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# One-pot synthesis of dihydropyrimidines *via* eco-friendly phosphorus derivatives catalysis.

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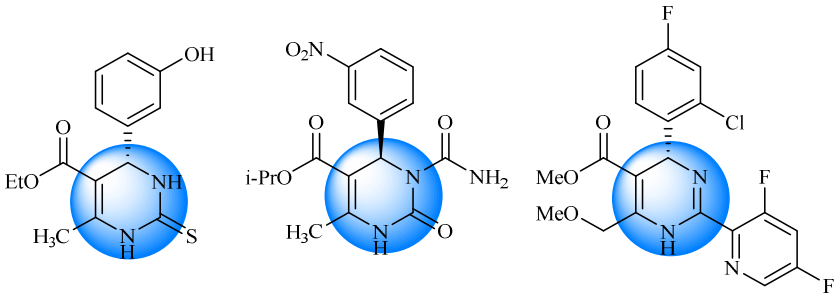
## Abstract

A straightforward, cost effective and eco-friendly protocol for the Biginelli reaction relying on the use of readily available hypophosphorous acid is presented. The methodology developed displays improvements compared to existing methods, is high-yielding, robust and was applied to a panel of dihydropyrimidines and thio-derivatives with various substituents. Related urea derivatives such as guanidines, benzimidazoles and benzothiazoles also reacted efficiently to afford more complex scaffolds. Thus, this rapid and convenient catalysis allows access to a wide diversity of structures including original biologically relevant heterocycles.

## Introduction

3,4-Dihydropyrimidin-2(1H)-one (DHPM) is a biologically relevant heterocycle with great interest thanks to its anticancer,[1] antifungal,[2] anti-hypertensive,[3] antimalarial,[4] anti-HIV[5] and anti-tubercular activities[6]. It is found in several drug candidates such as monastrol,[7] an effective non-tubulin-interacting mitosis inhibitor, SQ-32926,[8] a calcium channel antagonist with antihypertensive activity, or Bay 41-4109,[9] a potent human hepatitis B virus (HBV) inhibitor with an $IC_{50}$ of 53 nM (**Figure 1**).




**(*S*) Monastrol** **(*R*) SQ-32926** **(*S*) Bay 41-4109**

**Figure 1:** Examples of pharmacologically active DHPMs.

A straightforward way to produce the DHPM scaffold is the well-known Biginelli reaction.[10] This multicomponent reaction involves a one-pot cyclocondensation of ethyl acetoacetate, urea and an aromatic aldehyde. It follows the principles of diversity-oriented synthesis and is therefore useful to produce rapidly series of analogues with great structural diversity during drug discovery processes. The synthesis of DHPM derivatives is presently an active research area, efforts are currently dedicated to the development of new ecofriendly synthetic routes. Usual

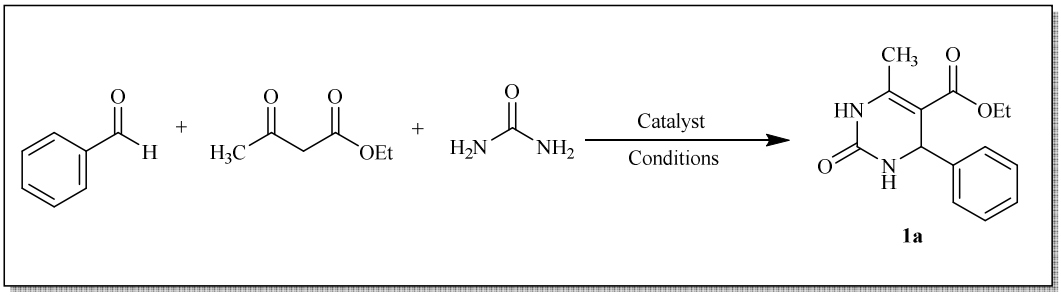
conditions for the Biginelli reaction are based on prolonged heating of the ternary mixture of reactants under strong Brønsted acidic conditions.[11,12] Other conditions have been reported for this reaction such as microwave-assisted transformations,[13,14] Mechanochemical conditions,[15,16] catalysis using adequate bases such as $K_2CO_3$,[17] Lewis acids such as $BF_3.Et_2O$,[18] lanthanum salts $LaCl_3$,[19] ionic liquids,[20,21] boric acid[22] or α-zirconium sulfophenylphosphonate.[23] Despite undeniable improvements, all these protocols still present drawbacks such as extended reaction times, high temperatures, use of hazardous chemicals or toxic solvents, high loadings of expensive heavy metal catalysts, or displaying low product yields.[24] One the other hand, sequential multistep strategies have been proposed to produce DHPM compounds with somewhat higher overall yields but lack the attractiveness of the one-pot procedure.[25] In this context, we found appealing to develop new conditions for the Biginelli reaction that overcome these drawbacks and will be closer to the precepts of green synthesis. Phosphorus derivatives particularly attracted our attention as they are widely available from phosphate, a natural resource almost inexhaustible (world resources of phosphate rock are more than 300 billion tons, with no imminent shortages according to USGS 2020).[26] Moreover, they have been recently proposed as efficient catalysts in several organic chemical processes such as the asymmetric hydrosilylation of alkenes,[27] or the production of 5-hydroxymethylfurfural.[28] Therefore, in continuation of our studies directed at the development of green processes,[29–34] we report here the screening of phosphorus derivatives for the catalysis of Biginelli reaction and their use to produce a panel of DHPM and related heterocycles under eco-friendly conditions.

