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Sustainable synthesis and Physicochemical study of fused Pyrimidones by using Natural catalyst

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Abstract

Pyrimidone derivatives have been synthesized by grinding 1,3-Diketone heterocycle, Aromatic Aldehyde and Urea/Thiourea with catalytic amount of Fresh limejuice as a natural catalyst. The comparative physiochemical studies were done with respect to the reaction conversion, purity, atom economy, simplicity of reaction and easy work-up of the multicomponent reaction. The actual structures of all the products confirmed by different chemical test along with Chromatographic analysis, melting point and spectral technique like IR, ^{1}H NMR and ^{13}C NMR.

Keywords: Catalysis, Grinding, natural acid, one pot synthesis, Biginelli reaction.

Introduction

The acid catalysed Biginelli reaction, which is a multicomponent reaction between carbonyl compounds like aldehyde or ketones, a β-ketoester or active methylene compounds and urea/thiourea, is a rapid and facile method for the synthesis of pyrimidones[1]. Heterocycles are very crucial in the study of medicinal chemistry due to versality in their structure and ability to interact with various biological targets. Pyrimidones and their derivatives have been integral in drug development, exemplified by drugs like Risperidone and sulphadimethoxine. Pyrimidone derivatives have been studied for their pharmacological properties, making significance role in pharmaceuticals. Natural substance like, Vitamin B series also contain heterocyclic pyrimidine ring. Fused pyrimidone show interesting biological properties like calcium channel blockers and antihypertensive agents[2].

Some pyrimidones have been discovered to improve the health of cancer patients[3]. Commercial importance of dihydropyrimidones derivatives have developed the catalytic route and techniques for their synthesis, such as H_2SO_4, Hydrochloric acid, fresh lime juice, transition metal-based nano-catalyst, the use of ultra sound, Microwave radiation, solar energy source and polymers supported reactions[3-6]. Derivatives of DHP have been reported to possess ulcer healing effect[7-9]. The DHP derivative known as barbitone is the earliest barbiturate hypnotic sedative and anticonvulsant[10].

Methodolgy

M.P. of all products were determined by open capillary tubes and are uncorrected. The TLC was performed to check the purity of all synthesized compounds. Proton Nuclear Magnetic Resonance (NMR) spectrum was recorded on Varian 600 MHz NMR using Deuterated Chloroform/DMSO-d_6 as medium and Tetramethylsilaneas an internal standard (chemical shifts observed in δ ppm). The IR spectrum was recorded on Bruker Alpha FTIR.

Reaction procedure: Procedure for the synthesis of Meldrum's Acid: A mixture of Acetone (10.0 mL), Malonic (11.2g) acid and Acetic anhydrides (12mL) are stirred at room temperature in presence of catalytic amount of Conc. Sulphuric acid for at least 5 to 6 hrs. After completion of reaction, the reaction mixture kept in a refrigerator for overnight. The product obtained is filtered, washed with cold water (to remove excess of water-soluble impurities), and dried. White crystalline solid of pure Meldrum's acid is obtained[11].

Scheme-1: Synthesis of Meldrum's acid (Compound 1).

General procedure for the synthesis of pyrimidones of Meldrum's acid: By conventional method: A mixture of Aromatic aldehydes (0.02 mol), Meldrum's acid (0.02 mol), and urea/thiourea (0.02 mol) was refluxed in ethanol with addition of few drops of Hydrochloric acid. The reaction progress was monitored by TLC. Upon completions of the reaction, the product obtained was poured onto cold water, separated solid

was filtered, washed with cold water, dried and weighed. Recrystallization was done from aqueous alcohol to obtain purified compound.

By green method: Equimolar mixture of Aryl aldehydes (0.02 mol), Meldrum's acid (0.02 mol), and urea/thiourea (0.02 mol) was grind with addition of few drops of fresh lime juice. The reaction progress was monitored by TLC. Upon completions of the reaction, the product obtained was poured onto cold water, separated solid was filtered, washed with cold water, dried and weighed. Recrystallization was done from aqueous alcohol to obtain purified compound.

Scheme-2: Synthesis of pyrimidone series (Compound 5 & 6).

Spectral data of purified Compounds: ***Compound 5a:*** *7H,8H,10H-8,10-Bisaza-2,4-dioxa-5,9-dioxo-7-phenylbicyclo [4.4.0] dec-1(6)-ene:* ^{1}H NMR values (δ ppm): 1.71 (6H,s,2xMe), 7.21 (5H,m,Aromatic- H), 8.15 (2H,s,2xNH), 8.25 (1H,s,CH), ^{13}C NMR values (δppm): 27.32(2xCH_3), 105.0 and 110.0 (tetrahedral C), 124.7 (CH), 116.36-131.7 (C=C & Ar-C), 160.47 (C=O),165.98 (C=O). IR values (cm^{-1}): 1675(C=O), 1720(C=O), 3285(NH).

