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$CaCl_2$ Catalysed C-acylation of Active Methylene Compounds

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Abstract

Calcium chloride was used as an effective catalyst for the synthesis of tricarbonyl compounds from active methylene compounds and acid chlorides. It is an inexpensive and readily available catalyst for the acylation of active methylene compounds in chloroform at room temperature.

Keywords: $CaCl_2$; C-acylation; Active Methylene Compound; eco-friendly

1 Introduction

The formation of carbon-carbon single bond is of fundamental importance in organic synthesis[1,2]. Acylation reactions are one of the important methods for the C-C bond forming reactions. Tricarbonyl compounds are shown to be act as analgesic, antipyretic, anti-inflammatory agents and also key intermediates in the synthesis of various heterocyclic compounds[3]. Surprisingly, only a limited number of procedures for the synthesis of tricarbonyl compounds have been developed. In most cases tricarbonyl compounds are prepared by *C*-acylation of 1,3-dicarbonyl compounds. Majority of the catalysts used are for the acylation reaction: strong bases such as EtONa [4], BaH_2 [5], EtMgBr [6], *n*-BuLi [7], or powerful reductive metals like Na [8], which are not suitable for sensitive substrates and Rathke [9] et. Al., developed a $MgCl_2$ promoted C-acylation of 1,3-dicarbonyl compounds. Lewis acids such as $SmCl_3$ [10], $InCl_3$, $AlCl_3$, $YbCl_3$, $Y(OTf)_3$, Mg metal, $MgCl_2$ like transition and alkaline metal catalysts were used for the acylation reaction on 1, 3-diketone and β-ketoester [11]. These catalysts are expensive and some catalysts need stoichiometric amounts to carry out the acylation reaction. The product yield is moderate. We have developed an efficient and cost-effective method for the synthesis of tricarbonyl compounds using calcium chloride as the catalyst. "Cheap metals for noble tasks" is the current trend in development of metal based catalysts. Calcium, the fifth most abundant element in the earth's crust (3.4 wt %) fits very well into this trend. This group 2 metal shows significant dose of metal Lewis-acidity, typical for group 3 reagents. Besides using as a routine drying agent in any organic laboratory, application of calcium and its compounds were less exploited in organic synthesis and it is beginning to gain momentum. With respect to green chemistry, calcium is considered as biocompatible and one of its compounds $CaCl_2$ could be considered as a mild green Lewis acid, and is eco-friendly, inexpensive and readily available [12]. $CaCl_2$ was used as a catalyst in some instances, in organic transformations such as for the synthesis of hexanoic acid. 2-(diethylamino)ethyl ester [13], Mannich bases [14], aminophosphonic esters [15,16], Biginelli reaction [17] and aldol reactions [18].

2 Experimental

As part of our synthetic interest on the use of $CaCl_2$ as a catalyst we have examined $CaCl_2$ as a catalyst for the C-acylation reaction on active methylene compounds, which could lead to the formation of tricarbonyl compounds. To find the optimal condition, the reaction was carried out with ethyl acetoacetate and acetyl chloride. Ethylacetoacetate was treated with acetyl chloride in the presence of triethylamine as a base in toluene as a solvent at 25 °C. No product formed even after heating at 60°C, for 6 h. In presence of the catalyst we observed the new spot formation in the thin layer chromatography and the reaction goes to completion only after using excess of acylating agent. The reaction was completed after 6 h, with 90% yield. In the absence of the catalyst there was no change of the reaction. The same reaction was carried out on ethyl acetoacetate with various solvents such as acetonitrile, toluene, nitromethane, chloroform and bases such as DMAP, Et_3N and DABCO. Then we have studied a variation in the quantity of the catalyst, 100 to 5 mol %. There was not much difference in the reaction yield. Finally, we found that 5 mol% of catalyst is enough to carry out the acylation reaction active methylene compound. Based on the standardization study, we found that the optimized condition for the acylation would be 5 mol% of $CaCl_2$ as the catalyst, triethyl amine as the base, $CHCl_3$ the solvent, and the reaction temperature would be room temperature. Then, using the optimum condition (entry 11 in Table 1), we attempted to synthesise a variety of active methylene compounds to establish the scope of

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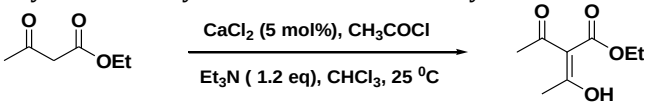
this method. The results are summarized in Table 2.

Table 1. Optimization of the Reaction Condition for Acylation of Ethyl Acetoacetate with Acetyl Chloride.



