling, the reaction was poured with stirring into ethyl acetate (40 ml) and petroleum ether (40 ml) leading to a solid. The title compound was obtained as a light brown solid (0.051g, 50.8%). The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample and with a sample of the compound 4b [A].

➤ **2-Amino-5-Methylphenol Hydrochloride (Compound 4b [A])**

To an oven dried 50-mL, three-necked, round-bottomed flask equipped with a thermometer, a reflux condenser fitted with a T-joint inlet, glass stoppers and a Teflon coated magnetic stirring bar was charged with N-(4-methylphenyl)-1-phenylethan-1-imine oxide (0.13g, 0.63 mmol, 1.0 equiv.) and THF (4ml). The mixture was stirred for 20 min at room temperature, then cooled to 0°C. Oxalyl chloride (0.09g, 0.69 mmol, 1.1 equiv.) was added dropwise during which the reaction was maintained less than 3°C. After the addition, the reaction was stirred at about 0 to 3°C for 30 min. and at room temperature for 2h. TLC analysis (eluent: butyl acetate/toluene / DCM = 1/2/6 v/v) indicated that the disappearance of nitrone. Concentrated hydrochloric acid (0.16 mL, 1.92mmol, 3 equiv.) was added to the reaction mixture, and the resulting mixture was heated for 4h at ca 72°C. Upon cooling, the reaction was poured with stirring into a mixture of acetate (40ml) and petroleum ether (40 ml) leading to a solid which was collected and washed with petroleum ether (2x25mL) and dried in vacuo first with a water aspirator and with an oil pump for 12 h to yield a grey solid (0.061g, 60.66%). The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample [Sigma-Aldrich Co.]. ^1H NMR (400MHz, CD_3OD): δ =7.17(1H, d, J =7.77Hz), 6.84 (1H, s), 6.77(1H, d, J =8.08Hz), 2.33(3H, s). ^{13}C NMR (100MHz, CD_3OD): δ =152.02, 142.00, 124.41, 121.64, 117.64, 116.70, 21.25 ppm. HRMS (ESI) m/z (M+1) $^+$ Calc'd for free amine $\text{C}_7\text{H}_9\text{NO}$: 124.0763. Found: 124.0756.

➤ **2-Chloro 4-Methylaniline Hydrochloride (Compound 4c [B])**

The title compound was prepared using 4-methylphenylnitrone (2.11g, 10 mmol), thionyl chloride (1.44g, 2.4 mmol) and THF (30ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (2.5mL, 30mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, the reaction was poured with stirring into

a mixture of ethyl acetate (50ml) and ether (50 ml) leading to a solid. The title compound was obtained as a yellow solid (1.01g, 56.7%). The obtained product was identified using HPLC analysis by comparison with an authentic sample. ^1H NMR (400MHz, CD_3OD): δ =7.52(1H, s), 7.49(1H, d, J =4.66 Hz), 7.32(1H, d, J =8.08Hz), 2.41(3H, s). ^{13}C NMR (100MHz, CD_3OD): δ =142.84, 132.12, 130.39, 128.93, 127.06, 125.75, 2.89 ppm. HRMS (ESI) m/z (M+1) $^+$ Calc'd for free amine $\text{C}_7\text{H}_8\text{ClN}$: 142.0424. Found: 142.0419.

➤ **Reaction of 4-Methoxyphenylnitrone with Oxalyl Chloride (Compounds 5b [A], [B] and [C])**

The reaction was conducted using 4-methoxyphenylnitrone (6.82g, 30 mmol, 1.0 equiv.), oxalyl chloride (4.19g, 33 mmol, 1.1 equiv.) and THF (60ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (7.8mL, 93.6mmol, 3.1 equiv.) for 4h at ca 72°C. Upon cooling, the reaction mixture was basified to pH=8. The organic compounds were extracted with ethyl acetate. The organic layer was separated, washed with water, and dried over anhydrous potassium carbonate. After the filtration, the organic layer was evaporated in vacuo to dryness. The resulting residue was subjected to HPLC and ^1H NMR analyses by comparison with purchased authentic samples and with the pure compound 5b[C] to determine the composition of these three aryl amines.

➤ **3-Chloro-4-Methoxyaniline Hydrochloride (Compound 5b [C])**

The reaction was conducted using 4-methoxyphenylnitrone (6.82g, 30 mmol, 1.0 equiv.), oxalyl chloride (4.19g, 33 mmol, 1.1 equiv.) and THF (60ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (7.8mL, 93.6mmol, 3.1 equiv.) for 4h at ca 72°C. The entire reaction mixture was poured with stirring into a mixture of ethyl acetate (200ml) and petroleum ether (400 ml) leading to a solid. The title compound was obtained as a light grey solid (2.24g, 38.5%). The obtained product was identified using HPLC analysis by comparison with a purchased authentic sample. ^1H NMR (400MHz, CD_3OD): δ =7.47(1H, d, J =2.49Hz), 7.36 (1H, d, J =8.86Hz, J =2.64Hz), 7.25(1H, d, J = 9.01 Hz), 3.96(3H, s). ^{13}C NMR (100MHz, CD_3OD): δ =157.08, 125.88, 124.73, 123.89, 114.35, 57.09 ppm. HRMS (ESI) m/z (M+1) $^+$ Calc'd for free amine $\text{C}_7\text{H}_8\text{ClNO}$: 158.0373. Found: 158.0366.

➤ **Reaction of 4-Methoxyphenylnitrone with Thionyl Chloride (Compounds 5c [B] and [C]):**

The reaction was conducted using 4-methoxyphenylnitrone (0.227g, 1.0 mmol, 1.0 equiv.), thionyl chloride (0.14g, 1.17 mmol, 1.17 equiv.) and THF (30ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.25mL, 3mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, the reaction mixture was basified to pH=8. The organic compounds were extracted with ethyl acetate. The organic layer was separated, washed with water, and dried over

anhydrous potassium carbonate. After the filtration, the organic layer was evaporated in vacuo to dryness. The resulting residue was subjected to HPLC and ^1H NMR analyses by comparison with purchased authentic samples to determine the composition of the two aryl amines: 2-chloro-4-methoxyaniline and 3-chloro-4-methoxyaniline.

➤ **Reaction of 4-Ethoxyphenylnitrone with Trichloro Acetyl Chloride (Compounds 6a [A], [B] and [C])**

The reaction was conducted using 4-ethoxyphenylnitrone (0.24g, 1 mmol, 1.0 equiv.), trichloroacetyl chloride (0.19g, 1.04 mmol, 1.04 equiv.) and THF (4ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.25mL, 3mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, the reaction mixture was basified to pH=8. The organic compounds were extracted with ethyl acetate. The organic layer was separated, washed water, and dried over anhydrous potassium carbonate. After the filtration, the organic layer was evaporated in vacuo to dryness. The resulting residue was subjected to HPLC and ^1H NMR analyses by comparison with purchased authentic samples and with a sample of the compound 6b [C] to determine the composition of the three aryl amines.

➤ **Reaction of 4-Ethoxyphenylnitrone with Oxalyl Chloride (Compounds 6b [A], [B] and [C])**

The reaction was conducted using 4-ethoxyphenylnitrone (0.24g, 1 mmol, 1.0 equiv.), oxalyl chloride (0.14g, 1.1 mmol, 1.1 equiv.) and THF (4ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.25mL, 3 mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, the reaction mixture was basified to pH=8. The organic compounds were extracted with ethyl acetate. The organic layer was separated, washed water, and dried over anhydrous potassium carbonate. After the filtration, the organic layer was evaporated in vacuo to dryness. The resulting residue was subjected to HPLC and ^1H NMR analyses by comparison with authentic samples and with a sample of the compound 6b [C] to determine the composition of aryl amines.

