Green synthesis of ethyl N-(cyclohexyl(methyl)amino)-2oxoindolin-3-ylideneamino)(4-fluorophenyl)methylformimidate derivative

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Abstract- A series of ethyl N-(cyclohexyl(methyl)amino)-2oxoindolin-3-ylideneamino)(4-fluorophenyl)methylformimidate derivative (8a-8e) were prepared by the reaction of ethyl N-substituted 2-oxoindolin-3-ylideneamino)methylformimidate **6** and N-methylcyclohexanamine **7** to passing HCl/H_2S through solution of substituted 4- substituted isocyano methanamine **1** and absolute ethanol. Ethyl N-(4- substituted)(-2-oxoindolin-3-ylideneamino)methylformimidate **6** were synthesized from the reaction of synthesized compound ethyl N-amino(4-substituted)methylformimidate **4** and isatin(1-H, indole 2,3-dione) are added to each other and finally compound (6a-6e) were form. This reaction known as Schiff reaction. The spectral study of newly synthesized compounds was characterized on the basis of elemental analysis, IR, H^1 NMR, ^{13}C-NMR and mass spectra.

Index Terms- Ethyl N-amino(substituted)methylformimidate , Isatin , Schiff base, Mannich base, ethyl N-(cyclohexyl(methyl)amino)-2oxoindolin-3-ylideneamino)(4-fluorophenyl)methylformimidate.

I. INTRODUCTION

Isatin(1H-indole-2,3-dione) become a popular topic due to its various uses. The chemistry of isatin and its derivatives are particularly interesting part because they have potential application in medicinal chemistry. Isatin showing potent anticonvulsant activity at low concentration of all possible derivatives.

Many more isatin derivative, are versatile substitute act as a pharmacological and biological compound,showing biological properties such as- antibacterial[1] , antifungal[2] , antidepresent[3], anti inflammatory[4].

Schiff bases are biological active compounds uses in industrial and pharmacological field. It synthesized by Schiff reaction[5-6] , mostly, Schiff bases derived from various heterocycles have been reported to possesses anticonvulsant [7] cytotoxic [8], antimicrobial [9], antifungal activities [10].antiproliferative [11].

Mannich bases having important role and applicable part of pharmaceutical chemistry. They have been encountered with antibacterial [12], antiviral [13], analgesic and anti-inflammatory [14], antimalarial [15], anticonvulsant [16].

Biologically property prompted us to synthesize new isatin derivatives bearing ethyl N-(cyclohexyl(methyl)amino)-2oxoindolin-3-ylideneamino)(4-fluorophenyl)methylformimidate. Identification of the chemical structures of the synthesized compounds were confirmed by the help of their IR, MS and H^1NMR spectral data. The medicinal activity synthesized compounds were tested by cup-plate method.

II. RESULT AND DISCUSSION

In the present study ethyl N-amino(4-fluorophenyl)methylformimidate **4** were prepare were passing H_2S/ HCl through solution of absolute ethanol, followed symmetric ether(diethyl ether) . The most favorable conditioning compound, ethyl N-(cyclohexyl(methyl)amino)-2oxoindolin-3-ylideneamino)(4-fluorophenyl)methylformimidate **8** were synthesized from the reaction of N-substituted 2-oxoindolin-3-ylideneamino)methylformimidate **6** and N-methylcyclohexanamine **7** by the mannich reaction[17,18]. The compound **6** is known as Schiff base it synthesized by of indole 2,3 –dione **5** and ethyl N-amino(4-substituted)methylformimidate by the solvent free multi component condensation reaction[19-21]. Compound **4** show absorption bands around 3380 cm^{-1} , 1675 cm^{-1} for 1^o –NH_2 ,N=CH respectively. And another compound **6** show absorption band around 1675 cm^{-1} , 1720cm^{-1} ,1660 cm^{-1} N=CH, C=N respectively. All the synthesized compound generally have 3-4 Aromatic absorption band 1450,1500,1562 cm^{-1}. The characteristic NH protons of compounds **4** were detected around δ 9.00 ppm. The H^1 NMR spectra for resultant compound **(8a-e)** exhibit four separate peaks appear in the region δH 7.90,7.10,7.54,8.23 for Ar-H respectively and 10.86 N-H. Another three peak exhibit appear in the region δH 7.05,7.12 for Ar-H ,2.0 (NH_2), 7.36 (N=CH-O), 3.46, 1.06 for sp^3 CH_2 &CH_3 respectively.

