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Research Article

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Synthesis of 4-Iminothiazolidinones by Using [bmIm] OH

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ABSTRACT

An evaluation of task specific basic ionic liquid [bmIm] OH for the synthesis of 4-iminothiazolidinone ring from 2-chloro-N-(4-morpholinophenyl) acetamide followed by Knovengel condensation with aryl aldehyde using [bmIm] OH , in absence of solvent with good yields than the conventional reagent. Green reaction conditions and reusability of catalyst are the most remarkable features of this synthetic method.

Keywords: Basic ionic liquid; [bmIm] OH; 4-Iminothiazolidinone ring; Knovengel condensation; Aryl aldehyde

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INTRODUCTION

Thiazolidinone as evident from literature, it was noted that lot of research has been carried out on thiazolidin-4-one pharmacophore. Admantanyl analogue of thiazolylimino-5-arylidene-thiazolidin-4-ones1 [1] was reported to show antibacterial activity was reported by Omar et al. Recently, Vicini et al. reported antibacterial activity of 2-thiazolylimino-5-arylidene-thiazolidin-4-ones [2] and its benzothiazolyl analogues. Recently, task specific basic ionic liquids used as molecular tools for green synthetic chemistry [3]. Mehnert [4] et al. reported the synthesis and applications of a task specific basic ionic liquid, 1-n-butyl-3-methylimidazolium hydroxide [bmIm] OH in 2002. Later on Ranu [5] et al. modified the previously reported synthetic procedure for preparation of [bmIm] OH and reported its diverse applications in synthetic organic chemistry. We used the tailor-made, task-specific and stable ionic liquid [bmIm] OH for the synthesis of iminothiazolidinones and its Knoevengel reaction with aryl aldehydes. The results of this attempt are summarized in the next part of this article (Figure 1).

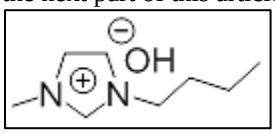


Figure 1: Structure of 1-n-butyl-3-methylimidazolium hydroxide ([bmIm] OH)

EXPERIMENTAL SECTION

Progress of reaction was monitored by silica gel-G coated TLC plates in Ethyl acetate: Hexane system (5:5). The spot was visualized by exposing dry plate in iodine vapours. Melting points were determined by the melting point determination apparatus (TEMPO) in open capillary tubes and are uncorrected. Proton NMR spectra were recorded on Bruker Advance II 400 and 200 NMR Ultra Shield Spectrometer using CDCl3 as a solvent and tetramethyl silane as internal standard. Chemical shift value is expressed in delta parts per million (ppm).

General Procedure for Preparation 2-(4-Aryl-limino)-Thiazolidin-4-one (2)
A mixture of 2-chloro-N-(4-morpholinophenyl)acetamide (1 gm, 1eq) and ammonium thiocyanate (0.342 gm, 0.004 mol) in [bmIm]OH) (0.93 gm, 2eq) was stirred at 45°C for 2 hrs. The mixture was cooled; the solid obtained was separated by filtration and recrystallized from ethanol to give 0.96 gm (88%) of 2-(4-morpholinophenylimino) thiazolidin-4-one.

General Procedure for Preparation of 5-(benzylidene)-2-(4-Ary-limino) Thiazolidin-4-one (3)
A mixture of 2-(4-morpholinophenylimino)-thiazolidin-4-one (0.1 gm, 1eq) and aryl aldehyde (0.38 mmol) in [bmIm] OH (0.11 gm, 1.2eq) was stirred at room temperature for 1 hour. After completion of the reaction (TLC check), cold water (10 ml) was added to reaction mixture, solid separated was filtered and the crude product was recrystalized using absolute ethanol to get appropriate arylidine derivatives 3(a-o) of 2-(4-morpholinophenylimino)-thiazolidin-4-one.

