CHAPTER IV

Metal-free, additive-free coupling of nitroarenes with arylboronic acids for the synthesis of diaryl ethers under amiable conditions.

IV. A. Introduction

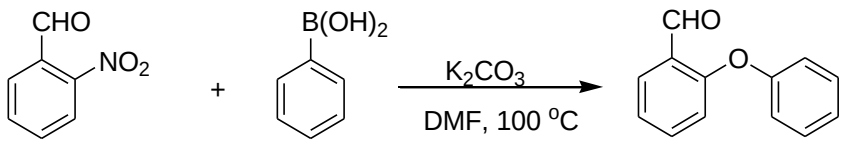
Diaryl ethers constitute a vital class of organic compounds on account of their biological activities and pharmaceutical applications.[1] They are utilized in polymer science and are employed as precursors in many organic synthesis reactions. They even serve as important ligands in some metabolic processes.[2] Synthesis of diaryl ethers through C-O bond formation reactions is hence an area of interest for many years.[3] Till date, the most popular methodology for the synthesis of diaryl ethers is the Cu catalysed Ullman type coupling of aryl halides with phenols.[4] Earlier the processes developed generally required stoichiometric amount of Cu. Search for improving atom-economy, minimizing waste discharge lead to development of several other transition metal catalyzed analogues of the variant of the reaction.[5] Cu catalysed processes involving low catalytic loading have also been achieved recently.[6] Another limitation of the process is the use of aryl halides which are hazardous and produce hazardous by-products during the reaction.

Recently, both Zheng *et. al.* and Peng *et. al.* individually developed a new synthetic strategy for diaryl ethers through the reaction of nitro arenes with aryl boronic acids.[7-8] This method has emerged as a good alternative because nitroarenes and arylboronic acids are greener than aryl halides and phenols used in previous methods. Other advantages include the easy availability and stability of substrates and their substituted derivatives. However, these works used Rh and Pd metals as catalysts respectively. These heavy transition metals are costly and toxic when discharged in environment after use. Zhang *et. al.* later carried out the reaction employing nano CuO as catalyst in the presence of Oxone (potassium peroxymonosulfate) as additive.[9] Considering the fact that chemical waste discharges containing heavy transition metals in the environment can cause several hazards, we tried to investigate the scope of the coupling reaction of nitroarenes with arylboronic acids in metal-free conditions. In this context, we herein report a transition metal-free and additive-free coupling of nitro arenes with aryl boronic acids for the formation of diaryl ethers. The reaction is eco-friendly, cost-effective and uses lesser reaction time as compared to previous reports.

IV. B. Present work: Results and Discussion

Initially, we investigated the scope of the coupling reaction of nitroarenes with arylboronic acids in metal-free conditions. We started with the attempt of coupling *o*-nitrobenzaldehyde with phenyl boronic acid at 100^{o} C with K_2CO_3 as base in DMF (Dimethyl formamide) as solvent (Scheme IV. 1).

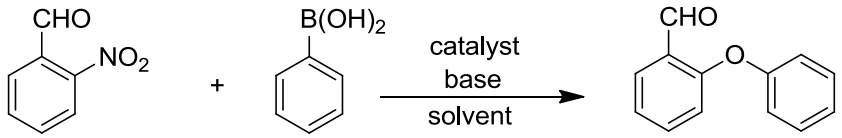
Scheme IV. 1. Coupling of *o*-nitrobenzaldehyde with phenyl boronic acid



Full conversion of *o*-nitrobenzaldehyde was observed in three hours. The corresponding C-O coupling product was obtained in 32% yield upon isolation. Subsequently, we optimised the suitable reaction parameters for the reaction (**Table IV. 1**). Various inorganic bases like Cs_2CO_3, NaOH, KO*t*Bu and LiOH were found effective for the reaction and provided varying yields of the ether product. Among these Cs_2CO_3 provided the best yield of 55%. Organic bases like pyridine and triethylamine were totally ineffective for the reaction and did not yield any product in 10 hours. No desired conversion was observed again, when the reaction was conducted in the absence of base.

