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Der Pharma Chemica, 2014, 6(5):101-104
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Green synthesis of biginelli products of meldrum acid

Vijay V. Dabholkar*, Mustaqeem Mohammed A., Navnath B. Shinde and Omprakash G. Yadav

Organic Research Laboratory, Department of Chemistry, Guru Nanak College, G.T.B Nagar, Mumbai

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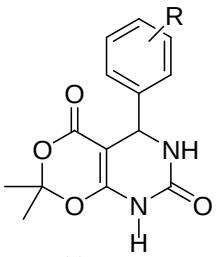

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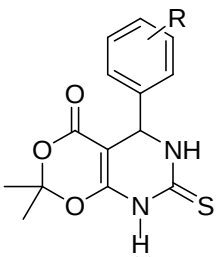

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ABSTRACT

A simple and efficient method has been devised for the synthesis of 3,3-dimethyl-7H,8H,10H-8,10-diaza-2,4-dioxa-5,9-dioxo-7-(substituted) phenylbicyclo [4.4.0] dec-1(6)-ene ***(5)*** *and 3,3-dimethyl-7H,8H,10H-8,10-diaza-2,4-dioxa-5-oxo-9-thioxo-7-(substituted) phenylbicyclo [4.4.0] dec-1(6)-ene* ***(6)****, by a one-pot three component cyclocondensation reaction of 1,3 dicarbonyl compound (Meldrum), aromatic aldehyde, and urea/thiourea using catalytic amount of fresh lemon juice in refluxing ethanol. Representative samples were screened for their anti-microbial activities against gram-negative bacteria and gram-positive bacteria using disc diffusion method. The structures of the products were confirmed by IR,* ^{1}H, ^{13}C *NMR and elemental analysis.*

Keywords: Aromatic aldehydes, Dihydropyrimidine, Meldrum acid.

INTRODUCTION

Nitrogen, oxygen and sulphur containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activity[1]. Pyrimidone and their derivatives are considered to be important for drugs and agricultural chemicals. As it is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities [2]. Pyrimidone derivatives possess several interesting biological activities such as antitumor[3], antiviral[4], antifungal, anticancer[5], antibacterial[6], antiinflammator[7], analgesic[8], antagonist[9], antifolate[10], anti-HIV, atiproliferative[11], antiplatelet, antithrombotic[12], antifilarial[13] activities, etc. Logically, we focused our attention on protonation of heteroatom in organic transformation by natural acids. Recently, we reported that Fresh Lemon Juice as Natural Catalyst efficiently catalyzes the Knoevenagel and Biginelli reactions[14]. To our satisfaction we found that the use of stoichiometric amount of Lemon Juice resulted in quantitative yield of the corresponding pyrimidone derivative under reflux condition. However, no result was obtained when condensation is carried without employing catalyst [14]. The literature study reveals that pyrimidone is an important pharmacophore[15] and exhibits outstanding biological activities. More recently pyrimidones have emerged as the integral backbones of

several calcium channel blockers[16].The acid-catalyzed Biginelli reaction, which is a three-component reaction between aldehyde, ß-ketoester and urea/ thiourea, is a rapid and facile method for the synthesis of pyrimidones, which are interesting compounds with a potential pharmaceutical applications.Now a day's multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry for various reasons[17].MCR strategies offer significant advantages over conventional multistep synthesis[18]. MCR condensations involve three or more compounds reacting in a single event, but consecutively to form a new product, which contains the essential parts of all the starting materials[19].Thus, the pharmacophoric activity of pyrimidones prompted the design and synthesis of 7H,8H,10H-8,10-diaza-2,4-dioxa-5,9-dioxo-7-(substituted) phenylbicyclo [4.4.0] dec-1(6)-ene **(5)** and 7H,8H,10H-8,10-diaza-2,4-dioxa-5-oxo-9-thioxo-7-(substituted) phenylbicyclo [4.4.0] dec-1(6)-ene **(6) (Scheme)**

MATERIALS AND METHODS

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer

Meldrum acid required for synthesis was obtained by reported procedure[14].

General Procedure:

Synthesis Of 3, 4-Dihydropyrimidin-2(1H)-One:

Mixture of Meldrum (0.05 mol), Aromatic aldehydes (0.05 mol) and urea/thiourea (0.05 mol) was refluxed on a water bath in ethanol in the presence of catalytic amount of lemon juice. The progress of the reaction was monitored by TLC. After completions of the reaction, the concentrated reaction mixture was cooled and poured onto ice-cold water, solid separated was filtered off, washed with water, dried, and recrystallized from absolute alcohol to obtain pure compound.

