Organic reactions in ionic liquids: ionic liquid-accelerated facile synthesis of 3-alkyl-2,4-thiazolidinediones

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The room temperature ionic liquid [bmim]PF_6 is a new green solvent for the N-alkylation of 2,4-thiazolidinones. Significant rate enhancement and improved yields have been observed.

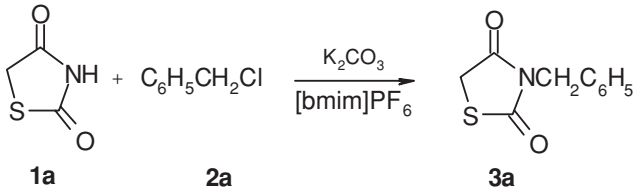
Keywords: ionic liquid, N-alkylation, 2,4-thiazolidinediones

3-Alkyl-2,4-thiazolidinediones are a class of important synthetic intermediates, and possess diverse biological and pharmaceutical activities.[1] For example, pioglitazone and rosiglitazone were launched recently for type II diabetes mellitus.[2] Most of the synthetic methods of 3-alkyl-2,4-thiazolidinediones were involve by N-alkylation of 2,4-thiazolidinediones with alkyl halides in presence of strong base such as NaOEt refluxing in DMF. This is difficult to recycle and heads to environmental contamination.[3]

Ionic liquids, a new type of solvents for green chemistry, have been studied recently because they are stable, nonvolatile, and easy to recycle. Many important reactions have been carried out in ionic liquids.[4] Seddon *et al*. reported the alkylation of indole in a [bmim]PF_6 ionic liquid and obtained almost exclusive N-substituted products. The reaction showed high regioselectivity and gave good yields.[5] Encouraged by this, we examined the N-alkylation of 2,4-thiazolidinediones with alkyl halides in the presence of K_2CO_3 in ionic liquids which would provide a facile synthesis of 3-alkyl-2,4-thiazolidinediones.

For this study, we synthesised the room temperature ionic liquids *n*-butylpyridinium tetrafluoroborate ([bpy]BF_4), 1-*n*-butyl-3-methylimidazoliumtetrafluoroborate ([bmim]BF_4) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphorate ([bmim]PF_6) according to the procedures reported in the literature.[6]

Firstly, we examed the efficiency of different solvents for the benzylation of 2,4-thiazolidinedione (**1a**) (Scheme 1). Significant rate enhancement and improved yields have been observed using ionic liquids as solvent (see Table 1). The results showed that the room temperature ionic liquid, [bmim]PF_6 was the best solvent in terms of yields and reaction times. The reaction of 2,4-thiazolidinedione (**1a**) with benzyl chloride (**2a**) using K_2CO_3 as a base in DMF needed 10 h under refluxing temperature and yielded 70% 3-benzyl-2,4-thiazolidinedione (**3a**), while in [bmim]PF_6, 90% yields of **3a** was obtained only in 2 h. at 60°C. For the room temperature ionic liquids [bmim]BF_4 and [bpy]BF_4, the yields 84% and 81% were obtained after 6h.

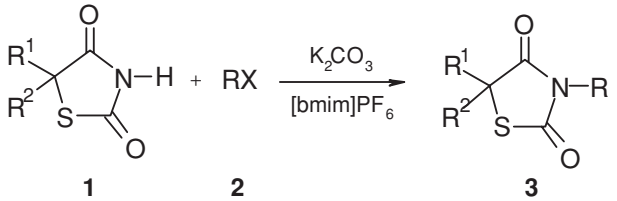


Scheme 1

Subsequently, we investigated the scope of the alkylation of 2,4-thiazolidinediones (1) with various alkyl halides (2) in the ionic liquid [bmim]PF_6 in the presence of K_2CO_3 (Scheme 2).

Either the 2,4-thiazolidinedione, or the (un)substituted 5-benzylidiene-2,4-thiazolidinediones reacted with alkyl halides containing chloro group, bromo group or iodo group smoothly in the ionic liquid [bmim]PF_6 under the mild conditions, and only produced the N-substituted products. The reaction of CH_3I with thiazolidinediones proceeded successfully at 30°C for 1–1.5 h. And the other alkyl halides also reacted easily with thiazolidinediones at 60°C with good yields. However 4-NO_2–$C_6H_4CH_2Cl$ and $ClCH(CH_3)CO_2C_2H_5$ needed longer reaction time. The results are summarised in Table 2. All the products were characterized by ^1H NMR, IR, elemental analysis and the melting points which were consistent with the literature data.

The ionic liquid can be typically recovered by firstly extracting out the product, then washing with water followed by vacuum drying. No obvious decrease in yields was observed while reusing the recovered solvent. The results are summarised in Table 3.



