Keggin and Dawson-type polyoxometalates as efficient catalysts for the synthesis of 3,4-dihydropyrimidinones: experimental and theoretical studies

Liza Saher, Malika Makhloufi-Chebli, Leila Dermeche, Baya Boutemeur-Khedis, Cherifa Rabia, Artur M.S. Silva, Maamar Hamdi

PII: S0040-4039(16)30186-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.02.077
Reference: TETL 47352

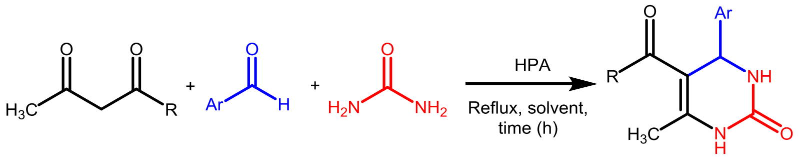
To appear in: *Tetrahedron Letters*

Received Date: 5 January 2016
Revised Date: 16 February 2016
Accepted Date: 19 February 2016

Please cite this article as: Saher, L., Makhloufi-Chebli, M., Dermeche, L., Boutemeur-Khedis, B., Rabia, C., Silva, A.M.S., Hamdi, M., Keggin and Dawson-type polyoxometalates as efficient catalysts for the synthesis of 3,4-dihydropyrimidinones: experimental and theoretical studies, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.02.077

Keggin and Dawson-type polyoxometalates as efficient catalysts for the synthesis of 3,4-dihydropyrimidinones: experimental and theoretical studies

Liza Saher,[a,b] Malika Makhloufi-Chebli,[a,b] Leila Dermeche,[a,c] Baya Boutemeur-Khedis,[b] Cherifa Rabia,[c] Artur M. S. Silva[d,] and Maamar Hamdi[b,]**



3,4-Dihydropyrimidinones were synthesized by the Biginelli condensation using, using Keggin and Dawson type polyoxometalates as catalysts in acetonitrile and ethanol.

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Keggin and Dawson-type polyoxometalates as efficient catalysts for the synthesis of 3,4-dihydropyrimidinones: experimental and theoretical studies

Liza Saher,[a,b] Malika Makhloufi-Chebli,[a,b] Leila Dermeche,[a,c] Baya Boutemeur-Khedis,[b] Cherifa Rabia,[c] Artur M. S. Silva[d,]* and Maamar Hamdi[b,]*

[a]*Département de Chimie, Faculté des Sciences, Université Mouloud Mammeri, 15000, Tizi Ouzou, Algeria.*
[b]*Laboratoire de Chimie Organique Appliquée (Groupe Hétérocycles), Faculté de Chimie, Université des Sciences et de la Technologie Houari Boumediène, BP32, El-Alia 16111 Bab-Ezzouar, Alger, Algeria.*
[c]*Laboratoire de Chimie du Gaz Naturel, Faculté de Chimie, Université des Sciences et de la Technologie Houari Boumediène, BP 32, El-Alia, 16111 Bab-Ezzouar, Alger, Algeria.*
[d]*QOPNA, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Biginelli reaction
Dihydropyrimidinones
Polyoxometalates (POMs)
Multicomponent reactions (MCR)
Environmentally friendly processes

ABSTRACT

3,4-Dihydropyrimidinones were synthesized by a multicomponent condensation of an aldehyde, a β-keto ester and urea, in acetonitrile and ethanol using Keggin and Dawson type polyoxometalates as catalysts. Keggin heteropolyacid, $H_4SiMO_{12}O_{40,}$ is more efficient compared to Keggin and Dawson salts and to the Biginelli classical reaction conditions. It leads to good yields and short reaction times. Theoretical calculations let us to confirm the reaction mechanism.

