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Propylphosphonic Anhydride-catalyzed Tandem Approach for Biginelli Reaction Starting from Alcohols

Cigalli N. Revanna,[1,2] Goravanalli M. Raghavendra,[3] T. A. Jenifer Vijay,[3] Kanchugarakoppal S. Rangappa,[3] Doddamedur G. Badregowda,[1] and Kempegowda Mantelingu*[3]

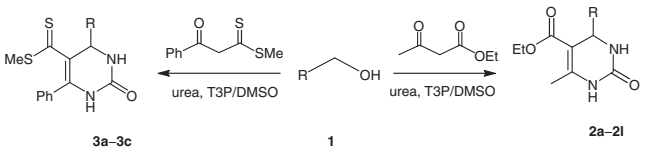
[1]*Yuvaraja's College, University of Mysore, Mysore-570005, India*

[2]*Syngene International Limited, Jigini Link Road, Bangalore 560099, India*

[3]*Department of Studies in Chemistry, University of Mysore, Mysore-570006, India*

(E-mail: mantelingu@chemistry.uni-mysore.ac.in)

An efficient and highly convergent route to dihydropyrimidinones (DHPMs) has been developed by one-pot three-component oxidative cyclocondensation of a variety of alcohols, β-ketoesters/β-oxodithioester and urea in the presence of T3P®/DMSO. This new approach consistently has the advantage of tandem and good yields (65–88%).



Scheme 1.

Domino processes and multicomponent reactions (MCRs) in an environmentally benign and atom-economic fashion play important roles in organic synthesis especially for the synthesis of bioactive heterocycles.[1] 3,4-Dihydropyrimidin-2-ones (DHPMs) and their derivates have been receiving much attention in recent years owing to their enormous application in the field of drugs and pharmaceuticals.[2–4] They occupy an important place in the realm of natural and synthetic organic chemistry due to their broad range of biological, including antiviral, antitumor, antibacterial, and anti-inflammatory activities and as HIV agents.[5–9] They also attracted considerable interest due to their promising activities as calcium channel blockers and orally active antihypertensive agents. A very recent important highlight in this aspect is the identification of the structurally rather simple DHPM monastrol as a mitotic kinesis EG_5 motor protein inhibitor and potential new lead for the development of anticancer drugs.[10] In 1893, Italian chemist Pietro Biginelli first reported the synthesis of DHPMs by multicomponent cyclocondensation,[11] involving reaction among a β-ketoester, an aldehyde, and urea under strong acidic conditions. Under strong acidic conditions the yields are very low, around 20%. To enhance the efficiency of the Biginelli condensation, various catalysts and reaction conditions have been studied including classical conditions, microwave-assisted irradiation, solid support, ionic liquids,[12] Lewis acid well as protic acid promoters such as $BF_3 \cdot OEt_2$,[13a] $InCl_3$,[13b] $LaCl_3 \cdot 7H_2O$,[13c] $FeCl_3 \cdot 6H_2O$,[13d] $Mn(OAc)_2$,[14a] $LiClO_4$,[14b] H_2SO_4,[14c] $HClO_4 \cdot SiO_4$.[14d] Zumpe et al. reported propylphosphonic anhydride (T3P®)-catalysed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones from aldehydes.[14e]

Recently, tandem oxidative processes (TOP) in which oxidation of alcohols combined with the subsequent elaboration of the carbonyl intermediates (aldehyde) have gained considerable attention among synthetic chemists.[15,16] Although a lot of work has been done for developing bimolecular TOP processes, the literature records only a few examples of combining alcohol oxidation with a multicomponent reaction (MCR) in a one-pot process.[17]

Aldehydes are ubiquitous substrates in many powerful MCRs. However, they are in general, more volatile, toxic, or unstable, especially because of aerial oxidation, than their corresponding alcohols. Thus, in many cases aldehydes must be purified just before their use because the presence of other products affects not only the concentration of the active aldehyde but also that the impurities often interfere with chemical reactions involving the aldehyde. The difficulties associated with the development of one-pot oxidation–MCR processes are self-evident due to the presence of multifunctionalities/multiintermediates and the complexity of the reaction mechanism intrinsic to MCRs. Thus, the use of a single vessel oxidation–MCR protocol would widen significantly the versatility and scope of the aldehyde-based MCRs. There have been only two reports on the Biginelli reaction starting directly from alcohols.[18] Very few reports on dihydropyrimidinones synthesis using β-oxodithioesters have appeared. However, to best of our knowledge this is the first report for the synthesis of dihydropyrimidinones starting from alcohols and β-oxodithioesters (Scheme 1).[19,20]

In continuation of our recent work on the synthesis of heterocycles by the development of new methodology,[21–24] in this paper, we report for the first time T3P®–DMSO-mediated tandem approach for the promoted Biginelli reactions. T3P®-catalyzed Biginelli reaction applied to the one-pot three-component oxidative condensations of a variety of alcohols, β-ketoester, and urea for the synthesis of DHPMs which is simple and high yielding. The one-pot procedure should prove highly advantageous for labile aldehydes in particular.

