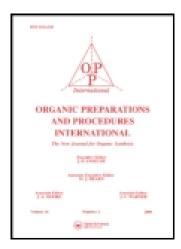
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Synthesis of 3,4-Dihydropyrimidin-2(1H)ones using Sodium Bisulfate as a Catalyst under Solvent-free Conditions

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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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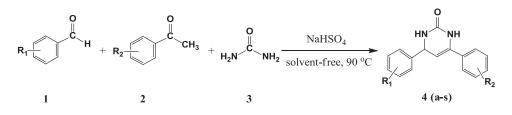
Pyrimidinones or dihydropyrimidinones (DHPMs) are important heterocycles that have drawn much attention due to their biological¹ and pharmacological² action as well as their potent calcium channel blocking activity.^{3–5} Thus, the synthesis of these compounds has attracted considerable interest in recent 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 FeCl₃·6H₂O/TMSCl in CH₃CN.⁷ Later, other catalysts such as NaI/TMSCl,⁸ Co(OAc)₂/TMSCl,⁹ tBuONa/MWI,¹⁰ PTSA/MWI,¹¹ AlCl₃ or AlBr₃ in CH₃CN,¹² I₂,¹³ ZnI₂/MWI,¹⁴ Fe(NO₃)₃·9H₂O,¹⁵ and AlCl₃/KI under N₂ atmosphere¹⁶ *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 NaHSO₄ 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 NaHSO₄ 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(1H)-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

Product	R_1	R_2	Time (min)	Yield (%)	$mp(^{\circ}C)$	Lit. (°C)
4a	Н	Н	20	84	217–219	218–219 ⁸
4b	2-Cl	Н	13	92	209-211	see Table 2
4c	2,4-Cl ₂	Н	8	89	213-215	see Table 2
4d	$2-NO_2$	Н	10	82	225-226	see Table 2
4e	3-NO ₂	Н	17	91	201-202	see Table 2
4f	$4-NO_2$	Н	7	90	197–198	see Table 2
4g	2-CH ₃ O	Н	30	75	230-232	see Table 2
4h	3-OH	Н	30	76	211-212	see Table 2
4i	Н	4-CH ₃ O	40	85	209-210	209-21111
4j	4-Cl	4-CH ₃ O	45	86	261-262	263-26510
4k	$2-NO_2$	4-CH ₃ O	15	74	213-215	see Table 2
41	3-NO ₂	4-CH ₃ O	60	89	198-200	see Table 2
4m	$4-NO_2$	4-CH ₃ O	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-C1	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 1

 Preparation of 5-Unsubstituted 3,4-dihydropyrimidin-2(1H)-ones Catalyzed by NaHSO4