Screening of various solvents was then performed. In addition to DMF, the reaction also proceeded well in case of polar aprotic solvents like DMSO (dimethyl sulphoxide) and Dioxane. However, comparatively low boiling DCE (1,2-dichloroethene) produced no observable conversion when the reaction was conducted at 84^{o}C. This might be due to the high activation energy of the reaction. Again, polar protic solvents like ethanol, ethylene glycol and water were inefficient for the reaction. To compare the reaction yield with that in presence of some green metals like iron and gold, we used $Fe(acac)_3$ (Iron(III) acetylacetonate) and $HAuCl_4$ (hydrogen tetrachloroaurate III) as catalysts for the reaction. Similar results were obtained with yields 53% and 55% respectively. Hence, the best suitable reaction conditions for our reaction system turned out to be as in entry 2, table IV. 1.

Table IV. 1. Optimization of reaction conditions



Entry	Base	Solvent	Catalyst	Yield[d] (%)
1	K_2CO_3	DMF	--	32
2	**Cs_2CO_3**	**DMF**	**--**	**55**
3	NaOH	DMF	--	25
4	KO*t*Bu	DMF	--	23
5	LiOH	DMF	–	30
6	Pyridine	DMF	--	–
8[b]	$N(C_2H_5)_3$	DMF	--	–
9[b]	--	DMF	--	–
10	Cs_2CO_3	DMSO	--	52
11[c]	Cs_2CO_3	DCE	--	–
12	Cs_2CO_3	Dioxane	--	51
13	Cs_2CO_3	Water	--	–
14[c]	Cs_2CO_3	EtOH	--	--
15	Cs_2CO_3	ethylene glycol	--	--
16	Cs_2CO_3	DMF	$Fe(acac)_3$	53
17	Cs_2CO_3	DMF	$HAuCl_4$	55

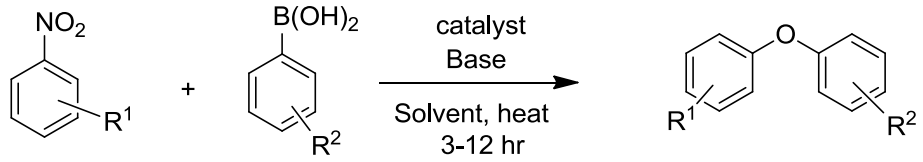
[a]Reaction Conditions: *o*-nitrobenzaldehyde (1 mmol), Phenyl boronic acid (1.2 equiv), Base (1.5 equiv), solvent 2-3mL, temperature - 100^{o}C, time - 3hr. [b]Reaction conducted for 10 hours. [c]Reaction conducted at the boiling points of the solvents under refluxing conditions. [d]Isolated Yields.

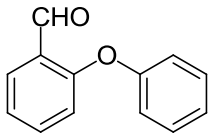
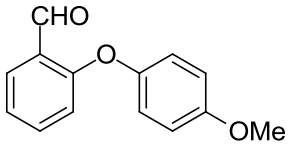
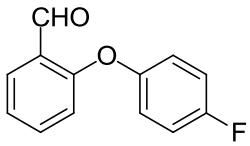
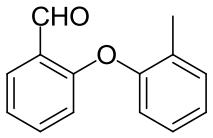
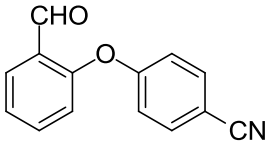
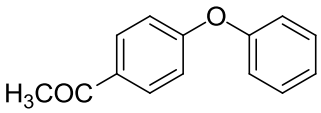
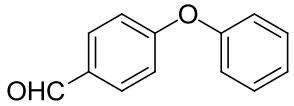
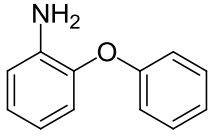
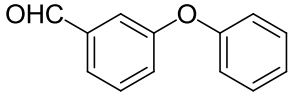
With these optimised conditions in hand, we proceeded forward to check the general applicability of the reaction methodology. Different types of nitroaryls were reacted with variety of aryl boronic acids under the optimised conditions. Efficient coupling reaction was observed with variety of substrates and the products were obtained in reasonable yields. In case of arylboronic acids the reaction was feasible with various substrates irrespective of the presence of electron donating or withdrawing substituents. In a general approach different aryl boronic acids were coupled with *o*-nitrobenzaldehyde. *p*-methoxyphenyl boronic acid, *p*-

fluorophenyl boronic acid, *o*-methylphenyl boronic acid and *p*-cyanophenyl boronic acid reacted to give the corresponding ether products in yields of 43%, 41%, 37% and 30% respectively. Hence, the reaction was successful for a range of phenyl boronic acids irrespective of the positioning of the groups on the basic skeleton (**Table IV. 2, entry 2-5**).