Scheme 2

Table 1 The reaction of 2,4-thiazolidinedione (**1a**) with benzyl chloride (**2a**) in different solvents to form **3a**

Entry[a]	Solvent	Reaction temp/°C	Reaction time/h	Yield/%[b]
1	[bmim]PF_6	60	2	90
2	[bmim]BF_4	60	6	84
3	[bpy]BF_4	60	6	81
4	DMF	Reflux	10	70

[a]All reactions were run with 2,4-thiazolidinedione (**1a**, 1mmol), benzyl chloride (**2a**, 1.1mmol) and K_2CO_3 (0.6mmol) in different solvents (2ml).
[b]Isolated yield based on 2,4-thiazolidinedione (**1a**)

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Table 2 The reactions of 2,4-thiazolidinediones (1) with alkyl halides (2) in ionic liquid [bmim]PF_6 to form 3[a]

Products	R^1, R^2	RX(2)	Temp./°C	Time/h	Yield/%[b]
3a	R^1= R^2=H	$C_6H_5CH_2Cl$	60	2	90
3b	BTZD[c]	$C_6H_5CH_2Cl$	60	2	94
3c	4-CH_3O-BTZD	$C_6H_5CH_2Cl$	60	2	92
3d	R^1= R^2=H	4-$NO_2C_6H_4CH_2Cl$	60	3	80
3e	BTZD	4-$NO_2C_6H_4CH_2Cl$	60	4	83
3f	BTZD	CH_2=$CHCH_2Cl$	60	4	78
3g	BTZD	$C_2H_5CO_2CH(CH_3)Cl$	60	6	70
3h	BTZD	$CH_3(CH_2)_3Br$	60	2	88
3i	BTZD	$(CH_3)_2CHI$	60	3	87
3j	R^1= R^2=H	CH_3I	30	1.5	89
3k	BTZD	CH_3I	30	1	95
3l	4-CH_3-BTZD	CH_3I	30	1	93
3m	4-CH_3O-BTZD	CH_3I	30	1	91

[a]All the reactions were run with thiazolidinediones (**1**, 1mmol), alkyl halides (**2**, 1.1mmol) and K_2CO_3 (0.6mmol) in [bmim]PF_6 (2ml).
[b]Isolated yields based on thiazolidinediones (**1**).
[c]BTZD stands for 5-benzylidene-2,4-thiazolidinedione.

Table 3 Results obtained using recycled ionic liquid

Entry [a]	Product	Cycle	Yield/%[b]
1	**3a**	1	90
2	**3a**	2	91
3	**3a**	3	90
4	**3a**	4	89

[a]All reactions were run with 2,4-thiazolidinediones (**1a**, 1mmol), benzyl halide(**2a**, 1.1mmol) and K_2CO_3 (0.6mol) in [bmim]PF_6 (2ml).
[b]Isolated yields based on 2,4-thiazolidinedione (**1a**).

In conclusion, we have developed a facile method of preparation of 3-alkyl-2,4-thiazolidinediones under mild conditions, which avoid using strong base and avoid the comprehensive process in the traditional solvents in literature. Moreover, ionic liquid [bmim]PF_6 is an attractive clean synthetic alternative to classical molecular solvents for N-alkylation of thiazolidinones with alkyl halides and give significant rate accelerations and improved yields of products. Separation of products from the ionic liquids is very convenient and the ionic liquid can be recycled.

Experimental

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

3-benzyl-2,4-thiazolidinedione (**3a**), *typical procedure*: 2,4-thiazolidinedione(0.117 g, 1 mmol), benzyl chloride (0.14 g, 1.1 mmol), K_2CO_3 (0.083 g, 0.6 mmol) were added to [bmim]PF_6 (2 ml).The resulting mixture was stirred at 60°C for 2h. Then the reaction mixture was extracted with Et_2O (4×15ml). The remaining ionic liquid suspension was washed with water, and reused after drying in vacuum. The combined ether solution was evaporated under reduced pressure. The crude product was purified by preparative TLC (EtOAC–*n*-hexane, 1: 4) to give the product **3a** (0.186 g, 90%) as a pale yellow solid.

M.p. 60–62°C, lit.[3d] 62–63°C. IR 3061, 2938, 1749, 1678 ^{1}H NMR δ 7.33–7.42 (5H, m, ArH), 4.79 (2H, s, N–CH_2–Ph), 3.97 (2H, s, CH_2–S).

3-benzyl-5-benzylidene-2,4-thiazolidinedione (**3b**): M.p. 133–134°C, lit.[3e] 132.5–134°C. IR 3035, 1730, 1684, 1604. ^{1}H NMR 7.93 (1H, s, ArCH=), 7.281–7.529 (10H, m, ArH), 4.92 (2H, s, N–CH_2).