Spectroscopic Data of Representative Compounds
2-(4-morpholinophenylimino)-thiazolidin-4-one:
White solid; M. P.: 137-139°C.
^{1}H NMR (DMSO-d6, 400 MHz): δ 3.03- 3.06 (t, J=4.8 Hz, 4H), 3.71- 3.73 (t, J=4.8 Hz, 4H), 4.07 (s, 2H), 6.90-6.92 (d, 2H), 7.41- 7.43 (d, 2H), 10.19 (s, 1H exchangeable with D2O). IR (KBr): 3053, 1705, 1627 cm^{-1}. MS (m/z): 278.9[M$^+$ +1].

5-(Benzilidene)-2-(4-morpholinophenylimino)-thiazolidin-4-one:
Pale Yellow solid; M. P.: 164-166°C.
1H NMR ($CDCl_3$, 400 MHz): δ 3.11 (t, J=4.7 Hz, 4H), 3.74 (t, J=4.7 Hz, 4H), 7.04- 7.08 (d, 2H), 7.36-7.48 (m, 5H), 7.74- 7.77 (d, 2H), 7.79 (s, 1H), 10.18 (bs, 1H, exchangeable with D2O). IR (KBr): 3158, 1730, 1564, 1100 cm^{-1}. MS (m/z): 366.5 [M$^+$+1].

5-(4-Hydroxybenzilidene)-2-(4-morpholinophenylimino)-thiazolidin-4-one:
Pale Yellow solid; M. P.: 187-189°C.
1H NMR (DMSO-d6, 200 MHz): δ 3.11 (bs, 4H), 3.74 (bs, 4H), 6.85- 6.99 (m, 5H), 7.45- 7.64 (m, 4H), 10.16 (bs, 1H, exchangeable with D2O). IR (KBr): 3156, 1732, 1658, 1567, 1109, 930 cm^{-1}.; MS (m/z): 382.5 [M$^+$ +1].

5-(4-Methoxoxybenzilidene)-2-(4-morpholinophenylimino)-thiazolidin-4-one:
Yellow solid; M.P.: 188-190°C.
1H NMR (DMSO-d6, 400 MHz): δ 3.16 (bs, 4H), 3.80 (bs, 4H), 3.86 (s, 3H), 6.81(d, 2H), 6.98 (d, 2H), 7.15 (d, 2H), 7.51(d, 2H), 7.71(s, 1H), 10.27 (bs, 1H, exchangeable with D2O). IR (KBr): 3105, 1708, 1645, 1516 and 1118 cm^{-1}. MS (m/z): 396.3 [M$^+$ +1].

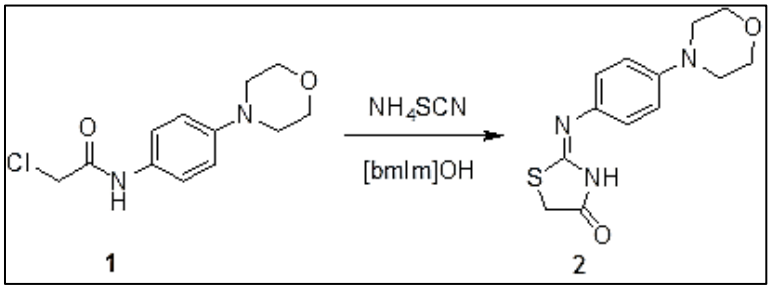
5-(4-Phenylbenzilidene)-2-(4-morpholinophenylimino)-thiazolidin-4-one:
Yellow solid; M.P: 217-219°C.
1H NMR ($CDCl_3$, 400 MHz): δ 3.09 (t, J=4.8 Hz, 4H), 3.72 (t, J=4.8 Hz, 4H), 7.05- 7.07 (d, 2H), 7.38- 7.39 (t, 1H), 7.42- 7.44 (t, 2H), 7.52- 7.54 (d, 2H), 7.57- 7.59 (d, 2H), 7.64- 7.66 (d, 2H), 7.74- 7.76 (d, 2H), 7.81(s, 1H), 10.17 (bs, 1H, exchangeable with D2O). IR (KBr): 3351, 3162, 1730, 1650, 1565, 1100 cm^{-1}.; MS (m/z): 442.1 [M$^+$+1].