On the other hand, in case of nitroarenes, those which are electron deficient due to the presence of a group of negative mesomeric effect at para or ortho position to the nitro group were found suitable for the reaction. Accordingly as observed, *o*-nitrobenzaldehyde reacted with phenylboronic acid to provide the resultant ether product in 55% yield (**Table IV. 2, entry 1**). *p*-nitroacetophenone and *p*-nitrobenzaldehyde underwent coupling with phenylboronic acid to yield corresponding products in 63% and 46% yields respectively (**Table IV. 2, entry 6-7**). However, no formation of desired product was observed in case of *o*-nitroaniline and *m*-nitrobenzaldehyde (**Table IV. 2, entry 8-9**).

Table IV. 2. Coupling reaction between various arylboronic acids and nitroarenes

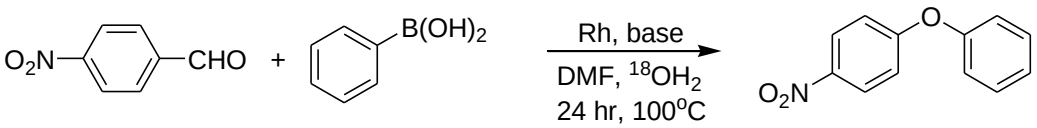


Entry	R_1	R_2	Product	Time (hr)	Yield (%)
1	2-CHO	H		3	55
2	2-CHO	4-OMe		12	43
3	2-CHO	4-F		3	41
4	2-CHO	3-CH_3		3	37
5	2-CHO	4-CN		12	30
6	4-$COCH_3$	H		5	63
7	4-CHO	H		3	46
8	2-NH_2	H		10	--
9	3-CHO	H		10	--

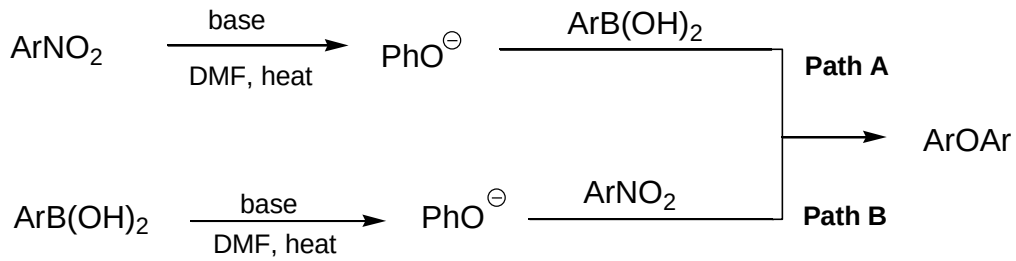
[a]Reaction Conditions: nitroarene (1 mmol), Aryl boronic acid (1.2 equiv), Cs_2CO_3 (1.5 equiv), solvent 2-3mL, temperature - 100°C.

Actual mechanistic pathway for the reaction is yet not confirmed; still, an insight can be drawn from the previous work of Wu *et. al*. (**Scheme IV.2**).[7] ^{18}O isotope labelling experiments suggest that the Oxygen of the ether linkage comes from the water molecules present in the solvent. Two types of plausible reaction pathways are suggested. One in which the nitroarene undergo nucleophilic attack by water and leads to the formation of a phenoxide ion. This intermediate can further couple with the aryl boronic acid (Path A) to produce the ether product. In the other possibility, the aryl boronic acid may undergo oxidative hydroxylation to produce the phenoxide intermediate (Path B) and that in turn lead to the ether product after coupling with the nitroarene.

Scheme IV. 2: Mechanistic study by Wu and co-workers



(a) isotope labelling experiments



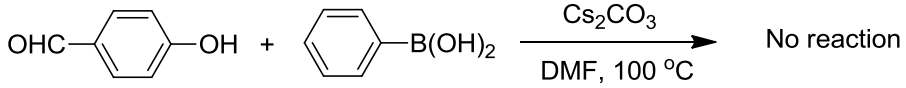
(b) Plausible reaction pathways

To develop an idea about the probable pathway of this transition metal free etherification reaction, we carried out some controlled experiments. If the reaction follows 'Path A' then the phenoxide ion intermediate should react with aryl boronic acid to give the corresponding coupling product. To investigate that, we attempted the coupling of *p*-hydroxybenzaldehyde with phenyl boronic acid under our optimised conditions. The reaction did not proceed and this ruled out the possibility of 'Path A' (Scheme IV. 3a). Now, if 'Path B' is the probable pathway for the reaction, then the intermediate phenoxide ion should react with the nitroarene to provide the corresponding ether product. We conducted the coupling of phenol and *p*-nitrobenzaldehyde under our optimised reaction conditions. The desired coupling product