➤ **3-Chloro-4-Ethoxyaniline Hydrochloride (Compound 6b [C])**

The reaction was conducted using 4-ethoxyphenylnitrone (0.24g, 1mmol, 1equiv.), Oxalyl chloride (0.14g, 1.1mmol) and THF(4ml), Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.25mL, 3mmol, 3 equiv.) for 4h at ca 72°C, The entire reaction mixture was poured with stirring into a mixture of acetonitrile (20ml) and CH_2Cl_2 (5ml) leading to a solid. The obtained compound was subjected to HPLC analysis by comparison with a purchased authentic sample. The title compound was obtained as a light grey solid (0.08g, 38.5%). ^1H NMR (400MHz, CD_3OD): δ =7.45(1H, d, J =2.62Hz), 7.32(1H, dd, J =8.84Hz, J =2.62Hz), 7.22 (1H, d, J =8.84Hz), 4.18(2H, q, J =7.4Hz), 1.45 (3H, t, J =7.4Hz). ^{13}C NMR (100MHz, CD_3OD): δ =156.35, 125.83,

124.84, 124.68, 123.75, 115.27, 66.32, 14.87 ppm. HRMS (ESI) m/z (M+1)⁺ Calc'd for free amine C₈H₁₀ClNO: 172.0530. Found: 172.0521. .

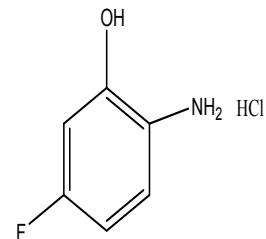
➤ **Reaction of 4-Ethoxyphenylnitrone with Thionyl Chloride (Compounds 6c [B] and [C])**

The reaction was conducted using 4-ethoxyphenylnitrone (0.24g, 1.0 mmol, 1.0 equiv.), thionyl chloride (0.14g, 1.17 mmol, 1.17 equiv.) and THF (4ml). Acid hydrolysis was conducted by using concentrated hydrochloric acid (0.25mL, 3mmol, 3 equiv.) for 4h at ca 72°C. Upon cooling, a sample of the reaction mixture was taken out, dissolved in methanol, and basified to pH=8. Ethyl acetate was added, and the sample was agitated. The supernatant liquid was subjected to HPLC and ¹H NMR analyses by comparison

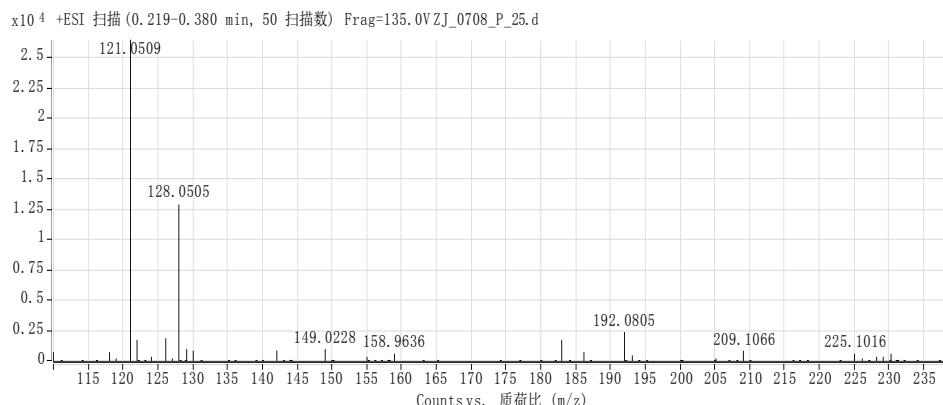
with authentic samples to determine the composition of the two aryl amines: 2-chloro-4-ethoxyaniline and 3-chloro-4-ethoxyaniline.

Part two: HRMS and ¹H & ¹³C NMR

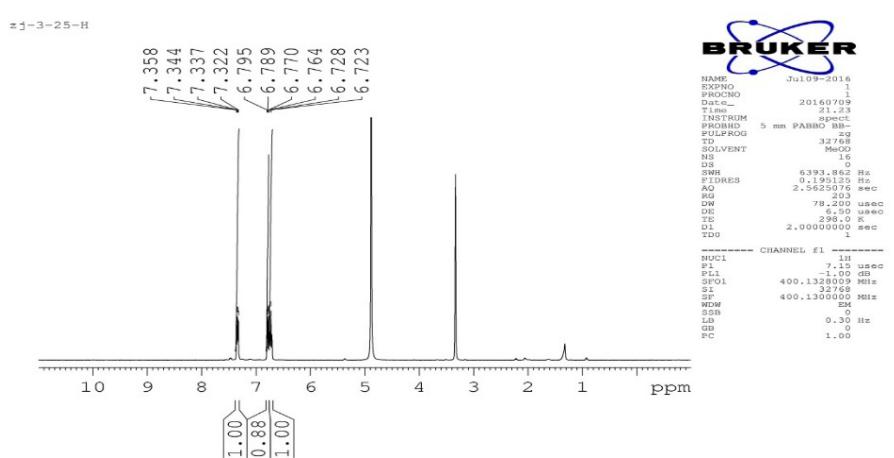
Compound 1a[A]: 2-Amino-5-Fluorophenol Hydrochloride [C₆H₆FNO]



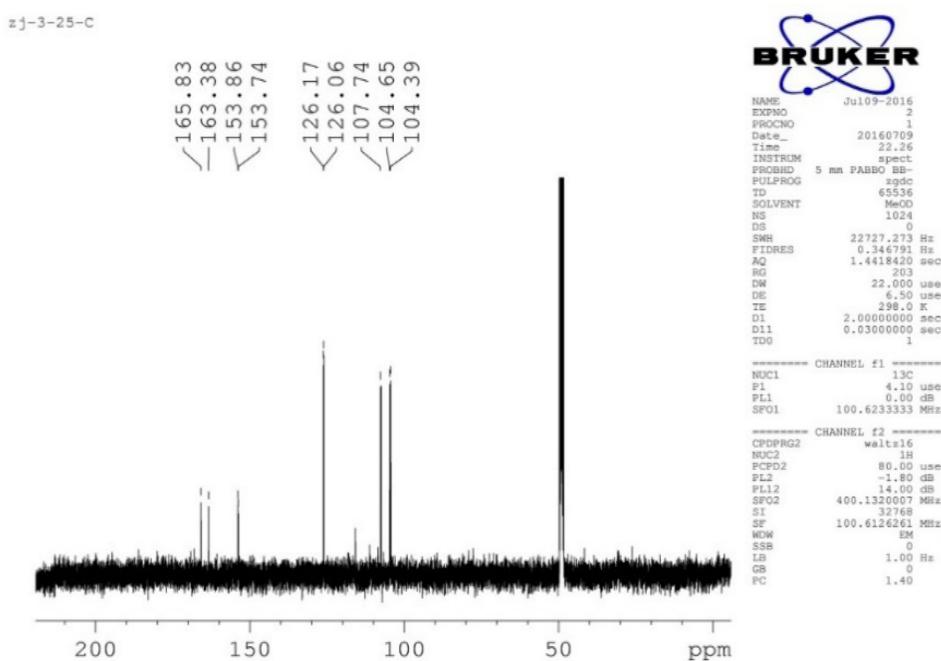
HRMS (ESI)



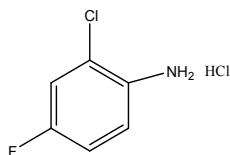
¹H NMR (400MHz, CD₃OD)



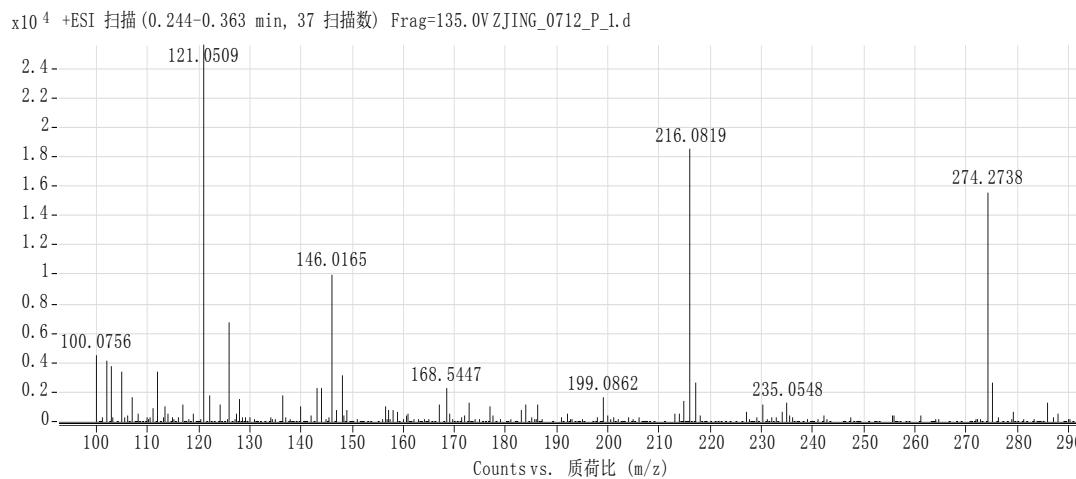
¹³C NMR (100MHz, CD₃OD)