			Flomant	Analysi	(Found)		
			Elementa	al Analysis	s (Found)	IR	
	Cmpd	mp (°C)	С	Η	Ν	(cm^{-1})) ¹ H NMR (δ)
	4 b	209–211	67.49	4.60	9.84	3340	10.36 (s, 1H, NH), 9.54 (s, 1H,
			(67.65)	(4.54)	(9.73)	3308	NH), 7.42-6.37 (m, 9H, ArH),
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$						1650	5.63 (s, 1H, =CH), 5.45
							(s, 1H, CH)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	4 c	213-215	60.21	3.79	8.78	3428	10.28 (s, 1H, NH), 8.90 (s, 1H,
			(60.06)	(3.85)	(8.70)		NH), 7.95-6.28 (m, 8H, ArH),
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$						1669	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	4d	225-226					
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			(65.22)	(4.36)	(14.35)		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$						1673	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$							
			67 00				
4f197–19865.084.4414.23345910.17 (s, 1H, NH), 5.45 (s, 1H, CH)4f197–19865.084.4414.23345910.17 (s, 1H, NH), 8.70 (s, 1H, CH)4f(65.24)(4.37)(14.12)3317NH), 8.43-7.30 (m, 6H, ArH), 6.25-6.17 (m, 1H, ArH), 5.82 (s, 1H, =CH), 5.46 (s, 1H, CH)4g230–23272.845.759.99344110.01 (s, 1H, NH), 8.79 (s, 1H, CH)4g230–23272.845.759.99344110.01 (s, 1H, NH), 8.79 (s, 1H, CH)4g211–21272.165.3010.5234449.98 (s, 1H, NH), 9.40 (s, 1H, NH)	4 e	201–202					
			(64.89)	(4.53)	(14.31)		
$ \begin{array}{c} \mbox{CH} \\ \mbox{4f} & 197-198 & 65.08 & 4.44 & 14.23 & 3459 & 10.17 (s, 1H, NH), 8.70 (s, 1H, (65.24)) & (4.37) & (14.12) & 3317 & NH), 8.43-7.30 (m, 6H, ArH), (65.24) & (4.37) & (14.12) & 3317 & NH), 8.43-7.30 (m, 6H, ArH), (6.25-6.17 (m, 1H, ArH), 5.82) & (s, 1H, =CH), 5.46 (s, 1H, CH) \\ \mbox{4g} & 230-232 & 72.84 & 5.75 & 9.99 & 3441 & 10.01 (s, 1H, NH), 8.79 (s, 1H, CH), (73.00) & (5.64) & (10.12) & 3321 & NH), 7.97-6.31 (m, 9H, ArH), (73.00) & (5.64) & (10.12) & 3321 & NH), 7.97-6.31 (m, 9H, ArH), (647) & 5.63 (s, 1H, =CH), 5.43 (s, 1H, CH), 3.80 (s, 3H, OCH_3) \\ \mbox{4h} & 211-212 & 72.16 & 5.30 & 10.52 & 3444 & 9.98 (s, 1H, NH), 9.40 (s, 1H, NH) \\ \end{array} $						1668	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$							
(65.24) (4.37) (14.12) 3317 NH), 8.43-7.30 (m, 6H, ArH), 1662 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 5.75 9.99 3441 10.01 (s, 1H, NH), 8.79 (s, 1H, (73.00) (5.64) (10.12) 3321 NH), 7.97-6.31 (m, 9H, ArH), 1647 5.63 (s, 1H, =CH), 5.43 (s, 1H, CH), 3.80 (s, 3H, OCH ₃) 4h 211–212 72.16 5.30 10.52 3444 9.98 (s, 1H, NH), 9.40 (s, 1H,	46	107 100	(5.00	4 4 4	14.00	2450	,
