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Synthesis and Characterization of Derivative derived from 1, 4-Dihydropyrimidine

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Abstract

In our present work A new modification in biginelli product has been developed and formation as well as characterization of ethyl 2-(butylsulfanyl)-4- (4-hydroxyphenyl) -6-methyl-1, 4-dihydropyrimidine-5- carboxylate, ethyl-4- (4-bromophenyl)-2-(butylsulfanyl)-6-methyl-1, 4-dihydropyrimidine-5-carboxylate, ethyl-2-(butylsulfanyl)-6-methyl-4-phenyl-1, 4-dihydropyrimidine-5-carboxylate, ethyl2-(butylsulfanyl)-4- (4-fluorophenyl)-6-methyl-1, 4-dihydropyrimidine-5-carboxylate, ethyl-2-(butylsulfanyl)-6-methyl-4 (3-nitrophenyl)-1, 4-dihydropyrimidine-5-carboxylate. Involving linkage of n-butyl group to Sulphur atom which is having the same biological activity. The compound obtain in the first stage was subjected for further reaction with n-butyl bromide in presence of weak base pyridine.

Keywords: Dihydropyrimidine, pyridine, AlCl3, EAA, thiourea, methanol, ethanol.

Introduction

Multicomponent reaction are the reactions which are having less hazardous impact on environment, because of which this reaction plays dominating role in chemical science, this are the reaction in which more than two component react in at a same time to give a product with effective atom economy so far manufacturing units are concerned the reaction was first proposed by bignelli[1] and is referred to as Biginelli Reaction, multicomponent reaction is an important tool in designing the drug such as dihydropyrimidine DHPM which are having Anti carcinogenic, antiviral anti mitotic properties.

Various modifications are done since biginelli first proposed it involving various catalyst[2] for improving the rate of reaction many such catalyst are $AlCl_3$, $FeCl_3$. $6H_2O$, Lewis Acid catalyst including $Mg(ClO_4)$ lanthanide series catalyst the nano catalyst were also used to improve rate and yield of the given reaction[3]. The vast biological activities of this drug have attracted the attention of synthetic organic chemist to synthesize this molecule.

As a part of our research in synthesizing the compound derive from DHPM[4] in our present work we have carried out the reaction involving DHPM and n butyl bromide linking the n Butyl group to sulphur atom in dihydro pyrimidine-2-thione ,and this compound also shows same biological activity such as DHPM[7]

Experimental details: The Chemicals used Are SD Fine Chemicals and are used without purifying them. The melting Point of synthesize compound was recorded in capillary sealed at one end and were uncorrected[1]. H NMR (200MHz) spectra was recorded using AVANCE200 spectrophotometer having chloroform-d the solvent and tri methyl silane as standard reference, IR Spectrum was recorded on Nicolet IS5 FTIR using Germanium Crystal

Methodology

General Procedure of Synthesis Butyl Derivative of Di Hydro Pyrimidine, Stage 1: A mixture of the substituted derivative of benz aldehyde 1mol, Thiourea 1.2mol, ethyl acetoacetate (EAA) 1.0mol was taken in a round bottom flask fitted with a condenser and caped with a guard tube added a catalytic amount of $AlCl_3$ and HCl 0.2mol, the solvent used was methanol the reaction mixture was heated and stirred and monitor the reaction using TLC till the product gets formed pour the reaction mixture in an ice cooled distilled water and stir until the product get precipitate outs as a white powder dry the compound and recrystallized it by hot ethanol and record the melting point.

Stage 2: Taken the compound obtain in first stage in 1mol, butyl bromide 1mol, methanol as solvent in a round bottom flask and sonicate by adding 6-8 drops of pyridine in a reaction mixture and monitor the reaction using TLC once the reaction gets complete separate it in an ice cold distilled water and dry the product and recrystallize by hot ethanol.