^{13}C-NMR spectra of compounds (**6a-e)** δ (ppm): 14.70 ($\underline{C}H_3$), 62.8 ($\underline{C}$H2CH3), Ar-C: substitute ring(128.58-158.20), Ar-C isatin ring(118.32-141.8),163.11(N=C), 165.82 (C=O).

III. EXPERIMENTAL SECTION

General: - Reagents and solvents (they are used in these reactions) were obtained from commercial sources or natural sources and used without further purification. Melting points were determined by the Toshniwal apparatus and reported uncorrected. The spectral and elemental analyses of synthesized compounds were carried out at the National Chemical Laboratory Pune (Maharashtra) and Central Drug Research Institute Lukhnow (U.P). The purity of these compounds were checked on

thin layer chromatography (TLC) of silica mesh 120-160 in various non-aqueous solvent system, e.g. Benzene, dichloromethane. Proton Nuclear Magnetic Resonance (H^1 NMR) spectra were recorded on a Bru-ker NMR spectrophotometer (Germany) (400MHz) in deuterated dimethyl sulfoxide (DMSO-d6) at room temperature. Me_4Si was used as an internal reference. IR spectra (KBr) were recorded on a Magna FT IR–550 spectrophotometer. The microwave-assisted reactions were carried out in a commercial multimode MW oven it has equipped with inverter technology and also attached with a magnetic stirrer and reflux condenser, operating at 1000W generating 2400 MHz frequency. Mass spectra of synthesized compounds were recorded on Kratos 50 mass spectrometer is work at 70 eV.

