Chapter-2

TBHP Mediated Solvent-Free Cascade C_{sp}^3-H Bond Functionalization of Methyl Arene with Active Methylene Compounds using Et_3N- as a Catalyst

2.1 Introduction

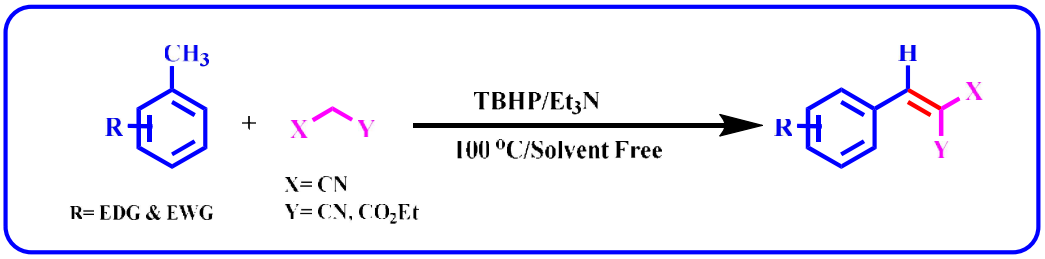
Methyl arenes are the most inexpensive and profuse naturally available substrates, which obtained from crude oil and as a by-product in the production of gasoline and coke. Methyl arenes can serve as the best substrates for the construction of any relevant fine chemicals for the industry due to their easy availability and economic favourability[1]. Recently the selective and controlled oxidation of the benzylic carbon-hydrogen (C–H) bond of methylarene[2][3][4][5] has emerged as an inspiring and challenging topic for the chemist. The conventional method for getting benzaldehyde are non–selective, tiresome, poisonous, and operationally tricky[6][7][8][9]. In this perspective, the direct selective oxidation of methyl arenes to benzaldehydes[10][11][12][13][14][15] is of vital importance. Hence, there is a need of straight, operationally simple, high yielding, green, waste-free, environmentally friendly protocols using benign oxidants and a high–atom economical pathway. The study of Neumann et al. and Pappo et al. on the controlled oxidation of benzaldehydes from methylarenes in high yields [16][17][18] prompted us to develop a method that uses methylarenes as a green, inexpensive, and readily available substrate for the *in-situ* generation of benzaldehydes.

The architecture of C=C bond formation has been a challenge for synthetic organic chemists because it is broadly used in the synthesis of important intermediates

or end-products for perfumes, pharmaceuticals, calcium antagonists, and polymers. Many organic reactions like Heck reaction, Witting reaction, and Knoevenegal condensation give substituted alkenes [19][20]. Knoevenegal condensation yields selective E-alkene [21][22][23][24], which is applied to therapeutic drugs [25], natural products [26], herbicides [27], insecticides, functional polymers [28], and fine chemicals [29] , while other synthetic methods lead to both E/Z alkenes. Recently several attempts have also been made for this reaction in the literature [21-24]. Although all reports have their own merits. However, some of them suffer from certain boundaries, such as costly catalysts, long reaction times, tiresome procedures for preparations of catalysts, and tedious workup conditions. Despite these efforts, the direct access to alkenes through sp^3C-H bond functionalization of methyl arenes (sustainable surrogates) with active methylene compounds is still in high demand (**Scheme 2.1**).

In recent years, there has been developing stress on exploiting and designing environment-friendly, solvent-free reactions[30][31][32] to reduce the amount of toxic waste and by-products arising from chemical processes stimulated by inflexible environment protection laws. Due to the emergent concern for the influence of the organic solvent on the environment as well as on the human body, organic reactions without the use of conventional organic solvents have attracted the attention of synthetic organic chemists. Although some modern solvents, such as ionic liquids and water, have been extensively studied recently, not using a solvent at all is absolutely the best option. The development of solvent-free organic reactions is thus gaining prominence.

As a part of our interest in the C-H functionalization of alkylaryl & their derivatives, we attempted to develop a metal-free oxidative condensation of methyl arenes with malononitrile using trimethylamine (10%) as a catalyst and *tert*-butyl hydroperoxide (TBHP)(3 equivalent) as an oxidant (**Scheme 2.1**). This is a metal-free, practical, inexpensive, non-toxic and environmentally benign method.



Scheme 2.1 Et_3N catalyzed C-H functionalization of methylarene with malononitrile/ ethyl cyanoacetate under solvent-free condition.

2.2 Results and discussion

In order to increase the efficiency of the product, the effect of various parameters such as the effect of mol % of catalyst, type of oxidant, amount of oxidant, temperature, solvents, and molar proportion of the reactants was examined in detail by taking a model reaction of toluene (**1a**) with malononitrile (**2**) in the presence of Et_3N as the catalyst and TBHP as an oxidant under solvent-free conditions at 100°C. As a solvent-free synthesis has achieved great interest, it was essential to examine the reaction under solvent-free conditions. However, the reaction failed to respond when the reactions were carried out in the absence of either catalyst, oxidant or both catalyst and oxidant. Delightfully, the yield of the product was increased by increasing the temperature (**Table 2.1 entries 4&5**) in the presence of 10 mol% of DBU catalyst and 2 equivalent of TBHP oxidant. Various oxidants like H_2O_2, Oxone, $K_2S_2O_8$, and Benzoyl Peroxide were examined (**Table 2.1 entries 6-9**) under solvent-free

conditions, but poor results were obtained. The use of various catalysts such as $Ba(OH)_2$, $^tBuO^-K^+$ and KOH (**Table 2.1, entries 10-12**) endorsed the reaction to a significant level. Further, to increase the efficiency of the product, the amount of catalyst and oxidant was varied because it had a high impact on the yield of the product. To our surprise, 82% yield of the product was obtained using 15 mol% of Et_3N as a catalyst and 3 equivalent of TBHP as an oxidant at 100^0C in 2 h (**Table 2.1 entry 14**). The use of TBHP (decane) instead of TBHP (aq) decreased the reaction yield significantly **(Table 2.1 entry 15**). To examine the effect of solvent, the model reaction was carried out using 15 mol% of Et_3N and 3 eqivalent of TBHP in various organic solvents such as water, ethanol, THF, benzene, acetonitrile, and chloroform **(Table 2.1 entries 18-23)**. The results are shown in table 2.1 and clearly indicate that the solvent-free condition was the best condition among all examined solvents in terms of product yield.

