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Biginelli reaction starting directly from alcohols

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ABSTRACT

An efficient of one-pot oxidative access to 3,4-dihydropyrimidin-2-(1*H*)-ones directly from aromatic alcohols under mild conditions is reported. The protocol involves 1-methylimidazolium hydrogen sulphate [Hmim]HSO_4 catalyzed oxidation of aromatic alcohols to aromatic aldehydes with $NaNO_3$ followed by their cyclocondensation with 1,3-dicarbonyl compounds and urea in the same reaction vessel at 80 °C within 2–4 h to afford 3,4-dihydropyrimidin-2-(1*H*)-ones in 55–97% overall yields. Thus, the present work utilizing alcohols instead of aldehyde in Biginelli reaction is a valid and green alternative to the classical synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones.

One-pot sequential multi-step reactions are of increasing academic, economical, and ecological interest because they address fundamental principles of synthetic efficiency and reaction design.[1] 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.[2,3] 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.[4]

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 mutli-functionalities/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.

Biginelli reaction[5] is one of the fundamental strategies involving a three-component condensation of ethyl acetoacetate, benzaldehyde, and urea for the synthesis of 4-aryldihydropyrimidinones (DHPMs) and their derivatives which occupy an important place in the realm of natural and synthetic organic chemistry.[6–9] The reaction can be carried out in a one-pot fashion in alcoholic solution in the presence of a catalytic amount of hydrogen chloride. A major drawback of the classical Biginelli reaction is the poor to moderate yields, particularly when substituted aromatic aldehydes are employed. In recent years, several synthetic procedures for the preparation of DHPMs have been made to improve and modify this reaction.[10,11] However, to the best of our knowledge, there has been only one report on the Biginelli reaction starting directly from alcohols.[4c]

Ionic liquids (ILs) are emerging as effective promoters and solvents for green chemical reactions. Especially, one of the most important advantages of ILs is the behavior of solvophobic interactions that generate an internal pressure which promotes the association of the reagents in a solvent and shows an acceleration of MCRs in comparison to conventional solvents.[12] Recently, Brønsted acidic ionic liquids have been deemed promising alternatives for acid catalyzed reactions and play a dual solvent–catalyst role in a variety of reactions including esterification of carboxylic acids, protection of alcohols and carbonyl groups, oxidation of alcohols, alcohol dehydrodimerization, pinacol/benzopinacol rearrangement, Mannich reactions, and cleavage of ethers.[13,14]

Our continued quest for the development of environmentally friendly alternatives[15] along with the recent investigations involving oxidation of alcohols and the subsequent trapping of carbonyl intermediates with appropriate nucleophiles in one-pot operation[15d,e] has led us to develop a green protocol for the Biginelli reaction starting directly from alcohols. Herein, we report a Brønsted acidic ionic liquid [Hmim]HSO_4 catalyzed sequential oxidation of aromatic alcohols with $NaNO_3$ followed by their

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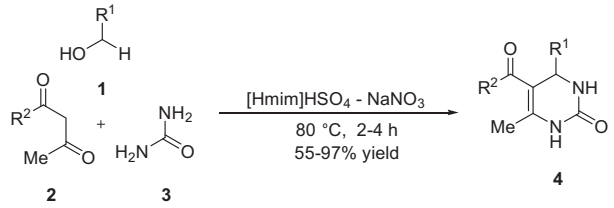
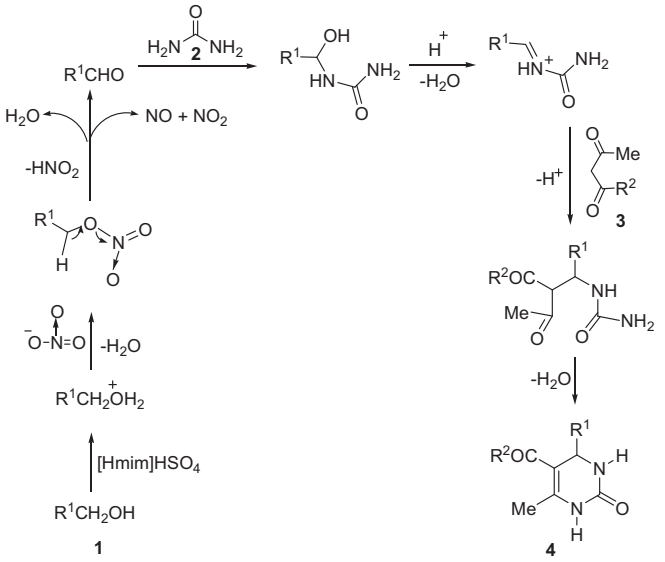


