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Synthesis, Characterisation And Biological Evaluation Of Dihydropyrimidone Derivatives Employing A Novel Nickel Based Organometallic Reagent As A Catalyst Under Solvent Free Condition

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Abstract:

Pyrimidones constitute a class of heterocyclic compounds with multifold applications in various fields of chemistry and medicine. The pharmaceutically important scaffold, has been synthesised by different researchers over a century of a work all over the world. Variety of chemical reagents and conditions have been used in this regard but prominently the Lewis acids are normally employed. In the present paper, we would like to report herein the green method for synthesising the dihydropyrimidone derivatives, commencing from the aromatic aldehydes, ethyl acetoacetate and urea under the catalysis of a novel nickel based organometallic reagent without employing any organic solvent for the conduct of a reaction . The work up is easy and the product formation takes place in very high yield. The products are characterised by IR and ^{1}H NMR spectroscopic spectral data.

Keywords: Biginelli reaction, Nickel based reagent, dihydropyrimidone derivatives

Introduction:

Pyrimidones are heterocyclic compounds with important pharmaceutical applications. Pyrimidine pharmacophore is an important and integral part of DNA and RNA and play an essential role in several biological processes and also have considerable chemical and pharmacological utility as antibiotics, antibacterial, cardiovascular as well as agrochemical and veterinary product. The Biginelli reaction is a multi-component chemical reaction to synthesize dihydropyrimidones. This reaction occurs between an aldehyde, a ß-ketoester and urea catalyzed by an acid.

Dihydropyridines are the most important heterocyclic ring systems with great potential for pharmaceutical applications. There are several methods reported as modifications to the original Biginelli reaction.

The ability of $SnCl_2$ .2 H_2O as catalyst to promote the Biginelli three-component condensation reaction from a diversity of aromatic aldehydes, ethyl acetoacetate and urea or thiourea is described in a neutral media[1] The preparation of *N*-aryl and *N*-alkyl acetoacetamides, and their utility as a catalyst for the synthesis of Dihydropyrimidone derivatives in good to excellent yields, using both conventional and microwave heating methods has been reported in the literature [2]. Dihydropyrimidines were shown to possess novel calcium antagonists with potent and long-lasting vasodilative and anti-hypertensive activity [3] . By exhaustively applying retrosynthetic analysis to the cognate MCR to identify and exploit alternative entry points into the overall reaction manifold, several such re-engineered MCRs [4] were proposed. Among the MCRs, those with isocyanides have developed into popular organic-chemical reactions in the pharmaceutical industry for the preparation of compound libraries of low-molecular druglike compounds. With a small set of starting materials, very large libraries can be built up within a short time, which can then be used for research on medicinal substances. MCRs are also increasingly being employed in the total synthesis of natural products. MCRs and especially MCRs with isocyanides [5] offer many opportunities to attain new reactions and basic structures. A simple, efficient and practical procedure for the Biginelli reaction using strontium (II) triflate [$Sr(OTf)_2$] as a novel catalyst is described under solvent-free conditions . The catalyst exhibited remarkable reactivity and it is reusable. Some of dihydropyrimidiones showed strong pesticidal activity[6]. An efficient and clean method was developed for the one-pot synthesis of pyrimidinones by ytterbium chloride catalyzed Biginelli-type reaction of aromatic aldehyde, cyclopentanone, and urea or thiourea under solvent-free conditions [7].

A green protocol for the Biginelli reaction was reported using Bronsted ionic liquid [8] (Btto) (p-TSA) under solvent free condition . 3,4-Dihydropyrimidones were synthesised in excellent yield using ionic liquid under microwave irradiation [9]. The 1-butyl-3-methylimidazolium-based ionic liquid has been used for the three component Biginelli reaction with good catalytic efficacy [10]. The ionic liquid $(DABCO)(SO_3H)_2$ Cl_2 was also shown to effect the Biginelli condensation reaction [11]. Fe_3 O_4 nanoparticles , SiO_2 shell CPTES, morpholine collectively used as a catalyst for the synthesis of Dihydropyrimidones [12]. An efficient synthesis of 3,4-dihydropyrimidones was catalysed by molten $(Et_3NH)(HSO_4)$ [13]. Tetrabutyl ammonium acetate was found to be an efficient catalyst for the synthesis of dihydropyrimidones with very good anti-oxidant and antibacterial activity [14]. Triethyl ammonium acetate under neutral medium has been reported to be a catalyst for the synthesis of 3,4-dihydropyrimidone derivatives in excellent yield [15].

Bronsted acidic ionic liquid (C_2O $_2$ BBTA)(TFA) was reported to catalyse the three component Biginelli reaction for the synthesis of dihydropyrimidones [16]. Lanthanide triflate was employes as a catalyst for the synthesis of 3,4-dihydropyrimidones and the reaction was carried out under solvent free condition [17]. Boric acid acetic acid combination was effectively used as a catalyst to effect the Biginelli reaction [18] .