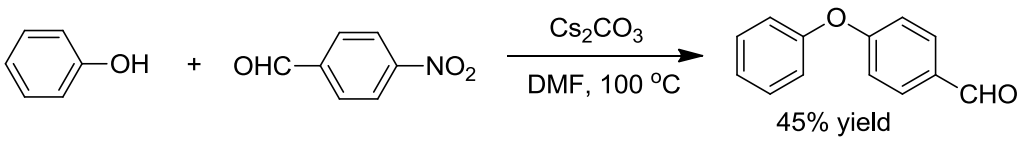
was obtained in 45% yield (scheme IV. 3b). This indicates that the reaction proceeds through the proposed 'Path B' for its completion. Hence, we can conclude that at first the phenoxide ion type intermediate is generated by the action of water under basic conditions on aryl boronic acid moiety. This nucleophile attacks on the aromatic C of the nitroarene bound with the nitro group substituting the latter to give the ether product. This mechanism is also in accordance with our previous observations. During the optimisation of reaction conditions we observed that the reaction was not feasible with protic solvents because that may lead to protonation of the phenoxide ion intermediate causing its deactivation. Again, the presence of an electron withdrawing group with negative mesomeric effect at *o*- or *p*- position of nitro group in nitroarene is desired for increasing the electron deficiency at the reaction centre for effective nucleophilic substitution to take place.

Scheme IV. 3. Control experiments

a)



b)



IV. C. Conclusion

In summary, we have developed a transition metal free, ligand free, additive free C-O coupling reaction leading to the formation of ether compounds. The reaction is easy to perform and utilises comparatively less toxic substrates as compared to aryl halides and phenols used in trivial methods of etherification. Variety of nitroarenes and aryl boronic acid moieties can be coupled using this methodology. A concise observation based study of the plausible reaction mechanism is also discussed.

IV. D. Experimental Section

II. D. Experimental

II. D. 1. General Comments

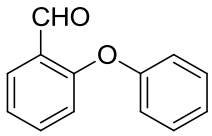
Unless stated otherwise, all reagents such as Palladium acetate, arylboronic acids and solvents were used as received from commercial suppliers. NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Products were purified using column chromatography on silica gel (60-120 mesh). Ethyl acetate and petroleum ether (60-80 ^{o}C) were used as eluents. Progress of reaction was monitored using silica gel TLC.

II. D. 2. General procedure for the synthesis of biaryl ethers

An oil bath was pre-heated to maintain a temperature of 100 ^{o}C. In a 25 mL round bottom flask, 1 mmol *o*-nitrobenzaldehyde, 1.2 mmol of aryl boronic acid 1.5 equiv Cs_2CO_3 and 2-3mL DMF was taken. The reaction mixture was stirred in the hot oil bath on a magnetic stirrer. Progress of the reaction was monitored with the help of TLC. After the reaction was completed, the reaction mixture was diluted with 30 mL of water and the organic layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified through column chromatography using petroleum ether and ethyl acetate as an eluent.

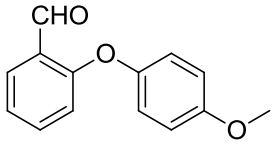
II. D. 3. Spectral Analysis

1. 2-Phenoxybenzaldehyde (Table IV.2, entry 1)[7]



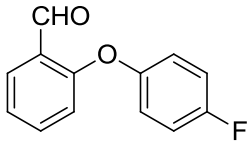
Colourless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.90 (d, *J* = 8.1 Hz, 1H) 7.05-7.09 (m, 2H), 7.18-7.21 (m, 2H), 7.37-7.42 (m, 2H), 7.48-7.54 (m, 1H), 7.94 (dd, *J* =7.8 Hz, 1.8 Hz, 1H),10.53 (s, 1H), ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 118.5, 119.4, 123.3, 124.3, 126.9, 128.4, 130.1, 135.7, 156.4, 160.0, 189.4.

