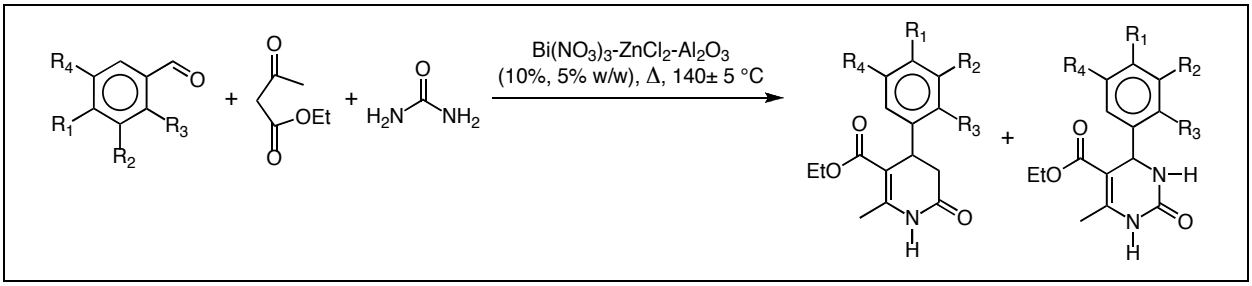
Simple and Efficient One-pot Synthesis of 3,4-Dihydro-2-pyridones via Solid-Supported Bi(III)nitrate catalyzed Double Michael Addition-Azaannulation

Jagjeet Singh [1], Summon Koul [1, 1a], Ajay P. S. Pannu [2], Rattan L. Sharma [1] and Tej K. Razdan *[1]

[1]Department of Chemistry, University of Jammu, Ambedkar Road, Jammu-180006, India.
[1a] Present address : Advinus Therapeutics, International Bio-Tech Park, Genesis Squre, Hinjewadi, Pune-411057
[2]Department of Chemistry, G. N. D. University, Amritsar, Punjab 154003, India.

Received March 29, 2007



4-Aryl-5-carboethoxy-6-methyl-2,3-dihydro-2-pyridones were obtained, in high yield, by heating ternary mixtures of appropriate aldehydes, ethylacetoacetate and compounds possessing NH_2-C=X functionality, in presence of immobilized Bi(III)nitrate and co-catalyst Zn(II)chloride, under solventless conditions. The reaction proceeds smoothly at 140±5°C and seems to involve double Michael addition-azaannulation.

J. Heterocyclic Chem., **45**, 349 (2008).

INTRODUCTION

2-Pyridones and their partially or fully reduced forms constitute the core nucleus of several naturally occurring products [1]. The compounds derived from these nuclei exhibit a wide spectrum of pharmacodynamic properties, such as anti-microbial [2], antifungal [3], and angiotensin converting enzyme inhibiting [4] properties. Some of the compounds inhibit DNA enzymes [5] and a few other products have become potential candidates for anti-tumor [6] and anti-viral [7] therapy. A majority of these products are useful psychotherapeutic agents [8]. Therefore, the synthesis of 2-pyridone derivatives continues to be a subject of great interest. Several methodologies [9], mostly involving oxidation of pyridinium salts [10], Dieckmann-like [11] and Knoevengel's, reactions [12], have been documented for the synthesis of 2-pyridones. Most of these methodologies suffer with one or the other drawback, such as multi-step laborious processes, involvement of stringent or environmentally hazardous reaction conditions, expensive rare-earth catalysts, sometimes in stoichiometric amounts, and low to moderate yield of products. Furthermore, little attention has been paid to the direct synthesis of dihydro-2-pyridone derivatives. This together with our interest in the exploration of the catalyst potential of the readily available, inexpensive, biocompatible and non-toxic Bi(III) nitrate in the synthesis of nitrogen heterocycles prompted us to undertake the synthesis of 3,4-dihydro-2-pyridones, using Bi(III) nitrate immobilized on neutral alumina as catalyst. Herein, we report an efficient, one-pot solid-supported straight forward and environmentally benign synthesis of these products from aryl aldehydes, using catalyst Bi (III) nitrate, immobilized on neutral alumina, in the presence of co-catalyst Zn (II) chloride.

RESULTS AND DISCUSSION

4-Aryl-5-carboethoxy-6-methyl-3,4-dihydro-2-pyridones were synthesized from appropriate aryl aldehyde **1a**-**1m**, ethylacetoacetate **2** and urea **3a**, in the presence of the catalyst Bi(III) nitrate, immobilized on neutral alumina, and co-catalyst Zn(II) chloride. Earlier [13], Bi(III) nitrate, immobilized on alumina, has been found to efficiently catalyze the Michael addition under solventless conditions. This led us to presume that in the presence of immobilized Bi(III) nitrate an aldehyde and ethyl-acetoacetate (1:2 moles) may form 1,5-diketones, *via* aldol condensation and Michael addition, which on subsequent regiospecific, aza-annulation may lead to target compounds. However, this hypothesis failed when ternary mixtures of arylaldehydes, ethylacetoacetate, urea (1:2:1 mole) and the catalyst 10% (w/w) Bi(III) nitrate on Al_2O_3, were heated, at 140 ± 5°C, under solvent less conditions. These reactions afforded mainly 4-aryl-5-carboethoxy-6-methyl-1,4-dihydropyrimidones [11]. Therefore, it occurred to us that it may be possible to divert the preferential Michael addition with urea by catalyst manipulation, using a co-catalyst with relatively higher activity than Bi(III) nitrate. Since, our primary goal has been to make use of inexpensive and biocompatible

metal salts, we chose Zn(II) chloride as co-catalyst. The catalyst was prepared by adsorbing Bi(III) nitrate (10% w/w) on neutral alumina and impregnating the activated Bi(III) nitrate-Al_2O_3 mixture, with co-catalyst Zn(II) chloride (5% w/w). The heterocatalyst mixture was activated, at 110 ± 5 °C, for 4 hours, in a thermostatically controlled hot-air oven. The catalyst mixture was reactivated at the same temperature, each time before use.