Results and Discussion

Spectral analysis of the synthesized compound: Spectral Data of Compound 4a: IR 3300-3150 cm-1 (NH), 1680-1653cm-1 (C=O, ester), 1611-1530cm-1 (Aromatic ring), 1495cm-1(C-O), 1130-1151cm-1(C-C): 1H NMR 7.25 ppm (s,

chloroform-d), 7.23ppm (multiplet, 5H), 4.2ppm (quartet,2H), 3.2ppm (bs,NH), 2.8ppm (triplet, 2H, S-CH_2), 2.3ppm (singlet, 3H, CH_3), 2.15ppm (singlet, 1H, C#H), 1.6ppm (multiplet, 2H, CH_2), 1.3ppm (multiplet, 2H, CH_2) 1.1ppm (triplet, 3H. CH_3) 0.9 ppm (triplet, 3H, CH_3) (# chiral proton).

Spectral Data of Compound 4b: IR 3470-3459cm-1(OH) 3300-3150 cm-1 (NH),1670-1645cm-1(C=O,ester), 1615-1540cm-1 (Aromatic ring), 1435cm-1(C-O), 1168-1126cm-1(C-C): 1H NMR 7.25ppm (singlet, chloroform-d), 7.1ppm (doublet, 2H, Ar-H), 6.75ppm (doublet, 2H, Ar-H) 5.45ppm (bs, 1H, OH) 4.4ppm (quartet, 2H), 3.1ppm (bs, NH), 2.8ppm (triplet, 2H, S-CH_2), 2.1ppm (singlet, 3H, CH3), 2.0ppm (singlet,1H,C#H), 1.7ppm (multiplet, 2H, CH2), 1.2ppm (multiplet,2H,CH_2) 1.1ppm (triplet,3H.CH_3) 0.9ppm(triplet,3H,CH_3) (# chiral proton).

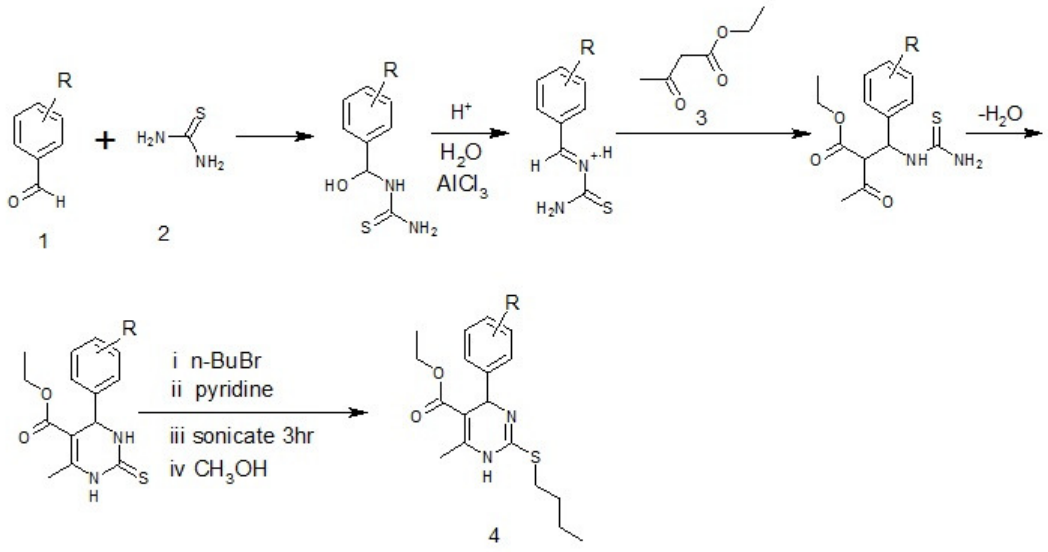
Spectral Data of Compound 4c: IR 3300-3150 cm-1 (NH), 1670-1655cm-1 (C=O, ester), 1610-1570cm-1 (Aromatic ring), 1465cm-1(C-O), 1170-1153cm-1(C-C) 823cm-1(C-F): 1H NMR 7.25ppm (singlet, chloroform-d), 7.1ppm (doublet, 2H, Ar-H), 6.75ppm (doublet, 2H, Ar-H), 4.2ppm (quartet, 2H), 3.3ppm (bs, NH), 2.7ppm (triplet, 2H, S-CH_2), 2.4ppm (singlet, 3H, CH_3), 2.1ppm (singlet, 1H,C#H), 1.4ppm (multiplet, 2H,CH_2), 1.1ppm (multiplet, 2H,CH_2) 0.9ppm (triplet, 3H.CH_3) 0.8ppm (triplet,3H,CH_3) (# chiral proton).