Table 2.1 Optimization of reaction conditions for the Synthesis of **3a**[a]

Entry	Catalyst	Mol %	oxidant	Equivalent	Time(min)	Temp (°C)	Solvent	Yield (%)[b]
1.	-		-	-	120	80	-	–
2.	Et_3N	10	-	-	120	80	-	-
3.	-	-	TBHP (aq)	2	120	80	-	-
4.	DBU	10	TBHP (aq)	2	120	80	-	15
5.	DBU	10	TBHP (aq)	2	120	100	-	22
6	Et_3N	10	H_2O_2	3	120	100	-	35
7	Et_3N	10	Oxone	3	120	100	-	Traces
8	Et_3N	10	$K_2S_2O_8$	3	120	100	-	40
9	Et_3N	10	Benzyl Peroxide	3	120	100	-	38
10.	Ba(OH)2	10	TBHP (aq)	2	120	100	-	28
11.	t-K^+-BuO^-	10	TBHP (aq)	2	120	120	-	32
12.	KOH	10	TBHP (aq)	2	120	100	-	36
13.	Et_3N	10	TBHP (aq)	2	120	100	-	60
14.	**Et_3N**	**15**	**TBHP (aq)**	**3**	**120**	**100**	**-**	**82**
15	Et_3N	15	TBHP (dec)	3	120	100	-	58
16.	Et_3N	10	TBHP (aq)	4	120	100		78
17.	Et_3N	20	TBHP (aq)	3	120	100	-	79
18	Et_3N	10	TBHP (aq)	3	120	100	H_2O	60
19	Et_3N	10	TBHP (aq)	3	120	100	EtOH	55
20	Et_3N	10	TBHP (aq)	3	120	100	THF	54
21	Et_3N	10	TBHP (aq)	3	120	100	Benzene	48
22	Et_3N	10	TBHP (aq)	3	120	100	MeCN	55
23	Et_3N	10	TBHP (aq)	3	120	100	$CHCl_3$	46

[a]Toluene- Malononitrile (1:1)
[b]Isolated Yield

The reaction of toluene (**1**) with malononitrile (**2**) was investigated in detail using different molar proportions of reactants (**Table 2.3**). A perusal of the table clearly indicates that the best result was obtained using Toluene (**1a**) and malononitrile (**2**) in the molar proportion 1:1 with 15 mol% of catalyst and 3 eq. of oxidant TBHP in 2h under solvent-free conditions (**Entry 2, Table 2.2).**

Table 2.2 Effect of molar ratio on condensation of Toluene with Malononitrile on yield of product.

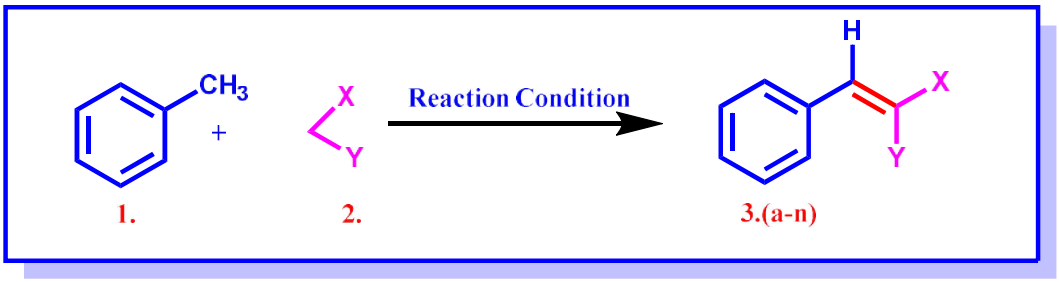
Entry	Molar ratio Toluene: Malononitrile	Time (min)	Yield (%)
1	1 : 0.5	120	60
2	**1 : 1**	**120**	**80**
3	1 : 2	120	65
4	1 : 5	120	Trace

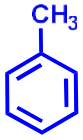
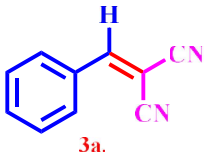
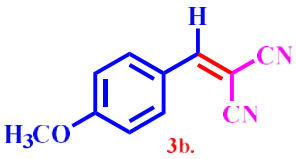
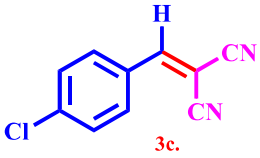
Reaction condition: Toluene and Malononitrile were refluxed in the presence of (aq)TBHP and Et_3N under solvent-free condition

