Organic Reactions in Ionic Liquids; Ionic Liquid-Accelerated Three-Component Reaction: A Rapid One-Pot Synthesis of 3-Alkyl-5-[(*Z*)-arylmethylidene]-1,3-thiazolidine-2,4-diones

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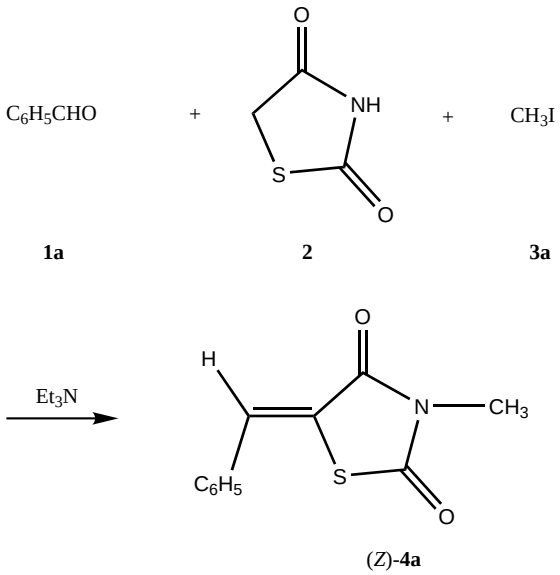
Abstract: A rapid one-pot synthesis of 3-alkyl-5-[(*Z*)-arylmethylidene]-1,3-thiazolidine-2,4-diones is described that occurs in recyclable ionic liquid [bmim]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate). Significant rate enhancement and good selectivity have been observed.

Key words: three-component reaction, 1,3-thiazolidine-2,4-diones, ionic liquid

Combinatorial chemistry has gained importance as a tool for the synthesis of a wide variety of useful compounds including pharmaceuticals.[1] In this context, the multiple component condensation (MCC) approach is especially appealing due to the fact that products are formed in a single step and diversity can be achieved simply by varying the reacting components. 3-Alkyl-5-arylmethylidene-1,3-thiazolidine-2,4-diones are an important class of synthetic intermediates in organic synthesis and many of these compounds display biological and pharmaceutical activities, such as anticonvulsant, antithelmintic, antitubercular, insecticidal, bactericidal, fungicidal, etc.[2] Generally, 3-alkyl-5-arylmethylidene-1,3-thiazolidine-2,4-diones were prepared by the alkylation of 5-arylmethylidene-1,3-thiazolidine-2,4-diones or the condensation of 3-alkyl-1,3-thiazolidine-2,4-diones with aromatic aldehydes in refluxing DMF or toluene.[3] These methods require first the preparation of the intermediates, 5-arylmethylidene-1,3-thiazolidine-2,4-diones or 3-alkyl-1,3-thiazolidine-2,4-diones and give low total yields. To the best of our knowledge, there is no report in the literature on the synthesis of 3-alkyl-5-arylmethylidene-1,3-thiazolidine-2,4-diones in a one-pot operation with an aromatic aldehyde, 1,3-thiazolidine-2,4-dione and an alkyl halide. In addition, the use of harmful organic solvents is undesirable from the view of present environmental consciousness. Hence, the development of rapid and eco-friendly synthesis of 3-alkyl-5-arylmethylidene-1,3-thiazolidine-2,4-diones is a challenging task.

Room temperature ionic liquids, especially those based on the 1-*n*-alkyl-3-methylimidazolium cation, have shown great promise as an attractive alternative to conventional solvents. They offer an eco-friendly reaction medium for a variety of organic transformations, as they are non-volatile, recyclable, non-explosive, easy to handle and thermally robust. To date, some of the more important reactions have been carried out and investigated in ionic liquids.[4] As part of a program to investigate the range of organic reactions possible in ionic liquids,[5] we have made an attempt to provide a convenient and rapid synthesis of 3-alkyl-5-arylmethylidene-1,3-thiazolidine-2,4-diones by ionic liquid-accelerated three-component reaction.

First, we investigated the three-component reaction of benzaldehyde (**1a**) and 1,3-thiazolidine-2,4-dione (**2**) with methyl iodide (**3a**) (Scheme 1). The results are presented in Table 1.



