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Design and Synthesis of Classical Dihydropyrimidone Derivatives from Azosalicyaldehydes

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ABSTRACT

A series of classical Dihydropyrimidone (DHP) derivatives were synthesize from o-hydroxy aldehydes. Azosalicyaldehydes *were prepared from various substituted anilines with salicylaldehyde by the reported process. These* Azosalicyaldehydes *were reacts with ethylacetoacetate and urea in presence of $ZnCl_2$ catalyst under 70-80°C temperature gives reported DHP products rather than oxygen bridged tricyclic product. The present method is founds eco-friendly, highly efficient, and clean method for the selective synthesis of DHP derivatives.*

Keywords: Classical DHP derivative, Azosalicyaldehydes, $ZnCl_2$ catalyst, Selective transformation, Tricyclic oxygen bridged derivative

INTRODUCTION

The Dihydropyrimidinones (DHPMs) have displayed remarkable and multifaceted biological activities, such as antiviral, antitumor, antibacterial, and antiinflammatory properties as well as calcium channel modulating activity [1]. Consequently, the synthesis of DHP derivatives bearing diverse substitution attends has attracted significant attention since its discovery in 1893 by the Italian chemist Pietro Biginelli [2]. Out of the five major bases in nucleic acids, three are pyrimidine derivatives, which comprises of cytosine (1), uracil (2) and thymine (3) (Figure 1). Because of their involvement as bases in DNA and RNA, they have become very important in the world of synthetic organic chemistry. Among them, the Biginelli multicomponent reaction, involving a multicomponent condensation of aldehyde, β-ketoester and urea, provides an easy access to the preparation of DHPMs, because multicomponent reactions (MCRs) are considered with high facileness, efficiency and economy in organic chemistry [3]. Literature includes number of research articles in which various substituted aliphatic and aromatic aldehydes were used for this transformation. In addition to use of heterocyclic aldehydes were used for same [4,5]. It is still highly valuable to develop new direct approaches for the efficient synthesis of DHPMs due to the continued importance of the DHP core in organic and medicinal chemistry.

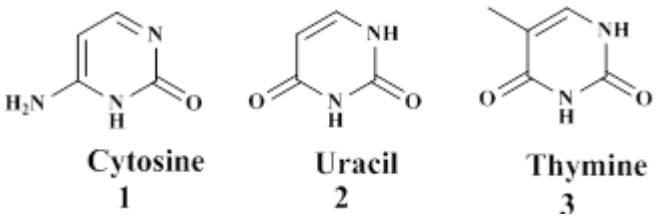


Figure 1: Pyrimidine derivatives cytosine (1), uracil (2) and thymine (3)

In particular, condensed heterocycles bearing a hydroxyaryl group as well as nitrogen-containing heterocycles derived from salicylaldehyde have been reported as anticancer [6], antihypertensive agents [7], neuropeptide Y antagonists [1] and calcium channel blockers [8].

The presence of both electrophilic and nucleophilic reaction centers in salicylaldehyde enables condensations to proceed in various possible directions. The direction control would open pathways for selectively obtaining different classes of heterocyclic compounds [9]. Simultaneously, the selectivity inevitably dictated by the variation of the reaction conditions [10].

In the literature various *o*-hydroxyl aldehydes were reported, among these azosalicyaldehyde is an important *o*-hydroxy substituted aldehyde. Furthermore, azosalicyaldehyde take more engrossed due to its importance in the field of pharmacology. Biological importance of azo compounds are well known for their use as antibacterial, antifungal anti-neoplastic, antidiabetic, antiseptics, anticancer, anti-inflammatory and other useful chemotherapeutic agents [11].

Recent year, chemist attracted towards the green synthesis of heterocyclic compounds. Use non-hazardous solvent as water [12], use of easy work up protocols and use of homogeneous catalysts as NH_4Cl [13] for the synthesis of heterocyclic compounds, which again take much attention. Current work, we use homogeneous catalyst zinc chloride, which gave us advantages in work up of reaction process.

In the present report, we describe the successful synthesis of expected *o*-hydroxy derivative of DHP from one pot reaction of various substituted azosalicyaldehyde with ethylacetoacetate and urea. The homogeneous $ZnCl_2$ catalyst, it was tested for synthesis of dihydropyrimidone derivatives. As results, catalyst showed 100% conversion of reactant to classical DHP derivatives. This process gives simple way of selective transformation of DHP; it avoided formation of tricyclic oxygen bridged product. In addition, present protocol needs just filtration and washing of product with cold water for the separation of catalyst from products, which shows unique green method impression for this protocol among other reported acid catalysts.