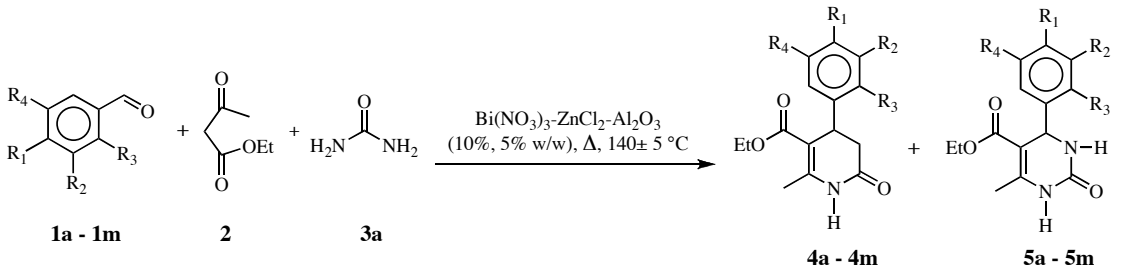
Compounds **4a-4m** were obtained by heating, at 140 ± 5 °C, the ternary mixtures of aryl aldehyde **1a-1m**, ethylacetoacetate **2** and urea **3a** (1:2:1 mole) in the presence of the heterocatalyst mixture Bi(III) nitrate-Al_2O_3-Zn(II) chloride, in proportion of the mass of substrates (calc. conc. of Bi(III) and Zn(II) ions approx. 5 mol. % and 2.5 mol. %), in thermostatically controlled hot-air oven. The reaction was monitored by tlc of the chloroform extract of the aliquots drawn out, from a simultaneously run separate experimental vessel, at 0.5 hour intervals. On completion of the reaction (4-5 hrs), the products were isolated with hot chloroform, the solvent was removed and the compounds were purified by column chromatography on silica gel, using graded solvent systems. Two products **4a**-**4m** (52-69%) and **5a**-**5m** (21-40%) were obtained (Table 1). The products were analyzed by spectral methods *viz*. HRMS, IR, ^{1}H-NMR, ^{13}C-NMR and DEPT-135°. The products **5a**-**5m** were found to be 4-aryl-5-carboethoxy-6-methyl-1,4-dihydro-pyrimidones and their identity was further confirmed by their co-tlc and mixed mp, with the authentic samples available to us, and the literature [11].

The ^{1}H-NMR spectra of **4a**-**4m** displayed characteristic resonance signals at δ 1.16 (t, J=7.0 Hz, 3H, $CO_2CH_2CH_3$), 2.23 (s, 3H, =C-CH_3), 2.30 (dd, J=14.2, 3.2 Hz, 2H, H-3), 4.01 (q, J=7.0 Hz, CO_2CH_2), 4.23 (d, J=3.2 Hz, H-4), 5.26 (s br, 1H, NH), besides the expected aromatic proton signals. The ^{13}C-NMR signals were assigned on the basis of DEPT 135°. The mass fragmentation was consistent with the assigned structures, with molecular ion peak as the base peak and major peaks arising out of loss of ethyl radical, carbon monoxide and arylimine.

The structures of **4a**-**4m** were further confirmed by the X-ray analysis of **4e**, as a representative compound, and comparison of their spectral data with **4e**. Compound **4e** crystallized in triclinic forms with cell dimensions: a = 7.685 Å, b = 8.232 Å, c = 11.846 Å and α = 92.8, β = 100.1, γ = 108.5 (Table 3). The ORTEP diagram of **4e** is given in Fig. 1 the X-ray data of the compound has been tabulated in Table 3-6. The 2-pyridone nucleus assumes a quasi chair conformation with bond angles C_2-C_1-N_1 115.7, C_1-C_2-C_3, 127.1; C_2-C_3-C_4; 190.0° and C_4-C_5-N_1, 120.4°.

To generalize this reaction we carried out the reactions of aldehydes **1a-1m**, ethylacetoacetate **2** and the catalyst mixture with acetamide **3b**, benzamide **3c**, buiret **3d** and semicarbazide **3e**, at 140 ± 5°C. Except for the reaction with **3e**, which yielded multi-component mixtures and were not analyzed, all other reactions afforded mainly 3,4-dihydro-2-pyridones (62-82%) (Table 2). The reaction with **3c** also formed benzoic acid as a minor product.

Scheme I



	R^1	R^2	R^3	R^4
1a.	H	H	H	H
1b.	OCH_3	H	H	H
1c.	Cl	H	H	H
1d.	OCH_3	OCH_3	H	H
1e.	H	H	Cl	H
1f.	H	H	OH	H
1g.	H	Cl	OH	H
1h.	Br	H	H	H
1i.	OCH_3	OH	H	H
1k.	CN	H	H	H
1l.	C_5H_5O	H	H	H
1m.	NO_2	H	H	H

Although, the exact role of co-catalyst Zn(II) chloride is not well understood its necessity in the formation of 3,4-dihydro-2-pyridones was evident from the fact that in its absence, the reactions of **1a**, **2** and **3**, catalyzed by Bi(III) nitrate-Al_2O_3, led to the formation of 4-aryl-5-carbo-ethoxy-6-methyl-1,4-dihydropyrimidones as the main product. Also, the same products were obtained when $ZnCl_2$, immobilized on neutral alumina was used as a catalyst, in the absence of Bi(III) nitrate.

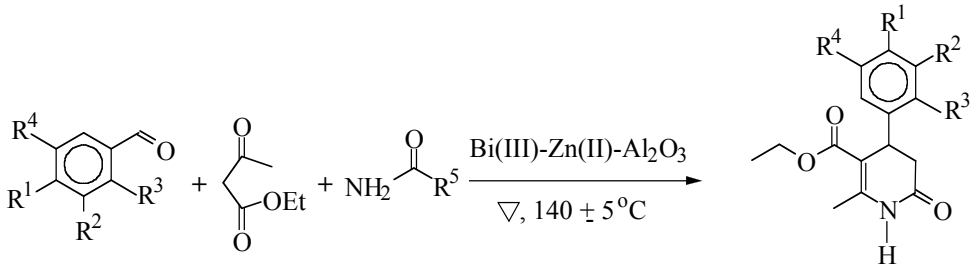
Mechanistically, the reaction of arylaldehyde, ethylacetoacetate and compounds possessing NH_2–C=X group may be rationalized as to involve Aldol condensation followed by Michael addition and subsequent aza-annulation with amines (Scheme 3) to form azetidine intermediate, on one side, and pyrimidone, on the other. The intermediate azetidine, most probably, undergoes Zn (II) mediated rearrangement to form thermodynamically more stable conjugate imine.

Table 1

Percentage yield of **4a-4m** and **5a-5m** using urea.

Product	yield percent	Microwave yield%	Time	Product	yield percent	Microwave yield %
4a	66	68	10	**5a**	20	15
4b	67	72	10	**5b**	30	20
4c	65	68	12	**5c**	28	18
4d	69	74	13	**5d**	28	18
4e	58	63	15	**5e**	40	25
4f	56	64	14	**5f**	40	35
4g	58	62	13	**5g**	40	30
4h	60	60	13	**5h**	38	20
4i	58	64	12	**5i**	33	25
4j	68	71	14	**5j**	21	20
4k	52	66	15	**5k**	36	26
4l	67	64	10	**5l**	31	25
4m	66	63	14	**5m**	30	20

Scheme II



1a-1m **2** **3b-3d** **4a-4m**

(79-88%)

Table 2

Percentage yield of **4a-4m** using **3b-3d**.

