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Synthesis and Crystal structure studies of Diethyl-(6-chloro-2-carbazolyl) Methyl malonate an intermediate in the synthesis of Anti-inflammatory drug Carprofen

Gaonkar Santosh L.[1], Mahendra M.[2], Nanjunda Swamy S,[3], Shetty Nitinkumar S.[1]
[1]Dept of Chemistry, Manipal Institute of Technolgy, Manipal University, Manipal, Karnataka, INDIA
[2]Department of Studies in Physics, University of Mysore, Mysore, INDIA
[3]Dept of Biotechnology, Sri Jayachamarajendra College of Engineering, Mysore, INDIA

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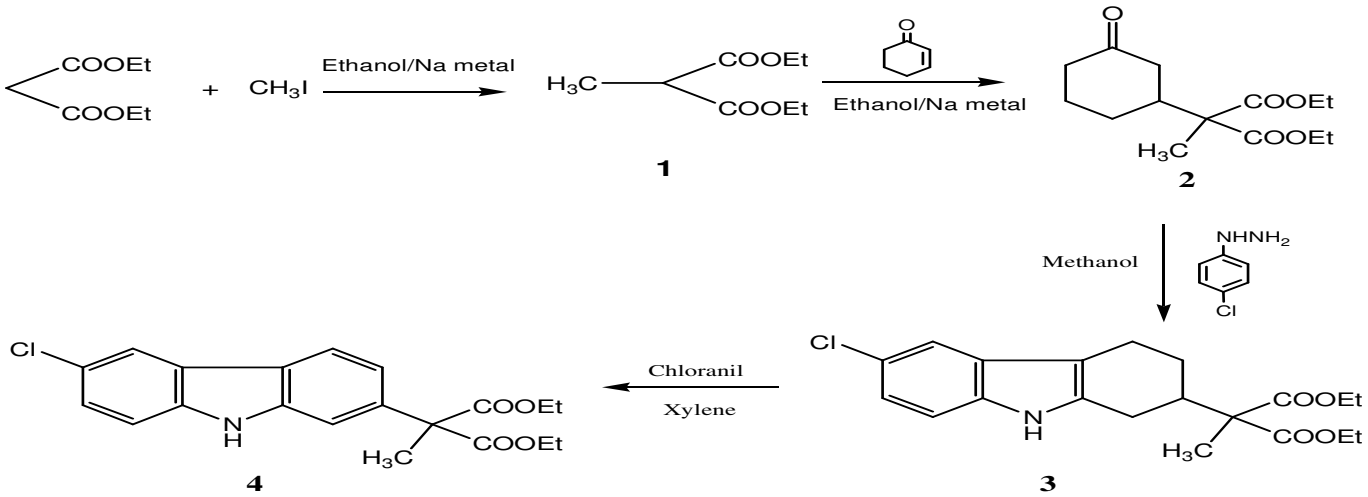
Abstract

Diethyl-(6-chloro-2-carbazolyl)methyl malonate, an intermediate in the synthesis of anti-inflammatory drug Carprofen and number of biologically active heterocycles, was synthesized and X-ray studies have been performed. The crystal structure analysis shows the title compound crystallizes in triclinic class under the space group P-1 with cell parameters, a = 9.3408(11) °A, b = 10.4853(12) °A, c = 11.1601(13) °A α = 113.623(6)°, β = 105.130(6)°, γ = 93.040(6)° and Z=2. The molecule exhibits N-H-O type intermolecular hydrogen bond.

Keywords: Anti-inflammatory drug carprofen biologically active heterocycles, intermolecular hydrogen bond.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutic agents. They inhibit the biosynthesis of prostaglandins, preventing their interactions with pain receptors to other mediators of inflammation. Carprofen is a well-known nonsteroidal anti-inflammatory analgesic with antipyretic activity[1-2]. Although its mechanisms of action and pharmacokinetics are well documented[3], carprofen has its own special properties[4-6]. It has a halflife of 10 to 12 hours and has shown no fecal blood loss. It is effective for acute and chronic pain while being unique in causing no gastrointestinal effects[7-10]. It is also used for treatment of peptic ulcer diseases[11] and shows broad spectrum of activities[12]. The title Diethyl-(6-chloro-2-carbazolyl) methyl malonate is an intermediate in the synthesis of carprofen and number of biologically active heterocycles. In continuation of our studies on biologically active heterocycles[13-16] and to study structural confirmation details, we report herein the synthesis and crystal structure of the title compound.



