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An efficient synthesis of 4-aryl-7-benzylidene-hexahydro-2*H*-cyclopenta[*d*] pyrimidin-2-ones/thiones catalyzed by *p*-dodecylbenzenesulfonic acid

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ABSTRACT

A new and efficient method has been developed for the synthesis of 4-aryl-7-benzylidene-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-ones through Biginelli-like reaction of cyclopentanone, with urea/thiourea and aromatic aldehyde employing *p*-dodecylbenzenesulfonic acid (DBSA) as a recyclable catalyst under solvent-free condition. The recovered catalyst was recycled for further runs. The product formation takes place via a cross-aldol condensation of benzaldehyde with cyclopentanone in the presence of DBSA to produce benzylidene intermediate and subsequent Michael addition. The present approach offers the advantages of short reaction time, mild reaction conditions, high yields and convenient operation. All the products were obtained in good to excellent yields and the structures of the synthesized compounds were established by advanced spectroscopic data.

Keywords*: Biginelli reaction; p-Dodecylbenzenesulfonic acid; Cyclopenta[d]pyrimidin-2-one; One-pot synthesis.*

1. Introduction

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 [1]. This approach is known as Biginelli reaction or Biginelli condensation [2]. Biginelli compounds are important medicinal synthones which exhibit a wide range of biological activities, making Biginelli reaction an interesting approach for the synthesis of such compounds [3]. Biginelli compounds are used in several calcium channel blockers [4], antihypertensive drugs [5], α1a-adrenergic antagonists [6-7], HIV-1 replication inhibitors [8], and anticancer drugs [9]. Batzelladine B, an alkaloid isolated from a marine sponge, contains a dihydropyrimidine unit and shows anti-HIV activity [10].

Due to the wide range of application of compounds containing dihydropyrimidine units, the synthesis of this type of compounds has attracted considerable attention and a series of methods have been developed which includes the one-pot three-component condensation of *β*-dicarbonyl compounds, aromatic aldehydes and urea or thiourea in the presence of promoters such as cellulose sulfuric acid [11], Iron(III) tosylate [12], decatungstodivanadogermanic heteropoly acid [13], CuO-CeO_2 nanocomposite [14], molybdate sulfuric acid [15], mesoporous aluminosilicate (AlKIT-5) [16], thiamine hydrochloride [17], chloroacetic acid [18], $Yb(PFO)_3$ [19] and melamine trisulfonic acid [20].

The scope of this reaction was gradually extended by the variation of all three building blocks, allowing access to a large number of multi functionalized dihydropyrimidines of medicinal use. The classical Biginelli reaction has been considerably extended by use of cycloalkanones instead of 1,3-dicarbonyl compounds. Use of TMSCl as a Lewis acid allowed one-pot chemoselective multicomponent Biginelli reactions between cycloalkanones, urea or thiourea, and aldehydes [21]. However, the use of stoichiometric amounts of TMSCl as additional reagent and mixed DMF/CH_3CN as reaction solvent seemed to be necessary to obtain satisfactory results. Furthermore, TMSCl is toxic, corrosive, and

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environmental unfriendly. An efficient and clean method was developed for the one-pot synthesis of pyrimidinones by an ytterbium chloride catalyzed Biginelli-type reaction of aromatic aldehyde, cyclopentanone, and urea or thiourea under solvent-free conditions [22]. A Biginelli-type three-component reaction involving cyclopentanone, aromatic aldehyde, and urea or thiourea for preparation of pyrimidinone derivatives under neat conditions was reported by Lei et al. [23]. This condensation reaction can also take place smoothly in the presence of vitamin B1 in EtOH at 80ºC in good yield [23]. However, many of these existing methodologies suffer from one or more disadvantages such as prolonged reaction times, low yields, use of harmful organic solvents, and requirement of excess of catalyst and reagents, and harsh reaction conditions. Keeping in view the disadvantages associated with reported protocols as well as increasing importance of pyrimidinones in pharmaceutical chemistry, there still remains a high demand for the development of more general, efficient, and eco-friendly protocol to assemble such scaffolds.