Scheme 1

We found that in the presence of Et_3N, the reaction of benzaldehyde (**1a**) and 1,3-thiazolidine-2,4-dione (**2**) and methyl iodide (**3a**) in 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquid resulted in the formation of 3-methyl-5[(*Z*)-phenylmethylidene]-1,3-thiazolidine-2,4-dione (**4a**) in 83% yield. The reaction proceeded smoothly at room temperature and was com-

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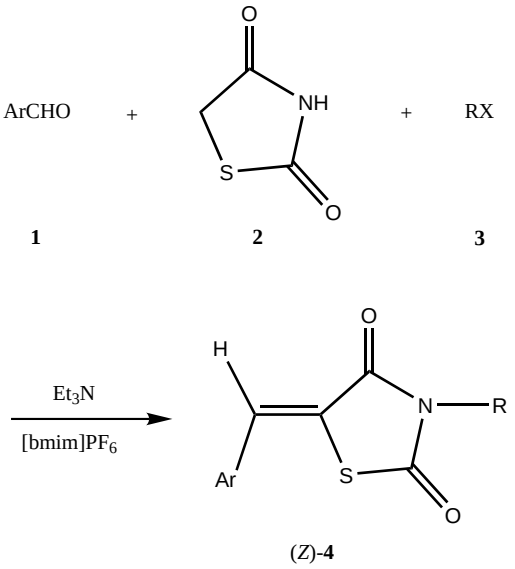
Table 1 Three-Component Reaction of **1a**, **2** and **3a** in Different Solvents to Form **4a**[a]

Solvent	Time (h)	Temp (°C)	Yield (%)[b]
[bmim]PF_6	2	25	83
[bmim]PF_6	8	25	10[c]
DMF	10	25	40
MeCN	10	25	26
toluene	10	25	13

[a] All the reactions were run with benzaldehyde (**1a**; 0.053 g, 0.5 mmol), 1,3-thiazolidine-2,4-dione (**2**; 0.059 g, 0.5 mmol), and MeI (**3a**; 0.085 g, 0.6 mmol) in different solvents (2 mL) using Et_3N (0.061 g, 0.6 mmol) as a base.
[b] Isolated yields based on 1,3-thiazolidine-2,4-dione (**2**).
[c] Using K_2CO_3 as a base.

pleted within 2 hours. When the Et_3N was replaced by K_2CO_3, the yield of **4a** was only 10% even after a long reaction period of 8 hours. Furthermore, we have performed the reactions in other solvents such as DMF, MeCN and toluene to compare the efficiency of the ionic liquid. The yields of **4a** were 40%, 26%, and 13%, respectively, even after a reaction period of 10 hours. It is obvious that the ionic liquid [bmim]PF_6 can truly accelerate the three-component reaction of benzaldehyde (**1a**) and 1,3-thiazolidine-2,4-dione (**2**) with methyl iodide (**3a**) to form 3-methyl-5-[(*Z*)-phenylmethylidene]-1,3-thiazolidine-2,4-dione (**4a**) which was characterized by ^1H NMR, IR, and melting point, which were in good accordance with the literature data.[2c]

Then, the scope of the reactions of different aromatic aldehydes **1** with 1,3-thiazolidine-2,4-dione (**2**) and various alkyl halides **3** was investigated (Scheme 2). We found that the three-component reaction of aldehydes **1** with 1,3-thiazolidine-2,4-dione (**2**) and alkyl halides **3** occurred easily in [bmim]PF_6 in the presence of Et_3N to form the corresponding 3-alkyl-5-[(*Z*)-arylmethylidene]-1,3-thiazolidine-2,4-diones **4**. The results are summarized in Table 2. In fact, simple stirring of a mixture of aldehydes **1**, 1,3-thiazolidine-2,4-dione (**2**), alkyl halides **3** and Et_3N in [bmim]PF_6 at room temperature for methyl iodide (**3a**) or at 60 °C for other alkyl halides (**3b**–**e**) for 2–4 hours gave, after extraction with diethyl ether, the desired 3-alkyl-5-[(*Z*)-arylmethylidene]-1,3-thiazolidine-2,4-diones **4** in good yields and the reaction was found to be generally applicable. Different aromatic aldehydes containing electron-withdrawing substituent, such as nitro group, or electron-releasing substituent, such as methoxy group reacted successfully. Several alkyl halides containing chloro group, bromo group or iodo group succeeded



Scheme 2

Table 2 Reaction of Aromatic Aldehydes **1**, with 1,3-Thiazolidine-2,4-dione (**2**) and Alkyl Halides **3** in [bmim]PF_6