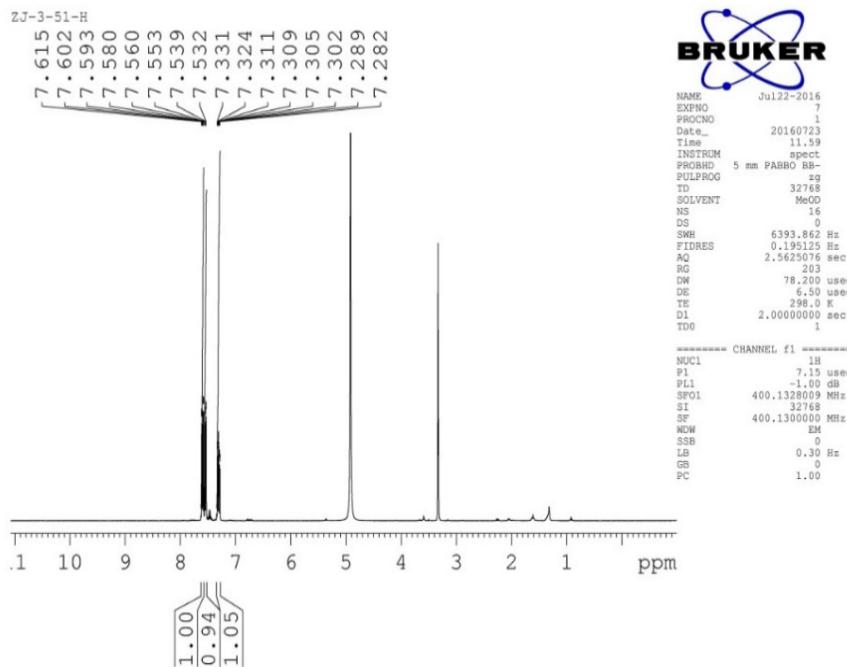
Compound 1c [B]: 2-chloro-4-fluoroaniline hydrochloride [C₆H₆ClFN]



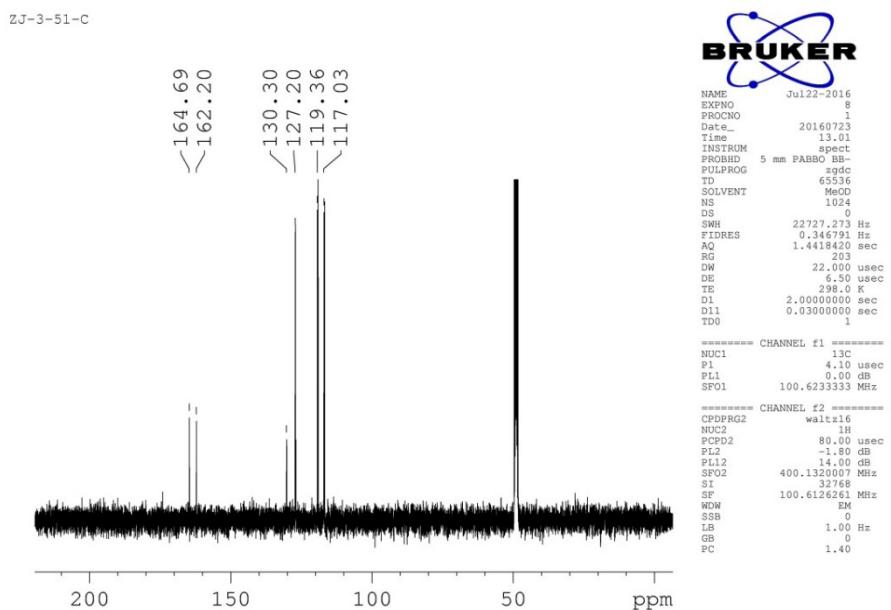
HRMS (ESI)



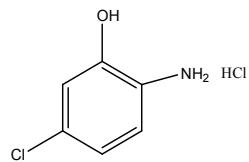
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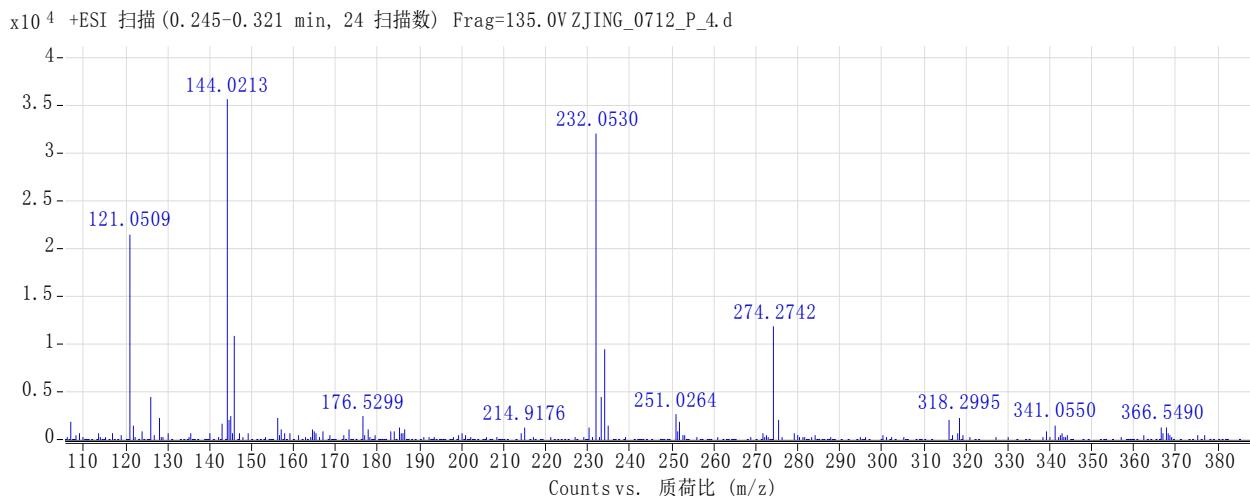
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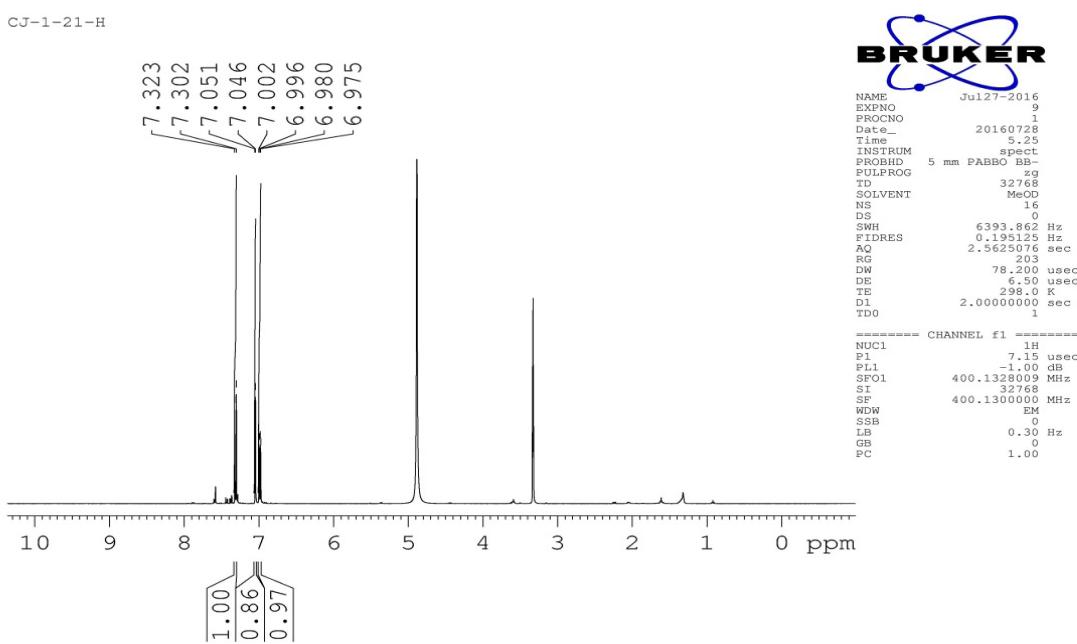
Compound 2a[A]: 2-amino-5-chlorophenol (C_6H_6ClNO)



