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Graphical Abstract

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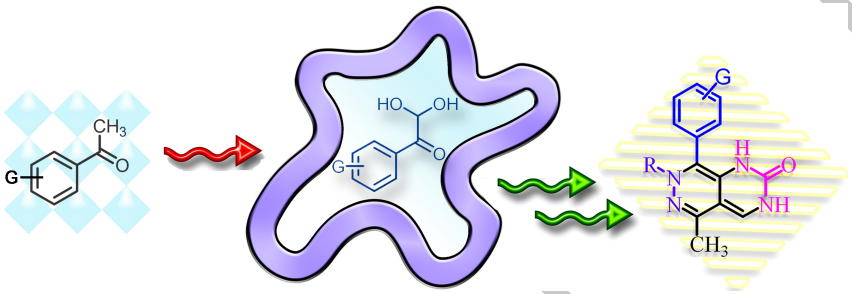

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Regiospecific strategies for the synthesis of novel dihydropyrimidinones and pyrimidopyridazines catalyzed by molybdate sulfuric acid

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ABSTRACT

The one-pot reactions of aryl glyoxals with acetylacetone and urea using molybdate sulfuric acid (5 mol%) lead to the novel functionalized 5-acetyl-4-(aryloyl)-3,4-dihydropyrimidinones, which readily undergo the Knorr condensation with hydrazines to produce new pyrimido[4,5-*d*]pyridazines. The present strategies are in accordance with green chemistry principles through the use of a safe and recyclable catalyst under solvent-free conditions.

The chemistry of heterocyclic compounds containing a nitrogen atom has been widely studied. Among these, dihydropyrimidinones are important in biological and pharmaceutical research.[1-3] The most common method for the synthesis of dihydropyrimidinones and the corresponding dihydropyrimidine-thiones (DHPMs) is via the Biginelli reaction. Accordingly, much attention has been paid to the study of the Biginelli reaction due to the important biological and pharmaceutical merits of DHPMs.[4] For example, functionalized dihydropyrimidine-2-ones have shown biological activities such as antibacterial,[5] antiviral,[6] and antitumour.[7] Besides, several reports on the synthesis and biological evaluation of pyrimido-fused heterocycles such as pyrimido[4,5-*d*]pyridazin-8(7*H*)-ones,[8] pyrano[2,3-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines,[9] and 2,4-diaminopyrido[2,3-*d*]pyrimidines[10] are available in the literature. Multicomponent reactions (MCRs) are increasingly emerging as powerful tools for rapidly generating complex molecules with potential biological properties.[11] In addition, organic synthesis based on green strategies has been widely investigated because of stringent environmental and economic regulations.[12] Molybdate sulfuric acid (MSA) is a safe, stable, and recyclable solid acid and, is a suitable catalyst for many organic reactions. On the other hand, according to green chemistry principles, the use of low amounts of a recyclable catalyst and the avoidance of organic solvents are important factors.[13]

In continuation of our interest on the synthesis of fused heterocycles,[14-16] we herein describe simple and efficient strategies for the synthesis of new dihydropyrimidinones and pyrimidopyridazines. The increasing demand for clean syntheses of fine chemicals has stimulated chemists to explore and develop new strategies in accordance with green chemistry principles.

After several experiments, we found that new aryloyl-3,4-dihydropyrimidinones **4** could be obtained via a one-pot, multicomponent reaction of aryl glyoxals **1**, urea (**2**), and acetylacetone (**3**) in the presence of molybdate sulfuric acid (MSA) under solvent-free conditions. Aryl glyoxals **1** were obtained by selenium dioxide oxidation of the corresponding aryl ketones.[17] Subsequently, compounds **4** were used as suitable 1,4-diketones for the synthesis of new pyrimido[4,5-*d*]pyridazines via the Knorr condensation with hydrazines **5**. The reactions were also catalyzed by MSA under solvent-free conditions (Scheme 1).[18,19]

By employing these methods, a number of novel fused heterocycles were obtained (Tables 1 and 2).

The structures and purities of the presented products were deduced from their FT-IR, elemental analysis, and NMR spectral data. As a representative example, the ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of **4a** exhibited two singlets due to the nitrogen protons (δ = 10.61 and 10.10), and a doublet (δ = 7.35) and singlet (δ = 7.20) corresponding to the aromatic protons. The resonance for the protons of the two methyl groups appeared at δ = 1.94 as a singlet.