Scheme 1. Preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones directly from aromatic alcohols.

condensation with urea and dicarbonyl compounds in the same vessel at 80 °C for an overall time period of 2–4 h to afford 3,4-dihydropyrimidin-2(1*H*)-ones in 55–97% yields (Scheme 1).

Initially, we studied the tandem oxidative cyclocondensation of benzyl alcohol (3 mmol), urea (3 mmol) and ethyl acetoacetate (3 mmol) in the presence of $[Hmim]HSO_4$ (1.2 mmol) with $NaNO_3$ (3 mmol) at 80 °C, disappointingly no reaction took place even after stirring the reaction mixture for 10 h. However, to our delight, we observed the formation of 3,4-dihydropyrimidin-2(1*H*)-ones when urea and ethyl acetoacetate were added to the reaction after the oxidation of the alcohol to the aldehyde was complete.

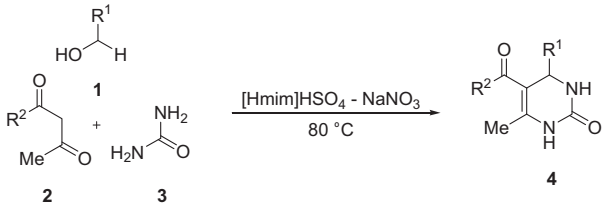
To explore the scope and limitations of this reaction, we extended the procedure to various aryl substituted alcohols carrying either electron-releasing or electron-withdrawing substituents in the *ortho*, *meta*, and *para* positions. Aryl alcohols with a strong electron-withdrawing group (such as nitro group) required a relatively longer time for completion of the reaction (Table 1, entries 4, 8, 11, and 14) whereas alcohols carrying electron-donating substituents gave excellent yields of DHPMs (Table 1, entries 3, 6, 7, 10, and 12) in a shorter reaction time. Another important feature of this procedure is the compatibility with a variety of functional groups such as ethers, nitro, hydroxyl, and halides under the present reaction conditions. Both β-ketoesters and acetylacetone reacted smoothly under the reaction conditions (Table 1) affording the corresponding 3,4-dihydropyrimidinones in excellent yields. Aliphatic alcohols were unreactive under the present reaction conditions (Table 1, entries 15 and 16).



Scheme 2. Plausible mechanism for one-pot oxidative Biginelli reaction.

We also attempted the oxidative Biginelli reaction using $[Hmim]NO_3$ as well as $NaNO_3$–$[Hmim]H_2PO_4$ separately under the same reaction conditions. The reaction was unsuccessful in the former case indicating the need for an acidic hydrogen which is absent in $[Hmim]NO_3$ to catalyze the oxidation of alcohols to aldehyde (Scheme 2). However, the reaction proceeded with the $NaNO_3$–$[Hmim]H_2PO_4$ system but relatively low yields of

Table 1
Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones[a]



