Research Article

One Pot Synthesis of β-Phosphonomalonates at Room Temperature Using Tetrabutylammonium Bromide as an Efficient Catalyst

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Abstract

A one pot solvent free procedure has been developed for the synthesis of β-phosphonomalonates by reacting of various aromatic aldehydes, malononitrile and triethyl phosphite through tandem Knoevenagel-phospha-Michael reaction at room temperature catalyzed by tetrabutylammonium bromide (5 mol%) as an efficient and eco-friendly catalyst with excellent yield (82-93%), easy work-up and short reaction time. The synthesized derivative of β-phosphonomalonates characterized and confirmed by FT-IR, ^{1}HNMR, ^{13}CNMR and HRMS data. This methodology is new, simple and efficient for the synthesis of β-phosphonomalonates with mild reaction condition, ease of handling, inexpensive way and good efficacy.

Keywords: Solvent-free**,** Aldehydes, Knoevenagel-phospha-Michael reaction mechanism**,** β-phosphonomalonates**,** Tetrabutylammonium bromide.

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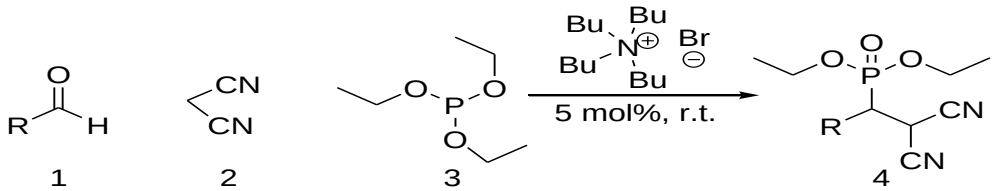
Introduction

Organophosphorous compounds including β-phosphonomalonates have wide range of applicability in the field of agriculture as plant growth regulators [1], antibiotics [2], metabolic probes [3], peptide mimetics [4], enzyme inhibitor [5] and in treatment of bone disorder [6]. Various methods are reported for the synthesis of β-phosphonomalonates by using acids [7-8], base [9], microwave [10], radical initiators [11], transition metal (Palladium) [12], 1,5,7-triazabicyclo[4.4.0]dec-5-ne (TBD) [13], nano sized zinc oxide [14], $Al(OTf)_3$ [15], phosphomolybdic acid [16], 3-aminopropylated silica gel [17], nano n-propylsulfonated γ-Fe_2O_3 [18], diethyl amine [19], ethylenediamine diacetate [20], molecular iodine [21], silica bonded 2-hydroxy ethylammonium acetate [22], iron doped single walled carbon nanotubes [23], heterogeneous catalyst (clay supported heteropolyacid) [24] and polystyrene supported DABCO [25].

Reported methods for the synthesis of β-phosphonomalonates suffer long reaction time, drastic reaction conditions, low yield and use of expensive and toxic reagents. So, designing of efficient and green methodology for the synthesis of β-phosphonomalonates essentially required. The use of ionic liquid as catalyst got more attention recently because of a wide range of properties such as the ability to act as both catalyst and solvent [26]. In present work, we report a one-pot synthesis of β-phosphono malonates using tetrabutylammonium bromide (TBAB) as a highly efficient catalyst (**Scheme 1**) which offered several advantages including mild reaction conditions, short reaction time, easy workup and high yield. To the best of our knowledge, we are first to apply tetrabutylammonium bromide (TBAB) as an efficient catalyst for the synthesis of β-phosphono malonates.



Scheme 1 Synthesis of β-phosphono malonates

Experimental Details

All the reagents and chemicals were purchased from Hi-Media Biosciences and were used without further purification. Melting Points were determined by MFRS Laboratory equipment. IR spectra were recorded on PerkinElmer FT-IR spectrophotometer. ^{1}H NMR and ^{13}CNMR spectra were recorded on 400 MHz JEOL JNM ECS400 instrument using $CDCl_3$. HRMS values were measured by a Waters Micromass Q-Tof Micro spectrometer.

General procedure for the synthesis of β phosphono malonates derivatives

Substituted benzaldehyde (5m mole), malononitrile (5m mole) and triethyl phosphite (5m mole) were mixed with 5 mol% of TBAB in a round bottom flask and stirred at room temperature (Scheme1). After some time the reaction mixture was solidified indicating the completion of the reaction, which was further confirmed by TLC using hexane and ethyl acetate (80:20) solvent system and visualized using iodine vapors and UV detection. The obtained solid crude product was washed with water and recrystallized from ethanol to get pure product.

Result and Discussion

The reaction conditions were optimized by the representative reaction taking derivative of benzaldehyde, malononitrile and triethyl phosphite as starting material and tetrabutylammonium bromide as catalyst (Scheme 1) under solvent free condition (**Table 1**). The reaction carried out without catalyst took longer time (5.5 hr) and afforded low yield (55%). The reaction without a catalyst under reflux condition took 1.5 hr to complete affording 67% yield. The reaction carried out using tetrabutylammonium bromide (20 mol %) as catalyst completed within 10 min affording 92% yield.

Table 1 Effect of different condition for the synthesis of Diethyl 1-(phenyl)-2,2 dicyano ethyl phosphonate with TBAB catalyst

Entry[a]	Condition	Mol[b]%	Time	Yield[c] (%)
1	Without Catalyst, Reflux	-	1.5hr	67
2	Without Catalyst, room temp	-	5.5 hr	55
3	TBAB, room temp	20	10 min	92
4	TBAB, room temp	10	10 min	92
5	TBAB, room temp	5	10 min	93
6	TBAB, room temp	2	30 min	81

[a]Reaction Condition: Benzaldehyde (5mmol), malononitrile (5 mmol), triethyl phosphate (5 mmol), Tetrabutylammonium bromide, monitored by TLC
[b]mol % of tetrabutylammonium bromide
[c]Isolated yields

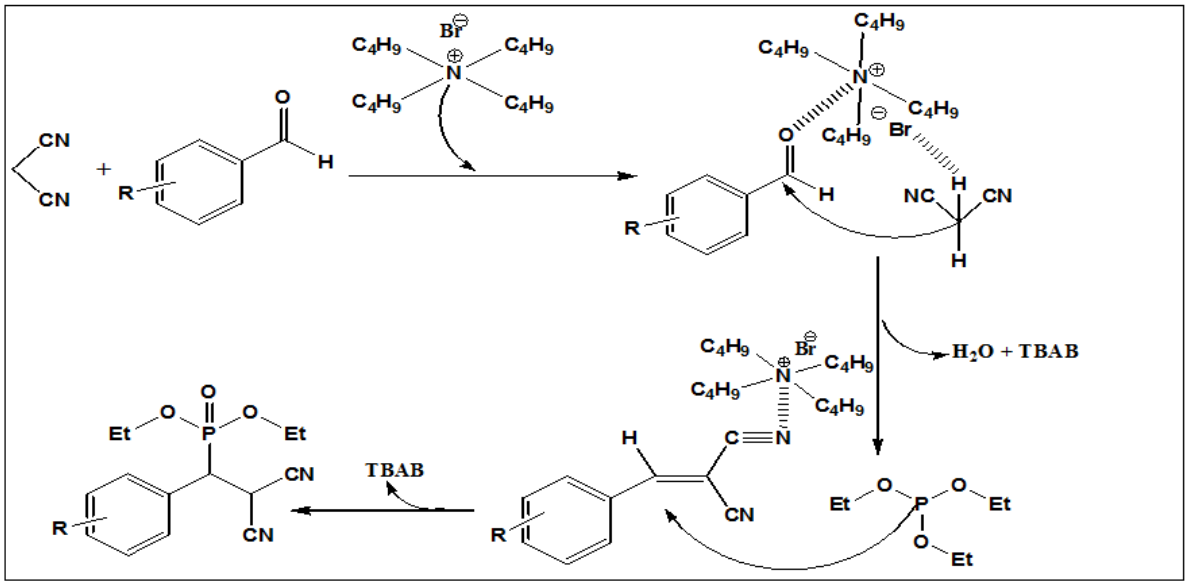
This clearly shows the importance of catalyst. The reaction was carried out at room temperature by taking a variable quantity of catalyst and it was found that 5 mol% of tetrabutylammonium bromide was the optimum quantity of catalyst. The same amount of catalyst was used for the synthesis of all the derivatives and all the reactions were carried out at room temperature under solventless condition. The reaction time and yield for different derivatives synthesized are depicted in **Table 2**. All the reaction completed within 2 to 30 minutes. The reaction time for the synthesized product having strong electron withdrawing group (4-NO_2, 2,3 dichloro, 3- NO_2,) on benzene ring was shorter (entries 4c, 4f and 4g).

Table 2 Tetrabutylammonium bromide (TBAB) catalyzed synthesis of β- phosphono malonates

Entry	Prod.	R	t/min	Yield[a]/%	M.P./ ^{0}C		Spectroscopic data [ref.]
					Found	Reported [ref.]	
1	4a	3,4-$(OCH_3)_2$-C_6H_3	20	93	98-99	-	[19]
2	4b	4-Cl-C_6H_4	10	90	97-98	98 [20]	[20, 21]
3	4c	4-NO_2-C_6H_4	2	89	103-104	104-105 [23]	[23]
4	4d	4-OH-C_6H_4	20	82	79-81	-	[17]
5	4e	C_6H_5	8	92	56-57	56-58 [20]	[20]
6	4f	2,3-$(Cl)_2$-C_6H_3	5	93	70-72	-	-
7	4g	3-NO_2-C_6H_4	6	85	75-76	-	[19]

[a]Yield of isolated products

The plausible mechanism of reaction carried out by Knoevenagel condensation followed by phospho- micheal addition has been shown in **Scheme 2**. The carbonyl groups of aldehyde are activated by tetrabutylammonium bromide for nucleophilic attack. Comparison between the present protocol and also the reported protocols (**Table 3**) clearly indicates the prevalence of present protocol in terms of cost, simplicity, short reaction time and high yield over the reportable ones.



Scheme 2 Plausible mechanism for the formation of β-phosphonomalonates

Table 3 Comparison between various reported method and the present method for the synthesis of β-phosphonomalonates

Entry	Catalyst	Mol%	Time	Condition	Solvent	Yield(%)	Ref.
1	1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)	20	30 min	RT	Toluene	96	[13]
2	$Al(OTf)_3$	10	45 min	Reflux	n-Hexane	93	[15]
3	Phosphomolybdic acid	2	30 min	80^0C	-	88	[16]
4	Diethyl amine	10	15min	RT	-	95	[19]
5	Ethylenediamine diacetate (EDDA)	20	12hr	RT	Ethanol	86	[20]
6	Molecular iodine	10	2hr	50^0C	-	90	[21]
7	Iron doped single walled carbon nanotubes	10	1hr	50^0C	-	97	[23]
8	Clay supported heteropolyacid	5mg	25 min	Ultrasonication	-	97	[24]
9	Tetra butyl ammonium bromide (TBAB)	5	2-15 min	RT	-	90-95	this work

Spectral analysis

Compound **4a**: Yellow crystals; yield: 90%; m.p.: 98-99^0C; IR (KBr) (cm^{-1}): 2222(CN str.), 1271(P=O str.); ^{1}HNMR ($CDCl_3$, 400MHz): 1.009 (t, 3H, J=7.32Hz), 1.46 (m, 3H, J=7.32Hz), 3.38(m,4H), 3.79 (dd, 1H), 3.93(s,3H), 3.97(s,3H), 4.11(dd,1H), 7.63(d,1H), 7.38-7.4 (m,2H) ppm; ^{13}CNMR ($CDCl_3$, 400MHz): 13.76(CH_3), 19.83(CH_3), 24.22(CH), 56.06(CH_3), 56.26(CH_3), 56.40(CH), 78.86(CH_2), 111.15(CN), 114.49(CN), 124.33, 127.00, 128.29, 149.57, 154.9, 159.24 ppm.

