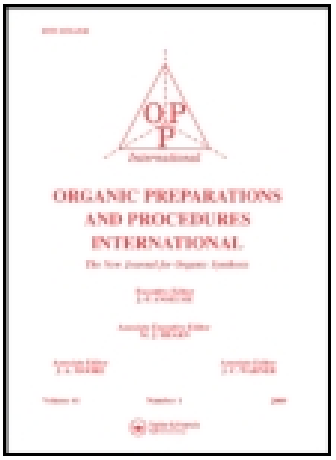

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Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones using Sodium Bisulfate as a Catalyst under Solvent-free Conditions

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OPPI BRIEF

Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones using Sodium Bisulfate as a Catalyst under Solvent-free Conditions

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Pyrimidinones or dihydropyrimidinones (DHPMs) are important heterocycles that have drawn much attention due to their biological[1] and pharmacological[2] action as well as their potent calcium channel blocking activity.[3–5] Thus, the synthesis of these compounds has attracted considerable interest in recent years.[6]

Multicomponent reactions (MCRs) are highly flexible, chemo-selective, convergent and atom-efficient processes. Over the past decade, a very efficient way to access heterocycles has been the use of MCRs. In 2004, Wang *et al*. first reported MCR preparation methods for the synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones from aromatic aldehydes, aromatic ketones and urea in the presence of $FeCl_3 \cdot 6H_2O$/TMSCl in CH_3CN.[7] Later, other catalysts such as NaI/TMSCl,[8] $Co(OAc)_2$/TMSCl,[9] tBuONa/MWI,[10] PTSA/MWI,[11] $AlCl_3$ or $AlBr_3$ in CH_3CN,[12] I_2,[13] ZnI_2/MWI,[14] $Fe(NO_3)_3 \cdot 9H_2O$,[15] and $AlCl_3$/KI under N_2 atmosphere[16] *etc*. have been used as well. However, the majority of these methods suffer from one or more disadvantages such as high toxicity of the solvent, high reaction temperature (140°C), the need for an additional promoter (TMSCl) or the use of microwave irradiation. As part of our studies toward the green synthesis of heterocycles,[17] we now report an efficient procedure for the preparation of 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones *via* the one-pot condensation of aromatic aldehydes, acetophenones and urea in the presence of $NaHSO_4$ at 90°C without solvent and promoter (*Scheme 1*).

We initiated our study with 2-nitrobenzaldehyde, acetophenone, and urea as a model reaction to determine the best experimental conditions. Solvent, the amount of catalyst and suitable reaction temperature were investigated. It was shown that 50% molar amount of $NaHSO_4$ under solvent-free conditions at 90°C gave the best results.

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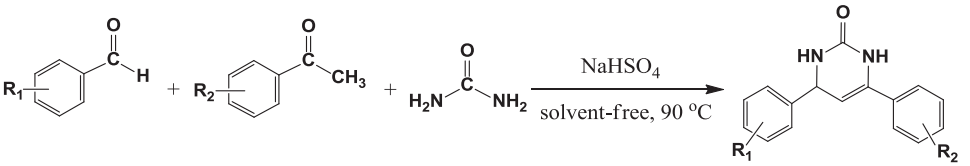

On the basis of these results, various substituted aromatic aldehydes treated with acetophenones and urea under these optimized reaction conditions to investigate the scope of this Biginelli-type reaction. The results are summarized in *Table 1*. It could be seen that all reactions proceed smoothly to afford the corresponding 5-unsubstituted 3,4-dihydropyri-midin-2(1*H*)-ones in short reaction times with excellent yields. Neither electron-withdrawing nor electron-donating groups on the aromatic ring affected the reaction significantly, either in the yield of product or the rate of the reaction. In addition, one aliphatic aldehyde (propio-naldehyde), an unsaturated aldehyde (cinnamaldehyde) and an aliphatic ketone (acetone) were also utilized in this reaction; unfortunately, after 3 h only dark colored sticky materials were formed and none of the desired products could be obtained. The condensation of benzaldehyde, acetophenone and thiourea under these

Table 1
Preparation of 5-Unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones Catalyzed by $NaHSO_4$