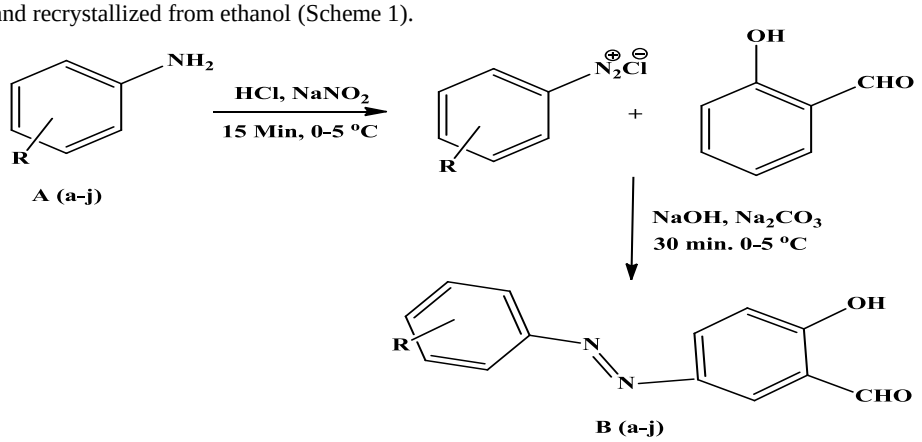
EXPERIMENTAL

General

All the chemicals were obtaining from commercial suppliers and used after further purification. All the melting points were determined in open capillary tubes and are uncorrected. The IR spectra (in cm^{-1}) were record on a perkin-Elmer spectrophotometer in KBr pellets. ^{1}HMR spectra were record on Varian Gemini (200 MHz) spectrometer using Dimethyl Sulfoxide (DMSO) as solvent and TMS as an internal standard.^{13}C-NMR spectrum recorded on 50 MHz in DMSO solvent, in δ ppm. All chemical shifts values were report in δ scale downfield from Tetramethylsilane (TMS). TLC checked homogeneity of the compound on silica gel plates.

General procedure for the synthesis of azo-salicylaldehyde from aniline

At first make, a solution of aniline (10 mmol) in the water (5 ml) add the conc. HCl in it then this combined solution was keep in ice water bath. Above solution is diazotized with solution of sodium nitrite (10 mmol), dissolved in water (3.5 ml) during a period of 15 min. maintaining the temperature at 0-5°C. This cold solution was added in the solution of Salicyaldehyde (10 mmol) in water (50 ml), containing sodium hydroxide (0.4 g) and sodium carbonate (7.3 g), during a period of 30 min. again this must be occurs in above temp. The reaction mixture was stir for 1 h. in ice bath. Then allow it to attained room temperature. Slowly after then, I had been stirred it for another 4 h. at room temperature obtained the solid product was filter and recrystallized from ethanol (Scheme 1).



Scheme 1: Where R = H, NO_2, Cl, Br, CH_3

General procedure for the synthesis of ethyl 4-(2-hydroxy-5-(phenyldiazenyl) phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives

At first combined azoaldehydes (2 mmol), ethylacetoacetate (2 mmol) and urea (3 mmol) in an unstopped Erlenmeyer flask, followed by addition of $ZnCl_2$ (0.42 mmol). Then resulting mixture heated on a water bath at 70-80°C with stirring until solidification occurs. After complication of reaction the solid product is grind to fine powder, collect under vacuum, rinsed with water and 95% ethanol and finally dried and recrystallization with ethanol solvent. Synthesized compounds further characterized by IR and ^{1}H NMR spectroscopy (Scheme 2).

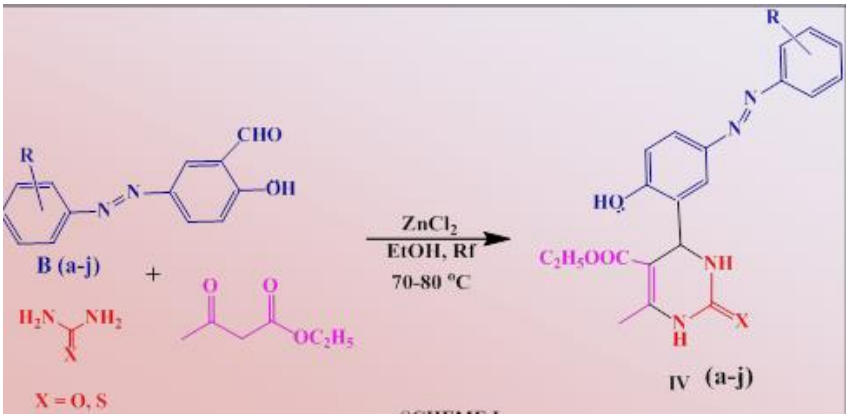
Spectral characterization of synthesized azosalicyaldehydes