Spectral Data of Compound 4d: IR 3327-3126 cm-1 (NH),1667-1641cm-1(C=O,ester),1600-1530cm-1 (Aromatic ring), 1453cm-1(C-O), 1127-1056cm-1(C-C) 8231m-1(C-F): 1H NMR 7.25ppm (singlet, chloroform-d), 7.3ppm (doublet, 2H, Ar-H), 6.55ppm (doublet, 2H, Ar-H), 4.2ppm (quartet, 2H), 3.4ppm(bs, NH), 2.8ppm(triplet, 2H, S-CH_2), 2.4ppm (singlet, 3H, CH3), 2.15ppm (singlet, 1H, C#H), 1.7ppm (multiplet, 2H, CH_2), 1.3ppm (multiplet, 2H, CH_2) 1.0ppm (triplet, 3H.CH_3) 0.9ppm (triplet, 3H, CH_3) (# chiral proton).

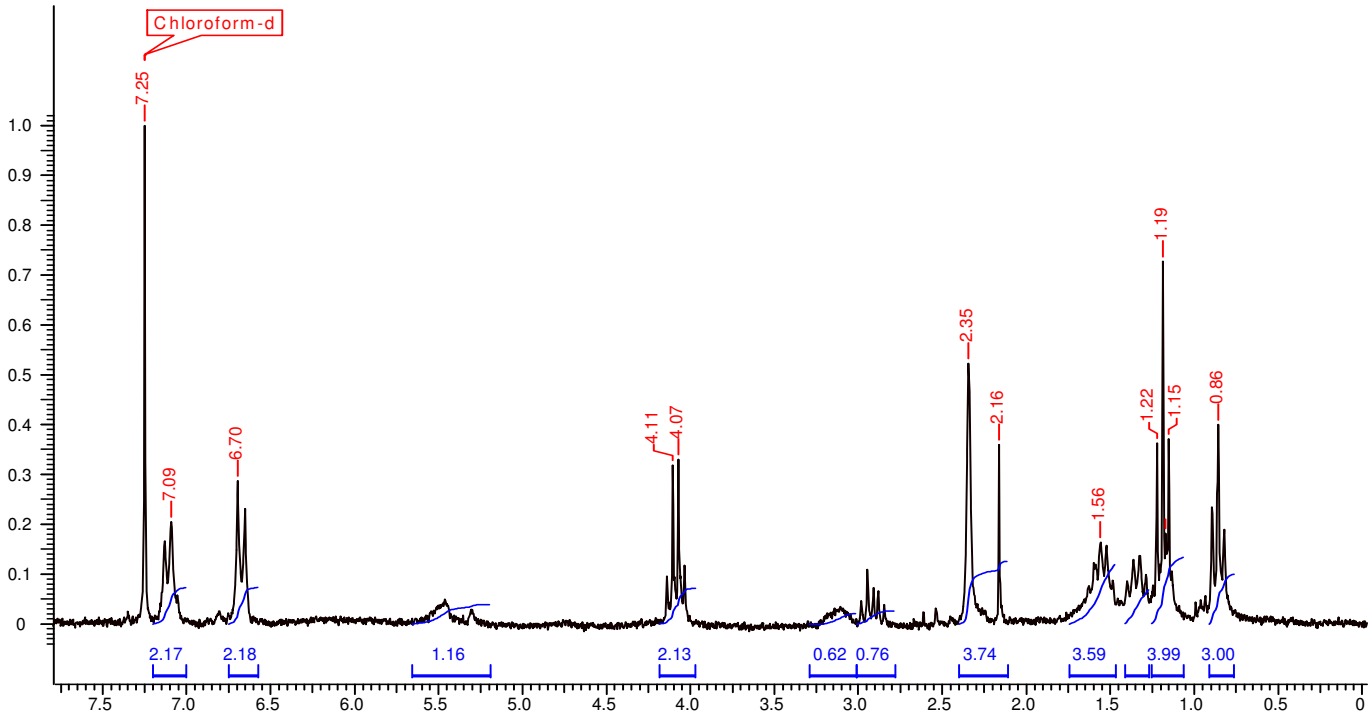
Spectral Data of Compound 4e: IR 3350-3116 cm-1 (NH), 1663-1612cm-1(C=O, ester), 1603-1523cm-1 (Aromatic ring), 1423cm-1(C-O), 1157-1032cm-1(C-C) 690-781cm-1(C-F) : 1H NMR 7.25ppm (singlet, chloroform-d), 7.9ppm(doublet, 1H, Ar-H), 7.6ppm (doublet, 1H, Ar-H), 7.4ppm (double doublet, 1H, Ar-H) 6.9ppm (double doublet, 1H, Ar-H) 4.1ppm (quartet, 2H), 3.23ppm (bs,NH), 2.6ppm (triplet, 2H, S-CH_2), 2.4ppm (singlet, 3H, CH_3), 2.1ppm (singlet, 1H, C#H), 1.5ppm (multiplet, 2H, CH_2), 1.3ppm (multiplet, 2H, CH_2) 1.0ppm (triplet, 3H.CH_3) 0.95ppm (triplet, 3H, CH_3) (# chiral proton).