1. **Introduction**[*]

Multicomponent reactions (MCRs) are of great importance in both organic and medicinal chemistry for various reasons.[1] They offer significant advantages compared to conventional synthesis. Thus, MCR condensations involve three or more compounds that react in a one-pot reaction to form a new product. The Biginelli reaction is one of the most important multicomponent reactions for the synthesis of dihydropyrimidinones, consisting in the acid-catalyzed cyclocondensation reaction of an aldehyde, a β-keto ester, and a urea (or thiourea).[2]

Over the past decade, dihydropyrimidin-2(1*H*)-ones (DHPMs) and derivatives have attracted considerable attention in organic and medicinal chemistry because of their pharmacological and therapeutic properties.[3] Certain derivatives have emerged due to their potential antiviral, antitumor, antibacterial and anti-inflammatory activities.[3-5] More recently, functionalized DHPMs are considered potent calcium channel blockers,[6] antihypertensive agents,[7] α-1a adrenergic antagonists[8] and neuropeptide Y (NPY) antagonists.[9]

The original Biginelli protocol for the DHMPs preparation consisted in heating a mixture of the three components (1 equiv of an aldehyde **1**, 1 equiv of a β-keto ester **2**, and 1.5 equiv of urea **3**), in ethanol with a catalytic amount of HCl.[2,4] This procedure leads in one-pot reaction to the desired DHMPs, but in low yields, particularly for substituted aromatic and aliphatic aldehydes.[7] This drawback led to modifications of the classical Biginelli's protocol in the development of multistep synthetic strategies involving Lewis acids, e.g. $BF_3.OEt_2$, polyphosphate esters, and reagents like $InCl_3$, $Mn(OAc)_3$, trimethylsilyltriflate, $LaCl_3.7H_2O$, $CeCl_3.7H_2O$, $LiClO_4$, $Yb(OTf)_3$, $ZrCl_4$ or $ZrOCl_2$ clays, among others.[8,10-24] However, many of these methods use longer reaction times, strong acidic conditions, and stoichiometric amounts of catalysts, and in addition are difficult to handle especially on a large scale.

The Keggin-type polyoxometalates are believed to have extensive prospects of application in synthetic chemistry. Their acidic and oxidizing properties are dependent of the composition and nature of components and can be modified according to the reaction needs. Moreover, they are easily to handle, non-volatile and non-explosive. Heteropolyacids (HPA) have been extensively studied as acid catalysts for many reactions in our laboratory,[25-27] and have also found industrial applications in several processes.[28] Herein we will report on the synthesis of DHPMs by the Biginelli reaction, in the presence of an acid

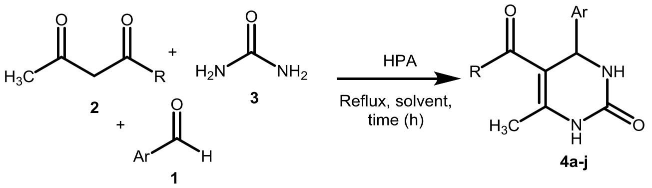
---

[*] Corresponding author. Tel.: +351 234370714 / +21 321 508 581; fax: +351 234370084. Email address: artur.silva@ua.pt (A.M.S. Silva) prhamdi@gmail.com (M. Hamdi).

catalyst of Keggin-type ($H_4SiMo_{12}O_{40}$) and of Dawson-type (α-$K_6P_2W_{18}O_{62}$, β-$(NH_4)_6P_2W_{18}O_{62}$, $K_6P_2W_{12}Mo_6O_{62}$) and in the presence of a series of Keggin-type phosphomolybdates ($H_3PMo_{12}0_{40}$, $H_4PMo_{11}VO_{40}$, $K_3HPMo_{11}VO_{40}$ and $(NH_4)_3PMo_{12}O_{40}$).

2. Results and discussion

Biginelli protocol was carried out using two solvents EtOH (polar protic) and MeCN (polar aprotic) and HPA catalysts under reflux conditions (Scheme 1). The condensation of methyl/ethyl acetoacetate, benzaldehyde and urea in refluxing ethanol (or acetonitrile), for 1.5 h in the presence of $H_4SiMo_{12}O_{40}$ catalyst (5 mol %), yielded various 3,4-dihydropyrimidin-2(1*H*)-ones **4a-j** in moderate to good yield (52-82%) (Table 1). Higher yields were obtained in the case of using aldehydes with electron-withdrawing **4i,j** and electron-donating **4d,e** substituents (Entries 4, 5, 9 and 10) and also using acetonitrile as the solvent. These results show that this method using $H_4SiMo_{12}O_{40}$ as the catalyst is effective and permit an improvement in the classical Biginelli's methodology.