scheme

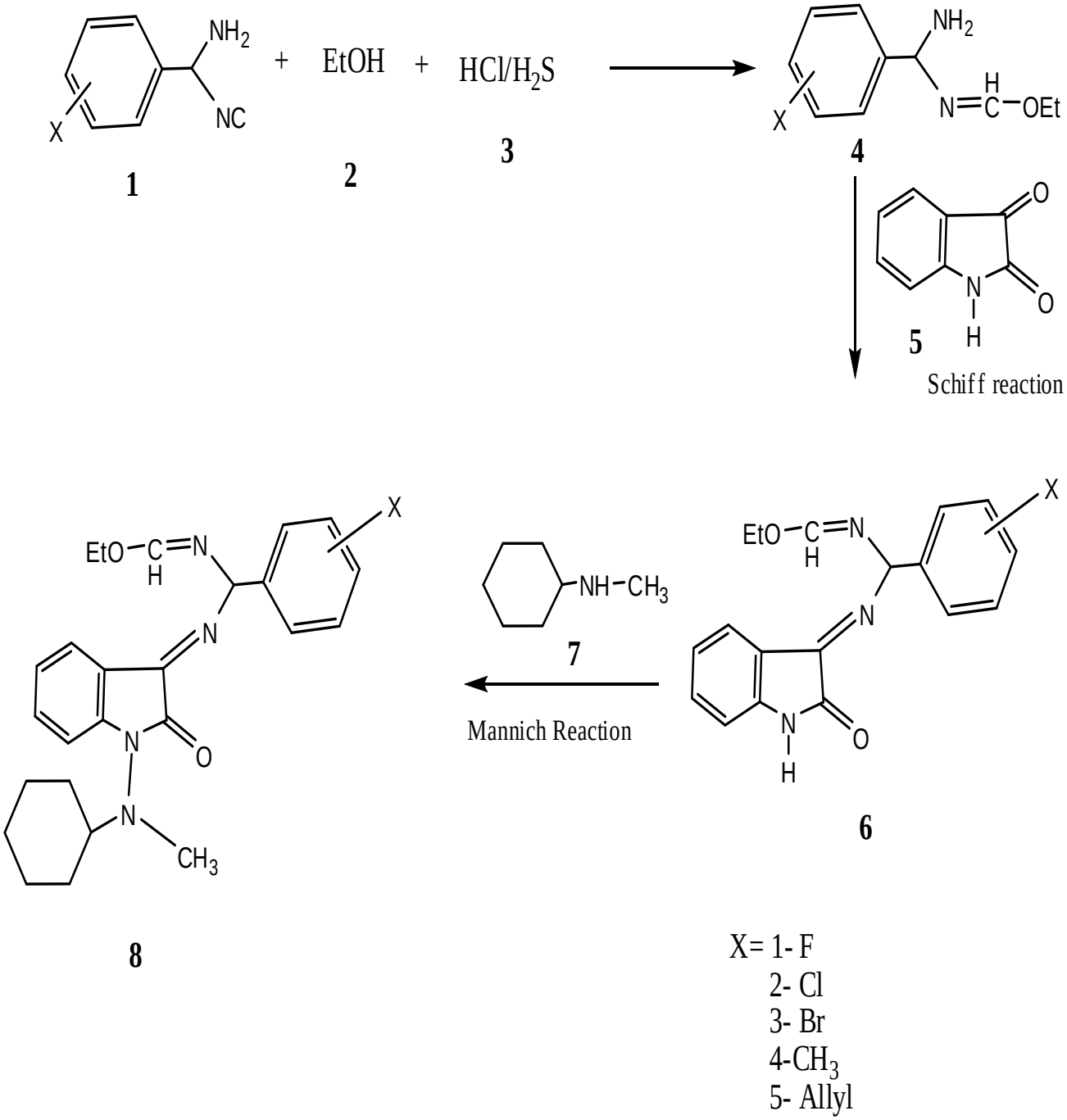
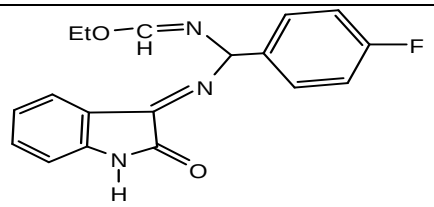
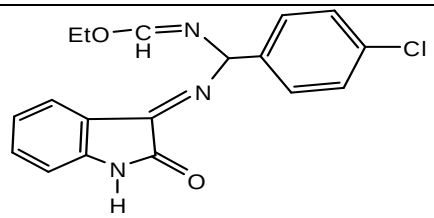
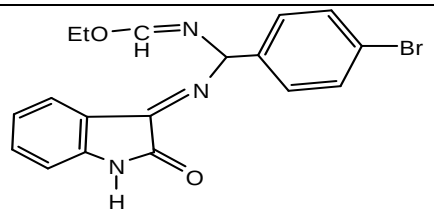
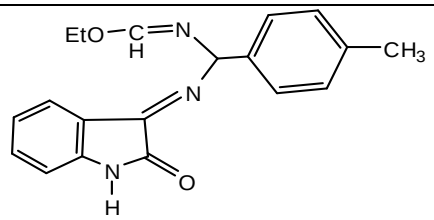
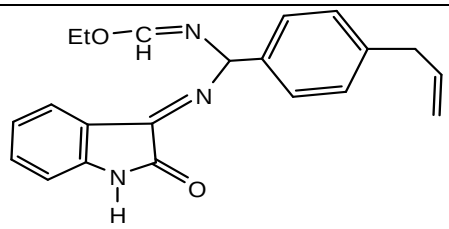
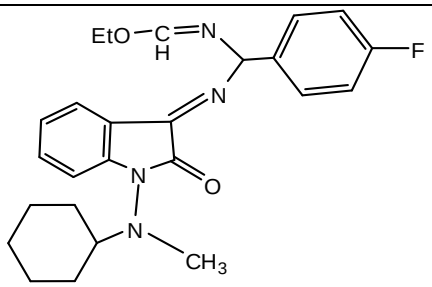
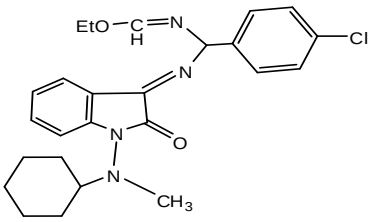
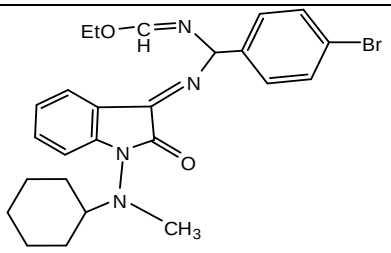
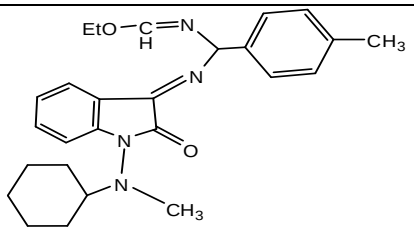
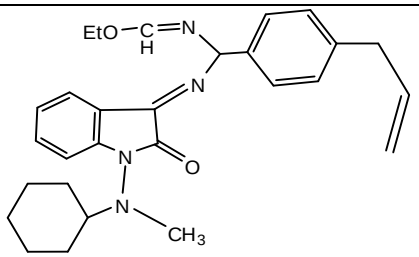