Table-1
Physical and Analytical Data for Compound 4a-4e

Compound	R	Reaction Time step i (hr)	Reaction Time step ii (min)	Yield	Mp^{0}C
4a	H	6.8	67	74.12%	121-122^0 C
4b	p-OH	5.6	72	67.89%	132-133^{0}C
4c	p-F	7.2	75	39.27%	134-136^{0}C
4d	m-NO_2	4.3	63	47.82%	146-147^{0}C
4e	p-Br	5.7	52	51.23%	113-115^{0}C

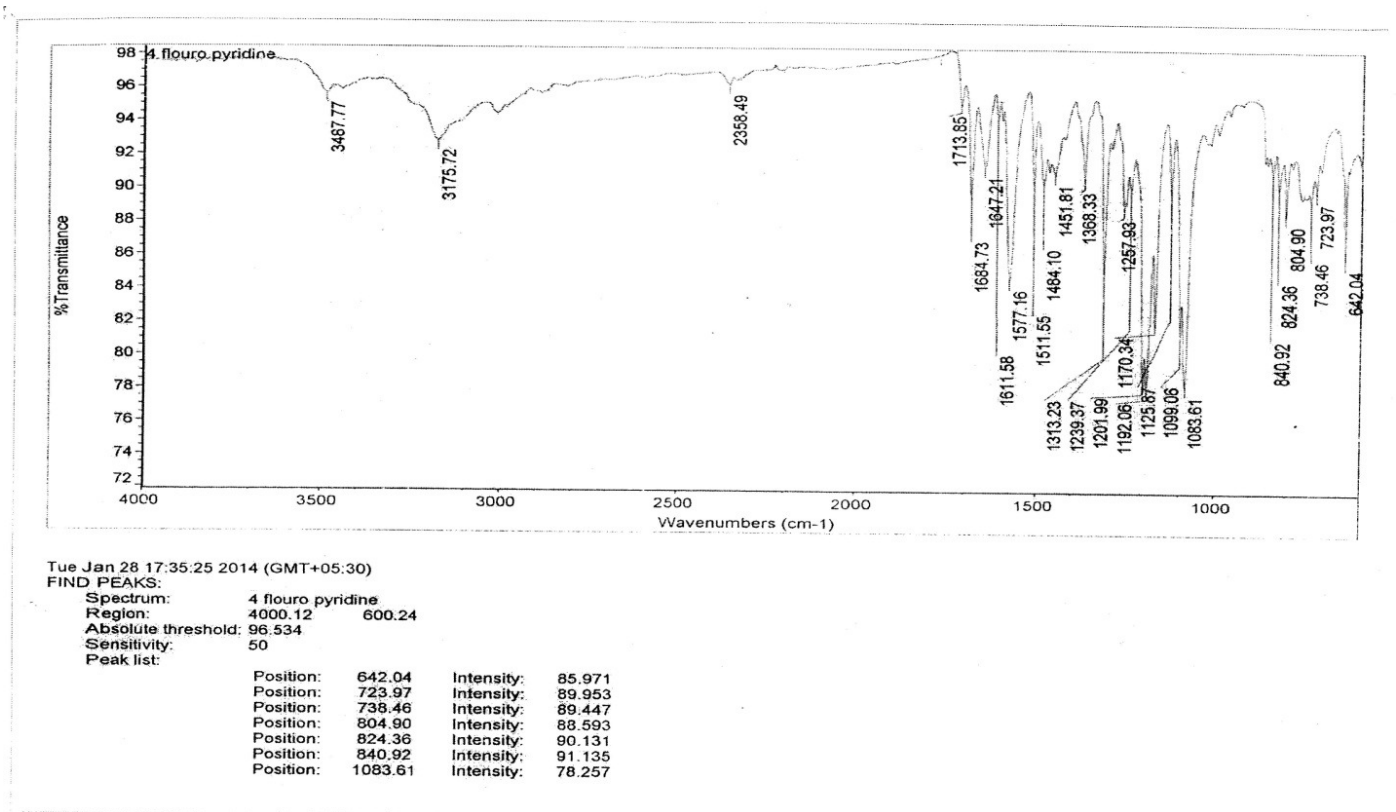


Scheme-1
General reaction R= -H, -NO_2, -OH, -F, -



Br

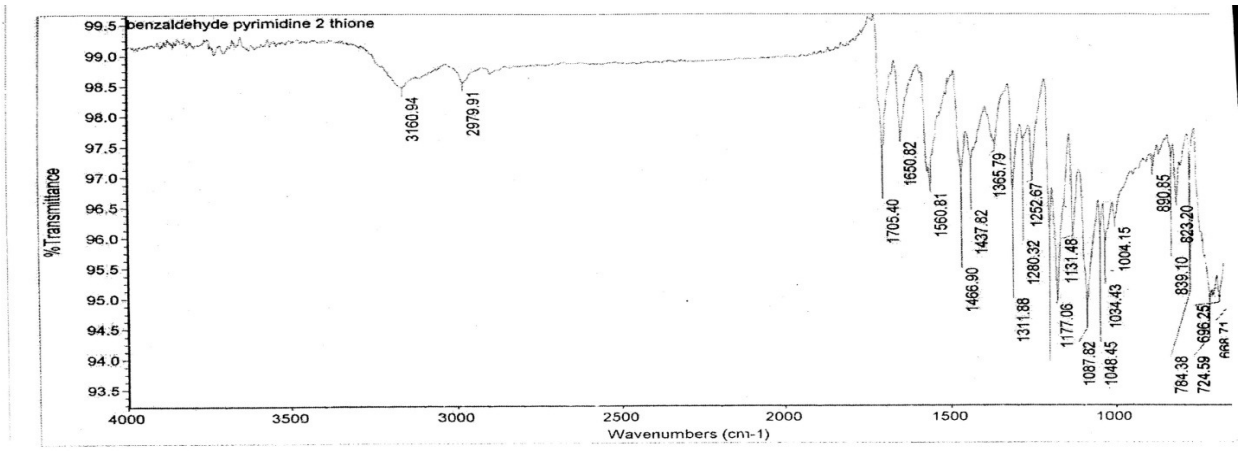
Figure-1
NMR Spectra of 4b at 200MHz



Tue Jan 28 17:35:25 2014 (GMT+05:30)
FIND PEAKS:
Spectrum: 4 flouro pyridine
Region: 4000.12 600.24
Absolute threshold: 96.534
Sensitivity: 50
Peak list:

Position:	642.04	Intensity:	85.971
Position:	723.97	Intensity:	89.953
Position:	738.46	Intensity:	89.447
Position:	804.90	Intensity:	88.593
Position:	824.36	Intensity:	90.131
Position:	840.92	Intensity:	91.135
Position:	1083.61	Intensity:	78.257