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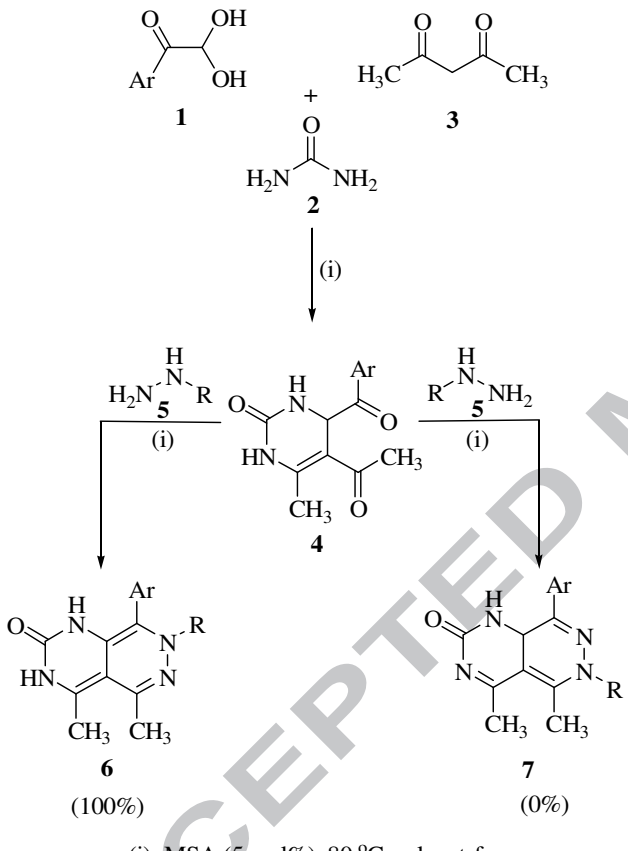
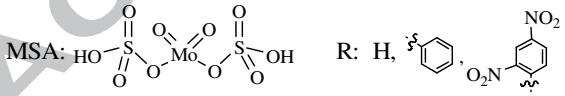
It is interesting to note that the Knorr reaction proceeded with regiospecificity in this method and only one structural isomer was formed. During the reaction, no trace was found by thin-layer chromatography (TLC) of the possible alternative product **7**. One of the ways to prove the exclusive formation of adducts **6** rather than adducts **7** was the disappearance of the signal for the methine hydrogen (usually at δ = 4-7) and the appearance of two NH signals. For example, in the case of compound **6b,** as an example, the disappearance of the methine hydrogen and the appearance of two protons for the NH groups were confirmed. The ^{1}H NMR spectrum of **6b** exhibited two sharp singlets identified as two methyl group protons (δ = 2.05 and 2.08). The multiplets (δ = 7.15-7.55) corresponded to the protons of the phenyl groups. The NH protons appeared as two distinct signals at δ = 10.23 and δ = 10.64. The proton decoupled ^{13}C NMR spectrum of **6b** showed 16 distinct resonances in agreement with the proposed structure.



(i): MSA (5 mol%), 80 °C, solvent-free.

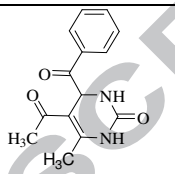
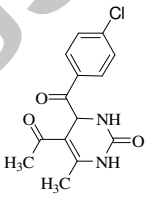
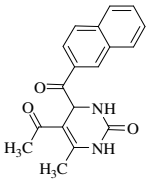
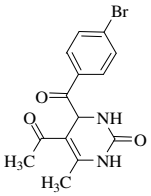
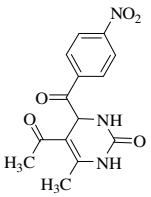


Scheme 1. Synthesis of aryloyl-3,4-dihydropyrimidinones **4** and pyrimido[4,5-*d*]pyridazines **6**

It should also be mentioned that the reactions did not proceed in the absence of the catalyst, even after long reaction times (about 12 h).

A suggested mechanism for the two-step process is shown in Scheme 2. Protonation of the hydroxyl group of the aryl glyoxal by the Brønsted acid MSA generates an electrophilic center which participates in a Knoevenagel condensation to form an α,β-unsaturated ketone as a reactive intermediate. Interception of the intermediate by urea through a 1,4-addition followed by dehydration, produces compounds **4**. In the second step for the formation of pyrimido[4,5-*d*]pyridazines **6**, MSA also acts as an efficient catalyst which can release a proton and activate the δ-dicarbonyl, thus, the energy of the transition state decreases and the rate of the nucleophilic displacement increases. After nucleophilic attack of the hydrazine on the activated carbonyls and dehydration, the final products **6** are formed.