## Results and discussion

Our interest first focused on common readily accessible phosphorus derivatives to test the catalytic activity for the Biginelli reaction. These derivatives were selected for their availability, their safety and eco-friendly features. They encompass synthesized organic derivatives, mineral acids, natural ores and recycled industrial waste (**Table 1**).

The catalytic activity was assayed on a model Biginelli reaction with benzaldehyde, ethyl acetoacetate and urea as substrates (**Table 1**). The catalyst loading was first set up at 20 mol% to evaluate the reactivity of various phosphorus derivates, compared to most efficient procedures described in the literature (**Table 1**, **entries 1-7**). Hypophosphorous acid was found to be the best reagent to promote this three-component reaction with 99% conversion after 6h in ethanol at reflux, and was therefore selected for further optimization. Decreasing the reaction time from 6h to 4h still retained high conversion (97%) whereas decreasing the amount of catalyst led to lower yields (**Table 1, entries 8-10**). Thus, the ratio of hypophosphorous acid was maintained at 20 mol% and several solvents and temperatures were assayed. Aqueous conditions proved clearely detrimental because of solubility issues. Acetonitrile or solvent-free conditions gave interesting results, even if they presented lower conversions than ethanol (**Table 1, entries 11-14**). Finally, decreasing the temperature to 50°C or 20°C led to a significant drop in the reaction rate (**Table 1, entries 15-16**).

**Table 1:** Screening and optimization of reaction conditions for the synthesis of dihydropyrimidinone **1a**




| Entry | Catalyst | Amount of catalyst | Solvent | Time | Temperature (°C) | Yields [a] (%) |
|---|---|---|---|---|---|---|
| **Reference 1** [35] | $H_3[PW_{12}O_{40}]$ | 0.1g | ethanol | 5h | 80 | 95 |
| **Reference 2** [23] | α-zirconium sulfophenylphosphonate | 12% | --- | 18h | 80 | 89 |
| **1** | **---** | --- | ethanol | 8h | 80 | 13 |
| **2** | phosphoric acid | 20% | ethanol | 6h | 80 | 91 |
| **3** | *N*-(phosphonomethyl)iminodiacetic acid hydrate | 20% | ethanol | 6h | 80 | 80 |
| **4** | 2-ethylhexylphosphate [b] | 20% | ethanol | 6h | 80 | 96 |
| **5** | hypophosphorous acid | 20% | ethanol | 4h, 6h | 80 | 97, 99 |
| **6** | phosphogypsum [c] | 20% | ethanol | 6h | 80 | 12 |
| **7** | apatite [d] | 20% | ethanol | 6h | 80 | 3 |
| **8** | hypophosphorous acid | 10% | ethanol | 6h | 80 | 81 |
| **9** | hypophosphorous acid | 5% | ethanol | 6h | 80 | 74 |
| **10** | hypophosphorous acid | 1% | ethanol | 6h | 80 | 60 |
| **11** | hypophosphorous acid | 20% | water | 6h | 80 | 28 |
| **12** | hypophosphorous acid | 20% | ethanol/water, 50/50 | 6h | 80 | 44 |
| **13** | hypophosphorous acid | 20% | acetonitrile | 6h | 80 | 93 |
| **14** | hypophosphorous acid | 20% | solvent-free | 6h | 80 | 85 |
| **15** | hypophosphorous acid | 20% | ethanol | 6h | 20 | 32 |
| **16** | hypophosphorous acid | 20% | ethanol | 6h | 50 | 77 |

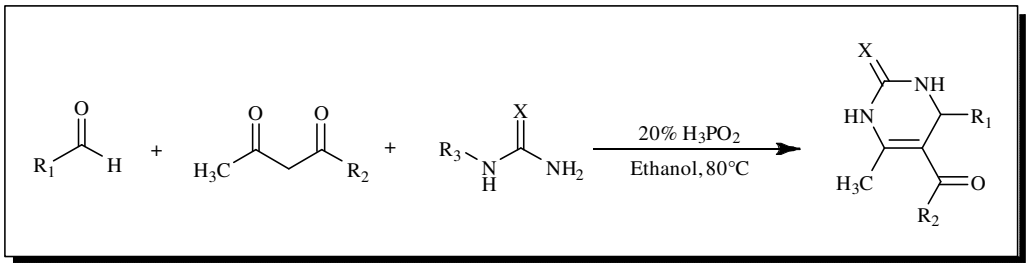
[a]: Conversion based on LCMS analyses at 280 nm. [b]: 2-ethylhexylphosphate (MPE) was synthesized by a procedure adapted from the literature.[36] [c]: by-product formed after the attack of phosphate rock with sulfuric acid (ore transformed in Jorf Al Asfar plant, Morocco).[d]: Natural phosphate from an ore extracted in Khouribga region (Morocco)