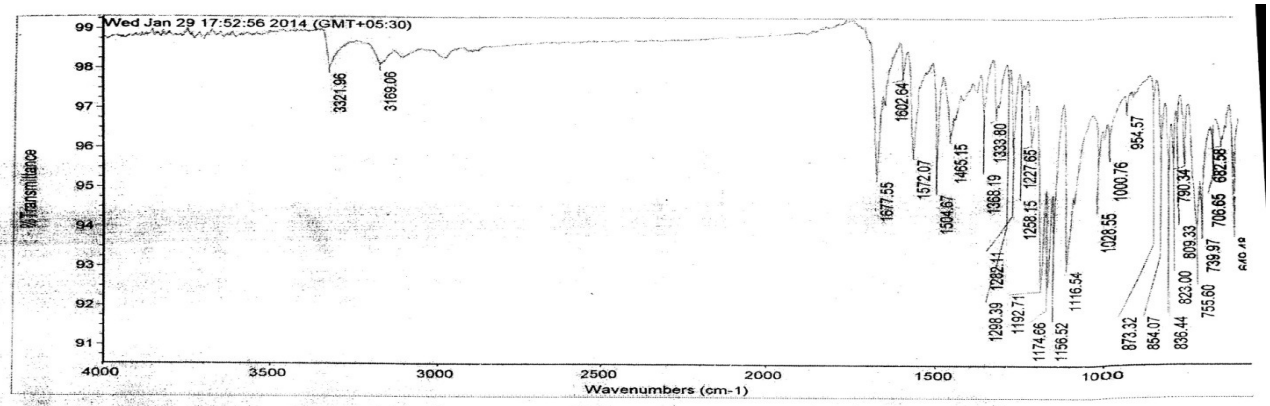
Figure-2
IR SPECTRA of 4a



Wed Jan 29 17:19:49 2014 (GMT+05:30)
FIND PEAKS:
Spectrum: benzaldehyde pyrimidine 2 thione
Region: 4000.12 600.24
Absolute threshold: 98.782
Sensitivity: 50
Peak list:

Position:	642.04	Intensity:	94.601
Position:	668.71	Intensity:	95.282
Position:	696.25	Intensity:	95.010
Position:	724.59	Intensity:	94.990
Position:	784.38	Intensity:	97.259
Position:	823.20	Intensity:	96.656
Position:	839.10	Intensity:	97.317

Figure-3
IR SPECTRA of 4b



Wed Jan 29 17:54:43 2014 (GMT+05:30)
FIND PEAKS:
Spectrum: Wed Jan 29 17:52:56 2014 (GMT+05:30)
Region: 4000.12 600.24
Absolute threshold: 98.543
Sensitivity: 50
Peak list:

Position:	649.48	Intensity:	93.937
Position:	682.58	Intensity:	96.187
Position:	706.65	Intensity:	96.275
Position:	739.97	Intensity:	94.395
Position:	755.60	Intensity:	94.018
Position:	790.34	Intensity:	95.667
Position:	809.33	Intensity:	96.650
Position:	873.32	Intensity:	97.227
Position:	954.57	Intensity:	97.026
Position:	1000.76	Intensity:	96.373
Position:	1028.55	Intensity:	95.875
Position:	1116.54	Intensity:	93.113
Position:	1156.52	Intensity:	93.936
Position:	1174.66	Intensity:	92.510
Position:	1192.71	Intensity:	92.535
Position:	1227.65	Intensity:	96.234
Position:	1258.15	Intensity:	97.477
Position:	1282.11	Intensity:	96.082
Position:	1298.39	Intensity:	97.794
Position:	1333.80	Intensity:	96.880
Position:	1368.19	Intensity:	96.982
Position:	1465.15	Intensity:	96.362
Position:	1504.67	Intensity:	95.781
Position:	1572.07	Intensity:	95.947
Position:	1602.64	Intensity:	97.886
Position:	1677.55	Intensity:	95.375
Position:	3169.06	Intensity:	98.126
Position:	3321.96	Intensity:	98.078

4 flouro 14 dihydro pyrimidine 2 thione 2 Page 1

Figure-4
IR SPECTRA of 4c

A clear and most efficient way of synthesizing various derivative of dihydro pyrimidine was performed with better yield and quality, various aspect of reaction was consider such as effect of different functional group namely electron donating and withdrawing effect which in some case cause reduce in the yield of the product, the compound synthesize could be furthered tested for its biological activity with anti-bacterial anti-carcinogenic properties

Conclusion

In conclusion we have illustrated the new reaction modifications involving biginelli product by reacting the dihydro pyrimidine with nbutyl bromide in presence of pyridine acting as a base, the second step of the reaction was carried using sonicator, it was found that methanol was effective solvent other than water. Application of this method can be widely used in synthesizing large number of such derivative having biological importance

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