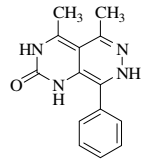
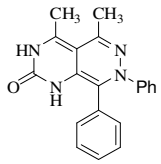
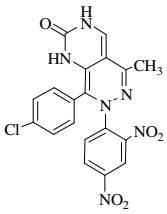
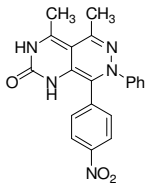
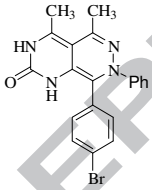
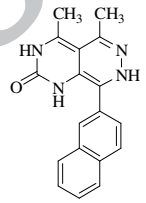
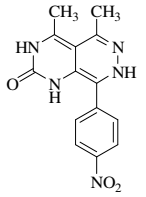
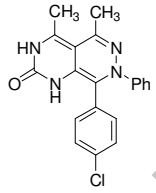
Table 1. Synthesis of 5-acetyl-4-(aryloyl)-3,4-dihydropyrimidinones using MSA under solvent-free conditions.

Entry	Ar	Product	Yield[a] (%)	Time (h)	Mp (ºC)
1	C_6H_5	 **4a**	70	5	212-214
2	4-Cl-C_6H_4	 **4b**	75	4	180-182
3	2-naphthyl	 **4c**	80	5	165-167
4	4-Br-C_6H_4	 **4d**	85	4	170-172
5	4-O_2N-C_6H_4	 **4e**	75	4	195-197

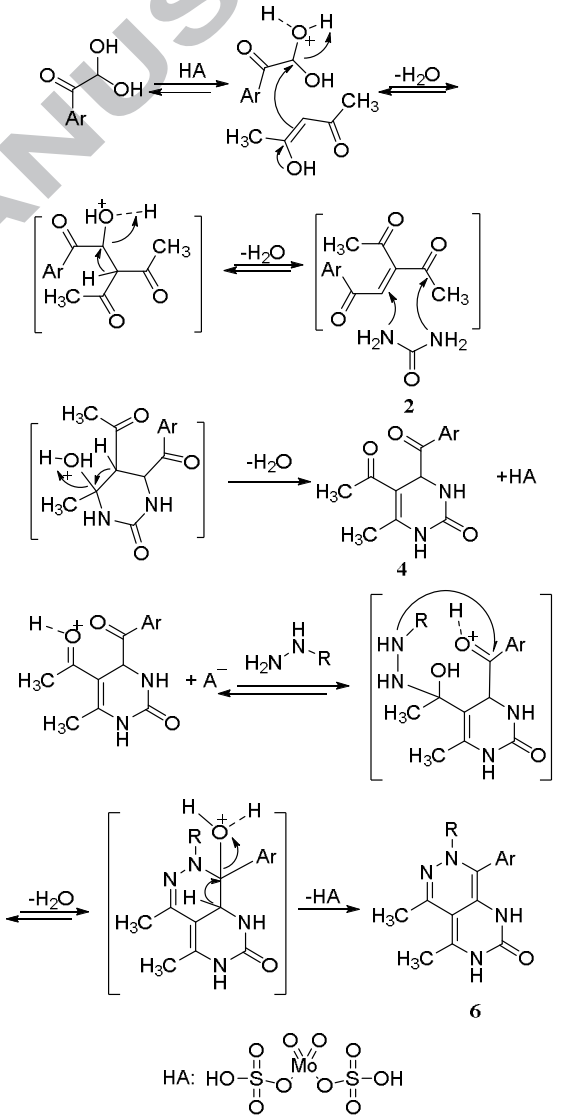
[a] Isolated yield.

An attempt to prepare compounds **6** in a one-pot process proved unsuccessful.

Table 2. Synthesis of pyrimido[4,5-*d*]pyridazines using MSA under solvent-free conditions.

Entry	Substrate	Product	Yield[a] (%)	Time (min)	Mp (ºC)
1	**4a**	 **6a**	78	60	308-310
2	**4a**	 **6b**	84	60	313-315
3	**4b**	 **6c**	83	60	224-226
4	**4e**	 **6d**	80	65	275-277
5	**4d**	 **6e**	88	50	212-214
6	**4c**	 **6f**	85	90	290-292
7	**4e**	 **6g**	79	65	258-260
8	**4b**	 **6h**	77	60	215-217

[a] Isolated yield.