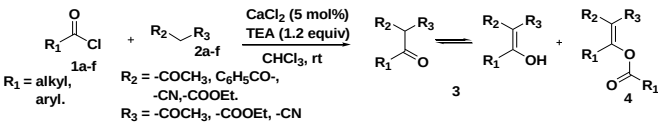
Entry	Solvent	Base	Catalyst mol% ($CaCl_2$)	Time (hr)	Yield (%)
1	$C_6H_5CH_3$	Et_3N	5	6	90
2	$C_6H_5CH_3$	DMAP	5	8	88
3	$C_6H_5CH_3$	DABCO	5	7	83
4	CH_3CN	DMAP	5	8	75
5	CH_3CN	Et_3N	5	6	85
6	CH_3CN	DABCO	5	9	78
7	CH_3NO_2	DMAP	5	8	85
8	CH_3NO_2	Et_3N	5	7	86
9	CH_3NO_2	DABCO	5	7	86
10	$CHCl_3$	DMAP	5	8	78
11	$CHCl_3$	Et_3N	5	6	95
12	$CHCl_3$	DABCO	5	8	85
13	$CHCl_3$	Et_3N	10	6	95
14	$CHCl_3$	Et_3N	20	6	94
15	$CHCl_3$	Et_3N	50	6	94
16	$CHCl_3$	Et_3N	100	6	94

3 Results and Discussion

The reaction of diethyl malonate with acetyl chloride gave the corresponding *C*-acylated diketone (3aa) in good yield (90%). Ethyl benzoylacetate was treated with acetyl chloride the desired product (3ae) was isolated in 87%. Ethyl acetoacetate and diethyl malonate was treated with trichloroacetyl chloride gave the corresponding *C*-acylated diketone (3bd) and (3ba) respectively in good yield. Further, *n*-butyrylchloride was treated with different active methylene compounds such as Ethyl acetoacetate, diethylmalonate, ethylcyano acetate, acetylacetone and malononitrile (entry 7-10 in Table 2) that gives the products in good yield.

In the case of diethylmalonate (2a) with two equivalents of n-butyryl chloride as acylating agent under standardized reaction condition. We observed that the reaction was complete in 7 h. The desired product (4ca) was in 90% yield after column purification. The ^{1}H-NMR shows five protons more in the aromatic region than expected for mono acylation product. Later it was confirmed that this is due to the O-butrylation on C-butrylated product. It means that primarily C-benzoylation takes place, the product enolized form contains more acidic -OH proton because of this the C-acylated product undergo O-benzoylation. Even when one equivalent of benzoyl chloride was used the same product was observed.

Table 2. CaCl2 Catalysed Acylation of Various Active Methylene Compounds



Active methylene compounds: diethyl malonate (2a), malononitrile (2b), ethyl cyanoacetate (2c), ethyl acetoacetate (2d), ethyl benzoyl acetate (2e), acetyl acetone (2f).

Acid Chlorides: Acetyl chloride (1a), trichloro acetylchloride(1b), n-butyl chloride (1c), benzoyl chloride (1d), 4-OMe-C_6H_4COCl (1e), 4-NO_2-C_6H_4COCl (1f).

Entry	R_1	R_2	R_3	Time	Yield (%)
1	CH_3-	-$COCH_3$	-COOEt	6	95(3ad)
2	CH_3-	-COOEt	-COOEt	6	90 (3aa)
3	CH_3-	-COC_6H_5	-COOEt	7	87 (3ae)
4	CH_3-	-CN	-COOEt	6	95 (3ac)
5	CCl_3-	-$COCH_3$	-COOEt	8	95 (3bd)
6	CCl_3-	-COOEt	-COOEt	7	92 (3ba)
7	$CH_3(CH_2)_2$-	-$COCH_3$	-COOEt	6	86 (3cd)
8	$CH_3(CH_2)_2$-	-CN	-COOEt	7	93 (3cc)
9	$CH_3(CH_2)_2$-	-$COCH_3$	-$COCH_3$	6	76 (3cf)
10	$CH_3(CH_2)_2$-	-CN	-CN	6	94 (3cb)
11	C_6H_5-	-$COCH_3$	-COOEt	6	83 (3dd)
12	C_6H_5-	-CN	-COOEt	6	94 (3dc)
13	C_6H_5-	-CN	-CN	6	73 (3db)
14	C_6H_5-	-$COCH_3$	-$COCH_3$	6	71 (3df)
15	$CH_3(CH_2)_2$-	-COOEt	-COOEt	7	90 (4ca)
16	C_6H_5-	-COOEt	-COOEt	6	87 (4da)
17	C_6H_5-	-COC_6H_5	-COOEt	6	91 (4de)
18	4-OMe-C_6H_4-	-COOEt	-COOEt	6	28 (3ea)

Further, benzoylchloride (1d) was used for acylating agents of C-acylation on different active methylene compounds (entry 11-13 in table 2) gave the desired products was isolated in good yield. In the case of benzoyilation of diethyl malonate and ethylbenzoyl acetate (entry 16 and 17 in Table 2) gave the O- benzoylation on C- benzoylation product. Single crystal X-ray for the product 4de (entry 17 in Table 2) unambiguously solved the structure. It means C-benzoylated product enolized and further acylation took place on the -OH to get the O-benzoylation product. With one equivalent of benzoyl chloride also we observed the same product

formation.Then, 4-methoxy benzoylchloride (1e) was treated with diethyl malonate to give the corresponding products C-acylated product entry 18 and 4-nitrobenzoyl chlorides was treated with diethyl malonate to give the corresponding 4-Nitro ethyl benzoate in 87% yield.

X- Ray crystallography

Good quality single crystals of compound **4de** were used for data collection using a Bruker SMART APEX-II diffractometer [19] at room temperature (296 K) equipped with graphite-monochromatic Mo-Kα radiation (λ = 0.71073 Å). Integration and cell refinement were carried out using Bruker SAINT. Absorption corrections were performed by multi-scan method using SADABS [19]. The molecular structures were solved by direct methods (SHELXS-97) and refinement by full-matrix least-squares on F^2 (SHELXL-97) [20]. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms involved in hydrogen bonding were located in electron-density maps, while the other hydrogen atoms were placed in their geometrically idealized positions and constrained to ride on their parent atoms. The program PLATON [21] was used to generate hydrogen bond table, while MERCURY [22] was used for all graphical representation of the results.