Entry	Product	R^1	R^2	Time (h)	Yield[b] (%)	Mp (°C)	
						Found	Reported
1	**4a**	C_6H_5	OEt	3	94	201–202	202–203[10d]
2	**4b**	2-ClC_6H_4	OEt	3.5	92	215–219	215–218[10d]
3	**4c**	2-HOC_6H_4	OEt	2	97	202–204	201–203[10d]
4	**4d**	4-$O_2NC_6H_4$	OEt	4	62	206–208	207–208.5[10d]
5	**4e**	4-ClC_6H_4	OEt	3.5	91	214–215	213–215[10d]
6	**4f**	4-MeC_6H_4	OEt	2.5	95	214–217	216–218[10e]
7	**4g**	4-$MeOC_6H_4$	OEt	2	96	207–208	208–209[10e]
8	**4h**	3-$O_2NC_6H_4$	OEt	4	59	230–232	232–234[10e]
9	**4i**	4-$O_2NC_6H_4$	Me	4	62	227–229	230[10d]
10	**4j**	4-$MeOC_6H_4$	Me	2	96	169–171	168–170[10d]
11	**4k**	4-$O_2NC_6H_4$	OMe	4	65	236–238	235–237[10d]
12	**4l**	4-$MeOC_6H_4$	OMe	2	95	191–193	192–194[10d]
13	**4m**	4-ClC_6H_4	OMe	3.5	92	204–207	204–207[10d]
14	**4n**	3-$O_2NC_6H_4$	OMe	4	55	277–279	278–280[10f]
15	**4o**	*n*-Butyl	OEt	6	—		157–158[10b]
16	**4p**	*n*-Propyl	OEt	6	—		155–157[11f]

[a] Reaction condition: alcohol (3 mmol), urea (3.0 mmol), β-dicarbonyl compound (3 mmol), $NaNO_3$ (3 mmol) and $[Hmim]HSO_4$ (1.20 mmol) at 80 °C for 2–4 h.[16]
[b] Isolated yields.

3,4-dihydropyrimidin-2(1*H*)-ones (28–39%) were obtained. This is probably due to the lower Brønsted acidity associated with $[H_2PO_4]$. Thus, $[Hmim]HSO_4$ plays a dual role, that is, as an acid catalyst and as a solvent for both the oxidation of alcohols and the subsequent condensation with urea and 1,3-dicarbonyl compounds. A plausible mechanism for the present one-pot oxidative cyclocondensation of aromatic alcohols, urea, and 1,3-dicrbonyl compounds is depicted in Scheme 2.

In summary, we have developed a new method for an efficient Biginelli reaction starting directly from alcohols using $NaNO_3$–$[Hmim]HSO_4$ system. The protocol involves $[Hmim]HSO_4$ catalyzed oxidation of alcohols to aldehydes with $NaNO_3$ at 80 °C followed by their cyclocondensation with the urea and dicarbonyl compounds to afford 3,4-dihydropyrimidin-2(1*H*)-ones in a one-pot operation. Thus, the present work could find useful applications in view of the power of the Biginelli reaction and that the concept could be extended as a valid and green alternative to other MCRs involving aldehyde substrates.

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16. *A typical procedure for the formation of 3,4-dihydropyrimidin-2-(1H)-ones* **4**: A mixture of an aryl alcohol (3 mmol), sodium nitrate (3 mmol), and $[Hmim]HSO_4$ (1.20 mmol) was heated with stirring at 80 °C for 5–30 min in a round-bottomed flask. After oxidation of the aromatic alcohol (monitored by TLC, *n*-hexane/ethyl acetate, 80:20), β-dicarbonyl compound (3 mmol) and urea (3.0 mmol) were added. The mixture was heated with stirring at 80 °C for 1.5–4 h. On completion of the reaction, as indicated by TLC (*n*-hexane/ethyl acetate: 60:40), the reaction mixture was cooled to rt, then cold water was added. The precipitated product was separated by simple filtration. The crude product was recrystallized from ethanol to obtain an analytical sample of **4**. The structure of the products was confirmed by comparison of their mp, TLC, IR, and ^1H NMR data with authentic samples obtained commercially or prepared by the literature method.[10b,d–f,11f]