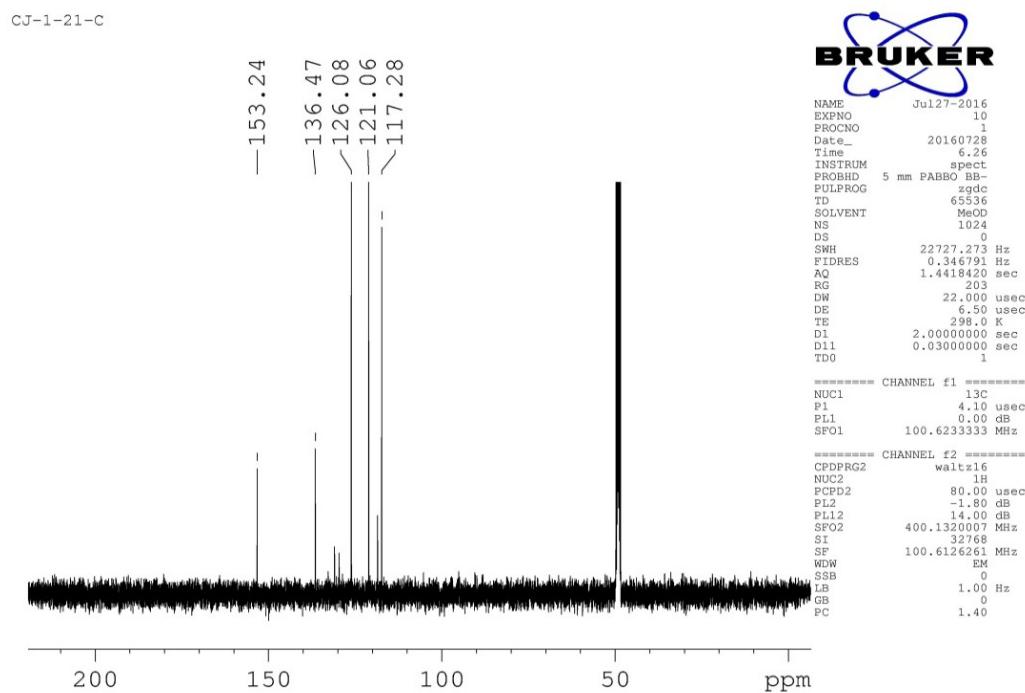
HRMS (ESI)



¹H NMR (400MHz, CD₃OD)

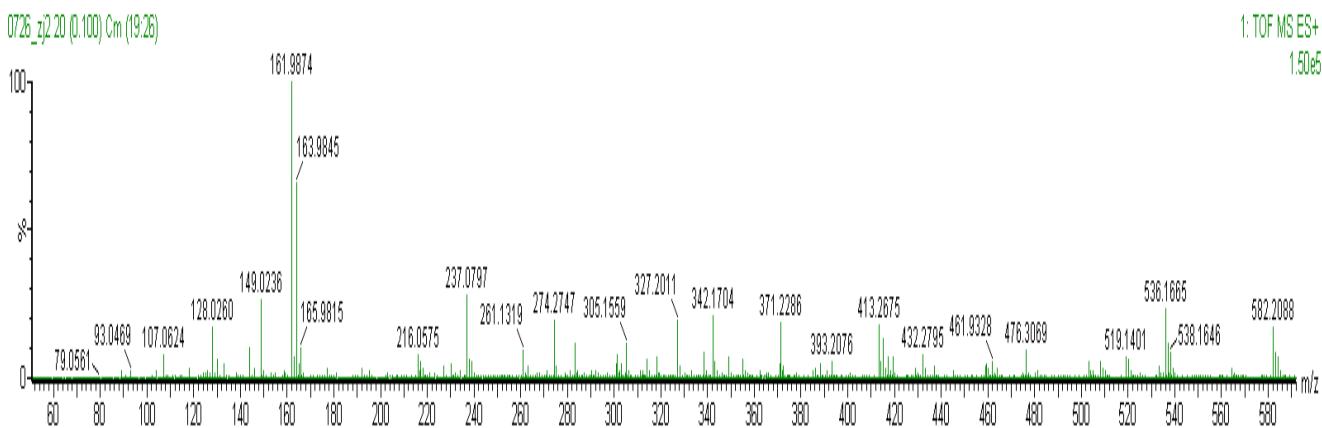


¹³C NMR (100MHz, CD₃OD)

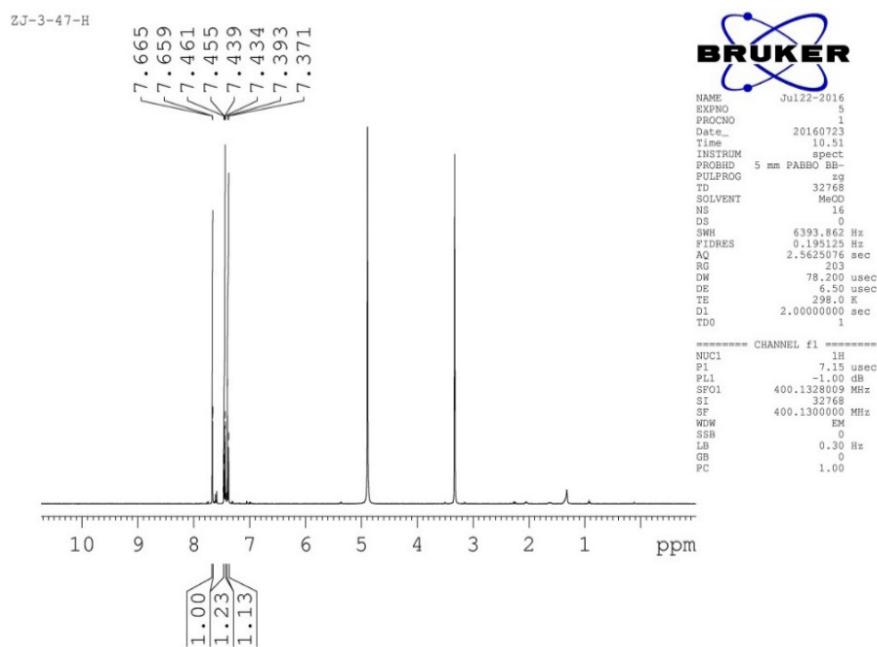


Compound 2c[B]: 2,4-dichloroaniline(C₆H₅Cl₂N)