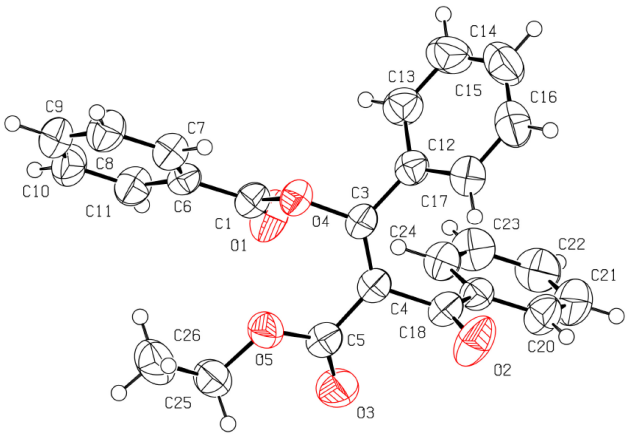


Fig. 1 ORTEP diagram of compound **4de**

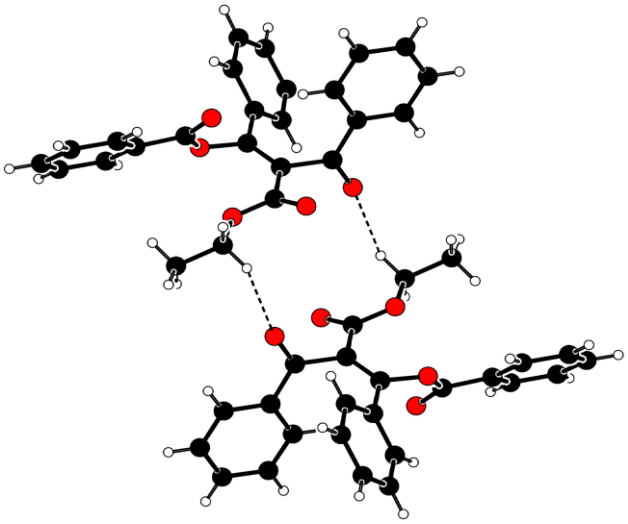


Fig. 2 Hydrogen bonding interaction in compound **4de**

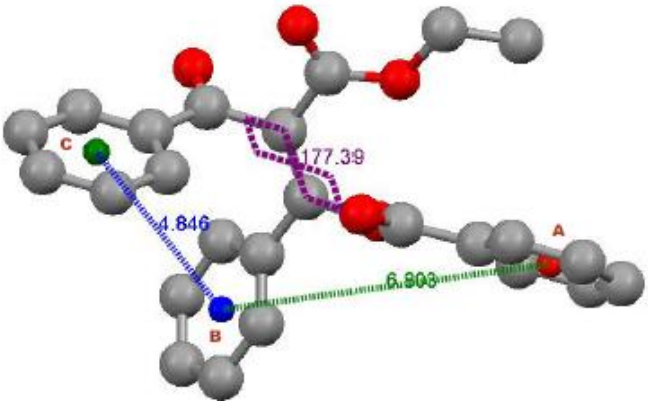


Fig. 3 Hydrogen bonding interaction in compound **4de**

Parameters	X
Empirical formula	$C_{26}H_{22}O_5$
Formula weight	400.41
Temperature (K)	296(2)
Crystal system	Monoclinic
space group	P21/n
Unit cell dimension (Å, °) , a , α	11.1632(2) , 90
b , β	11.7208(2) , 97.766(1)
c, γ	16.2030(2), 90
Volume (Å^3)	2100.58(6)
Z, Calculated density (Mg/m^3)	4, 1.266
Absorption coefficient (mm^{-1})	0.088
F(000)	840
Crystal size (mm)	0.28 x 0.25 x 0.21
θ range for data collection	2.1 to 27.9°
Limiting indices	-12=<h=<14;-5=<k=<13; -21=<l =<21
Reflections collected/ unique	21848/4980,[R(int)=0.0405]
Completeness to θ = 25.00°	99.9 %
Refinement method	Full-matrix least- squares on F2
Data/ restraints/ parameters	4980 / 0 / 272
Goodness-of-fit on F2	1.023
Final R indices [I>2σ(I)]	R1 = 0.041; wR2 = 0.097
R indices (all data)	R1 = 0.068; wR2 = 0.112
Largest diff. peak and hole	0.205 ; -0.164 e.Å^{-3}

4 Conclusions

In summary an efficient and simple C-C bond forming reaction, acylation was achieved using $CaCl_2$ as the catalyst. This C-C bond formation reaction was observed on active methylene compounds such as diethyl malonate, ethyl acetoacetate, ethyl benzoyl acetate, ethyl cyanoacetate, acetyl acetone and malonanitrile. The reaction was successful by simply using 5 mol% of $CaCl_2$ catalyst. This is in contrast to the procedures already reported for the preparation of similar compounds where the use of stoichiometric quantity of the catalyst is necessary.