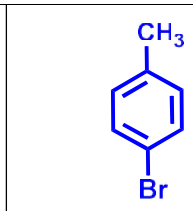
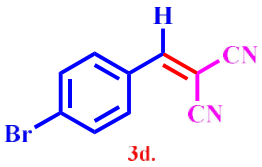
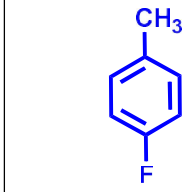
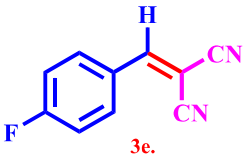
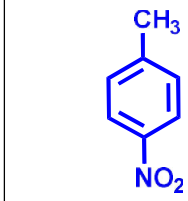
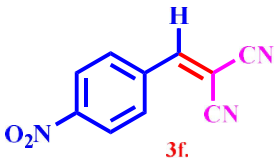
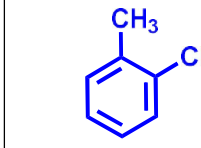
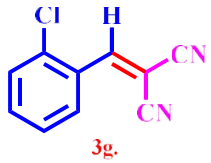
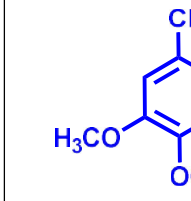
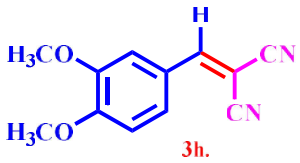
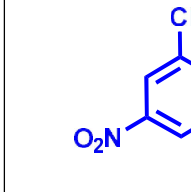
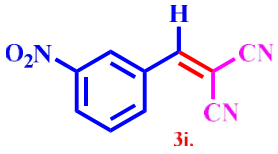
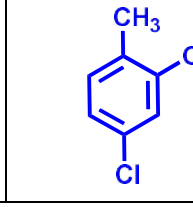
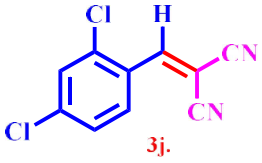
Under the optimized reaction conditions, a variety of active methylene compounds (**2a and 2b**) were allowed to react with toluene (**1a**), 4-methoxytoluene **(1b)**, 4-chlorotoluene **(2C)**, 4-bromotoluene **(2d),** 4-florotoluene **(2e),** 4-nitrotoluene **(2f),** 2-chlorotoluene **(2g),** 3,4-dimethoxytoluene (**2h**), 3-nitrotoluene (**2i**) 2,4-dichlorotoluene (**2j**) 4-methyltoluene **(2k),** 2-methylnapthelene **(2l),** to demonstrate the universal applicability of this methodology. The results are summarized in **Table 2.3**. In most cases, the yield of products was good. According to this result, the effect of electron deficiency and the nature of the substituents on the aromatic rings showed some effect on this condensation reaction. The reaction gave higher yields of the desired

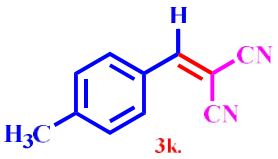
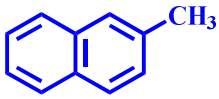
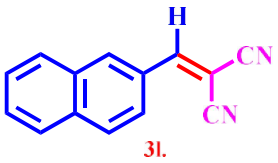
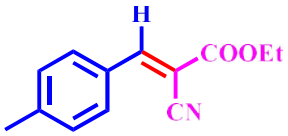
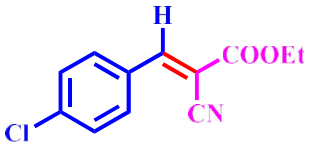
product when the aromatic rings bear an electron-withdrawing group (**Table 2.3**), probably because the electron-withdrawing group increases the polarity of the carbonyl group of *in-situ* generated aromatic aldehyde as compared to the electron donating group. In addition, malononitrile proved to be slightly more efficient than the ethyl cyanoacetate, may be due to the weak electron-withdrawing nature of the acetate group than the cyanide group.

Table 2.3 C-H functionalization of methyl arene with an active methylene compound



Entry	1	2	3[a]	Yield[b] %
1			 3a.	82
2			 3b.	81
3			 3c.	88

4			 3d.	**87**
5			 3e.	**85**
6			 3f.	**90**
7			 3g.	**86**
8			 3h.	**80**
9			 3i.	**86**
10			 3j.	**86**

