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Highly effectual synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones using *N*,*N*,*N*′,*N*′-tetramethylethylenediaminium-*N*,*N*′-disulfonic acid hydrogen sulfate as a dual-functional catalyst

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Abstract: The highly effectual synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones *via* the one-pot multicomponent reaction of acetophenones with arylaldehydes and urea in the presence of trimethylsilyl chloride and a catalytic amount of the ionic liquid *N*,*N*,*N*′,*N*′-tetramethylethylenediaminium-*N*,*N*′-disulfonic acid hydrogen sulfate ([TMEDSA][HSO_4]$_2$) under solvent-free conditions has been described. The reaction results and conditions of the catalytic system have been compared with previously reported catalysts. [TMEDSA][HSO_4]$_2$ afforded better results in comparison with the reported catalysts in terms of one or more of these factors: yield, temperature, the reaction media, time, and generality. Moreover, a plausible reaction mechanism based on dual functionality of the catalyst has been proposed.

Keywords: 4,6-diarylpyrimidin-2(1*H*)-one; ionic liquid; multicomponent reaction; *N*,*N*,*N*′,*N*′-tetramethylethylenediaminium-*N*,*N*′-disulfonic acid hydrogen sulfate ([TMEDSA][HSO_4]$_2$); solvent-free.

1 Introduction

During the last decade, ionic liquids (ILs) have been extensively used as reaction media, catalysts, and reagents for organic reactions, due to various exclusive advantages, e.g. chemical and thermal stability, low flammability, very low vapour pressure, wide liquid range, environmental friendliness, and their good capability for dissolving organic and inorganic compounds [1–10]. Among them, Brønsted acidic ILs have been especially designed for use as catalysts and reagents for organic transformations [2–10].

Performing organic transformations using environmentally friendly methods is particularly desirable. Some interesting examples are multicomponent reactions (MCRs), in which at least three starting materials are reacted in a one-pot reaction to a single product without the separation of any intermediates [11–14]. MCRs offer significant advantages over conventional multistep protocols because of their flexibility and their convergent and atom-economic nature. Thereby, MCRs often save energy and time, increase yields, and reduce side products and the application of volatile organic solvents [11–14]. Another green technique that has been extensively applied recently in organic synthesis is the solvent-free reaction condition, offering especially advantages from an ecological point of view, combined with operational simplicity [15–17].

Pyrimidinone-containing heterocycles show a wide range of biological, medicinal, and therapeutic activities, e.g. they have been used as non-peptide antagonists for the human luteinizing hormone-releasing hormone receptor [18], for their antiproliferative and cytodifferentiating activities in human cells [19] and their antihistaminic activity [20]. They may be integral backbones of several calcium channel blockers [21] and of antitumor [22], antifolate [23], and antimalarial [23] agents. Fluorescence and zinc ion recognition properties have been also reported for pyrimidinone derivatives [24].

One of the best protocols for the synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones, a significant class of pyrimidinones, is the one-pot MCR of acetophenones with arylaldehydes and urea in the presence of a catalyst, such as concentrated HCl in IL [24]; $Bi(TFA)_3$ in IL [25]; large-pore zeolites [26]; atomized sodium [27]; $H_6P_2W_{18}O_{62}\cdot 18H_2O$ [28]; sulfamic acid [29]; SBA-Pr-SO_3H [30]; NaOH [31]; concentrated HCl in 2-propanol [32]; 2,4,6-trichloro-1,3,5-triazine-$Zn(OTf)_2$ (or -$Bi(OTf)_3$) [33]; HBF_4-SiO_2 [34], $H_3PMo_{12}O_{40}$ [35]; I_2 [36]; and 1,8-diazabicyclo[5,4,0] undec-7-ene [37]. Nonetheless, many of these catalysts have at least one of the following disadvantages: prolonged reaction times, moderate yields, need for elevated reaction temperatures, utilization of volatile organic solvents, non-generality (arylaldehydes possessing electron-withdrawing substituents, such as the nitro group, could not be utilized in the reaction), and poor agreement with green chemistry protocols.

