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Synthesis of Some Arylidene Heterobicyclic Compounds using Nano Al_2O_3-SO_3H under Sonication Conditions

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Abstract

The condensation of aromatic aldehydes, cyclopentanone and urea promoted by nano Al_2O_3-SO_3H and HCl (aq) as heterogeneous and homogeneous catalysts, respectively, have been developed for the synthesis of some arylidene heterobicyclic compounds. In this synthesis, we have used two methods with sonication and thermal condition that have several advantages such as excellent yields and short reaction times. The ultrasonic device used in this study includes an ultrasonic bath equipped with a thermal system designed and built in our laboratory.

Keywords: Arylidene heterobicyclic compounds, Nano Al_2O_3-SO_3H, HCl (aq),Sonication condition, Cyclopentanone.

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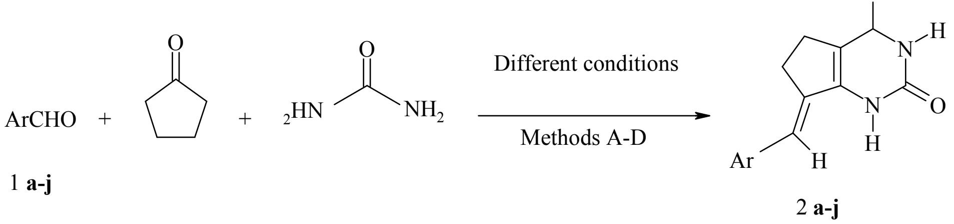
Introduction

One of the most famous reactions in the organic chemistry is Biginelli reaction. This reaction is used for synthesis of six-membered heterocyclic compounds, 1,2,3,4-tetrahydropyrimidinone and 3,4-dihydropyrimidine-2(1*H*)-one (DHPM), which are important constituents that often exist in the biologically active natural products as well as in the synthetic compounds of medicinal interest [1,2]. They also exhibit antibacterial, antifungal, antiviral, anti-inflammatory effects, antihypertensive and anticancer activities [3-7]. The earliest of these seems to be the discovery of the reaction which was reported in 1893, wherein Biginelli heated benzaldehyde, ethyl acetoacetate and urea in concentrated hydrochloric acid to obtain the now well-known 3,4-DHPM. [8] However, this reaction generally requires severe conditions and long reaction times in which it gives low yields. To overcome these drawbacks, several protocols for the synthesis of DHPMs have been developed to improve and modify this reaction [9-16]. Recently the application of cyclic ketone and *β*-diketone instance of ethyl acetoacetate was reported in the three-components condensation with different aldehydes and urea / thiourea [17-19].

Sound waves are a form of vibrational energy with continuous frequencies. Usually; they aredivided according to their functions, provided on the target substances. It contains low frequency, high energy, and power ultrasound in the kHz range. Moreover, high frequency, low energy, and the diagnostic ultrasound in the MHz range were considered as well. [20] Low frequency and high intensity ultrasound generates the strong shear and the mechanical forces. It has extensively been used in the synthesis of some 3,4-dihydropyrimidinone derivatives [21-23].

In recent years, the application of solid acid catalysts as promoter in organic transformations has been another area of growing interest in the organic synthesis because they are low toxicity and recyclable catalysts. Using the alumina sulfonic acid and nano alumina sulfonic acid opened an interesting field in the synthesis of organic compounds [24-30].The main objective of the present study is to use the nano alumina sulfonic acid as a solid acid catalyst in the synthesis of some arylidene heterobicyclic compounds under thermal and son-thermal conditions. (Scheme 1) Furthermore, we used this catalyst and HCl (aq) under the sono-thermal condition for the synthesis of these compounds. (Scheme 1).



Scheme 1.One-pot synthesis of some 4-Ar-7-benzylidene-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-ones under different conditions.

Experimental

All reagents were purchased from Merck and Aldrich and used without any further purification. ^{1}H NMR spectra were recorded on Bruker Avance 500 MHz spectrometer in DMSO-d6 with TMS as an internal standard. The FT-IR spectra were recorded on Perkin Elmer Spectrum RX in a FT-IR spectroscopy. Melting points were determined by electrothermal SI550 apparatus. The ultrasonic device used was a bath instrument Ultramet Sonic cleaner Bvehleb Ltd Apparatus that equipped to thermal system (Was designed by myself).