Compound **4b**: Yellow crystals; yield: 90%; m.p.: 97-98^0C; IR (KBr) (cm^{-1}): 2225(CN str.), 1280(P=O str.); ^{1}HNMR ($CDCl_3$, 400MHz): 1.03(t, 3H, J=7.32Hz), 1.45 (m, 3H, J=7.32Hz), 3.72 (dd, 1H), 3.8-3.9(m, 4H), 4.11(dd, 1H), 7.52 (d, 2H), 7.82(d, 2H) ppm; ^{13}CNMR ($CDCl_3$, 400MHz): 13.82(CH_3), 19.90(CH_3), 24.29(CH), 59.22(CH), 83.41(CH_2), 112.47(CN), 113.57(CN), 128.94, 129.37, 130.98, 141.28, 158.46 ppm.

Compound **4c**: Yellow crystals; yield: 89%; m.p.: 103-104^0C; IR (KBr) (cm^{-1}): 2230(CN str.), 1341(N=O str.), 1211(P=O str.); ^{1}HNMR ($CDCl_3$, 400MHz): 1.33(t,3H, J=7.32Hz), 1.43 (t,3H, J=7.32Hz), 3.72 (dd, 1H), 4.04(t,4H), 4.13(dd,1H), 7.56 (d,2H), 8.26(d,2H) ppm; ^{13}CNMR ($CDCl_3$, 400MHz): 13.75(CH_3), 19.86(CH_3), 24.03(CH), 59.04(CH), 87.67(CH_2), 111.73(CN), 112.75(CN), 123.86, 124.78, 131.45, 135.91, 150.43, 157.01 ppm.

Compound **4d**: Brown crystals; yield: 72%; m.p. 79-81^0C; IR (KBr) (cm^{-1}): 3347(OH str.), 2223(CN str.), 1256(P=O, str.); ^{1}HNMR ($CDCl_3$, 400MHz): 0.97 (t,3H, J=7.32Hz), 1.26 (t,3H, J=7.32Hz),3.96 (dd, 1H), 4.01(dd,1H), 4.29(m,4H), 5.08(OH,s), 7.02 (d,2H), 7.7(d,1H), 7.8(d, 1H) ppm; ^{13}CNMR ($CDCl_3$, 400MHz):

13.74(CH_3), 19.83(CH_3), 24.10(CH), 59.11(CH), 64.21(CH_2), 64.26(CH_2), 113.96(CN), 115.06(CN), 117.30, 122.94, 128.98, 131.12, 134.05, 159.37 ppm.

Compound **4e**: Cream crystals; yield: 92%; m.p. 56-57^{0}C; IR (KBr) (cm^{-1}): 2231(CN str.), 1316(P=O, str.). ^{1}HNMR ($CDCl_3$, 400MHz): 1.25 (t,3H, ^{3}J=7.32Hz), 1.34 (t,3H, ^{3}J=7.32Hz), 3.23 (dd, 2H), 3.71(m,2H), 4.11(m,2H), 7.54 (t,1H), 7.6(t,2H), 7.9(d, 2H) ppm; ^{13}CNMR ($CDCl_3$, 400MHz): 13.72(CH_3), 19.83(CH_3), 24.10(CH), 59.11(CH), 82.89(CH_2), 112.65(CN), 113.82(CN), 129.73, 130.83, 131.01, 134.75, 160.10 ppm.

Compound **4f:** Cream crystals; yield: 91%; m.p. 70-72^{0}C; IR (KBr) (cm^{-1}): 2234(CN str.), 1264(P=O, str.); ^{1}HNMR ($CDCl_3$, 400MHz): 1.02(t,3H, J=7.32Hz), 1.25 (t,3H, J=7.32Hz), 3.23 (dd, 2H), 3.73(m,4H), 7.40 (t,1H), 7.69(d,1H), 8.02(d, 1H) ppm; ^{13}CNMR ($CDCl_3$, 400MHz): 13.74(CH_3), 19.83(CH_3), 29.83(CH), 45.89(CH), 87.50(CH_2), 111.57(CN), 112.90(CN), 127.83, 128.27, 131.13, 135.03, 135.26, 156.19 ppm. HRMS m/z (M^+) calculated for $C_{14}H_{15}O_3N_2PCl_2$: 361.13; found: 360.33.

Compound **4g**: Brown crystals; yield: 85%; m.p. 75-76^{0}C; IR (KBr) (cm^{-1}): 2234(CN str.), 1538(N=O str.), 1355(P=O, str.); ^{1}HNMR ($CDCl_3$, 400MHz): 1.0045 (t,3H, J=7.32Hz), 1.22 (t,3H, J=7.32Hz), 3.18 (dd, 1H), 3.71(m,4H), 4.06 (t.1H), 7.7(t,1H), 7.87 (s,1H), 8.32(d,1H), 8.6(d, 1H) ppm; ^{13}CNMR ($CDCl_3$, 400MHz): 13.71(CH_3), 19.82(CH_3), 24.01(CH), 59.00(CH), 86.80(CH_2), 111.77(CN), 112.79(CN), 125.66, 128.36, 131.11, 132.08, 134.99, 148.71, 157.18 ppm.

Conclusion

In summary, we have developed highly efficient, an eco-friendly method for the synthesis of β-phosphonomalonate derivatives via Knoevenagel condensation followed by a Phosphomicheal addition in solventless condition, in the presence of tetrabutylammonium bromide as a catalyst with less reaction time and high yield.