Over the past years, DBSA in organic synthesis has been widely used for carrying out various organic transformations in water as well as under solvent-free conditions [24–34] due to its low toxicity, air and water compatibility, operational simplicity, and remarkable ability to suppress side reactions in acid sensitive substrates. DBSA has been used extensively as catalyst for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles [24], dibenzo[*a,j*]xanthenes [25], 1,8-dioxo-octahydroxanthene [26], 3,4-dihydropyrimidins [27], esterification [28], bis(indol-3-yl)alkanes [29], 1, 1- diacetates [30], tetrahydro benzo[*b*]pyrans [31], α,ά-bis(substituted benzylidene)cycloalkanones [32], indeno[1,2-*d*]pyrimidines [33] and 3,3-arylidene bis(4-hydroxycoumarin) [34].

Our main strategy in this work is to develop a solvent-free organic reaction enhancement methodology, which is extremely fast and cleaner than conventional reactions, and lead to higher atom economy. In continuation of our interest in the area of useful synthetic methodology [35-38] herein, we report a simple, efficient, and one-pot reaction of aldehyde, cyclopentanone and urea/thiourea using DBSA at 80˚C for the preparation of 4-aryl-7-benzylidene-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-ones/thiones in high yields (Scheme 1).

2. Experimental

2.1. Chemicals and analysis

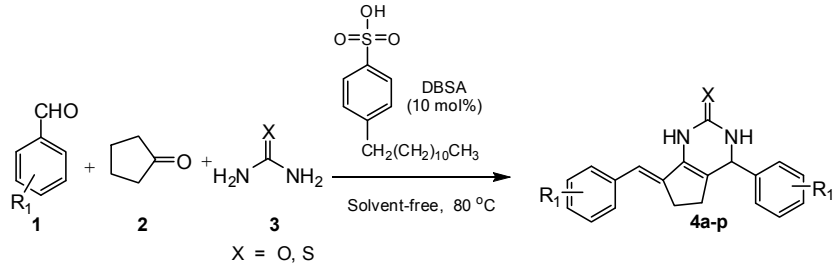
Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained using Bruker DRX- 500 Avance at ambient temperature, using TMS as internal standard. FT-IR spectra were obtained as KBr discs on Shimadzu spectrometer. Mass spectra were determined on a Varion-Saturn 2000 GC/MS instrument. Elemental analysis was measured by means of Perkin Elmer 2400 CHN elemental analyzer flowchart. All yields refer to isolated products unless otherwise stated.

2.2 General procedure for the preparation of 4a-p

A mixture of aldehyde (1 mmol), cyclopentanone (1 mmol), urea/thiourea (1.2 mmol), and DBSA (10 mol %) under solvent-free condition was heated to 80˚C, with stirring, for 1.0 – 1.5 h to complete the reaction (monitored by TLC). After cooling to room temperature, the reaction was quenched with 20 ml of H_2O and stirred for 10 min. The pure product was isolated by filtration, followed by recrystallization from ethanol. The IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis data of the synthesized compounds are given below.

3. Results and Discussion

To obtain the best reaction conditions, the reaction of benzaldehyde (1 mmol), cyclopentanone (1 mmol), and urea (1.2 mmol), was examined in the presence of 10 mol% of DBSA as catalyst in the presence of various solvents (Table 1, entries 1-6). When the reaction mixture was refluxed for 3 h, undesired products were detected. In view of the current interest in environmentally benign catalytic processes, a procedure performed under solvent-free conditions would be more ideal, and therefore we decided to carry out this reaction under solvent-free conditions at



Scheme 1. DBSA-catalyzed synthesis of various substituted 4-aryl-7-benzylidene-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-ones/thiones.

Table 1. Synthesis of 7-benzylidene-4-phenyl-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*] pyrimidin-2-ones in the presence of DBSA as catalyst in different reaction conditions.[a]

Entry	Solvent	Catalyst (mol %)	Temp (°C)	Time (h)	Yield (%)[b]
1	1,4-Dioxane	10.0	Reflux	3.0	39
2	CH_3CN	10.0	Reflux	3.0	43
3	EtOH	10.0	Reflux	3.0	74
4	DMF	10.0	Reflux	3.0	47
5	$CHCl_3$	10.0	Reflux	3.0	41
6	Water	10.0	Reflux	3.0	68
7	Solvent-free	10.0	80	1.2	93
8	Solvent-free	10.0	r.t	3.0	51
8	Solvent-free	10.0	50	3.0	63
10	Solvent-free	10.0	60	2.5	72
11	Solvent-free	10.0	70	2.0	85
12	Solvent-free	10.0	90	1.2	93
13	Solvent-free	0.0	80	3.0	26
14	Solvent-free	4.0	80	2.0	53
15	Solvent-free	8.0	80	1.5	80
16	Solvent-free	12.0	80	1.2	94

[a]Reaction conditions: benzaldehyde (1 mmol), cyclopentanone (1 mmol) and urea (1.2 mmol)
[b]Isolated yield.