Scheme 1

Chemistry: Diethyl malonate was methylated using CH_3I in presence of sodium metal in ethanol medium. The resulting product diethyl methyl malonate **1** was coupled with cyclohexenone in presence of sodium metal in ethanol to gave diethyl ester **2.** The diethyl ester **2** was refluxed with p-chloro phenyl hydrazine to gave tetrahydrocarbazole **3**, which was oxidized in presence of chloranil to gave the title compound **4** in good yield and purity (scheme 1). The formation of the product was confirmed on the basis of X-ray studies, ^{1}H NMR, ^{13}C NMR and elemental analyses. ^{1}H NMR ($CDCl_3$) of **4** shows a triplet at δ 1.26 for 6 protons due to two CH_3 groups, a quartet at δ 4.24 for 4 protons due to two CH_2 groups and a singlet at δ 2.01 for 3 protons due to CH_3 group of diethyl malonate side chain. A broad singlet observed at δ 8.42 due to NH group of carbazole ring. Aromatic protons are observed in the region δ 6.96-7.68. ^{13}C NMR showed all the peaks in the expected region.

Material and Methods

Preparation of diethyl methyl malonate 1: A three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, under nitrogen atmosphere, was charged ethanol (100 ml). Sodium metal (4.3 g, 0.187 mol) was charged lot wise and stirred till clear solution. A dropping funnel was charged with diethyl malonate (25 g, 0.156 mol), added drop wise over 20-30 min. The mixture was stirred for 1 hr at rt. The reaction mixture was cooled to 5-10 ^{0}C. Methyl iodide (24.3 g, 0.171 mol) in ethanol (25 ml) was charged into a dropping funnel and added drop wise to the reaction mixture for a period of 30 min. After the addition the reaction mixture was stirred at rt for 5 hr. Ethanol was removed and the residual mass was added water and extracted into methylene dichloride (2 X 50 ml), washed with water and dried. The condenser was attached along with fractionating column and the product was distilled at 58-62 ^{0}C at 0.5 mm Hg to yield 21.25 g (78%).

Preparation of α-methyl-3-oxocyclohexanemalonic acid diethyl ester 2: A three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, under nitrogen atm, was charged ethanol (50 ml). Sodium metal (0.4 g, 17.39 mmol) was charged and stirred till clear solution. Diethyl methyl malonate (18.12 gm, 0.104 mol) was charged to reaction mixture at room temperature. A dropping funnel was charged with cyclohexenone (10 g, 0.104 mol) in ethanol (20 ml), added dropwise for 30 min. The mixture was heated to reflux and maintained for 2-3 h. The reaction mixture was cooled to 5-10 ^{0}C and neutralized with acetic acid. Ethanol was removed and the residue left behind was extracted into methylene dichloride (2 X 50 ml), washed with water and dried. Condenser was attached along with fractionating column and the product was distilled at 140-146^{0}C at 0.5 mm Hg to yield 22.04 g (78%).

Preparation of diethyl-(6-chloro-1,2,3,4-tetrahydro-2-carbazolyl)methylmalonate 3: A three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, under nitrogen atm, was charged ethanol (25 ml) and α-methyl-3-oxocyclohexanemalonic acid diethyl ester **2** (10 g, 36.99 mmol). 4-Chlorophenyl hydrazine hydrochloride (6.64 g, 37.08 mmol) was charged and the mixture was stirred at rt for 2 hrs. The temperature was raised to reflux and maintained for 2 hr. The mixture was cooled, and the solid formed was filtered to gave diethyl -(6 -chloro-1,2,3,4 -tetrahydro-2-carbazolyl) methyl-malonate **3** as off white solid to yield 11.33 g (81 %). mp 128 – 130 ^{0}C.