Supporting Materials

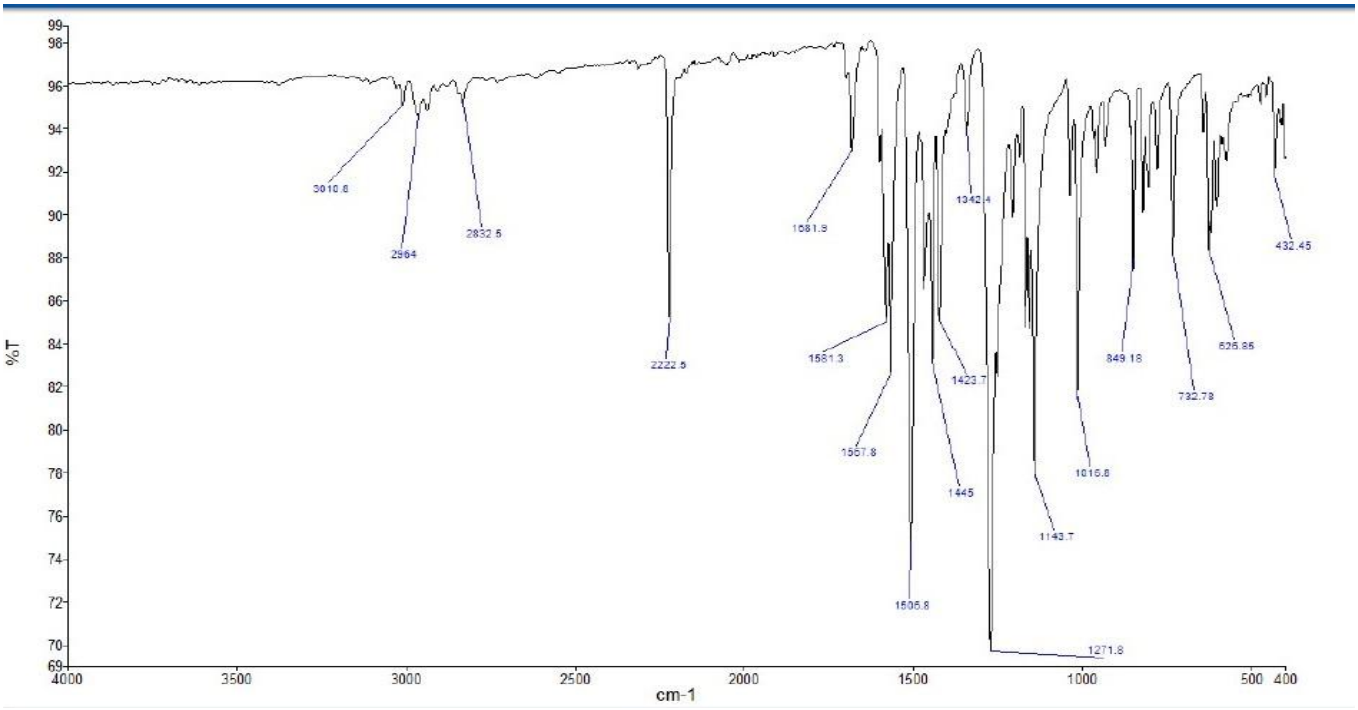


Figure 1 FTIR spectrum of **4a**

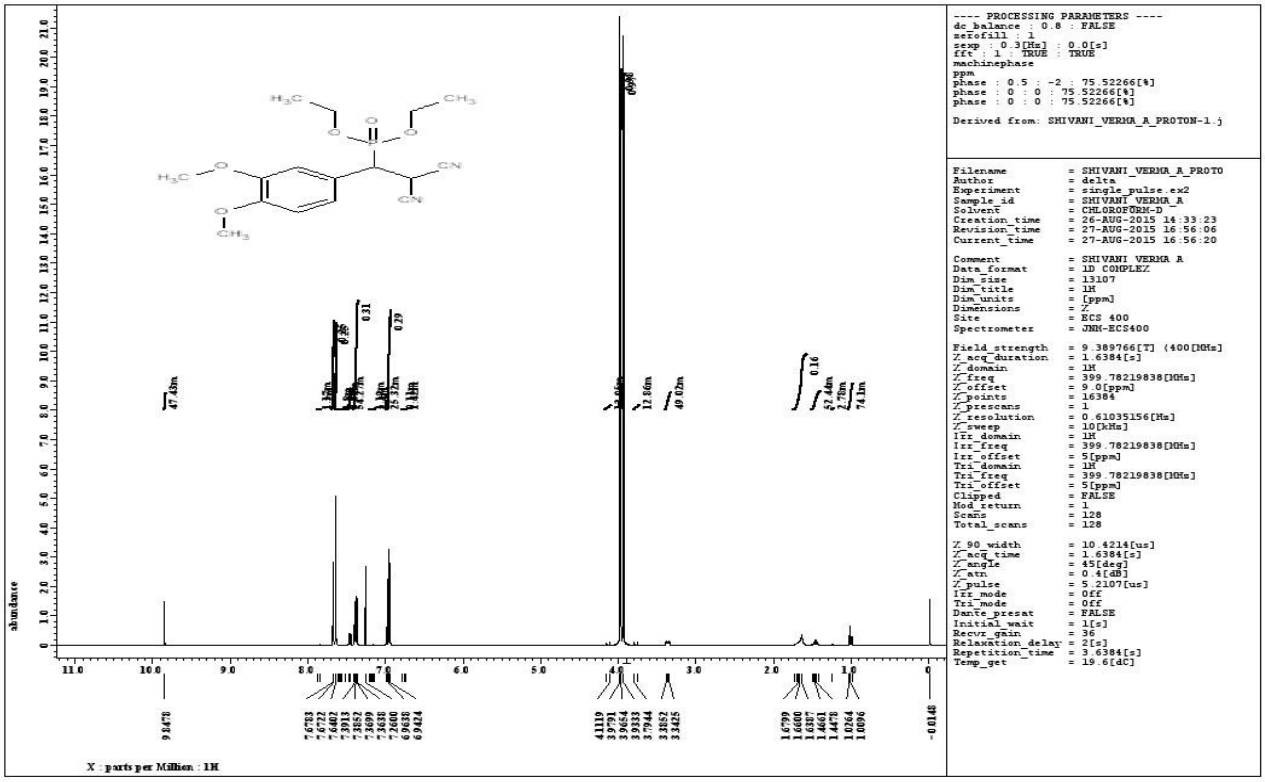


Figure 2 ^{1}HNMR (400Mz) spectrum of **4a** in $CDCl_3$

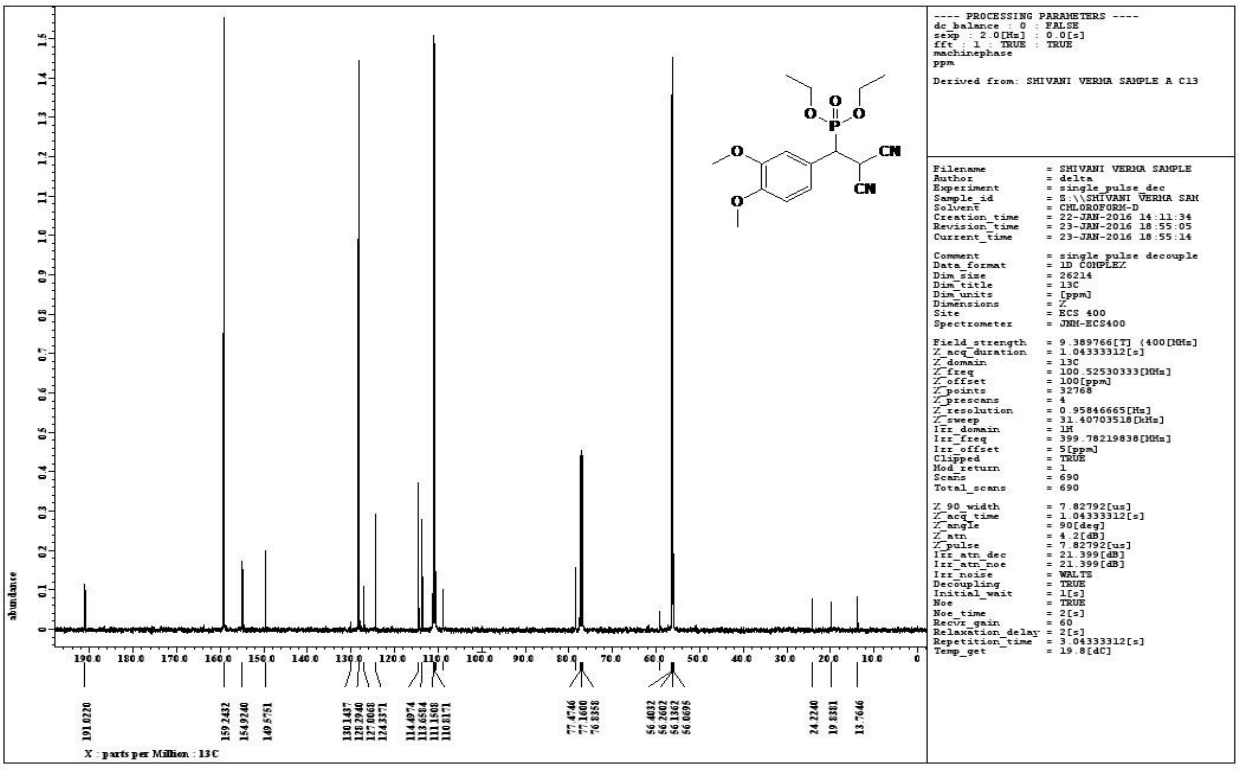


Figure 3 ^{13}CNMR (400Mz) spectrum of **4a** in $CDCl_3$

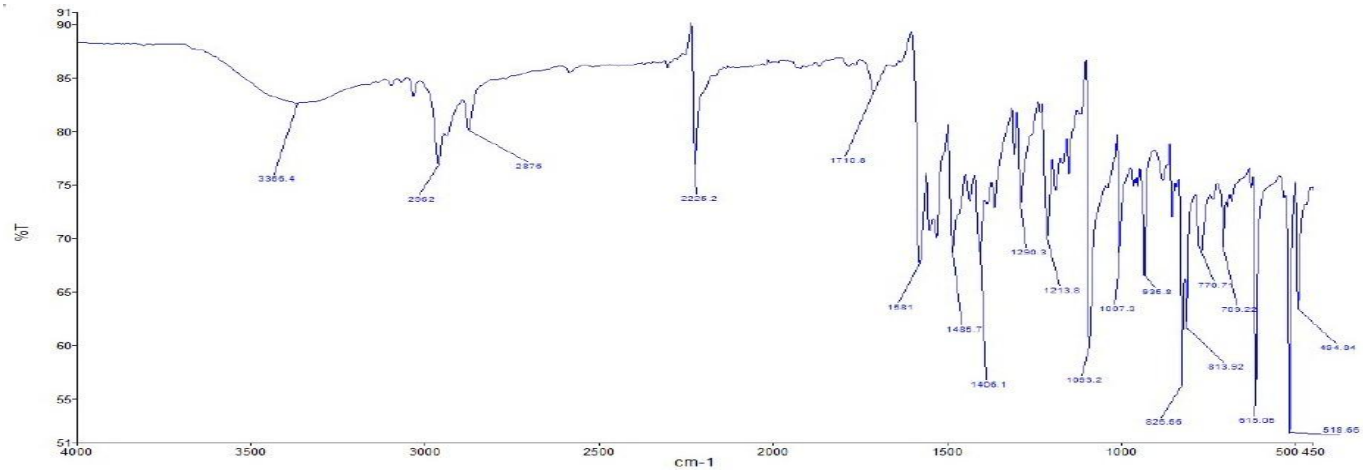


Figure 4 FTIR spectrum of **4b**

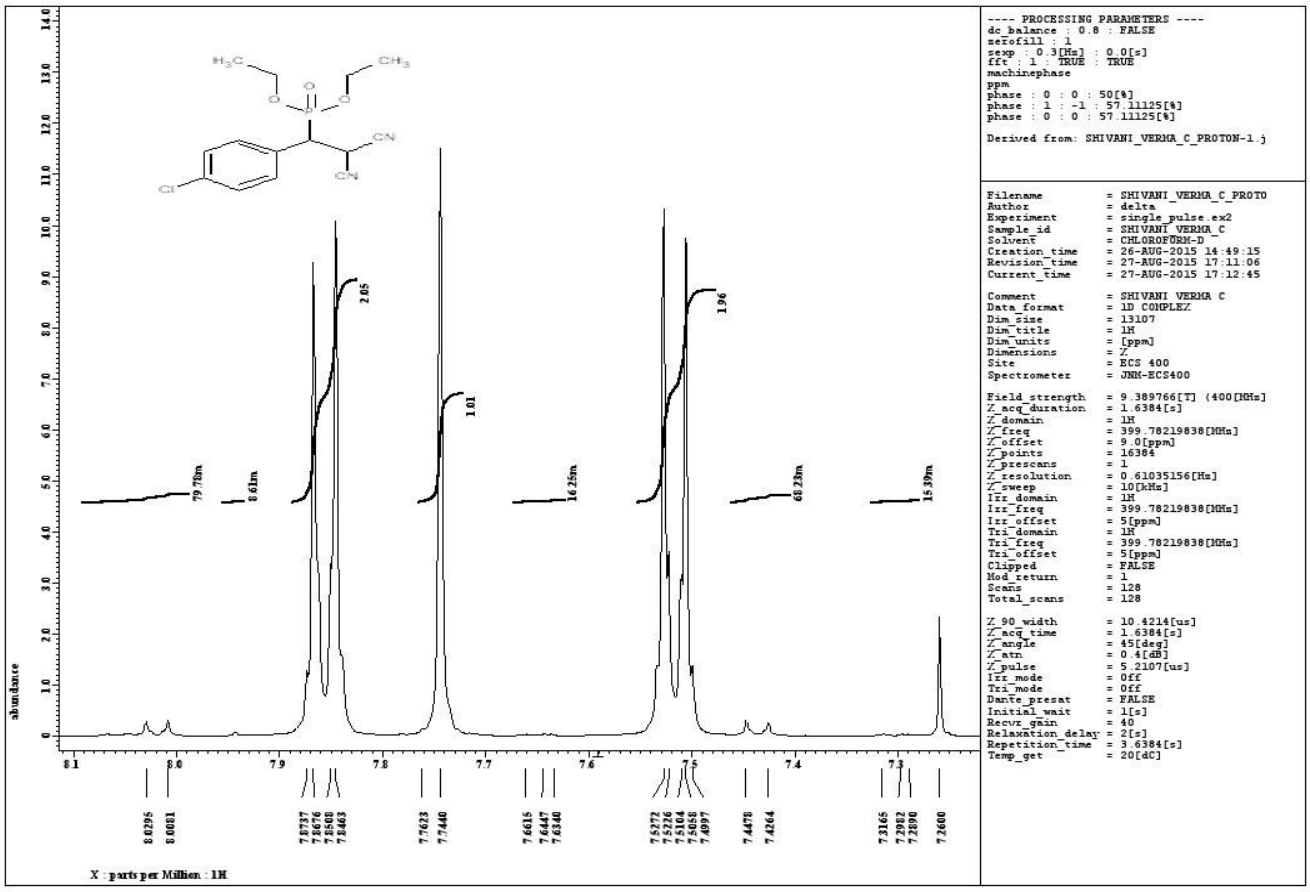