5-(3-Indollidene)-2-(4-morpholinophenylimino)-thiazolidin-4-one:
Yellow solid; M.P: 179-181°C.
1H NMR ($CDCl_3$, 400MHz): δ 3.15 (t, J=4.6 Hz, 4H), 3.80 (t, J=4.6 Hz, 4H), 7.07- 7.09 (d, 2H), 7.25- 7.29 (m, 3H), 7.31- 7.33 (t, 2H), 7.43- 7.44 (d, 2H), 7.74- 7.76 (d, 2H), 7.64- 7.66 (d, 2H), 7.84- 7.86 (d, 1H), 8.14 (s, 1H), 8.88 (bs, 1H) 10.53 (bs, 1H, exchangeable with D2O). IR (KBr): 3303, 2958, 2872, 1684, 1634, 1598, 1417, 1130 cm^{-1}. MS (m/z): 405.3 [M$^+$+1].

5-(2-Furylidine)- 2-(4-morpholinophenylimino)-thiazolidin-4-one
Yellow solid; M.P: 117-119°C.
1H NMR ($CDCl_3$, 400 MHz): δ 3.08 (t, J=4.8 Hz, 4H), 3.74 (t, J=4.8 Hz, 4H), 6.51- 6.53 (q, 1H), 6.69- 6.70 (d, 1H), 7.04-7.08 (d, 2H), 7.54 (s, 1H), 7.58 (d, 1H), 7.73- 7.76 (d, 2H), 10.23 (bs, 1H, exchangeable with D2O). IR (KBr): 3169, 1740, 1656, 1570, 1115 cm^{-1}. MS (m/z): 356.2 [M$^+$+1].

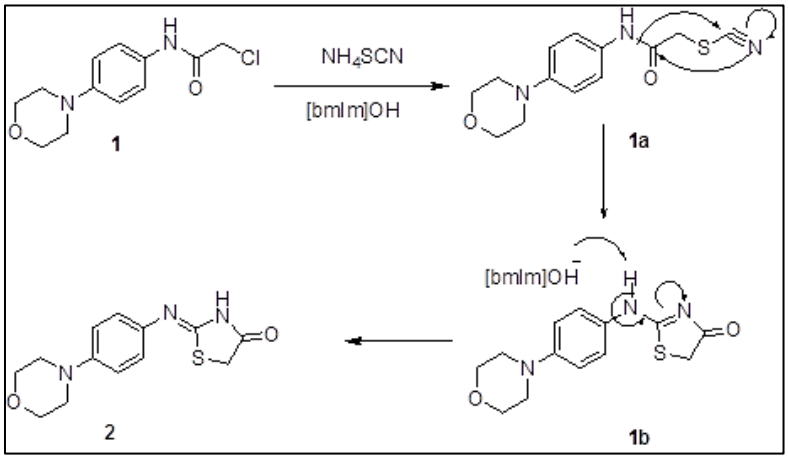
RESULTS AND DISCUSSION

In conventional method the synthesis of 2-(4-morpholinophenylimino)-thiazolidin-4-one was carried out using ammonium thiocynate in absolute ethanol at 80-90°C [6]. The yield of the required product was relatively low as compare to the other steps. The lower yield may be due to the formation of 2-amino-thiazolidin-4-one tautomer. It was reported in the literature that the formation of 2-imino-thiazolidin-4-one tautomer is more favour in the basic media [7]. Considering this observation it was thought that use of basic medium for the synthesis may improve the yield of 2-imino-thiazolidin-4-one. It leads us to conception that task specific basic ionic liquids can be used as basic and green reaction medium as well as solvent in the reaction.