2. 2-(4-Methoxyphenoxy)benzaldehyde (Table IV.2, entry 2)[7]



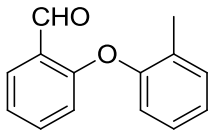
Colourless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 3H), 6.80 (d, *J* = 8.4, 0.9 Hz, 1H), 6.91-6.94 (m, 2H) 7.01-7.05 (m, 2H), 7.10-7.14 (m, 1H), 7.43-7.50 (m, 1H), 7.91 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 10.6 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.7, 115.2, 117.0, 121.2, 122.5, 126.1, 128.4, 135.7, 149.2, 156.6, 161.1, 189.5.

3. 2-(4-Fluorophenoxy)benzaldehyde (Table 2, entry 3)[7]



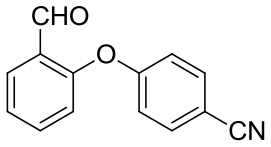
Colourless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.82-6.85 (dd, *J*= 8.4 Hz, 0.9 Hz, 1H), 7.03-7.12 (m, 4H), 7.15-7.21 (m, 1H), 7.47-7.53 (m, 1H), 7.93 (dd, *J*= 7.8 Hz, 1.8 Hz, 1H), 10.50 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 116.6, 116.9, 117.7, 121.0, 121.2, 123.3, 126.6, 128.6, 135.8, 151.9, 157.8, 160.2, 161.0, 189.2.

4. 2-(*o*-Tolyloxy)benzaldehyde (Table IV.2., entry 4)[7]



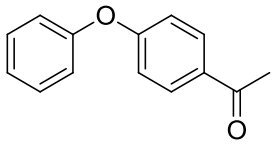
White solid, mp: 50 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.11-7.16 (m, 1H), 7.21-7.24 (m,1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.44-7.47 (m, 1H), 7.93-7.94 (m, 1H), 10.60 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 116.5, 120.2, 122.5, 125.0, 125.8, 127.5, 128.5, 130.1, 131.8, 135.8, 153.5, 160.4, 189.4.

5. 2-(4-Cyanophenoxy)benzaldehyde (Table IV.2., entry 5)[10]



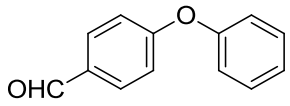
Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04 (d, *J* =8.50 Hz, 1H), 7.35 (t, *J* =7.50 Hz, 1H), 7.10-7.07 (m, 2H), 7.68-7.61 (m, 3H), 7.98 (dd, *J* =8.00, 1.50 Hz, 1H), 10.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 107.2, 118.4, 118.5, 120.5, 125.4, 127.9, 129.4, 134.4, 136.1, 157.2, 160.9, 188.4.

6. 1-(4-Phenoxyphenyl)ethanone (Table IV.2, entry 6)[7]



White solid; mp: 49 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.57 (s, 3H), 6.98-6.99 (m, 2H), 7.00-7.10 (m, 2H), 7.20-7.26 (m, 1H), 7.37-7.42 (m, 2H), 7.94 (dd, *J* = 6.9 Hz, 2.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.4, 117.3, 120.2, 124.6, 130.1, 130.6, 131.9, 155.5, 162.0, 196.8.

7. 4-Phenoxybenzaldehyde (Table IV.2, entry 7)[7]