11			 3k.	**83**
12			 3l.	**86**
13			 3m.	**86**
14			 3n.	**85**

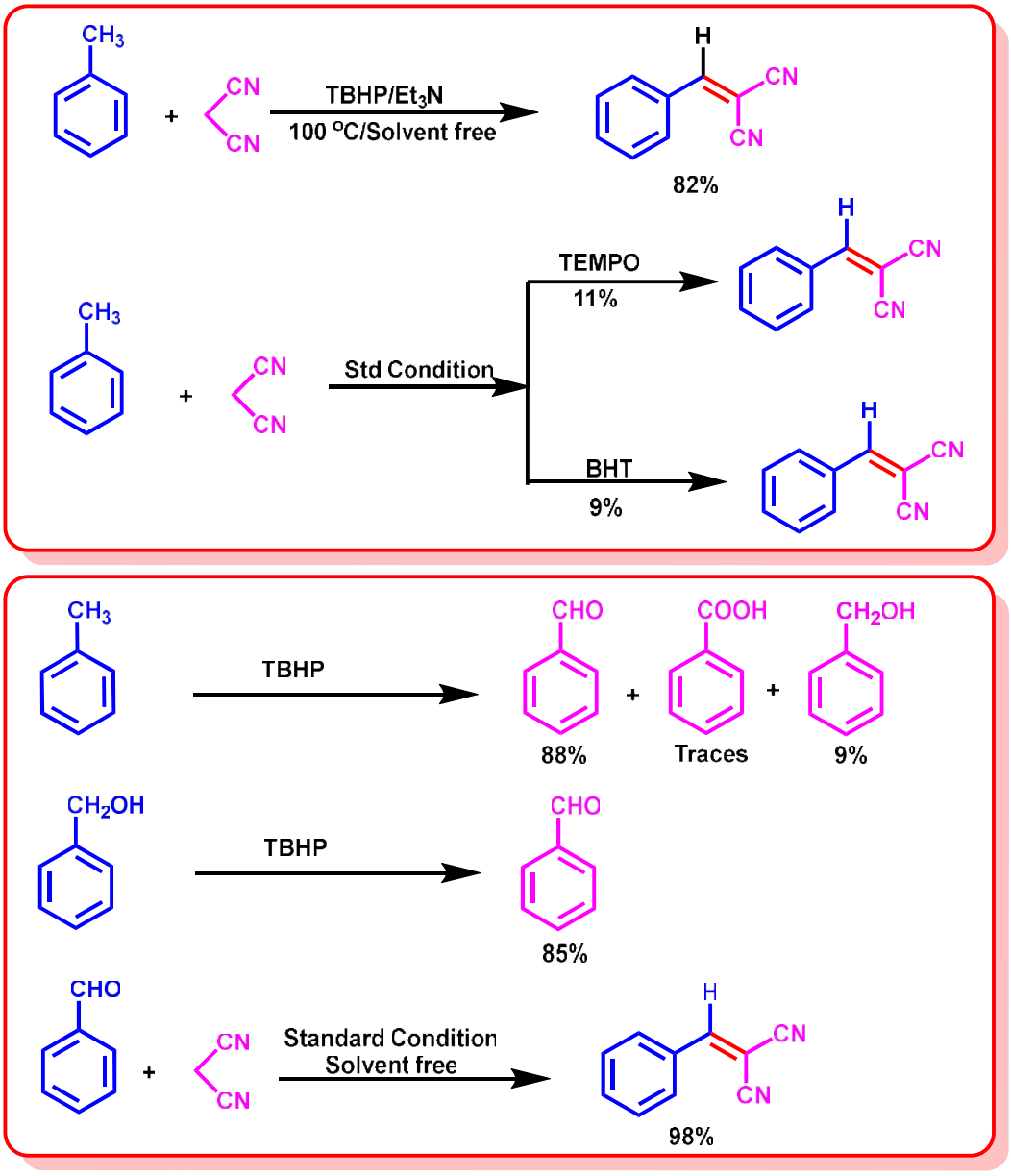
[a] Products were characterized by ^{1}H, ^{13}C NMR and IR analysis.

[b] Isolated yield.

2.3 Control experiment

In order to establish the reaction mechanism, some controlled experiments were carried out in the presence of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) (3 equivalent) and BHT(3 equivalent) under optimized reaction conditions. In the presence of TEMPO, 11% of product was obtained while in the case of BHT 9% of the product was formed. This data confirms the involvement of radical intermediate in the reaction. A blank experiment was carried out by taking toluene with TBHP, which resulted in 85% of benzaldehyde, 10% of benzyl alcohol and trace amounts of benzoic acid. To confirm the intermediacy of benzyl alcohol, it was allowed to undergo the

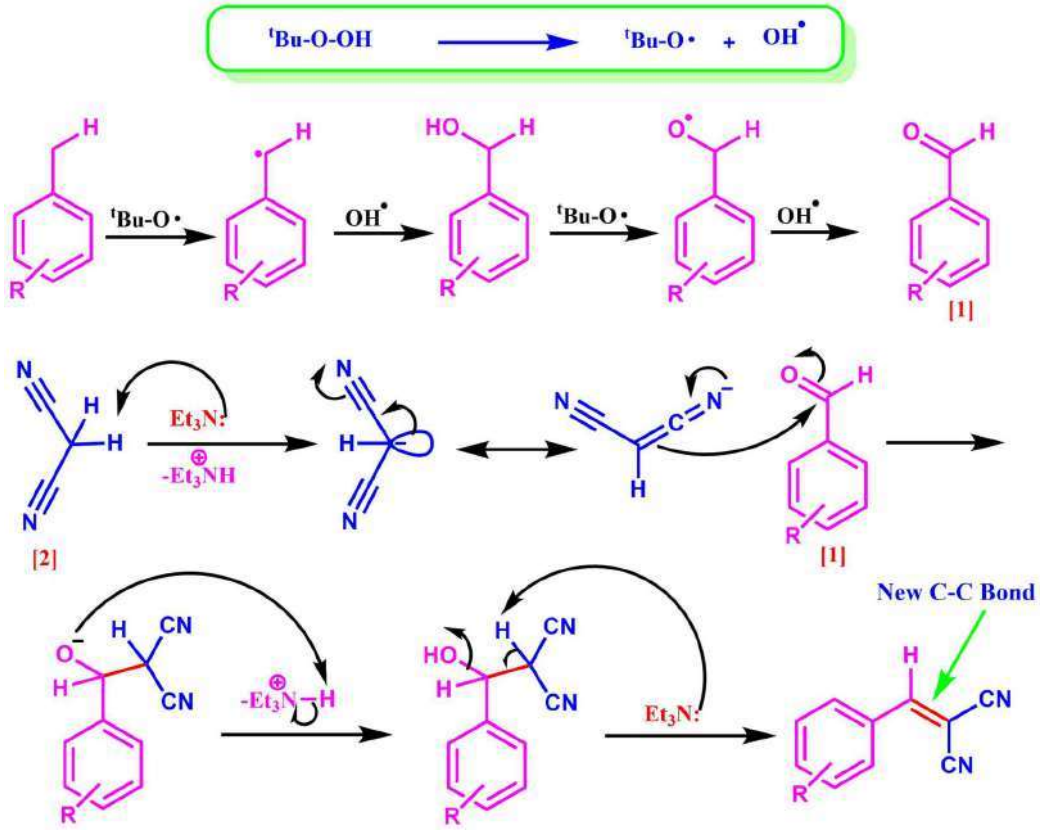
standard reaction and produced the benzaldehyde in 95% yield. Finally, the intermediacy of benzyl alcohol was further confirmed by using it in the Synthesis of alkene under standard reaction conditions.