Product	R_1	R_2	Time (min)	Yield (%)	mp (°C)	Lit. (°C)
4a	H	H	20	84	217–219	218–219[8]
4b	2-Cl	H	13	92	209–211	*see Table 2*
4c	2,4-Cl_2	H	8	89	213–215	*see Table 2*
4d	2-NO_2	H	10	82	225–226	*see Table 2*
4e	3-NO_2	H	17	91	201–202	*see Table 2*
4f	4-NO_2	H	7	90	197–198	*see Table 2*
4g	2-CH_3O	H	30	75	230–232	*see Table 2*
4h	3-OH	H	30	76	211–212	*see Table 2*
4i	H	4-CH_3O	40	85	209–210	209–211[11]
4j	4-Cl	4-CH_3O	45	86	261–262	263–265[10]
4k	2-NO_2	4-CH_3O	15	74	213–215	*see Table 2*
4l	3-NO_2	4-CH_3O	60	89	198–200	*see Table 2*
4m	4-NO_2	4-CH_3O	10	95	191–193	*see Table 2*
4n	2-NO_2	4-Cl	10	88	219–220	*see Table 2*
4o	3-NO_2	4-Cl	20	73	202–203	*see Table 2*
4p	4-NO_2	4-Cl	12	94	195–197	*see Table 2*
4q	4-Cl	4-NO_2	45	92	193–194	*see Table 2*
4r	2-NO_2	4-NO_2	15	87	216–217	*see Table 2*
4s	3-NO_2	4-NO_2	40	90	193–195	*see Table 2*

Table 2
Spectral Data of Compounds **4b**-**4h**, **4k**-**4s**

Cmpd	mp (°C)	Elemental Analysis (Found)			IR	^{1}H NMR (δ)
		C	H	N	(cm^{-1})	
4b	209–211	67.49 (67.65)	4.60 (4.54)	9.84 (9.73)	3340 3308 1650	10.36 (s, 1H, NH), 9.54 (s, 1H, NH), 7.42-6.37 (m, 9H, ArH), 5.63 (s, 1H, =CH), 5.45 (s, 1H, CH)
4c	213–215	60.21 (60.06)	3.79 (3.85)	8.78 (8.70)	3428 3293 1669	10.28 (s, 1H, NH), 8.90 (s, 1H, NH), 7.95-6.28 (m, 8H, ArH), 5.67 (s, 1H, =CH), 5.45 (s, 1H, CH)
4d	225–226	65.08 (65.22)	4.44 (4.36)	14.23 (14.35)	3480 3301 1673	10.25 (s, 1H, NH), 8.73 (s, 1H, NH), 7.87-7.51 (m, 6H, ArH), 6.88 (d, 2H, $J = 7.8$ Hz, ArH), 6.55 (t, 1H, $J = 7.8$ Hz, ArH), 5.71 (s, 1H, =CH), 5.45 (s, 1H, CH)
4e	201–202	65.08 (64.89)	4.44 (4.53)	14.23 (14.31)	3440 3297 1668	10.15 (s, 1H, NH), 8.70 (s, 1H, NH), 8.17-6.99 (m, 8H, ArH), 6.26-6.19 (m, 1H, ArH), 5.83 (s, 1H, =CH), 5.45 (s, 1H, CH)
4f	197–198	65.08 (65.24)	4.44 (4.37)	14.23 (14.12)	3459 3317 1662	10.17 (s, 1H, NH), 8.70 (s, 1H, NH), 8.43-7.30 (m, 6H, ArH), 7.04-6.98 (m, 2H, ArH), 6.25-6.17 (m, 1H, ArH), 5.82 (s, 1H, =CH), 5.46 (s, 1H, CH)
4g	230–232	72.84 (73.00)	5.75 (5.64)	9.99 (10.12)	3441 3321 1647	10.01 (s, 1H, NH), 8.79 (s, 1H, NH), 7.97-6.31 (m, 9H, ArH), 5.63 (s, 1H, =CH), 5.43 (s, 1H, CH), 3.80 (s, 3H, OCH_3)
4h	211–212	72.16 (72.01)	5.30 (5.17)	10.52 (10.65)	3444 3350 1652	9.98 (s, 1H, NH), 9.40 (s, 1H, NH), 7.12-6.03 (m, 10H, ArH and -OH), 5.67 (s, 1H, =CH), 5.45 (s, 1H, CH)

(Continued on next page)