2-hydroxy-5-(phenyldiazenyl)benzaldehyde (B-a)

Brown solid; Yield 80%; M.p. 126-128°C; IR (KBr, cm^{-1}): 3208 (O-H stretch), 2872 (aromatic C-H stretch), 1664 (aromatic aldehyde C=O stretch), 1620, 1570 (aromatic C=C stretch), 1475 (N=N stretch), 1284 (C-O stretch); ^{1}H-NMR spectrum (200MHz, DMSO, in δ ppm): 8.1 (s, ^{1}H), 7.4-7.6 (dd, 4H), 6.6 (m, 2H), 6.4 (m, 1H).

5-((3-chlorophenyl)diazenyl)-2-hydroxybenzaldehyde (B-c)

Yellow solid, Yield: 80%, m.p.: 175-177°C IR (KBr) in cm-1: 3193 (-OH), 2882 C-H), 1661 (-CHO), 1646 (Ar-H), 1487 (N=N), 1450 (C-N), 1285 (C-O), 587,793 (Ar-Cl). ^{1}H-NMR spectrum (200 MHz, DMSO, in δ ppm): 8.2 (s, ^{1}H), 7.8 (m, 3H), 7.3-7.5 (m, 2H), 6.8 (m, ^{1}H).



Scheme 2: Synthesis. Where, R=H, NO_2, Cl, Br, CH_3

2-hydroxy-5-((4-bromophenyl)diazenyl)benzaldehyde B-d

Yellow solid, Yield*:* 82%, IR (KBr) in cm^{-1}: 3208 (-OH), 2872 (C-H), 1722 (-CHO), 1620, 1664 (Ar-H), 1475 (N=N), 1393 (C-N). ^{1}H-NMR spectrum (200 MHz, DMSO, in δ ppm): 8.18 (d, ^{1}H), 8.08 (s, ^{1}H), 7.92 (d, 2H), 7.40 (d, 1H), 7.24 (d, 2H).

2-hydroxy-5-((4-nitrophenyl)diazenyl)benzaldehyde (B-e)

Orange solid; Yield 83%; M.p. 185-187°C; IR (KBr, in cm^{-1}): 3400 (O-H stretch), 3100 (aromatic C-H stretch), 1660 (aromatic aldehyde C=O stretch), 1600, 1570 (aromatic C=C stretch),1520 (NO_2 asymmetric stretch), 1475 (N=N stretch), 1340 (NO2 symmetric stretch), 1280 (C-O stretch), 850 (aromatic out of plane bend); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ:7.21 (d, ^{1}H), 8.06 (d, 2H), 8.26 (dd, ^{1}H), 8.33 (d, ^{1}H), 8.43 (d, 2H,).

Spectral analysis of final DHP derivatives containing azo moiety

(E)-ethyl4-(2-hydroxy-5-(phenyldiazenyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate Iva

Brown solid, IR (KBr, in cm^{-1}): 3463 (N-H), 3351 (N-H), 3218 (-OH), 2980 (C-H), 1741 (CO-Ester), 1616, 1580 (Ar-H), 1478 (N=N). 1H NMR (500 MHz, $CDCl_3$, ppm) δ: 6.8-7.2 (m, 5H), 7.5-7.8 (m, 3H), 5.1 (s, 1H), 4.2 (q, 2H), 2.3 (s, 3H), 1.4 (t, 3H).

(E)-ethyl 4-(2-hydroxy-5-((2-nitrophenyl)diazenyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate IVb

Yellowish brown, IR (KBr, in cm^{-1}): 3470 (N-H), 3356 (N-H), 3224 (-OH), 2910 (C-H), 1746 (CO-Ester), 1625, 1585 (Ar-H), 1482 (N=N). 1H NMR (500 MHz, $CDCl_3$, ppm) δ: 7.8-8.2 (dd, 2H), 7.2-7.4 (d, 2H), 6.3-6.5 (m, 3H), 4.8 (s, 1H), 4.3 (q, 2H), 2.5 (s, 3H), 1.2 (t, 3H).