In the continuation of our work on the preparation and catalytic application of *N*,*N*,*N*′,*N*′-tetramethylethylenediaminium-*N*,*N*′-disulfonic acid

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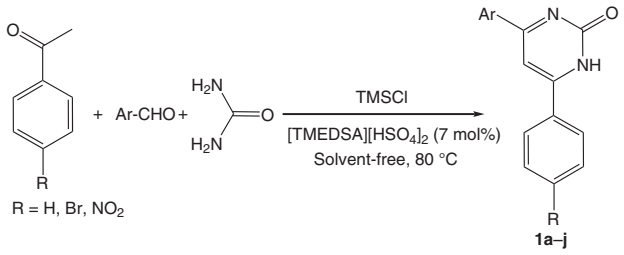
hydrogen sulfate ([TMEDSA][HSO_4]$_2$) published in this journal [5], we report here the utilization of this IL as a highly effective, homogeneous, and dual-functional catalyst for the solvent-free preparation of 4,6-diarylpyrimidin-2(1*H*)-ones *via* one-pot MCR of acetophenones with arylaldehydes and urea in the presence of trimethylsilyl chloride (TMSCl). This method avoids many of the above-mentioned drawbacks.

2 Results and discussion

Firstly, we studied the influence of the amount of catalyst and reaction temperature on the solvent-free reaction of acetophenone with 4-nitrobenzaldehyde and urea in the presence of TMSCl (Scheme 1). The main results are summarized in Table 1. As the data indicate, catalyst-free condition is not effective (Table 1, entry 1), and the best results were obtained when 7 mol% of [TMEDSA][HSO_4]$_2$ was utilized at 80°C (Table 1, entry 3). Increasing the amount of catalyst and the temperature did not improve the reaction time and yield (Table 1, entries 4 and 6). The reaction was also examined using 7 mol% of the catalyst at 80°C in the absence of TMSCl, in which only a low yield of the product was obtained (Table 1, entry 7). These results prove that [TMEDSA][HSO_4]$_2$ and TMSCl are essential for the reaction.



Scheme 1: The synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones **1a–1j**.

Table 1: The solvent-free condensation of acetophenone with 4-nitrobenzaldehyde and urea in the presence of TMSCl and [TMEDSA][HSO_4]$_2$.

Entry	Catalyst amount, mol%	Temp., °C	Time, min	Yield, %[a]
1	–	80	45	64
2	4	80	45	73
3	7	80	35	95
4	10	80	35	95
5	7	70	50	68
6	7	85	35	95
7	7[b]	80	40	71

[a]Isolated yields; [b]This reaction was examined in the absence of TMSCl.

After optimization of the catalyst amount and temperature, diverse arylaldehydes were reacted with acetophenones and urea in the presence of TMSCl and [TMEDSA][HSO_4]$_2$. The results are displayed in Table 2. As it can be seen, benzaldehyde and arylaldehydes bearing electron-withdrawing, electron-donating, or halogen substituents afforded the corresponding products in high yields and short reaction times. The reactions were also effectively promoted when differently substituted acetophenones were utilized. According to these excellent results, we can claim that [TMEDSA][HSO_4]$_2$ is a highly effective and general catalyst for this MCR synthesis. It is noteworthy that in all the reactions, the 4,6-diarylpyrimidin-2(1*H*)-ones were obtained without the formation of any by-products. In some cases, however, few amounts of unreacted starting materials remained.

A plausible mechanism, based on literature data [29], is proposed for the reaction (Scheme 2). [TMEDSA][HSO_4]$_2$ acts as dual-functional catalyst, as it is shown in the mechanism. Acidic hydrogens play two roles: (i) activation of carbonyl groups to accept nucleophilic attack (steps 2 and 6) and (ii) assistance for removing H_2O (step 8). Anion also plays two roles: (i) assistance for removing H_2O (step 8) and (ii) activation of nucleophiles (steps 2, 4 and 6). This role of hydrogen sulfate anion is confirmed according to the literature in the synthesis of hexahydroquinolines [2]. The high efficiency of [TMEDSA][HSO_4]$_2$ for the reaction can be attributed to its dual functionality and also its possession of four acidic protons.