Preparation of nano alumina sulfonic acid

A 50 mL suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution of alkali trap. The suspension of chlorosulfonic acid (1 mL) in dry CH_2Cl_2 (3 mL) was added dropwise to powder nano Alumina (1 g) for 1 h at room temperature while the mixture was stirred slowly. Then, the mixture was shaken for 1 h. After completion of the addition, the residual HCl was eliminated by suction. At the end, the mixture was washed with dry CH_2Cl_2. Finally, nano alumina sulfonic acid as a white solid powder (2.2 g) was obtained. [30,31]

General procedure for the synthesis of 2a-j compounds using nano Al_2O_3-SO_3H as catalyst

A) Under thermal condition

A mixture of aromatic aldehydes (10 mmol), cyclopentanone (10 mmol), urea (10 mmol) and nano Al_2O_3-SO_3H (0.05 g) was heated at 120 °C under solvent-free condition. The progress of the reaction wasmonitored by TLC using *n*-hexane/ethyl acetate (5:1) as eluent. After the reaction was complete, the system was cooled to room temperature. Then, the product was washed with water, followed by crystallization from ethanol. The catalyst was separated by simple filtration and reused several times.

B) Under sono-thermal condition

The same mixture (method A) was sonicated under the reflux conditions in EtOH. The progress of the reaction and separation of the products is considered the same as method A.

General procedure for the synthesis of 2a-j compounds using HCl (aq) as catalyst

C) Under thermal condition

A mixture of aromatic aldehydes (10 mmol), cyclopentanone (10 mmol), urea (10 mmol) and 3 drops of HCl (aq) was heated under reflux conditions. TLC monitoring of the reaction using nhexane/ethyl acetate (5:1) as eluent was followed until total disappearance of the cyclopentanone compound was observed. After cooling to room temperature, the mixture was washed with cold water, and then the crude product was recrystallized from ethanol.

D) Under sono-thermal condition

The same mixture (method C) was sonicated under the reflux conditions in EtOH. The progress of the reaction and separation of the products is considered the same as method C.

Result and discussion

In continuation of our studies on developing inexpensive and environmentally benign methodologies for the organic reactions, especially with the use of nano solid acid catalysts. [24-26] In this study, we used Al_2O_3-SO_3H and HCl (aq) as the catalysts under thermal and son-thermal conditions for the Biginelli condensation reaction of cyclopentanone with a vast variety of aldehydes and urea. To the best of our knowledge, there is no literature reporting on arylidene heterobicyclic synthesisunder these conditions. (Methods A-D) A mixture of benzaldehyde (1**a**), cyclopentanone, urea and nano Al_2O_3-SO_3H (24–180 nm) as a catalyst were used under different conditions. In this reaction different solvents such as water, ethanol and acetonitrile (10 mL for each one) were used at room temperature and thermal condition. According to the data reported in Table 1, the best condition was achieved as a mixture of the following materials as benzaldehyde, cyclopentanone and urea by molar ratio 1:1:1 in the presence of 0.05 g of nano Al_2O_3-SO_3H under solvent-free at a temperature of 120 °C.

Table 1. Optimization synthesis of 7-benzylidene-1,3,4,5,6,7-hexahydro-4-phenyl-2H-cyclopenta [d] pyrimidin-2-one product (2a) using nano Al_2O_3-SO_3H catalyzed under different conditions.

Entry.	Solvent (mL)	Amount of catalyst (g)	T (°C)	Time (min)[a]	Yield (%)[b]
1	Water (10)	0.1	r.t.	120	22
2	EtOH (10)	0.1	r.t	120	35
3	CH_3CN (10)	0.1	r.t	120	33
4	Solvent free	0.1	r.t	120	38
5	EtOH (10)	0.1	reflux	60	64
6	CH_3CN (10)	0.1	reflux	60	54
7	Solvent-free	0.1	80	45	84
8	Solvent-free	0.1	100	45	91
9	Solvent-free	0.1	120	5	97.3
10	Solvent-free	0.1	140	5	97.4
11	Solvent-free	0.05	120	5	97

[a] Times are given after maximum progression of the reaction. [b] Isolated yield.

However, similar mixture was sonicated under different conditions. Data are reported in Table 2. The best condition was achieved with the same mixture and the molar ratio of the materials were achieved in the presence of 0.05 g of nano Al_2O_3-SO_3H in ethanol under reflux condition.

Table 2. Optimization synthesis of product (2**a**) using nano Al_2O_3-SO_3H catalyzed under ultrasonic bath wave conditions.