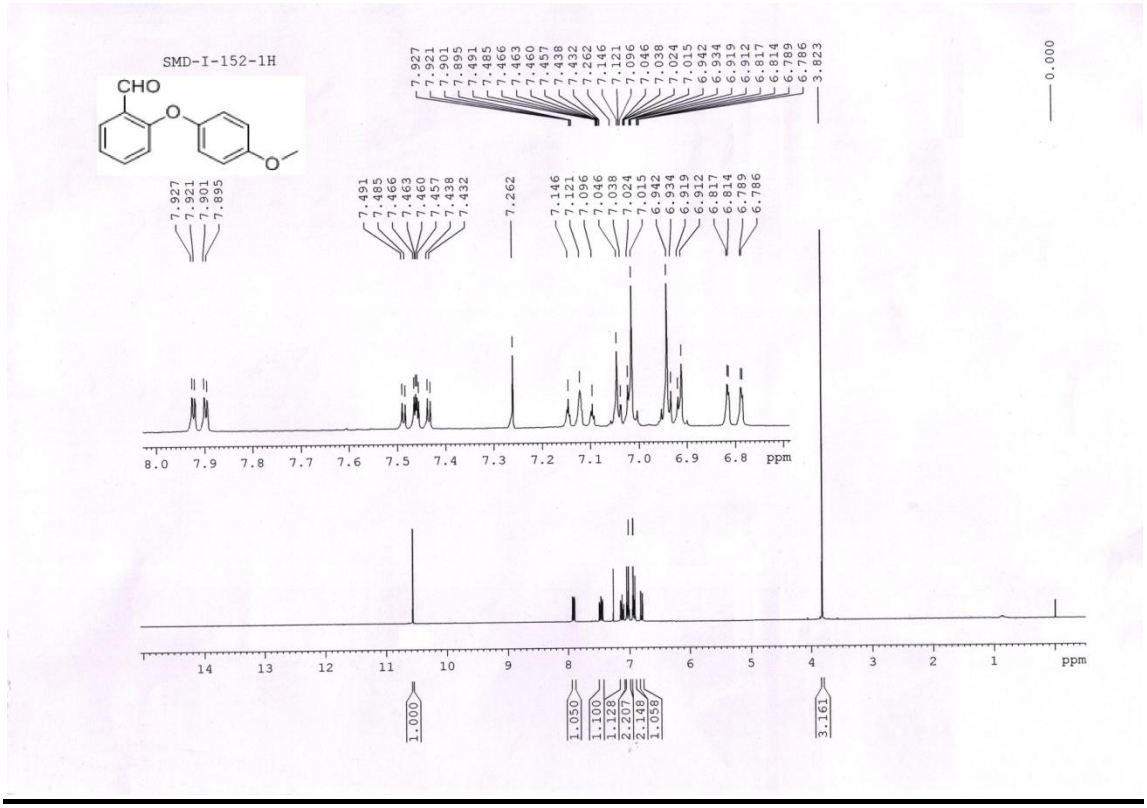


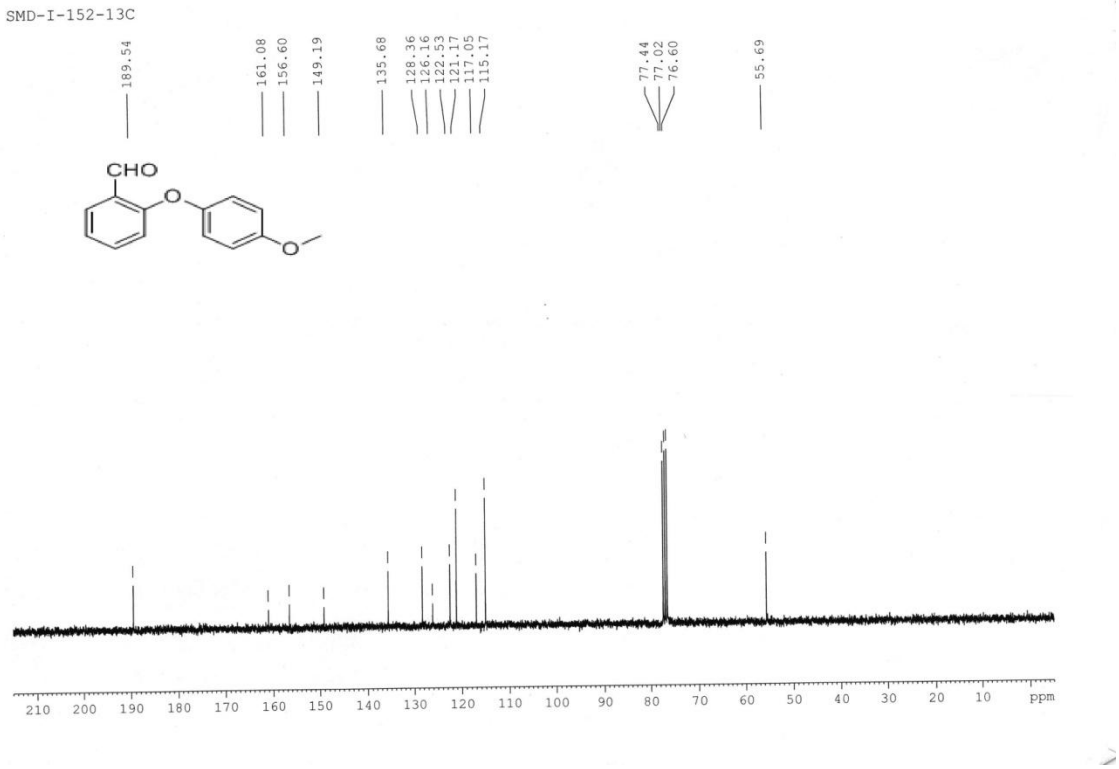
Colourless liquid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00-7.10 (m, 4H), 7.20-7.26 (m, 1H), 7.40-7.45 (m, 2H), 7.84 (dt, *J* = 9.6 Hz, 4.8 Hz, 2.7 Hz, 2H), 9.90 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 117.6, 120.4, 124.9, 130.2, 131.3, 132.0, 155.1, 163.2, 190.8.