Treatment of alcohol (2 mmol), ethyl acetoacetate (2 mmol), and urea (3 mmol) in the presence of T3P® (4 mmol) in DMSO/ethyl acetate (1:2) at room temperature for 1–2 h followed by heating with ethyl acetate afforded the corresponding 3,4-dihydropyrimidones. The results are summarized in Table 1. The yields of products were generally >94% as assessed by LC-MS.[27,28] Another, important feature of this protocol is survival of a variety of functional groups such as OCH_3, OH, NO_2, Br, and Cl under the reaction conditions. To explore the scope and limitations of these reactions, we extended the procedure to various aryl-substituted alcohols carrying either electron-releasing (**2a**–**2e**) or electron-withdrawing (**2f**–**2h**), heterocyclic (**2i** and **2j**), aliphatic (**2k** and **2l**) substituents. The same process was successfully extended to β-oxodithioesters to the corresponding

Table 1. T3P®/DMSO-catalyzed synthesis of dihydropyrimidinones **2a**–**2l**

Entry	R	Product	Yield/%[a]
1	4-(OMe)–C_6H_4	**2a**	85[b]
2	4-(OH)–C_6H_4	**2b**	84[d]
3	Piperidyl	**2c**	79[c]
4	4-(O*i*-Pr)–C_6H_4	**2d**	86[c]
5	4-(NMe_2)–C_6H_4	**2e**	85[e]
6	2-(Br)–C_6H_4	**2f**	88[c]
7	4-(Cl)–C_6H_4	**2g**	82[b]
8	4-(NO_2)–C_6H_4	**2h**	79[d]
9	4-Thiazolyl	**2i**	68[c]
10	3-C_6H_4N	**2j**	75[c]
11	Ethyl	**2k**	67[c]
12	Propyl	**2l**	65[c]

[a]Yields refer to those of pure isolated products characterized by ^{1}H NMR and LCMS. [b]Ref 20, [c]ref 21, [d]ref 25, and [e]ref 26.

Table 2. T3P®-catalyzed synthesis of 5-methylsulfanylthiocarbonyl-substituted dihydropyrimidinones **3a**–**3c**

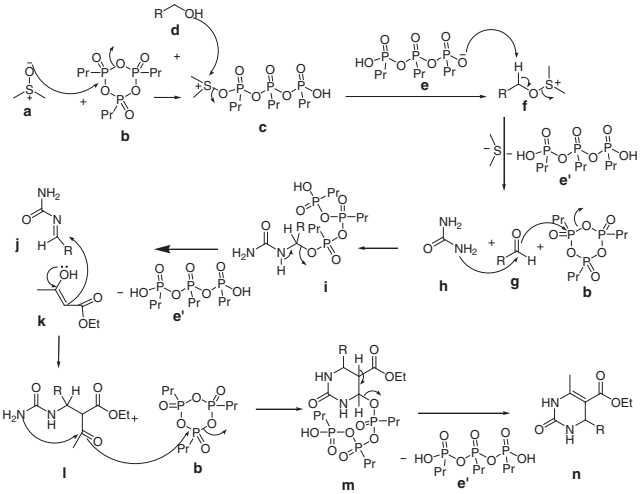
Entry	R	Product	Yield/%[a]
1	4(F)-C_6H_4	**3a**	80[b]
2	4-(Cl)-C_6H_4	**3b**	84[b]
3	4-(Br)-C_6H_4	**3c**	79[b]

[a]Yields refer to those of pure isolated products characterized by ^{1}H NMR and LCMS. [b]Ref 20.

dihydropyrimidinones in good yield (Table 2). Table 2 shows the generality of the present protocol, which is equally effective for β-oxodithioesters. In most cases, the reactions proceeded smoothly to produce the corresponding DHPMs in high yields. Aromatic alcohols containing either electron-donating or electron-withdrawing substituents produced improved yields as compared to the classical Biginelli protocol.