Scheme 2. Suggested mechanism for the synthesis of dihydropyrimidinones and pyrimidopyridazines using MSA.

Additionally, the activity of the MSA was investigated in the synthesis of **6a** over three runs, during which a small appreciable loss was observed in the catalytic activity (Figure 1).

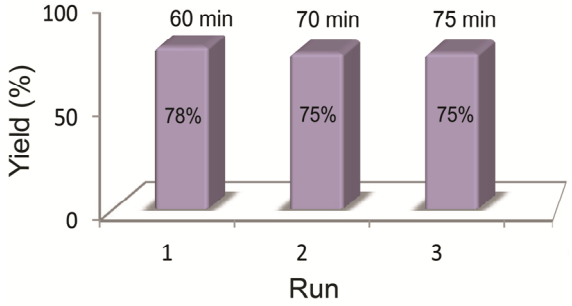


Figure 1. Recyclability of the MSA catalyst in the synthesis of **6a** over three runs.

In summary, we have shown that the three-component reaction of aryl glyoxals, urea, and acetylacetone catalyzed by molybdate sulfuric acid provides a simple one-pot entry for the synthesis of functionalized aryloyl-3,4-dihydropyrimidinones. Moreover, the aryloyl-3,4-dihydropyrimidinone derivatives undergo condensation with hydrazines to produce novel pyrimido[4,5-*d*]pyridazines. The simple operation and work-up procedure, compatibility with green chemistry principles, and high yields of products are notable features of this work. The presence of transformable functionalities in the products makes them potentially valuable substrates for further synthetic manipulations.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at …

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18. *Preparation of 5-acetyl-4-(aryloyl)-3,4-dihydropyrimidinones* (**4**)
A mixture of **1** (1 mmol), **2** (1.5 mmol), **3** (1 mmol), and MSA (0.05 mmol) was stirred and heated at 80 °C in a preheated oil bath for the appropriate amount of time. After completion of the reaction as indicated by TLC (EtOAc/hexane, 1:4), the mixture was cooled to room temperature, then crystallized from EtOH to afford the pure product **4**. The catalyst was separated by filtration and washed with Et_2O, dried at 70 °C for 45 min, and reused in another reaction.
5-Acetyl-4-(benzoyl)-6-methyl-3,4-dihydropyrimidinone (**4a**). Light yellow solid, IR (KBr): 3057, 1720, 1648, 1591, 1448, 1027 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ= 10.61 (s, 1H), 10.10 (s, 1H), 7.35 (d, 4H, *J* = 5.6 Hz), 7.20 (s, 1H), 5.55 (s, 1H), 1.94 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ= 193.15, 183.00, 153.88, 129.96, 128.79, 126.50, 124.11, 119.60, 112.66, 103.85, 57.38, 23.25; Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.31; H, 5.40; N, 10.73.
19. *Preparation of pyrimidopyridazines* (**6**).
A mixture of **4** (1 mmol), **5** (1 mmol) and MSA (0.05 mmol) was stirred and heated at 80 °C in a preheated oil bath for the appropriate amount of time. After completion of the reaction as indicated by TLC (EtOAc/hexane, 1:4), the mixture was dissolved in hot EtOH and the catalyst was separated by filtration. The solvent was removed under vacuum and the product was purified by crystallization from EtOH. The catalyst was washed with Et_2O, dried at 70 °C for 45 min, and reused in another reaction.
4,5-Dimethyl-7,8-diphenylpyrimido[4,5-*d*]pyridazin-2(1*H*,3*H*,7*H*)-one (**6b**). Light yellow solid, IR (KBr): 3450, 3030, 2995, 2990, 2890, 1690, 1650, 1490, 1100 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ= 10.64 (s, 1H), 10.23 (s, 1H), 7.55-7.50 (m, 4H), 7.43-7.36 (m, 1H), 7.31-7.27 (m, 4H), 7.18-7.15 (m, 1H), 2.08 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ= 154.72, 148.09, 139.75, 138.80, 130.90, 129.72, 129.05, 129.05, 127.85, 126.69, 124.81, 124.56, 119.31, 110.78, 110.76, 12.72, 11.97; Anal. Calcd. for $C_{20}H_{18}N_4O$: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.95; H, 5.36; N, 16.80.