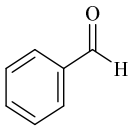
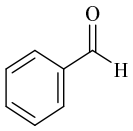
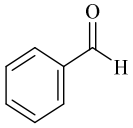
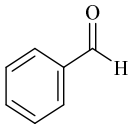
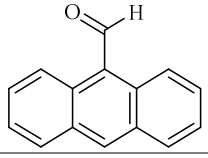
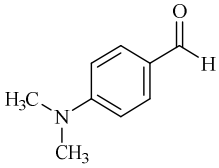
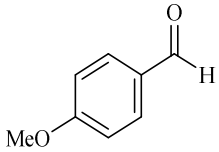
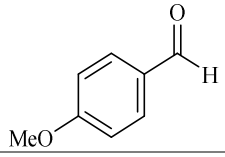
From a mechanistic point of view, the urea derivative reacts with the aldehyde to form an hemiaminal product. Hypophosphorous acid (pKa 1.2) is believed to protonate this hemiaminal, promoting its dehydration to an iminium intermediate, which subsequently reacts with ethyl acetoacetate. Final cyclodehydration provides the desired DHPM derivative (see below **Figure 2**).[37,38]

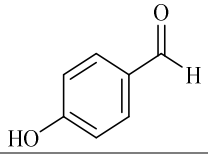
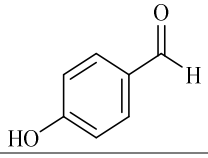
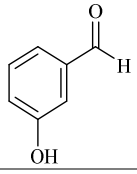
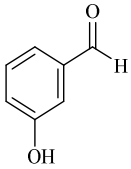
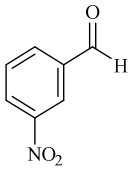
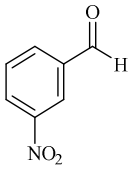
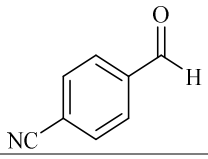
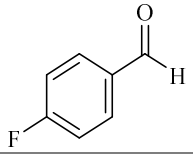
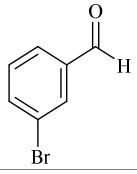
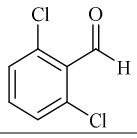
With these optimized conditions in hand (heating in ethanol at 80°C for 4h in the presence of 20% of hypophosphorous acid), the scope of the protocol was studied by reacting various (hetero)aromatic/aliphatic aldehydes, diketones and (thio)urea derivatives (**Table 2**). All compounds were recovered by simple filtration and

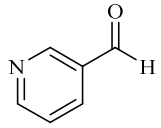
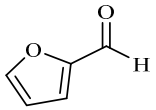
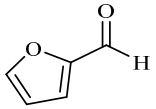
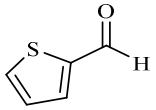
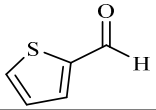
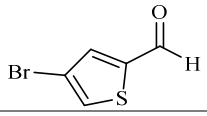
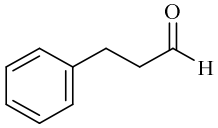
washing after ice-cooling of the reaction mixture and were purified by recrystallization. Under these conditions, model dihydropyrimidinone **1a** was obtained with 96% yield.

**Table 2:** Scope and limitations of the proposed conditions.[a] Synthesis of 3,4-dihydropyrimidin-2(1H)-(thi)ones **1a-y**




| Entry | $R_1$ | $R_2$ | $R_3$ | X | Product [b] | Yield [c] (%) |
|---|---|---|---|---|---|---|
| **1** |  | OEt | H | O | **1a** | 96 |
| **2** |  | Me | H | O | **1b** | 94 |
| **3** |  | Me | H | S | **1c** | 98 |
| **4** |  | OEt | Me | S | **1d** | 98 |
| **5** |  | OEt | H | O | **1e** | 93 |
| **6** |  | OEt | H | O | **1f** | 94 |
| **7** |  | OEt | H | O | **1g** | 97 |
| **8** |  | Me | H | O | **1h** | 98 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **9** |  | OEt | H | O | **1i** | 92 |
| **10** |  | Me | H | O | **1j** | 94 |
| **11** |  | OEt | H | O | **1k** | 98 |
| **12** |  | OEt | H | S | **1l** | 97 |
| **13** |  | OEt | H | O | **1m** | 97 |
| **14** |  | Me | H | O | **1n** | 96 |
| **15** |  | OEt | H | O | **1o** | 82 |
| **16** |  | OEt | H | O | **1p** | 91 |
| **17** |  | Me | H | O | **1q** | 94 |
| **18** |  | OEt | H | O | **1r** | 90 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **19** |  | OEt | H | O | **1s** | 89 |
| **20** |  | OEt | H | O | **1t** | 95 |
| **21** |  | OEt | H | S | **1u** | 92 |
| **22** |  | OEt | H | O | **1v** | 84 |
| **23** |  | OEt | H | S | **1w** | 79 |
| **24** |  | OEt | H | O | **1x** | 78 |
| **25** |  | OEt | H | O | **1y** | 92 |

