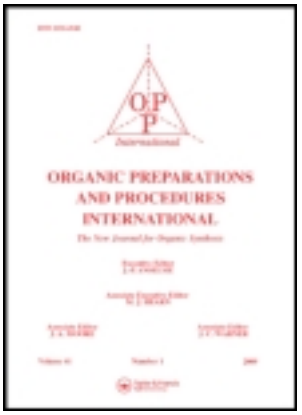

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Javad Safaei-Ghomi [a] & Mohammad Ali Ghasemzadeh [a]

[a] Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, 51167, Kashan, I. R. Iran

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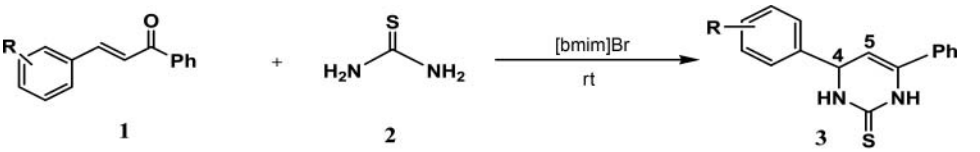
Preparation of 4,6-Diaryl-3,4-dihydropyrimidine-2(*1H*)-thiones in an Ionic Liquid

Javad Safaei-Ghomi and Mohammad Ali Ghasemzadeh

Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, 51167 Kashan, I. R. Iran

Pyrimidine derivatives have a wide range of medicinal application because of their diverse biological activities, such as anti-microbial,[1] anti-tumor, and anti-fungal activities;[2] they are also considered to be important for drugs and agricultural chemicals.[3–5] Many of the recent methods reported for the synthesis of pyrimidine derivatives[6–11] suffer from drawbacks such as long reaction times, complicated work-up, unsafe reaction conditions, and low yields. Over the past decade, ionic liquids have been received increasing attention in organic chemistry because of their environmentally benign nature, high polarity, and good thermal stability. Often shorter reaction times, high yields, cleaner reaction products, and high selectivity are observed in ionic liquid as reaction media.[12,13] In continuation of our studies on the application of ionic liquids media,[14–16] we found that 1-*n*-(butyl)-3-methylimidazolium bromide ([bmim]Br) has several advantages over other ionic liquids.[17,18] The use of [bmim]Br have been reported in reactions such as oxidation of thiols,[19] alkyl arenes, and alcohols;[20,21] the preparation of phenacyl esters[22] and of 3-acetoacetylcoumarin derivatives;[23] and the demethylation of methyl aryl ethers.[24] This reagent is safe, easy handled, environmentally benign, and presents fewer disposal problems. The present investigation describes the preparation of pyrimidine-2-thione derivatives **3** in [bmim]Br.



1 **2** **3**

3a) R = H; **3b)** R = 2-CH_3; **3c)** R = 3-CH_3; **3d)** R = 4-CH_3;

3e) R = 4-MeO; **3f)** R = $N(Me)_2$; **3g)** R = 3-Cl; **3h)** R = 4-Cl

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Address correspondence to Javad Safaei-Ghomi, Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, 51167 Kashan, I. R. Iran. E-mail: safaei@kashanu.ac.ir

Application of the ionic liquid as solvent and catalyst at room temperature shortened the reaction time of the generation for pyrimidines from 6 h under classical conditions[25,27] to 40–50 min (see Table 1) and the yields improved 20%–30% as compared with the base heating method.[25,27] The spectrometric data of products are shown in *Table 2*. These results can be explained by the catalytic and coordinative properties of [bmim]Br as previously discussed.[29–32]

Michael addition between α,β-unsaturated carbonyl compounds and nucleophiles may be performed by the use of activated vinyl compounds bearing alkyl or aryl groups. Thus the reaction between thiourea and chalcones containing various substituents was carried out in both common and ionic liquids media. *Table 1* shows that chalcones bearing both electron-withdrawing and electron-donating groups afforded the corresponding pyrimidine-2-thiones. However, with R = *o*- or *p*-nitro groups, the yields were poor even after a prolonged time and the work-up was complicated compared with chalcones bearing other substituents.

Experimental Section

All melting points are uncorrected and were determined in capillary tubes on Boetius melting point microscope. FT-IR spectra were recorded on a Nicolet Magna 550 spectrometer (KBr). [bmim]Br was purchased from Fluka. ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker 400 MHZ spectrometer in dimethyl sulfoxide-d_6 (DMSO-d_6) as solvent using tetramethylsilane (TMS) as an internal standard; the chemical shift values are in δ. All reactions were monitored and checked by thin layer chromatography (TLC) using hexane/ethyl acetate (7:3) and spots were examined using a UV lamp.