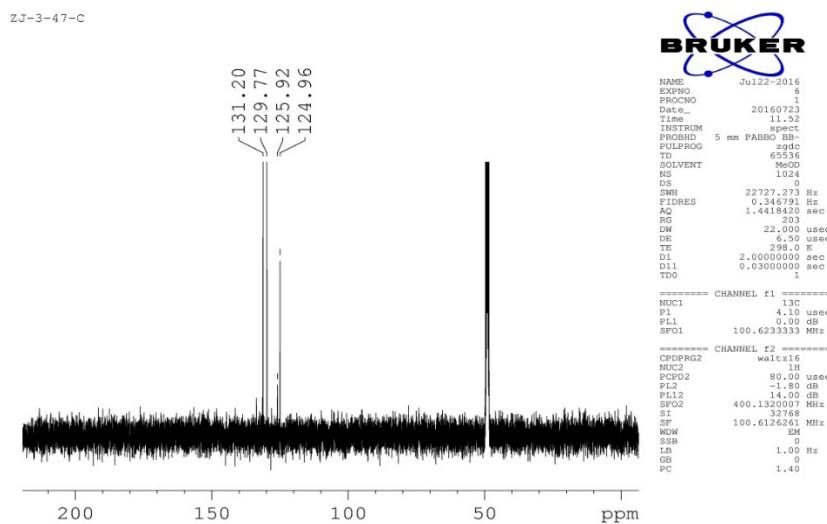
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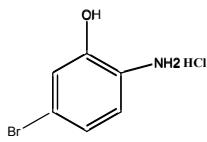
¹H NMR (400MHz, CD₃OD)



¹³C NMR (100MHz, CD₃OD)

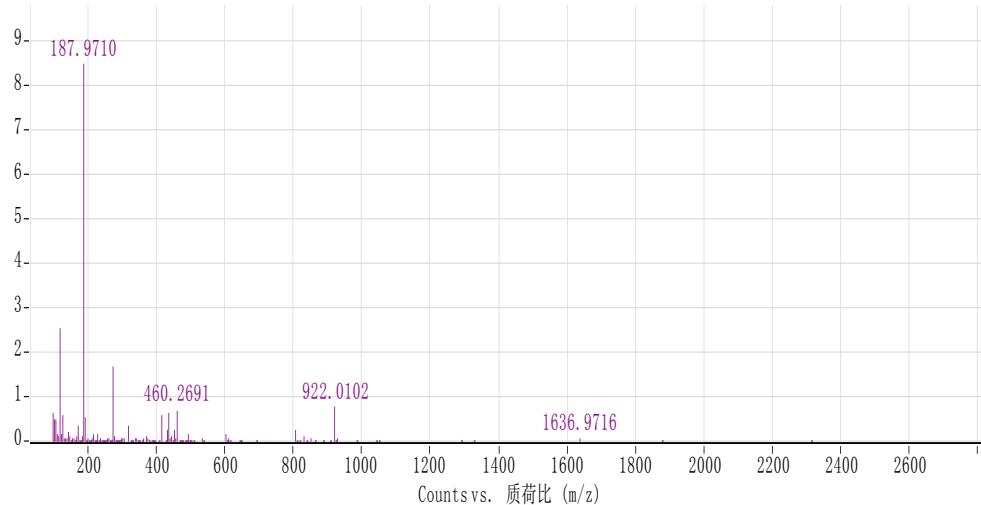


3a[A]. 2-Amino-5-Bromophenol (C_6H_6BrNO)

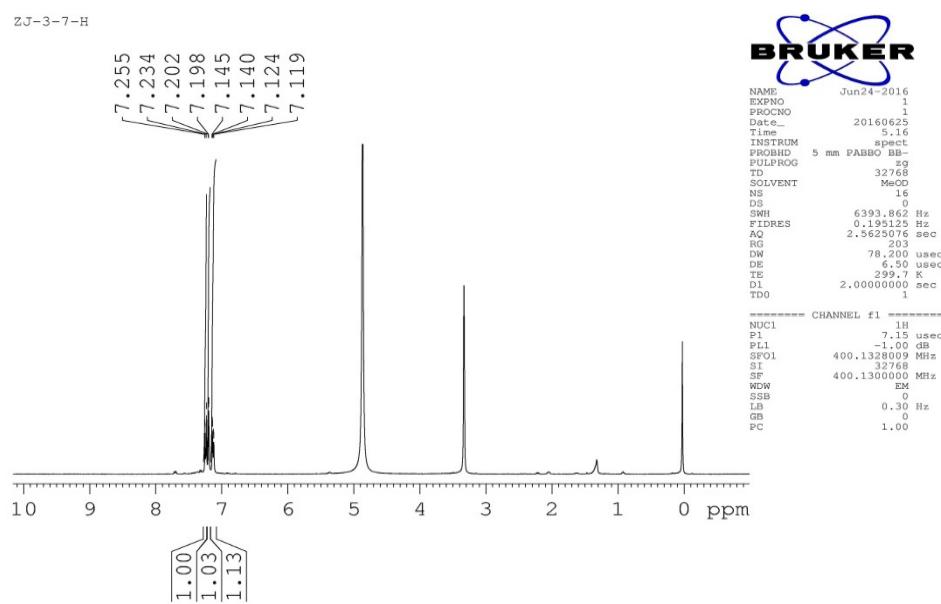


HRMS (ESI)

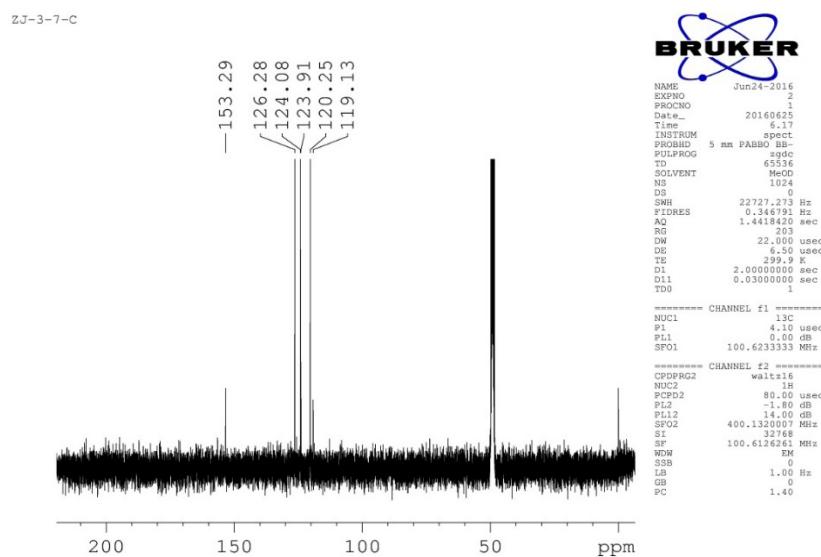
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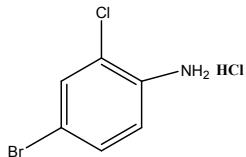
¹H NMR (400MHz, CD₃OD)



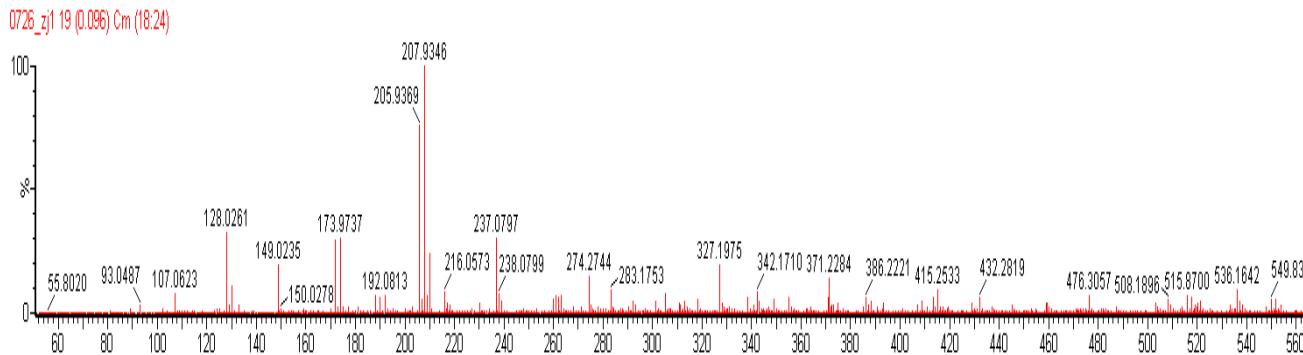
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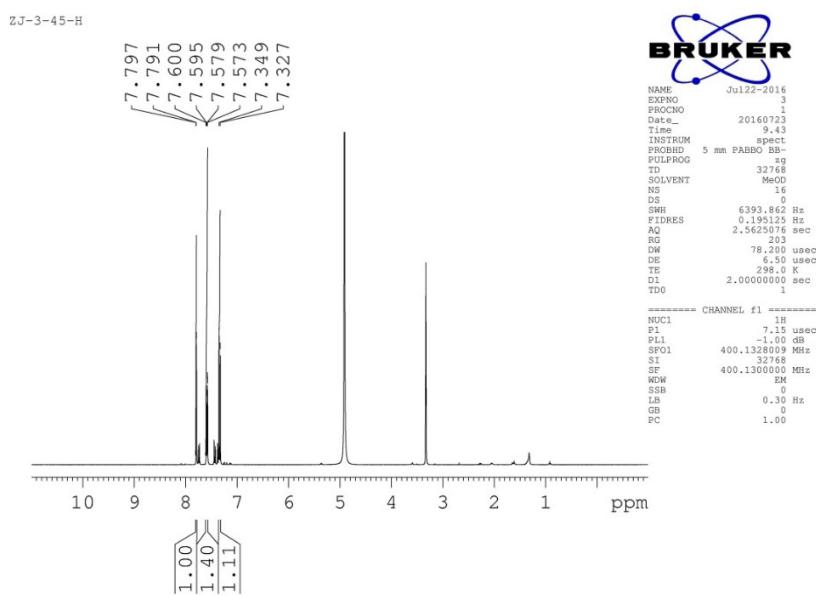
3c[B]: 4-bromo-2-chloroaniline (C₆H₅BrClN)