Figure 5 Expended ^{1}HNMR (400Mz) spectrum of **4b** in $CDCl_3$

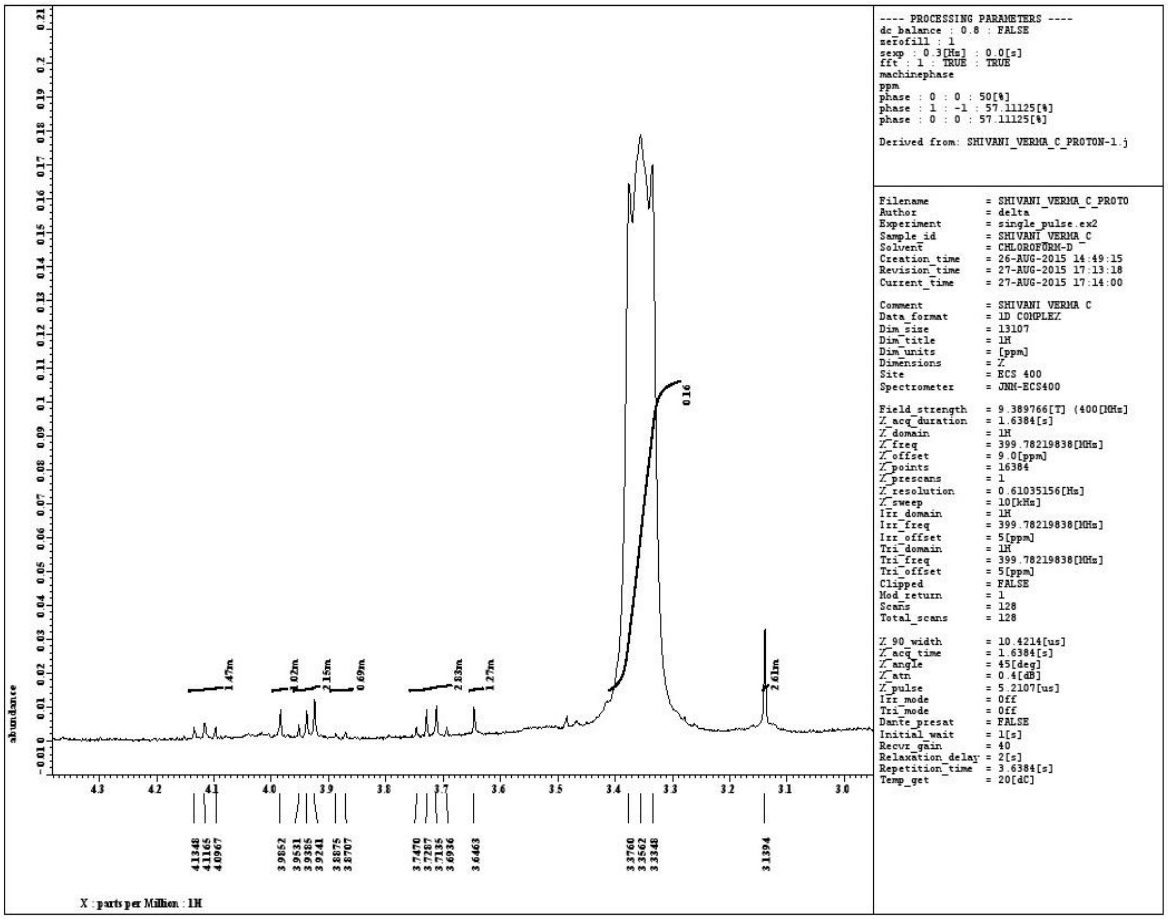


Figure 6 Expended ^{1}HNMR (400Mz) spectrum of **4b** in $CDCl_3$

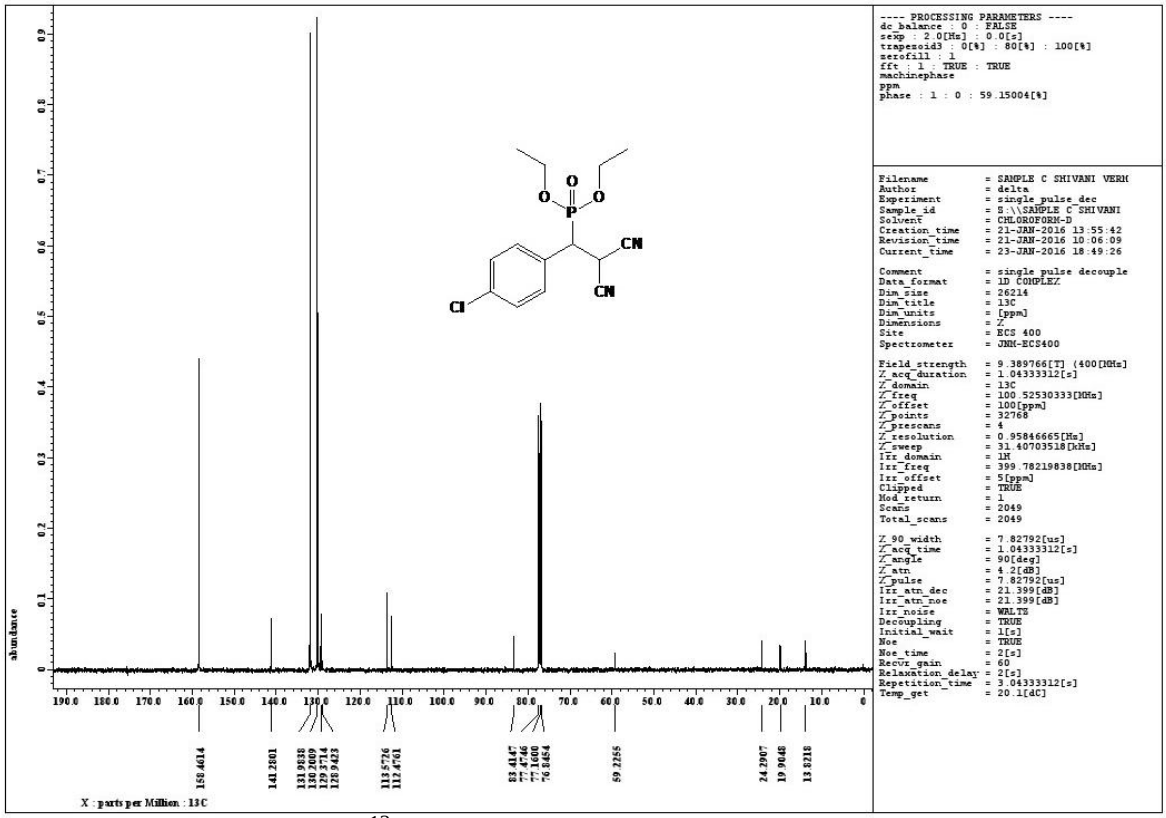


Figure 7 ^{13}CNMR (400Mz) spectrum of **4b** in $CDCl_3$

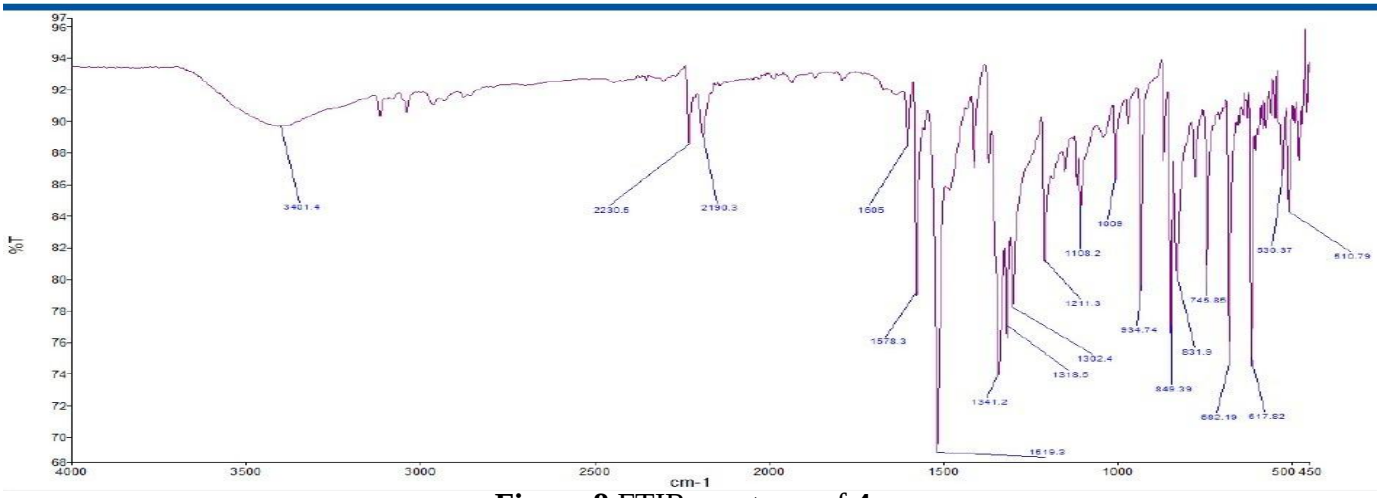


Figure 8 FTIR spectrum of **4c**

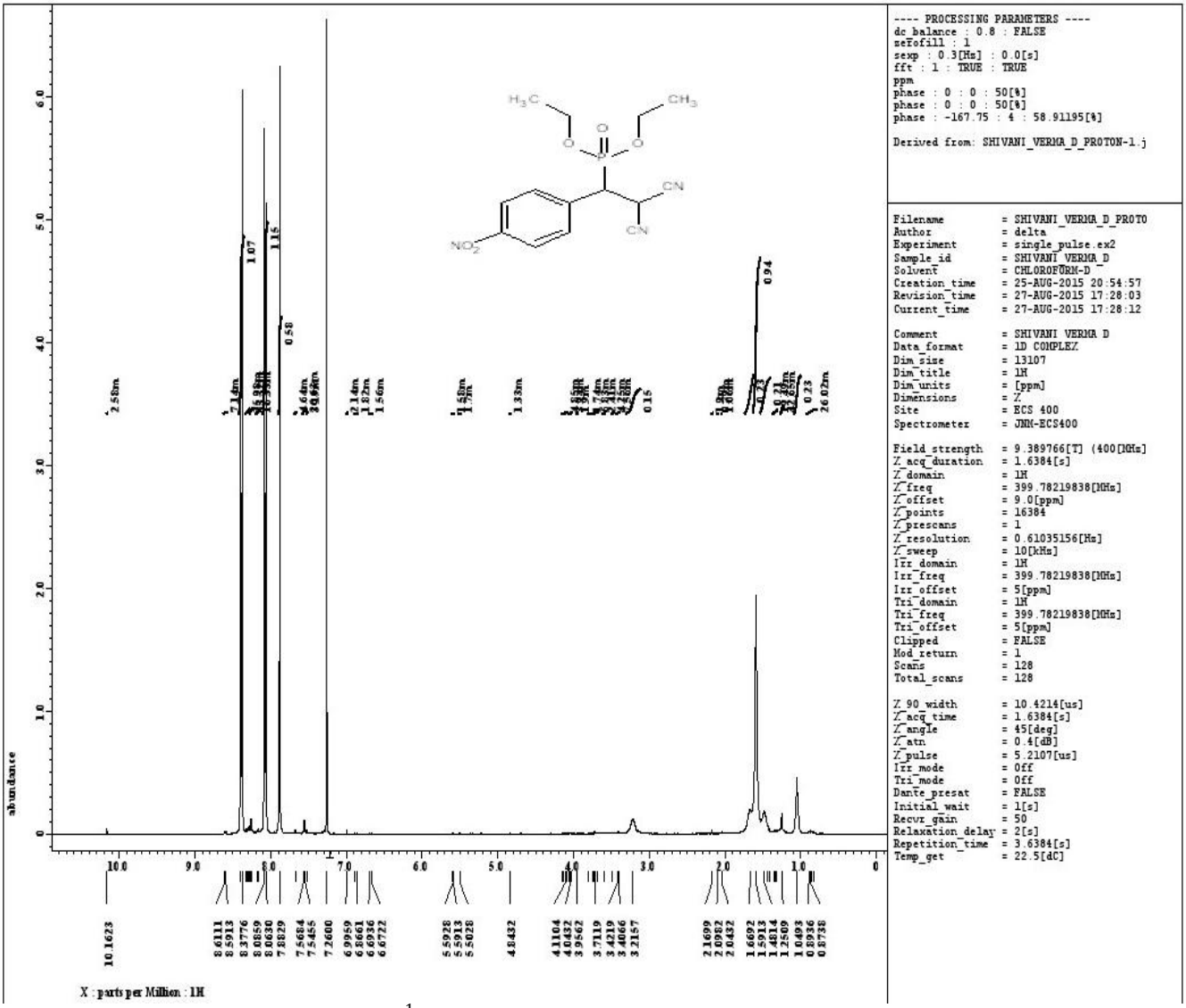


Figure 9 ^{1}HNMR (400Mz) spectrum of **4c** in $CDCl_3$