[a] Reaction conditions: aldehyde (1 mmol), β-dicarbonyl derivative (1.2 mmol), urea derivative (1.2 mmol) for 6h at 80°C, [b]: All products were characterized by $^{1}H$ NMR, $^{13}C$ NMR and LC-MS compared with those reported in the literature, [c]: Isolated yields.

Derivatives bearing electron-donating groups, such as 4-dimehylamino, 4-methoxy, 4-hydroxy, and 3-hydroxy, respectively, at different positions on the ring reacted in efficient way with both ethyl acetoacetate and acetylacetone as $R_2$ and (thio)urea $R_3$ to produce the corresponding DHPMs **1f-l** in excellent isolated yields (**92–98%**) (**Table 2, entries 6-12**). A benzaldehyde derivative with an electron-accepting nitro or cyano group on the ring showed also a good reactivity to afford the products **1m-o** in good isolated yields ranging from **82%-97% (Table2, entries 13-15).** Benzaldehyde derivatives with halogen atoms at different positions on the aromatic ring (4-fluoro, 2,6-dichloro, and 3-bromo) also underwent reaction to form the corresponding products (**1p-r**) in good isolated yields that ranged from **91–94%** (**Table2, entries 16-18**). Heteroaromatic aldehydes, such as 3-pyridine-aldehyde, 2-furylaldehyde, thiophene-2-aldehyde and 4-bromo-thiophene-2-aldehyde led to the corresponding products with the same efficiency **78%-95%** (**Table 2, entries 19-24**). Remarkably, the aliphatic phenethylaldehyde were also converted to their DHPM products with 92% yield **(Table 2, entries 25**).

In summary, the developed protocol proved robust upon variation of the substituents on the benzaldehyde both in terms of electronic nature and position. Moreover, these optimized reaction conditions are suitable for heteroaromatic aldehydes as well as for aliphatic phenethylaldehyde that reacted with the same efficiency. The scope of the reaction proved also broad towards replacement of β-ketoester by 1,3-diketone or using substituted urea and thiourea derivatives. In all cases, high yields were achieved after a straightforward isolation and

purification procedure. All the synthesized compounds were fully characterized (see experimental part) and showed analytical data in accordance with the literature, except for **5**, **20** and **23** that represent new compounds.

To extend the scope of the present methodology, the synthesis of fused-dihydropyrimidinones and more complex heterocycles was attempted by extrapolating the urea reagent. We first tried the reaction with 2-aminobenzimidazole in view to obtain a 1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine tricyclic scaffold. The reaction could occur by condensation of 2-aminobenzimidazole and the aldehyde under hypophosphorous acid catalysis. Subsequent reaction with a 1,3-dicarbonyl compound and cyclodehydration should provide the desired heterocycle. The reaction was performed with five different (hetero)aromatic aldehydes allowing the formation of the corresponding 1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidines **2a-2e** with satisfactory yields, ranging from 61% to 92% (**Table 3**).

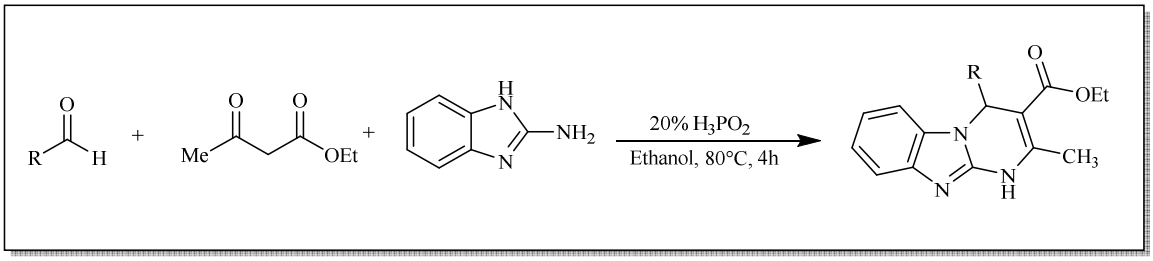



**Table 3:** Synthesis of 1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidines **2a-2e** by Biginelli type tricomponent reaction in the presence of hypophosphorous acid.