3,3-dimethyl-7H,8H,10H-8,10-diaza-2,4-dioxa-5,9-dioxo-7-(4-methoxy) phenylbicyclo [4.4.0] dec-1(6)-ene **(5c)**

Yield:71 %; m.p.=214-216 °C : Calcd for $C_{15}H_{16}N_20_5$: C,59.21;H,5.26;N,9.21%.Found C,59.88;H,5.12,N,9.24%.IR (cm^{-1}): 1660(C=O), 1730(C=O), 3290(NH)**,** ^{1}H NMR(δ ppm): 1.72(6H,s,2xCH_3), 3.88 (3H,s,OCH_3), 7.2 (4H,m,Ar-H), 8.2 (2H,s,2xNH), 8.3 (1H,s,CH), , ^{13}C NMR(δ ppm): 27.325(2xCH_3), 55.70(OCH_3),105 and 110(tetrahedral carbon), 124.78 (CH), 116.36-131.7 (C=C,Ar-C),160.476 (C=O),165.985 (C=O).

3,3-dimethyl-7H,8H,10H-8,10-diaza-2,4-dioxa-5,9-dioxo-7-(4-hydroxy) phenylbicyclo [4.4.0] dec-1(6)-ene **(5d)**.

Yield: 80%; m.p.=220-223°C ; Calcd for $C_{14}H_{14}N_20_5$: C,57.93;H,4.57;N,9.15%.Found C,57.22;H,4.52,N,9.34%.IR (cm^{-1}): 1660(C=O), 1750(C=O), 3290(NH)**,** ^{1}H NMR(δ ppm): 1.72(6H,s,2xCH_3), 6.9 (1H,s,CH), 7.2-7.3 (4H,m,Ar-H), 7.8 (1H,s,OH), 10.6 (1H,s, NH), 9.72(1H,s,NH), ^{13}C NMR(δ ppm):, 27.325(2xCH_3),104.12 and 115(tetrahedral carbon), 116.36-123.525 (C=C,Ar-C), 124.78 (CH), 160.477 (C=O),163.82 (C=O).

3,3-dimethyl-7H,8H,10H-8,10-diaza-2,4-dioxa-5-oxo-9-thioxo-7-(4-methoxy) phenylbicyclo [4.4.0] dec-1(6)-ene **(6c)**

Yield: 74%; m.p.=120-123°C ; Calcd for $C_{15}H_{16}N_20_4S$: C,56.52;H,5.0;N,8.75%.Found C,56.82;H,5.2,N,8.54%.IR (cm^{-1}): 1680 (C=O), 1240 (C=S), 3310(NH)**,**^{1}H NMR(δ ppm): 1.72(6H,s,2xCH_3), 3.88 (3H,s,OCH_3), 7.05-7.16 (4H, m,Ar- H), 8.2 (2H,s,2×NH), 8.4(1H,s,CH), ^{13}C NMR(δ ppm):, 27.325(2xCH_3), 104.12 and 109(2x tetrahedral carbon), 120.53-130.788 (C=C,Ar-C), 156.982 (C=O), 163.512 (C=S).

3,3-dimethyl-7H,8H,10H-8,10-diaza-2,4-dioxa-5-oxo-9-thioxo-7-(4-hydroxy) phenylbicyclo [4.4.0] dec-1(6)-ene **(6d)**

Yield: 74%; m.p.=202-204°C ; Calcd for $C_{14}H_{14}N_20_4S$: C,54.91;H,4.57;N,9.15%.Found C,54.69;H,4.62,N,9.34%.IR (cm^{-1}): 1670 (C=O), 1230(C=S), 3330(NH),3450(OH)**,**^{1}H NMR(δ ppm):, 1.72(6H,s,2xCH_3), 6.72 (1H,s,CH), 6.9 (1H,s,OH),7.22-7.40 (4H,m,Ar- H), 11.0 (2H,s,2xNH), ^{13}C NMR(δ ppm):, 27.221(2xCH_3), 103.12 and 111.23(2x tetrahedral carbon), 114.3-138.2 (C=C,Ar-C), 157.3 (C=S), 167.3 (C=S).

