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P-Dodecylbenzenesulfonic acid (DBSA), a Brønsted acid-surfactant catalyst for Biginelli reaction in water and under solvent free conditions

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Abstract

We report herein the use of *p*-dodecylbenzenesulfonic acid (DBSA) as a catalyst for a one-pot Biginelli reaction to afford 3,4-dihydropyrimidinone derivatives in good to excellent yields. This reaction proceeds efficiently in water and under solvent free conditions. Comparisons of results indicate that although the yields are high and comparable for both methods, the reaction times are considerably shorter under solvent free conditions.

Keywords: Biginelli reaction; Dihydropyrimidinone; *P*-Dodecylbenzenesulfonic acid (DBSA)

In 1893, Pietro Biginelli reported the first synthesis of 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) by a one pot condensation reaction of aromatic aldehydes and ethylacetoacetate urea under a strongly acidic condition [1]. Dihydropyrimidinones (DHPMs) exhibit a wide range of biological activities such as antiviral, antitumor, antibacterial and anti-inflammatory actions [2]. Some marine natural products containing the dihydropyrimidinone-5-carboxylate units such as batzelladine alkaloids have been found to be potent HIV (gp-120-CD4) inhibitors [3]. Thus the synthesis of these heterocyclic compounds is of current interest. Recently, numerous improved procedures using $FeCl_3$/HCl [4], $LaCl_3$-graphite [5], PPh_3 [6], $SbCl_3$ [7], $PhB(OH)_2$ [8], $InBr_3$ [9], Dowex [10], baker's yeast [11], heteropoly acids [12], $CuCl_2{\cdot}2H_2O$ [13], NBS [14], I_2 [15], covalently anchored sulfonic acid on silica [16] and TCCA [17] are reported. Many of these protocols suffer from the use of expensive catalysts, prolonged reaction times and low yields. Thus search for newer and more efficient methods are needed. Recently, organic reactions in water without the use of harmful organic solvents have attracted much attention. *p*-Dodecylbenzenesulfonic acid (DBSA) is a Brønsted acid-surfactant-combined catalyst, composed of an acidic group and a hydrophobic moiety that has been studied as a catalyst in organic chemistry [18]. The behavior of DBSA as a catalyst has been studied in Mannich type reactions [19] and also in esterification of various carboxylic acids and alcohols [20]. In this study, we report our results for the synthesis of DHPMs using DBSA in environmentally benign conditions.

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1. Experimental

IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer (KBr). ^{1}H NMR spectra were recorded on a varian 300 MH_Z spectrometer. Melting points were determined using an Electrotermal 9100 and are uncorrected. Reactions were monitored by thin layer chromatography and products were identified fully or by comparison of melting points and spectroscopic data with those previously reported.

1.1. General procedure for synthesis of DHPM using DBSA (in water)

A mixture of urea (0.168 g, 2.8 mmol), benzaldehyde or substituted benzaldehydes (2 mmol), β-ketoester (2 mmol) and DBSA (0.4 mmol) in water (5 mL) was heated at 54 °C for 7 h. Upon cooling, solid material precipitated from the solution (Table 2). The precipitates were filtered off, washed with water and were recrystalized from EtOH to afford pure DHPMs as yellow-white solids.

1.2. General procedure for synthesis of DHPM using DBSA (solvent free)

A mixture of urea (0.168 g, 2.8 mmol), benzaldehyde or substituted benzaldehyde (2 mmol), β-ketoesters (2 mmol) and DBSA (0.4 mmol) was heated at 100 °C, while stirring for 30 min. The solid material which precipitated upon cooling was recrystalized from EtOH to afford pure DHPMs (Table 2).

Compound **4e** (0.54 g, 81%) mp 231–233 °C (found: C, 49.55; H, 4.43; N, 8.22. $C_{14}H_{15}BrN_2O_3$ requires C, 49.57; H, 4.46; N, 8.26%); ν_{max}/cm^{-1} 3353 and 3222 (NH), 1694 and 1646 (C=O); ^{1}H NMR (300 MHz; DMSO-d_6; Me_4Si): δ 1.05 (t, 3H, CH_3CH_2), 2.23 (s, 3H, Me), 3.9(q, 2H, CH_2), 5.1 (d, 1H, 4-H), 7.1–7.5 (m, 4H, Ph), 7.7(s, 1H, 3-H), 9.23(s, 1H, 1-H); ^{13}C NMR (75 MHz; DMSO-d_6; Me_4Si): δ 14.05, 17.79, 53.47(C-4), 59.25(CH_2), 98.74(C-5), 120.29, 128.53, 131.3, 144.18, 148.72(C-6), 151.91, 165.18.