Table 1 :- Physical and analytical data of synthesized compounds

product	X	Mol. Formula & Mol. Weight	Mol. Structure	m.p.	Time(min)	Yield %
6a	F	$C_{18}H_{16}N_3O_2F$ 319		170	125-130	58
6b	Cl	$C_{18}H_{16}N_3O_2Cl$ 337		176	125-130	62
6c	Br	$C_{18}H_{16}N_3O_2Br$ 371		205	155-168	63
6d	CH_3	$C_{19}H_{19}N_3O_2$ 317		185	124-136	60
6e	Allyl	$C_{21}H_{24}N_3O_2$ 342		154	143-150	66

product	X	Mol. Formula & Mol. Weight	Mol. Structure	m.p.	Time(min)	Yield %

8a	F	$C_{15}H_9N_2O_4Br$ 351		176	120-125	54
8b	Cl	$C_{16}H_{12}N_2O_4$ 296		185	125-130	62
8c	Br	$C_{17}H_{14}N_2O_4$ 310		215	145-158	58
8d	CH_3	$C_{17}H_{13}N_2SO_4F$ 359		190	114-126	56
8e	C_2H_5	$C_{17}H_{13}N_2SO_4Cl$ 376		164	135-145	60

Synthesis of Schiff Bases (6a-e):-

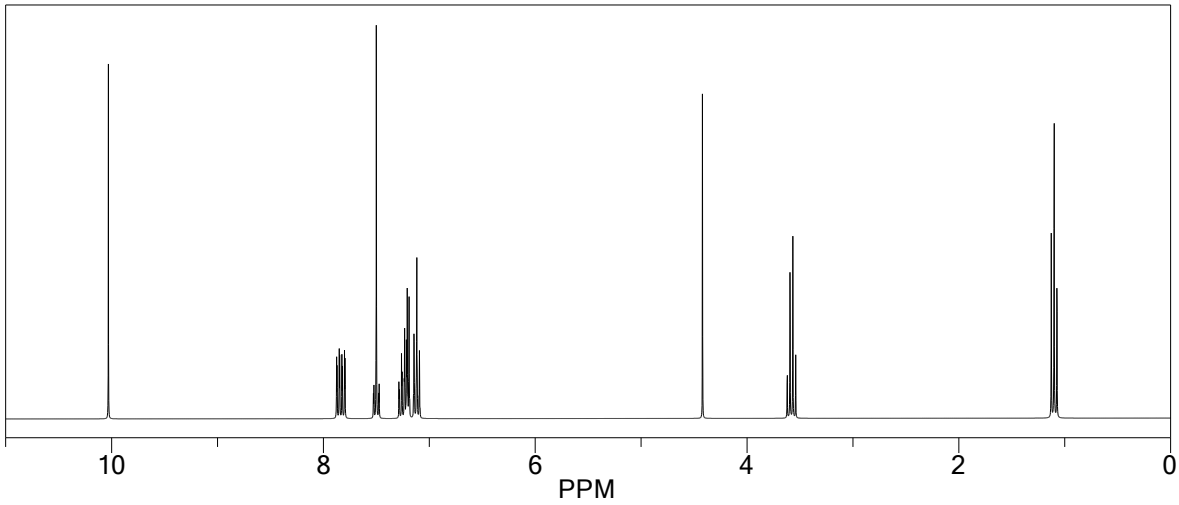
Equimolar quantities (0.01 mol) of isatin and the corresponding amino compound 4a-e were warm dry toluene containing glacial acetic acid (0.5 mL). The reaction mixture was refluxed for 4-5 h and then kept at room temperature overnight. The resultant solid was washed with dilute ethanol, dried and recrystallized from ethanol-water (1:2) mixture to afford compounds 6a-e.