Scheme 2.2 Control experiments using radical trapping agents

2.4 Mechanism

Based on the reported literature, controlled experiments, and isolation of the products, the following plausible mechanism was proposed (**Scheme 2.3**). TBHP oxidizes the methyl arene to aromatic aldehyde via a radical pathway. Now aromatic aldehyde condenses with malononitrile in the presence of triethylamine. Triethylamine abstracts the H^+ ion from malononitrile, and then this ion condenses with an aromatic aldehyde to give the product i.e. alkene.



Scheme 2.3 Mechanism of C-H functionalization of methyl arene with malononitrile /ethyl cyanoacetate under solvent-free condition

2.5 Conclusion

In summary, a novel and efficient Et_3N catalyzed sp^3 C –H bond functionalization of methyl arenes with active methylene compounds has been designed under solvent-free conditions to provide alkenes/E-alkene. In addition to the broad substrate scope and functional group compatibility, the reaction is effortless and metal-free. Considering its operational ease, effortless availability of substrates and mild reaction conditions, this approach should discover crucial applications in organic Synthesis.

2.6 Experimental Section

2.6.1 General experimental procedure

Under air, a mixture of toluene (1 mmol), active methylene compound (1 mmol), aqueous TBHP (3 mmol), and triethylamine(15mol%) were taken in a 10 mL glass vial containing a Teflon coated magnetic stirrer bar, and the reaction mixture was further heated up to 100 °C for 2 h. After completion of the reaction (TLC), water was added. The reaction mixture was filtered and partitioned between water and ethyl acetate. The organic layer was dried and evaporated by using a rotary evaporator. The residue thus obtained was further subjected to silica gel column chromatography using a mixture of ethyl acetate and hexane as eluent.

2.6.2 Physical and spectral data of representative compounds:

2-Benzylidenemalononitrile(3a)

White solid, m.p.83-84 °C; 82% yield; **^{1}H NMR (500 MHz, $CDCl_3$).** δ 7.93 (d, *J* = 7.7 Hz, 1H), 7.81 (s, 1H), 7.75 – 7.56 (m, 1H), 7.59 (dd, *J* = 26.9, 19.1 Hz, 1H). **^{13}C**

NMR (126 MHz, $CDCl_3$). δ 159.96 (s), 134.64 (s), 130.20 (d, *J* = 137.0 Hz), 113.14 (d, *J* = 145.7 Hz), 82.92 (s).

2-(4-Methoxybezylidene)malononitrile(3b)

Yellow solid, m.p.167-168 °C; 81% yield; **^{1}H NMR (500 MHz, $CDCl_3$).** δ 7.93 (d, *J* = 8.9 Hz, 2H), 7.68 (s, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 3.94 (s, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)**. δ 164.79 (s), 158.85 (s), 133.42 (s), 123.98 (s), 115.10 (s), 114.40 (s), 113.31 (s), 78.51 (s), 55.77 (s).

2-(4-Chlorobezylidene) malononitrile(3c)

White solid, m.p.163-164 °C; 88% yield; **^{1}H NMR (500 MHz, $CDCl_3$).** δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.76 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$).** δ 158.30 (s), 141.16 (s), 131.85 (s), 130.09 (s), 129.31 (s), 113.46 (s), 112.35 (s), 83.39 (s).

2-(4-Bromobezylidene) malononitrile (3d)

White solid, m.p.173-174 °C; 87% yield; **^{1}H NMR (500 MHz, DMSO).** δ 8.52 (s, 1H), 8.14 – 7.56 (m, 4H).**^{13}C NMR (126 MHz, DMSO).** δ 160.74 (s), 133.14 (s), 132.60 (s), 130.84 (s), 128.80 (s), 114.53 (s), 113.47 (s), 82.77 (s).

2-(4-Fourobezylidene)malononitrile (3e)

White solid, m.p.152-153 °C; 85% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.05 – 7.90 (m,2H), 7.78 (s, 1H), 7.25 (t, *J* = 8.4 Hz, 2H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 167.16 (s), 165.09 (s), 158.41 (s), 133.46 (d, *J* = 9.5 Hz), 127.41 (d, *J* = 3.3 Hz), 117.30 (s), 117.12 (s), 113.62 (s), 112.54 (s), 82.40 (d, *J* = 2.6 Hz).

2-(4-Nitrobezylidene)malononitrile (3f)

Light yellow solid, m.p.160.2-163 °C; 90% yield; **^{1}H NMR (500 MHz, DMSO)** δ 8.72 (s, 1H), 8.43 (d, *J* = 8.9 Hz, 2H), 8.14 (d, *J* = 8.7 Hz, 2H).**^{13}C NMR (126 MHz, DMSO)** δ 159.29 (s), 149.70 (s), 131.44 (s), 124.38 (s), 113.62 (s), 112.51 (s), 85.94 (s).