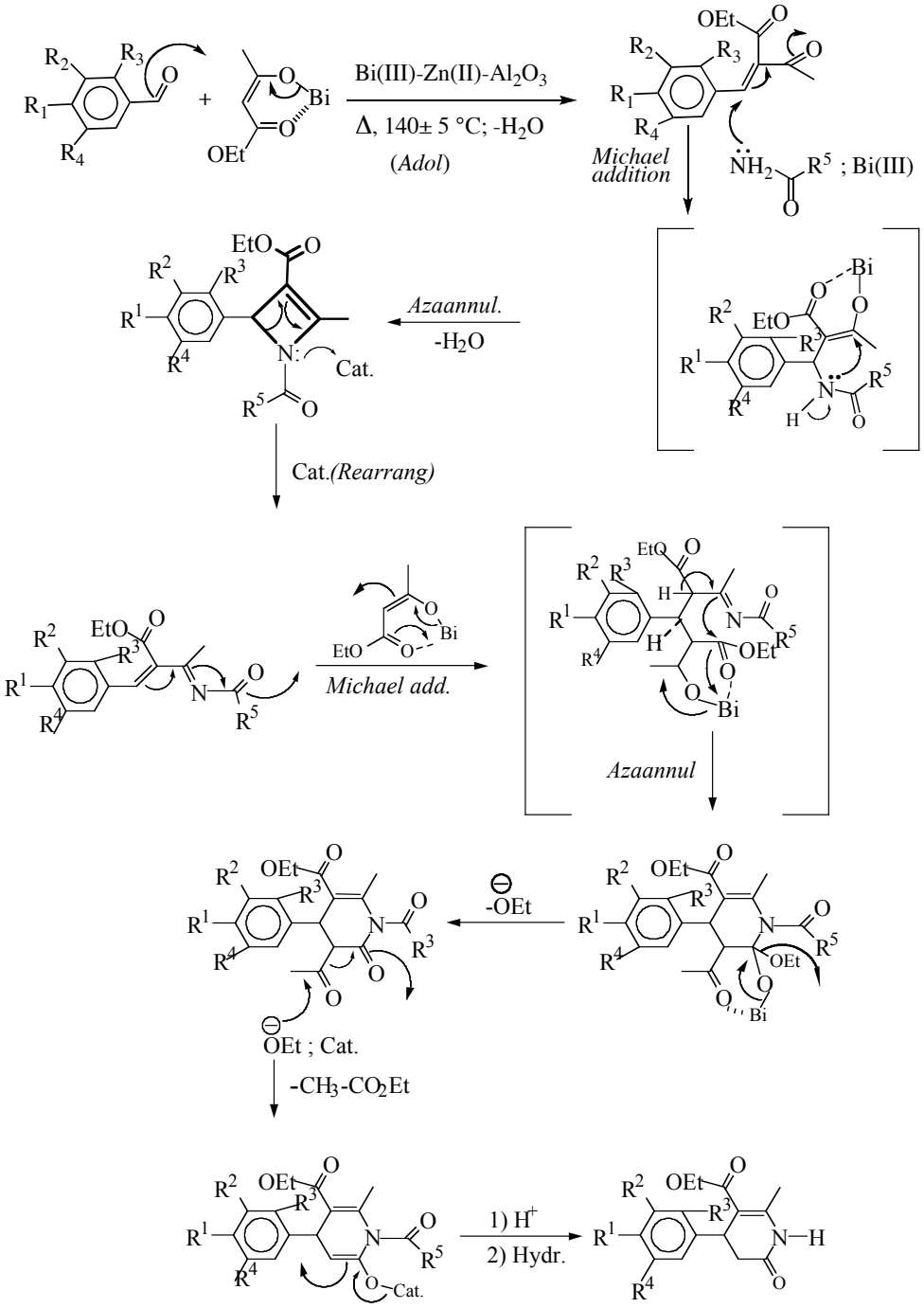
Compound	**3b**	**3c**	**3d**
4a	82	72	81
4b	85	80	84
4c	80	76	71
4d	80	80	76
4e	76	70	66
4f	60	55	32
4g	79	80	75
4h	77	69	71
4i	62	54	49
4j	80	70	85
4k	79	68	72
4l	70	60	62
4m	62	58	66

Subsequent, conjugate addition by six-membered enolised ester Bi(III) complex and regiospecific aza-annulation may lead to the formation of 3-acetyl-4-aryl-5-carboethoxy-6-methyl-3,4-dihydropyridine-2-one which on further hydrolytic disproportionation *via* an enolate ion may form 4-aryl-5-carboethoxy-6-methyl-3,4-dihydro-pyridine-2-one.

The reaction is temperature dependent with the optimum temperature being 140 ± 5 °C. We have also optimized the concentration of Bi(III) nitrate and Zn(II) chloride on neutral alumina and found that 10% (w/w) Bi(III) nitrate and 5%(w/w) Zn(II) chloride on neutral alumina showed the best performance, when the heterocatalyst mixture was used in proportion by weight of the substrates such that the approximate concentration of Bi(III) nitrate and Zn(II) chloride remained within 10 mole percent and 5 mole percent, respectively.

Since, the application of microwave irradiation is becoming increasingly popular in carrying out solventless thermal

Scheme III



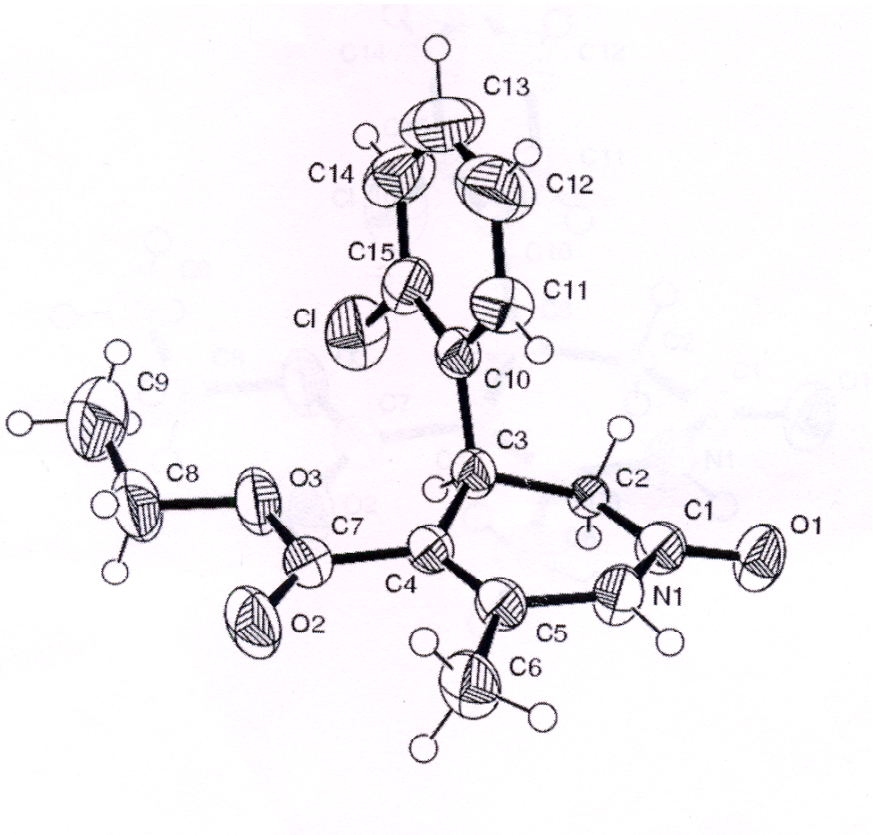


Figure 1. ORTEP diagram of **4e**.

reactions, we repeated the reactions of **1a-1d**, **2**, **3a** and the catalyst in domestic microwave (4.250 MHz) using Makhopadyay *et.al*'s procedure [14]. The reactions were complete within 10-20 mins without any appreciable increase in the percentage yield (Table 1).

