Tetrahedron Letters 52 (2011) 6328–6330

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

p-Sulfonic acid calixarenes as efficient and reusable organocatalysts for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones

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ARTICLE INFO

Article history:
Received 21 April 2011
Revised 13 August 2011
Accepted 16 August 2011
Available online 19 September 2011

Keywords:
Calixarene
p-Sulfonic acid calix[4]arene
Organocatalysis
Biginelli reaction
3,4-Dihydropyrimidin-2(1*H*)-one
3,4-Dihydropyrimidin-2(1*H*)-thione

ABSTRACT

A new and efficient methodology is proposed for obtaining 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones through Biginelli reactions. It is based on the use of less than the stoichiometric amount of *p*-sulfonic acid calixarenes as organocatalysts. A number of aromatic aldehydes as well as urea or thiourea can be employed for successfully synthesizing the corresponding Biginelli adducts. The described methodology is devoid of metal-containing catalysts, which in turn is very attractive for safely producing 3,4-dihydropyrimidin-2-(1*H*)-ones/-thiones of pharmacological interest. In addition, the catalyst efficiency is not compromised after its successive use in reactions. This is the first report about the application of calixarenes as catalysts in the multicomponent Biginelli reaction.

Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of a metal-free organic compound.[1] Increased interest in organocatalysis is due to its operational simplicity, low toxicity and cost, and also high tolerance to molecular oxygen and traces of water. In addition, products from reactions catalyzed by non-metallic organic compounds are desirable to food, pharmaceutical, and cosmetic industries.[2]

Multicomponent reactions (MCRs) are very attractive tools to obtain complex molecules from one-pot procedures. In 1893, the Italian chemist Pietro Biginelli reported the cyclocondensation of ethyl acetoacetate, urea, and an aryl aldehyde in the presence of an acid, furnishing 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs or Biginelli adducts) as products.[3] This approach is known as Biginelli reaction or Biginelli condensation.[4] Compounds bearing a DHPM moiety have shown promising biological activities, making Biginelli reaction an interesting approach for the synthesis of such compounds. Several studies have shown a variety of inorganic Brønsted–Lowry acids as catalysts in Biginelli reaction and more recently, Lewis acids have gained special attention for this purpose.[5] The use of ionic liquids,[6] microwave irradiation,[7] solid-phase reagents,[8] baker's yeast[9] or polymer-supported catalysts,[10] zelolite,[11] dodecyl sulfonic acid[12], and PEG[13] has also been reported. Only a few examples of organocatalysts have been described for Biginelli reaction.[14]

Calixarenes, macrocycles formed from the condensation of *p*-substituted phenols with formaldehyde in basic medium, have been widely used as ligands in organometallic catalysis.[15] Nevertheless, their roles as organocatalysts are still poorly investigated.[16] The *p*-sulfonic acid calixarenes **7** and **10** (Table 1) have been reported as catalysts in Mannich-type reactions,[17] while compound **10** was also successfully employed as a catalyst in allylic alkylation reactions.[18]

Herein we describe an efficient and simple method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones through Biginelli reactions by using calixarenes[19] (Table 1) as organocatalysts.

Preliminary studies focused on the screening of calixarenes **5–10** as catalysts in Biginelli reactions containing ethyl acetoacetate (**1**), 4-hydroxybenzaldehyde (**2a**), and urea (**3a**).[20] The yield of calixarene-free reactions was lower than 12% (Table 1, entry 1). The use of *tert*-butyl-calixarenes **5** or **8** has raised the yields by 4.7-fold (Table 1, entries 2 and 3). Similar results were obtained by using calixarenes **6** or **9** (Table 1, entries 4 and 5). These results suggest that neither *tert*-butyl group nor calixarene cavity size is critical for catalytic efficiency. On the other hand, substitution of *tert*-butyl for a sulfonyl group (calixarenes **7** and **10**) allowed obtaining Biginelli adducts in yields higher than 70% (Table 1, entries 6 and 7). Furthermore, the reaction time was considerably reduced, without affecting the yield, when calixarenes **7** or **10** were used at 0.5 mol % (Table 1, entries 8 and 9). The improvement of reaction yield from the use of sulfonated calixarenes is likely due to their increased acidity.[18,19,21] To explore the role of calixarenes spatial