2-(2-Chlorobezylidene)malononitrile (3g)

White solid, m.p.95-96 °C; 86% yield; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 8.28 (d, *J* = 0.5 Hz, 1H), 8.20 (dd, *J* = 4.6, 4.1 Hz, 1H), 7.57 (dd, *J* = 6.2, 2.4 Hz, 2H), 7.51 – 7.41 (m, 1H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 156.06 (s), 136.33 (s), 135.06 (s), 130.72 (s), 129.51 (s), 129.09 (s), 127.81 (s), 113.23 (s), 111.94 (s), 85.81 (s).

2-(2,4-Methoxybezylidene)malononitrile (3h)

White solid, m.p.114-115 °C; 80% yield; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.68 – 7.65 (m, 1H), 7.39 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 3.96 (d, *J* = 25.7 Hz, 2H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 159.15 (s), 154.92 (s), 149.58 (s), 128.17 (s), 124.30 (s), 114.42 (s), 113.59 (s), 111.16 (s), 110.89 (s), 78.42 (s), 56.33 (s), 56.08 (s).

2-(3-Nitrobezylidene)malononitrile (3i)

White solid, m.p.162-163 °C; 90% yield; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 8.69 (d, *J* = 1.6 Hz, 1H), 8.54 – 8.43 (m, 1H), 8.33 (d, *J* = 0.8 Hz, 1H), 7.94 (s, 1H), 7.82 (s, 1H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 157.12 (s), 148.68 (s), 134.94 (s), 131.54 (d, *J* = 128.9 Hz), 131.54 (d, *J* = 128.9 Hz), 128.24 (s), 125.53 (s), 112.71 (s), 111.69 (s), 86.74 (s).

2-(2,4-Dichlorobezylidene)malononitrile (3j)

White solid, m.p.99-100 °C; 86% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.21 (s, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 2.1 Hz, 1H), 7.46 (dd, *J* = 8.6, 2.0 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 154.54 (s), 140.95 (s), 137.07 (s), 130.66 (s), 130.07 (s), 128.30 (s), 127.42 (s), 112.96 (s), 111.71 (s), 85.97 (s).

2-(4-Methylbezylidene)malononitrile (3k)

White solid, m.p.134-135 °C; 83% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.82 (d, *J* = 8.3 Hz, 1H), 7.74 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 2.47 (s, 2H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 159.84 (s), 146.43 (s), 132.47 – 131.04 (m), 128.51 (s), 114.06 (s), 112.92 (s), 81.13 (s), 22.01 (s).

2-(Naphthalen-2-ylmethylene)malononitrile (3l)

Yellow solid, m.p.175-176 °C; 86% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.29 (d, *J* = 0.9 Hz, 1H), 8.08 (dd, *J* = 8.7, 1.9 Hz, 1H), 8.03 – 7.86 (m, 4H), 7.78 – 7.50 (m, 2H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 159.72 (s), 135.90 (s), 134.45 (s), 132.64 (s), 130.01 (s), 129.68 (d, *J* = 1.7 Hz), 128.57 (s), 128.05 (s), 127.76 (s), 124.23 (s), 114.02 (s), 112.88 (s), 82.28 (s).

(Z)-Ethyl 3-(4-methylphenyl)-2-cyanoacrylate (3m)

White solid, m.p.112-113 °C; 86% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (s, 1H), 7.94 – 7.78 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.35 (d, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.37 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.67 (s), 154.87 (s), 144.61 (s), 131.22 (s), 130.01 (s), 128.87 (s), 115.71 (s), 101.56 (s), 62.53 (s), 21.80 (s), 14.15 (s).

(Z)-Ethyl 3-(4-chlorophenyl)-2-cyanoacrylate (3n)

White solid, m.p.89-90 ºC; 85% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.21 (s, 1H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 4.61 – 4.20 (m, 2H), 1.49 – 1.37 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.24 (s), 153.40 (s), 139.59 (s), 132.22 (s), 129.69 (s), 115.28 (s), 103.50 (s), 62.89 (s), 14.15 (s).