We have devised a simple, straight forward, cost-effective one-pot solventless methodology for the preparation of 4-aryl-5-carboethoxy-6-methyl-3,4-dihydro-2-pyridones from aldehydes, ethylacetoacetate and urea derivatives using a heterocatalyst mixture of Bi(III) nitrate-Zn(II) chloride-Al_2O_3. The reaction seems to proceed *via* a cascade sequence of reactions involving double Michael addition and aza-annulation. The reaction shows high functional group tolerance and does not affect the sensitive functionalities like nitrilo and nitro group. The added advantage of this methodology is the non-toxicity and biocompatibility of the catalyst mixture.

EXPERIMENTAL

General. IR spectra were measured on KBr discs using a Perkin Elmer R X 1-FTI R instrument. ^{1}H-NMR spectra were measured using Varian Gemini-200 (200 MHz) and JEOL-FT-NMR-AL (300 MHz). ^{13}C-NMR, DEPT 135° spectra were measured on JEOL-FT-NMR-300 (75.45 MHz). HRMS were recorded on JEOL mass spectrometer. Mp's were determined with Metler FP-82 hot stage apparatus and are uncorrected. Column chromatography was carried out on silica gel (Sisco Research Lab. 60-120 mesh). TLC was done on silica gel G (Sisco Research Lab) plates.

Preparation of Catalyst Mixture. Bi(III) nitrate (10% w/w, 5 g) in hot MeOH-Me_2CO (1:1v/v, 100 mL) was added to neutral alumina (45 gm) and the mixture stirred for 24 hr. at room temperature. The solvent was removed under reduced pressure and the residue was activated at 110 ± 5°C for 8 hr., in a thermostatically controlled hot-air oven. The activated mixture was cooled in a desiccator. To this mixture Zn(II) chloride (5% w/w; 2.5 g) in dry acetone (100 mL) was added and the mixture was again stirred for 6 hrs at room temperature under anhydrous conditions. After removing the solvent, under pressure, the catalyst mixture was again activated at 110 ± 5°C for 10 hr. The catalyst mixture was preserved in a desiccators and reactivated at 110 ± 5°C, for 2 hr, each time before use.

General Procedure for the preparation of 3,4-dihydro-2-pyridones. The aldehydes **1a-1m** (1 x 10^{-3} moles), ethylaceto-acetate (2 x 10^{-3} moles) and compounds possessing NH_2-C=X, *viz* urea, CH_3CONH_2, $PhCONH_2$, $NH_2CO.NH.CONH_2$ and $NH_2.NH.CO.NH_2$ ($1x10^{-3}$ moles) were mixed with the catalyst, in proportion by the mass of substrates, and stirred mechanically for 1 hr. The reaction mixture was heated at 140 ± 5 °C in a thermostatically controlled hot-air oven. To monitor the reactions by tlc separate experiments were simultaneously conducted. Aliquots were drawn out at 0.5 hr intervals and reaction was monitored by comparative tlc of the chloroform extracts, using pet. ether-chloroform graded solvent system. On completion of the reaction (4-5 hr) the products were isolated with hot $CHCl_3$ in a soxhlet extractor. The organic layer was washed with water, 1 *M*

NH_4OH and water. The organic layer was dried over anhyd. Na_2SO_4, filtered and purified by column chromatography, using pet. ether-$CHCl_3$ graded solvent systems. The products were crystallized from $CHCl_3$-pet. ether (bp 40°- 60 °C).

5-Carboethoxy-6-methyl-4-phenyl-3,4-dihydro-pyridine-2-one (4a). Colorless crystals, mp. 102-103°C. IR: ν_{max} 3117, 2969, 1724, 1648, 1466, 1420, 1386, 1290, 1222, 1091, 1028, 782 cm^{-1}. ^{1}H-NMR($CDCl_3$, 200MHz): δ 1.16 (3H, t, J = 7.0 Hz), 2.17 (3H, s), 2.37 (2H, d, J = 3.4 Hz), 3.68 (1H, d, J = 3.4 Hz), 6.07 (1H, s br, NH), 7.10-7.46 (5H, m). ^{13}C-NMR ($CDCl_3$): δc 13.7, 17.5, 43.5, 54.3, 59.9, 110.3, 120.8, 125.7, 127.9, 128.4, 139.5, 165.6, 171.3. HRMS: m/z (rel. int.) 259.1216 (M^+) (calcd. for $C_{15}H_{17}NO_3$, 259.1209) (100), 231(30), 217(60), 203(36), 189(38), 159(55), 145(54), 104(26), 77(87). *Anal.* calcd. for $C_{15}H_{17}NO_3$: C, 69.48 ; H, 6.60 ; N, 5.40 .Found: C, 69.49 ; H, 6.62 ; N, 5.39.

5-Carboethoxy-6-methyl-4-(4-methoxy)phenyl-3,4-dihydro-pyridin-2-one (4b). Colorless crystals, mp 137-138°C. IR: ν_{max} 2995, 2874, 2265, 1685, 1578, 1510, 1445, 1410, 1340, 1305, 1285, 1040 1017, 866 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 7.1 Hz), 1.87 (1H, s), 2.22 (3H, s), 2.40 (2H, dd, J = 1.4, 3.7 Hz), 3.75 (3H, s), 3.93 m (1H, d, J = 3.7, 1.7 Hz), 3.98 (2H, q, J = 7.1 Hz), 6.80 (2H, d, J = 8.7 Hz), 7.16 (2H, d, J = 8.7 Hz). ^{13}C-NMR ($CDCl_3$): δc 18.6, 24.1, 40.6, 55.3, 60.0, 101.5, 109.5, 109.7, 118.6, 136.3, 148.3, 153.3, 165.7. MS : m/z (rel. int.) 289.1323 (M^+) (calcd. for $C_{16}H_{19}NO_4$, 289.1315) (100), 274(34), 261(47), 247(59), 233(33), 189(52), 175(50), 134(42), 107(69), 92(49). *Anal.* calcd. for $C_{16}H_{19}NO_4$: C, 66.42 ; H, 6.61; N, 4.84. Found: C, 66.41; H, 6.62; N, 4.83.

