One-pot three-step synthesis of 3-aryl-2-benzoylimino-4-thiazolidinones in the ionic liquid [bmim$^+$][PF$_6^-$]

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3-Aryl-2-acylimino-4-thiazolidinones are efficiently formed in 1-*n*-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF$_6$] as solvent in a one-pot three-step procedure. The ionic solvent could be recovered and recycled four times with no diminution in yields.

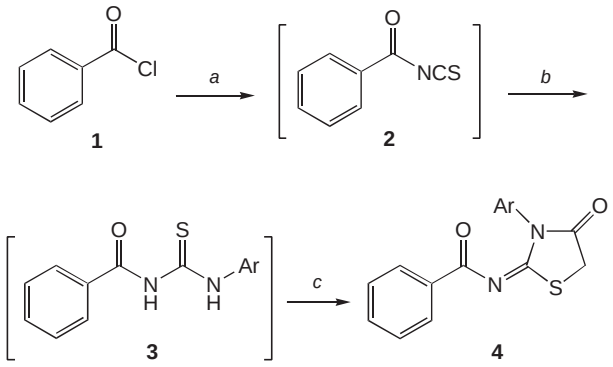
Keywords: thiocyanates, ionic liquids, thiazolidinones, acylimines

The search for alternative synthetic technologies that are cleaner, safer and more efficient than methods currently employed is an important goal both in the plant and in the laboratory.[1] In reducing the amount of waste and the use of environmentally undesirable solvents, room temperature ionic liquids[2] have received a good deal of attention in recent years as environmentally benign reaction media for organic synthesis due to their reusability whilst offering an inert, dipolar medium compatible with much conventional chemistry. Moreover, the switch from an organic solvent to ionic liquids reduces air pollution by solvents and produces a cleaner waste stream.

One-pot synthesis has the great advantage that the desired compounds can be prepared without the need to isolate and purify intermediates. From the environmental and economic points of view, green chemistry commonly prefers one-pot synthesis, largely because the separation of intermediates requires added unit operations, and leads to problems of waste disposal and feedstock losses. Unfortunately, few attempts have been made to investigate one-pot multi-step organic synthesis in ionic liquids. Only two examples, a two-step aza-Diels–Alder reaction[3] and a three-step parallel synthesis of isoxazolines,[4] have been reported in the literature, and therefore research in the area has much scope for extension.

Thiazolidinones are an interesting class of compound due to their biological activities, having generated much interest as antiinflammatory agents,[5] anticonvulsant drugs,[6] fungicides,[7] herbicides[8] and acaricides[9] in the pharmaceutical and agrochemical industry. However, few efforts have been made in the development of synthetic methods for 3-aryl-2-acylimino-4-thiazolidinones. Previous published syntheses were carried out in multi-batch fashion, employing *N*-acyl-*N'*-arylthioureas as intermediates, synthesised from *in situ* generated acyl isothiocyanates and aromatic amines in volatile, toxic and/or flammable solvents such as acetone,[10] acetonitrile,[11] benzene,[12] and chloroform.[13] Treatment of *N*-acyl-*N'*-arylthioureas with ethyl chloroacetate/ KOH/ DMF [14] or ethyl bromoacetate / NaOAc/ EtOH [15] afforded 3-aryl-2-acylimino-4-thiazolidinones in moderate yields. These methods require additional work-up to isolate the intermediates and thus produce waste. In view of the value of thiazolidinones as drug candidates and the demand for eco-conscious chemical processes, access to an efficient procedure permitting synthesis of the title compounds in a one-pot operation may be of value.

In continuation of our research program aimed at greener synthesis and the development of new methods for the expeditious preparation of biologically relevant heterocycles, here we report an efficient and eco-friendly one-pot three-step procedure for the synthesis of 3-aryl-2-benzoylimino-4-thiazolidinones using ionic liquid [bmim][PF$_6$] as sole reaction medium. This protocol involves three sequential reaction steps using one batch of ionic liquid (Scheme 1). The experimental procedure is quite simple, convenient and avoids tedious work-up procedures for the isolation of intermediates. Ammonium thiocyanate in [bmim][PF$_6$] was treated with one equivalent of benzoyl chloride **1** and the benzoyl isothiocyanate **2** thus formed was reacted with various aromatic amines (1 equiv.) to give *N*-benzoyl-*N'*-arylthiourea **3**. The product was directly used in the next step without any work-up or isolation. Subsequent cyclisation of **3** with ethyl bromoacetate (1.2 equiv.) in the presence of sodium acetate led to the desired 3-aryl-2-acylimino-4-thiazolidinones **4**. This protocol is a combination of green techniques that effectively improve the environmental performance of the reactions such as (1) the use of ionic liquid as sole reaction medium (the least environmentally threatening solvent), (2) the recycling of the reaction medium (an important way to reduce wastes), and (3) the performance of these reactions in one-pot operation (a perfect manner allows tedious work-up and energy waste to be avoided as well as the production of waste to be minimised at source).