1. Synthesis of ethyl N-(4-fluorophenyl)((E)-2-oxoindolin-3-ylideneamino)methylformimidate**(6a)**

mp*- 170^0 C , Yield- 58 %

IR (KBr cm^{-1}), 2133 cm^{-1} (C=N), 1450,1504,1564 cm^{-1} (C=C substitute Ar-H), H^1 NMR (400 MHz, $CDCl_3$) δH–7.10(1H, d, Ar-H) , 7.18(1H, d,Ar-H) , 1.10(1H, t ,sp^3 C-H), 7.47(1H,s,-CH=N-) , 7.74(2H, q ,sp^3 C-H) , 3.54(1H, d, isatin benzene Ar-H)

^{13}C-NMR δ (ppm): 14.72 ($\underline{C}H_3$), 116.62 ($\underline{C}$H2CH3), 128.38, 113.25, 156.35(Ar-C: substitute ring ,117.92, 130.19,113.3 (Ar-C isatin ring),161.91(N=C), 163.82 (C=O).



2. Synthesis of ethyl N-(4-chlorophenyl)((E)-2-oxoindolin-3-ylideneamino)methylformimidate**(6b)**

mp*- 176^0 C , Yield- 62 %

IR (KBr cm^{-1}), 2136 cm^{-1} (C=N), 1450,1500,1562 cm^{-1} (C=C substitute Ar-H), H^1 NMR (400 MHz, $CDCl_3$) δH–7.08(1H, d, Ar-H) , 7.15(1H, d,Ar-H) , 1.09(1H, t ,sp^3 C-H), 7.45(1H,s,-CH=N-) , 7.72(2H, q ,sp^3 C-H) , 3.50(1H, d, isatin benzene Ar-H)

^{13}C-NMR δ (ppm): 14.70 ($\underline{C}H_3$), 116.8 (CH2CH3), 128.58, 114.35, 156.00 (Ar-C: substitute ring ,118.32, 131.79,113.8 (Ar-C isatin ring),162.11(N=C), 164.42 (C=O).

3. Synthesis of ethyl N-(4-bromoophenyl)((E)-2-oxoindolin-3-ylideneamino)methylformimidate**(6c)**

mp*- 205^0 C , Yield- 63 %

IR (KBr cm^{-1}), 2130 cm^{-1} (C=N), 1448,1502,1562 cm^{-1} (C=C substitute Ar-H), H^1 NMR (400 MHz, $CDCl_3$) δH–7.08(1H, d, Ar-H) , 7.15(1H, d,Ar-H) , 1.09(1H, t ,sp^3 C-H), 7.44(1H,s,-CH=N-) , 7.70(2H, q ,sp^3 C-H) , 3.50(1H, d, isatin benzene Ar-H)

^{13}C-NMR δ (ppm): 14.68 ($\underline{C}H_3$), 116.56 (CH2CH3), 127.88, 113.25, 155.65(Ar-C: substitute ring) ,117.62, 129.79,113.3 (Ar-C isatin ring),160.91(N=C), 163.82 (C=O).