80°C. Under the solvent-free conditions, the reaction proceeded to completion in 1.2 h (Table 1, entry 7). The effect of temperature plays an important role in the multi-component reaction of benzaldehyde, cyclopentanone and urea. It was examined in different temperatures, including room temperature, 50, 60, 70, 80 and 90 °C under solvent-free conditions and the results are shown in Table 1. Temperature increase leads to an increasing in the yield. The yields of product for a reaction temperature of room temperature, 50, 60, 70 and 80°C are 51, 63, 72, 85 and 93% respectively (Table 1, Entries 7-11). The increasing on the reaction temperature to 90°C did not affected to increase the product yield (Table 1, Entry 12). The greatest yield in the shortest reaction time was obtained under solvent-free conditions at 80°C. Thus 80°C was chosen as the ideal temperature to continue with the analysis of other reaction variables.

The effective amount of DBSA catalyst was also investigated (Table 1, entries 7 and 13-16). Generally, the reaction rate and yield increased with the amount of catalyst. It was found that 10 mol% of catalyst was the appropriate amount for the reaction. Smaller amounts gave a low yield even after a long reaction time, while greater amounts did not cause an obvious increase in the yield of product (Fig. 1).

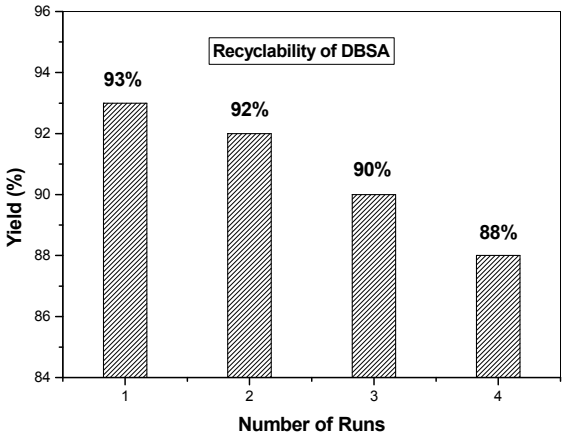


Fig. 1. Recycling of the catalyst DBSA for the synthesis of 7-benzylidene-4-phenyl-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-ones

Hence, the optimal amount of catalyst chosen was 10 mol% in the subsequent reactions using the molar ratio of 1:1:1.2 of benzaldehyde, cyclopentanone and urea respectively.

The formation of the product 7-benzylidene-4-phenyl-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-ones (Scheme 1) indicates that the product is formed by the condensation of benzaldehyde, cyclopentanone, and urea at a 2:1:1 ratio. But the reaction at this ratio of substrate gave the yield lower than that obtained at a 1:1:1.2 ratio (Table 2, entry 2). This means that excessively used cyclopentanone and urea played important roles in promoting the conversion of benzaldehyde to the product (Table 2, entries 3 and 4). Hence best yield is obtained at a 1:1:1.2 mol ratio of benzaldehyde, cyclohexanone, and urea. The reason for this is not yet clear.

With the optimized conditions in hand, to explore the generality of the reaction, we extended our study to different aromatic aldehydes to prepare a series of 4-aryl-7-benzylidene-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-ones (Table 3). In all the cases the corresponding products were obtained in good to excellent yields. However, with aromatic aldehydes with electron-withdrawing groups as substrates, the reaction time is shorter than those with electron-donating groups. Though *meta*- and *para*-substituted aromatic aldehydes gave good results (Table 3, entries 1, 4-8, 10, 11, and 13-15), *ortho*-substituted aromatic aldehydes gave lower yields because of the steric effects (Table 3, entries 2, 3, 9, 12 and 16). The use of thiourea was able to facilitate the transformation by giving evidently similar yield of products than the entries using urea (Table 3, entries 8–16).

The recyclability of the catalyst in the reaction of benzaldehyde (1 mmol), cyclopentanone (1 mmol), and urea (1.2 mmol) in the presence of DBSA (10 mol%) was checked. Upon completion of the reaction, the mixture was poured into crushed ice with stirring.