Compound 5b: *7H,8H,10H-8,10-Bisaza-2,4-dioxa-5,9-dioxo-7-(p-chloro)phenylbicyclo [4.4.0] dec-1(6)-ene:* ^{1}H NMR value (δ ppm): 1.74 (6H,s,2xMe), 7.31 (5H,m,Aromatic-H), 8.22 (2H,s,2xNH), 8.25 (1H,s,CH), ^{13}C NMR value (δppm): 27.32(2xMe), 105 and 112 (tetrahedral C), 122.78 (CH), 116.36-131.7 (C=C,Aryl-C), 160.47 (C=O), 165.98 (C=O). IR (cm^{-1}): 1675(C=O), 1720(C=O), 3290(NH).

Compound 5c: *7H,8H,10H-8,10-Bisaza-2,4-dioxa-5,9-dioxo-7-(p-methoxy) phenylbicyclo [4.4.0] dec-1(6)-ene:* ^{1}H NMR values (δppm): 1.73(6H,s,2xMe), 3.88 (3H,s,OMe), 7.23 (4H,m,Aromatic-H), 8.22 (2H,s,2xNH), 8.31 (1H,s,CH), ^{13}C NMR values (δppm): 27.325(2xCH_3), 55.75(OCH_3),105.0 and 110.0 (tetrahedral C), 124.78 (CH), 116.36-131.7 (C=C,Aryl-C), 160.476 (C=O), 165.985 (C=O). IR values (cm^{-1}): 1670(C=O), 1720(C=O), 3295(NH).

Compound 6a: *7H,8H,10H-8,10-Bisaza-2,4-dioxa-5-oxo-9-thioxo-7-phenylbicyclo [4.4.0] dec-1(6)-ene:* ^{1}H NMR values (δ ppm):1.72(6H,s,2xMe),, 7.0-7.15 (5H, m,Aromatic- H), 8.22 (2H,s,2×NH), 8.4(1H,s,CH), ^{13}C NMR values (δppm):, 27.32(2xCH_3), 104.12 and 109(tetrahedral carbon), 120.53-130.78 (C=C,Aryl-C), 156.98 (C=O), 163.512 (C=S). IR values (cm^{-1}):1685 (C=O), 1230 (C=S), 3315(NH).

Compound 6b: *7H,8H,10H-8,10-Bisaza-2,4-dioxa-5-oxo-9-thioxo-7(p-chloro)phenylbicyclo [4.4.0] dec-1(6)-ene:* ^{1}H NMR values (δ ppm): 1.71(6H,s,2xMe), 7.0-7.15 (5H,m,Aromatic-H), 8.31 (2H,s,2×NH), 8.39(1H,s,CH), ^{13}C NMR values (δppm): 27.29 (2xCH_3), 104.12 and 109.0 (tetrahedral carbon), 120.53-130.788 (C=C,Aryl-C), 156.80 (C=O), 162.412 (C=S). IR values (cm^{-1}): 1680 (C=O), 1240 (C=S), 3310(NH).

Compound 6c: *7H,8H,10H-8,10-Bisaza-2,4-dioxa-5-oxo-9-thioxo-7(p-methoxy)phenylbicyclo [4.4.0] dec-1(6)-ene:* ^{1}H NMR values (δ ppm): 1.72(6H,s,2xMe), 3.71(3H,s,-OMe), 7.0-7.15 (5H,m,Aromatic-H), 8.2 (2H,s,2×NH), 8.45(1H,s,CH), ^{13}C NMR values (δppm): 27.33(2xCH_3), 56.85(-OCH_3), 104.12 and 109.0 (tetrahedral carbon), 120.53-130.788 (C=C,Ar-C), 156.98 (C=O), 162.51 (C=S). IR values (cm^{-1}): 1685 (C=O), 1230 (C=S), 3315(NH).

Table-1: Characterization data of Pyrimidones 5 (NH_2CONH_2 derivatives) and Thiopyrimidones 6 (NH_2CSNH_2 derivatives).