4g 230–232 72.84 5.75 9.99 3441 10.01 (s, 1H, NH), 8.79 (s, 1H, CH) 4g 230–232 72.84 5.75 9.99 3441 10.01 (s, 1H, NH), 8.79 (s, 1H, CH) 4g 4g 230–232 72.84 5.75 9.99 3441 10.01 (s, 1H, NH), 8.79 (s, 1H, CH) 4g 4g 230–232 72.84 5.75 9.99 3441 10.01 (s, 1H, NH), 8.79 (s, 1H, CH) 4g 4g 230–232 72.84 5.75 9.99 3441 10.01 (s, 1H, NH), 8.79 (s, 1H, CH) 4g 4g 230–232 72.84 5.63 (s, 1H, NH), 9.40 (s, 1H, NH) 1647 5.63 10.52 3444 9.98 (s, 1H, NH), 9.40 (s, 1H, NH) 1647	41	197–198					
6.25-6.17 (m, 1H, ArH), 5.82 (s, 1H, =CH), 5.46 (s, 1H, CH) 4g 230–232 72.84 5.75 9.99 3441 10.01 (s, 1H, NH), 8.79 (s, 1H, CH) (73.00) (5.64) (10.12) 3321 NH), 7.97-6.31 (m, 9H, ArH), 1647 5.63 (s, 1H, =CH), 5.43 (s, 1H, CH), 3.80 (s, 3H, OCH ₃) 4h 211–212 72.16 5.30 10.52 3444 9.98 (s, 1H, NH), 9.40 (s, 1H, NH)			(03.24)	(4.57)	(14.12)		
4g 230–232 72.84 5.75 9.99 3441 10.01 (s, 1H, NH), 8.79 (s, 1H, CH) (73.00) (5.64) (10.12) 3321 NH), 7.97-6.31 (m, 9H, ArH), 1647 5.63 (s, 1H, =CH), 5.43 (s, 1H, CH), 3.80 (s, 3H, OCH ₃) 4h 211–212 72.16 5.30 10.52 3444 9.98 (s, 1H, NH), 9.40 (s, 1H, NH)						1002	
4g 230–232 72.84 5.75 9.99 3441 10.01 (s, 1H, NH), 8.79 (s, 1H, (73.00) (5.64) (10.12) 3321 NH), 7.97-6.31 (m, 9H, ArH), 1647 5.63 (s, 1H, =CH), 5.43 (s, 1H, CH), 3.80 (s, 3H, OCH ₃) 4h 211–212 72.16 5.30 10.52 3444 9.98 (s, 1H, NH), 9.40 (s, 1H,							
4g 230–232 72.84 5.75 9.99 3441 10.01 (s, 1H, NH), 8.79 (s, 1H, (73.00) (5.64) (10.12) 3321 NH), 7.97-6.31 (m, 9H, ArH), 1647 5.63 (s, 1H, =CH), 5.43 (s, 1H, CH), 3.80 (s, 3H, OCH ₃) 4h 211–212 72.16 5.30 10.52 3444 9.98 (s, 1H, NH), 9.40 (s, 1H,							
(73.00) (5.64) (10.12) 3321 NH), 7.97-6.31 (m, 9H, ArH), 1647 5.63 (s, 1H, =CH), 5.43 (s, 1H, CH), 3.80 (s, 3H, OCH ₃) 4h 211–212 72.16 5.30 10.52 3444 9.98 (s, 1H, NH), 9.40 (s, 1H,	4 9	230-232	72.84	5.75	9,99	3441	,
1647 5.63 (s, 1H, =CH), 5.43 (s, 1H, CH), 3.80 (s, 3H, OCH ₃) 4h 211–212 72.16 5.30 10.52 3444 9.98 (s, 1H, NH), 9.40 (s, 1H, 1H)	.9	200 202					
1H, CH), 3.80 (s, 3H, OCH ₃) 4h 211–212 72.16 5.30 10.52 3444 9.98 (s, 1H, NH), 9.40 (s, 1H, NH)			(10.00)	(0.01)	(10.12)		
4h 211–212 72.16 5.30 10.52 3444 9.98 (s, 1H, NH), 9.40 (s, 1H,						10.7	
	4h	211-212	72.16	5.30	10.52	3444	
1652 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