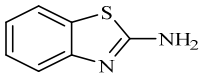
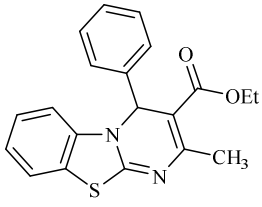
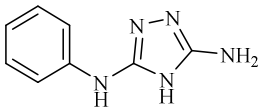
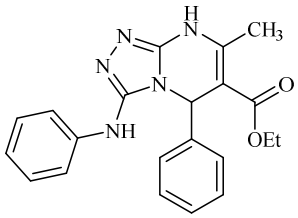
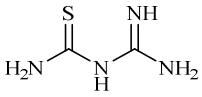
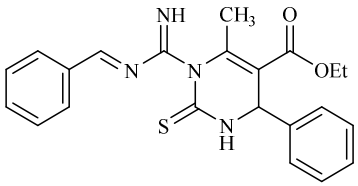
| Entry | R | Product [a] | Yield [b] (%) |
|---|---|---|---|
| **1** | $C_6H_4$ | **2a** | 70 |
| **2** | 4-OMe-$C_6H_4$ | **2b** | 84 |
| **3** | 3-Br-$C_6H_4$ | **2c** | 92 |
| **4** | 2-Thiophene | **2d** | 77 |
| **5** | 3-OH-$C_6H_4$ | **2e** | 61 |

[a]: All products were characterized by $^1$H NMR, $^{13}$C NMR and HR-MS / LC-MS, [b]: Isolated yields.

To further explore the efficiency of hypophosphorous acid to produce more complex scaffolds *via* the Biginelli reaction, the conditions developed were applied to other urea derivatives: 2-aminobenzothiazole, $N^3$-phenyl-4*H*-1,2,4-triazole-3,5-diamine and *N*-amidinothiourea (**Table 4**). The reaction proceeded smoothly with 2-aminobenzothiazole furnishing, after cyclocondensation, the desired 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine derivative **3** with 84% yield. Interestingly, the obtained product **3** showed a tautomeric dearomatisation behavior on the benzothiazole core, as already reported for 2-aminobenzothiazole derivatives linked to electron-

withdrawing groups.[39] The reaction also proceeded with $N^3$-phenyl-4*H*-1,2,4-triazole-3,5-diamine to provide 5,8-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidine analog **4** with 43% yield. Finally, these conditions were attempted with *N*-amidinothiourea as substrate to study the regioselectivity of the cyclocondensation. Indeed, two reaction products **6** and **6'** can be possibly formed (**Figure 2**). A full selectivity was obtained towards the cyclisation *via* the thiourea part, relative to the guanidine part. However, a second benzaldehyde condensation occurred on the terminal guanidine nitrogen of **6**, leading to the corresponding imine derivate **5** in 72% yield.

**Table 4**: Synthesis of complex heterocyclic systems by Biginelli-like reaction using urea analogues

| **$R_3$** | **Product** [a] | **Yield** [b] **(%)** |
|---|---|---|
|  |  **3** | 84 |
|  |  **4** | 43 |
|  |  **5** | 72 |

[a]: All products were characterized by $^1$H NMR, $^{13}$C NMR and HR-MS / LC-MS, [b]: Isolated yields.