Entry[a]	ArCHO	RX	Product	Temp (°C)	Time (h)	Yield (%)[b]
1	PhCHO (**1a**)	MeI (**3a**)	**4a**	25	2	83
2	4-$MeOC_6H_4CHO$ (**1b**)	MeI (**3a**)	**4b**	25	2	81
3	4-$NO_2C_6H_4CHO$ (**1c**)	MeI (**3a**)	**4c**	25	2	62
4	PhCHO (**1a**)	$PhCH_2Cl$ (**3b**)	**4d**	60	3	85
5	4-$MeOC_6H_4CHO$ (**1b**)	$PhCH_2Cl$ (**3b**)	**4e**	60	3	84
6	4-$NO_2C_6H_4CHO$ (**1c**)	$PhCH_2Cl$ (**3b**)	**4f**	60	3	70
7	PhCHO (**1a**)	4-$NO_2C_6H_4CH_2Cl$ (**3c**)	**4g**	60	4	68
8	PhCHO (**1a**)	$Me(CH_2)_2CH_2Br$ (**3d**)	**4h**	60	3	79
9	PhCHO (**1a**)	Me_2CHI (**3e**)	**4i**	60	3	75

[a] All reactions were run with aldehydes **1** (0.5 mmol), 1,3-thiazolidine-2,4-dione (**2**; 0.5 mmol), alkyl halides **3** (0.6 mmol) and Et_3N (0.6 mmol) in [bmim]PF_6 (2 mL).
[b] Isolated yields based on 1,3-thiazolidine-2,4-dione (**2**).

for primary and secondary alkyl halides especially. The *Z* or *E* configuration of all the products was determined by the prospective method to calculate the chemical shifts of the protons on variously substituted olefins. Sohda et al. have reported the calculated value of the methine protons of *Z* products in ^{1}H NMR spectra to be 7.90 ppm, which is consistent with our tested value, and the value of *E*-products to be 7.42 ppm. In addition, the *Z*-products are more stable than the *E*-types.[6]

The ionic liquid can be typically recovered by extracting out the product first, then washing the residue with water followed by vacuum drying. The recovered ionic liquid can be reused with no appreciable decrease in yield. The results are summarized in Table 3.

Table 3 Results Obtained Using Recycled Ionic Liquid [bmim]PF_6

Entry[a]	Product	Cycle	Yield (%)[b]
1	**4a**	1	83
2	**4a**	2	83
3	**4a**	3	82
4	**4a**	4	84

[a] All reactions were run with benzaldehyde (**1a**; 0.053 g, 0.5 mmol), 1,3-thiazolidine-2,4-dione (**2**; 0.059 g, 0.5 mmol), and CH_3I (**3a**; 0.085 g, 0.6 mmol) in presence of Et_3N (0.061 g, 0.6 mmol) in [bmim]PF_6 (2 ml) at 25 °C.
[b] Isolated yields based on 1,3-thiazolidine-2,4-dione

Under the same conditions, the reaction of rhodanine (2-thioxo-1,3-thiazolidine-4-one) with benzaldehyde (**1a**) and MeI (**3a**) was also investigated. But the expected product, 3-methyl-5-[(*Z*)-phenylmethylidene]-2-thioxo-1,3-thiazolidine-4-one was not observed.

In conclusion, we have provided a convenient and rapid synthesis of 3-alkyl-5-[(*Z*)-arylmethylidene]-1,3-thiazolidine-2,4-diones **4** by ionic liquid accelerated three-component reaction. The simple operation combined with easy recovery and reuse of the reaction media ([bmim]PF_6), makes this process economic and environmentally benign.

Melting points are uncorrected. IR spectra were recorded as KBr pellets on Vector-22 IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker (400 MHz) spectrometer using TMS as an internal standard. Elemental analyses were performed on Carlo Erba EA 1106 instrument.

3-Methyl-5-[(*Z*)-phenylmethylidene]-1,3-thiazolidine-2,4-dione (4a); Typical Procedure

Benzaldehyde (**1a**; 0.053 g, 0.5 mmol), 1,3-thiazolidine-2,4-dione (**2**; 0.059 g, 0.5 mmol), MeI (**3a**; 0.085 g, 0.6 mmol) and Et_3N (0.061 g, 0.6 mmol) were added to [bmim]PF_6 (2 ml).The resulting mixture was stirred at 25 °C for 2 h. Then the reaction mixture was extracted with Et_2O (4 × 15 mL). The remaining ionic liquid suspension was washed with H_2O, and reused after drying in vacuum. The combined Et_2O solution was evaporated under reduced pressure. The crude product was purified by preparative TLC (EtOAC–*n*-hexane, 1: 4) to give **4a** (0.091 g, 83%) as a pale yellow solid; mp 125–128 °C (Lit.[3e] mp 130 °C).

IR (KBr): 3017, 2925, 1742, 1672 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.93 (1 H, s, ArC*H*=), 7.50–7.54 (5 H, m, ArH), 3.28 (3 H, s, NCH_3).