Reaction time is very short and moderate to very high yield of the triketone was obtained. Benzoylation on ethylbenzoyl acetate and diethyl malonate, butyrylation on diethylmalonate, leads to C-acylation followed by O-acylation in one step. $CaCl_2$ is a heterogeneous, inexpensive, easily available, eco friendly catalyst and simple work up procedure. The resulting tri carbonyl compounds could be used as some important precursor in many organic reactions, and some important biologically active compounds.

Acknowledgements

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Supporting Information

General experimental conditions

All the commercial reagents and solvents were used without further purification unless otherwise stated. All yields reported are based on isolated compounds. TLC separations were carried out on silica gel plates with UV indicator from Aldrich; visualization was by UV fluorescence or by staining with iodine vapor. NMR spectra were recorded on FT-NMR Bruker 400MHz spectrometer as $CDCl_3$ / DMSO solutions with TMS as internal reference.

For compounds already known in the literature Melting Point and ^1H NMR values are given and compared with the spectral data already known and suitable references are also mentioned.

General Procedure A:

A. General procedure for the preparation of tricarbonyl compounds

A mixture of β-ketoester with triethyl amine as a base and 5 mol % of $CaCl_2$ as a catalyst in chloroform solvent. The reaction was carried out at moisture sensitive condition. The reaction mixture was stirred for 40 min at room temperature (25°C). Then the reaction was cooled at 0°C, the acid chloride was added drop wise. After the acid chloride addition cooling was removed, then the stirring was continued for around 6 h, the reaction was completed then the reaction mixture was quenched with $NaHCO_3$ still pH should attain neutral.

1. Synthesis of 2-acetyl-3-hydroxy- but-2-enoic acid ethyl ester (3aa)

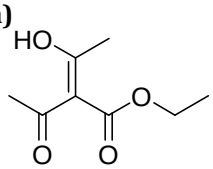

Fig. 3.1 Structure of 2-acetyl-3-hydroxy- but-2-enoic acid ethyl ester (3aa)

A solution of ethylacetoacetate (1000 mg, 7.68 mmol), NEt_3 (933 mg, 9.22mmol) and $CaCl_2$ (42 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25°C). Then the reaction was cooled at 0°C, the acetyl chloride (1210 mg, 15.36 mmol) was added drop wise. After the acetyl chloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The **2-acetyl-3-hydroxy- but-2-enoic acid ethyl ester** (3aa) was obtained (1255 mg, 7.30 mmol) in 95 % yield.

^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, *J* = 6.8 Hz, 3H, -CH_2CH_3), 2.3 (s, 6H, -$COCH_3$), 4.20 (q, *J* = 7.2 Hz, 2H, -CH_2CH_3). Mass Data: m/z: 172.07

2. Synthesis of 2-acetyl-malonic acid diethyl ester (3ba)

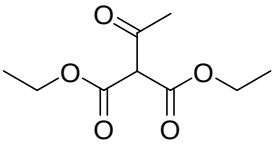

Fig. 3.2 Structure of 2-acetyl-malonic acid diethyl ester (3ba)

A solution of diethyl malonate (1000 mg, 6.24 mmol), NEt_3 (758 mg, 7.49 mmol) and $CaCl_2$ (34 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25°C). Then the reaction was cooled at 0°C, the acetyl chloride (980 mg, 12.48 mmol) was added drop wise. After the acetyl chloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-acetyl-malonic acid diethyl ester (3ba) was obtained (1135 mg, 5.618 mmol) in 90 % yield.

^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 4.4 Hz, 6H, -CH_2CH_3), 2.13 (s, 1.5H, -$COCH_3$), 2.25 (s, 1.5H, -$COCH_3$), 3.3 (s, 1H, -*CH*), 4.17 (q, *J* = 7.2 Hz, 4H, -CH_2CH_3).

Mass Data: m/z: 202.00

3. Synthesis of 2-Benzoyl-3-hydroxy-but-2-enoic acid ethyl ester and 2-(Hydroxy-phenyl-methylene)-3-oxo-butyric acid ethyl ester (3ca)

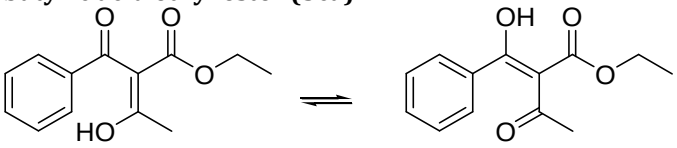

Fig. 3.3 Structure of 2-Benzoyl-3-hydroxy-but-2-enoic acid ethyl ester and 2-(Hydroxy-phenyl-methylene)-3-oxo-butyric acid ethyl ester (3ca)

A solution of Ethyl benzoylacetate (1000 mg, 5.21 mmol), NEt_3 (633 mg, 6.25 mmol) and $CaCl_2$ (29 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room

temperature (25°C). Then the reaction was cooled at 0°C, the acetyl chloride (820 mg, 10.41 mmol) was added drop wise. After the acetyl chloride addition cooling was removed, and then the stirring was continued for 7 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The **2-Benzoyl-3-hydroxy-but-2-enoic acid ethyl ester and 2-(Hydroxy-phenyl-methylene)-3-oxo-butyric acid ethyl ester** (3ca) was obtained (1060 mg, 4.53 mmol) in 87 % yield. The product was exist as syn and anti isomers in the proton NMR spectrum.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.2 Hz, 1.5H, -CH_2*CH_3*), 1.07 (t, *J* = 7.2 Hz, 1.5H, -CH_2*CH_3*), 1.84 (s, 3H, -CO*CH_3*), 1.95 (s, 1.5H, -CO*CH_3*), 2.29 (s, 1.5H, -CO*CH_3*), 2.51 (s, 3H, -CO*CH_3*), 4.05 (q, *J* = 7.2 Hz, 1H, -*CH_2*CH_3), 4.13 (q, *J* = 6.8 Hz, 2H, -*CH_2*CH_3) 7.6 (m, Ar-H). Mass Data: m/z: 234.09