Table 2. Effects of ratio of substrates on the synthetic reaction of **4a**.[a]

Entry	Time (h)	**1a:2:3a**	Yield (%)[b]
1	1.2	1:1:1.2	93
2	1.2	2:1:1.2	70
3	1.2	2:1:2.4	85
4	1.2	2:2:1.2	88

[a]Reaction conditions: benzaldehyde (**1a**), cyclopentanone (**2**) and urea (**3a**) heating at 80°C in the presence of DBSA under solvent-free condition.
[b]Isolated yield.

The crude product was filtered, washed with cold water and recrystallized from hot ethanol. After the separation of the product, CH_2Cl_2 (20 mL) was added, and the catalyst was removed by filtration. The recovered catalyst was washed two times with an aliquot of fresh CH_2Cl_2 (2×10 mL), then drying to ready for later run. As shown in Fig. 1, the recycled catalyst was used for further runs, the yields ranged from 93% to 88%.

The suggested mechanism of the DBSA catalyzed transformations is shown in Scheme 2. As reported in the literature [22], at first the protonation of carbonyl compounds is taking place. The protonated cyclopentanone equilibrate with their enol form. The nucleophilic attack of the enol form to the protonated aldehyde following by the removing of water lead to the formation of a benzylidene intermediate (this step of the reaction generally named as cross-aldol condensation). The benzylidene intermediate further protonated and equilibrate with their enol form (5-benzylidenecyclopent-1-enol intermediate) which entangled in the attack to the protonated aldehyde to form 2-arylidene-5-(hydroxy(aryl)methyl) cyclopentanone. This intermediate protonated on the hydroxyl group which entangled in the reaction with nitrogen nuclophile from urea. The cyclization reaction following by the imine-enamine tautomerization lead to the formation of the targeted molecules (Scheme 2).

4. Conclusions

In conclusion, we describe here an efficient method for the synthesis of 7-benzylidene-4-phenyl-1,3,4,5,6,7-hexahydro-2*H*- cyclopenta[*d*]pyrimidin-2- ones/thiones by DBSA catalyzed reaction of aromatic aldehyde, cyclopentanone, and urea or thiourea under solvent-free condition at 80°C. The reaction presented here has several advantages including that it is one-pot and it is practically simple.

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Table 3. Synthesis of various 4-aryl-7-benzylidene-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*] pyrimidin-2-ones/thiones.[a]