Scheme 1 One-pot synthesis of thiazolidinones **4** in [bmim][PF$_6$].
Reagents and conditions: (*a*) NH_4SCN, 0 °C → r. t., 30 min; (*b*) $ArNH_2$, r. t., 20 min; (*c*) $BrCH_2COOEt$, NaOAc, 80 °C, 2–3 h.

As the first step, we investigated the effects of solvents on the one-pot approach. Four different solvents, [bmim][BF$_4$], [bmim][PF$_6$], acetonitrile and *N*-methyl-2-pyrrolidone (NMP), were screened using the synthesis of **4b** as a model under the similar reaction conditions (80 °C). The yields of the desired products were 75%, 77%, 74% and 63%, respectively. There were no considerable differences in reaction rates and yields either with [bmim][BF$_4$] or with [bmim][PF$_6$]. In our procedure, the latter was chosen due to its hydrophobic nature, which allows the water-soluble by-products to be readily removed by water washing.

Since one of the initial goals of this research effort was to develop a one-pot process to combine these reactions with

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enhanced yield and efficiency, we further compared the yields in one-pot synthesis with those in stepwise synthesis using [bmim][PF_6] as solvent. The intermediate **3b** was either isolated after standard work-up or directly used in the next step. Product **4b** was obtained in total 70 % yield in the stepwise process, while in 77% yield *via* the one-pot process. Therefore, the one-pot synthesis is preferable to the stepwise process whether from the standpoint of total yield or from the convenience of the process.

The scope and generality of this process were further examined with respect to a range of aromatic amines under optimised conditions (Table 1). It should be noted that the substituents with different electronic and steric effects would affect the reaction rates and yields. The electron-donating groups favored the formation of product as demonstrated for **3b** and **3e**, while the presence of electron-withdrawing groups (**3d, 3g, 3h, 3i** and **3j**) required longer reaction times to give similar yields. It should be mentioned here that the *ortho*-substituted substrate required longer reaction times to obtain comparable yields with the *para*-substituted one, which due presumably to steric reasons. For instance, **3e** gave 75% yield of the corresponding **4e** in 2 h, while a diminished yield (67%) was obtained even after 3h when the methoxyl group was present at the *ortho* position (**3f**).

Having established the practicability of this procedure, using **4b** and **4c** as model products, attention was next focused on the recycling of [bmim][PF_6] for environmental and economic reasons. As shown in Figure 1, the ionic liquids used in both systems could be recycled at least five times with essentially no change in the reaction outcome. On completion of the reaction, in the case of **4b**, the salts were firstly leached with water. The weakly soluble product was collected by filtration (77% yield after purification). The ionic liquid was then separated from the aqueous layer and dried *in vacuo* at 100 °C for 1 h. The same batch of ionic liquid could be reused in four successive runs, affording similar isolated yields of **4b** (80%, 78%, 76%, 80%). It is noted that even a little higher yields than in the first run were obtained in the second, third and fifth runs. Analogous results were also obtained in the synthesis of **4c**.

In summary, we have demonstrated a straightforward and green method for the synthesis of 3-aryl-2-benzoylimino-4-thiazolidinones in satisfactory yields via one-pot process using [bmim][PF_6] as reaction medium. The experimental procedure is quite simple and convenient. The combination of a one-pot strategy with recoverable ionic liquids makes this procedure environmentally benign, economic and user-friendly.

Experimental

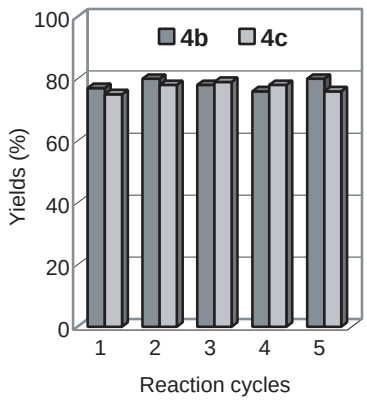

Fig. 1. Recycling studies on [bmim][PF_6] in the synthesis of 4b and 4c

Table 1 One-pot synthesis of thiazolidinones in [bmim][PF_6]

Entry	Ar	Time/h[a]	Yield/%[b]
a	C_6H_5	2	78
b	4-$CH_3C_6H_4$	2	77
c	4-ClC_6H_4	2	75
d	4-$NO_2C_6H_4$	3	74
e	4-$CH_3OC_6H_4$	2	75
f	2-$CH_3OC_6H_4$	3	67
g	3-FC_6H_4	3	70
h	4-FC_6H_4	3	77
i	3-Cl-4-FC_6H_3	3	72
j	3,4-$F_2C_6H_3$	3	78

[a]reaction time of step c, Scheme 1.
[b]all yields refer to isolated products which were characterised by m.p. data and spectral analysis.