Scheme 1: Formation of 2-imino-thiazolidin-4-one

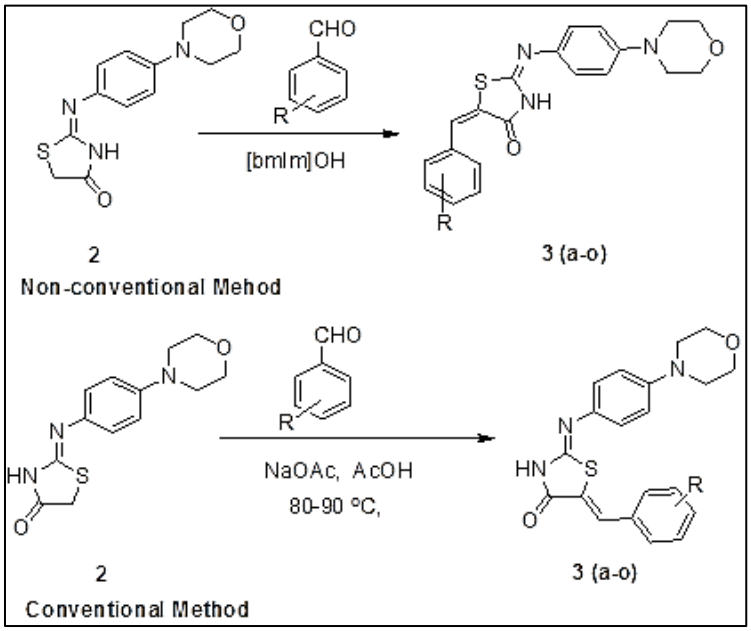
The reaction of 2-chloro-N-(4-morpholinophenyl)acetamide 1 was carried out with ammonium thiocynate in presence of one equivalent [bmIm]OH at room temperature. The formation of desired product was observed in the reaction mixture and after 30 min, 39% of desired 2-(4-morpholinophenylimino)-thiazolidin-4-one 2 was isolated. The yield was not improved significantly on continuing the reaction for longer time and by heating the reaction mixture at 50-60°C for several hours. In the reaction mixture some insoluble material was observed, this may be the reason for lower reaction yield. To overcome this problem, the reaction was carried out using two equivalent of [bmIm] OH at 45°C this resulted into the clear homogenous reaction mixture. The significant improvement in the yield of the reaction was observed and around 88% of 2-(4-morpholinophenylimino) thiazolidin-4-one 8 was isolated after 2 hours (Scheme 1). The IR, ^{1}H NMR and mass analysis data was found to matches well with the data of earlier synthesized compound. The ionic liquid used in the reaction was recovered from aqueous layer and washed with diethyl ether to remove any organic impurities and dried under vacuum to get the pure ionic liquid and is reuse for the above reactions. The plaussible mechanism of formation of 2-imino-thiazolidin-4-one was proposed in which basic ionic liquid favours the formation of 2 by converting amino tautomer 1b to imino tautomer 2 by providing the required basic medium (Scheme 2).



Scheme 2: The plausible reaction pathway for synthesis of 2

It was reported that [bmIm] OH catalyzes Knoevengel condensation reaction of rhodanine [8-12], but there were no reports in literature for Knoevengel condensation of 2-imino-thiazolidin-4-one using such ionic liquid. We thought that [bmIm] OH can be used as base in Knoevengel condensation of 2-(4-morpholinophenylimino) thiazolidin-4-one 2 (Scheme 3). The 2-(4-morpholino phenyl imino) - thiazolidin-4-one 2 was treated with 4-arylaldehyde in two