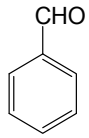
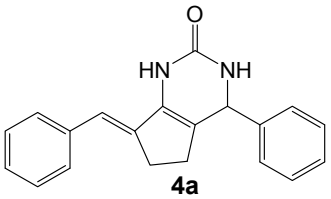
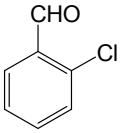
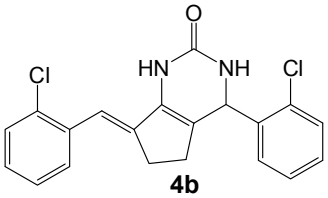
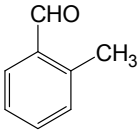
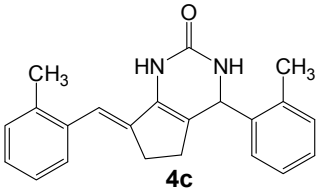
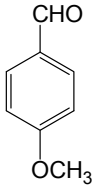
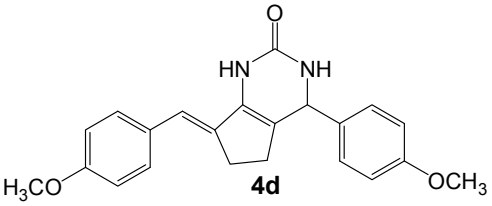
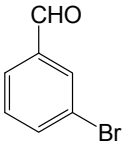
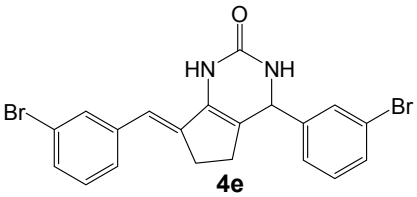
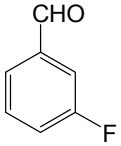
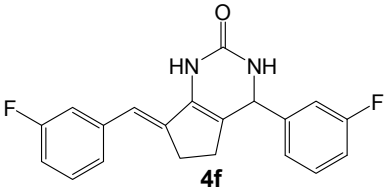
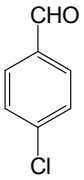
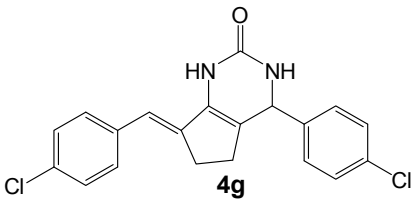
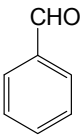
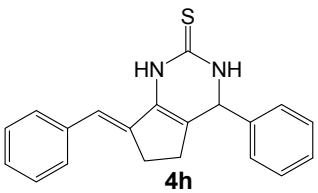
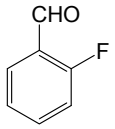
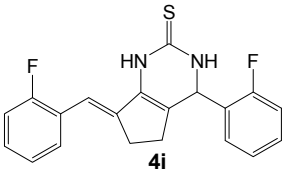
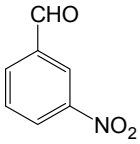
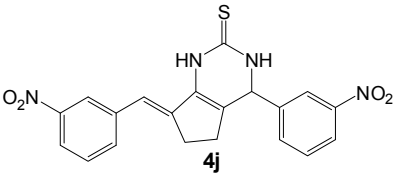
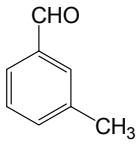
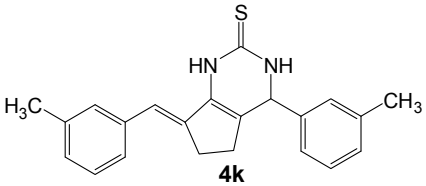
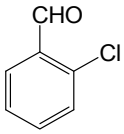
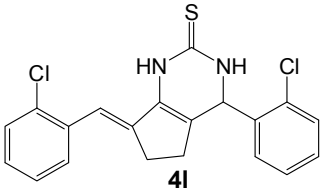
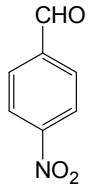
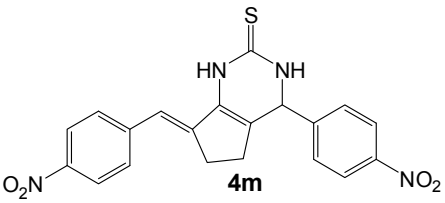
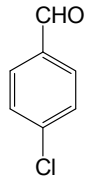
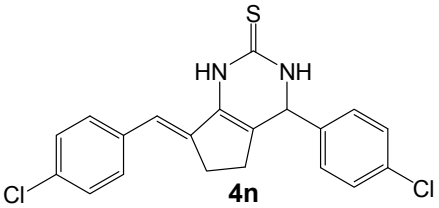