All reagents were purchased from commercial suppliers and used without further purification, with the exception of ionic liquids [bmim][PF_6][16] and [bmim][BF_4],[17] which were prepared as described elsewhere. Melting points were determined on a X-4 micro-melting point apparatus. FTIR spectra were obtained on a Nicolet Nexus 470 infrared spectrometer in KBr discs and ^{1}H NMR spectra were recorded on a 500 MHz Bruker AM 500 spectrometer with TMS as internal standard. Elemental analysis was performed on an Italian Mod. 1106 analyser and the results were found to be in good agreement with the calculated values.

General procedure: A 50 ml flask equipped with a dropping funnel was charged with NH_4SCN (0.38 g, 5 mmol) and [bmim][PF_6] (5 ml) and was cooled in an ice-water bath. Freshly distilled benzoyl chloride (0.71 g, 5 mmol) was added dropwise to the magnetically stirred suspension. After 10 min the mixture was warmed to room temperature and stirred for a further 20 min (disappearance of starting material was monitored by TLC). Aromatic amine (5 mmol) was then added to the same reaction vessel at room temperature and the mixture was stirred for 20 min more. On completion, ethyl bromoacetate (1.00 g, 6 mmol) and anhydrous sodium acetate (0.49 g, 6 mmol) was added to the flask, and the mixture was heated at 80 °C for the period (2-3 h) specified in Table 1. After consumption of *N*-benzoyl-*N'*-arylthioureas by TLC monitoring, the salts were firstly leached with water (5ml × 2), and the crude product was collected by filtration. Recrystallization from ethanol gave pure products as white or yellowish crystalline solids.

3-Phenyl-2-benzoylimino-4-thiazolidinone (**4a**): m.p. 237 °C (lit.[15] 240–241 °C). IR: ν_{max} (KBr, cm^{-1}) 1735, 1632, 1509, 1380, 1324, 1206, 1165. NMR: δ_H ($CDCl_3$, 500 MHz): 4.00 (s, 2H, CH_2), 7.32–7.42 (m, 4H, ArH), 7.43–7.55 (m, 2H, ArH), 7.55–7.60 (m, 2H, ArH), 7.99 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 2H, ArH).

3-(4-Tolyl)-2-benzoylimino-4-thiazolidinone (**4b**): m.p. 226 °C (lit.[15] 225–227 °C). IR: ν_{max} (KBr, cm^{-1}): 1745, 1647, 1493, 1360, 1319, 1375, 1193, 1160, 1080. NMR: δ_H ($CDCl_3$, 500 MHz) 2.50 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 7.24 (d, *J* = 8.3 Hz, 2H, ArH), 7.37 (m, 4H, ArH), 7.51 (t, *J* = 7.4 Hz, 1H, ArH), 8.00 (d, *J* = 7.3, 2H, ArH).

3-(4-Chlorophenyl)-2-benzoylimino-4-thiazolidinone (**4c**): m.p. 205 °C (lit.[15] 202–204 °C). IR: ν_{max} (KBr, cm^{-1}): 1740, 1637, 1509, 1478, 1319, 1201, 1088. NMR: δ_H ($CDCl_3$, 500 MHz) 4.00 (s, 2H, CH_2), 7.32 (m, 2H, ArH), 7.40 (m, 2H, ArH), 7.49–7.58 (m, 3H, ArH), 8.01 (d, *J* = 7.1 Hz, 2H, ArH).

3-(4-Nitrophenyl)-2-benzoylimino-4-thiazolidinone (**4d**): m.p. 205–207 °C. IR: ν_{max} (KBr, cm^{-1}) 1725, 1625, 1600, 1580, 1500, 1380, 1320, 1200, 1175. NMR: δ_H (acetone-d_6, 500 MHz): 4.20 (s, 2H, CH_2), 7.43 (t, *J* = 7.5 Hz, 2H, ArH), 7.57 (d, *J* = 7.5 Hz, 1H, ArH), 7.87 (d, *J* = 9.0 Hz, 2H, ArH), 8.01 (q, J_1 = 1.0 Hz, J_2 = 1.3 Hz, 2H, ArH), 8.50 (d, *J* = 9.1 Hz, 2H, ArH). Anal: Found: C, 56.43; H, 3.27; N, 12.59. $C_{16}H_{11}N_3O_4S_2$ requires C, 56.30; H, 3.25; N, 12.31 %.