3-benzyl-5-(4-methoxyphenylmethlene)-2,4-thiazolidinedione (**3c**): M.p. 144–146°C. IR 3011, 2932, 1736, 1673. ^{1}H NMR 7.87 (1H, s, ArCH=), 6.98–7.48 (9H, m, ArH), 4.91(2H, s, N–CH_2), 3.76 (3H, 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-(4-nitrobenzyl)-2,4-thiazolidinedione (3d): M.p. 116–117°C ,lit.[3d] 117–118°C. IR 1756, 1675, 1527. ^{1}H NMR 8.19–8.21 (2H,d, ArH), 7.53–7.56 (2H, d, ArH), 4.80 (2H, s, N–CH_2), 4.29 (2H, s, CH_2–S).

3-(4-nitrobenzyl)-5-benzylidene-2,4-thiazolidinedione (**3e**): M.p. 188–190°C. IR 3081, 1741, 1683. ^{1}H NMR 8.20 (2H, d, ArH), 7.99 (1H, s, ArCH=), 7.56–7.64 (7H, m, ArH), 4.98 (2H, 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-allyl-5-benzylidene-2,4-thiazolidinedione (**3f**): M.p. 88–90°C,lit.[3h] 88°C. IR 3064, 2937, 1735, 1686. ^{1}H NMR 7.87 (1H, s, ArCH=), 7.39–7.49 (5H, m, ArH), 5.81–5.88 (1H, m, –CH=CH_2), 5.22–5.30 (2H, m, =CH_2), 4.31–4.33 (2H, d, NCH_2).

3-(1-ethyl propionate)-5-benzylidene-2,4-thiazolidinedione (**3g**): M.p. 88–90°C. IR 22982, 1747, 1687. ^{1}H NMR 7.92 (1H, s, ArCH=), 5.06–5.08 (1H, m, NCH), 4.22–4.27 (2H, m, OCH_2), 1.23–1.32 (6H, m, CH_3). Anal. Calcd. for $C_{15}H_{15}NO_4S$ C% 59.02, H% 4.92, N% 4.59, Found C% 59.08, H% 4.94, N% 4.57.

3-n-butyl-5-benzylidene-2,4-thiazolidinedione (**3h**): M.p. 80–82°C. IR 3035, 2960, 2874, 1745, 1675, 1605. ^{1}H NMR 7.91 (1H, s, ArCH=), 7.28–7.55 (5H, m, ArH), 3.76–3.79 (2H, t, NCH_2), 1.66–1.77. (2H, m, CH_2–CH_2*–CH_2), 1.36–1.41 (2H, m,*CH_2CH_3), 0.95-0.99 (3H, t,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-benzylidene-2,4-thiazolidinedione (**3i**): M.p. 68–70°C. IR 2980, 1740, 1686. ^{1}H NMR 7.87 (1H, s, ArCH=), 7.49–7.51 (5H, m, ArH), 4.66–4.73 (1H, m, NCH), 1.49–1.51 (6H, d, 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.

3-methyl-2,4-thiazolidinedione (**3j**): M.p. 39–40°C, lit[3f] 40–42°C. IR 2924, 1746, 1676. ^{1}H NMR 3.96 (2H, s, CH_2-S), 3.11 (3H, s, NCH_3).

3-methyl-5-benzylidene-2,4-thiazolidinedione (**3k**): M.p. 125–128°C, lit.[3g] 130°C. IR 3017, 2925, 1742, 1672. ^{1}H NMR 7.93 (1H, s, ArCH=), 7.50–7.54 (5H, m, ArH), 3.28 (3H, s, NCH_3).

3-methyl-5-(4-methylphenylmethlene)-2,4-thiazolidinedione (**3l**): M.p. 146–148°C. IR 2943, 1732, 1682. ^{1}H NMR 7.90 (1H, s, ArCH=), 7.27–7.44 (4H, m, ArH), 3.26 (3H, s, NCH_3), 2.42(3H, s, Ar–CH_3). Anal. Calcd. for $C_{12}H_{11}NO_2S$ C% 61.80, H%4.72, N% 6.01, Found C% 61.83, H% 4.73, N% 6.05.

3-methyl-5-(4-methoxyphenylmethlene)-2,4-thiazolidinedione (**3m**): M.p. 145–147°C. IR 2950, 1735, 1681. ^{1}H NMR 7.88 (1H, s, ArCH=), 7.27–7.49 (2H, m, ArH), 6.99–7.02 (2H, m, ArH), 3.88 (3H, s, OCH_3), 3.25 (3H, 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.

Received 11 February 2005; accepted 29 March 2005
Paper 05/3068

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