4. Synthesos of 2-Cyano-3-hydroxy-but-2-enoic acid ethyl ester (3ac)

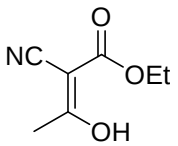

Fig. 3.4 Structure of 2-Cyano-3-hydroxy-but-2-enoic acid ethyl ester (3ac)

A solution of Ethyl cyanoacetate (1000 mg, 8.85 mmol), NEt_3 (1074 mg, 10.62 mmol) and $CaCl_2$ (48 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25°C). Then the reaction was cooled at 0°C, the acetyl chloride (1381 mg, 17.70 mmol) was added drop wise. After the acetyl chloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-Cyano-3-hydroxy-but-2-enoic acid ethyl ester (3ac) was obtained (1303 mg, 8.41 mmol) in 95 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.2 Hz, 3H, -CH_2*CH_3*), 2.35 (s,1H, -*CH_3*), 4.34 (q, *J* = 7.2 Hz, 2H, -*CH_2*CH_3), 13.63 (s, 1H, -OH). ^{13}C NMR ($CDCl_3$) : δ 13.91, 21.16, 62.43, 81.24, 114.68, 169.94, 188.05.

5. Synthesis of 2-Acetyl-4,4,4-trichloro-3-hydroxy-but-2-enoic acid ethyl ester (3ab)

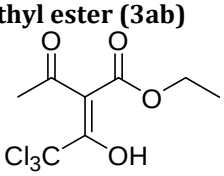

Fig. 3.5 Structure of 2-Acetyl-4,4,4-trichloro-3-hydroxy-but-2-enoic acid ethyl ester (3ab)

A solution of Ethyl acetoacetate (1000 mg, 7.69 mmol), NEt_3 (934 mg, 9.23 mmol) and $CaCl_2$ (42 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25°C). Then the reaction was cooled at 0°C, the trichloro acetylchloride (2800 mg, 15.38 mmol) was added drop wise. After the trichloro acetylchloride addition cooling was removed, and then the stirring was continued for 8 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-Acetyl-4,4,4-trichloro-3-hydroxy-but-2-enoic acid ethyl ester (3ab) was obtained (2000 mg, 7.27 mmol) in 95 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, *J* = 7.2 Hz, 3H, -CH_2*CH_3*), 1.78 (s, 3H, -CO*CH_3*), 3.87 (q, *J* = 6.8 Hz, 2H, -*CH_2*CH_3). Mass Data: m/z: 304.9

6. Synthesis of 2-(2,2,2-trichloro-1-hydroxy-ethylidene)-malonic acid diethyl ester (3bb)

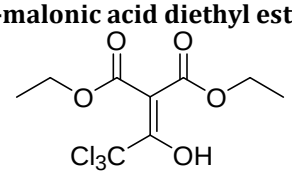

Fig. 3.6 Structure of 2-(2,2,2-trichloro-1-hydroxy-ethylidene)-malonic acid diethyl ester (3bb)

A solution of Diethyl malonate (1000 mg, 6.25 mmol), NEt_3 (758 mg, 7.50 mmol) and $CaCl_2$ (34 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25°C). Then the reaction was cooled at 0°C, the trichloro acetylchloride (2272 mg, 12.50 mmol) was added drop wise. After the trichloro acetylchloride addition cooling was removed, and then the stirring was continued for 7 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with

$NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-(2,2,2-trichloro-1-hydroxy-ethylidene)-malonic acid diethyl ester (3bb) was obtained (1750 mg, 5.75 mmol) in 92 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 6H, -CH_2*CH_3*), 4.24 (q, *J* = 7.2 Hz, 4H, -*CH_2*CH_3). ^{13}C NMR ($CDCl_3$) : δ 13.7, 29.67, 54.34, 62.5, 135.38, 162.34.

Mass Data: m/z:334.9

7. Synthesis of 2- Acetyl-3-oxo-hexanoic acid ethyl ester (3ac)

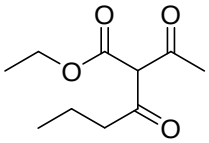

Fig. 3.7 Structure of 2- Acetyl-3-oxo-hexanoic acid ethyl ester (3ac)

A solution of Ethyl acetoacetate (1000 mg, 7.68 mmol), NEt_3 (932 mg, 9.20 mmol) and $CaCl_2$ (42 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the n-butrylchloride (1650 mg, 15.37 mmol) was added drop wise. After the n-butrylchloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The **2- Acetyl-3-oxo-hexanoic acid ethyl ester** (3ac) was obtained (1330 mg, 6.65 mmol) in 86 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.4 Hz, 3H, -CH_2CH_2*CH_3*), 1.20 (t, *J* = 6.4 Hz, 3H, -CH_2*CH_3*), 1.63 (m, 2H, -CH_2*CH_2*CH_3), 2.26 (s, 3H, -CO*CH_3*), 2.32 (t, *J* = 6.4 Hz, 3H, -*CH_2*CH_2CH_3), 4.12 (q, *J* = 6.0 Hz, 2H, -*CH_2*CH_3), 5.58 (s, 1H, -*CH*). ^{13}C NMR ($CDCl_3$) : δ 13.4, 13.7, 18.2, 18.3, 36.1, 60.0, 110.3, 163.8, 165.9, 170.7, 198.5.