equivalent basic ionic liquid [bmIm] OH, 5-(4-arylidene)-2-(4-morpholinophenylimino)-thiazolidin-4-one 3(a-o) was obtained in excellent yields. In the IR spectrum of compound 3c a absorption band at 3105 cm^{-1} correspond to the presence of free NH group of amide. The carbonyl bond shows absorption band at 1645 cm^{-1}. The band at 1708 cm-1 was due to the absorption band of C=N bond of iminothiazodiline group. In 1H NMR spectrum of the compound 9c, the disappearance of singlet of methylene proton of 2-imino-thiazolidin-4-one ring at 4.08 ppm strongly indicates the formation of desired Knoevengel condensation product. Two broad singlets at 3.16 and 3.80 ppm each integrating for four protons were assigned to the protons of the methylene groups attached to the N- and O- atoms respectively. A singlet at 3.86 ppm was assigned to the protons of methyl group attached to O-atom. The four doubletes at 6.81, 6.98, 7.15 and 7.51 ppm integrating for two protons respectively was assigned to the four aromatic protons of methoxybenzene group and aromatic protons of benzene ring attached to the iminothiazolidin-4-one ring. Singlet at 7.71 ppm integrating for one proton was assigned to the olefinic proton. The amide proton resonated at 10.28 ppm as a broad singlet exchangeable with D2O. The mass spectrum showed a peak at m/z = 396.3 (M+ +1) was in tune with the molecular formula C21H21N3O3S. All the spectral values and analysis data confirmed that the structure of 5-(4-methoxybenzylidene)-2-(4-morpholinophenylimino)-thiazolidin-4-one 9c. The formation of condensation product 3 indicates that the basic ionic liquid [bmIm] OH acts as a catalyst as well as solvent for the Knoevengel condensation of 2-imino-thiazolidin-4-one 8 with aryl aldehydes.



Scheme 3: Knoevengel condensation of 2-(4-morpholinophenylimino) thiazolidin-4-one (3)

The yield of the formation of 2-(4-morpholinophenylimino)-thiazolidin-4-one 3 by non-conventional method (88%) using ionic liquid [bmIm]OH is better than the conventional method (65%) using ethanol and Sodium acetate. The reaction conditions used for non-conventional method are relatively mild and work up is also easy. Comparative study for the formation of iminothiazolidinone from 2-chloro-N-(4-morpholinophenyl) acetamide and ammonium thiocynate by conventional method and non-conventional method concludes that the non-conventional method is superior over the conventional method. The Knoevengel condensation of 2-(4-morpholinophenylimino) thiazolidin-4-one with different aromatic aldehydes by conventional method requires high temperature (100-110°C) and hazardous solvent such as acetic acid. Whereas, the Knovengel condensation reaction using [bmIm]OH gave comparatively higher yields of condensation products under mild and green reaction conditions (Table 1).

Table 1: Comparative study of conventional and non-conventional method (Knovengel product)

Sr. No.	Aldehyde	Conventional method		Non- conventional method	
		% yield	Reaction time (hr)	% yield	Reaction time (hr)
3a	Benzaldehyde	75	2	81	1
3b	4-Hydroxy benzaldehyde	86	4	91	1
3c	4- Methoxy benzaldehyde	90	2	93	2
3d	Biphenylcarboxaldehyde	85	2	93	2
3e	Indol-3-carboxaldehyde	68	3	87	2
3f	Furfuraldehyde	70	3	93	1
3g	2,4-Dimethoxybenzaldehyde	88	2	89	3
3h	3-Bromo-4-flouro benzaldehyde	67	2	75	3
3i	p-Toulaldehyde	76	5	76	3
3j	3-Flouro-4-methoxy benzaldehyde	79	3	86	3
3k	4- Bromo benzaldehyde	82	2	91	1
3l	4-Nitro benzaldehyde	92	1	95	0.5
3m	4-Cyano benzaldehyde	94	1	83	1
3n	2,4,6-Trimethoxybenzaldehyde	88	2	94	2
3o	4-Hydroxy,3-methoxybenzaldehyde	67	5	77	3

CONCLUSION

Conclusively, we have reported the task-specific and stable ionic liquid [bmIm] OH for the synthesis of iminothiazolidinones and its Knoevengel reaction with aryl aldehydes gives better yields than the conventional synthetic method using base and solvent.

ACKNOWLEDGMENT

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