Preparation of diethyl-[6-chloro-2-carbazolyl]methylmalonate 4: A three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, under nitrogen atm, was charged xylene (50 ml), diethyl-(6-chloro-1,2,3,4-tetrahydro-2-carbazolyl)methylmalonate 3 (10 g, 26.46 mmol) and *p*-chloranil (13.28 g, 54 mmol). The mixture was heated to 150-155^{0}C and maintained for 6 h. The mixture was cooled to rt, insolubles were filtered. The filtrate was washed with 1N NaOH, water and dried. Xylene was removed under vacuum and the residue left behind was crystallized from acetic acid to gave 4 as white crystalline solid to yield 7.2 g (73 %). mp 135-137 ^{0}C (Lit.[17] mp 134-136 ^{0}C); ^{1}H NMR ($CDCl_3$): δ 1.26 (6H, t, *J* = 7.3 Hz, 2XCH$_2$*CH$_3$*), 2.01 (3H, s, *CH$_3$*), 4.24 (4H, q, *J* = 7.3 Hz, 2XC*H$_2$*CH$_3$), 6.96-7.68 (6H, m, Ar*H*), 8.42 (1H, bs, N*H*); ^{13}C NMR ($CDCl_3$): δ 14.6 (2C), 22.3, 57.6, 60.9 (2C), 112.2, 112.8, 119.1, 119.5, 121.4, 121.7, 124.6, 126.3, 126.6, 130.1, 135.4, 169.8 (2C); Anal. Calcd for $C_{20}H_{20}ClNO_4$: C, 64.26, H, 5.39, N, 3.75 %. Found: C, 64.39, H, 5.47, N, 3.70%.

X-ray Crystal structure determination of 4: A single crystal of **4** of dimensions 0.25×0.25×0.24 mm was chosen for X-ray diffraction studies. The measurements were made on a Bruker APEX-II CCD area detector with graphite monochromated radiation (MoK*α*). Raw data was processed and reduced by using APEX2 and SAINT[18]. The peaks were indexed successfully with primitive lattice and were consistent with the centrosymmetric space group P-1. A multi-scan absorption correction was applied (absorption coefficient μ = 0.225 mm^{-1}), and the maximum and minimum transmission factors were 0.9480 and 0.9459. After the correction, the resulting 4772 data were used in the least squares refinement.

The structure was solved by direct methods using SHELXS[19]. All the non-hydrogen atoms were revealed in the first map itself. Initially fullmatrix least-squares refinement using 4772 reflections with isotropic temperature factors for all the non-hydrogen atoms was carried out by SHELXL[20]. Subsequent refinements were carrried out with anisotropic thermal parameters for non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms which were placed at chemically acceptable positions. After eight cycles of refinement the final residual indices saturated to R1 = 0.0.0706 for 4772 reflections. An isotropic extinction parameter was refined to a final value of 0.04. The weighting parameters were 0.09 and 0.59. Successful convergence was indicated by the maximum shift/error of 0.000 for the last cycle of least squares refinement. The details of

crystal data and refinement are given in table 1 (CCDC NO.775402)[21].

Results and Discussion

The final positional coordinates of all the atoms, bond distances and bond angles are given in tables 2–4 respectively. The bond distances and bond angles are in good agreement with the related compounds values[22,23]. However, there may be slight bond length variations across the C13 substituent position of carbazole ring (see table 3). Also, bond length and angles of the diethyl ester group are slightly deviated from the usual standard values (see table 3 and 4). Figure 1 represents the ORTEP diagram[24] of the molecule **4** with thermal ellipsoids at 50% probability. The carbazolyl moiety is highly planar with maximum deviation of 0.010 Å at C13. 6-chloro group is essentially planar with the carbazole moiety, while diethyl methyl malonate group and carbazole ring system are non-coplanar to each other. This non-coplanarity can be viewed with a dihedral angle of 82.6° between the planes and indicates approximately perpendicular orientation. The terminal carbon atoms C21 and C26 of diethyl-ester groups shows slightly high thermal displacement parameters, and this may be due to some steric hindrance factor and high electron withdrawing character. The structure exhibits intermolecular hydrogen bond of the type N-H…O (N10-H10-O23), which helps in stabilizing the crystal structure. It has a length of 2.927(3) Å and an angle of 161° with their symmetry equivalent position 1-x,1-y,1-z. The molecules when extended along the three directions indicated that they are interlinked by the hydrogen bonds forming infinite chains with good π-π stacking interactions.