5-Carboethoxy-6-methyl-4(4-chloro)phenyl-3,4-dihydro-pyridin-2-one (4c). Colorless crystals, mp. 178-179°C. IR: ν_{max} 3001, 2875, 2776, 2250, 1695, 1628, 1570, 1530, 1510, 1445, 1366, 1340, 1290, 1060, 1017, 960 cm^{-1}. ^{1}H-NMR (300 MHz,$CDCl_3$): δ 1.19 (3H, t, J = 7.1 Hz), 2.13 (3H, s), 2.39 (2H, d, J = 3.1 Hz), 4.07 (1H, d, J = 3.1 Hz), 4.20 (2H, q, J = 7.1 Hz), 5.80 (1H, s br), 7.44 (2H, *d*, J = 8.4 Hz), 7.75 (2H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$): δc 14.5, 19.6, 43.2, 53.1, 60.0, 101.1, 121.2, 127.6, 133.5, 137.3, 148.0, 148.7, 154.5, 154.6, 165.3. MS: m/z (rel. int.) 293.0892, 295.0798 (M^+) (Calc. for $C_{15}H_{16}ClNO_3$, 293.0819, 295.0789), 275(36), 273(28), 265(39), 253(36), 251(68), 223(46), 237(67), 179(55), 138(16), 112(72), 77(48). *Anal.* calcd. for $C_{15}H_{16}ClNO_3$: C, 61.33 ; H, 5.49 ; N, 4.76. Found: C, 66.41; H, 5.52; N, 4.78.

5-Carboethoxy-6-methyl-4(3,4-dimethoxy)phenyl-3,4-dihydro-pyridin-2-one (4d). Colorless crystals, mp 112-113°C. IR: ν_{max} 3174, 2973, 2603, 2265, 1699, 1605, 1578,1515, 1445, 1340, 1305, 1278, 1210, 1160, 1017, 984cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.20 (3H, t, J = 7.2 Hz), 2.34 (3H, s), 2.58 (2H, d, J = 3.7 Hz), 3.62 (3H, s), 3.67 (3H, s), 3.85 (1H, d, J = 3.7 Hz), 4.07 (2H, q, J = 7.1 Hz), 5.90 (1H, s br), 6.67 (1H, d, J = 3.1 Hz), 6.89 (1H, d, J = 8.6 Hz), 7.12 (1H, d, J = 8.6 Hz). ^{13}C-NMR ($CDCl_3$): δc 14.1, 18.6, 20.6, 40.3, 55.3, 55.8, 60.0, 101.5, 109.8, 111.0, 118.6, 136.3, 148.6, 148.9, 153.4, 165.7. MS: m/z (rel. int) 319.1432 (M^+) (Calc. for $C_{17}H_{21}NO_5$ 319.1420), 281(23), 277(63), 263(42), 249(38), 219(55), 205(62), 164(59), 77(76). *Anal.* calcd. for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.62 ;N, 4.38. Found: C, 63.95; H, 6.64; N, 4.39.

5-Carboethoxy-6-methyl-4-(2-chloro)phenyl-3,4-dihydro-pyridin-2-one (4e). Colorless crystal, mp 154-155°C. IR: ν_{max} 3244, 3117, 2969, 1700, 1648, 1599, 1466, 1420, 1386, 1313, 1290, 1222, 1091, 1028, 782. ^{1}H-NMR ($CDCl_3$, 200MHz): δ 1.05 (3H, t, J = 6 Hz), 2.42 (3H, s), 2.74 (2H, d, J = 3.2 Hz), 3.97 (1H, d, J = 3.2 Hz), 3.99 (2H, q, J = 6.6 Hz), 5.72 (1H, s br), 7.21 (1H, dd, J = 7.2, 3.0 Hz), 7.35 (2H, m), 7.39 (1H, dd, J = 7.2, 3.0 Hz). ^{13}C-NMR , s), ($CDCl_3$) δc 14.6, 18.9, 45.8, 57.2, 61.2, 109.5, 121.2, 133.5, 136.5, 146.9, 147.6, 148.0, 155.3, 155.7. MS: m/z (rel. int.) 295.0786, 293.0812 (M^+) (Calc. for $C_{15}H_{16}ClNO_3$, 295.0789, 293.0819) (100), 267(52), 265(68), 252(57), 237(35), 223(42), 193(58), 179(56), 138(42), 112(44), 77(82). *Anal.* calcd. for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.76.Found: C, 61.35; H, 5.51; N, 4.75.

5-Carboethoxy-6-methyl-4-(2-hydroxy)phenyl-3,4-dihydro-pyridin-2-one (4f). Colorless crystals mp. 208-209°C. IR: ν_{max} 3462, 3120, 2964, 2827, 1708, 1682, 1655, 1519, 1461, 1385, 1323, 1282, 1238, 1139, 1096, 1027, 866 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO): δ 1.26 (3H, t, J = 7.1 HZ), 1.87 (3H, s), 2.37 (2H, s), 3.12 (2H, d, J = 3.4 Hz), 4.30 (2H, q, J = 7.1 Hz), 6.07 (1H, s br), 6.81 (2H, dd, J = 8.1, 2.3 Hz), 7.12 (1H, m), 7.22 (1H, dd, J = 8.1, 2.3 Hz). ^{13}C-NMR δc 14.8, 18.5, 39.4, 55.3, 60.7, 110.9, 113.5, 128.3, 133.6, 136.3, 140.3, 146.5, 151.0, 153.9, 165.3. MS: m/z (rel. int.) 275.1149 (M^+) (Calcd. for $C_{15}H_{17}NO_4$, 275.1158) 247(45), 233(62), 219(38), 205(37), 175(51), 151(53), 120(44), 93(76). *Anal.* calcd. For $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.08. Found: C, 65.44 ; H, 6.20 ; N, 5.07.

5-(Carboethoxy)-4-(3,5-dichloro)phenyl-6-methyl-3,4-dihydro-pyridin-2-one (4g). Colorless crystals, mp 189-190°C. IR: ν_{max} 3100, 2965, 2830, 1700, 1682, 1658, 1510, 1467, 1385, 1323, 1282, 1236, 1140, 1096, 1030, 868cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.19 (3H, t, J = 7.1Hz), 2.23 (3H, s), 2.30 (2H, s), 4.01 (2H, q, J = 7.1 Hz), 4.23 (1H, d,J = 3.4 Hz), 5.19 (1H, s br), 7.42 (1H, d, J = 2.4 Hz), 7.76 (1H, dd, J = 8.2,2.4 Hz),8.12 (1H, d, J = 8.2 Hz). ^{13}C-NMR (DMSO-d_6): δc 15.3, 18.6, 46.8, 55.0, 61.2, 108.3, 121.5, 133.6, 142.2, 147.5, 148.0, 148.6, 152.3, 156.7, 165.5. MS: m/z (rel. int) 331.0458, 327.0440 (M^+) (Cal. for $C_{15}H_{15}NO_3Cl_2$, 331.0450, 327.0431) (100), 301(36), 299(39), 286(61), 272(35), 258(34), 228(48), 214(51), 173(36), 147(74). *Anal.* calcd for: $C_{15}H_{15}NO_3Cl_2$: C, 54.89; H, 4.60; N, 4.26. Found: C, 54.87; H, 4.59; N, 4.27.

