Ionic liquid-accelerated N-arylation of 5-arylidene-2,4-thiazolidinediones with diaryliodonium salts

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An efficient method for the synthesis of N-aryl-5-arylidene-2,4-thiazolidinediones has been developed involving the N-arylation of 5-arylidene-2,4-thiazolidinediones derivatives with diaryliodonium salts in the ionic liquid [bmim]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate).

Keywords: ionic liquid, N-arylation, 2,4-thiazolidinediones derivatives, diaryliodonium salts

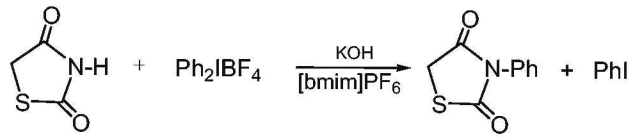
Thiazolidinone derivatives are a bio-active group of heterocyclic compounds.[1,2] They have again attracted interest because of their antidiabetic activities and pioglitazone and rosiglitazone have been launched for type 2 diabetes mellitus.[3,4] The common method of synthesising N-aryl-thiazolidinedione moieties utilised the condensation of chloroacetic acid with the aryl-substituted thiourea followed by acid hydrolysis. Another method utilised the reaction of aryl isocyanates with ethyl thioglycolate in the presence of sodium metal.[5] These preparations are unsatisfactory because of their long time reaction, harmful solvents and low yields.

The applications of hypervalent iodine compounds in organic synthesis are interesting.[6,7] Recently we showed that diaryliodonium salts are efficient electrophilic arylating reagents, and ionic liquids can accelerate the arylation reactions rates of the diaryliodonium salts.[8] Relative to conventional molecular solvents, ionic liquids have many advantages.[9,10] We considered that the preparation of N-aryl-5-arylidene-2,4-thiazolidinediones in ionic liquids, coupled with the high electrophilic reactivity of diaryliodonium salts, would be useful.

First, we examined the efficiency of different solvents for the N-phenylation of 2,4-thiazolidinedione with diphenyliodonium in the presence of KOH (see Scheme 1). The results, summarised in Table 1, show that the ionic liquid [bmim]PF_6 gave the best results in terms of yields and reaction times. As can be seen from Table 1, the ionic liquids compared with classical molecular solvents, have the advantages of accelerating rate and increasing yield. For example, the preparation of N-phenyl-2,4-thiazolidinedione (**3a**) needed refluxing for 12 long hours in the classical molecular solvents dimethylformamide or acetonitrile. Yet, the same reaction was successful in ionic liquid [bmim]PF_6 at only 80 °C within 2 h, and gave higher yield (80%). Furthermore, the temperature of the reaction in the ionic liquid, 80 °C, is lower than that using the solvent dimethylformamide (b.p. 158 °C), and is approximately equivalent to that using acetonitrile (b.p. 81 °C).

The ionic liquid can be typically recovered by extracting the product, and then washing with water followed by vacuum drying. No obvious decrease of yields was observed while reusing the recovered solvent. The results are summarised in Table 2.

We investigated the reactions of 5-arylidene-2,4-thiazolidinediones (**1**) with diaryliodonium tetrafluoroborate (**2**) at 80 °C in the ionic liquid [bmim]PF_6 in the presence of KOH (see Scheme 2). The results summarised in Table 3, show that 5-arylidene-2,4-thiazolidinediones (Ar = 4-CH_3–Ph, 4-CH_3O–Ph, 3,4-$(CH_3O)_2$–Ph, 4-NO_2–Ph, Ph, Ph–CH=CH, 2-furyl) reacted smoothly with diphenyliodonium tetrafluoroborates and gave adequate yields (50%–85%) after 2–4 h at 80 °C in the ionic liquid [bmim]PF_6 in the presence of KOH. The reactions



1a **2** **3a**

Scheme 1

Table 1 Reactions of 2,4-thiazolidinedione (**1a**) with diphenyliodonium salts (**2**) to form 3-phenyl-2,4-thiazolidinedione (**3a**) in different solvents in the presence of KOH

Entry[a]	Solvent	Temp/°C	Time/h	Yield/%[b]
1	DMF	Reflux	12	46
2	CH_3CN	Reflux	12	39
3	[bmim]PF_6	80	2	80
4	[bmim]BF_4	80	6	72
5	[bpy]BF_4	80	6	60

[a]All reactions were run with 2,4-thiazolidinedione (**1a**, 0.5 mmol) and diphenyliodonium salts (**2**, 0.55 mmol) in solvents (5 ml) in the presence of KOH (0.5 mmol).
[b]Isolated yields based on 2,4-thiazolidinedione (**1a**).