(E)-ethyl4-(5-((3-chlorophenyl)diazenyl)-2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate IVc

Yellow solid, IR (KBr, in cm^{-1}): 3305 (N-H), 3192 (N-H), 3076 (-OH), 2883 (C-H), 1740 (CO-Ester), 1618, 1574 (Ar-H), 1487 (N=N), 684,882 (Ph-sub.). ^{1}H NMR (500 MHz, CDCl3, ppm) δ: 8.4 (s, ^{1}H), 7.4-7.7 (m, 4H), 6.5 (dd, 2H), 4.9 (s, 1H), 4.2 (q, 2H), 2.3 (s, 3H), 1.3 (t, 3H).

(E)-ethyl4-(5-((4-bromophenyl)diazenyl)-2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate. IVd

Yellowish Brown solid, IR (KBr, in cm^{-1}): 3317 (N-H), 3185 (N-H), 3050 (-OH), 2878 (C-H), 1736 (CO-Ester), 1620, 1580 (Ar-H), 1478 (N=N), 680,860 (Ph-sub.). ^{1}H NMR (500 MHz, CDCl3, ppm) δ: 8.4 (d, 2H), 7.8 (d, 2H), 6.5-6.7 (m, 3H), 5.1 (s, ^{1}H), 4.4 (q, 2H), 2.2 (s, 3H), 1.3 (t, 3H).

(E)-ethyl 4-(2-hydroxy-5-(p-tolyldiazenyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate. IVf

Pale grey solid, IR (KBr, in cm^{-1}): 3375 (N-H), 3330 (N-H), 3186 (-OH), 2875 (C-H), 1735 (CO-Ester), 1622, 1564 (Ar-H), 1469 (N=N), 740,886 (Ph-sub.). 1H NMR (500 MHz, CDCl3, ppm) δ: 7.6 (d, 2H), 7.4 (d, 2H), 6.5-6.8 (m, 3H), 4.6 (s, 1H), 4.5 (q, 2H), 2.2 (s, 3H), 1.8 (s, 3H), 1.3 (t, 3H).

RESULTS AND DISCUSSION

We synthesis of DHP derivatives using various substituted azosalicyaldehyde. This research work start with preparation of azosalicyaldehyde using reported method from substituted anilines and Salicyaldehyde. This synthesized azosalicyaldehyde used for one-pot synthesis of DHP derivatives (4), reaction was performed using azosalicyaldehyde 1, urea 2 and ethyacetoacetate 3. Reaction was accomplished by heating reaction mixture at 70-80°C temperature at appropriate time (Scheme 1). All obtained results summarized in Tables 1 and 2. All synthesized products are conformed by spectral and analytical data.

Selection of Zinc chloride done based on comparing the performance of various homogeneous catalysts in different conditions; observed results were summarizing in Table 1. For this we carried out reaction of 5-phenylazosalicyaldehyde with ethylacetoacetate and urea as classical reaction. We start with, reaction carried out in catalyst free condition in ethanol solvent; at 80°C temperature it gives only 55% of yield. In addition to that, same reaction carried out solvent free and catalyst free but it fail to gives satisfactory result. Role for solvent observed by changing solvent ethanol to DMF and reaction mixture reflux at 120°C, this gives near about 50% transformation of reactants in to desired product. For the further investigation, we keep ethanol as solvent for this present classical reaction. Catalyst $FeCl_3.6H_2O$ (10% mol) gives 66% of yield in ethanol by refluxing reaction mixture at 80°C temperature. Furthermore, 10% mole of Zinc acetate (Zn $(OAc)_2$) and Zinc Sulfate ($ZnSO_4.7H_2O$) gives satisfactory 65 and 68% yield respectively in ethanol at reflux condition.