8. Synthesis of 2-(1-Butyryloxy-butylidene)-malonic acid diethyl ester (4bc)

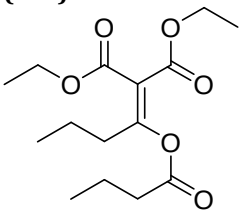

Fig. 3.8 Structure of 2-(1-Butyryloxy-butylidene)-malonic acid diethyl ester (4bc)

A solution of Diethyl malonate (1000 mg, 6.24 mmol), NEt_3 (757 mg, 7.48 mmol) and $CaCl_2$ (34 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the n-butrylchloride (1338 mg, 12.48 mmol) was added drop wise. After the n-butrylchloride addition cooling was removed, and then the stirring was continued for 7 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-(1-Butyryloxy-butylidene)-malonic acid diethyl ester (4bc) was obtained (1700 mg, 5.66 mmol) in 90 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J* = 6.4 Hz, 6H, -CH_2CH_2*CH_3*), 1.26 (t, *J* = 6.0 Hz, 3H, -CH_2*CH_3*), 1.58 (m, 2H, -CH_2*CH_2*CH_3), 1.71 (m, 2H, -$OCOCH_2$*CH_2*CH_3), 2.44 (t, *J* = 6.4 Hz, 2H, -*CH_2*CH_2CH_3), 2.61 (t, *J* = 6.4 Hz, 2H, -OCO*CH_2*CH_2CH_3), 4.22 (q, *J* = 6.0 Hz, 4H, -*CH_2*CH_3). ^{13}C NMR ($CDCl_3$) : δ 13.4, 13.9, 14.1, 18.10, 18.34, 41.00, 41.53, 60.14, 166.68, 170.00.

9. Synthesis of 2-Cyano-3-hydroxy-hex-2-enoic acid ethyl ester (3dc)

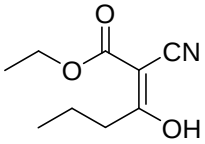

Fig. 3.9 Structure of 2-Cyano-3-hydroxy-hex-2-enoic acid ethyl ester (3dc)

A solution of Ethyl cyanoacetate (1000 mg, 8.85 mmol), NEt_3 (1074 mg, 10.62 mmol) and $CaCl_2$ (48 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the n-butrylchloride (1890 mg, 17.68 mmol) was added drop wise. After the n-butrylchloride addition cooling was removed, and then the stirring was continued for 7 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column

chromatography. The 2-Cyano-3-hydroxy-hex-2-enoic acid ethyl ester (3dc) was obtained (1500 mg, 8.19 mmol) in 93 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, 3H, -CH_2CH_2*CH_3*), 1.29 (t, *J* = 7.2 Hz, 3H, -CH_2*CH_3*), 1.67 (m, 2H, -CH_2*CH_2*CH_3), 2.52 (t, *J* = 7.6 Hz, 2H, -*CH_2*CH_2CH_3), 4.26 (q, *J* = 6.8 Hz, 2H, -*CH_2*CH_3) 13.60 (s, 1H, -OH).

Mass Data: m/z: 182.1

10. Synthesis of 3- acetyl-heptane-2,4-dione (3ec)

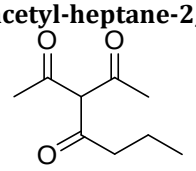

Fig. 3.10 Structure of 3- acetyl-heptane-2,4-dione (3ec)

A solution of Acetyl acetone (1000 mg, 10.00 mmol), NEt_3 (843 mg, 8.33 mmol) and $CaCl_2$ (55 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the n-butrylchloride (2142 mg, 20.00 mmol) was added drop wise. After the n-butrylchloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 3- acetyl-heptane-2,4-dione (3ec) was obtained (1300 mg, 7.64 mmol) in 76 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 6.4 Hz,3H, -CH_2CH_2*CH_3*), 1.63 (m, 2H, *J* = 6.4 Hz, 2H, -CH_2*CH_2*CH_3), 2.14 (s, 3H, -CO*CH3*), 2.23 (s, 3H, -CO*CH3*), 2.33 (t, *J* = 7.2 Hz, 2H, -*CH_2*CH_2CH_3), 6.00 (s, 1H, -CH). ^{13}C NMR ($CDCl_3$) : δ 14.13, 22.70, 23.75, 38.73, 68.17, 128.8, 130.89.