4. Synthesis of ethyl N-(4-methylophenyl)((E)-2-oxoindolin-3-ylideneamino)methylformimidate**(6d)**

mp*- 185^0 C , Yield- 60 %

IR (KBr cm^{-1}), 2117 cm^{-1} (C=N), 1444,1502,1558 cm^{-1} (C=C substitute Ar-H), H^1 NMR (400 MHz, $CDCl_3$) δH–7.04(1H, d, Ar-H) , 7.13(1H, d,Ar-H) , 1.07(1H, t ,sp^3 C-H), 7.42(1H,s,-CH=N-) , 7.68(2H, q ,sp^3 C-H) , 3.48(1H, d, isatin benzene Ar-H)

^{13}C-NMR δ (ppm): 14.64 ($\underline{C}H_3$), 115.86 (CH2CH3), 127.18, 112.85, 155.15(Ar-C: substitute ring) ,117.12, 129.19,113.3 (Ar-C isatin ring),159.70(N=C), 162.12 (C=O).

5. Synthesis of ethyl N-(4-allylphenyl)((E)-2-oxoindolin-3-ylideneamino)methylformimidate**(6e)**

mp*- 154^0 C , Yield- 66 %

IR (KBr cm^{-1}), 2122 cm^{-1} (C=N), 1448,1510,1568 cm^{-1} (C=C substitute Ar-H), H^1 NMR (400 MHz, $CDCl_3$) δH–7.09(1H, d, Ar-H) , 7.21(1H, d,Ar-H) , 1.13(1H, t ,sp^3 C-H), 7.47(1H,s,-CH=N-) , 7.70(2H, q ,sp^3 C-H) , 3.50(1H, d, isatin benzene Ar-H)

^{13}C-NMR δ (ppm): 15.15 ($\underline{C}H_3$), 116.28 (CH2CH3), 128.08, 113.15, 155.85(Ar-C: substitute ring) ,117.12, 129.69,113.75 (Ar-C isatin ring),160.07(N=C), 162.82 (C=O).

Synthesis of Mannich Base(8a-e):-

The corresponding Schiff bases 6a-e (0.002 mol) were dissolved in absolute ethanol (100 mL).

Then formaldehyde (37%, 0.5 mL) and piperidine (0.002 mol) were added drop wise with vigorous stirring. After combining all reagents, the reaction mixture was stirred at room temperature for 12-14 h.

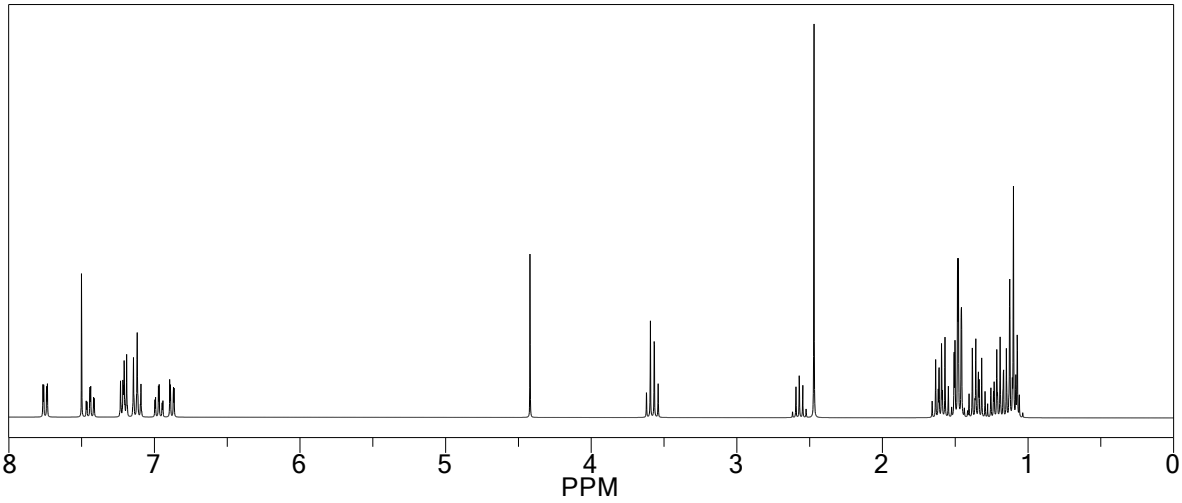
The mixture was cooled, and the solid product was filtered after this washed with petroleum ether. The solid that separated was recrystallized from ethanol-dioxane (1:2) to yield the title compounds 8a-e.