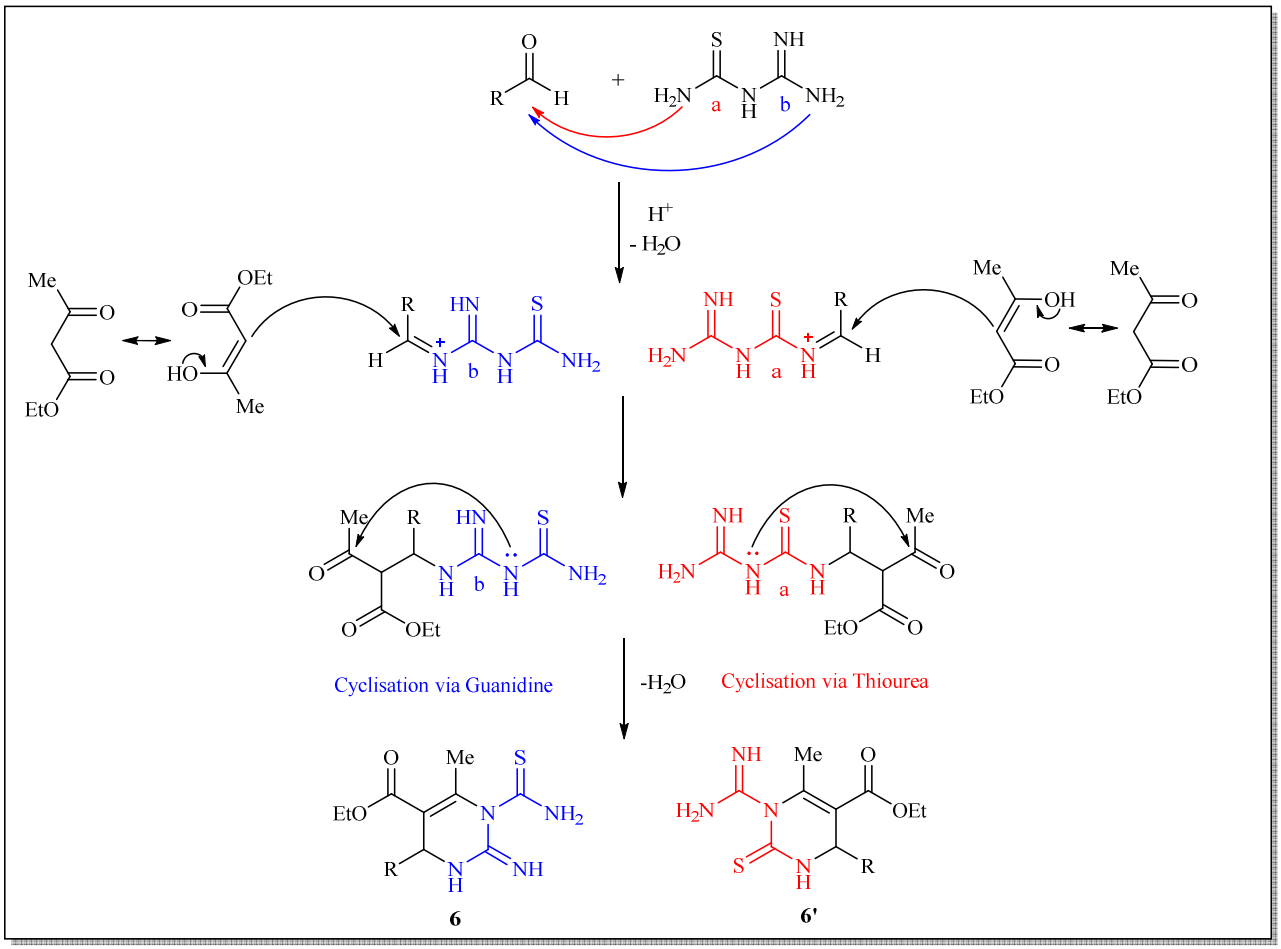



**Figure 2**: Reaction mechanism and possible regioisomer products for the three-component reaction with *N*-amidinothiourea

Ultimately, our hypophosphorous acid conditions successfully provided the desired heterocycles with all the substrates tested. From the synthesized compounds, **3** has already been described, obtained in the presence of TMGT (1,1,3,3-*N,N,N',N'*- tetramethylguanidinium trifluoroacetate) ionic liquid at 100°C for 5h with only 66% yield, [40] whereas **4** and **5** are new compounds. These experiments further underline the advantages of the use of $H_3PO_2$ as green catalyst to provide a broad scope of products with improved yields and shorter reaction times, while relying on environmentally benign procedure and easy workups.

Beyond the establishment of efficient conditions based on the use of readily available hypophosphorous acid, the developed methodology is particularly interesting to open access to complex heterocycles with biologically relevant structures. Indeed, the 1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine tricyclic scaffold presents a benzimidazole condensed ring system that has shown interesting anticancer activities against a panel of cancer cell lines and the 4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine core has demonstrated efficiency in antibacterial and antimycobacterial models.[41] Moreover, the new scaffolds **4** and **5** possess very interesting structural features to be evaluated for potential future applications in anticancer, inflammation and antibacterial models.

In summary, we developed an efficient hypophosphorous acid-based protocol for the Biginelli reaction, showing effectivity improvements compared to the existing methods, and advantages in the context of green chemistry as it is catalyzed by a readily available simple chemical: $H_3PO_2$, and does not require the use of toxic metals or solvents. Moreover, it displays a broad scope in terms of substrates, exemplified through the synthesis of 33 compounds DHPM, thio derivatives, as well as new bi- and tricyclic structures such as benzo[4,5]imidazo[1,2-*a*]-pyrimidine, 4H-pyrimido[2,1-*b*]benzothiazole and 5,8-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidine. Overall, the methodology presented allows a rapid, versatile and ecofriendly access to a great diversity of functionalized DHPMs and related structures with potential biological interest.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.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**Keywords***: Phosphate derivatives catalysis, Biginelli reaction, dihydropyrimidines, one-pot protocol, fused heterocycles*


## References


1. Kapoor TM, Mayer TU, Coughlin ML, Mitchison TJ. Probing spindle assembly mechanisms with monastrol, a small molecule inhibitor of the mitotic kinesin, Eg5. *J Cell Biol*. 2000;150(5):975-988.
2. Singh OM, Singh SJ, Devi MB, Devi LN, Singh NI, Lee S-G. Synthesis and in vitro evaluation of the antifungal activities of dihydropyrimidinones. *Bioorg Med Chem Lett*. 2008;18(24):6462-6467.
3. Rovnyak GC, Atwal KS, Hedberg A, et al. Dihydropyrimidine calcium channel blockers. 4. Basic 3-substituted-4-aryl-1, 4-dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents. *J Med Chem*. 1992;35(17):3254-3263.
4. October N, Watermeyer ND, Yardley V, Egan TJ, Ncokazi K, Chibale K. Reversed Chloroquines Based on the 3, 4-Dihydropyrimidin-2 (1H)-one Scaffold: Synthesis and Evaluation for Antimalarial, β-Haematin Inhibition, and Cytotoxic Activity. *ChemMedChem Chem Enabling Drug Discov*. 2008;3(11):1649-1653.
5. Fatima S, Sharma A, Saxena R, et al. One pot efficient diversity oriented synthesis of polyfunctional

styryl thiazolopyrimidines and their bio-evaluation as antimalarial and anti-HIV agents. *Eur J Med Chem*. 2012;55:195-204.