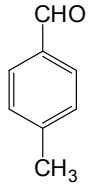
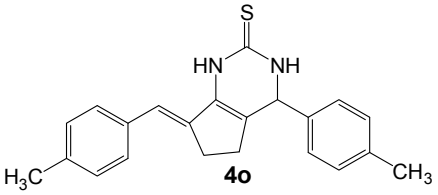
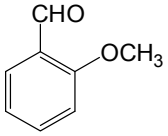
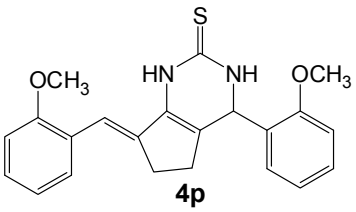
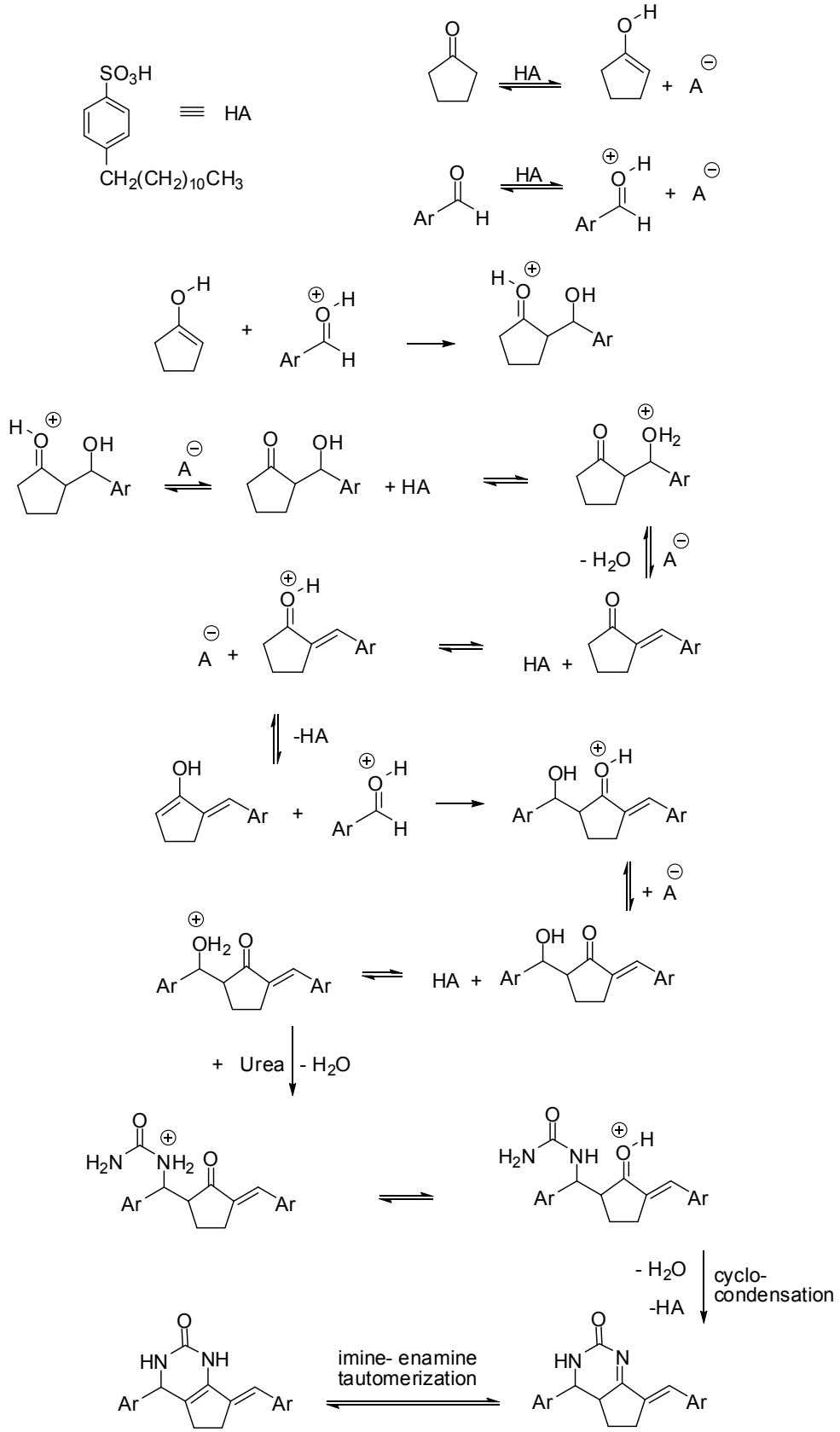
Entry	Aldehyde	Product	Time (h)	Yield (%)[b]	m.p. (°C)
1		 **4a**	1.2	93	208–210
2		 **4b**	1.6	86	218–220
3		 **4c**	1.8	84	222–224
4		 **4d**	1.4	87	212–214
5		 **4e**	1.0	90	228–230
6		 **4f**	1.0	92	226–228
7		 **4g**	1.0	90	207–209
8		 **4h**	1.2	90	226–228

Table 3. *(Continued)*.

9		 **4i**	1.4	87	202–204
10		 **4j**	1.0	94	210–212
11		 **4k**	1.5	88	215–217
12		 **4l**	1.5	86	201–203
13		 **4m**	1.0	94	203–205
14		 **4n**	1.0	90	207–209
15		 **4o**	1.5	88	208–210
16		 **4p**	1.6	83	222–224

[a]Reaction conditions: aromatic aldehydes (1 mmol), cyclopentanone (1 mmol) and urea/thiourea (1.2 mmol) heating at 80°C in the presence of DBSA (10 mol %) under solvent-free condition.
[b]Isolated yields.



Scheme 2. A plausible mechanism of DBSA-catalyzed synthesis of various substituted 4-aryl-7-benzylidene-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-ones/thiones.

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