Mass Data: m/z:170.4

11. Synthesis of 2-(1-Hydroxy-butylidene)-malononitrile (3fc)

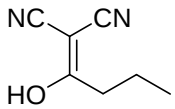

Fig. 3.11 Structure of 2-(1-Hydroxy-butylidene)-malononitrile (3fc)

A solution of Malononitrile (1000 mg, 15.15 mmol), NEt_3 (1839 mg, 18.18 mmol) and $CaCl_2$ (83 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the n-butrylchloride (3250 mg, 30.30 mmol) was added drop wise. After the n-butrylchloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-(1-Hydroxy-butylidene)-malononitrile (3fc) was obtained (1950 mg, 14.30 mmol) in 94 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.2 Hz,3H, -CH_2CH_2*CH_3*), 1.64 (m, 1H, *J* = 7.6 Hz, 1H, -CH_2*CH_2*CH_3), 2.48 (t, 1H, *J* = 7.6 Hz, 1H, -CH_2*CH_2*CH_3), 3.17 (m, *J* = 4.8 Hz, 2H, -*CH_2*CH_2CH_3). ^{13}C NMR ($CDCl_3$) : δ 13.82, 22.89, 37.48, 46.99, 117.88, 119.04, 171.34.

Mass Data: m/z:136.5

12. Synthesis of 2-Benzoyl-3-oxo-butyric acid ethyl ester (3ad)

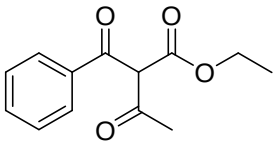

Fig. 3.12 Structure of 2-Benzoyl-3-oxo-butyric acid ethyl ester (3ad)

A solution of ethyl acetoacetate (1000 mg, 7.68 mmol), NEt_3 (933 mg, 9.22 mmol) and $CaCl_2$ (42 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the benzoylchloride (1875 mg, 15.36 mmol) was added drop wise. After the benzoylchloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-(Hydroxy-phenyl-methylene)-3-oxo-butyric acid ethyl ester **and 2-Benzoyl-3-hydroxy-but-2-enoic acid ethyl ester** (3ad) was obtained (1500 mg, 6.40 mmol) in 83 % yield. The product was exist as syn and anti isomers in the proton NMR spectrum.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.2 Hz, 3H, -CH_2*CH_3*), 2.48 (s, 3H, -CO*CH_3*), 4.21 (q, *J* = 7.2 Hz, 1H, -*CH_2*CH_3), 5.82 (s, 1H, -CO*CH*CO-), 7.48 (m, 2H, Ar-H), 7.60 (m, 1H, Ar-H), 8.08 (m, 2H, Ar-H). ^{13}C NMR ($CDCl_3$) : δ 14.26, 18.26, 29.6, 60.26, 110.45, 128.63, 130.12, 133.84, 163.95, 164.17, 166.03

Mass Data: m/z: 233.7

13. Synthesis of 2-(Benzoyloxy-phenyl-methylene)-malonic acid diethyl ester (4bd)

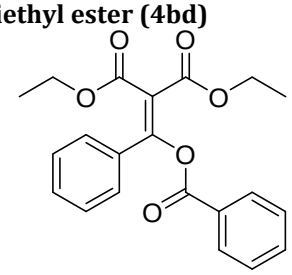

Fig. 3.13 Structure of 2-(Benzoyloxy-phenyl-methylene)-malonic acid diethyl ester (4bd)

A solution of Diethyl malonate (1000 mg, 6.24 mmol), NEt_3 (758 mg, 7.49 mmol) and $CaCl_2$ (34 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the benzoylchloride (1523 mg, 12.49 mmol) was added drop wise. After the benzoylchloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-(Benzoyloxy-phenyl-methylene)-malonic acid diethyl ester (4bd) was obtained (2000 mg, 5.43 mmol) in 87 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 6.8 Hz, 6H, -CH_2*CH_3*), 4.19 (q, *J* = 7.2 Hz, 4H, -*CH_2*CH_3), 7.5 (m, 10H, Ar-H). ^{13}C NMR ($CDCl_3$) : δ 14.2, 60.8, 128.2, 129.4, 130.4, 132.7, 166.4

Mass Data: m/z: 369.7

14. synthesis of 3-benzoyl-pentane-2,4-dione (3df)

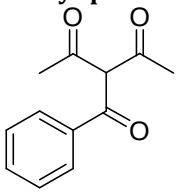

Fig. 3.14 Structure of 3-benzoyl-pentane-2,4-dione (3df)

A solution of Acetyl acetone (1000 mg, 10.00 mmol), NEt_3 (843 mg, 8.33 mmol) and $CaCl_2$ (55 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the benzoylchloride (2811 mg, 20.00 mmol) was added drop wise. After the benzoylchloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 3- acetyl-heptane-2,4-dione (3ec) was obtained (1350 mg, 7.14 mmol) in 71 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15-2.43 (6H, -CO*$CH3$*), 6.22 (s, 1H, -CH), 7.46 (m,2H, Ar-H), 7.60 (m,1H, Ar-H), 8.05 (m,2H, Ar-H). Mass Data: m/z: 203.5

15. Synthesis of 2-Cyano-3-hydroxy-3-phenyl-acrylic acid ethyl ester (3dd)

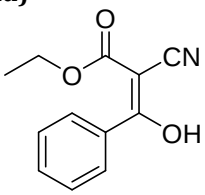

Fig. 3.15 Structure of 2-Cyano-3-hydroxy-3-phenyl-acrylic acid ethyl ester (3dd)