Conclusion

In conclusion, Diethyl-(6-chloro-2-carbazolyl)methyl malonate a well-known intermediate for the synthesis of number of biologically active heterocycles was synthesized and the structure of the compound was confirmed by single crystal x-ray studies.

Acknowledgements

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Table1
Experimental X-ray Crystallography Details

Empirical formula	$C_{20}H_{20}Cl\ NO_4$
Formula weight	373.82
Temperature	296(2)K
Wavelength	0.71073°A
Crystal system	Triclinic
Space group	P-1
Cell dimensions	a = 9.3408(11) Å, b = 10.4853(12) Å, c = 11.1601(13) Å, dα = 113.623(6)°, β = 105.130(6)°, √ = 93.040(6)°
Volume	951.25(19) $Å^3$
Z	2
Density (calculated)	1.305 Mg/m^3
Absorption coefficient	0.225 mm^{-1}
F_{000}	392
Crystal size	0.25 ×0.25 ×0.24 mm
Theta range for data collection	2.09 to 28.40
Index ranges	$-12 \le h \le 12$, $-14 \le k \le 13$, $-14 \le l \le 14$
Reflections collected	17118
Independent reflections	4722[R (int) = 0.0298]
Refinement method	Full-matrix least-squares on F^2
Max. and min. transmission	0.9480 and 0.9459
Data / restraints / parameters	4722 / 0 / 231
Goodness-of-fit on F^2	1.065
Final R indices [I > 2σ (I)]	$R1$ = 0.0706, $\omega R2$ = 0.1999
R indices (all data)	$R1$ = 0.0865, $\omega R2$ = 0.2164
Extinction coefficient	0.046(7)
Largest diff. peak and hole	0.880 and -0.642 e. $Å^{-3}$

Table-2
Atomic Coordinates and Equivalent Thermal Parameters of the Non-Hydrogen Atoms

Atom	x	y	z	U_{eq}
C11	0.07099(11)	0.57833(8)	0.25461(10)	0.0857(3)
N10	0.3757(2)	1.1664(2)	0.5053(2)	0.0487(5)
C4	0.3161(2)	0.9419(2)	0.3363(2)	0.0432(5)
C14	0.5308(2)	1.2765(2)	0.4076(2)	0.0435(5)
C13	0.5825(3)	1.2490(2)	0.2958(2)	0.0435(5)
C11	0.4662(3)	1.0004(2)	0.1920(2)	0.0485(5)
C8	0.4103(2)	1.0273(2)	0.3022(2)	0.0423(5)
C22	0.5458(3)	1.4362(2)	0.2120(2)	0.0522(6)
C9	0.4440(2)	1.1654(2)	0.4093(2)	0.0419(5)
O24	0.4452(2)	1.3400(2)	0.1014(2)	0.0689(6)
C3	0.2464(3)	0.8004(2)	0.2703(3)	0.0500(5)
C15	0.6640(3)	1.3709(2)	0.2818(2)	0.0469(5)
C2	0.1606(3)	0.7544(3)	0.3339(3)	0.0555(6)
C12	0.5508(3)	1.1108(2)	0.1895(2)	0.0500(5)
C17	0.7614(3)	1.3179(3)	0.1874(3)	0.0579(6)
O18	0.7470(3)	1.3292(3)	0.0831(2)	0.0816(7)
C5	0.2980(3)	1.0323(2)	0.4630(2)	0.0458(5)
C6	0.2109(3)	0.9834(3)	0.5247(3)	0.0556(6)
C7	0.1428(3)	0.8430(3)	0.4588(3)	0.0598(6)
O23	0.5443(3)	1.5603(2)	0.2532(2)	0.0845(7)
O19	0.8669(3)	1.2594(3)	0.2397(3)	0.0867(7)
C25	0.3264(4)	1.3854(4)	0.0227(4)	0.0858(10)
C20	0.9617(7)	1.1980(7)	0.1524(7)	0.1542(18)
C21	1.0616(7)	1.1379(7)	0.2151(7)	0.1542(18)
C26	0.2342(8)	1.2614(7)	-0.0932(7)	0.195(4)
C16	0.7644(3)	1.4876(3)	0.4212(3)	0.0590(6)