2.6.3.1 Spectral Data of Product 2-Benzylidenemalononitrile (2a)

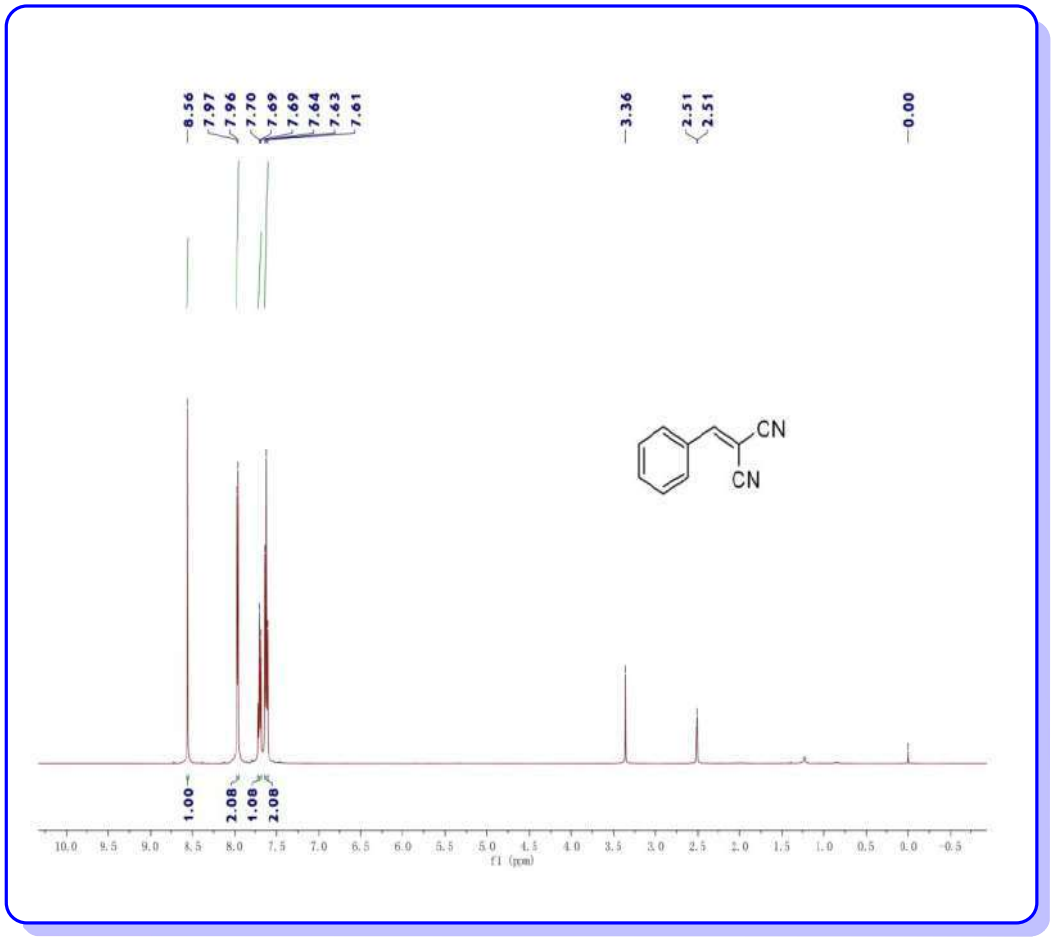


Figure 2.1 ^{1}H NMR of 2-Benzylidenemalononitrile (2a)

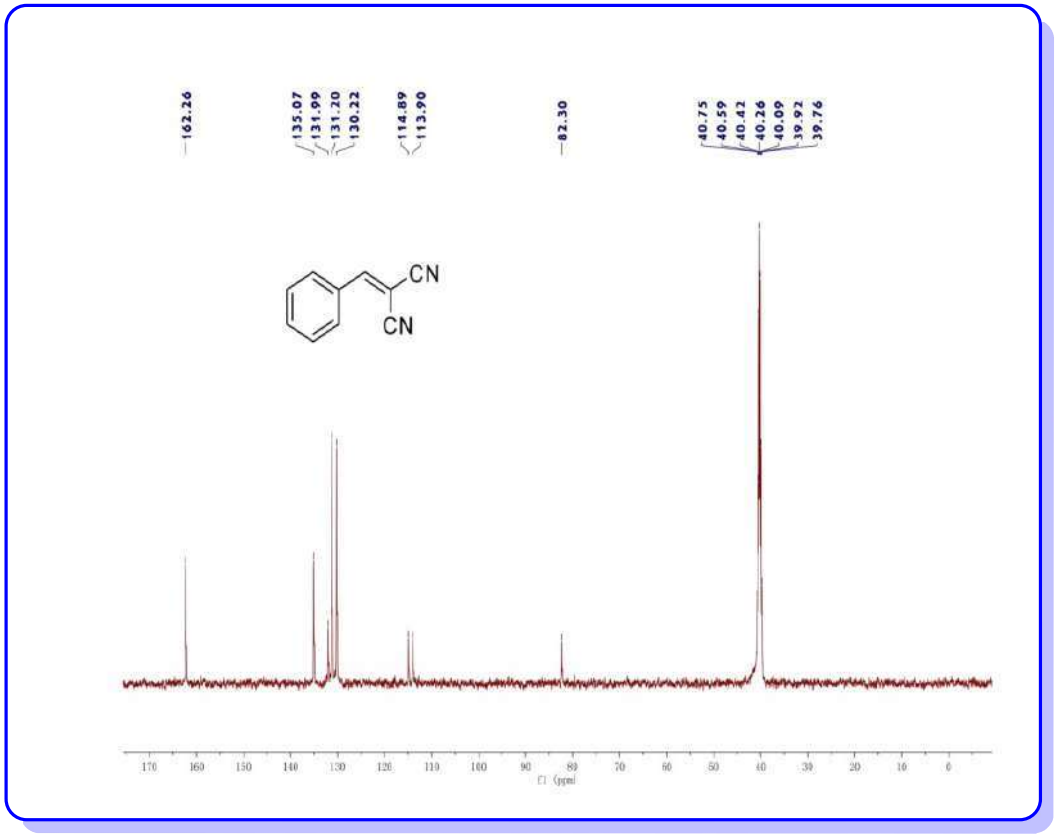


Figure 2.2 ^{13}C NMR of 2-Benzylidenemalononitrile (2a)