Table 1
Preparation of Pyrimidines (**3**) under Base and Ionic Liquid Conditions

Cmpd	mp(°C)	lit. mp	Base-Catalyzed		In [bmim]Br	
			Time (h)	Yield (%)	Time (min)	Yield (%)
3a	182–184	184[25]	5.5	68	40	92
3b	175–177	——[a]	6	64	45	85
3c	183–185	——[b]	6	66	42	88
3d	196–198	197–198[26]	6	**66**	42	90
3e	123–124	123–124[27]	6	60	45	87
3f	162–164	——[c]	6	60	45	88
3g	192–194	193–194[28]	5	70	35	95
3h	180–182	181–182[28]	5	72	30	95

[a]*Anal.* Calcd. For $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99; S, 11.44. Found: C, 72.88; H, 5.66; N, 10.05; S, 11.35.
[b]*Anal.* Calcd. For $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99; S, 11.44. Found: C, 72.83; H, 5.76; N, 10.01; S, 11.38.
[c]*Anal.* Calcd. For $C_{18}H_{19}N_3S$: C, 69.87; H, 6.19; N, 13.58; S, 10.36. Found: C, 69.93; H, 6.15; N, 13.55; S, 10.33.

Table 2
Spectroscopic Data of Compounds **3b**, **3c**, **3f**

Cmpd	IR (Cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)
3b	3255 (NH), 1677 (C=N), 1165 (C=S)	2.1 (s, 3H, CH_3), 4.87 (d, 1H, 4-CH) 5.12 (d, 1H, 5-CH C=CH), 6.91–7.30 (m, 9H, Ar-H), 8.85 (bs, 1H, NH), 9.60 (bs, 1H, NH).	22.3, 56, 101.8, 125.45, 125.8, 127.5, 127.9, 128.7, 129.2, 133.4, 133.8, 134.7, 137.5, 144.3, 175.2
3c	3169 (NH), 1667 (C=N), 1194 (C=S)	2.08 (s, 3H, CH_3), 4.85 (d, 1H, 4-CH) 5.15 (d, 1H, 5-CH), 6.83–7.31 (m, 9H, Ar-H), 8.85 (bs, 1H, NH), 9.64 (bs, 1H, NH).	21.6, 55.1, 101.7, 124, 126.2, 127.3, 127.9, 128.6, 129.1, 129.3, 133.75, 134.6, 138.2, 144.5, 177.3
3f	3196 (NH), 1666 (C=N), 1191 (C=S)	2.74 (s, 6H, $N(Me)_2$), 5 (m, 2H, 4-CH, 5-CH), 6.83–7.25 (m, 8H, Ar-H), 8.64 (bs, 1H, NH), 9.60 (bs, 1H, NH)	56.52, 79.67, 102.04, 112.22, 125.64, 126.26, 127.98, 128.19, 130.29, 134.46, 138.7, 150.54, 176.12

General Procedures for the Synthesis of Pyrimidine-2-thiones 3a–3h

***Base-catalyzed Method*:** A mixture of chalcone (5 mmol), thiourea (0.38 g, 5 mmol), and potassium hydroxide (0.5 g) in ethanol (20 ml) was refluxed (magnetic stirring) on oil bath at 70°C–80°C for 6 h. The reaction mixture was left standing for overnight and then was concentrated under reduced pressure. The solid obtained was collected, washed with water, and recrystallized from ethanol.

***[bmim]Br Method*:** A mixture of chalcone (5 mmol), thiourea (0.38 g, 5 mmol), and [bmim]Br (0.763 g, 3.5 mmol) was stirred at room temperature for the period of time shown in Table 1. After completion of the reaction as indicated by TLC using hexane/ethyl acetate (7:3), the reaction mixture was extracted with ether (3 × 10 ml). The organic layer was evaporated under reduced pressure and the product was recrystallized from ethanol. The immiscible ionic liquid phase was recovered and heated for 3 h under vacuum (1 mbar) for further uses. The best results were obtained with a ratio of [1:1:0.7] mmols of chalcone, thiourea, and [bmim]Br.

***General Procedure for the Large-scale Synthesis of 4,6-Diphenyl-3,4-dihydropyrimidine-2(1H)-thione (3a) by the [bmim]Br Method*:** To a 500 ml round-bottomed flask equipped with a large stir bar was added 1,3-diphenyl-2-propen-1-one (1a) (20.8 g, 0.1 mol), thiourea (7.6 g, 0.1 mol), and [bmim]Br (15.26 g, 0.07 mol). The reaction mixture was stirred at room temperature for 2 h. Progress of the reaction was continuously monitored by TLC using hexane/ethyl acetate (7:3). After the reaction was completed, the mixture was extracted with ether (3 × 50 ml). The organic layer was evaporated under

vacuum and the solid obtained was recrystallized from ethanol to produce 20.5 g (77%) of pure product (**3a**). The catalyst was recovered as mentioned in previous procedure.

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