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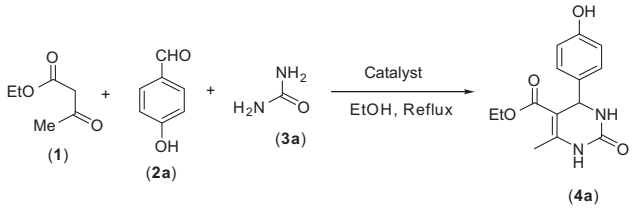
0040-4039
doi:10.1016/j.tetlet.2011.08.175

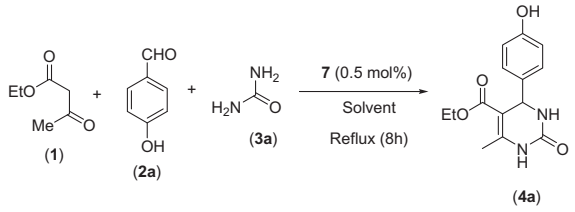
Table 1
Screening of calixarenes as organocatalysts for Biginelli reactions[a]



Entry	Catalyst (mol %)	Time (h)	Yield (%)
1	—	24	12
2	5 (0.15)	24	56
3	8 (0.15)	24	51
4	6 (0.15)	24	54
5	9 (0.15)	24	53
6	7 (0.15)	24	77
7	10 (0.15)	24	72
8	7 (0.50)	8	81
9	10 (0.50)	8	75
10	PHSA (0.50)	8	69
11	PHSA (2.0)	8	74
12	PHSA (3.0)	8	68

[a] Reagents and conditions[20]: 4-hydroxybenzaldehyde/ethyl acetoacetate/urea (molar ratio = 1:1.5:1.5). PHSA, *p*-hydroxybenzenesulfonic acid.

Table 2
Effect of solvents on the yield of calixarene **7**-catalyzed Biginelli reactions[a]



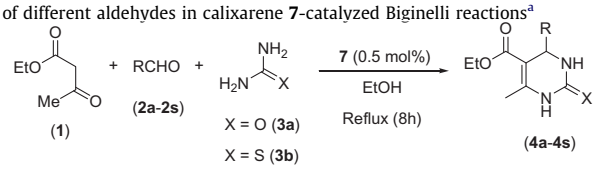
Entry	Solvent	Yield (%)
1	Ethanol	81
2	Tetrahydrofuran	NP
3	1,4-Dioxane	18
4	Acetonitrile	31
5	Methanol	52
6	Hexane	NP

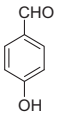
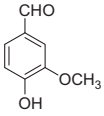
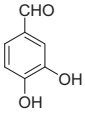
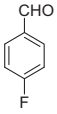
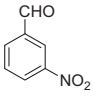
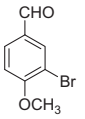
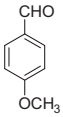
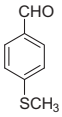
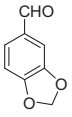
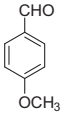
[a] Reagents and conditions[20]: 4-hydroxybenzaldehyde/ethyl acetoacetate/urea (molar ratio = 1:1.5:1.5). NP, no product detected under the tested experimental conditions.

arrangement on the catalysis efficiency, we used *p*-hydroxybenzenesulfonic acid (PHSA) as a catalyst. PHSA (Table 1, entries 10–12) was less efficient than calixarenes **7** and **10**. This indicates that the sulfonyl and phenolic groups in calixarene structures are not solely responsible for the achievement of good reaction yields. Overall, calixarene **7** was an organocatalyst slightly more efficient than **10** (Table 1, entries 8 and 9). Large scale reactions carried out with aldehydes, urea, and ethylacetoacetate at 30, 45, and 45 mmol, respectively, provided similar good yields of Biginelli adducts.