4a Ar = C_6H_5, R = OMe, **4b** Ar = 4-OHC_6H_4, R = OMe, **4c** Ar = 4-ClC_6H**4**, R = OMe **4d** Ar = 4-$NO_2C_6H_4$, R = OMe, **4e** Ar = 4-$OCH_3C_6H_4$, R = OMe, **4f** Ar = C_6H_5, R = OEt **4g** Ar = 4-OHC_6H_4, R = OEt, **4h** Ar = 4-ClC_6H_4, R = OEt, **4i** Ar = 4-$NO_2C_6H_4$, R = OEt **4j** Ar = 4-$OCH_3C_6H_4$, R = OEt.

Scheme 1. Synthesis of various substituted 3,4-dihydropyrimidin-2(1*H*)-ones using heteropolyacid catalyst, using refluxing EtOH or CH_3CN.

Table 1. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones **4a-j** (structural characterisation at SI) using $H_4SiMo_{12}O_{40}$ (5 mol%) heteropolyacid as catalyst, under refluxing ethanol or MeCN.

Entry	Compound (solvent)	Ar	R	Yield (%)	Mp (°C) (Mp)^{Lit}
1	**4a** (EtOH) (MeCN)	C_6H_5	OMe	52 64	207-209 (209-211)[32]
2	**4b** (EtOH) (MeCN)	4-OHC_6H_4	OMe	70 76	238-240 -
3	**4c** (EtOH) (MeCN)	4-ClC_6H_5	OMe	73 77	201-203 (204-207)[32]
4	**4d** (EtOH) (MeCN)	4-$NO_2C_6H_4$	OMe	78 80	233-236 (236-238)[32]
5	**4e** (EtOH) (MeCN)	4-$OCH_3C_6H_3$	OMe	74 76	194-195 (192-194)[32]
6	**4f** (EtOH) (MeCN)	C_6H_5	OEt	60 65	203-205 (202-204)[30]
7	**4g** (EtOH) (MeCN)	4-OHC_6H_4	OEt	63 70	225-228 (228-230)[31]
8	**4h** (EtOH) (MeCN)	4-ClC_6H_5	OEt	65 68	210-212 (209-211)[31]
9	**4i** (EtOH) (MeCN)	4-$NO_2C_6H_4$	OEt	79 82	207-209 (209-212)[31]
10	**4j** (EtOH) (MeCN)	4-$OCH_3C_6H_3$	OEt	69 75	200-202 (199-202)[31]

[a] Isolated yields. [b] All the compounds are known and were characterized by NMR and IR spectroscopy and mass spectrometry.

In order to evaluate the effect of the catalyst the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones **4a-j** was also performed with $H_3PMo_{12}O_{40}$. In this case the highest yields were obtained in MeCN and using electron-withdrawing **4i,j** and electron-donating **4d,e** substituents (Table 2, entries 4, 5, 9 and 10). However, these results were lower than those obtained with $H_4SiMo_{12}O_{40}$. The difference in the obtained yields are more pronounced (up to 10%) in the case of other substituents, showing that $H_4SiMo_{12}O_{40}$ is more active than $H_3PMo_{12}O_{40}$ (Table 2). This catalytic behaviour could be explained by the number of protons existing in $SiMo_{12}O_{40}$ ($4H^+$) that is greater than that of $PMo_{12}O_{40}$ ($3H^+$) and not by the acidity strength. In the Keggin-type heteropolyacid, all protons are equivalent and have the same strength unlike conventional acids (H_2SO_4, H_3PO_4).

Table 2. Synthesis of DHPMs **4a-j** using $H_3PMo_{12}O_{40}$ (5 mol%) as catalyst, under refluxing ethanol or MeCN.

Entry	Product	Yield (%)	
		EtOH	MeCN
1	**4a**	51	61
2	**4b**	61	65
3	**4c**	62	66
4	**4d**	75	77
5	**4e**	70	72
6	**4f**	58	59
7	**4g**	62	68
8	**4h**	61	68
9	**4i**	77	78
10	**4j**	67	70

All the aforementioned reactions delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing both, electron-donating and electron-withdrawing substituents. Substrates with electron-withdrawing groups gave relatively higher yields (Table 1 and 2), and this fact was confirmed by theoretical calculations using the PM6 semi-empirical Hamiltonian method,[29] which proved to give useful evidence for the yields by estimating the Mulliken charges. The results show that the aldehyde carbon (CHO) is more positive in both solvents when the substituent is an electron-withdrawing group (Table 3). Hence the ranking of increasing reactivity of the aldehyde carbonyl group are as follows: Ph < 4-ClPh < 4-OHPh < 4-OCH_3Ph) < 4-NO_2Ph. Therefore the obtained yields have varied in the same direction.

