Tetrahedron Letters 54 (2013) 5974–5978

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Catalyst free, regioselective one-pot three-component synthesis of thiazol-2-imine derivatives in ionic liquid

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ARTICLE INFO

Article history:
Received 17 June 2013
Revised 12 August 2013
Accepted 17 August 2013
Available online 27 August 2013

Keywords:
Amine
Phenyl isothiocyanate
β-Nitroacrylate
Thiazol-2-imines
Regioselectivity and ionic liquid

ABSTRACT

A one-pot three-component approach for the synthesis of thiazol-2-imines has been described by the reaction of amine, phenyl isothiocyanate and β-nitroacrylate in [Hbim]BF_4 ionic liquid. The method is applicable for aromatic, benzylic, aliphatic and cyclic amines. Reusable reaction media, regioselectivity, mild reaction condition, catalyst free and high yield of products are the salient features of this protocol.

Thiazole moiety is found as a core unit in various pharmaceuticals as well in agrochemicals such as acrecides, insecticides and plant growth regulators.[1] Particularly, 2-iminothiazoline has been shown to possess different biological activities[2] such as anti-inflammatory, analgesic and kinase (CDK1, CDK5 and GSK3) inhibition,[3] antifungal,[4] melanin-reducing activity (skin whitening agent)[5] and as platelet GPIIb/IIIa receptor antagonists.[6] Recently, Pifithrin (Pft-α) having 2-iminothiazoline skeleton has been projected as a possible lead for the treatment of major neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Stroke and cancer therapy (Fig. 1).[7]

There are various methods for the synthesis of iminothiazolines. Hantzsch condensation reaction was the first method reported for the synthesis of 2-aminothiazole moiety using α-haloketone and thiourea as starting materials.[8] Subsequently other alternative methods have been reported including copper-catalysed N-phenylation of 2-aminobenzothiazole derivatives,[9] condensation of thiazol-2(3*H*)-imines with 4-chloro and 4-isothiocyanato acridines,[3] cycloaddition of 5-imino-1,2,4-thiazolidin-3-ones with both electrophilic and nucleophilic unsaturated compounds such as enamines and ester enolates.[10] Another method is based on the ring expansion of 1-aryl methyl-2-(thiocyanatomethyl) aziridine with an acyl chloride in the presence of $TiCl_4$.[11] In addition to this the synthesis of thiazol-2-imines was also accomplished by the reaction of substituted amines with isothiocyanates.[12] Some of the methods for the synthesis of thiazol-2-imines comprise the use of *N*,*N*′-dialkylthiourea and in situ generated α-bromoketones in one-pot protocol, which is limited to symmetrical thioureas and a few selected ketones.[13] Recently, the three component reaction of phenacyl bromide or 2-chloro-1,3-dicarbonyl compound, amine and phenyl isothiocynate has been reported to give thiazol-2-imines.[14] Murru et al.[15] reported the one-pot reaction of enolisable ketones and disubstituted thioureas in presence of 1,10-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT) as a brominating agent to give thiazol-2-imines. Though the reported methods are satisfactory for the synthesis of thiazol-2-imines, some drawbacks like harsh reaction condition, low yield, prolonged reaction time and use of polar, volatile and hazardous organic solvents have been encountered. In addition to this some of the methods are limited to

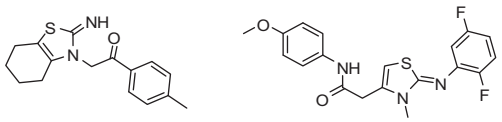

Figure 1. Representative examples of biologically active thiazol-2-imine derivatives.

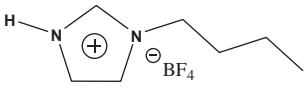

Figure 2. Chemical structure of 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF_4 ionic liquid.

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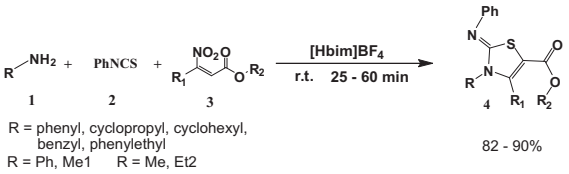
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.08.056



Scheme 1. Three component synthesis of substituted thiazol-2-imines under catalyst-free condition by using $[Hbim]BF_4$ as a reaction medium.

Table 1
Screening of reaction media[a]

Entry	Reaction media	Time (min)	Yield[b] (%)
1	$[Hbim]BF_4$	55	90
2	$[Hbim]BF_4$	120	90
3	$[bmim]BF_4$	120	75
4	$[bmim]PF_6$	120	72
5	$[emim]BF_4$	120	65

[a] Reaction condition: aniline **1a** (1 mmol), phenyl isothiocyanate **2** (1 mmol) and β-nitroacrylates ((Z)-ethyl 3-nitrobut-2-enoate) **3a** (1 mmol) in 5 mL ionic liquid.
[b] Isolated yield.

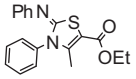
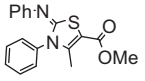
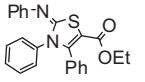
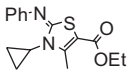
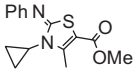
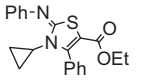
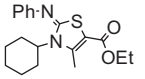
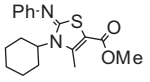
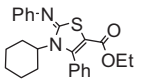
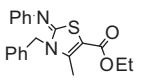
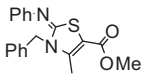
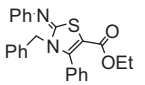
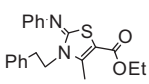
symmetrical thio urea and selected ketones and lack regioselectivity. In this regard it is desirable to develop efficient one pot method for the regioselective formation of thiazol-2-imines under mild reaction conditions.

Multicomponent reactions (MCRs) have recently emerged as valuable tools in pharmaceutical chemistry because of their wide range of applications such as atom economy, simplicity and time-saving features. MCRs are convergent reactions, producing an extremely high increase of molecular complexity in just one step.[16,17] Due to these significant useful attributes of MCRs, they have attracted more and more attention from the medicinal chemistry community.

The use of ionic liquids as a recyclable and environmentally benign medium has been attracting considerable attention for chemical transformations including non-catalytic reactions. The main advantage of ionic liquids is to reduce or eliminate the use of hazardous and toxic solvents.[18] In this context, ionic liquids have emerged as environmentally friendly substitutes for volatile organic compounds.[19]

Due to prominent biological activity of thiazol-2-imines and as a part of our ongoing interest in the application of ionic liquids[20]

Table 2
Synthesis of substituted thiazol-2-imines[a] in $[Hbim]BF_4$

Entry	R	R^1	R^2	Product	Time (min)	Yield[b] (%)
1		CH_3	Et	 **4a**	55	90
2		CH_3	Me	 **4b**	55	89
3		ph	Et	 **4c**	25	89
4		CH_3	Et	 **4d**	55	87
5		CH_3	Me	 **4e**	55	86
6		ph	Et	 **4f**	25	86
7		CH_3	Et	 **4g**	60	84
8		CH_3	Me	 **4h**	60	84
9		ph	Et	 **4i**	30	82
10		CH_3	Et	 **4j**	57	84
11		CH_3	Me	 **4k**	57	84
12		ph	Et	 **4l**	27	82
13		CH_3	Et	 **4m**	55	88

(*continued on next page*)