5-Carboethoxy-4-(4-fluorophenyl)-6-methyl-3,4-dihydro-pyridine-2-one (4h). Colorless crystals, mp 166-167°C. IR: ν_{max} 3000, 2968, 2845, 1698, 1660, 1515, 1475, 1380, 1326, 1292, 1236, 1145, 1090, 1030, 865cm^{-1}. ^{1}H-NMR (300 MH, $CDCl_3$): δ 1.21 (3H, t, J = 7.1 Hz), 2.50 (3H, s), 2.53 (2H, dd, J = 3.4, 1.8 Hz), 4.13 (2H, q, J = 7.1 Hz), 5.17 (1H, d, J = 3.4 Hz), 5.60 (1H, s br), 7.12 (2H, dd, J = 8.6, 2.9 Hz), 7.62 (2H, dd, J = 8.6, 2.9 Hz). ^{13}C-NMR ($CDCl_3$): δc 14.9, 18.6, 50.8, 53.1, 61.2, 98.9, 115.1, 128.1, 128.2, 140.9, 146.5, 159.9, 166.5, 165.8. MS: m/z (rel. int.) 277.1125 (M^+) (Calcd. for $C_{15}H_{16}FNO_3$, 277.1114) (100), 249(32), 221(66), 207(32), 177(67), 163(55), 122(63), 96(65), 77(72). *Anal.* calcd. for $C_{15}H_{16}FNO_3$: C, 64.97; H, 5.81; N, 5.05. Found: C, 64.96; H, 5.80; N, 5.07.

5-Carboethoxy-6-methyl-4(2-hydroxy-4-methoxy)phenyl-3,4-dihydropyridin-2-one (4i). Colourless solid mp 215-216 °C. IR ν_{max} 3500, 3047, 3005, 2846, 1656, 1600, 1578, 1511, 1445, 1340, 1305, 1263, 1212, 1170, 1017, 984 cm^{-1}. ^{1}H-NMR (300 MHz,DMSO-d_6): δ 1.02 (3H, t, J = 7.1 Hz), 2.0 (3H, s), 2.46 (2H, d, J = 3.2 Hz), 3.83 (3H, s), 3.92 (5H, q, d, J = 7.1, 3.2 Hz), 6.60 (1H, d, J = 3.2 Hz), 6.68 (1H, d, J = 8.0 Hz), 6.84 (1H, d, J = 8.0 Hz), 8.70 (1H, s br), 9.12 (1H, s, br). ^{13}C-NMR (DMSO-d_6): δc 14.8, 18.5, 44.8, 55.8, 56.4, 60.6, 99.2, 109.6, 112.3, 119.2, 144.01, 148.5, 149.6, 153.7, 156.5, 166.8 MS : m/z (rel. int.) 305.1253 (M^+) (Calcd. for $C_{16}H_{19}NO_5$, 305.1265), 277(28), 263(44), 261(58), 235(49), 233(52), 205(61), 191(52), 124(82), 110(61).*Anal.* calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.58. Found: C, 62.95; H, 6.28; N, 4.57.

5-Carboethoxy-6-ethyl-4-(3,4-dioxymethylene)-phenyl-3,4-dihydropyridin-2-one (4j). Colorless crystals mp 137-138 °C.

IR: ν_{max} 3060, 3004, 2837, 1659, 1598, 1572, 1446, 1422, 1336, 1293, 1256, 1172, 1113, 1071, 1035, 1018, 828, 778 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.19 (3H, t, J = 7.1 Hz), 2.34 (3H, s), 2.55 (2H, d, J = 3.7 Hz), 3.85 (1H, d, J = 3.7 Hz), 4.07 (2H, q, J = 7.1 Hz), 6.80 (1H, s), 6.84 (1H, d, J = 8.6 Hz), 7.18 (1H, dd, J = 8.6, 2.3 Hz). ^{13}C NMR ($CDCl_3$): δc 16.5, 19.8, 51.2, 53.4, 60.2, 101.1, 102.5, 112.5, 114.8, 118.6, 137.6, 149.9, 149.1, 154.2, 165.3. MS: m/z (rel. int.) 303.1101 (M^+) (Calcd. for $C_{16}H_{17}NO_5$, 303.1107), 275(49), 273(59), 230(66), 216(45), 211(35), 183(64), 175(56), 142(32). *Anal*. calcd. for $C_{16}H_{17}NO_5$: C, 63.35 ; H, 5.64 ; N, 4.61. Found: C, 63.34; H, 5.65; N, 4.60.

5-Carboethoxy-6-methyl-4-(4-cyano)phenyl-3,4-dihydropyridin-2-one (4k). Colorless crystals mp 168-169°C. IR: ν_{max} 3032, 3005, 2859, 1676, 1650, 1600, 1578, 1573, 1515 1490, 1447, 1340, 1305, 1260, 1212, 1170, 1017, 984 cm^{-1}. ^{1}H-NMR (200 MHz,$CDCl_3$) δ 1.12 (3H, t, J = 7.1 Hz), 2.29 (3H, s), 2.66 (2H, d, J = 3.2 Hz), 4.00 (2H, q, J = 7.1 Hz), 4.16 (1H, d, J = 3.5 Hz), 7.63 (2H, dd, J = 8.1 Hz), 7.83 (2H, dd, J = 8.1 Hz), 5.63 (1H, s br). ^{13}C-NMR ($CDCl_3$) : δc 12.4, 16.3, 40.4, 56.4, 59.5 108.0, 125.8, 130.5, 147.6, 148.3, 153.5, 163.5. MS: m/z (rel. int) 284.1172 ($M^{+\cdot}$) (Cal. For $C_{16}H_{16}N_2O_3$ 284.1161), 256(20), 242(58), 228(42) 214(47), 170(58), 129(35), 103(68), 77(81). *Anal*. calcd. for :$C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found : C, 67.58; H, 5.66; N, 9.84.

3-Carboethoxy-4-furfryl-6-methyl-3,4-dihydropyridin-2-one (4 l). Colorless crystals mp 110-111°C. IR: ν_{max} 3227, 3110, 2973, 1698, 1645, 1499, 1454, 1381, 1300, 1292, 1151, 1100, 1014, 927, 799cm^{-1}. ^{1}H-NMR (300 MHz,$CDCl_3$) δ 1.21 (3H, t, J = 7.1 Hz), 2.32 (3H, s), 2.82 (2H, d, J = 3.1 Hz), 4.13 (2H, q, J = 7.1 Hz), 5.44 (1H, d, J = 3.1 Hz), 5.63 (1H, s br), 6.10 (1H, d, J = 1.9 Hz), 6.27 (1H, dd, J = 0.9, 1.7 Hz), 7.32 (1H, dd, J = 1.7 Hz). ^{13}C-NMR ($CDCl_3$) δc 15.6, 19.4, 42.5, 60.8, 63.2, 99.6, 107.3, 130.5, 131.1, 133.4, 143.4, 153.1, 166.7. MS: m/z (rel. int.) 249.1012 (M^+) (Calc. for $C_{13}H_{15}NO_4$, 249.1001), 221(46), 207(58), 193(47), 179(56), 149(68), 135(44), 94(33), 67(78). *Anal*. calcd. for; $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.61. Found: C, 62.62; H, 6.04; N, 5.59.