TABLE I : Characterization data of compounds 5 (Urea derivative) and 6 (Thiourea derivative)

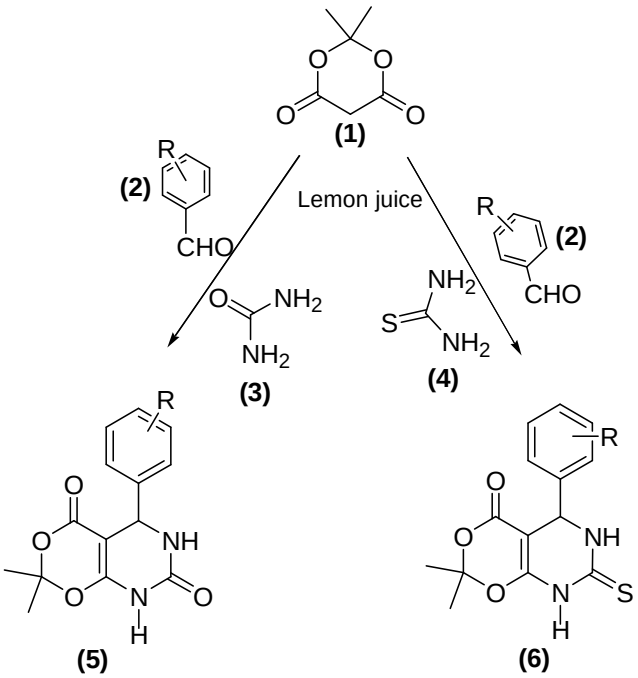
Compounds	R	Mol. Formula	m.p. °C	Yield %	Color
5a	H	$C_{14}H_{14}N_2O_4$	212-214	68	White
5b	4-Cl	$C_{14}H_{13}N_2O_4Cl$	170-174	64	White
5c	4-OCH_3	$C_{15}H_{16}N_2O_5$	130-132	77	Pale Green
5d	4-OH	$C_{14}H_{14}N_2O_5$	214-216	71	Dark Yellow
5e	3-OCH_3, 4-OH	$C_{15}H_{16}N_2O_6$	145-148	79	Orange
6a	H	$C_{14}H_{14}N_2O_3S$	200-202	69	Cream
6b	4-Cl	$C_{14}H_{13}N_2O_3SCl$	156-160	80	Pale Yellow
6c	4-OCH_3	$C_{15}H_{16}N_2O_4S$	120-123	74	Green
6d	4-OH	$C_{14}H_{14}N_2O_4S$	202-204	76	Buff
6e	3-OCH_3, 4-OH	$C_{15}H_{16}N_2O_5S$	138-141	70	Yellowish-orange

Antimicrobial And Antifungal Activities

All the newly synthesized compounds were evaluated for their antibacterial activities against gram-negative and gram-positive bacteria using disc diffusion method. The zone of inhibition was measured in mm and the activities was compared with standard drug.

The activities of representative compounds are reported in Table II.

General Scheme



RESULTS AND DISCUSSION

The target molecules 3,3-dimethyl-7H,8H,10H-8,10-diaza-2,4-dioxa-5,9-dioxo-7-(substituted) phenylbicyclo [4.4.0] dec-1(6)-ene **(5) (a-e)** and 3,3-dimethyl-7H,8H,10H-8,10-diaza-2,4-dioxa-5-oxo-9-thioxo-7-(substituted) phenylbicyclo [4.4.0] dec-1(6)-ene **(6) (a-e)**,were synthesized in good yield by the one pot reaction of aromatic aldehydes, Meldrum and urea/thiourea in refluxing ethanol using few drops of fresh lemon juice as catalyst.

TABLE II Antibacterial activity of compounds 5 and 6

Antibacterial Activity of compound 5 & 6				
Comp.	**Zone of inhibition (in mm)**			
	Gram Positive		**Gram negative**	
	S.aureus	***C.diphtheria***	***P.aeruginosa***	***E.coli***
5b	23	19	22	18
5c	21	17	21	17
5d	17	18	19	15
5e	16	17	15	19
6b	21	23	16	17
6c	21	22	17	16
6d	17	20	23	15
6e	16	22	22	17
Amphicilin trihydrate	26	28	24	21
DMSO	0	0	0	0

** Diameter of the disc was 6mm;*
Concentration of the compounds taken was about 100 µg/mL.

CONCLUSION

A number of new pyrimidones were prepared in good yield, representative compounds were further screened for their antimicrobial activity which showed good activities against gram positive as well as gram negative bacteria.

Acknowledgement
Authors are thankful to the Management of Guru Nanak College, G.T.B. Nagar, Mumbai for constant encouragement and providing necessary facilities. Authors are also thankful to, The Director, TIFR Mumbai for spectral data.

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