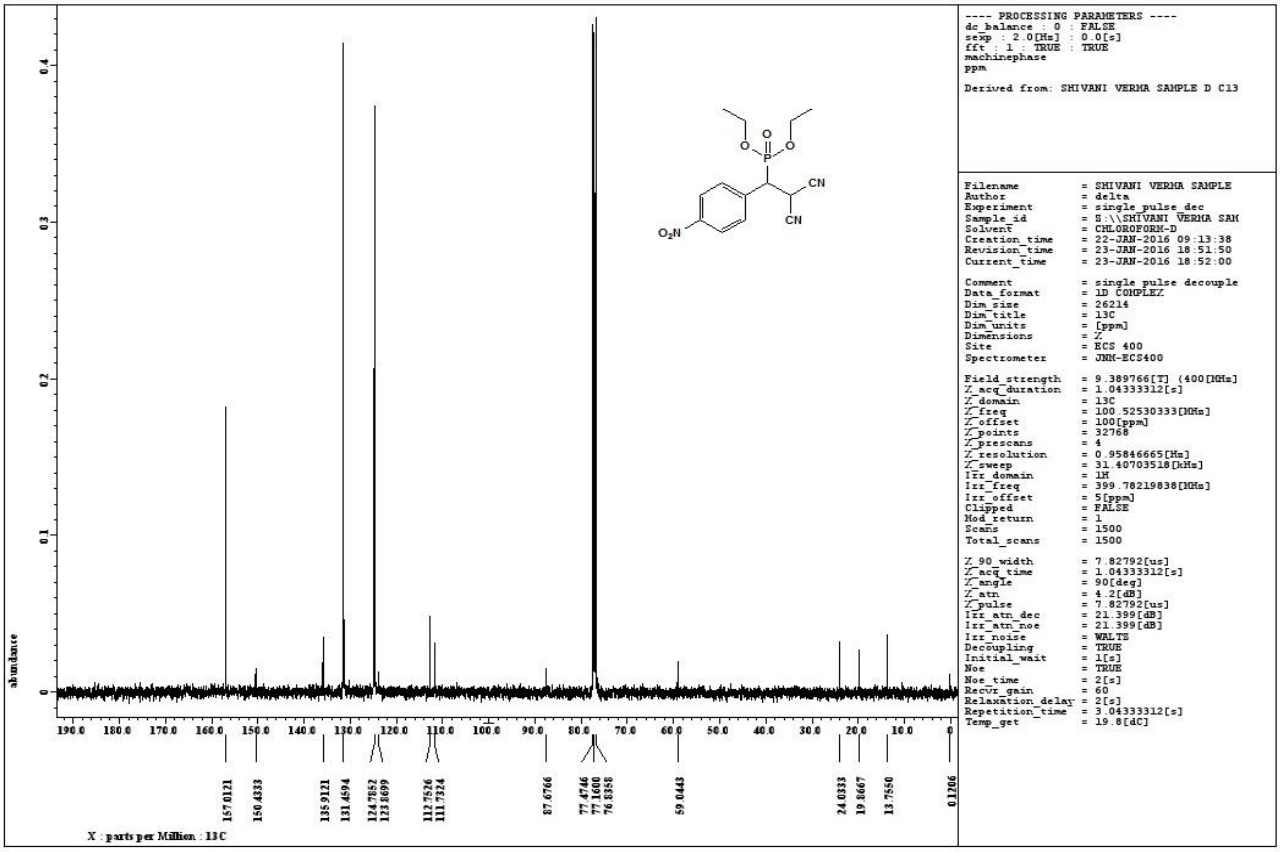


Figure 10 ^{13}CNMR (400Mz) spectrum of **4c** in $CDCl_3$

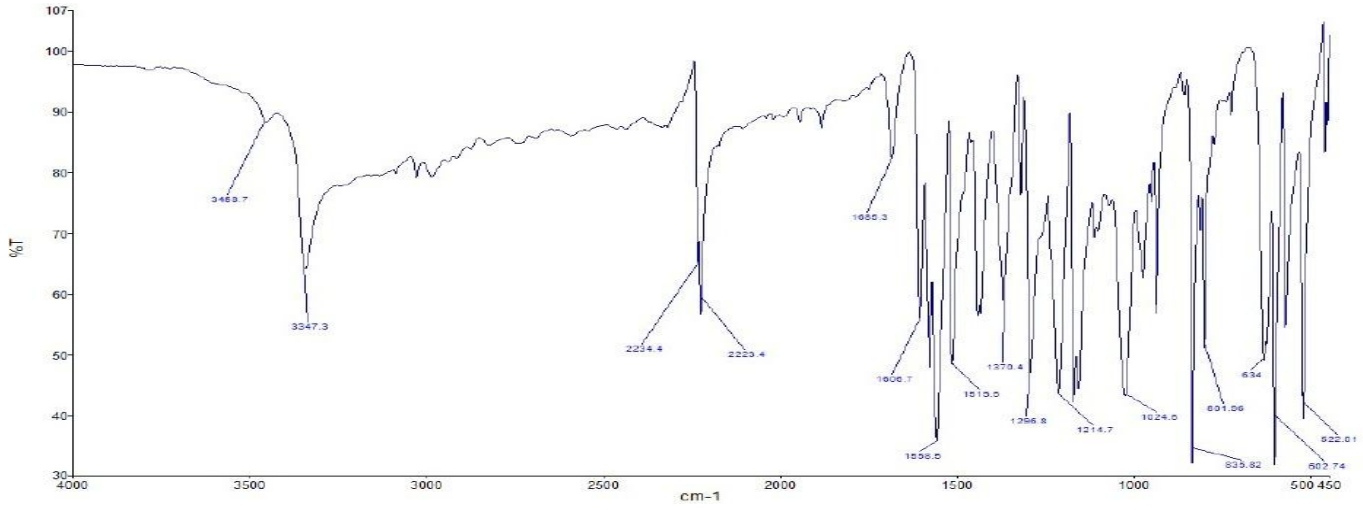


Figure 11 FTIR spectrum of **4d**

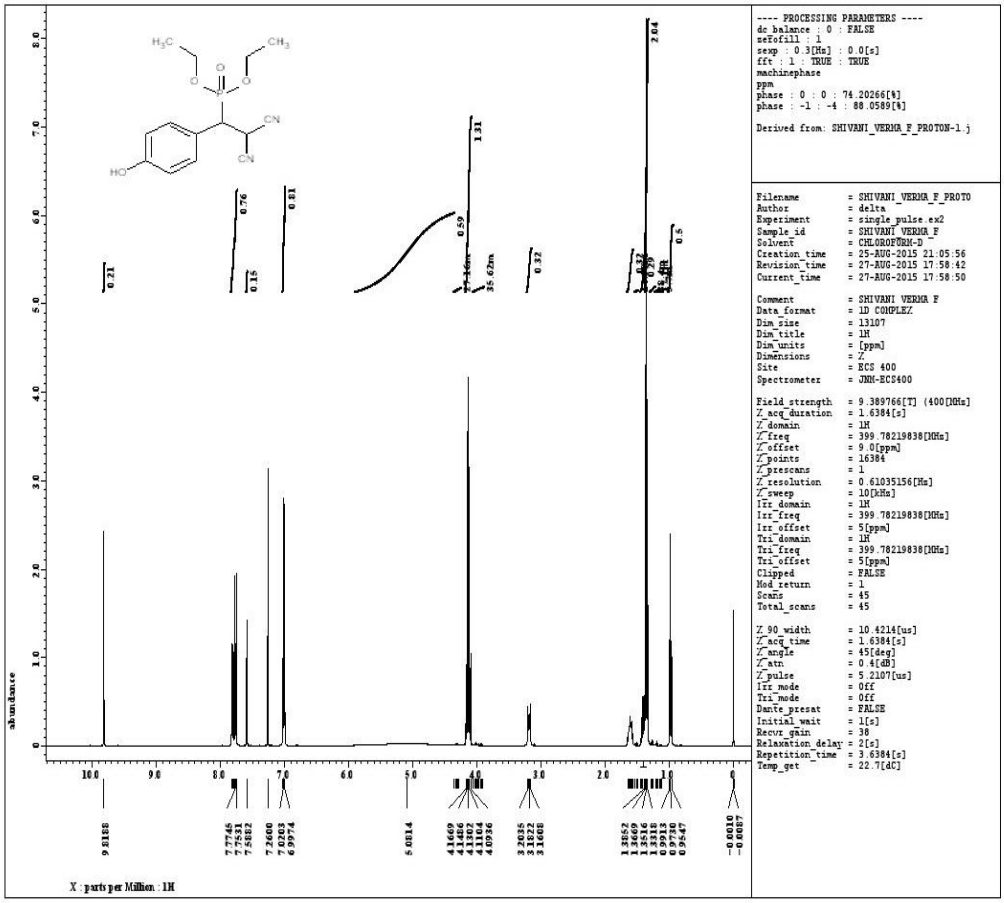


Figure 12 ^{1}HNMR (400Mz) spectrum of **4d** in $CDCl_3$

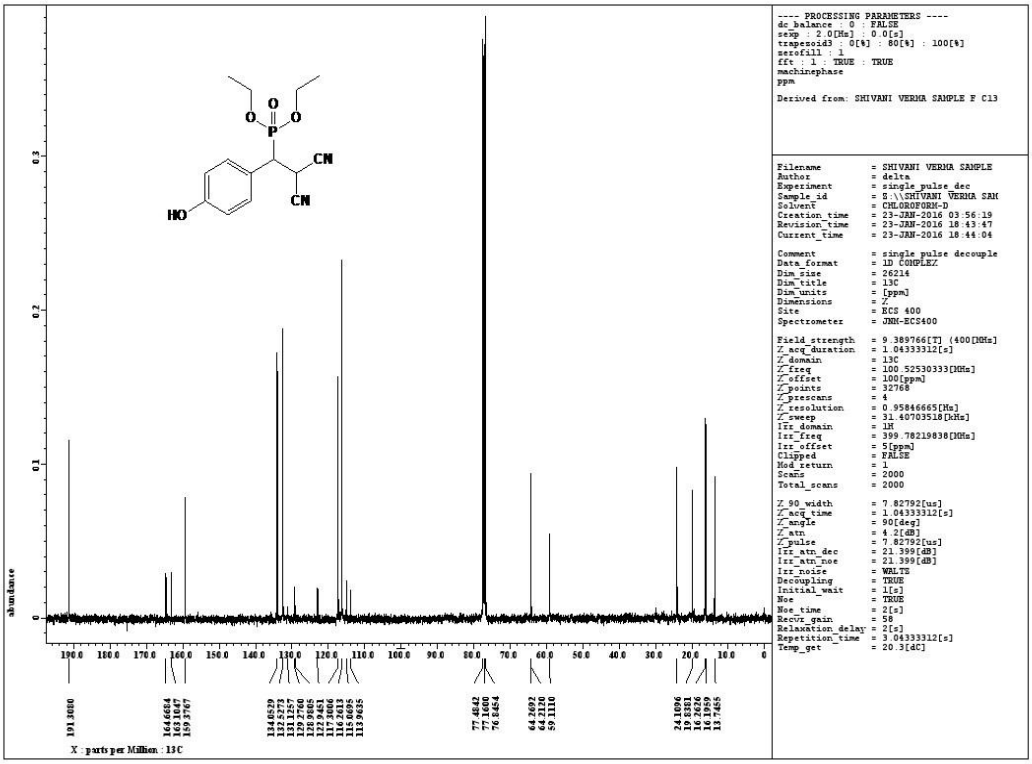


Figure 13 ^{13}CNMR (400Mz) spectrum of **4d** in $CDCl_3$

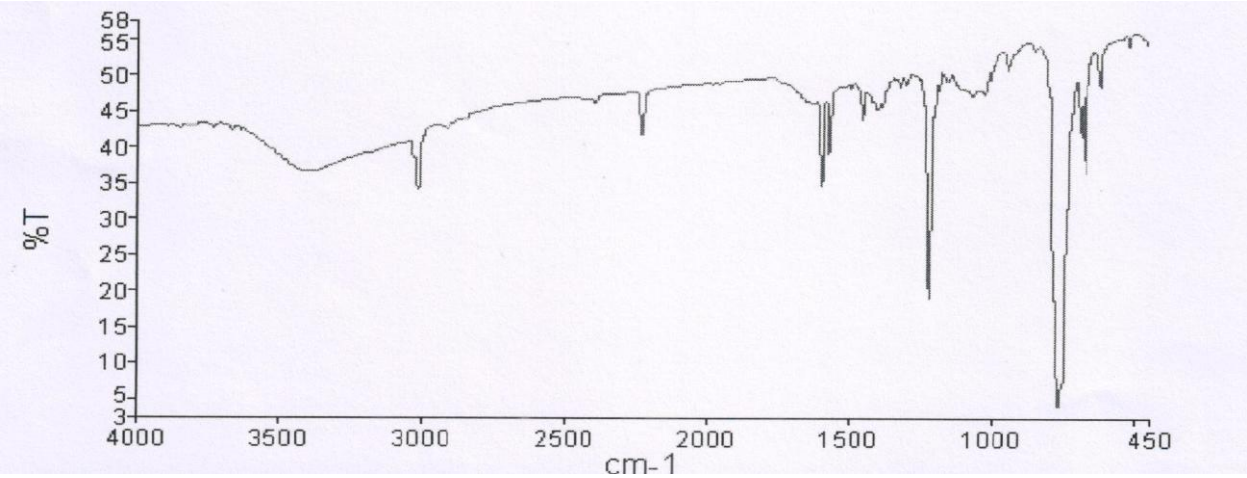


Figure 14 FTIR spectrum of **4e**.