Table 3

Crystal data and structure refinement for **4e**

Identification code	**4e**
Empirical formula	$C_{15}H_{16}ClNO_3$
Formula weight	293.74
Temperature	293(2) K
Wavelength	0.71069 A
Crystal system, space group	TRICLINIC, P-1
Unit cell dimensions	a = 7.685(5) A alpha = 92.800(5) deg. b = 8.232(5) A beta = 100.190(5) deg. C = 11.846(5) A gamma = 108.560(5) deg.
Volume	694.8(7) A^3
Z, Calculated density	2, 1.404 Mg/m^3
Absorption coefficient	0.281 mm^-1
F(000)	308
Crystal size	0.02x0.02x0.03 mm
Theta range for data collection	1.76 to 25.50 deg.
Limiting indices	0<=h<=8, -9<=k<=9, -14<=1<=14
Reflections collected / unique	2706/2497 [R (int) = 0.0251]
Completeness to theta = 25.50	96.4%
Absorption correction	None
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	2497 / 0 / 181
Goodness-of-fit on F^2	0.978
Final R indices [I>2sigma(I)]	R1 = 0.0612, wR2 = 0.1818
R indices (all data)	R1 = 0.1054, wR2 = 0.2089
Largest diff. peak and hole	0.420 and -0.578 e.A^-3

5-Carboethoxy-4(4-nitro)phenyl-6-methyl-3,4-dihydropyridin-2-one(4m). Pale yellow crystals mp 132-133°C. IR: ν_{max} 3010, 2876, 2825, 1690, 1672, 1656, 1530, 1460, 1385, 1325, 1285, 1238, 1140, 1090, 1025, 870 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, t, J = 7.1 Hz), 2.23 (3H, s), 2.51 (2H, dd, J = 3.6, 1.8 Hz), 3.32 (1H, d, J = 3.6 Hz), 4.01 (2H, q, J = 7.1 Hz), 7.51 (2H, d, J = 8.7 Hz), 8.20 (2H, d, J = 8.7 Hz). ^{13}C-NMR ($CDCl_3$) δc 18.6, 19.1, 53.6, 53.7, 60.1, 109.4, 123.8, 127.9, 146.6, 148.9, 151.6, 153.2, 163.9. MS: m/z (rel. int.) 303.0969 (M^+) (Calc. for $C_{15}H_{15}N_2O_5$, 303.0981), 275(46), 257(53), 247(58), 261(58), 233(37), 189(49), 148(56), 77(71). *Anal*. calcd .for :$C_{15}H_{15}N_2O_5$: C, 59.20 H, 5.30 N, 9.20. Found: C, 59.22; H, 5.26; N, 9.21.

Table 4

Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **4e**. U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	u(eq)
C (1)	4455 (5)	2457 (5)	9303 (3)	44 (1)
C (2)	3983 (4)	802 (4)	8902 (3)	27 (1)
C (3)	2135 (5)	-334 (5)	8283 (3)	39 (1)
C (4)	651 (5)	435 (5)	8519 (3)	38 (1)
C (5)	1133 (5)	2083 (5)	8940 (3)	41 (1)
C (6)	-161 (5)	3045 (5)	9154 (4)	57 (1)
C (7)	-1314 (5)	-686 (5)	8266 (3)	47 (1)
C (8)	-3419 (7)	-3471 (7)	7512 (5)	95 (2)
C (9)	-3509 (9)	-4853 (8)	6763 (6)	114 (2)
C (10)	2126 (5)	-595 (5)	7011 (3)	42 (1)
C (11)	2338 (6)	801 (6)	6358 (4)	60 (1)
C (12)	2435 (8)	651 (9)	5214 (4)	86 (2)
C (13)	2312 (8)	-917 (10)	4673 (5)	95 (2)
C (14)	2076 (7)	-2321 (8)	5287 (5)	80 (2)
C (15)	1985 (5)	-2163 (5)	6429 (4)	56 (1)
N (1)	2997 (4)	3102 (4)	9231 (4)	48 (1)
O (2)	-2661 (4)	-297 (4)	8406 (3)	67 (1)
O (3)	-1503 (4)	-2272 (4)	7835 (3)	66 (1)
O (1)	6055 (4)	3376 (4)	9741 (3)	63 (1)
Cl	1723 (2)	-3986 (2)	7139 (1)	82 (1)

Table 5

Bond lengths [A] and angles [deg.] for **4e**.

C (1) -O (1)	1.224 (4)	O (1) –C (1) –C (2)	124.1 (3)
C (1) -C (2)	1.332 (5)	O (1) –C (1) –N (1)	120.2 (3)
C (1) -N (1)	1.376 (5)	C (2) –C (1) –N (1)	115.7 (3)
C (2) -C (3)	1.466 (4)	C (1) –C (2) –C (3)	127.1 (3)
C (3) -C (10)	1.510 (5)	C (2) –C (3) –C (10)	110. 1 (3)
C (3) -C (4)	1.528 (5)	C (2) –C (3) –C (4)	109.0 (3)
C (4) -C (5)	1.333 (5)	C (10) –C (3) –C (4)	112. 4 (3)
C (4) -C (7)	1.468 (5)	C (5) –C (4) –C (7)	121.0 (3)
C (5) -N (1)	1.381 (5)	C (5) –C (4) –C (3)	120.8 (3)
C (5) –C (6)	1.500 (5)	C (7) –C (4) –C (3)	118.3 (3)
C (7) –O (2)	1.212 (4)	C (4) –C (5) –N (1)	120.4 (3)
C (7) –O (3)	1.332 (5)	C (4) –C (5) –C (6)	127.0 (3)
C (8) –C (9)	1.384 (7)	N (1) –C (5) –C (6)	112.6 (3)
C (8) –O (3)	1.458 (5)	O (2) –C (7) –O (3)	121.3 (4)
C (10) –C (15)	1.396 (5)	O (2) –C (7) –C (4)	127.1 (4)
C (10) –C (11)	1.400 (6)	O (3) –C (7) –C (4)	111.7 (3)
C (11) –C (12)	1.372 (6)	C (9) –C (8) –O (3)	110.6 (4)
C (12) –C (13)	1.381 (8)	C (15) –C (10) –C (11)	116.3 (4)
C (13) –C (14)	1.375 (8)	C (15) –C (10) –C (3)	123.8 (4)
C (14) –C (15)	1.369 (7)	C (11) –C (10) –C (3)	119.8 (3)
C (15) –Cl	1.729 (5)	C (12) –C (11) –C (10)	122.0 (5)
		C (11) –C (12) –C (13)	119.9 (5)
		C (14) –C (13) –C (12)	119.5 (5)
		C (15) –C (14) –C (13)	120.4 (5)
		C (14) –C (15) –C (10)	121.9 (5)
		C (14) –C (15) – Cl	117.3 (4)
		C (10) –C (15) – Cl	120.9 (3)
		C (1) –N (1) –C (5)	123.4 (3)
		C (7) –O (3) –C (8)	115.9 (3)

Symmetry transformation used to generate equivalent atoms:

Table 6

Anisotropic displacement parameters (A^2 x 10^3) for **4e**.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U11+ \ldots\ldots. +2h\ k\ a^*\ b^*\ U12]$