The influence of DMSO and various solvents on the synthesis of dihydropyrimidinone **2a** was studied, and results are summarized. We tried the reaction of alcohol **1a**, with ethyl acetoacetae and urea using T3P® (2.0 equiv) alone without DMSO both at room temperature and reflux condition, but no reaction was observed. Increasing the volume of DMSO in the ratio (EtOAc/DMSO) to 1:1, 1:2, 1:3, and 1:4 did not improve the yield. The optimization of solvents such as THF, DMF, toluene, acetonitrile, acetone, and benzene did not improve the yields. Ethyl acetate was chosen as the appropriate solvent with consideration to yield. Most of the synthesized compounds were known compounds which were adequately characterized by physical and spectral data and are in good agreement with those reported in the literature.

A possible mechanism of the oxidative and dehydrative cyclization to get dihydropyrimidinones is suggested in Scheme 2. DMSO **a** gets activated by T3P® **b** to give an electrophilic sulfur species **c**, which then reacts with alcohol **d** to give an aryloxysulfonium salt **f**. The hydrolyzed T3P® obtained as the by-product **e** acts as a base to pull out H of aryloxysulfonium salt **f** to form the aldehyde **g**. *P*,*P*′,*P*″-Tripropyltriphosphonic acid **e**′ and dimethyl sulfide are formed as the by-product. The second step in the probable mechanism of



Scheme 2. Proposed mechanism for the synthesis of dihydropyrimidinones.

the Biginelli reaction is the T3P®-catalyzed condensation of the urea **h** with aldehydes **g** affording a phosphonate intermediate **i**, which generates an *N*-acylimino Schiff base **j**. Subsequently, the enol form of the β-ketoester **k** attacks *N*-acylimino Schiff base **j** to generate an open chain ureide **l**, which readily cyclizes to a tetrahydropyrimidinone **m** derivative followed by the elimination of phosphonate intermediate molecules to give dihydropyrimidinones **n**.

In summary, we have developed a simple, convenient, and efficient method for the synthesis of DPHMs and a diverse set of 5-methylsulfanylthiocarbonyl-substituted 3,4-dihydropyrimidin-2(1*H*)-ones have been synthesized in good yields, starting from alcohols, using a T3P®/DMSO system. Our literature survey shows that this is the first example promoted by T3P®–DMSO in which β-ketoester/β-oxodithioester are as activated synthons used in a Biginelli reaction. The protocol involves T3P®-catalyzed oxidation of alcohols to aldehydes 0–25 °C followed by their cyclocondensation of β-ketoester/β-oxodithioesters, urea at 60–70 °C temperature using T3P® as an eco-friendly, homogeneous catalyst. This method is applicable to a wide range of substrates including aromatic, heterocyclic, α,β-unsaturated, aliphatic alcohols. This method is not only simple, but provides clean reactions with high yield (70–84%) and greatly decrease in environmental pollution.

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27 Typical procedure for the synthesis of 3,4-dihydropyrimidinones: To a solution of alcohol (1.0 mmol) in a mixture of solvents ethyl acetate (4 mL) and DMSO (2 mL), was added T3P® (2 mmol, 50% solution in ethyl acetate), the resulting reaction mixture was stirred at room temperature for 1–2 h under nitrogen atmosphere. The reaction was monitored by TLC. β-ketoester/β-oxodithioester (1.0 mmol) and urea (1.5 mmol) were added and stirred further 4–6 h at 60–70 °C. After completion of the reaction, solvent was evaporated and mixture was poured into crushed ice. Stirring was continued for several minutes. The solid product was filtered, washed with cold water and recrystallized from ethanol to get pure product. Detailed spectroscopic data of representative compounds are given below. **Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2a)**: Mp 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H, N*H*), 7.66 (s, 1H, N*H*), 7.15–6.84 (m, 4H, C_6H_4), 5.07 (s, 1H, C*H*), 3.96 (q, $J = 6.8$ Hz, 2H, OCH_2CH_3), 3.70 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3), 1.09 (t, $J = 6.8$ Hz, 3H, OCH_2CH_3). MS (ESI + ion): m/z 291.2. **Methyl 4-(4-bromophenyl)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbodithioate (3c)**: Mp 241–242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.61 (s, 1H, N*H*), 7.56 (s, 1H, N*H*), 7.46–7.39 (m, 7H, C_6H_4, C_6H_5), 7.33–7.31 (m, 2H, C_6H_4), 5.489 (s, 1H, C*H*), 2.28 (s, 3H, CH_3). MS (ESI + ion): m/z 418.8.
28 Experimental details and detailed spectroscopic data of all the compounds are available in Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.