1. Synthesis of ethyl N-(cyclohexyl(methyl)amino)-2-oxoindolin-3-ylideneamino)(4-fluorophenyl)methylformimidate **(8a).**

mp*- 176^0 C , Yield- 54 %

IR (KBr cm^{-1}), 2140 cm^{-1} (C=N), 2940cm^{-1}(sp^3 C-H for N-N) 1450,1500,1562 cm^{-1} (Ar. C=C), H^1 NMR (400 MHz, $CDCl_3$) δH–7.09(1H, d, Ar-H) , 7.14(1H, d,Ar-H) , 4.42(1H, s ,sp^3 C-H), 7.47(1H,s,-CH=N-) , 7.72(2H, q ,sp^3 C-H) , 1.10(3H,t,sp^3 C-H) , 3.50(1H, d, Ar-H) , 6.90(1H,dd, Ar-H) , 10H(due to cyclohaxane , multiplate), 2.40(3H,s,CH_3).

^{13}C-NMR δ (ppm): 14.70 ($\underline{C}H_3$), 62.8 (CH2CH3), Ar-C: substitute ring(128.58, 114.35, 156.00), Ar-C isatin ring(116.32, 129.79,112.8),163.11(N=C), 165.82 (C=O).



2. Synthesis of ethyl N-(4-chlorophenyl) -1-(cyclohexyl (methyl) amino)-2-oxoindolin-3-ylideneamino)methylformimidate**(8b).**

mp*- 185^0 C , Yield- 62 % ,

IR (KBr cm^{-1}), 2138 cm^{-1} (C=N), 2938cm^{-1}(sp^3 C-H for N-N) 1448,1500,1560 cm^{-1} (Ar. C=C), H^1 NMR (400 MHz, $CDCl_3$) δH–7.32(1H, d, Ar-H) , 7.12(1H, d, Ar-H) , 4.40(1H, s ,sp^3 C-H), 7.45(1H,s,-CH=N-) , 7.71(2H, q ,sp^3 C-H) , 1.10(3H,t,sp^3 C-H) , 3.48(1H, d, Ar-H) , 6.88(1H,dd, Ar-H) , 10H(due to cyclohaxane , multiplate), 2.38(3H,s,CH_3). ^{13}C-NMR δ (ppm): 14.70 ($\underline{C}H_3$), 62.8 ($\underline{C}$H2CH3), Ar-C: substitute ring(128.58, 126.35, 130.00), Ar-C isatin ring(116.32, 129.79,112.8),163.11(N=C), 165.82 (C=O)

3. Synthesis of ethyl N-(4-bromophenyl) -1-(cyclohexyl (methyl) amino)-2-oxoindolin-3-ylideneamino)methylformimidate**(8c).**

mp*- 215^0 C , Yield- 58% ,

IR (KBr cm^{-1}), 2136 cm^{-1} (C=N), 2935cm^{-1}(sp^3 C-H for N-N) 1445,1500,1558 cm^{-1} (Ar. C=C), H^1 NMR (400 MHz, $CDCl_3$) δH–7.73(1H, d, Ar-H) , 7.07(1H, d, Ar-H) , 4.38(1H, s ,sp^3 C-H), 7.43(1H,s,-CH=N-) , 7.70(2H, q ,sp^3 C-H) , 1.10(3H,t,sp^3 C-H) , 3.46(1H, d, Ar-H) , 6.86(1H,dd, Ar-H) , 10H(due to cyclohaxane , multiplate), 2.36(3H,s,CH_3).). ^{13}C-NMR δ (ppm): 14.70 ($\underline{C}H_3$), 62.8 ($\underline{C}$H2CH3), Ar-C: substitute ring(129.58, 129.35, 118.17), Ar-C isatin ring(116.32, 129.79,112.8),163.11(N=C), 165.82 (C=O)