Table-3
Bond Lengths (Å)

Atoms	Length	Atoms	Length
C11-C2	1.741(3)	C22-O24	1.312(3)
N10-C9	1.380(3)	C22-C15	1.534(4)
N10-C5	1.381(3)	O24-C25	1.453(4)
C4-C3	1.392(3)	C3-C2	1.382(3)
C4-C5	1.411(3)	C15-C17	1.527(3)
C4-C8	1.446(3)	C15-C16	1.545(3)
C14-C13	1.384(3)	C2-C7	1.391(4)
C14-C9	1.393(3)	C17-O18	1.192(3)
C13-C12	1.410(3)	C17-O19	1.318(4)
C13-C15	1.534(3)	C5-C6	1.389(3)
C11-C12	1.382(3)	C6-C7	1.379(4)
C11-C8	1.391(3)	O19-C20	1.468(5)
C8-C9	1.412(3)	C25-C26	1.434(6)
C22-O23	1.196(3)	C20-C21	1.354(7)

Table-4
Bond Angles (^{0})

Atoms	Angle	Atoms	Angle
C9-N10-C5	109.11(18)	C17- C15-C13	111.47(18)
C3-C4-C5	120.3(2)	C22-C15-C13	108.73(19)
C3-C4-C8	133.2(2)	C17-C15-C16	108.4(2)
C5-C4-C8	106.47(19)	C22-C15-C16	109.17(19)
C13-C14-C9	118.17(19)	C13-C15-C16	113.13(19)
C14-C13-C12	120.1(2)	C3-C2-C7	122.7(2)
C14-C13-C15	119.99(18)	C3-C2-C11	118.8(2)
C12-C13-C15	119.72(19)	C7-C2-Cl1	118.5(2)
C12-C11-C8	118.8(2)	C11-C12-C13	121.7(2)
C11-C8-C9	119.4(2)	O18-C17-O19	124.5(3)
C11-C8-C4	134.0(2)	O18-C17-C15	125.6(3)
C9-C8-C4	106.60(18)	O19-C17-C15	109.9(2)
O23-C22-O24	123.4(3)	N10-C5-C6	129.7(2)
O23-C22-C15	124.3(2)	N10-C5-C4	108.94(19)
O24-C22-C15	112.2(2)	C6-C5-C4	121.3(2)
N10-C9-C14	129.3(2)	C7-C6-C5	118.0(2)
N10-C9-C8	108.88(19)	C6-C7-C2	120.4(2)
C14-C9-C8	121.83(19)	C17-O19-C20	114.0(3)
C22-O24-C25	118.8(2)	C26-C25-O24	107.7(3)
C2-C3-C4	117.3(2)	C21-C20-O19	108.3(5)
C17-C15-C22	105.7(2)		