The promising results obtained with calixarene **7** prompted us to further investigate the effect of solvents on Biginelli reactions catalyzed by this macrocyclic compound. Ethanol (Table 2, entry 1) was the best solvent, followed by methanol, acetonitrile, and

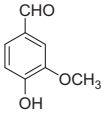
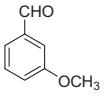
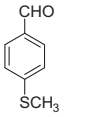
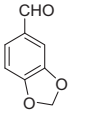
Table 3
Use of different aldehydes in calixarene **7**-catalyzed Biginelli reactions[a]



Product	Aldehydes (**2a–s**)	X	Yield (%)
4a		O	81
4b		O	79
4c		O	69
4d		O	76
4e		O	56
4f		O	91
4g		O	62
4h		O	68
4i		O	78
4j		O	89
4k		O	92
4l		O	71
4m	$CH_3CH_2CH_2CHO$	O	34
4n		O	38
4o		S	78

(*continued on next page*)

Table 3 (*continued*)

Product	Aldehydes (**2a–s**)	X	Yield (%)
4p		S	72
4q		S	74
4r		S	78
4s		S	64

[a] Reagents and conditions[20]: aldehyde/ethyl acetoacetate/urea/thiourea (molar ratio = 1:1.5:1.5).

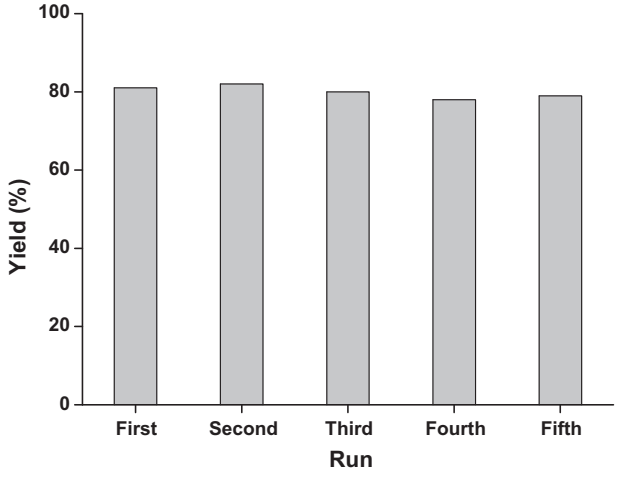


Figure 1. Reuse capacity of calixarene **7** in Biginelli reactions.

1,4-dioxane. Surprisingly, acetonitrile, a solvent commonly used in Biginelli reactions, provided poor yields (Table 2, entry 4). Tetrahydrofuran and hexane were not suitable solvents (Table 2).

After pursuing the best solvent, we evaluated the scope of calixarene **7**-catalyzed Biginelli reaction by using a variety of aldehydes. Aromatic aldehydes bearing electron-donating or electron-withdrawing groups were employed in Biginelli reactions and the expected products were obtained in good yields (Table 3). Non-aromatic aldehydes, however, were less reactive, affording moderate yields (Table 3, products **4m** and **4n**). Both urea and thiourea were suitable substrates as attested by the yields of corresponding formed DHPMs (Table 3).

We also checked whether or not calixarene **7** could be reused in such reactions (Fig. 1). Calixarene **7** was then recovered from the reaction medium through liquid–liquid extraction with water. After drying, the residue was used in successive reactions. Calixarene **7** was found to be efficient in reactions containing ethyl acetoacetate (**1**), 4-hydroxybenzaldehyde (**2a**), and urea (**3a**) even after five cycles of use (Fig. 1).

In conclusion, an efficient procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones was developed based on the use of *p*-sulfonic acid calix[4]arene **7** as an organocatalyst. A broad variety of aromatic aldehydes can be employed. The methodology here is environmentally friendly since it does not employ metal-based catalyst. This is, in turn, very attractive for safely obtaining 3,4-dihydropyrimidin-2-(1*H*)-ones/-thiones of pharmacological interest. To the best of our knowledge, this is the first report on the application of calixarenes as catalysts in multicomponent Biginelli reactions.

Acknowledgments

The authors are grateful to Dr. Luzia V. Modolo for critical reading of this manuscript. This work was funded by FAPEMIG, CAPES, and CNPq. D.L.S. and A.D.F. are supported by CNPq scholarship and research fellowship, respectively.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.175.

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20. General procedure for the synthesis of DHPMs: Aldehydes (3 mmol), ethylacetoacetate (4.5 mmol), and urea or thiourea (4.5 mmol) were dissolved in 3 mL of ethanol containing a calixarene (0.15–0.5 mol %). The mixture was heated under reflux and stirred for 8 h. Reactions were monitored by TLC. The mixtures were concentrated under vacuum, following the addition of few drops of cold water to precipitate the product. All products were characterized by NMR (^{1}H, ^{13}C), melting point and elemental analyses (Supplementary data).
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