A solution of Ethyl cyanoacetate (1000 mg, 8.85 mmol), NEt_3 (1074 mg, 10.62 mmol) and $CaCl_2$ (49 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the benzoylchloride (2157 mg, 17.68 mmol) was added drop wise. After the benzoylchloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-Cyano-3-hydroxy-3-phenyl-acrylic acid ethyl ester (3dd) was obtained (1810 mg, 8.34 mmol) in 94 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, 3H, -CH_2*CH_3*), 4.3 (q, 2H, -*CH_2*CH_3), 7.5 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$) : δ 14.14, 62.96, 79.0, 115.89, 128.63, 131.51, 133.35, 171.39, 183.04

Mass Data: m/z: 216.6

16.Synthesis of Benzoic acid 2-ethoxycarbonyl-3-diphenyl-propenyl ester (4cd)

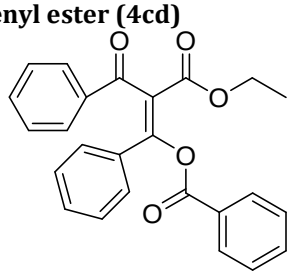

Fig. 3.16 Structure of Benzoic acid 2-ethoxycarbonyl-3-diphenyl-propenyl ester (4cd)

A solution of Ethyl benzoylacetate (1000 mg, 5.21 mmol), NEt_3 (631 mg, 6.24 mmol) and $CaCl_2$ (28.6 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the benzoylchloride (1270 mg, 10.41 mmol) was added drop wise. After the benzoylchloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The Benzoic acid 2-ethoxycarbonyl-3-diphenyl-propenyl ester (4cd) was obtained (1900 mg, 4.75 mmol) in 91 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.2 Hz, 3H, -CH_2*CH_3*), 4.0 (q, *J* = 7.2 Hz, 2H, -*CH_2*CH_3), 7.5 (m,15H, Ar-H). ^{13}C NMR ($CDCl_3$) : δ 13.7, 61.3, 123.1, 128.4, 128.5, 128.6, 128.7, 128.9, 130.4, 130.8, 133.3, 133.5, 133.9, 136.7, 157.1, 162.8, 164.3, 192.2

Mass Data: m/z: 400.4

17. Synthesis of 2-(Hydroxy-phenyl-methylene)-malononitrile (3fd)

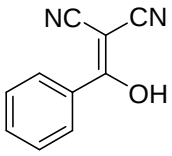

Fig. 3.17 Structure of 2-(Hydroxy-phenyl-methylene)-malononitrile (3fd)

A solution of Malononitrile (1000 mg, 15.15 mmol), NEt_3 (1840 mg, 18.18 mmol) and $CaCl_2$ (83 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the benzoylchloride (3700 mg, 30.30 mmol) was added drop wise. After the benzoylchloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-(Hydroxy-phenyl-methylene)-malononitrile (3fd) was obtained (1900 mg, 11.12 mmol) in 73 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.5 (m,5H, Ar-H). ^{13}C NMR ($CDCl_3$) :

29.79, 128.38, 128.54, 129.18, 129.33, 130.21, 133.89, 134.66, 162.43, 172.30.

18.Synthesis of 2-(4-Methoxy-benzoyl)-malonic acid diethyl ester (3be)

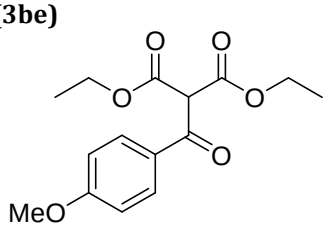

Fig. 3.18 Structure of 2-(4-Methoxy-benzoyl)-malonic acid diethyl ester (3be)

A solution of Diethyl malonate (750 mg, 4.68 mmol), NEt_3 (568 mg, 5.62 mmol) and $CaCl_2$ (26 mg, 5 mol%) in chloroform (20 mL) was taken in a100 mL of round bottom flask equipped with calcium chloride guard tube. The reaction mixture was stirred for 40 min at room temperature (25^{o}C). Then the reaction was cooled at 0^{o}C, the 4-methoxy benzoylchloride (1751 mg, 10.30 mmol) was added drop wise. After the 4-methoxy benzoylchloride addition cooling was removed, and then the stirring was continued for 6 h, the progress of the reaction was monitored by thin layer chromatography using hexane-ethyl acetate solvent system (95:5). The reaction was completed then the reaction mixture was quenched with $NaHCO_3$ solution still pH of the reaction should attain neutral pH. The reaction mixture extracted with chloroform. Organic layer was separated and the aqueous layer was extracted with chloroform, the combined organic layer was washed with water dried by (Na_2SO_4). The filtrate was concentrated and the crude product was purified by column chromatography. The 2-(4-Methoxy-benzoyl)-malonic acid diethyl ester (3be) was obtained (350 mg, 1.32 mmol) in 28 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, *J* = 4.4 Hz, 6H, -CH_2*CH_3*), 3.8 (s, 1H, -OCH_3), 4.25 (q, *J* = 6.8 Hz, 4H, -*CH_2*CH_3), 5.2 (s, 1H, -CH), 6.9 (d,4H, Ar-H), 7.8 (d,4H, Ar-H). ^{13}C NMR ($CDCl_3$) : δ 14.13, 55.00, 60.34, 113.35, 122.72, 131.30, 163.14, 165.98

Mass Data: m/z: 293.8