Finally, to put the results obtained with [TMEDSA][HSO_4]$_2$ as catalyst into a better perspective, we compared them with those of other reported catalytic systems. The results are summarized in Table 3. The table clearly demonstrates that [TMEDSA][HSO_4]$_2$ is superior in terms of one or more of these factors: yield, temperature, reaction media, time, and generality of application (arylaldehydes bearing electron-donating, electron-withdrawing, and halogen substituents). In addition, it should be mentioned that ultrasound or microwave irradiation has not been used in our reaction system.

3 Conclusion

We applied [TMEDSA][HSO_4]$_2$ as a catalyst for the synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones from differently substituted aromatic aldehydes, acetophenones, and urea. The benefits of this protocol consist of high yields, short reaction times, and generality of the reaction, as well as solvent-free conditions.

Table 2: The synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones catalyzed by $[TMEDSA][HSO_4]_2$ (Scheme 1).

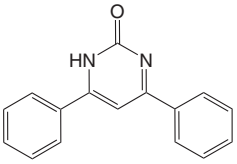
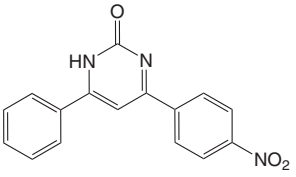
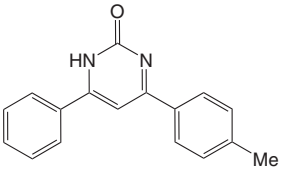
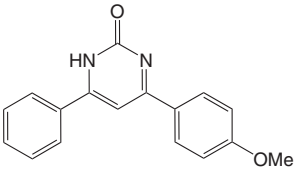
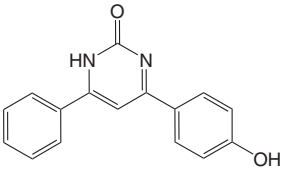
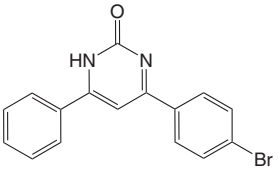
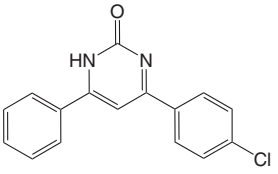
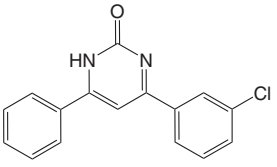
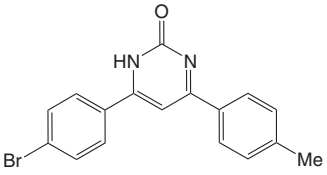
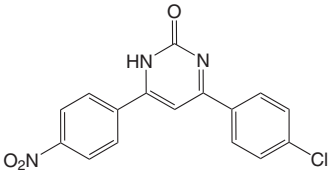
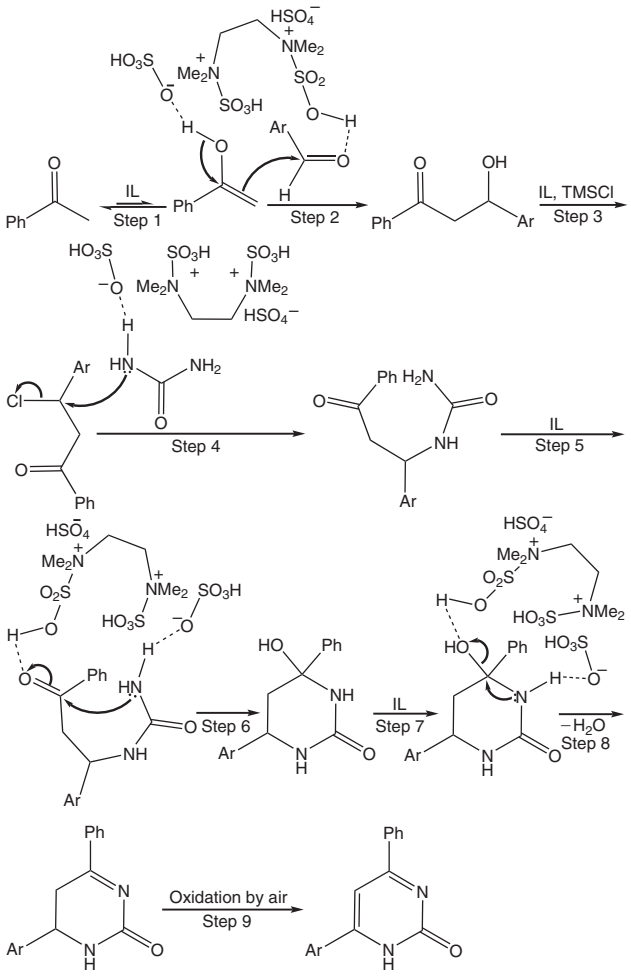
Comp. no.	Ar	Product	Time, min	Yield, %[a]	M. p., °C (Lit.)
1a[b]	C_6H_5		30	81	236–238 (235) [27]
1b[b]	$4\text{-}O_2NC_6H_4$		35	95	314–316 (>300) [24]
1c[b]	$4\text{-}MeC_6H_4$		30	87	285–287 (287–290) [28]
1d[b]	$4\text{-}MeOC_6H_4$		20	79	256–258 (257–260) [30]
1e[b]	$4\text{-}HOC_6H_4$		35	85	257–259 (258–261) [27]
1f[b]	$4\text{-}BrC_6H_4$		25	86	248–250 (251–254) [28]
1g[b]	$4\text{-}ClC_6H_4$		25	81	254–256 (258–260) [29]
1h[b]	$3\text{-}ClC_6H_4$		15	94	208–210 (210–212) [31]
1i[c]	$4\text{-}MeC_6H_4$		25	87	332–334 (335–337) [32]