6. Desai NC, Trivedi AR, Khedkar VM. Preparation, biological evaluation and molecular docking study of imidazolyl dihydropyrimidines as potential Mycobacterium tuberculosis dihydrofolate reductase inhibitors. *Bioorg Med Chem Lett*. 2016;26(16):4030-4035.

7. Kaan HYK, Ulaganathan V, Rath O, et al. Structural basis for inhibition of Eg5 by dihydropyrimidines: stereoselectivity of antimitotic inhibitors enastron, dimethylenastron and fluorastrol. *J Med Chem*. 2010;53(15):5676-5683.

8. Atwal KS, Rovnyak GC, Kimball SD, et al. Dihydropyrimidine calcium channel blockers. II. 3-Substituted-4-aryl-1, 4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters as potent mimics of dihydropyridines. *J Med Chem*. 1990;33(9):2629-2635.

9. Wichmann J, Adam G, Kolczewski S, Mutel V, Woltering T. Structure-activity relationships of substituted 5H-thiazolo [3, 2-a] pyrimidines as group 2 metabotropic glutamate receptor antagonists. *Bioorg Med Chem Lett*. 1999;9(11):1573-1576.

10. Biginelli P. Ueber aldehyduramide des acetessigäthers. *Berichte der Dtsch Chem Gesellschaft*. 1891;24(1):1317-1319.

11. Biginelli P. Derivati aldeiduredici degli eteri acetile dossal-acetico. *Gazz Chim Ital*. 1893;23:360-416.

12. Xiao L, Wei Z, Wang Y. One-pot synthesis of 3,4-dihydropyrimidine-2(1H)-ones and their derivatives. *Gongye Cuihua*. 2013;21(12):72-75. doi:10.3969/j.issn.1008-1143.2013.12.015

13. Kappe CO, Kumar D, Varma RS. Microwave-assisted high-speed parallel synthesis of 4-aryl-3, 4-dihydropyrimidin-2 (1H)-ones using a solventless Biginelli condensation protocol. *Synthesis (Stuttg)*. 1999;1999(10):1799-1803.

14. Kuraitheerthakumaran A, Pazhamalai S, Gopalakrishnan M. Microwave-assisted multicomponent reaction for the synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones and their corresponding 2 (1H)-thiones using lanthanum oxide as a catalyst under solvent-free conditions. *Arab J Chem*. 2016;9:S461-S465.

15. Bose AK, Pednekar S, Ganguly SN, Chakraborty G, Manhas MS. A simplified green chemistry approach to the Biginelli reaction using 'Grindstone Chemistry.' *Tetrahedron Lett*. 2004;45(45):8351-8353.

16. Ould M'hamed M, Alshammari AG, Lemine OM. Green high-yielding one-pot approach to Biginelli reaction under catalyst-free and solvent-free ball milling conditions. *Appl Sci*. 2016;6(12):431.

17. Kamal Raj M, Rao HSP, Manjunatha SG, et al. A mechanistic investigation of Biginelli reaction under base catalysis. *Tetrahedron Lett*. 2011;52(28):3605-3609. doi:10.1016/j.tetlet.2011.05.011

18. Chaltin P, Debyser Z, De Maeyer M, et al. Pyrimidine derivatives as novel viral replication inhibitors and their preparation and use in the treatment of HIV infection. *PCT Int Appl*. 2011;(WO2011015641A1):189pp.

19. Lu J, Bai Y, Wang Z, Yang B, Ma H. One-pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones using lanthanum chloride as a catalyst. *Tetrahedron Lett*. 2000;41(47):9075-9078.

20. Freitas EF, Souza RY, Passos STA, Dias JA, Dias SCL, Neto BAD. Tuning the Biginelli reaction mechanism by the ionic liquid effect: the combined role of supported heteropolyacid derivatives and acidic strength. *RSC Adv*. 2019;9(46):27125-27135.

21. Zarchi MAK, Hamidi Z. Synthesis of [P 4-VP]-Fe 3 O 4 supported Brønsted acid ionic liquid and its application as a highly efficient heterogeneous and reusable nanocatalyst in the Biginelli reaction under solvent-free conditions. *React Kinet Mech Catal*. 2018;125(2):1023-1037.

22. Meshram HM, Kumar AS, Kumar GS, Swetha A, Reddy BC, Ramesh P. Boric acid promoted an efficient and practical synthesis of fused pyrimidines in aqueous media. *Der Pharma Chem*. 2012;4(3):956-960.