Materials and methods :

Preparation of a Nickel based reagent ;

In a 50 mL round bottom flask placed 1 g of O-phenylene diamine (9.25 mmol) and dissolved it in 20ml of ethanol. An aqueous solution of nickel acetate (2.30 g, 9.25 mmol) was added to this and the reaction mixture was stirred at room temperature for 20 minutes . The adduct immediately formed . It was filtered and washed with alcohol and dried at 100 ^{o} C in an oven for 1 hour . The Complex was subjected to IR and EDAX analysis .

IR cm $^{-1}$: 3700, 3500, 1600, 1500, 500

EDAX analysis : C= 76.61 % , N = 12.45 % . O = 7.34 % , Ni = 3.60 %

Biginelli reaction :

In a 100 mL round bottom flask 1 g (9.4 mmol) of benzaldehyde , 1.2 g (9.4 mmol) of ethyl acetoacetate and 0.56 g Urea (9.4 mmol) was charged . The contents were heated on water bath for 3-4 hours . The three component addition takes place , which can be monitored by TLC technique . The crude product was filtered and purified by column chromatography using petroleum ether and ethyl acetate as eluents . The yield of the purified dihydropyrimidone ranges from 75-85 % . The purified products were further characterised by IR and 1 H NMR spectroscopic data . The findings are summerised in the result **Table 1**

Table 1

S.No.	Substrate 1 g	Ethyl acetoacetate g	Urea g	Catalyst g	Yield %
1	Benzaldehyde	1.2	0.56	0.2	75
2	4- Chloro benzaldehyde	1.2	0.56	0.2	82
3	2-Nitro benzaldehyde	1.2	0.56	0.2	78
4	4-hydroxy, 3-methoxy benzaldehyde	1.2	0.56	0.2	80
5	4- Methoxy benzaldehyde	1.2	0.56	0.2	84

Spectral Data :

1. Ethyl-6-methyl -4-(4-phenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate

IR (cm ¯1) : 3318, 1720, 1649, 1600, 1512, 1212

H NMR (ppm) : 1.14, t, 3H, 2.26, s, 3H, 3.91 , q, 2H, 5.12 , d, 1H, 5.90, s, 1H, 7.3, m, 5H, 9.09, s, 1H

2. Ethyl-6-methyl -4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate

IR (cm ¯1) : 3242, 3131, 2929, 1724,1703, 1649, 1487,1466, H NMR (ppm) : : 1.14, t, 3H, 2.26, s, 3H, 4.02 , q, 2H, 5.35 , d, 1H, 6.80, s, 1H, 7.2-7.8, m, 4H, 9.09, s, 1H

3. Ethyl-6-methyl -4-(2- nitrophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate

IR (cm ¯1) : 3443,3139, 2998, 1676, 1592, 1517, 1370, 1234

^{1} H NMR (ppm) : : 1.17, t, 3H, 2.32, s, 3H, 4.08 , q, 2H, 5.13 , d, 1H, 6.43-6.95 , m, 4H, 9.57, s, 1H , 10.2, s, 1H

4. Ethyl-6-methyl -4-(6-hydroxy -3 methoxy phenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate

IR (cm ¯1) : 3360,3276, 1720, 1640, 1471, 1417, 1083

^{1} H NMR (ppm) : : 1.4, t, 3H, 2.32, s, 3H, 3.70 , q, 2H, 4.7 , d, 1H, 5.13, d, 1H, 7.65,-8.0 m, 3H, 9.12, s, 1H , 9.8 s, 1 H

5. Ethyl-6-methyl -4-(4methoxy -phenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate

IR (cm ¯1) : 3242,2955, 1708, 1649, 1612, 1512, 1460

^{1} H NMR (ppm) : : 1.15, t, 3H, 2.25, s, 3H, 3.73 ,s,3H, 4.02 , q, 2H, 5.13 , d, 1H, 6.83-7.18, m, 4H , 7.57, s, 1H, 9.06, s, 1H

Biological activity of Dihydropyrimidones :

Compound		Inhibition zone in nm			
		Staphylococcus aureus	Klebsiella pneumochaniae	Aspergillusniger Fungi	Candida albicans Fungi
Compound 1		----	8mm	11mm	5mm
Compound 2		----	5mm	11mm	10mm
Compound 3		11mm	8mm	10 mm	13 mm
Compound 4		10mm	10mm	24 mm	13mm
Compound 5		07mm	8mm	8 mm	10 mm
Ciprofloxacin		20 mm	24 mm	-----	-----
Fluconazole		-----	------	32 mm	29 mm

Results and Discussion :

We have used a new , novel and eco-friendly reagent for the synthesis of dihydropyrimidone derivatives in very good to excellent yield . The reagent is stable and can be stored at room temperature for months . The preparative method is free of any organic solvent , so, it follows the norms of a green chemistry . the resultant compounds were screened for their anti-bacterial and anti-fungal activity . Most of the compounds showe moderate activity against bacteria and fungi .

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