Synthesized Compounds	-R	Molecular Formula	Melting point (°Celsius)	Percentage Yield	
				With Mineral acid (Reflux)	With Green catalyst (Griding)
5a	-H	$C_{14}H_{14}N_20_4$	212-214	66	68
5b	4-Chloro	$C_{14}H_{13}N_20_4Cl$	170-172	65	69
5c	4-methoxy	$C_{15}H_{16}N_20_5$	130-132	77	85
6a	-H	$C_{14}H_{14}N_20_3S$	200-202	69	75
6b	4-Chloro	$C_{14}H_{13}N_20_3SCl$	156-158	79	87
6c	4-methoxy	$C_{15}H_{16}N_20_4S$	120-122	72	82

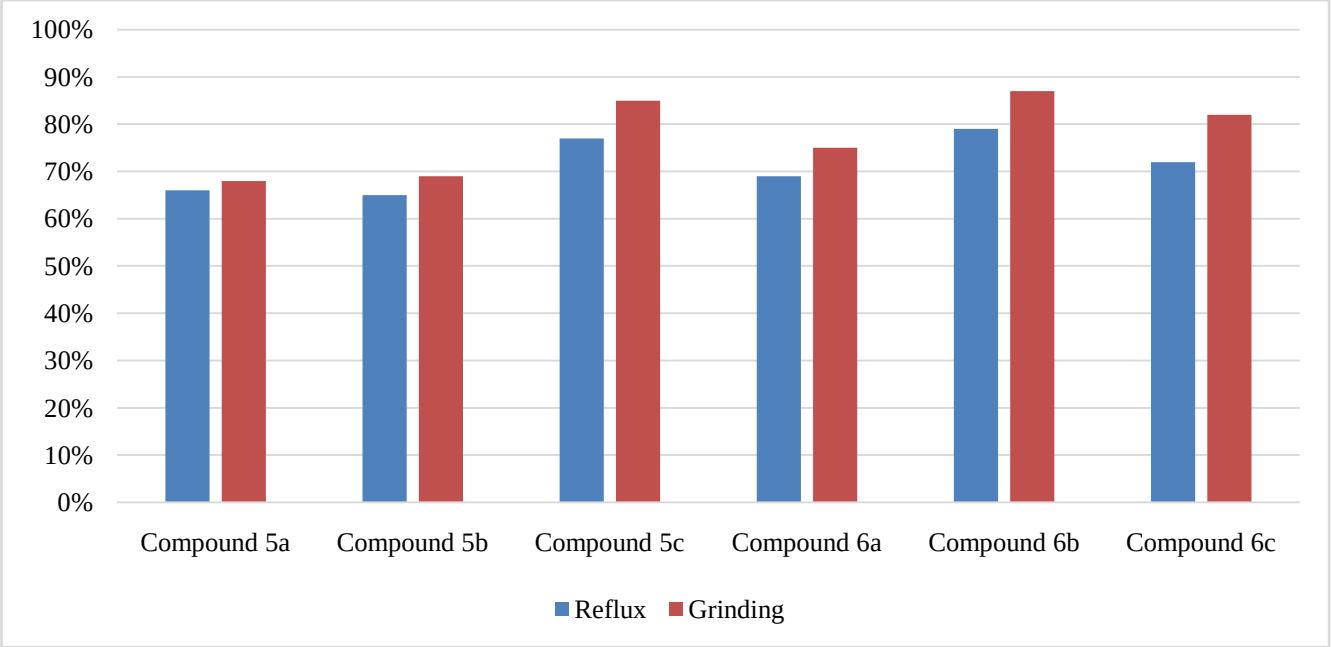

Figure-1: Comparative yields of conventional method (Reflux) and green method (Grinding).

Results and Discussion

The synthesized product spyrimidones of urea derivatives i.e 7H,8H,10H-8,10-Diaza-2,4-dioxa-5,9-dioxo-7-(substituted) phenylbicyclo[4.4.0]dec-1(6)-ene (5) (a-c) and Thiopyrimidones of thiourea derivatives i.e7H,8H,10H-8,10-Diaza-2,4-dioxa-5-oxo-9-thioxo-7-(substituted) phenylbicyclo [4.4.0] dec-1(6)-ene (6) (a-c), were prepared in better yield byone pot synthesis of aryl aldehydes, Meldrum's acid and Thiourea/urea using catalytic amount of freshly obtained lime juice as a natural source of catalyst by grinding method.

Conclusion

Nitrogen based six membered heterocyclic compound is a unique and important branch of medicinal chemistry that has gained a lot of importance recently. The development of new methodologies has received a lot of attention for the formation of highly functionalized molecules. Dihydropyrimidones and Dihydropyrimidinethiones were synthesized in appropriately better yield by using one pot reaction. Use of fresh lime juiceas a catalyst and grinding method was found to be very effective with high percentage of atom economy.

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