4. Synthesis of ethyl N-(4-bromophenyl) -1-(cyclohexyl (methyl) amino)-2-oxoindolin-3-ylideneamino)methylformimidate**(8d).**

mp*- 190^0 C , Yield- 56% ,

IR (KBr cm^{-1}), 2130 cm^{-1} (C=N), 2932cm^{-1}(sp^3 C-H for N-N) 1442,1500,1554 cm^{-1} (Ar. C=C), H^1 NMR (400 MHz, $CDCl_3$) δH–7.11(1H, d, Ar-H) , 7.07(1H, d, Ar-H) , 4.34(1H, s ,sp^3 C-H), 7.40(1H,s,-CH=N-) , 7.68(2H, q ,sp^3 C-H) , 1.10(3H,t,sp^3 C-H) , 3.40(1H, d, Ar-H) , 6.84(1H,dd, Ar-H) , 10H(due to cyclohaxane , multiplate), 2.34(3H,s,CH_3).). ^{13}C-NMR δ (ppm): 14.70 ($\underline{C}H_3$), 62.8 ($\underline{C}$H2CH3), Ar-C: substitute ring(127.58, 127.35, 133.90), Ar-C isatin ring(116.32, 129.79,112.8),19.17 (Ar-CH_3)163.11(N=C), 165.82 (C=O)

5. Synthesis of ethyl N-(4-bromophenyl) -1-(cyclohexyl (methyl) amino)-2-oxoindolin-3-ylideneamino)methylformimidate**(8e).**

mp*- 164^0 C , Yield- 60% ,

IR (KBr cm^{-1}), 2010 cm^{-1} (-C=C-H$_{str.}$) , 2130 cm^{-1} (C=N), 2934cm^{-1}(sp^3 C-H for N-N) 1444,1504,1556 cm^{-1} (Ar. C=C), H^1 NMR (400 MHz, $CDCl_3$) δH–7.13(1H, d, Ar-H) , 7.09(1H, d, Ar-H) , 4.36(1H, s ,sp^3 C-H), 7.44(1H,s,-CH=N-) , 7.70(2H, q ,sp^3 C-H) , 1.12(3H,t,sp^3 C-H) , 3.42(1H, d, Ar-H) , 6.84(1H,dd, Ar-H) , 10H(due to cyclohaxane , multiplate), 2.34(3H,s,CH_3).). ^{13}C-NMR δ (ppm): 14.70 ($\underline{C}H_3$), 62.8 ($\underline{C}$H2CH3), Ar-C: substitute ring(126.58, 126.35, 135.76), Ar-C isatin ring(116.32,129.79,112.8),37.26 (allylic CH_2) 134.27,113.72(allylic $CH_2 = CH_2$)163.11(N=C), 165.82 (C=O)

IV. Conclusions

The above detail study we can prove such as- facile, efficient and environmental or economical for the one-pot synthesis of a series of ethyl N-(cyclohexyl(methyl)amino)-2oxoindolin-3-ylideneamino)(4-fluorophenyl)methylformimidate (8a-e) with passing H_2S/HCL contain montmorillonite KSF and silica mesh 120-160 as a inorganic solid support. The advantages are -

(i) These reactions are solid support so no need of any solvent.
(ii) Obtained good yields.
(iii) No requirement for additional reagent/catalyst
(iv) Virtually no waste generation and
(v) Non inflammable and nontoxic reaction medium,
(vi) Ease of product isolation and further purification.

Acknowledgements

Financial support from CSIR-HRDG New Delhi (Govt.of India) provide SRF (NET), award No. (09/1025(0002)/2012-EMR-I) is gratefully acknowledgement. We also thankful to

Dr. Sudhanshu Sharma (chairman SGVU) Jaipur and they provided best laboratory facility to us for this work and NCL-Pune & RSIC Chandigarh for the elemental and spectral analyses.

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