IV. E. References

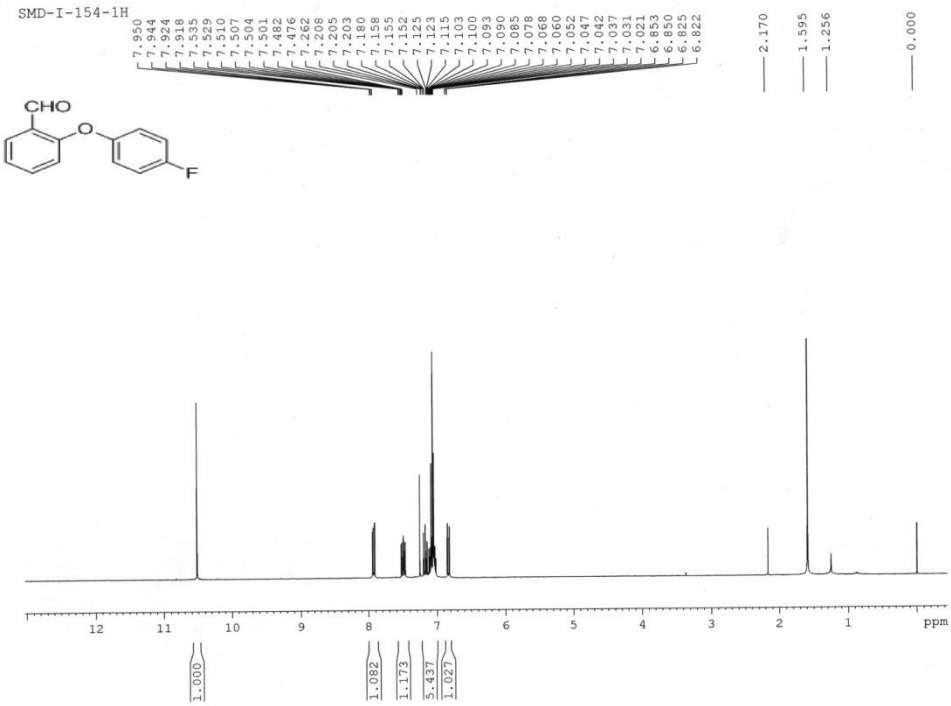
References are given in BIBLIOGRAPHY under Chapter IV (pp-126-127)