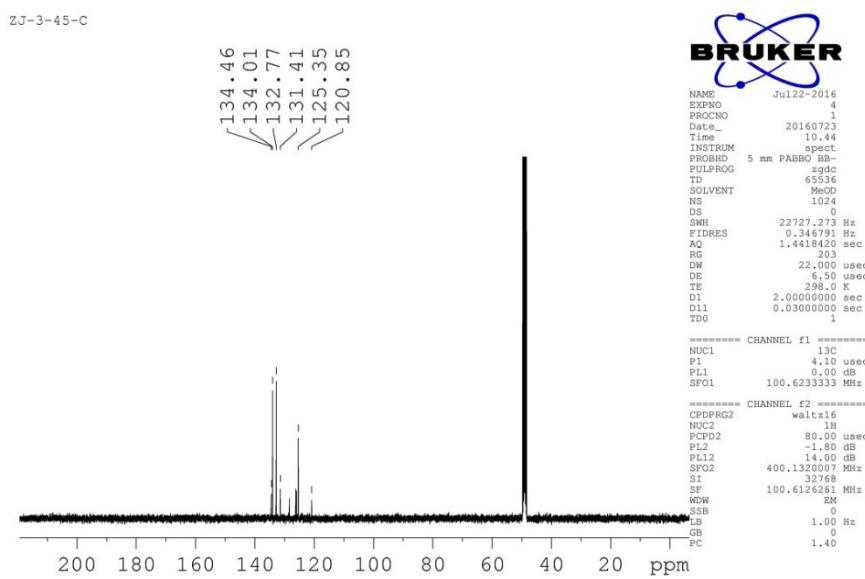
HRMS (ESI)



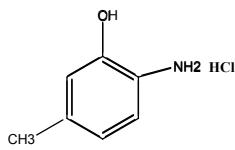
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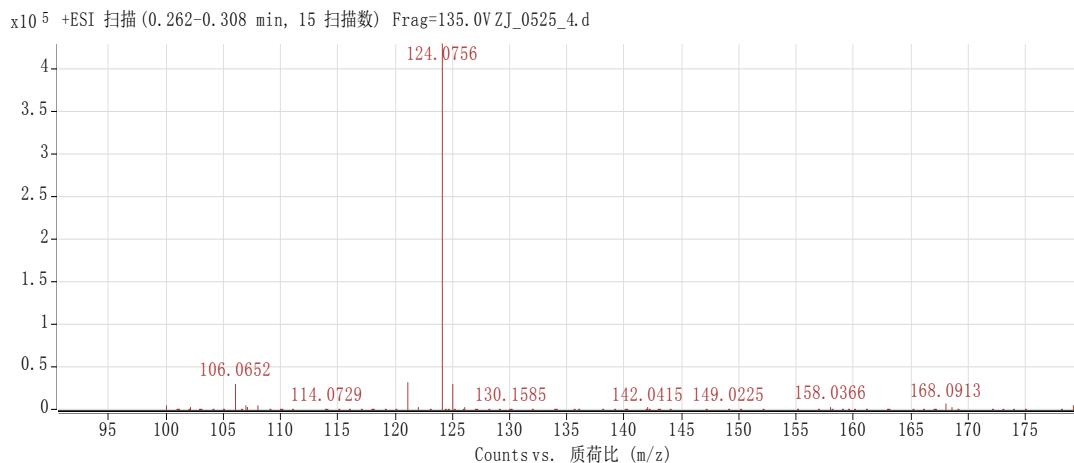
¹³C NMR (100MHz, CD₃OD)



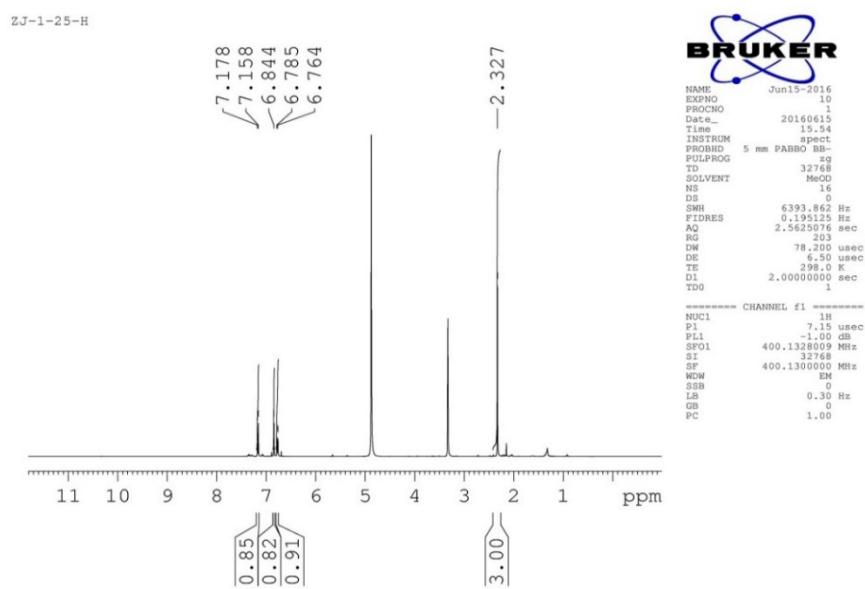
Compound 4b [A]. 2-amino-5-methylphenol (C_7H_9NO)