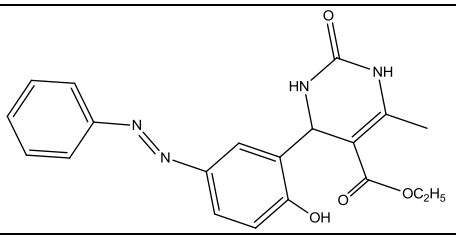
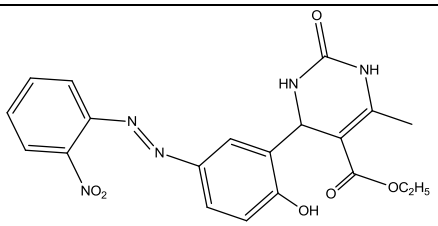
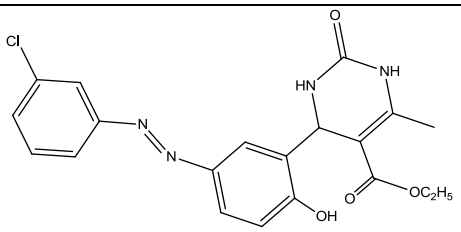
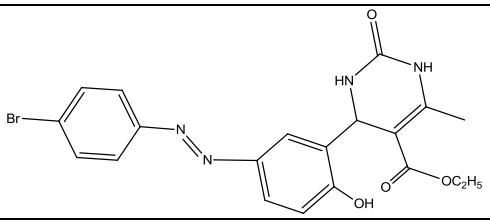
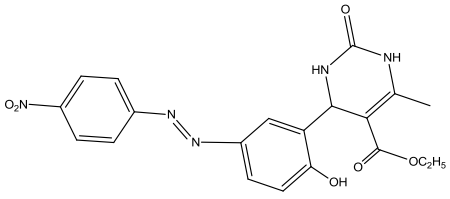
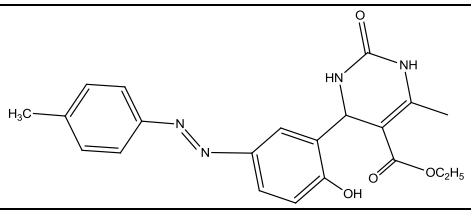
Result shows that the Zinc Chloride ($ZnCl_2$) is the better homogeneous catalyst among the above-mentioned catalysts. $ZnCl_2$ catalyst shows superior yield as 72% yield for the conversion of 5-phenylazosalicyaldehyde with ethylacetoacetate and urea in to classical dihydropyrimidone derivative in ethanol solvent and at 70-80°C temperature.

Table 1: Effect of various catalyst and solvent on the reaction of azasalicyaldehyds, ethylacetoacetate and urea

Entry	Catalyst	Solvent	Condition	Yield[(b)] (%)
1	No catalyst	Ethanol	Reflux at 80°C	55
2	No catalyst	Solvent free	Heat at 80°C	30
3	No catalyst	DMF	Reflux at 120°C	50
4	$FeCl_3$ 6 H_2O	Ethanol	Reflux at 80°C	66
5	$Zn(OAc)_2$	Ethanol	Reflux at 80-120°C	65
6	$ZnSO_4.7H_2O$	Ethanol	Reflux at 80-100°C	68
7	$ZnCl_2$	Ethanol	Reflux at 70-80°C	72

(a) Reaction conditions: EAA (2 mmol); 5-phenylazosalicyaldehyde (2 mmol); urea (3 mmol) and catalyst (10 mol%) in solvent free condition; (b) Isolated yield

Table 2: Analytical data of synthesized compounds 3(a-f)

Entry	Product	Yield[(b)] (in %)	Time of reaction in h[(c)]	M.P. (°C)
a		72	6	179
b		70	6	207
c		70	7	208
d		72	7	203
e		75	5	202
f		72	7	211

With the optimized conditions in hand, we proceeded to investigate the scope and generality of this procedure using rang of various substituted azosalicyaldehyde provided the corresponding azo derivative of DHP in good to excellent yield, as publicized in Table 2. As marked from Table 2, all substituted azosalicyaldehyde participated well in this cyclization reaction and affording the desired products of DHP in good to efficient yields. In addition, these reactions were complete in short reaction time and small amount of catalyst offered high to efficient yield.

From this result, we conclude that the $ZnCl_2$ is an efficient catalyst for the present transformation. This protocol is give higher yield in short time. All functional groups on the substituted Azosalicyaldehydes were unaffected during DHP transformation. Separation of catalyst from reaction mixture through the washing of crud product by H_2O, this was a key point of this work.

CONCLUSION

In summary, an efficient method for the synthesis of classical Biginelli product of DHP derivatives from *o*-hydroxy aldehydes has reported. This is the first time to synthesis of DHP derivatives from azo salicylaldehyde; it gives selective and facile transformation in desired DHP products and avoid development of tricyclic oxygen bridged derivative. Synthesized DHP derivatives consist of aza moiety, which inputs extra benefits in term of biological activities. Simplicity in reaction protocol, homogeneity of catalyst, high yields; easy work-up and purification of compounds are the key advantages of this method.

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