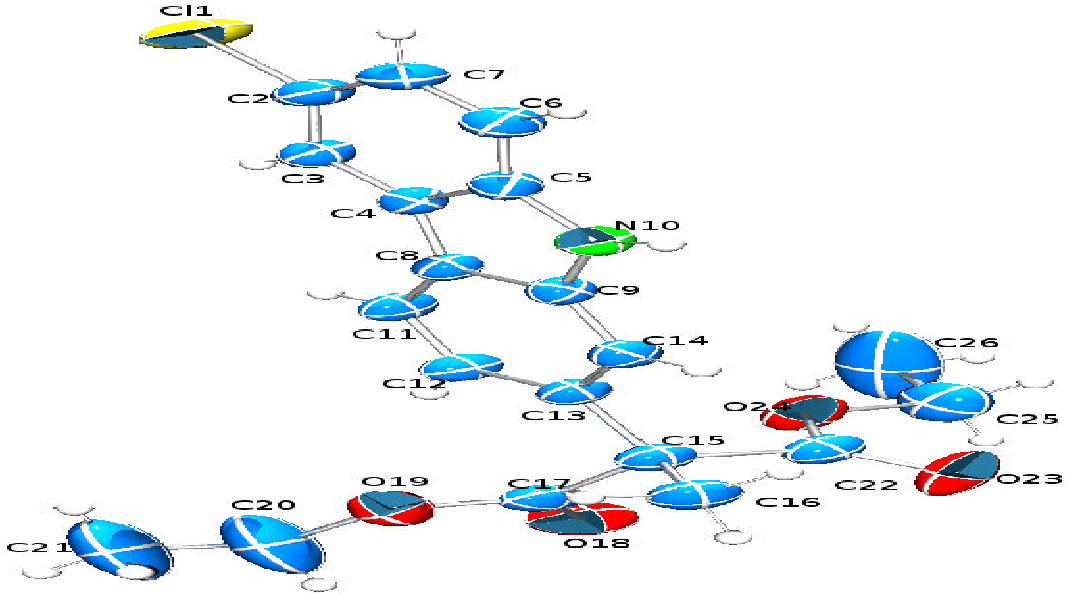

Figure-1
ORTEP diagram of the molecule 4 at 50% probability. Carbon, Oxygen, Nitrogen and Chlorine atoms are depeicted in blue, red, green and yellow colours, respectively