4k 213-215 62.76 4.65 12.92 3479 9.15 (s, 1H, N (62.90) 4k 213-215 62.76 4.65 12.92 3479 9.15 (s, 1H, N (3.01) 62.90) (4.54) (13.01) 3301 NH), 7.87-7 1672 6.88 (d, 2H, ArH), 6.56 (ArH), 5.71 (5.46 (s, 1H, OCH ₃) 4l 198-200 62.76 4.65 12.92 3438 10.15 (s, 1H, OCH ₃) 4l 198-200 62.76 4.65 12.92 3438 10.15 (s, 1H, OCH ₃) 4l 198-200 62.76 4.65 12.92 3438 10.15 (s, 1H, OCH ₃) 4l 198-200 62.76 4.65 12.92 3443 10.17 (s, 1H, IECH) (62.58) (4.73) (13.01) 3313 NH), 8.43-6 1669 5.83 (s, 1H, IH, CH), 3. 4n 219-220 58.28 3.67 12.74 3480 10.24 (s, 1H, IH, CH), 5.71 (s, 58.41) 4o 202-203 58.28 3.67 12.74 3440 10.15 (s, 1H, IECH) 4o	
	$\mathrm{MR}\left(\delta\right)$
	H), 8.73 (s, 1H,
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	51 (m, 5H, ArH)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	J = 7.4 Hz,
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	J, 1H, J = 7.4 Hz
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	s, 1H, = CH),
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	CH), 3.84 (s, 3H,
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	
$ \begin{array}{c} \mbox{4m} & 191-193 & 62.76 & 4.65 & 12.92 & 3447 & 10.17 ({\rm s}, 1{\rm H}, ={\rm CH}), 3.84 ({\rm s}, 1{\rm H}, {\rm cH}), 3.84 ({\rm s}, 1{\rm H}), 3.84 ({\rm s}, 1{\rm H}), 3.84 {\rm cH}), 3.84 ({\rm s}, 1{\rm H}), 3.84 {\rm cH}), 3.84 ({\rm s}, 1{\rm H}, {\rm cH}), 3.84 {\rm cH}), 3.84 ({\rm s}, 1{\rm H}), 3.84 {\rm cH}), 3.84 {\rm c$	VH), 8.70 (s, 1H,
$ \begin{array}{c} ({\rm s},1{\rm H},={\rm CH})\\ ({\rm CH}),3.84({\rm s})\\ ({\rm f}2.58) & ({\rm f}4.73) & (13.01) & 3313 & {\rm NH}),8.43-6\\ ({\rm f}62.58) & ({\rm f}4.73) & (13.01) & 3313 & {\rm NH}),8.43-6\\ ({\rm f}669 & 5.83({\rm s},1{\rm H},\\ {\rm H},{\rm CH}),3.\\ {\rm f}{\rm n} & 219-220 & 58.28 & 3.67 & 12.74 & 3480 & 10.24({\rm s},1{\rm H},\\ ({\rm 58.41}) & ({\rm 3.60}) & (12.82) & 3301 & {\rm NH}),8.14-7\\ ({\rm f}673 & 6.88({\rm d},2{\rm H},\\ {\rm ArH}),6.55({\rm s},1{\rm H},\\ {\rm f}5.45({\rm s},1{\rm H},\\ {\rm f}5.45({\rm s},1{\rm H},\\ {\rm f}68 & 6.99({\rm d},2{\rm H},\\ {\rm ArH}),6.25-\\ {\rm ArH}),5.82({\rm f}5.44({\rm s},1{\rm H},\\ {\rm f}7.4({\rm s},1{\rm H},\\ {\rm f$	00 (m, 7H, ArH)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$, 1H, ArH), 5.83
4m 191–193 62.76 4.65 12.92 3447 10.17 (s, 1H, 1) (62.58) (4.73) (13.01) 3313 NH), 8.43-6 1669 5.83 (s, 1H, 1H, CH), 3. 4n 219–220 58.28 3.67 12.74 3480 10.24 (s, 1H, 1H, CH), 3. 4n 219–220 58.28 3.67 12.74 3480 10.24 (s, 1H, 1H, CH), 3. 4n 219–220 58.28 3.67 12.74 3480 10.24 (s, 1H, 1H, CH), 3. 4n 219–220 58.28 3.67 12.74 3480 10.24 (s, 1H, 1H, CH), 3. 4n 202–203 58.28 3.67 12.74 3440 10.15 (s, 1H, 1H, CH), 5.71 4o 202–203 58.28 3.67 12.74 3440 10.15 (s, 1H, 1H, CH), 5.71 4o 202–203 58.28 3.67 12.74 3440 10.15 (s, 1H, 1H, CH), 5.82 4o 202–203 58.28 3.67 12.74 3440 10.15 (s, 1H, 1H, CH), 5.82 4p 195–197 58.28 3.67 12.74 3459 10.17 (s, 1H, 1H, CH), 5.82), 5.45 (s, 1H,