Table 2 (continued)

Comp. no.	Ar	Product	Time, min	Yield, %[a]	M. p., °C (Lit.)
1j[d]	4-ClC_6H_4		30	85	305–307 (308–310) [29]

[a]Isolated yields; [b]R (in Scheme 1) = H; [c]R (in Scheme 1) = Br; [d]R (in Scheme 1) = NO_2.



Scheme 2: The proposed mechanism for the preparation of 4,6-diarylpyrimidin-2(1*H*)-ones.

4 Experimental

4.1 General

All chemicals were bought from Merck or Fluka Chemical Companies with high-grade quality and used without any purification. $[TMEDSA][HSO_4]_2$ was synthesized according to our method reported previously [5]. The structures of known products were determined by comparing their melting points and spectroscopic data with those reported in the literature. TLC (on silica gel SIL G/UV 254 plates) was used for monitoring the progress of the reactions. Bruker Avance DPX, FT-NMR spectrometers were applied for running the ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) spectra. Melting points were measured on a Büchi B-545 apparatus in open capillary tubes.

4.2 General procedure for the synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones

$[TMEDSA][HSO_4]_2$ (0.07 mmol, 0.033 g) was added to a mixture of arylaldehyde (1 mmol), acetophenone (1 mmol), urea (1.5 mmol, 0.09 g), and TMSCl (1 mmol, 0.109 g), and the resultant mixture was stirred at 80°C. After completion of the reaction, as indicated by TLC, the mixture was cooled to room temperature, and the obtained solid was recrystallized from ethanol (95%) to afford the pure products.