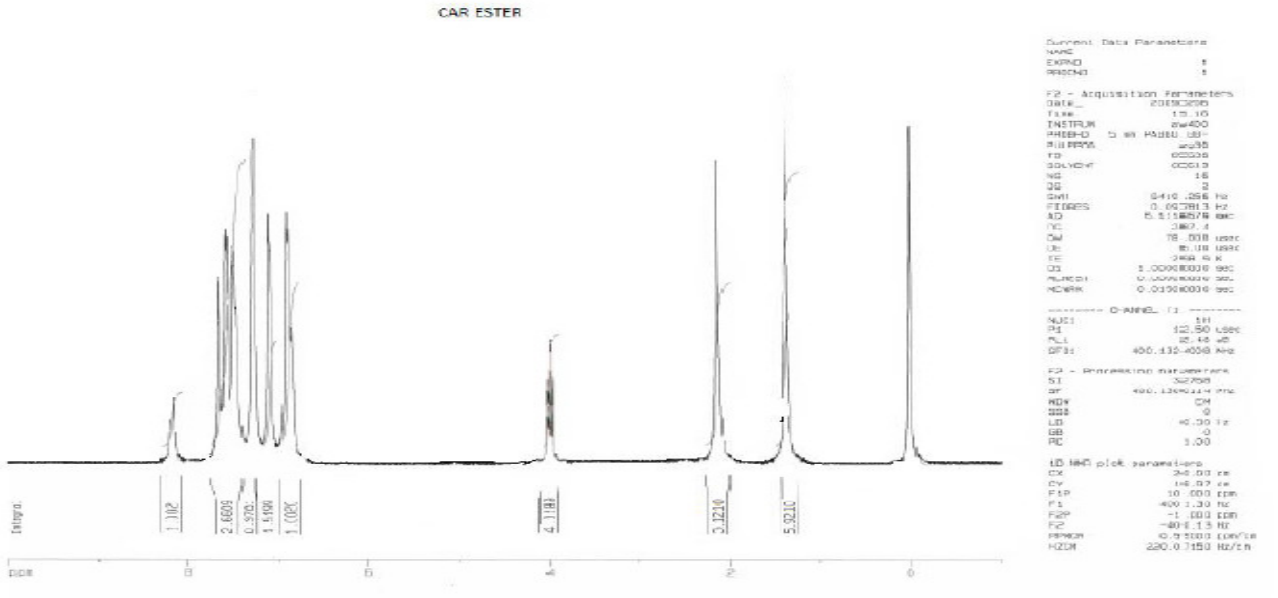

Figure-2
[1]HMNR Spectrum

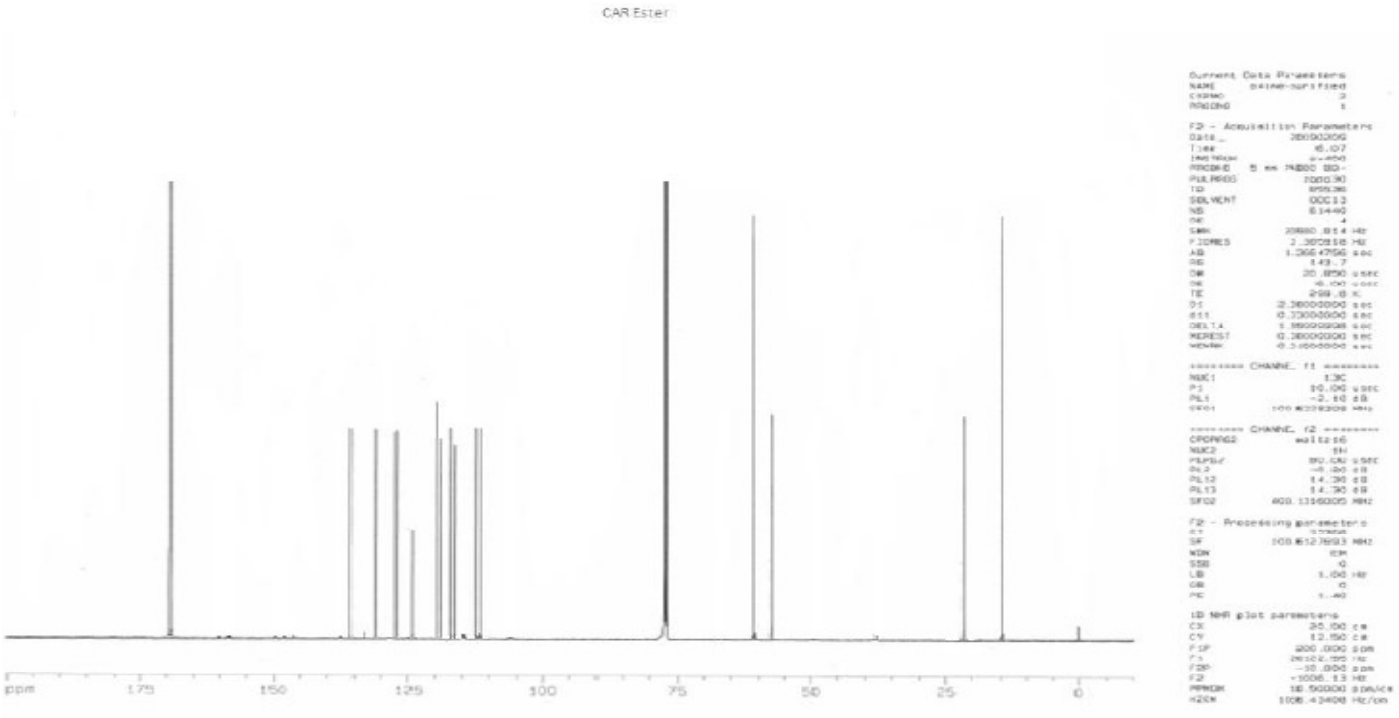

Figure-3
[13]CNMR Spectrum

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21. CCDC 775402- contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; email: deposit@ccdc.cam.ac.uk] **(2012)**

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