Compound **4h** (0.51 g, 81%) mp 167–170 °C (found: C, 70.75; H, 5.61; N, 8.67. $C_{19}H_{18}N_2O_3$ requires: C, 70.79; H, 5.63; N, 8.69%); ν_{max}/cm^{-1}3356 and 3219 (NH), 1704 and 1687 (C=O); ^{1}H NMR (300 MHz; DMSO-d_6; Me_4Si): δ 2.25(s, 3H, CH_3), 4.96 (q, 2H, CH_2), 5.15 (d, 1H, 4-H), 7.11–7.31(m, 10H, 2Ph), 7.74 (s, 1H, 3-H), 9.25 (s, 1H, 1-H); ^{13}C NMR (75 MHz; DMSO-d_6; Me_4Si): δ 17.84(CH_3), 53.91(C-4), 64.78(CH_2), 98.70(C-5), 126.27, 127.29, 127.52, 127.68, 128.25, 128.41, 136.50, 144.63, 149.26(C-6), 151.96, 165.04.

Compound **7a** (0.16 g, 23%) mp 198–201 °C (found: C, 48.22; H, 4.35; N, 8.15. $C_{14}H_{15}F_3N_2O_5$: C, 48.28; H, 4.34; N, 8.04%); ν_{max}/cm^{-1}3598(OH), 3343 and 3320 (NH), 1703 and 1623 (C=O); ^{1}H NMR (300 MHz; DMSO-d_6; Me_4Si): δ 1.87(s, 3H, CH_3), 3.72(s, 3H, CH_3), 3.02(d, 1H, 5-H), 4.76(d, 1H, 4-H), 7.13(s, 1H, OH), 7.55(s, 1H, 3-H), 7.67 (s, 1H, 1-H); 6.86-7.28(m, 4H, Ph); ^{13}C NMR (75 MHz; DMSO-d_6; Me_4Si): δ 30.47, 52.45, 55.09, 57.42, 80.40, 80.82, 113.85, 129.24, 153.55, 159.19, 204.15.

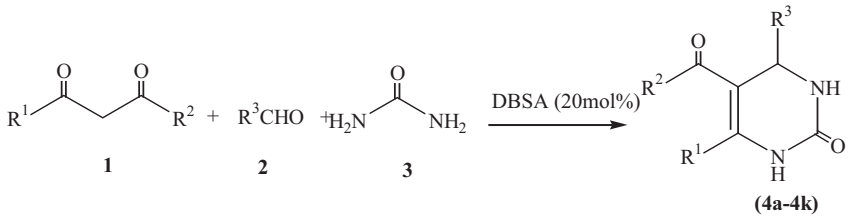
Compound **7b** (0.33 g, 45%) mp 215–217 °C (found: C, 42.87; H, 3.21; N, 11.48. $C_{13}H_{12}F_3N_3O_6$: C, 42.98; H, 3.33; N, 11.57%); ν_{max}/cm^{-1} 3588(OH), 3354 and 3316 (NH), 1726 and 1675 (C=O); ^{1}H NMR (300 MHz; acetone-d_6; Me_4Si): δ 1.88(s, 3H, CH_3), 3.66(d, 1H, 5-H), 5.13 (d, 1H, 4-H), 6.39(s, 1H, 3-H), 6.75(s, 1H, 1-H), 7.16(s, 1H, OH), 7.69–8.39(m, 4H, Ph); ^{13}C NMR (75 MHz; acetone-d_6; Me_4Si): δ 32.37, 55.10, 82.22, 122.38, 123.85, 124.62, 126.98, 131.09, 135.42, 141.15, 149.44, 154.62, 205.89.

2. Results and discussion

We wish to report the use of DBSA as a catalyst in Biginelli's reaction (Scheme 1). A summary of the optimized experiments is listed in Table 1. Our results show that the best yields are obtained in water at 54 °C (entry 5) and the optimum amount of DBSA is found to be 20 mol% (entry 5).

In order to investigate the scope of these reactions, various types of substituted benzaldehydes and different β-ketoesters were studied in water and under solvent free conditions. Comparison of the results obtained under the two conditions is reported in Table 2.

β-Ketoesters containing CF_3 groups, however, did not behave similarly. More careful analysis of spectroscopic data revealed that the products obtained from these starting materials were in fact the non dehydrated precursors of expected DHPMs (**7a**, **7b**). The mechanism of the reaction is depicted in Scheme 2. We later found evidence of similar



Scheme 1. Synthesis of DHPMs catalyzed by DBSA in H_2O.