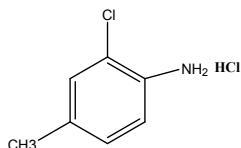
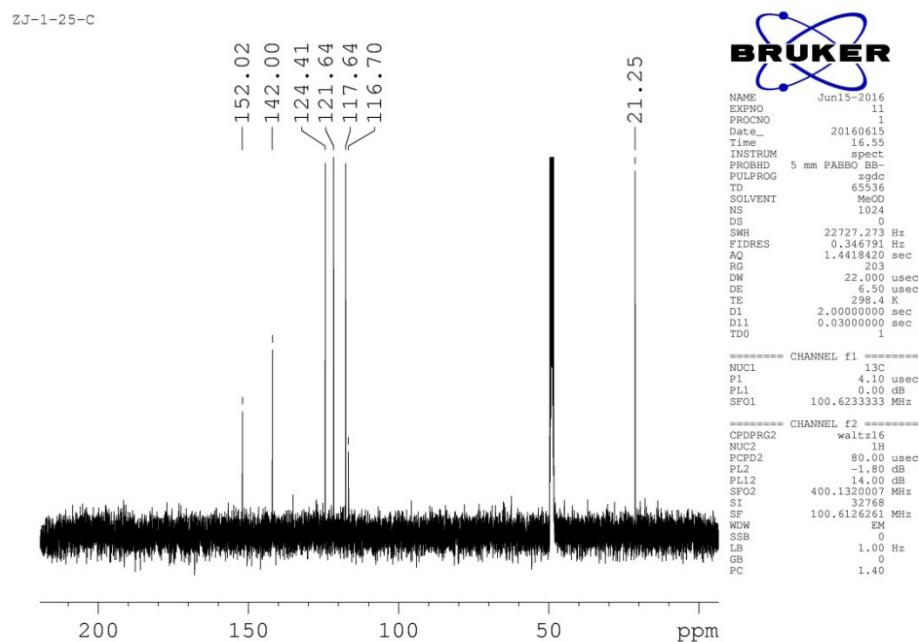
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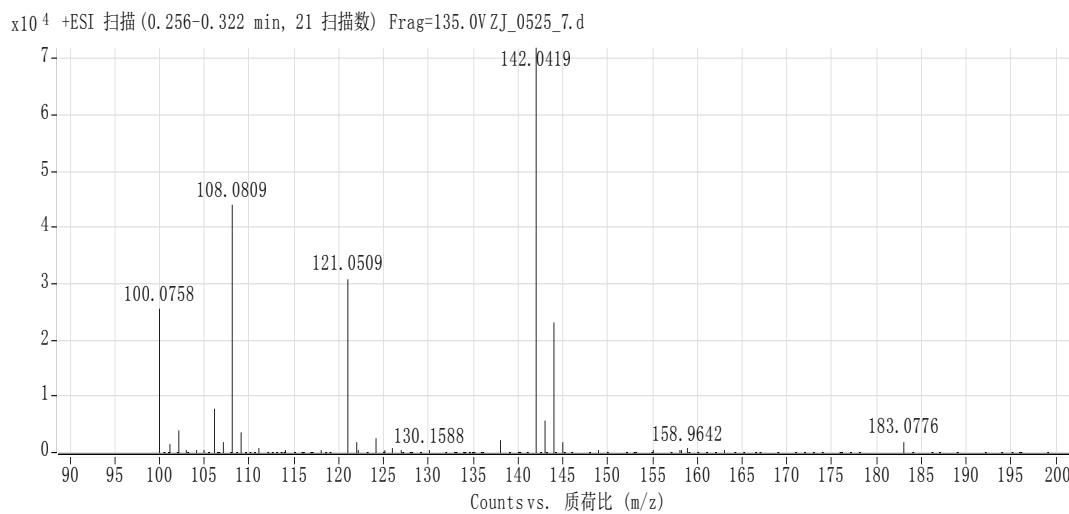
¹H NMR (400MHz, CD₃OD)



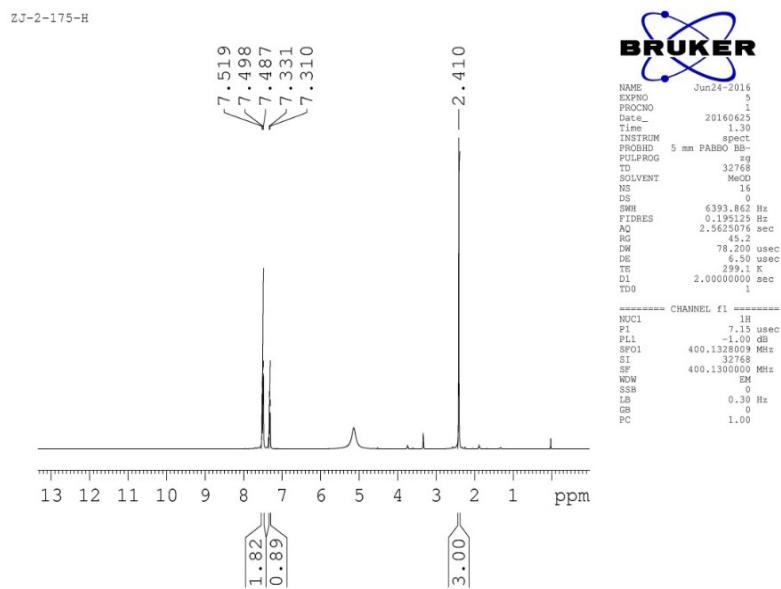
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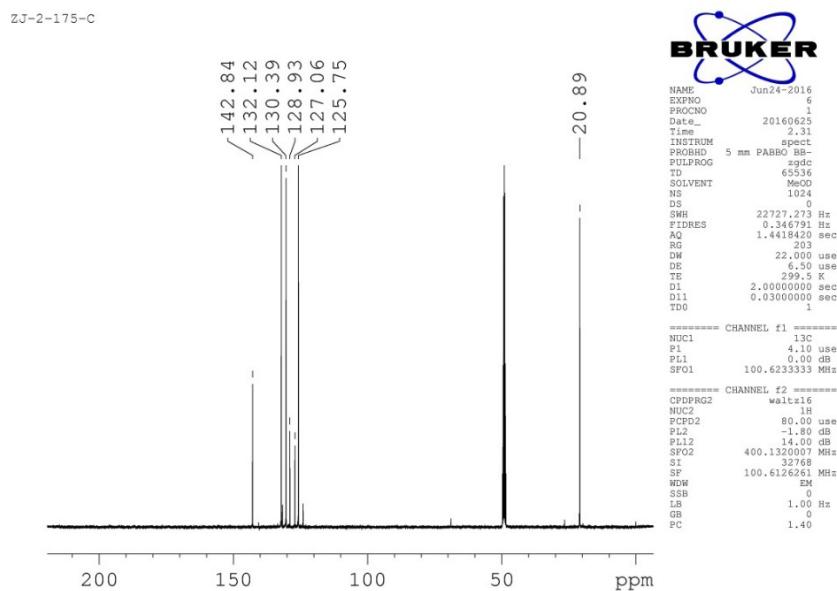
HRMS (ESI)



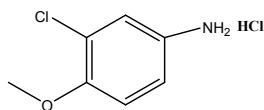
¹H NMR (400MHz, CD₃OD)



¹³C NMR (100MHz, CD₃OD)