Entry.	Solvent (mL)	Amount of catalyst (g)	T (°C)	Time (min)[a]	Yield (%)[b]
1	EtOH	0.1	r.t	45	73
2	CH_3CN	0.1	r.t	45	65
3	EtOH	0.1	reflux	30	94
4	CH_3CN	0.1	reflux	30	88
5	EtOH	0.05	reflux	30	93

[a] Times are given after maximum progression of the reaction. [b] Isolated yield.

Furthermore, this reaction was carried out with the HCl (aq) under different conditions. (Methods C and D) These data are reported in Tables 3 and 4. According to the data reported in the Table 3, the best result was achieved in HCl (aq) ($7.2 \times 10^{-3)}$ under reflux conditions.

Table 3. Optimization synthesis of product (2**a**) using HCl (aq) catalyzed under thermal conditions.

Entry.	Solvent (mL)	[HCl] (M)	T (°C)	Time (min)[a]	Yield (%)[b]
1	EtOH (10)	7.2×10^{-3}	r.t	120	23
2	EtOH (10)	7.2×10^{-3}	Reflux	30	90

The reaction was carried out at the same above conditions, but in ultrasonic conditions. The combination of ultrasound and heat (sono-thermal) decreases drastically the time of reaction compared with the reaction under thermal condition. (Time (15 min)) (Table 4)

Table 4. Optimization synthesis of product (2**a**) using HCl (aq) catalyzed under ultrasonic bath wave conditions.

Entry.	Solvent (mL)	[HCl] (M)	T (°C)	Time (min)[a]	Yield (%)[b]
1	EtOH (10)	7.2×10^{-3}	r.t	45	77
2	EtOH (10)	7.2×10^{-3}	Reflux	15	94

After the optimization of the different methods, this reaction was carried out with various aryl aldehydes under different methods.

Method A: using 0.05 g nano Al_2O_3-SO_3H as catalyst under solvent-free at 120 °C. These data are reported in the Table 5. As shown in this table, the substitution patterns and the electronic effect of substituents on the aryl ring can be effected on the reaction yield. (71-97%)

Table 5. Synthesis of some 4-Ar-7-benzylidene-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-ones in the presence of nano Al_2O_3-SO_3H as catalyst under solvent-free at the temperature of 120 °C (Method A).

Comp.	Ar	Time (min)	Yiled (%)[a]	Observed M.p	Reported M.p
2**a**	C_6H_5-	5	97	233-236	236-239 [17]
2**b**	2-Me-C_6H_4-	5	71	226-228	222-224 [32]
2**c**	4-Me-C_6H_4-	10	92	234-237	238-241 [17]
2**d**	2-Cl-C_6H_4-	5	95	229-232	232-234 [17]
2**e**	3-Cl-C_6H_4-	5	90	233-235	229-232 [17]
2**f**	4-Cl-C_6H_4-	5	88	256-258	252-255 [17]
2**g**	3-MeO-C_6H_4-	15	93	238-240	240-242 [33]
2**h**	4-MeO-C_6H_4-	10	85	249-251	250-252 [17]
2**i**	3-Br-C_6H_4-	5	91	225-227	228-230 [32]
2**j**	4-Br-C_6H_4-	5	95	218-220	219-222 [34]
2**k**	3-Me-C_6H_4-	5	70	251-253	

[a] Time is given after maximum progression of the reaction. [b] Isolated yield.

Method B: This reaction was carried out under sono-thermal condition in the ethanol solvent under reflux condition by using the same method A. (Table 6)

Table 6. Synthesis of the same compounds in the presence of nano Al_2O_3-SO_3H as catalyst under sono-thermal condition (Method B).

Comp.	Ar	Time (min)	Yiled (%)
2**a**	C_6H_5-	30	93
2**b**	2-Me-C_6H_4-	30	84
2**c**	4-Me-C_6H_4-	30	91
2**d**	2-Cl-C_6H_4-	30	86
2**e**	3-Cl-C_6H_4-	30	83
2**f**	4-Cl-C_6H_4-	30	80
2**g**	3-MeO-C_6H_4-	35	83
2**h**	4-MeO-C_6H_4-	30	81
2**i**	3-Br-C_6H_4-	35	88
2**j**	4-Br-C_6H_4-	35	92
2**k**	3-Me-C_6H_4-	30	85

Method C: In this method, synthesis of some dihydropyrimidinones was carried out by using 3 drops HCl (aq) in 10 mL ethanol as solvent under reflux conditions. These data are reported in the Table 7.