U12	U11	U22	U33	U23	U13
C(1)	27 (2)	54 (2)	51 (2)	-8 (2)	6 (2)
C(2)	19 (2)	34 (2)	30 (2)	-4 (1)	2 (1)
C(3)	30 (2)	39 (2)	47 (2)	-2 (2)	9 (2)
C(4)	29 (2)	45 (2)	41 (2)	-2 (2)	7 (2)
C(5)	29 (2)	48 (2)	47 (2)	-1 (2)	8 (2)
C(6)	39 (2)	56 (2)	81 (3)	-5 (2)	16 (2)
C(7)	34 (2)	57 (2)	45 (2)	-3 (2)	10 (2)
C(8)	52 (3)	83 (14)	120 (5)	-34 (2)	38 (3)
C(9)	83 (4)	91 (4)	129 (5)	-35 (4)	20 (4)
C(10)	27 (2)	48 (2)	49 (2)	-6 (2)	8 (2)
C(11)	57 (3)	69 (3)	53 (3)	3 (2)	17 (2)
C(12)	79 (4)	120 (5)	63 (3)	26 (3)	26 (3)
C(13)	83 (4)	157 (6)	49 (3)	-10 (4)	13 (3)
C(14)	70 (3)	105 (4)	67 (3)	-32 (3)	5 (3)
C(15)	38 (2)	61 (3)	65 (3)	-19 (2)	7 (2)
N(1)	32 (2)	42 (2)	68 (2)	-15 (2)	7 (2)
O(2)	32 (2)	74 (2)	96 (2)	-5 (2)	18 (2)
O(3)	36 (2)	52 (2)	97 (2)	-21 (2)	21 (2)
O(1)	29 (2)	61 (2)	91 (2)	-28 (2)	3 (1)
Cl	75 (1)	52(1)	120 (1)	-12 (1)	23 (1)

Acknowledgement. The author are thankful to Prof. Hundal G. N. D. University Amritsar for X-ray analysis, Dr. Simon Fraser (University, British Columbia, Canada) and Mrs. B. P. Wakhlu (R.R.L Jammu) spectral analysis.

REFERENCES

[1] (a) Schultz, A. *Chem. Rev* **1973**, *73*, 385. (b) Emtenas, H.; Alderin, L.; Almqvist, F. *J. Org. Chem.* **2001**, *66*, 6756. (c) Stilli, J. R.; Barta, N. S. Studies in Natural Product Chemistry Elsevier Science, Amsterdam, 1966; vol. 18, pp 315 (d) Bradley, J. C.; Buchi, G., *J. Org. Chem.* **1976**, *41*, 699.

[2] Kelly, T.; Bell, S.; Osashi, N.; Amtrong-Chong, J. *J. Am. Chem. Soc.* **1988**, *110*, 6471.

[3] (a) Cox, R.; O' Hagan, D. *J. Chem. Soc., Perkin Trans. I,* **1991**, 2537. (b) Mynderse, J. S.; Samlaska, S. K.; Fukuda, D. S.; DuBus, R. H.; Baker, P. J. *J. Antibiot.* **1985**, *38*, 1003.

[4] (a) O' Connor, S.; Somers, *P. J. Antibiot.* **1985**, *38*, 993. (b) Hunt, A. H.; Mynderse, J. S.; Samlaska, S. K.; Fukuda, D.; Maciak, G. M.; Kirst, H. A.; Occolowitz, J. L.; Swartzen-druber, J. K.; Jones, N. D. *J. Antibiot.* **1988**, *41*, 771.

[5] (a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888. (b)Aberg, V.; Hedenstrom, M.; Pinkner, J. S.; Hultgren, S. J.; Almqvist, F. *Org. Biomal. Chem.* **2005**, *3*, 3886.

[6] (a) Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255. (b) Potmesil,, M. Cancer Res., **1994**, *54*, 1431. (c) Rice-Evans, C. A.; Burdon, R. H., *Free Radical Damage and its Control*; Elsevier, Amsterdam, 1994.

[7] (a) Josien, H.; Curran, D. P. *Tetrahedron* 1997, 53, 8881. (b) Williams, D.; Lowder, P.; Gu, Y. G. *Tetrahedron Lett.* **1997**, *38*, 327.

[8] Kozkowski, A.; Campiani, G.; Sun, L. Q.; Wang, S.; saxena, A.; Doctor, B. *J. Am. Chem. Soc.* **1996**, *118*, 11357.

[9] (a) Aggarwal, V.; Singh, G.; Illa,H.; Jungrappa, H. *Synthesis* **1982**, 214. (b) Datta, A.; Illa,H.; Junjappa, H. *J. Org. Chem.* **1990**, *55*, 5589. (c) Chuit, C.; Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron* **1986**, *42*, 2293. (d) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. J. *Org. Chem.* **2000**, *65*, 2368. (e) Gurski-Birchler, A.; Liu, F.; Liebeskind, L. S. *J. Org. Chem.*

1994, *59*, 7737. (f) Tomas, M.; Suarez-Sobrino, A.; Gotor, V. *Tetrahedron Lett*. **1988**, *29*, 4855. (g) Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett*. **1996**, *37*, 4973. (h) Katrizky, A.; Belyakov, S.; Sorochinsky, A.; Henderson, A.; Chen, J. *J. Org. Chem*. **1997**, *62*, 6210. (i) Grosche, P.; Holtzel, A.; Walk, T. B., Trautwein, A. W.; Jung, G. *Synthesis*, **1999**, 1961. (j) Linn, J. A.; Gerritz, S. W.; Handlon, A. L.; Hyman, C. E.; Heyer, D. *Tetrahedron Lett*. **1999**, *40*, 2227. (k) Brun, E.; Gil, S. Mesters,R.; Parra, M., *Synthesis* **2000**, 273. (l) Paulvannan, K.; Chen, T., *J. Org. Chem*. **2000**, *65*, 6160. (m) Wagman, A. S.; Wnag, L.; Nuss, J. M. J. *Org. Chem*. **2000**, *65*, 9103. (n) Emtenas, H.; Ahlin, K.; Pinkner, J. S.; Hultgren, S. J.; Almqvist, F. *J. Comb. Chem.* **2002**, *4*, 630. (o) Cherry, K.; Abarbri, M.; Parrian J. L.; Duehene, A. *Tettrahedron. Lett.,* **2003**, *44*, 5791.

[10] Mohrle, H.; Neber,W. *Tetrahedron*, **1970**, *26*, 2953. (b) McKillop, A.; Boulton, A. Comprehensive Heterocyclic Chemistry, Pergamon Oxford, **1984**, vol., 2, p 67.

[11] Hung, D. L.; Knight, S. D.; Woods,R. M.; Pinkner, J. S.; Hultgren, *S. J. EMBOJ,* **1996**, *15*, 3792.

[12] Jones, G. *Org. React*, **1967**, *15*, 204.

[13] Kumar, A., Koul, S., Razdan, T. K.; Kapoor, K. K. *Tetrahedron Lett*., **2006**, *47*, 837.

[14] Mukhopadhyay, C.; Becker, F. F. and banik, B. K. *J. Chem. Res. Synop*. **2001**, *28* and refs. 10 and 11 therein and footnote 16.