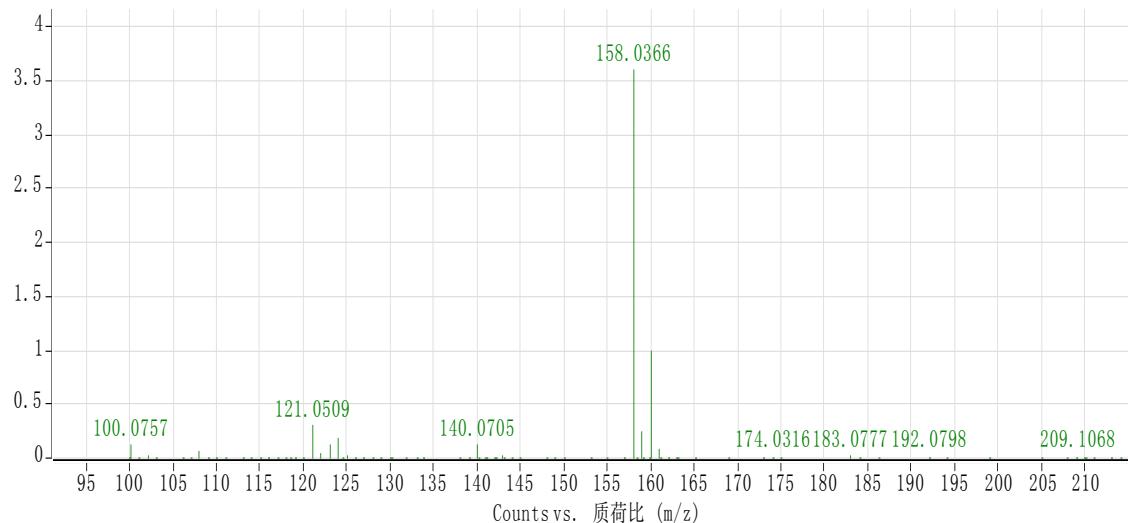


Compound 5b[C]. 3-chloro-4-methoxyaniline (C₇H₈ClNO) HCl

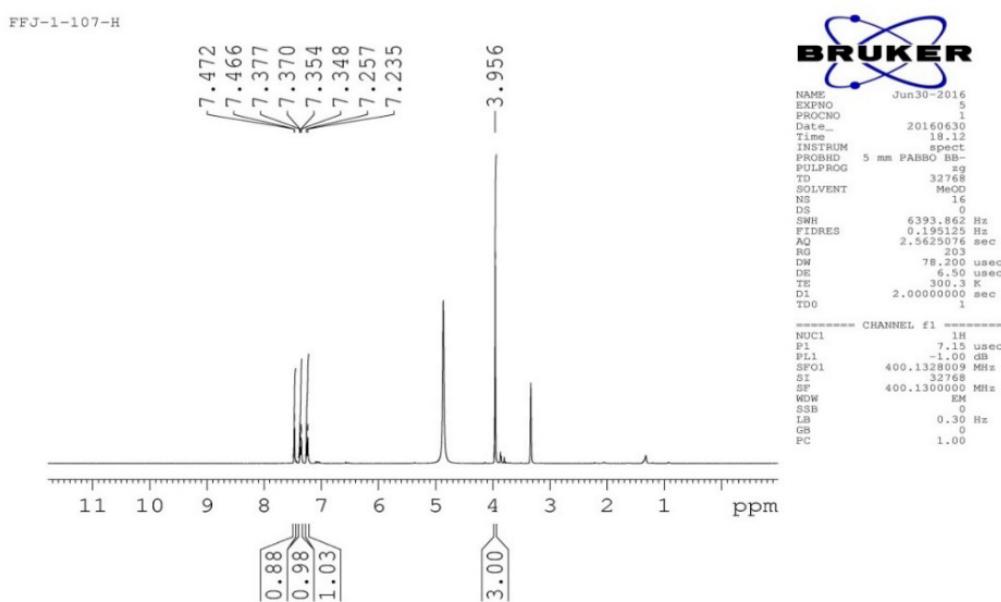


HRMS (ESI)

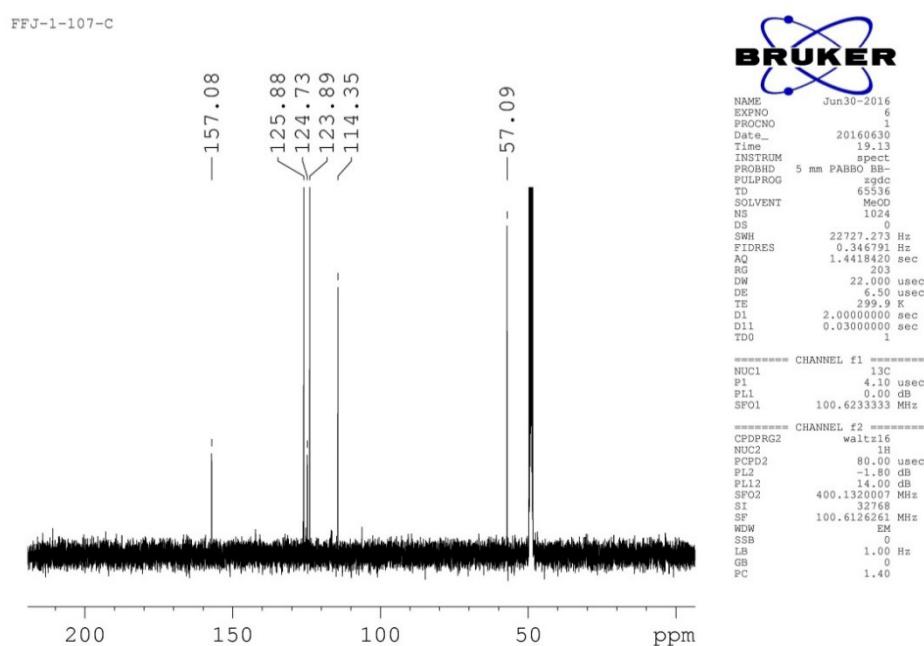
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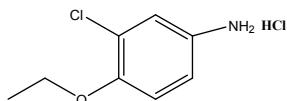
¹H NMR (400MHz, CD₃OD)



¹³C NMR (100MHz, CD₃OD)



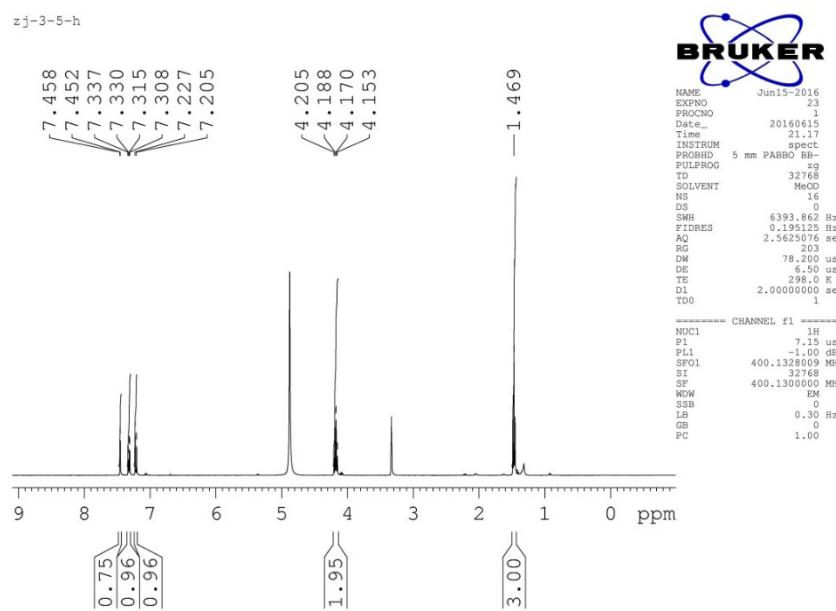
Compound 6b[C]: 3-chloro-4-ethoxyaniline (C₈H₁₀ClNO)



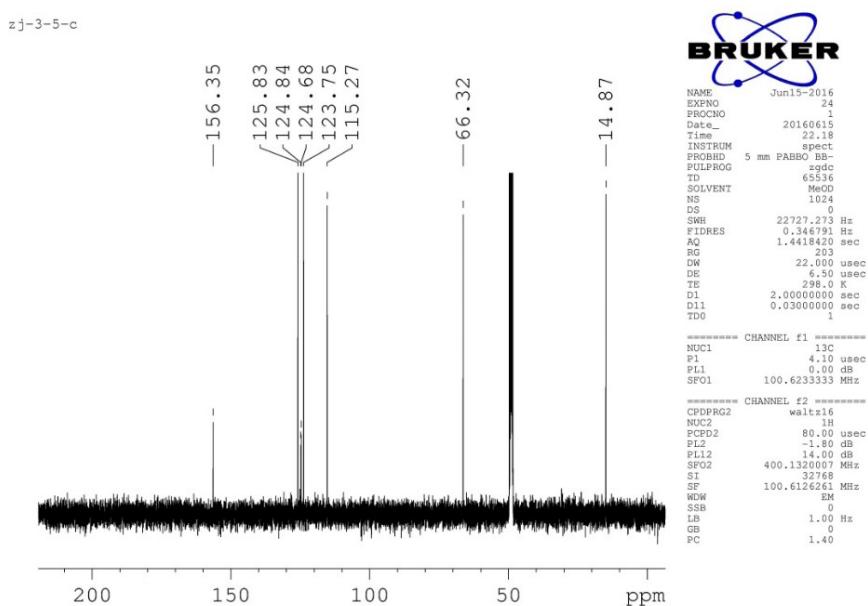
HRMS (ESI)



¹H NMR (400MHz, CD₃OD)



¹³C NMR (100MHz, CD₃OD)



Acknowledgement

We are indebted to National Science Foundation of China [Grant No. 21636001] for their generous financial support.

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