Table 2 Results obtained using recycled ionic liquid

Entry[a]	Product	Cycle	Yield/%[b]
1	**3a**	1	80
2	**3a**	2	78
3	**3a**	3	80
4	**3a**	4	81

[a]All reactions were run with 2,4-thiazolidinedione (0.5 mmol, 0.078 g) and diphenyliodonium tetrafluoroborate (0.55 mmol, 0.202 g) in [bmim]PF_6 (5 ml) in the presence of KOH (0.5 mmol) at 80 °C for 2 h.
[b]Isolated yields based on 2,4-thiazolidinedione.

also proceeded successfully for the substituted (Ar' = 4-CH_3–Ph, 4-CH_3O–Ph) diaryliodonium tetrafluoroborates without variation in the yield. All the products were characterised by ^{1}H NMR, IR, and the melting points which were consistent with the literature data[11-13]. Elemental analyses for the new compound also matches the calculated value.

As shown in Schemes 1 and 2, the iodoarene was another product as well as the N-aryl-2,4-thiazolidinediones in the reaction. It could be converted easily to the respective diaryliodonium salts in adequate yields as described in our previous work.[14]

In conclusion, an efficient, clean, and novel method for the synthesis of N-aryl-5-arylidene-2,4-thiazolidinediones has been developed using a non toxic arylation agent (diaryliodonium salts) which can be regenerated in adequate yield to replace aryl halides. Employment of ionic liquid rather than classical molecular solvents leads to mild reaction conditions. The ionic liquid can be recycled.

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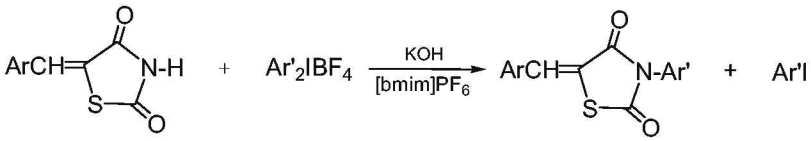

1 2 3

3b. Ar=Ph, Ar'=Ph; **3c**. Ar=4-CH_3-Ph,Ar'=Ph; **3d**. Ar=4-CH_3O-Ph, Ar'=Ph;
3e. Ar=3,4-$(CH_3O)_2$-Ph, Ar'=Ph; **3f**. Ar=4-NO_2-Ph, Ar'=Ph; **3g**. Ar=Cinnamyl, Ar'=Ph;
3h. Ar=Furfuryl,Ar'=Ph; **3i**. Ar=Ph, Ar'=4-CH_3-Ph; **3j**. Ar=Ph, Ar'=4-CH_3O-Ph

Scheme 2

Table 3 Reactions of 5-arylidene-2,4-thiazolidinediones (**1**) with diaryliodonium tetrafluoroborate (**2**) to form 3-aryl-5-arylidene-2,4-thiazolidinediones (**3**)[a]

Product(**3**)	Ar	Ar'	Time/h	Yield/%[b]
3b	Ph	Ph	2	83
3c	4-CH_3–Ph	Ph	2	85
3d	4-CH_3O–Ph	Ph	3	78
3e	3,4-$(CH_3O)_2$–Ph	Ph	4	69
3f	4-NO_2–Ph	Ph	3	74
3g	Ph–CH=CH	Ph	3	75
3h	2-Furyl	Ph	2	50
3i	Ph	4-CH_3–Ph	3	70
3j	Ph	4-CH_3O–Ph	3	71

[a]All reactions were run with 5-arylidene-2,4-thiazolidinediones (**1**, 0.5 mmol) with diaryliodonium tetrafluroborates (**2**, 0.6 mmol) in ionic liquid [bmim]PF_6 (5 ml) in the presence of KOH (0.5 mmol) at 80 °C.
[b]Isolated yields based on 5-arylidene-2,4-thiazolidinedione (**1**).

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 (400 MHz) spectrometer using TMS and d_6-DMSO as an internal standard and solvent. Elemental analysis was performed on Carlo Erba EA 1106 instrument.

3-Phenyl-2,4-thiazolidinedione (**3a**): *typical procedure*
2,4-Thiazolididione(0.5 mmol, 0.078 g) and diphenyliodonium tetrafluoroborate (0.55 mmol, 0.202 g) were added to [bmim]PF_6 (5 ml) in presence of KOH (0.5 mmol, 0.028 g).The resulting mixture was stirred at 80 °C for 2 h. Then the reaction mixture was extracted with Et_2O (4 × 15 ml). 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, 1:2) to give the product **3a** (0.077 g, 80%) as a pale yellow solid.