Table 1
Reaction of benzaldehyde, methyl acetoacetate and urea in water[a].

Entry	DBSA%	Time (h)	Temperature (°C)	Yield%
1	0	7	54	0
2	5	7	54	38.6
3	10	7	54	44.7
4	15	7	54	61.3
5	20	7	54	90
6	25	7	54	81
7	30	7	54	70
8	20	9	18	0
9	20	8	34	65.4
10	20	7	68	90

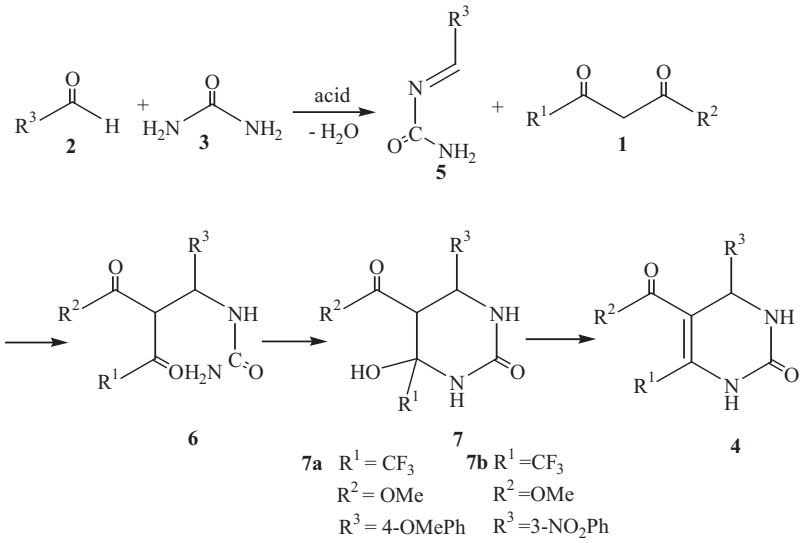
[a] benzaldehyde/methyl acetoacetate/urea, 1:1:1.4.

Table 2
DBSA catalyzed synthesis of dihydropyrimidinones in water or solvent free.

Compound	R^1	R^2	R^3	In water		Solvent free		mp (°C)	Lit. mp (°C)
				Time (h)	Yield (%)	Time (min)	Yield (%)		
4a	CH_3	OMe	C_6H_5	7	90	30	96	212–214	209–212 [21]
4b	CH_3	OEt	C_6H_5	7	89	30	92	204–207	202–205 [17]
4c	CH_3	OEt	4-$MeOC_6H_4$	8	78	20	80	213–218	215–216 [9]
4d	CH_3	OEt	4-$NO_2C_6H_4$	8	76	15	81	208–211	208–211 [21]
4e	CH_3	OEt	4-BrC_6H_4	7	81	15	88	231–233	–
4f	CH_3	OEt	3-ClC_6H_4	9	83	15	88	194–197	193–195 [9]
4g	CH_3	OEt	2-Naphthyl	7	69	20	72	279–281	–
4h	CH_3	OCH_2Ph	C_6H_5	8	81	10	89	167–170	–
4i	CH_3	OCH_2Ph	4-$MeOC_6H_4$	8	80	15	87	190–193	–
4j	CH_3	OCH_2Ph	2-ClC_6H_4	9	80	10	92	213–215	–
4k	CH_3	OCH_2Ph	3-$NO_2C_6H_4$	8	75	10	88	217–219	–
7a	CF_3	OMe	4-$MeOC_6H_4$	7	23	–	–	198–201	–
7b	CF_3	OMe	3-$NO_2C_6H_4$	9	45	–	–	215–217	–

behavior in previous reports [22]. It appears that the presence of CF_3 groups has two effects on the faith of this reaction. It slows down the overall rate of reaction (hence the low yields) and it also prohibits the dehydration step.

The reaction times are shorter under solvent free conditions than when water is used as solvent. Biginelli reaction requires strong acidic conditions. It is possible that water hinders the reaction to some extend by lowering the acidity and hence longer reaction times.



Scheme 2. Possible mechanism of the reaction.

3. Conclusion

In conclusion, we report the development of a one pot, simple, inexpensive, ecofriendly (non-toxic solvents and catalyst), benign and efficient method for Biginelli reaction. High yields and short reaction times are further positive features of this work.

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