Table 2
Spectral Data of Compounds **4b**-**4h**, **4k**-**4s** *(Continued)*

Cmpd	mp (°C)	Elemental Analysis (Found) C	H	N	IR (cm^{-1})	^{1}H NMR (δ)
4k	213–215	62.76 (62.90)	4.65 (4.54)	12.92 (13.01)	3479 3301 1672	9.15 (s, 1H, NH), 8.73 (s, 1H, NH), 7.87-7.51 (m, 5H, ArH), 6.88 (d, 2H, $J = 7.4$ Hz, ArH), 6.56 (t, 1H, $J = 7.4$ Hz, ArH), 5.71 (s, 1H, =CH), 5.46 (s, 1H, CH), 3.84 (s, 3H, OCH_3)
4l	198–200	62.76 (62.61)	4.65 (4.72)	12.92 (12.84)	3438 3300 1668	10.15 (s, 1H, NH), 8.70 (s, 1H, NH), 8.35-7.00 (m, 7H, ArH), 6.32-6.20 (m, 1H, ArH), 5.83 (s, 1H, =CH), 5.45 (s, 1H, CH), 3.84 (s, 3H, OCH_3)
4m	191–193	62.76 (62.58)	4.65 (4.73)	12.92 (13.01)	3447 3313 1669	10.17 (s, 1H, NH), 8.99 (s, 1H, NH), 8.43-6.18 (m, 8H, ArH), 5.83 (s, 1H, =CH), 5.46 (s, 1H, CH), 3.84 (s, 3H, OCH_3)
4n	219–220	58.28 (58.41)	3.67 (3.60)	12.74 (12.82)	3480 3301 1673	10.24 (s, 1H, NH), 8.73 (s, 1H, NH), 8.14-7.51 (m, 5H, ArH), 6.88 (d, 2H, $J = 7.5$ Hz, ArH), 6.55 (t, 1H, $J = 7.5$ Hz, ArH), 5.71 (s, 1H, =CH), 5.45 (s, 1H, CH)
4o	202–203	58.28 (58.16)	3.67 (3.57)	12.74 (12.85)	3440 3298 1668	10.15 (s, 1H, NH), 8.70 (s, 1H, NH), 8.33-7.33 (m, 5H, ArH), 6.99 (d, 2H, $J = 7.2$ Hz, ArH), 6.25-6.19 (m, 1H, ArH), 5.82 (s, 1H, =CH), 5.44 (s, 1H, CH)
4p	195–197	58.28 (58.39)	3.67 (3.61)	12.74 (12.56)	3459 3318 1662	10.17 (s, 1H, NH), 8.87 (s, 1H, NH), 8.43-6.19 (m, 8H, ArH), 5.83 (s, 1H, =CH), 5.46 (s, 1H, CH)
4q	193–194	58.28 (58.14)	3.67 (3.55)	12.74 (12.60)	3437 3308 1654	10.01 (s, 1H, NH), 8.87 (s, 1H, NH), 8.36-6.15 (m, 8H, ArH), 5.71 (s, 1H, =CH), 5.42 (s, 1H, CH)

(Continued on next page)

Table 2
Spectral Data of Compounds **4b**-**4h**, **4k**-**4s** *(Continued)*

Cmpd	mp (°C)	Elemental Analysis (Found) C	H	N	IR (cm^{-1})	^{1}H NMR (δ)
4r	216–217	56.47 (56.32)	3.55 (3.61)	16.46 (16.37)	3440 3301 1673	10.25 (s, 1H, NH), 8.73 (s, 1H, NH), 8.36-7.51 (m, 5H, ArH), 6.89 (d, 2H, $J = 7.8$ Hz, ArH), 6.56 (t, 1H, $J = 7.8$ Hz, ArH), 5.71 (s, 1H, =CH), 5.46 (s, 1H, CH)
4s	193–195	56.47 (56.61)	3.55 (3.60)	16.46 (16.38)	3438 3300 1668	10.15 (s, 1H, NH), 8.84 (s, 1H, NH), 8.36-8.13 (m, 2H, ArH), 7.78-7.33 (m, 3H, ArH), 7.00 (d, 2H, $J = 7.7$ Hz, ArH), 6.20 (t, 1H, $J = 7.6$ Hz, ArH), 5.83 (s, 1H, =CH), 5.45 (s, 1H, CH)

optimized conditions was also examined and it afforded the corresponding 3,4-dihydro-4,6-diphenyl-pyrimidin-2-(1*H*)-thione (mp. 249–251°C[11]) albeit in only 28% yield after 1 h.

In conclusion, the mild and solvent-free conditions, short reaction times, excellent yields, inexpensive, non-toxic, and commercially available catalyst, and broad substrate range make this procedure a useful process for the synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones.

Experimental Section

Mps were determined using an RY-1 micromelting point apparatus. Infrared spectra were recorded on a Scimitar 2000 series Fourier Transform instrument of VARIAN. ^{1}H NMR spectra were obtained on an Agilent 400-MR spectrometer in DMSO-d_6 using TMS as an internal standard. Mass spectra were determined on an Agilent 1100 series LC/MSD VL ESI instrument. Elemental analyses were carried out on EA 2400II elemental analyzer (Perkin Elmer). All reagents were from commercial sources.

General Procedure

A mixture of an aromatic aldehyde (10 mmol), an aromatic ketone (10 mmol), urea (0.90 g, 15 mmol), $NaHSO_4$ (5 mmol) was added into a 25 ml dried round-bottom flask. Then the reaction mixture was stirred at 90°C for an appropriate time. After completion of the reaction (as indicated by TLC using ethyl acetate-*n*-hexane, 1:4), the mixture was cooled to room temperature and the precipitated solid was collected and washed thoroughly with

water. The product was purified by recrystallization from 95% ethanol. All products were characterized by melting point, IR, ^{1}H NMR, MS and elemental analysis.

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