Table 3: Carbon Mulliken charge of the aldehyde group in the two different solvents.

Aldehyde	Substituent R	Charge of CHO	
		MeCN	EtOH
4-NO_2PhCHO	4-NO_2	0.192	0.192
PhCHO	H	-0.039	-0.039
4-ClPhCHO	4-Cl	-0.019	-0.019
4-OHPhCHO	4-OH	0.041	0.041
4-OCH_3PhCHO	4-OCH_3	0.095	0.095

In order to evaluate the effect of other catalysts the synthesis of **4i** was also carried out in MeCN under the same conditions in the presence of $K_3HPMo_{11}VO_{40}$, $H_4PMo_{11}VO_{40}$ and $(NH_4)_3PMo_{12}O_{40}$ (5mol %) (Table 4). The results evidenced the efficiency (82%) of the $H_4SiMo_{12}O_{40}$ catalyst compared to the phosphomolybdate-based catalysts $H_3PMo_{12}O_{40}$ and $H_4PMo_{11}VO_{40}$ (78 and 56%, respectively). $K_3HPMo_{11}VO_{40}$ and $(NH_4)_3PMo_{12}O_{40}$ salts were found inactive toward **4i** formation. These results show that the synthesis of DHPM **4i** requires a strong medium acidity.

Table 4. Synthesis of **4i** as function of POM composition.

Catalyst (5%mol)	Yield %
$H_3PMo_{12}O_{40}$	78
$H_4SiMo_{12}O_{40}$	**82**
$H_4PMo_{11}VO_{40}$	56
$K_3HPMo_{11}VO_{40}$	< 10
$(NH_4)_3PMo_{12}O_{40}$	Traces

We have also evaluated the effect of the catalyst amount (2-8 mol %) on the synthesis of DHPMs **4a** (EtOH) and **4j** (MeCN) using $H_4SiMo_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ (Table 5). In the presence of $H_4SiMo_{12}O_{40}$, the yields of **4a** and **4j** increase from 18 to 74% and from 25 to 78% respectively, with the increase of catalyst from 2 to 8 mol%, unlike to $H_3PMo_{12}O_{40}$ where the highest yields towards **4a** (51%) and **4j** (70%) were obtained with an amount of 5 mol% and ~~decreases~~ with an amount of 8 mol%, which is probably due to the oxidizing power of $H_3PMo_{12}O_{40}$ that is higher than that of $H_4SiMo_{12}O_{40}$.

Table 5. Effect of the amount of catalysts on the synthesis of DHPMs **4a** (EtOH) and **4j** (MeCN).

	Yields (%) at 2%mol		Yields (%) at 5%mo		Yields (%) at 8%mol	
	$H_3PMo_{12}O_{40}$	$H_4SiMo_{12}O_{40}$	$H_3PMo_{12}O_{40}$	$H_4SiMo_{12}O_{40}$	$H_3PMo_{12}O_{40}$	$H_4SiMo_{12}O_{40}$
4a EtOH	12	18	51	52	**24**	**74**
4j MeCN	21	25	70	75	**50**	**78**

The influence of stoichiometric amounts of the reactants on the synthesis of **4j** was also examined; being the reaction carried in reflux MeCN and using $H_3PMo_{12}O_{40}$ as the catalyst (5 mol%) (Table 6). An excess of ethyl acetoacetate (EtAcOAc) does not affect the yield, while an aldehyde excess increases the yield of **4j** in 12%.

Table 6. Effect of the reagents amount on the yields of DHPM **4j**.

Reagents amounts	Yield (%)
1 mmol 4-$OCH_3C_6H_4CHO$ + 1 mmol EtAcOAc + 1.5 mmol urea	70
1 mmol 4-$OCH_3C_6H_4CHO$ + 1.5 mmol EtAcOAc + 1.5 mmol urea	69
1.5 mmol 4-$OCH_3C_6H_4CHO$ + 1 mmol EtAcOAc + 1.5 mmol urea	82