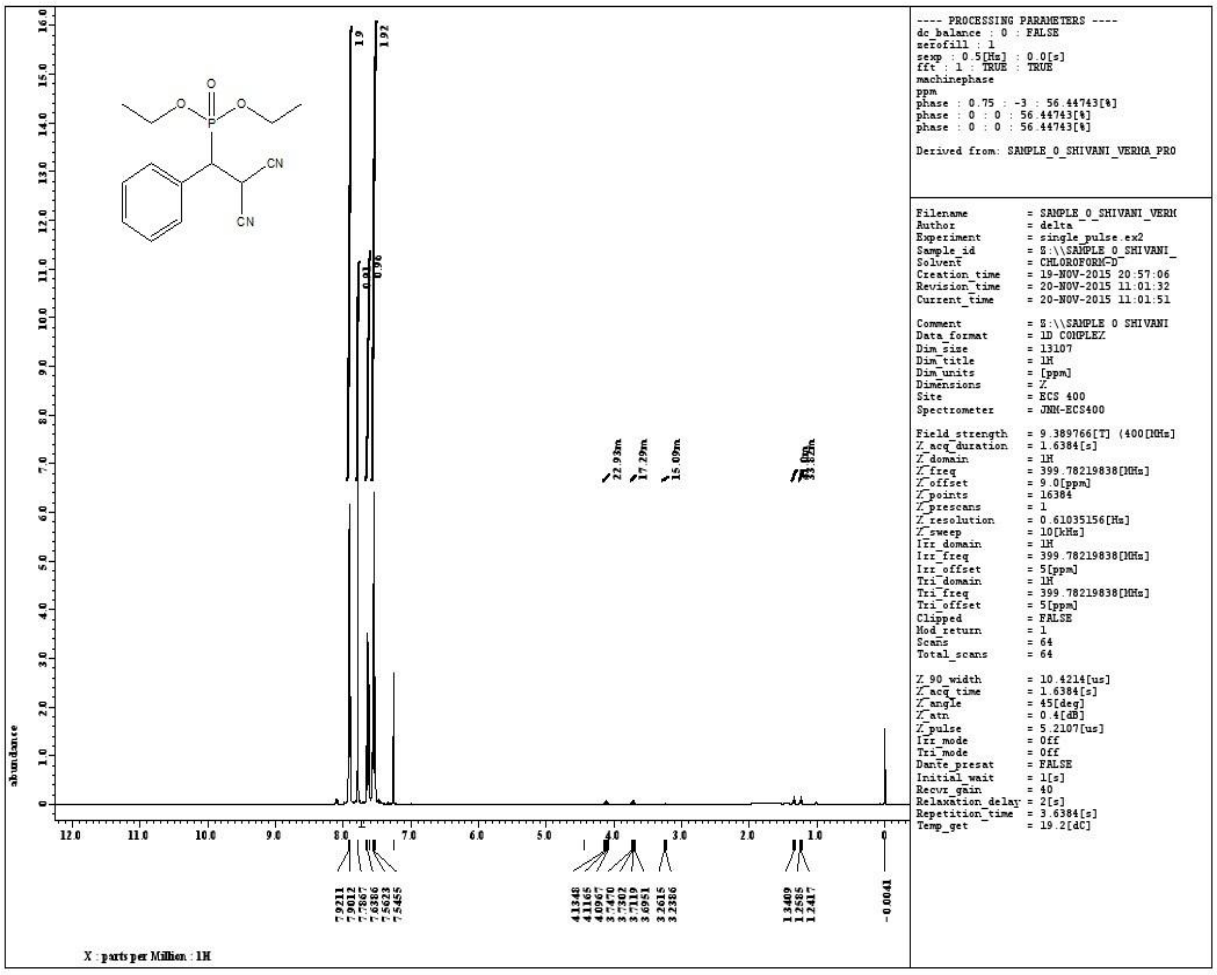


Figure 15 ^{1}HNMR (400Mz) spectrum of **4e** in $CDCl_3$

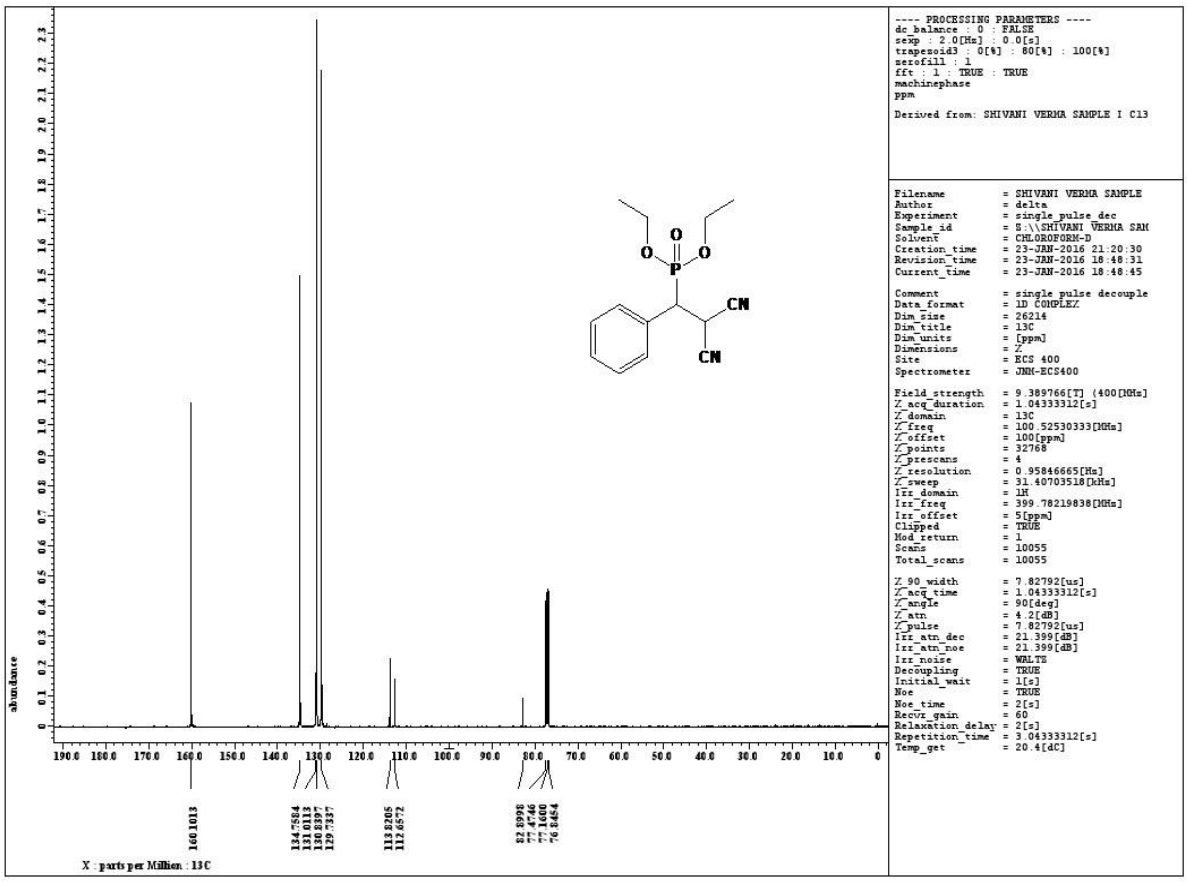


Figure 16 ^{13}CNMR (400Mz) spectrum of **4e** in $CDCl_3$

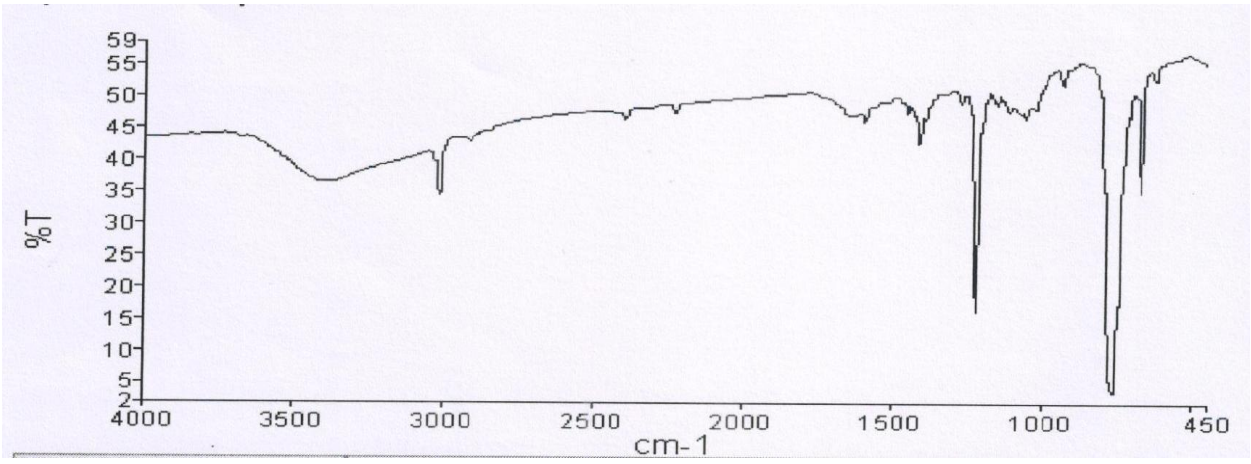


Figure 17 FTIR spectrum of **4f**

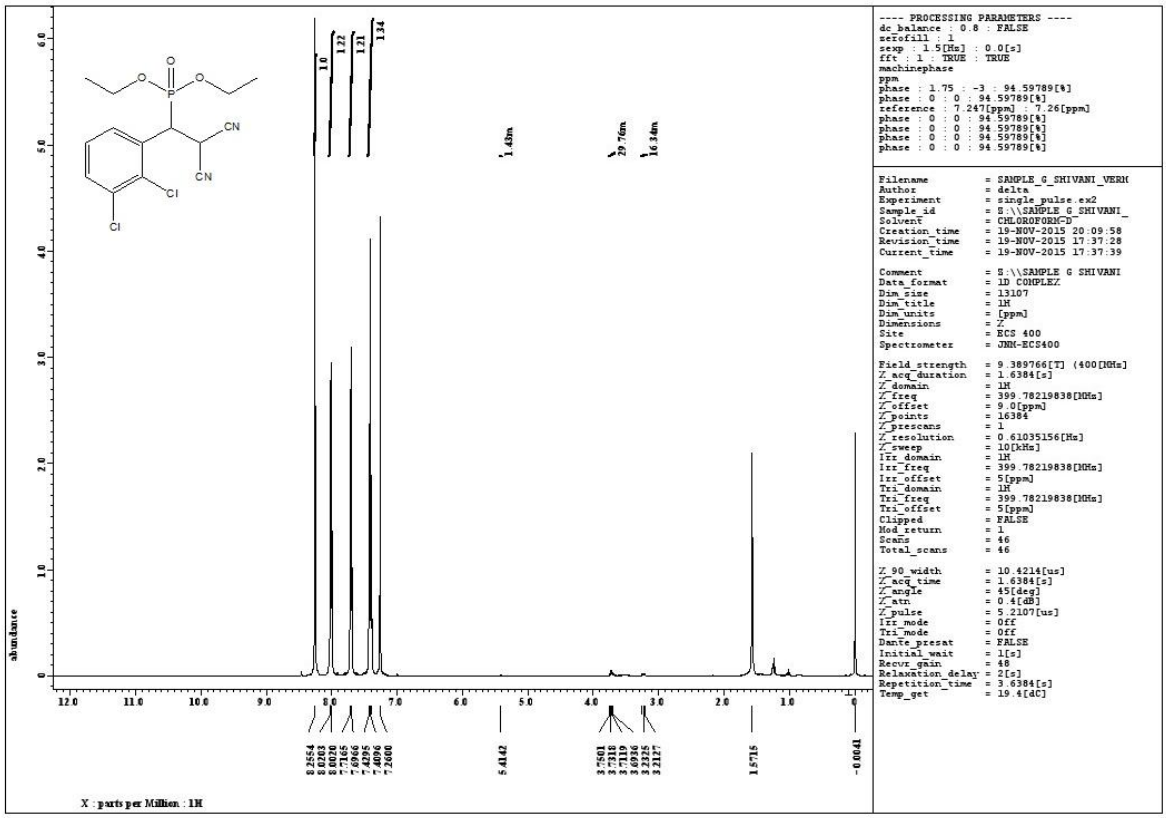


Figure 18 ^{1}HNMR (400Mz) spectrum of **4f** in $CDCl_3$

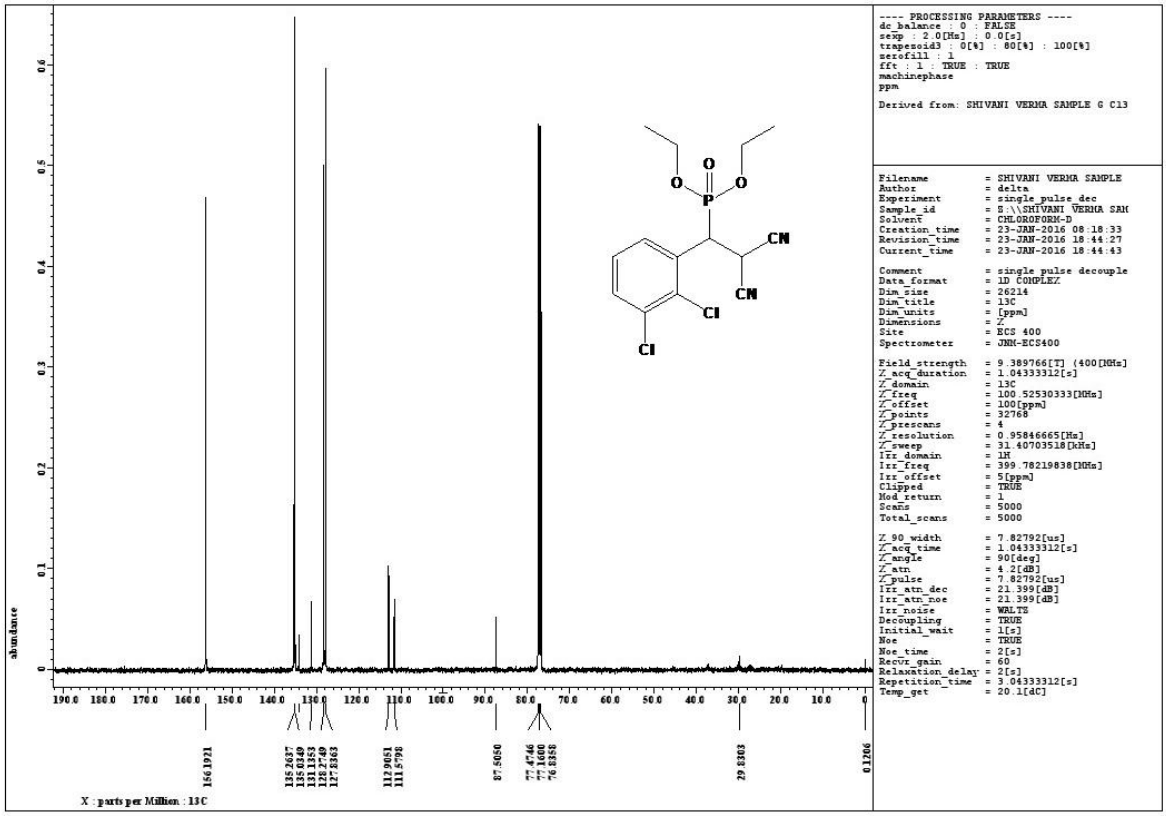


Figure 19 ^{13}CNMR (400Mz) spectrum of **4f** in $CDCl_3$

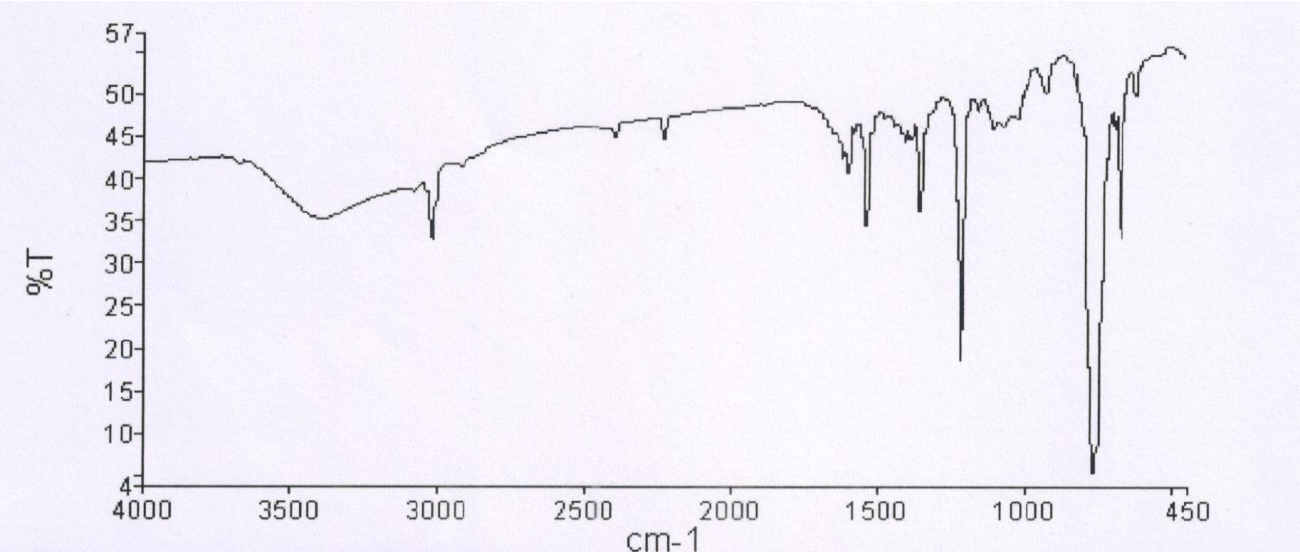


Figure 20 FTIR spectrum of **4g**

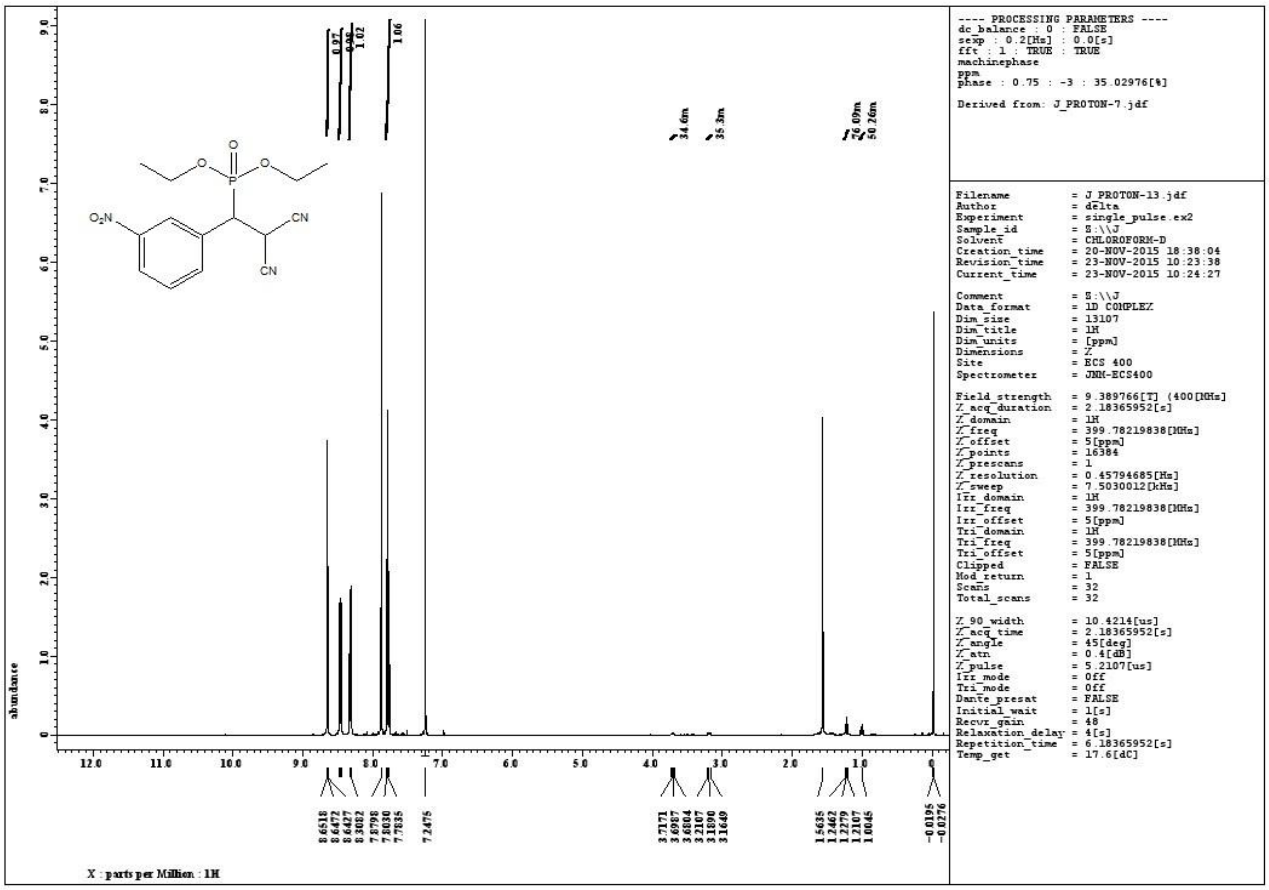


Figure 21 ^{1}HNMR (400Mz) spectrum of **4g** in $CDCl_3$

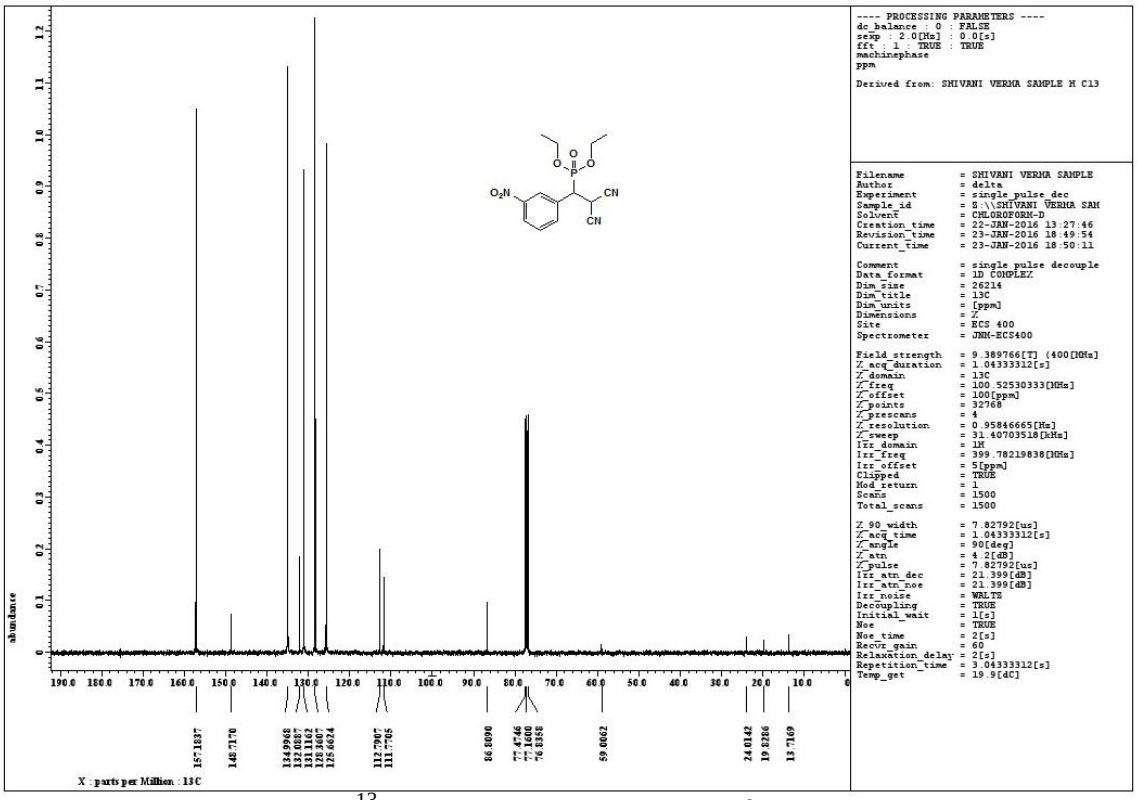


Figure 22 ^{13}CNMR (400Mz) spectrum of **4g** in $CDCl_3$

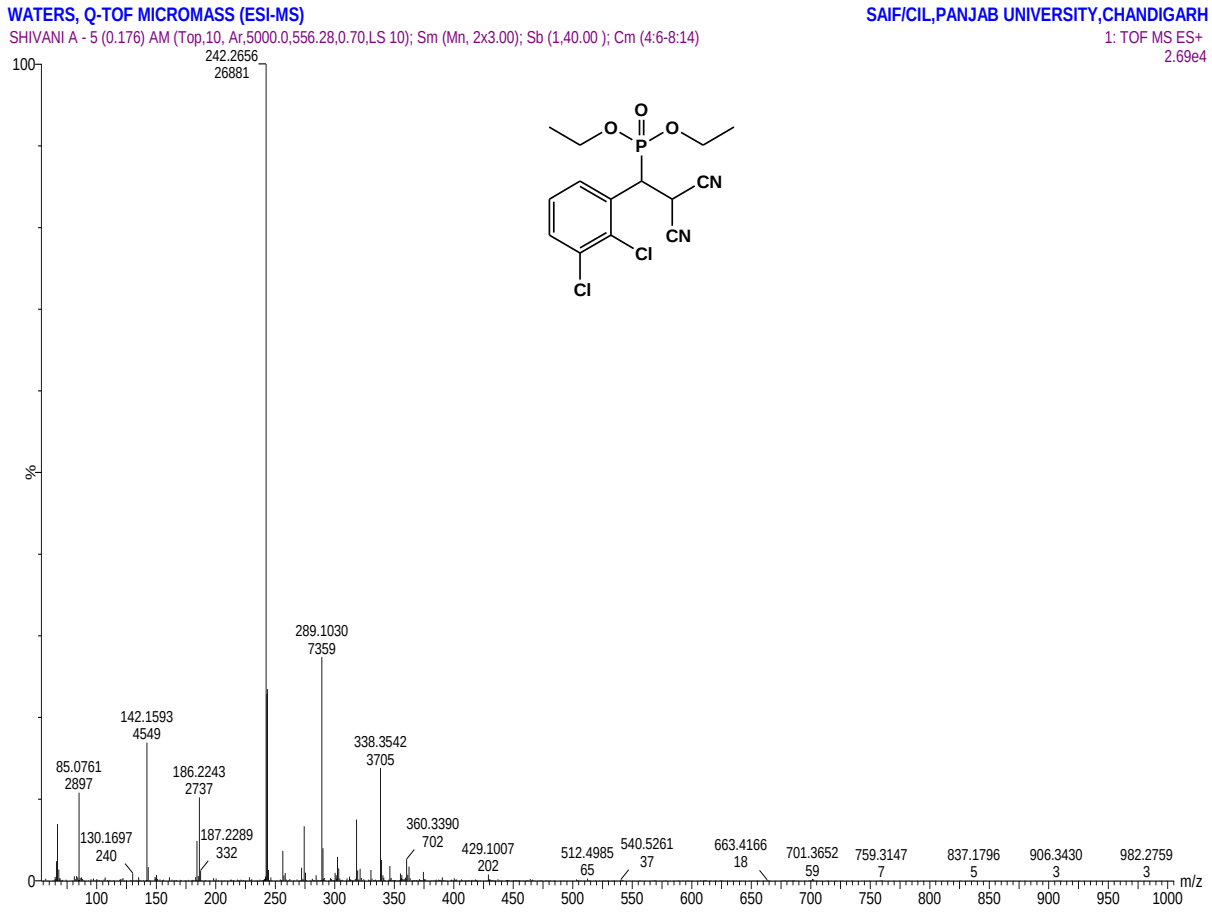


Figure 23 HRMS of **4f**

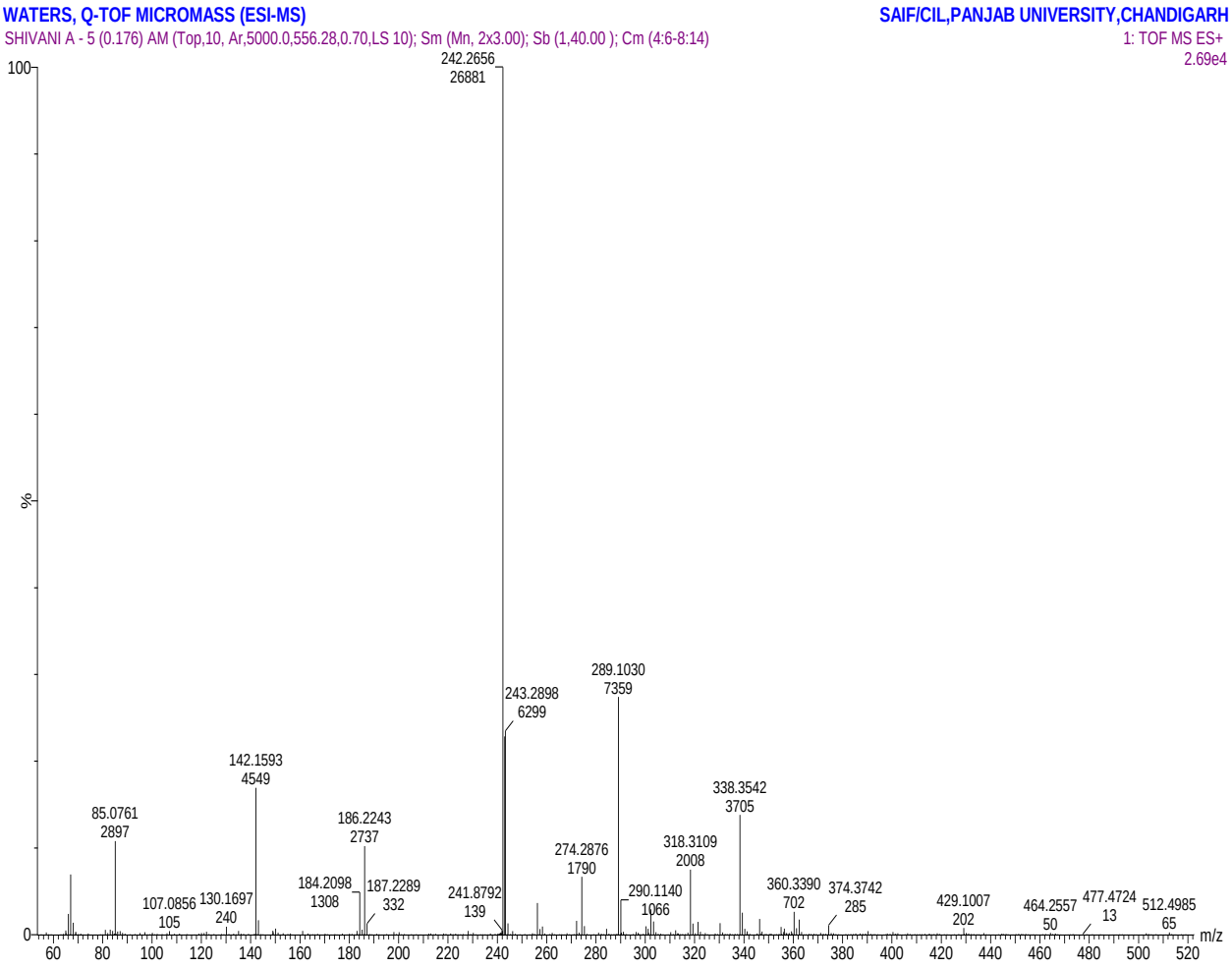


Figure 24 Expended HRMS of **4f**

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References