Table 7. Synthesis of the same compounds in the presence of 1-2 drops of HCl (aq) as catalyst in ethanol under thermal and sono-thermal conditions. (Methods C and D).

Comp.	Method C		Method D	
	Time (min)	Yield (%)	Time (min)	Yield (%)
2**a**	30	90	15	94
2**b**	30	63	15	82
2**c**	30	84	15	90
2**d**	60	81	30	92
2**e**	60	77	30	85
2**f**	60	79	30	87
2**g**	30	78	15	83
2**h**	30	80	15	88
2**i**	45	82	20	91
2**j**	45	80	20	93
2**k**	30	65	15	85

Method D: In this method the reaction was carried out under sono-thermal condition by using 3 drops of HCl (aq) in 10 mL ethanol (Table 7). The data reported in Table 7 show the effect of ultrasonic wave on carrying a decrease of the reaction time and increasing the isolated yields (Method D, Time 15-30 (min), Yield 91-94%).In summary, we have described an alternative and general method for the multicomponent synthesis of functionalized of some 4-Ar-7-benzylidene-1,3,4,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-ones using nano Al_2O_3-SO_3H and HCl (aq) as catalysts under different conditions. Each of these methods is an efficient method for this Biginelli condensation reaction.The prospect of the reusability of nano Al_2O_3-SO_3H catalyst has also been demonstrated without compromising on the yield of the product. These data are reported in the Table 8.

Table 8. Recyclability of nano Al_2O_3-SO_3H (0.05 g) for synthesis of product (2**a**) under solvent-free condition at 120 ˚C.

Entry	Yield (%) a	Time (min) b
1	97	5
2	94	5
3	91	5
4	88	5
5	85	5

Comparison synthesis data of somearylidene heterobicyclic compounds under thermal and son-thermal conditions using nano Al_2O_3-SO_3H and HCl (aq) as catalysts are show in the Figure 1.