^{1}H and ^{13}C Spectra of 2-(4-Methoxyphenoxy)benzaldehyde

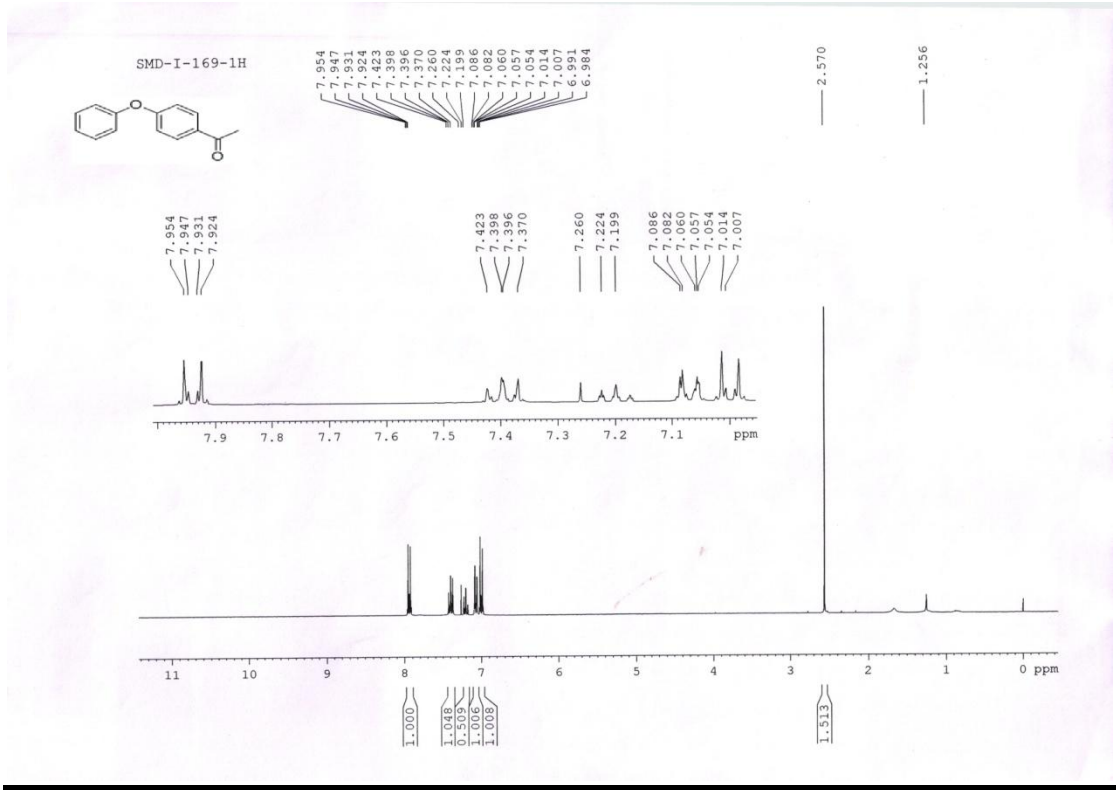


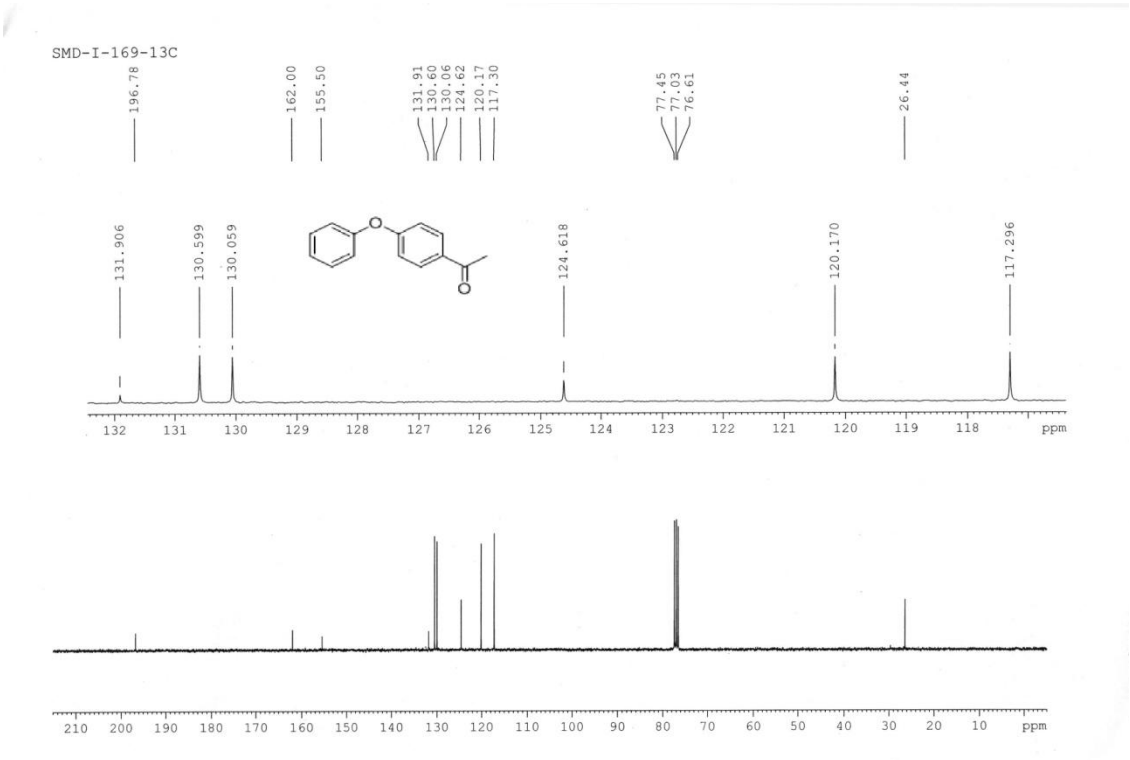


^{1}H and ^{13}C Spectra of 2-(4-Fluorophenoxy)benzaldehyde



^{1}H and ^{13}C Spectra of 1-(4-Phenoxyphenyl)ethanone





^{1}H and ^{13}C Spectra of 4-Phenoxybenzaldehyde