3-Phenyl-2,4-thiazolidinedione (**3a**): M.p. 137–139 °C, lit.[11] 135 °C; IR 2978, 1758, 1697, 1673, 1366, 1152; ^{1}H NMR 7.47–7.56 (5H, m, ArH), 4.16 (2H, s, CH_2).

3-Phenyl-5-benzylidene-2,4-thiazolidinedione(**3b**):M.p.205–206 °C, lit.[12] 208; IR 3156, 1754, 1696, 1610, 1368, 1165 cm^{-1}; ^{1}H NMR 7.42–7.62 (10H, m, ArH), 8.02 (1H, s, CH=).

3-Phenyl-5-(4-methylbenzylidene)-2,4-thiazolidinedione (**3c**): M.p. 190–191 °C, lit.[12] 192 °C; IR 3130, 3019, 1732, 1680, 1563 cm^{-1}; ^{1}H NMR 2.39 (3H, s, CH_3), 7.36–7.39 (9H, m, ArH), 8.03 (1H, s, CH=).

3-Phenyl-5-(4-methoxylbenzylidene)-2,4-thiazolidinedione (**3d**): M.p. 200–202 °C, lit.[12] 199–200 °C; IR 3140, 3025, 1741, 1690, 1585 cm^{-1}; ^{1}H NMR 3.89 (3H, s, OCH_3), 7.14 (2H, d, J = 8 Hz, ArH), 7.29–7.34 (5H, m, ArH), 7.49(2H, d, J = 8 Hz, ArH), 7.89 (1H, s, CH=).

3-Phenyl-5-(3,4-dimethoxybenzylidene)-2,4-thiazolidinedione (**3e**): M.p. 209–210 °C, lit.[12] 208–209 °C; IR 3124, 3040, 2895, 2799, 1735, 1690, 1510, 1155, 1279 cm^{-1}; ^{1}H NMR 3.81–3.83 (6H, s, OCH_3), 7.26–7.29 (3H, m, ArH), 7.35–7.38 (5H, m, ArH), 7.91 (1H, s, CH=).

3-Phenyl-5-(4-nitrobenzylidene)-2,4-thiazolidinedione (**3f**): M.p. 238–240 °C, lit.[12] 239 °C; IR 3210, 1711, 1688, 1612 cm^{-1}; ^{1}H NMR 7.40–7.42 (5H, m, ArH), 7.80 (2H, d, J = 8 Hz, ArH), 8.12 (1H, s, CH=), 8.34 (2H, d, J = 8 Hz, ArH).

3-Phenyl-5-cinnamylidene-2,4-thiazolidinedione (**3g**): M.p. 211–213 °C, lit.[12] 212–213 °C; IR 3198, 3034, 1720, 1686, 1620, 1318, 1140, 690 cm^{-1}; ^{1}H NMR 6.98 (1H, t, J = 11.6 Hz, CH=CH*–CH=), 7.70 (2H, d, J = 11.6 Hz, CH* =CH–CH*=), 7.34–7.50 (10H, m, ArH).

3-Phenyl-5-furfurylidene-2,4-thiazolidinedione (**3h**): M.p. 217–219 °C, lit.[12] 218–219 °C; IR 3140, 3035, 2814, 1730, 1689, 1613, 1338, 1032 cm^{-1}; ^{1}H NMR 6.80 (1H, t, J = 6 Hz, 3-furyl-H), 7.16 (1H, d, J = 6 Hz, 4-furyl-H), 7.45–7.53(5H, m, ArH), 7.73 (1H, d, J = 6 Hz, 5-furyl-H), 8.08 (1H, s, CH=).

3-(4-Methylphenyl)-5-benzylidene-2,4-thiazolidinedione (**3i**): M.p. 202–204 °C, lit.[13] 201 °C; IR 3034, 2977, 1750, 1693, 1620, 1353, 1192 cm^{-1}; ^{1}H NMR 2.39 (3H, s, CH_3), 7.37–7.40 (4H, m, ArH), 7.43–7.45(5H, m, ArH), 8.00 (1H, s, CH=).

3-(4-Methoxylphenyl)-5-benzylidene-2,4-thiazolidinedione (**3j**): M.p. 193–194 °C; IR 3047, 2981, 1755, 1697, 1614, 1364, 1150 cm^{-1}; ^{1}H NMR 3.79, (3H, s, OCH_3), 7.40–7.42 (4H, m, ArH), 7.57–7.58 (5H, m, ArH), 8.00 (1H, s, CH=). Anal. Calcd for $C_{17}H_{13}NO_3S$ C 65.58, H 4.28, N 4.50; Found C 65.40, H 4.51, N 4.46%.

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