3-(4-Methoxyphenyl)-2-benzoylimino-4-thiazolidinone (**4e**): m.p. 204 °C. IR: ν_{max} (KBr, cm^{-1}) 1740, 1642, 1499, 1478, 1365, 1319, 1275, 1190, 1140, 1083. NMR: δ_H ($CDCl_3$, 500 MHz) 3.92 (s, 3H, OCH_3), 4.20 (s, 2H, CH_2), 7.06 (m, 2H, ArH), 7.26 (m, 2H, ArH), 7.38 (d, *J* = 7.8 Hz, 2H, ArH), 7.53 (d, *J* = 6.3 Hz, 2H, ArH), 8.01 (dd, J_1 = 7.8 Hz, J_2 = 1.13 Hz, 2H, ArH). Anal: Found: C, 62.41; H, 4.37; N, 8.55. $C_{17}H_{14}N_2O_3S$ requires C, 62.57; H, 4.32; N, 8.58 %.

3-(2-Methoxyphenyl)-2-benzoylimino-4-thiazolidinone (**4f**): m.p. 167–169 °C. IR: ν_{max} (KBr, cm^{-1}) 1730, 1637, 1499, 1375, 1324, 1206, 1160, 1088. NMR: δ_H ($CDCl_3$, 500 MHz): 3.81 (s, 3H, OCH_3), 4.14 (s, 2H, CH_2), 7.12–7.52 (m, 7H, ArH), 7.93 (d, *J* = 7.9 Hz, 2H, ArH); Anal: Found: C, 62.35; H, 4.39; N, 8.50. $C_{17}H_{14}N_2O_3S$ requires C, 62.57; H, 4.32; N, 8.58 %.

3-(3-Fluorophenyl)-2-benzoylimino-4-thiazolidinone (**4g**): m.p. 209 °C. IR: ν_{max} (KBr, cm^{-1}) 1725, 1642, 1596, 1509, 1483, 1375, 1324, 1206, 1087, 1005. NMR: δ_H ($CDCl_3$, 500 MHz) 4.01 (s, 2H, CH_2), 7.12–7.18 (m, 1H, ArH), 7.19 (d, *J* = 7.2 Hz, 1H, ArH), 7.22–7.25 (m, 1H, ArH), 7.38 (t, *J* = 7.8 Hz, 2H, ArH), 7.48–7.59 (m, 2H, ArH), 8.01(d, *J* = 7.3 Hz, 2H, ArH); Anal: Found: C, 61.29; H, 3.57; N, 8.87. $C_{16}H_{11}FN_2O_2S$ requires C, 61.15; H, 3.53; N, 8.91 %.

3-(4-Fluorophenyl)-2-benzoylimino-4-thiazolidinone (**4h**): m.p. 194–195 °C. IR: ν_{max} (KBr, cm^{-1}) 1745, 1637, 1504, 1375, 1319, 1206, 1165, 1093. NMR: δ_H ($CDCl_3$, 500 MHz) 4.00 (s, 2H, CH_2), 7.34–7.42 (m, 4H, ArH), 7.52 (t, *J* = 7.3 Hz, 1H, ArH), 8.01 (d, *J* = 7.9 Hz, 2H, ArH); Anal: Found: C, 61.22; H, 3.58; N, 8.98. $C_{16}H_{11}FN_2O_2S$ requires C, 61.15; H, 3.53; N, 8.91 %.

3-(3-Chloro-4-fluorophenyl)-2-benzoylimino-4-thiazolidinone (**4i**): m.p. 196 °C. IR: ν_{max} (KBr, cm^{-1}) 1745, 1637, 1514, 1493, 1365, 1314, 1196, 1160. NMR: δ_H ($CDCl_3$, 500 MHz): 4.00 (s, 2H, CH_2), 7.35 (d, *J* = 8.1 Hz, 1H, ArH), 7.41 (d, *J* = 7.7 Hz, 2H, ArH), 7.48–7.51 (m, 1H, ArH), 7.54 (d, *J* = 7.4 Hz, 1H, ArH), 8.05 (d, *J* = 7.6 Hz, 2H, ArH); Anal: Found: C, 55.28; H, 2.88; N, 8.16. $C_{16}H_{10}ClFN_2O_2S$ requires C, 55.42; H, 2.91; N, 8.08 %.

3-(3,4-Difluorophenyl)-2-benzoylimino-4-thiazolidinone (**4j**): m.p. 203–204 °C. IR: ν_{max} (KBr, cm^{-1}) 1750, 1647, 1617, 1529, 1473, 1380, 1314, 1278, 1196, 1160, 1083. NMR: δ_H ($CDCl_3$, 500 MHz): 4.00 (s, 2H, CH_2), 7.13–7.20 (m, 1H, ArH), 7.36–7.46 (m, 4H, ArH), 7.52 (d, *J* = 7.3 Hz, 1H, ArH), 8.01 (d, *J* = 7.1 Hz, 2H, ArH); Anal: Found: C, 57.97; H, 3.12; N, 8.32. $C_{16}H_{10}F_2N_2O_2S$ requires C, 57.83; H, 3.03; N, 8.43 %.

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