The catalytic effect of tungsten-based Dawson polyoxometalates (α-$K_6P_2W_{18}O_{62}$, β-$(NH_4)_6P_2W_{18}O_{62}$, $K_6P_2W_{12}Mo_6O_{62}$), on the synthesis of **4j** in refluxing MeCN for 1.5 h [4-nitrobenzaldehyde (1.5 mmol), ethyl acetoacetate (1 mmol) and urea (1.5 mmol)] was also studied (Table 7). The experimental results show that α-$K_6P_2W_{18}O_{62}$, β-$(NH_4)_6P_2W_{18}O_{62}$ and $K_6P_2W_{12}Mo_6O_{62}$ are much less efficient compared to Keggin POMs. We found that the yields are too low because the Dawson-type salts does not present the required Bronsted acidity [such as the case of $(NH_4)_3PMo_{12}O_{40}$], which plays a major role in this type of reaction as opposed to its presence in Keggin-type catalysts giving them a greater advantage.

The mechanism of this reaction was studied by several researchers,[33-45] and each of them gave arguments for the formation of an intermediate from which DHPMs are formed. In order to explain the formation of the DHPMs, we have calculated the charges of the electrophilic and nucleophilic sites of the reagents via theoretical calculations using the PM6 semi-empirical Hamiltonian method to identify the entities that react first and deduced the most likely intermediate (Figure 1 reports the charges of each atom that participate in the reaction).

Table 7. Synthesis of **4i** (yield, %) using Dawson type POMs α-$K_6P_2W_{18}O_{62}$, β-$(NH_4)_6P_2W_{18}O_{62}$, $K_6P_2W_{12}Mo_6O_{62}$ as catalysts.

Catalyst	5%mol	8%mol
α-$K_6P_2W_{18}O_{62}$	20	30
β-$(NH_4)_6P_2W_{18}O_{62}$	35	60
$K_6P_2W_{12}Mo_6O_{62}$	17	27

In our previous work,[46] we have shown that β-diketones can exist in a tautomeric equilibrium, being the diketo form more stable in polar solvents against the keto-enol form that is more stable in non-polar solvents. Here we have chosen two polar solvents, being one protic (EtOH) and the other aprotic (MeCN). The protic solvent can replace the hydrogen of the enol function by a hydrogen bond with the β-diketone which can give the keto enol form, unlike in acetonitrile diketone form is more abundant.

The calculations of the atom loads of each reagent in both solvents show firstly that the urea nitrogen atoms do not change much in both EtOH and MeCN solvents, being slightly more negative in MeCN than in EtOH, and that the carbon of ethyl acetoacetate of the diketo form is more positive than in the keto-enol form in both solvents which increases the reactivity and the yield in MeCN (Figure 1).

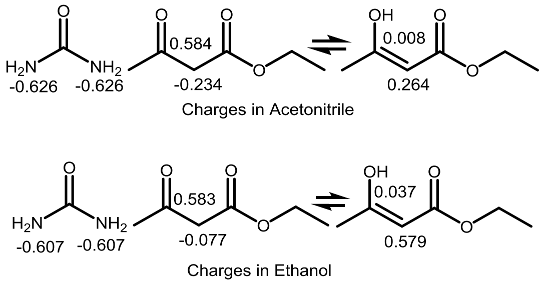
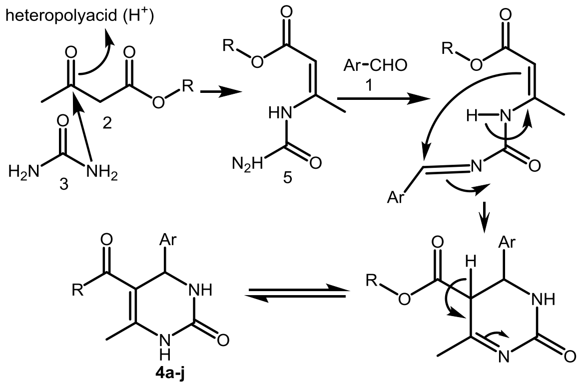


Figure 1. Charges of urea and ethyl acetoacetate in ethanol and acetonitrile using the Gaussion calculations.

On the other hand, the ketone carbon of ethyl acetoacetate in the diketo form is more positive (Figure 1) than the carbon of the aldehyde function in both solvents (Table 2), suggesting that the reactivity of urea **3** with methyl/ethyl acetoacetate **2** is the first step of the reaction, then intermediate **5** reacts with the aldehydes **1** to give 3,4-dihydropyrimidinones **4a-j**, confirming the mechanism proposed by Cepanec[41] and Litvic,[45] thus opposing to that proposed by Folkers and Johnson[33] and Kappe.[38]



Scheme 2. Proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones **4a-j** using heteropolyacids as catalysts.