5-[(*Z*)-(4-Methoxyphenyl)methylidene]-3-methyl-1,3-thiazolidine-2,4-dione (4b)

Mp: 145–147 °C.

IR (KBr): 3025, 2950, 1735, 1681 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.88 (1 H, s, ArC*H*=), 7.27–7.49 (2 H, m, ArH), 6.99–7.02 (2 H, m, ArH), 3.88 (3 H, s, OCH_3), 3.25 (3 H, s, NCH_3).

Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.83; H, 4.42; N, 5.62. Found: C, 57.84; H, 4.40; N, 5.66.

3-Methyl-5-[(*Z*)-(4-nitrophenyl)methylidene]-1,3-thiazolidine-2,4-dione (4c)

Mp 180–185 °C.

IR (KBr): 3080, 1706, 1670, 1599 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.22–8.25 (2 H, s, ArH), 7.89 (1 H, s, ArC*H*=), 7.76–7.81 (2 H, m, ArH), 4.25 (3 H, s, NCH_3).

Anal. Calcd for $C_{11}H_8N_2O_4S$: C, 50.00; H, 3.03; N, 10.60. Found: C, 50.03; H, 3.34; N, 10.55.

3-Benzyl-5-[(*Z*)-phenylmethylidene]-1,3-thiazolidine-2,4-dione (4d)

Mp 133–134 °C (Lit.[3d] mp 132.5–134.0 °C).

IR: 3035, 1730, 1684, 1604 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.93 (1 H, s, ArC*H*=), 7.28–7.52 (10 H, m, ArH), 4.92 (2 H, s, NCH_2).

3-Benzyl-5-[(*Z*)-(4-methoxyphenyl)methylidene]-1,3-thiazolidine-2,4-dione (4e)

Mp 144–146 °C.

IR (KBr): 3011, 2932, 1736,1673 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.87 (1 H, s, ArC*H*=), 6.98–7.48 (9 H, m, ArH), 4.91(2 H, s, NCH_2), 3.76 (3 H, s, OCH_3).

Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.46; H, 4.62; N, 4.31. Found: C, 66.49; H, 4.62; N, 4.33.

3-Benzyl-5-[(*Z*)-(4-nitrophenyl)methylidene]-1,3-thiazolidine-2,4-dione (4f)

Mp 204–207 °C.

IR (KBr): 3153, 1720, 1698, 1601 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.26–8.30 (2 H, m, ArH), 7.91 (1 H, s, ArCH=), 7.18–7.69 (7 H, m, ArH), 4.96 (2 H, s, NCH_2).

Anal. Calcd for $C_{17}H_{12}N_2O_4S$: C, 60.00; H, 3.53; N, 8.24: Found: C, 60.11; H, 3.57; N, 8.19.

3-(4-Nitrobenzyl)-5-[(*Z*)-phenylmethylidene]-1,3-thiazolidine-2,4-dione (4g)

Mp 188–190 °C.

IR (KBr): 3081, 1741, 1683 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.20 (2 H, d, *J* = 8.8 Hz, ArH), 7.99 (1 H, s, ArC*H*=), 7.56–7.64 (7 H, m, ArH), 4.98 (2 H, s, NCH_2).

Anal. Calcd for $C_{17}H_{12}N_2O_4S$: C, 60.00; H, 3.53; N, 8.24. Found: C, 59.95; H, 3.55; N, 8.27.

3-Butyl-5-[(*Z*)-phenylmethylidene]-1,3-thiazolidine-2,4-dione (4h)
Mp 80–82 °C.

IR (KBr): 3035, 2960, 2874, 1745, 1675, 1605 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.91 (1 H, s, ArC*H*=), 7.28–7.55 (5 H, m, ArH), 3.76–3.79 (2 H, t, *J* = 7.2 Hz, NCH_2), 1.66–1.77 (2 H, m, $CH_2CH_2CH_2$), 1.36–1.41 (2 H, m, CH_2CH_3), 0.95–0.99 (3 H, t, *J* = 7.2 Hz, CH_3).

Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.37; H, 5.75; N, 5.36: Found: C, 64.39; H, 5.75; N, 5.37.

3-Isopropyl-5-[(*Z*)-phenylmethylidene]-1,3-thiazolidine-2,4-dione (4i)
Mp 68–70 °C.

IR (KBr): 2980, 1740, 1686 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.87 (1 H, s, ArC*H*=), 7.49–7.51 (5 H, m, ArH), 4.66–4.73 (1 H, m, NCH), 1.49–1.51 (6 H, d, *J* = 5.2 Hz, CH_3).

Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.16; H, 5.26; N, 5.67. Found: C, 63.15; H, 5.27; N, 5.70.

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