4.2.1 Selected spectral data of the 4,6-diarylpyrimidin-2(1*H*)-ones

4.2.1.1 4-(4-Nitrophenyl)-6-phenylpyrimidin-2(1*H*)-one (1b)

^{1}H NMR (250 MHz, [D_6]DMSO, 25°C, TMS): δ = 6.90–6.97 (m, 3H, H_{Ar} and CH), 7.16–7.28 (m, 5H, H_{Ar}), 7.95–7.99 (m, 3H, H_{Ar} and NH). – ^{13}C NMR (62.5 MHz, [D_6]DMSO, 25°C, TMS): δ = 122.9, 126.8, 127.3, 127.6, 128.1, 128.5, 141.4, 146.2, 148.9, 153.9, 162.9, 164.8 [24].

4.2.1.2 4-(4-Methoxyphenyl)-6-phenylpyrimidin-2(1*H*)-one (1d)

^{1}H NMR (250 MHz, [D_6]DMSO, 25°C, TMS): δ = 3.85 (s, 3H, CH_3), 7.09–7.13 (m, 3H, H_{Ar} and CH), 7.53–7.66 (m, 4H, H_{Ar}), 8.10–8.20 (m, 4H, H_{Ar} and NH). – ^{13}C NMR (62.5 MHz, [D_6]

Table 3: Comparison of the results and reaction conditions of $[TMEDSA][HSO_4]_2$ with the reported catalysts.

Catalyst	Conditions	Time range	Yield range, %	Ref.
$[TMEDSA][HSO_4]_2$	Solvent-free, 80°C	15–35	79–95	This work
Concentrated HCl	[bmim][BF_4][a], 120°C	210–300	70–95	[24]
$Bi(TFA)_3$	[nbpy]$FeCl_4$[b], 70°C	80–160	60–96	[25]
Large-pore zeolites	Toluene, reflux	20–30	76–85[c]	[26]
Atomized sodium	THF, ultrasound, r. t.	10–15	86–90[c]	[27]
$H_6P_2W_{18}O_{62} \cdot 18H_2O$	Solvent-free, 70°C	4–10	90–95[c]	[28]
Sulfamic acid	Solvent-free, 70°C	15–60	90–99[c]	[29]
SBA-Pr-SO_3H	Solvent-free, 110°C	20–40	91–97[c]	[30]
NaOH	Solvent-free, 70°C	10–15	80–92[c]	[31]
Concentrated HCl	2-Propanol, r. t.	360	25–47[c]	[32]
TCT[d]-$Zn(OTf)_2$	Solvent-free, microwave	12–15	64–94	[33]
TCT[d]-$Bi(OTf)_3$	Solvent-free, microwave	10–15	74–93	[33]
HBF_4-SiO_2	Solvent-free, microwave	10	62–94	[34]
$H_3PMo_{12}O_{40}$	Solvent-free, 70°C	15–25	90–95[c]	[35]
I_2	Solvent-free, 80°C	5–15	90–96[c]	[36]
DBU[e]	Solvent-free, microwave	8–12	90–96[c]	[37]

[a]1-Butyl-3-methylimidazolium tetrafluroroborate; [b]*n*-Butylpyridinium tetrachloroferrate; [c]In this work, arylaldehydes bearing electron-withdrawing substituents (e.g. nitro groups) have not been applied; [d]2,4,6-trichloro-1,3,5-triazine; [e]1,8-diazabicyclo[5,4,0]undec-7-ene.

DMSO, 25°C, TMS): $\delta = 55.6$, 99.5, 113.5, 114.4, 124.9, 127.9, 128.2, 128.9, 130.1, 132.1, 133.1, 162.8, 164.2 [30].

4.2.1.3 4-(4-Chlorophenyl)-6-phenylpyrimidin-2(1*H*)-one (1g)

^{1}H NMR (250 MHz, [D_6]DMSO, 25°C, TMS): $\delta = 7.52$–7.65 (m, 6H, H_{Ar} and CH), 8.12–8.22 (m, 5H, H_{Ar} and NH). – ^{13}C NMR (62.5 MHz, [D_6]DMSO, 25°C, TMS): $\delta = 100.9$, 127.8, 128.8, 128.9, 129.7, 132.0, 132.9, 133.4, 136.8, 164.2, 164.5 [29].

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Graphical synopsis

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