3. Conclusion

Keggin-type polyoxometalates (phospho and silicomolybdic based HPAs) in an amount of 5 mol% have shown to be excellent acid catalysts for the one-pot synthesis of 3,4-dihydropyrimidinones in good yields, using an excess of aldehyde. The theoretical calculations have confirmed the mechanism of the reaction including the formation of the so called 'ureido-crotonate'. Tungsten-based Dawson POMs α-$K_6P_2W_{18}O_{62}$, β-$K_6P_2W_{18}O_{62}$ and $K_6P_2W_{12}Mo_6O_{62}$, in an amount of 5-8 mol% are less acidic and give lower yields than the Keggin-type POMs.

4. Experimental

4.1. Materials and Method

Melting points were determined on a Stuart scientific SPM3 apparatus fitted with a microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solutions on Bruker Avance 300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) spectrometer. Chemical shifts are reported in ppm (δ) using TMS as internal reference and coupling constants (J) are given in Hz. ^{13}C assignments were made using NOESY, HSQC, and HMBC (delays for one bond and long-range $J_{C/H}$ couplings were optimized for 145 and 7 Hz, respectively) experiments. Mass spectra are obtained with ESI$^+$. Positive-ion ESI mass spectra were acquired using a Q-TOF 2 instrument [diluting 1 μL of the sample chloroform solution (~10^{-5} M) in 200 μL of 0.1% trifluoroacetic acid/methanol solution. Nitrogen was used as the nebulizer gas and argon as the collision gas. The needle voltage was set at 3000 V, with the ion source at 80°C and desolvation temperature at 150°C. Cone voltage was 35 V].

4.2. Synthesis of Polyoxometalates

Pure Keggin-type heteropolyacids $H_3PMo_{12}O_{40}$, $H_4PMo_{11}VO_{40}$ and $H_4SiMo_{12}O_{40}$ were prepared according to the classic methods [47-49]. $(NH_4)_3PMo_{12}O_{40}$ was precipitated at pH < 1 as described by Cavani et al.[50] $K_6P_2W_{18}O_{62}$ and $(NH_4)_6P_2W_{18}O_{62}$ Dawson-type heteropoly-salts were synthesized according to the literature.[51] Mixed polyoxometalate $K_6P_2Mo_6W_{12}O_{62}$ was obtained from the hexavacant anion $[H_2P_2W_{12}O_{56}]^{12-}$ according to the method described by Contant et al.[52]

4.3. General procedure for the synthesis of 3,4-dihydropyrimidinones

In the presence of POM, the reaction of methyl/ethyl acetoacetate **1** (1 mmol), aldehydes **2** (1 mmol) and urea **3** (1.5 mmol) were carried out in refluxing MeCN (or ethanol) (10 mL) for 1.5 h. After the reaction was completed, as indicated by TLC analysis, the solvent was evaporated, the residue was dried and washed with water and the resulting solid was treated with hot ethanol and filtered again. The filtrate was concentrated to afford the recrystallized product. The products were characterized by IR, ^{1}H and ^{13}C NMR spectral data, mass spectrometry and by comparison with melting points of the reported compounds.

Acknowledgments

Thanks are due to University of Aveiro, FCT/MEC for the financial support to the QOPNA research Unit (FCT UID/QUI/00062/2013), through national funds and where applicable co-financed by the FEDER, within the PT2020 Partnership Agreement, and also to the Portuguese NMR Network. We thank Cristina Barros and Hilário Tavares (Department of Chemistry, University of Aveiro, 3810-193, Aveiro, Portugal) for performing the mass and NMR spectra.

Supplementary Material

Experimental procedures and structural characterization of 3,4-dihydropyrimidin-2(1*H*)-ones **4a-4j**.