[1] J. D. Smith, R.L. Hilderbrand, Metabolism of phosphonates in the role of Phosphonates in living systems, CRC:Press, Boca Raton, 1983, p31.
[2] F.R. Atherton, C.H. Hassall, R.W. Lambert, J. Med. Chem., 1986, 29, 29.
[3] D. V. Patel, K. Rielly-Gauvin, D.E. Ryono, Tetrahedron Lett., 1990, 31, 5587.
[4] P. Kafarski, B. Lejczak, Biological Activity of aminophosphonic acids, Phosphorous, Sulfur, Silicon Relat. Elem, 1991, p.193.
[5] A. Payman, K.H. Budt, J. Spanig, B. Stowasser, D. Ruppert, Tetrahedron Lett., 1992, 33, 4549.
[6] G.B. Kastig, M.D. Francis, J. Bone. Miner. Res., 1992,7, 513.
[7] K. Green, Tetrahedron Lett., 1989, 30, 4807.
[8] S. Sobhani, Z. Tashrifi, Tetrahedron, 2010, 66, 1429.
[9] D. Simoni, F.P. Invidiata, M. Manferdini, I. Lampronti, R. Rondanin, M. Roberti, G.P. Pollini, Tetrahedron Lett., 1998, 39,7615.
[10] R.A. Stockland, R.I. Taylor, L.E. Thompson, P.B. Patel, Org. Lett., 2005, 7, 851.
[11] L.B. Han, C.Q. Zhao, J. Org. Chem., 2005, 70, 10121.
[12] Q. Xu, L.B. Han, Org. Lett., 2006, 8, 2099.