2.6.3.2 Spectral Data of Product (Z)-Ethyl 3-(4-chlorophenyl)-2-cyanoacrylate(3n).

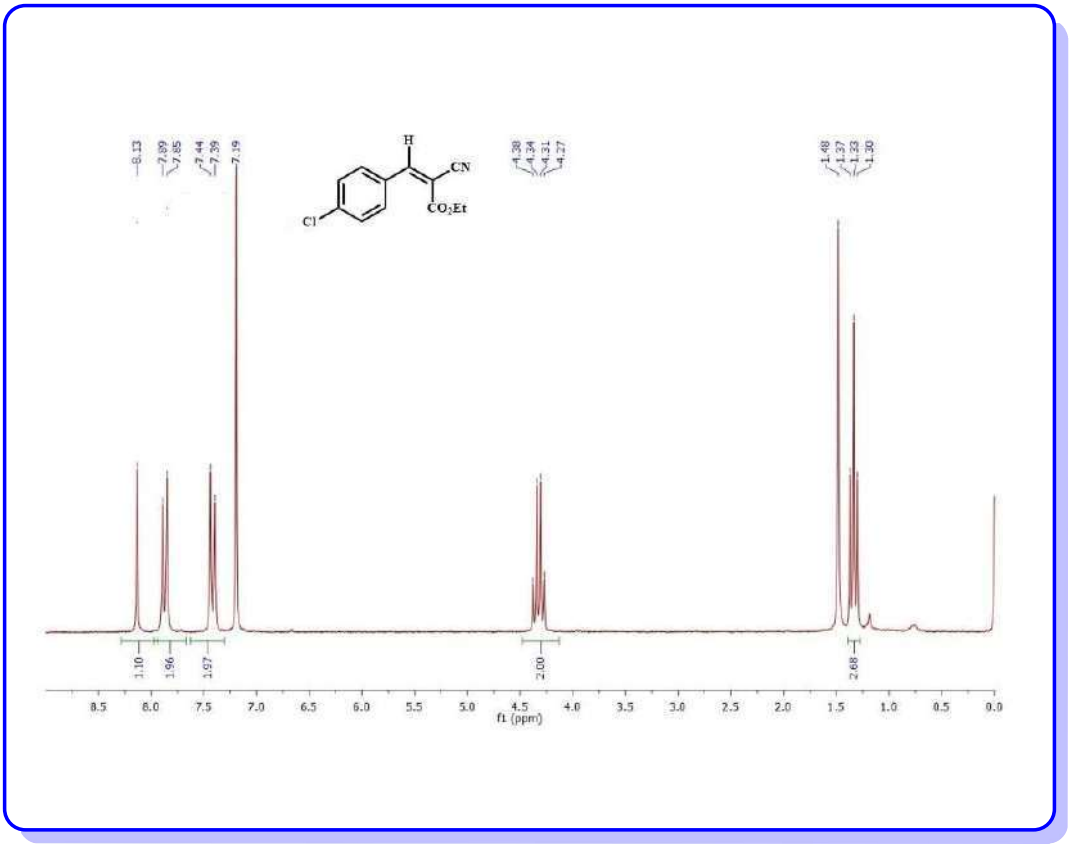


Figure 2.3 ^{1}H NMR of (Z)-Ethyl 3-(4-chlorophenyl)-2-cyanoacrylate(3n).

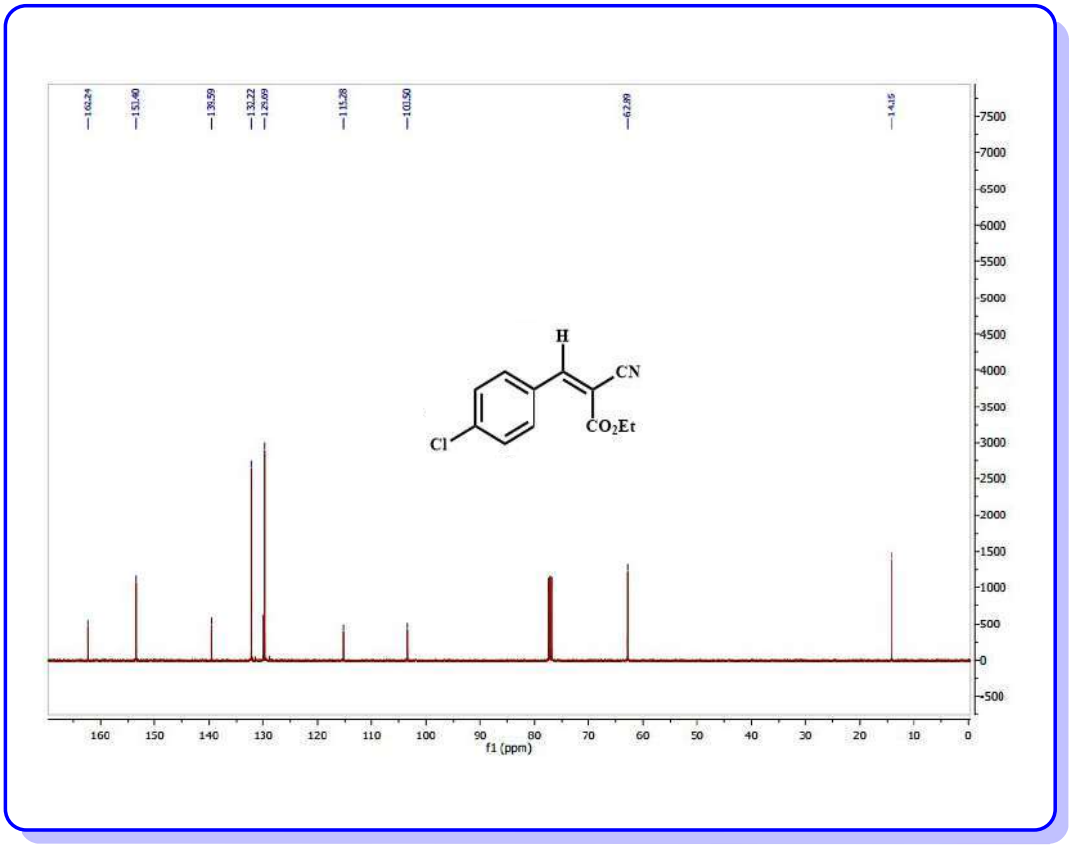


Figure 2.4 ^{13}C NMR of (Z)-Ethyl 3-(4-chlorophenyl)-2-cyanoacrylate(3n).

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