References and notes

1. Passerini three-component and Ugi four-component condensations are the most popular among many other reactions for their wide scope and synthetic utility. For reviews, see: (a) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321-3329. (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168-3210. (c) Raman, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, **44**, 1602-1643.
2. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360-413.
3. Aslam, M.; Verma, S. *Int. J. ChemTech. Res.* **2012**, *4*, 109-111.
4. Nevagi, R. J.; Narkhede, H. I. *Der Pharma Chem.*, **2014**, *6*, 135-139.
5. Kumar, P. S.; Idhayadhullal. A.; Abdul-Nasser, A. J.; Selvin, J. *J. Serb. Chem. Soc.* **2011**; *76*, 1-11.
6. Lloyd, J.; Finlay, H. J.; Vacarro, W.; Hyunh, T.; Kover, A.; Bhandaru, R.; Yan, L.; Atwal, K.; Conder, M. L.; Jenkins-West, T.; Shi, H.; Huang, C.; Li, D.; Sun, H.; Levesque, P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1436-1439.
7. (a) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, 34, 806-811. (b) Grover, G. J.; Dzwomczyk, S.; McMullen, D. M.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J. *J. Cardiovasc. Pharmacol.* **1995**, 26, 289-294. (c) Zorkun, I. S.; Sarac, S.; Celebib, S.; Erolb, K. *Bioorg. Med. Chem.* **2006**, 14, 8582-8589. (d) Sehon, C. A.; Wang, G. Z.; Viet, A. Q.; Goodman, K. B.; Dowdell, S. E.; Elkins, P. A.; Semus, S. F.; Evans, C.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Bentley, R. *J. Med. Chem.* **2008**, *51*, 6631-6634. (e) Chikhale, R. V.; Bhole, R. P.; Khedekar, P. B.; Bhusari, K. P. *Eur. J. Med. Chem.* **2009**, *44*, 3645-3653. (f) Alam, O.; Khan, S. A.; Siddiqui, N.; Ahsan, W.; Verma, S. P.; Gilani, S. J. *Eur. J. Med. Chem.* **2010**, *45*, 5113-5119.
8. (a) Silder, D. R.; Larsen, R. D.; Chartrain, M.; Ikemote, N.; Roerber, C. M.; Taylor, C. S.; Li, W.; Bills, G. F. *PCT Int. WO* **1999**/07695. (b) Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803-2816.
9. Bruce, M. A.; Pointdexter, G. S.; Johnson, G. *PCT Int. Appl. WO* **1998**/33791.
10. (a) Bose, D. S.; Sudharshan, M.; Chavhan, S. W. *Arkivoc* **2005**, *iii*, 228-236. (b) Hajelsiddig, T. T. H.; Saeed, A. E. M. *Int. J. Pharm. Sci. Res.* **2015**, *6*, 2191-2196.
11. Russowsky, D.; Lopes, F. A.; da Silva, V. S. S.; Canto, K. F. S.; Montes D'Oca, M. G.; Godoi, M. N. *J. Braz. Chem. Soc.* **2004**, 15, 165-169.
12. Reddy, Y. T.; Rajitha, B.; Reddy, P. N.; Kumar, B. S.; Rao, V. P. *Synth. Commun.* **2004**, *34*, 3821-3825.
13. Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 3305-3308.
14. Lu, J.; Bai, Y. *Synthesis* **2002**, 466-470.
15. Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1341-1345.
16. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864-3868, and references cited therein.
17. Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, 63, 3454-3457.
18. Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, 65, 6270-6272.
19. Reddy, C. V.; Mahesh, M.; Raju, P. V. V. K.; Babu, T. R.; Reddy, V. V. N. *Tetrahedron Lett.* **2002**, *43*, 2657-2659.
20. Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe, C. *Tetrahedron* **2002**, *58*, 4801-4807.
21. Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587-590.
22. Carlos, R. D.; Bernardi, D.; Kirsch, G. *Tetrahedron Lett.* **2007**, *48*, 5777–5780.
23. Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, 1799-1803.
24. Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Bodaghi-Fard, M. A. *Tetrahedron Lett.* **2003**, *44*, 2889-2891.
25. Ighilahriz, K.; Boutmeur, B.; Chami, F.; Rabia, C.; Hamdi, M.; Hamdi, S. M. *Molecules* **2008**, *13*, 779-789.
26. Hedidi, M.; Hamdi, S. M.; Mazari, T.; Boutemeur, B.; Rabia, C.; Chemat, F.; Hamdi, M. *Tetrahedron* **2006**, *62*, 5652-5655.
27. Bentarzi, Y.; Benadji, S.; Bennamane, N.; Rabia, C.; Nedjar-Kolli. *Res. J. Pharm., Biol. Chem. Sci.* **2013**, 1, 971-979.
28. (a) Okuhara, T.; Mizuno, N.; Misono, M. *Adv. Catal.* **1996**, 41, 113-252. (b) Kozhevnikov, I. V. *Chem. Rev.* **1998**, 98, 171-198. (c) Misono, M. *Chem. Commun.* **2001**, 1141-1152.
29. Dennington, R. D.; Keith, T. A.; Millam, J. M. *Gaaussian 09W and GausView 5.0.8. Semichem*, **2000–2008**.
30. Debache, A.; Boulcina, R.; Tafer, R.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Chin. J. Chem.* **2008**, *26*, 2112-2116.