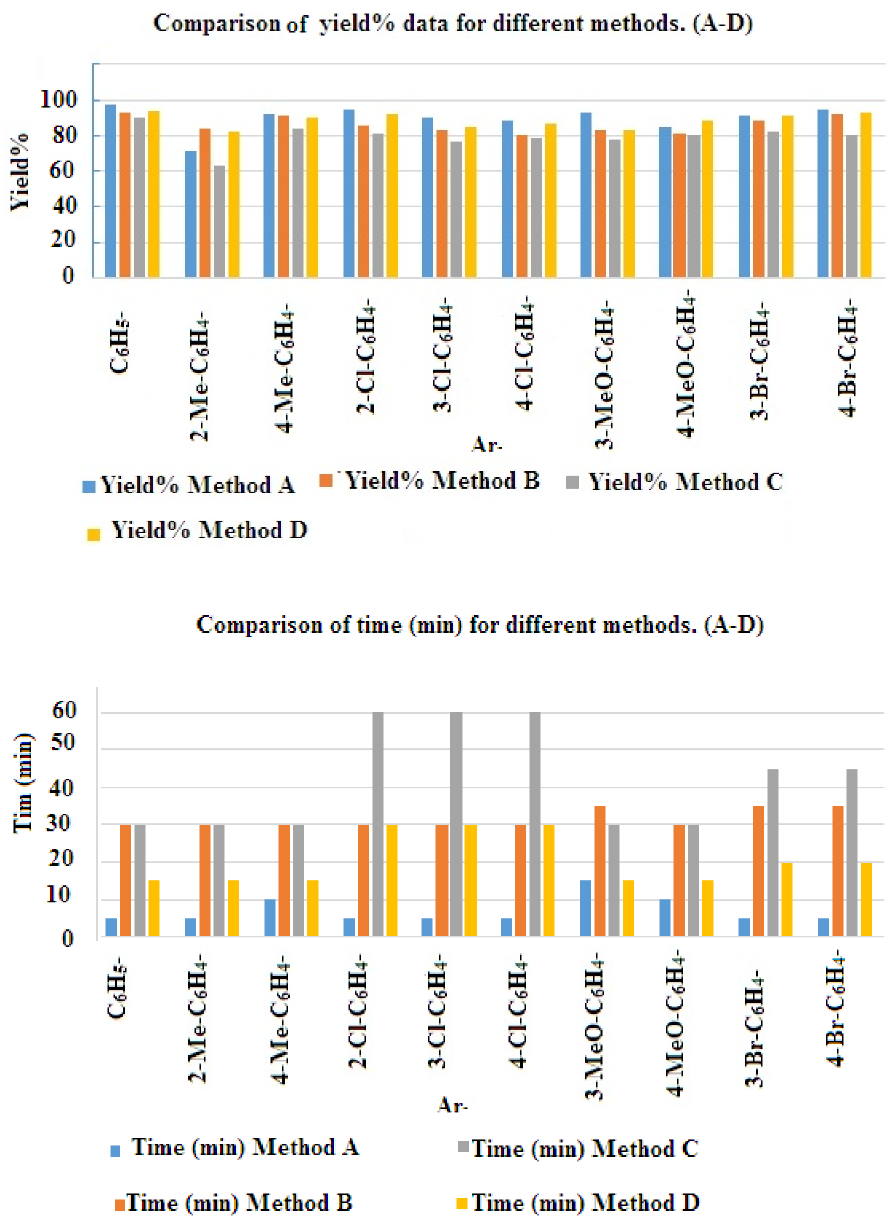


Figure 1. Diagrams for comparing yields and times for different synthesized methods (A-D).

Selected spectral data

7-benzylidene-1,3,4,5,6,7-hexahydro-4-phenyl-2*H*-cyclopenta[*d*]pyrimidin-2-one (2**a**)

M.p. 233–236 °C. -IR (KBr): 3408, 3206, 3115, 3020, 2846, 1670, 1465, 1443, 1352 cm^{-1}. -^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.87 (s, 1 H), 7.23–7.69 (m, 8 H), 6.71 (s, 1 H), 5.23 (s, 1 H), 2.83–2.96 (m, 2 H), 2.45-250 (m, 1 H), 2.10–1.93 (m, 1 H) ppm.

7-(2-methylbenzylidene)-1,3,4,5,6,7-hexahydro-4-(2-methylphenyl)-2*H*-cyclopenta[*d*]pyrimidin-2-one (2**b**)

M.p. 226–228 °C. -IR (KBr): 3236, 3113, 2922, 2849, 2359, 1678, 1590, 1490, 1457 cm^{-1}. -^{1}H NMR (500 MHZ, DMSO-d$_6$): δ = 8.92 (s, 1 H), 7.03– 7.35 (m, 8 H), 6.65 (s, 1 H), 5.38 (s, 1 H), 3.30-3.32 (m, 2 H), 2.69-2.72 (m, 1 H), 2.31(s, 3H), 2.27(s, 3H), 1.88 (m, 1 H) ppm.

7-(3-bromobenzylidene)-1,3,4,5,6,7-hexahydro-4-(3-bromophenyl)-2*H*-cyclopenta[*d*]pyrimidin-2-one (2**i**)

M.p. 225–227 °C. -IR (KBr): 3251, 2915, 2848, 2360, 1685, 1386, 1492, 1463, 1420 cm^{-1}. -^{1}H NMR (500 MHZ, DMSO-d$_6$): δ = 8.82 (s, 1 H), 7.25–7.47 (m, 8 H), 6.57 (s, 1 H), 5.17 (s, 1 H), 2.80–2.77 (m, 2 H), 2.33-2.41 (m, 1 H), 2.00–1.96 (m, 1 H) ppm.

7-(3-methylbenzylidene)-1,3,4,5,6,7-hexahydro-4-(3-methylphenyl)-2*H*-cyclopenta[*d*]pyrimidin-2-one (2**k**)

M.p. 251-253 °C. -IR (KBr): 3443, 3214, 3115, 2845, 1687, 1511, 1447 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.75 (s, 1 H), 7.03– 7.25 (m, 8 H), 6.55 (s, 1 H), 5.41 (s, 1 H), 2.75-2.79 (m, 1 H), 2.33-2.47 (m, 2 H), 2.27 (s, 3H), 2.33 (s, 3H), 1.95-1.97 (m, 1 H) ppm.

Conclusion

We have reported two methods for the synthesis of some arylidene heterobicyclic compounds under thermal and son-thermal conditions using nano Al_2O_3-SO_3H and HCl (aq) as catalysts. These methods have several advantages such as excellent yields and short reaction times. This condensation reaction can be developed under thermal and sonicated conditions. The main advantages of synthesis of these compounds under sono-thermal condition are short reaction times and high product yields.

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