[13] Z. Jiang, Y. Zhang, W. Ye, C.H. Tan, Tetrahedron Lett., 2007, 48, 5.
[14] M. Hosseini-Sarvari, S. Etemad, Tetrahedron, 2008, 64, 5519.
[15] S. Sobhani, A. Vafaee, Tetrahedron., 2009, 65, 7691.
[16] S. Sobhani, S. Rezazadeh, J. Iran. Chem. Soc., 2011, 8, 198.
[17] S. Sobhani, Z.P. Parizi, S. Rezazadeh, J. Organomet. Chem., 2011, 696, 813.
[18] S. Sobhani, Z.P. Parizi, N. Razavi, Appl. Catal. B, 2011, 409,162.
[19] M.A. Kulkarni, V.R. Pandurangi, U.V. Desai, P.P. Wadgaonkar, C. R. Chimie., 2012, 15, 745.
[20] S.R. Kolla, Y.R. Lee, Tetrahedron, 2012, 68, 226.
[21] S. Sobhani, R. Jahanshani, Synth. Comm., 2013, 43, 3247.
[22] S. Sobhani, M. Honarmand, Catal. Lett., 2013, 143, 476.
[23] H. Sharghi, S. Ebrahimpourmoghaddam, M.M. Doroodmand, Tetrahedron, 2013, 69, 4708.
[24] B.A. Dar, N. Pandey, S. Singh, R.K. Bamezai, M. Sharma, R.A. Vishwakarma, B. Singh, Tetrahedron Lett., 2014, 55, 623.
[25] Y.Q. Yu, D.Z. Xu, Tetrahedron, 2015, 71, 2853.
[26] R. Ratti, Advance in chemistry, 2014, 1.

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