23. Rosati O, Curini M, Montanari F, Nocchetti M, Genovese S. α-zirconium sulfophenylphosphonate as a catalyst for the synthesis of 3, 4-dihydropyrimidin-2 (1H)-one derivatives under solvent free conditions. *Catal Letters*. 2011;141(6):850-853.

24. Oliver Kappe C. 100 years of the biginelli dihydropyrimidine synthesis. *Tetrahedron*. 1993;49(32):6937-6963. doi:https://doi.org/10.1016/S0040-4020(01)87971-0

25. O'REILLY BC, Atwal KS. Synthesis of substituted 1, 2, 3, 4-tetrahydro-6-methyl-2-oxo-5-pyrimidinecarboxylic acid esters: The Biginelli condensation revisited. *Heterocycles (Sendai)*. 1987;26(5):1185-1188.

26. Bernhardt D, Reilly I. Mineral commodity summaries 2020. *US Geol Surv*. Published online 2020.

27. Feng Z, Xianghua L, Wei L, Guojun D. Application of Pd-Monodentate Phosphorus Catalysts in the Asymmetric Hydrosilylation Reactions of Alkenes. *CHINESE J Org Chem*. 2017;37(10):2555-2568.

28. Souleymanou M, Delcroix D. Production of 5-hydroxymethylfurfural in the presence of organic phosphorus catalysts. *PCT Int Appl*. 2017;(WO2017016923A1):19pp.; Chemical Indexing Equivalent to 166:157077.

29. Tachallait H, Safir Filho M, Marzag H, et al. A straightforward and versatile FeCl 3 catalyzed Friedel–Crafts C-glycosylation process. Application to the synthesis of new functionalized C-nucleosides. *New J Chem*. 2019;43(14):5551-5558.

30. Marzag H, Robert G, Dufies M, Bougrin K, Auberger P, Benhida R. FeCl3-promoted and ultrasound-assisted synthesis of resveratrol O-derived glycoside analogs. *Ultrason Sonochem*. 2015;22:15-21.

31. Malnuit V, Duca M, Manout A, Bougrin K, Benhida R. Tandem azide-alkyne 1, 3-dipolar cycloaddition/electrophilic addition: A concise three-component route to 4, 5-disubstituted triazolyl-nucleosides. *Synlett*. 2009;2009(13):2123-2126.

32. Alaoui S, Driowya M, Demange L, Benhida R, Bougrin K. Ultrasound-assisted facile one-pot sequential synthesis of novel sulfonamide-isoxazoles using cerium (IV) ammonium nitrate (CAN) as an efficient oxidant in aqueous medium. *Ultrason Sonochem*. 2018;40:289-297.

33. Spadafora M, Mehiri M, Burger A, Benhida R. Friedel–Crafts and modified Vorbrüggen ribosylation. A short synthesis of aryl and heteroaryl-C-nucleosides. *Tetrahedron Lett*. 2008;49(25):3967-3971.

34. Botubol-Ares JM, Cordón-Ouahhabi S, Moutaoukil Z, et al. Methylene-Linked Bis-NHC Half-Sandwich Ruthenium Complexes: Binding of Small Molecules and Catalysis toward Ketone Transfer Hydrogenation. *Organometallics*. 2021;40(6):792-803.

35. Chopda L V, Dave PN. Heteropoly-12-tungstophosphoric acid H3 [PW12O40] over natural bentonite as a heterogeneous catalyst for the synthesis of 3, 4-dihydropyrimidin-2-(1H)-ones. *Arab J Chem*. 2020;13(6):5911-5921.

36. Ihara T, Yano S, Kita K. Preparation of phosphate esters from phosphorus oxyhalides and alcohols. *Jpn Kokai Tokkyo Koho*. 1996;(JP08092262A):10 pp.

37. Nagarajaiah H, Mukhopadhyay A, Moorthy JN. Biginelli reaction: an overview. *Tetrahedron Lett*. 2016;57(47):5135-5149.

38. Kappe CO. A reexamination of the mechanism of the Biginelli dihydropyrimidine synthesis. Support for an N-Acyliminium ion intermediate1. *J Org Chem*. 1997;62(21):7201-7204.

39. Baladi T, Hamouda-Tekaya N, Gonçalves LCP, Rocchi S, Ronco C, Benhida R. Sulfonylguanidine

Derivatives as Potential Antimelanoma Agents. *ChemMedChem*. 2020;15(13):1113-1117.

40. Shaabani A, Rahmati A, Naderi S. A novel one-pot three-component reaction: Synthesis of triheterocyclic 4H-pyrimido[2,1-b]benzazoles ring systems. *Bioorg Med Chem Lett*. 2005;15(24):5553-5557. doi:10.1016/j.bmcl.2005.08.101

41. Bhoi MN, Borad MA, Jethava DJ, et al. Synthesis, biological evaluation and computational study of novel isoniazid containing 4H-Pyrimido [2, 1-b] benzothiazoles derivatives. *Eur J Med Chem*. 2019;177:12-31.