 (62.58) (4.73) (13.01) 3313 NH), 8.43-6 1669 5.83 (s, 1H, 1H, CH), 3. 4n 219–220 58.28 3.67 12.74 3480 10.24 (s, 1H, 3. (58.41) (3.60) (12.82) 3301 NH), 8.14-7 1673 6.88 (d, 2H, ArH), 6.55 40 202–203 58.28 3.67 12.74 3440 10.15 (s, 1H, 3. (58.16) (3.57) (12.85) 3298 NH), 8.33-7 1668 6.99 (d, 2H, ArH), 6.25- ArH), 5.82 5.44 (s, 1H, ArH), 6.25- ArH), 5.82 5.44 (s, 1H, (58.39) (3.61) (12.56) 3318 NH), 8.43-6 1662 5.83 (s, 1H, 	
4n 219–220 58.28 3.67 12.74 3480 10.24 (s, 1H, 1H, CH), 3. 4n 219–220 58.28 3.67 12.74 3480 10.24 (s, 1H, 1H, CH), 3. (58.41) (3.60) (12.82) 3301 NH), 8.14-7 1673 6.88 (d, 2H, ArH), 6.55 ArH), 5.71 5.45 (s, 1H, 1H, CH), 5.71 5.45 (s, 1H, 1H, 5.71) 5.45 (s, 1H, 1H, 5.71) 5.45 (s, 1H, 1H, 5.71) 5.45 (s, 1H, 1H, 5.71) 5.45 (s, 1H, 1H, 6.55) 10.15 (s, 1H, 1H, 1H, 6.25) ArH), 5.71 1668 6.99 (d, 2H, ArH), 6.25) ArH), 5.82 (s, 1H, 1H, 1H, 6.25) 1668 6.99 (d, 2H, ArH), 5.82 (s, 1H, 1H, 5.82) 4p 195–197 58.28 3.67 12.74 3459 10.17 (s, 1H, 1H, 5.82) (58.39) (3.61) (12.56) 3318 NH), 8.43-60 1662 5.83 (s, 1H, 1H, 5.83)	VH), 8.99 (s, 1H,
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1668 6.99 (d, 2H, ArH), 6.25- ArH), 5.82 (5.44 (s, 1H, (58.39) 4p 195–197 58.28 3.67 12.74 3459 10.17 (s, 1H, (s, 1H, (58.39) 10.17 (s, 1H, (3.61) 10.12 (s, 1H, (12.56) 10.12 (s, 1H, 3318 NH), 8.43-6 1662 1662 5.83 (s, 1H,	NH), 8.70 (s, 1H,
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(58.39) (3.61) (12.56) 3318 NH), 8.43-6 1662 5.83 (s, 1H,	<i>,</i>
1662 5.83 (s, 1H,	NH), 8.87 (s, 1H,
	19 (m, 8H, ArH)
1H, CH)	=CH), 5.46 (s,
•	NH), 8.87 (s, 1H,
	15 (m, 8H, ArH)
	=CH), 5.42 (s,
1H, CH)	1 .
(Contin	ued on next page,

 Table 2

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

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		Elemental Analysis (Found)			IR		
Cmpd	mp (°C)	С	Н	Ν	(cm^{-1})) ¹ H NMR (δ)	
4r	216–217	56.47	3.55	16.46	3440	10.25 (s, 1H, NH), 8.73 (s, 1H,	
		(56.32)	(3.61)	(16.37)	3301	NH), 8.36-7.51 (m, 5H, ArH),	
					1673	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)	
4 s	193–195	56.47	3.55	16.46	3438	10.15 (s, 1H, NH), 8.84 (s, 1H,	
		(56.61)	(3.60)	(16.38)	3300	NH), 8.36-8.13 (m, 2H, ArH),	
					1668	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)	

 Table 2

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

optimized conditions was also examined and it afforded the corresponding 3,4-dihydro-4,6-diphenyl-pyrimidin-2-(1H)-thione (mp. 249–251°C¹¹) 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(1H)-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. ¹H 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), NaHSO₄ (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, ¹H NMR, MS and elemental analysis.

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