31. Fazaeli, R.; Tangestaninejad, S.; Aliyan, H.; Moghadam, M. *Appl. Cat. A: Gen.* **2006**, *309*, 44-51.
32. Karade, H. N.; Sathe, M.; Kaushik**,** M. P. *Molecules* **2007**, *12*, 1341-1351.
33. Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55,* 3784-3791.
34. Sweet, F.; Fissekis, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 8741-8749.
35. O'Reilly, B. C.; Atwal, K. S. *Heterocycles.* **1987**, *26*, 1185-1188.
36. Atwal, K. S.; O'Reilly, B. C.; Gougoutas, J. Z.; Malley, M. F. *Heterocycles* **1987**, *26*, 1189-1192.
37. Atwal, K. S., Rovnyak, G. C., O'Reilly, B. C., Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898-5907.
38. Kappe, C. O. *J. Org. Chem.* **1997**, *62,* 7201-7204.
39. Saloutina, V. I.; Burgarta, Y. V.; Kuzuevaa, O. G.; Kappe, C. O.; Chupakhin, O. N. *J. Fluor. Chem.* **2000**, *103*, 17-23.
40. Saini, A.; Kumar, S.; Sandhu, J. S. *Indian J. Chem.* **2007**, *46B*, 1886-1889.
41. Cepanec, I.; Litvic, M.; Filipan-Litvic, M.; Grüngold, I. *Tetrahedron* **2007**, *63*, 11822-12827.
42. Ma, J. G.; Zhang, J. M.; Jiang, H. H.; Ma, W. Y.; Zhou, J. H. *Chin. Chem. Lett.* **2008**, *19*, 375-378.
43. De Souza, R. O. M. A.; da Penha, E. T.; Milagre, H. M. S.; Garden, S. J.; Esteves, P. M.; Eberlin, M. N.; Antunes, O. A. C. *Chem. Eur. J.* **2009**, *15*, 9799-9804.
44. Shen, Z-L.; Xu, X-P.; Ji, S-J. *J. Org. Chem.* **2010**, *75*, 1162-1167.
45. Litvic, M.; Vecenaj, I.; Ladisic, Z. M.; Lovric, M.; Vinkovic, V.; Litvic, M. F. *Tetrahedron* **2010**, *66*, 3463–3471.
46. Makhloufi-Chebli, M.; Hamdi, S. M.; Hamdi, M.; Rabahi, A.; Silva, A. M. S. *J. Mol. Liq.* **2013**, *181*, 89-96.
47. Sanchez, C.; Livage, L. P.; Fournier, M.; Jeannin, Y. J. *J. Am. Chem. Soc.* **1982**, *104*, 3194-3202.
48. Deltchef, C. R.; Fournier, M.; Franck, R.; Thouvenot R. *Inorg. Chem.* **1983**. *22*, 207-216.
49. Rabia, C.; Bettahar, M. M.; Launay, S.; Herve, G.; Fournier, M. *J. Chem. Phys.* **1995**, *92*, 1442-1456.
50. Cavani, F.; Mezzogori, R.; Pigamo, A.; Trifiro, F. *Surf. Chem. Catal.* **2000**, *3*, 523-531.
51. Randall, W. J.; Lyon, D. K.; Domaille, P. J.; Finke, R.G. *Inorg. Synth.* **1998**,*32*, 242-268.
52. Contant, R.; Abbessi, M.; Thouvenot, R.; Hervé, G. *Inorg. Chem.* **2004**, *43*, 3597-3604.

Highlights

- 3,4-Dihydropyrimidinones were synthesized by a multicomponent condensation reaction

- Keggin-type polyoxometalates (5 mol%) were excellent acid catalysts for synthesis

- The semi-empirical theoretical calculations have confirmed the reaction mechanism