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A CONVENIENT SYNTHESIS OF 5-ARYLIDENETHIAZOLIDINE-2,4-DIONES CATALYZED BY ALKALINE IONIC LIQUID

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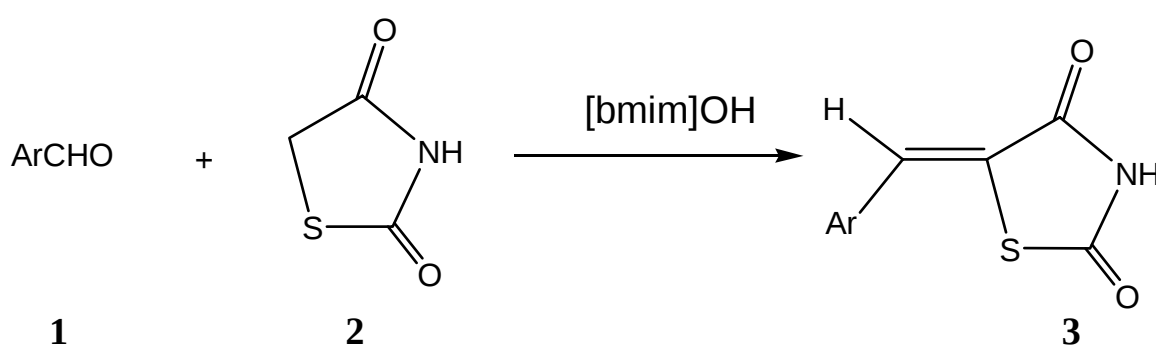
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Abstract – A series of 5-arylidene-thiazolidine-2,4-diones was synthesized by the Knoevenagel condensation of thiazolidine-2,4-dione with aromatic aldehydes with alkaline ionic liquid 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) as dual solvent and catalyst. This method provides many advantages such as being environmentally benign, simple work-up, short reaction times, obtaining in good to excellent yields, and the reusability of ionic liquid.

5-Arylidene-thiazolidine-2,4-diones constitute an important class of chemically, biologically and pharmaceutically significant compounds.^{1,2} For example, they are key intermediates for the synthesis of anti-diabetic drugs such as troglitazone, pioglitazone, rosiglitazone, englitazone.³ The conventional synthesis of 5-arylidene-thiazolidine-2,4-diones involves the Knoevenagel condensation of aromatic aldehydes with thiazolidine-2,4-dione catalyzed by organic base or salt in refluxing volatile organic solvent such as benzene,¹ toluene,⁴ acetic acid,^{4,5} ethanol,^{2,6,7} etc. However, these reactions require long reaction times (16-24 h), tedious work-up procedures, and sometimes only moderate yields obtained. Recently, some methods have been developed such as facilitated by solid base,⁸ ionic liquids,⁹ solid condensation,¹⁰ or MW irradiation.^{11,12} Although the condensation reactions could be completed in short times, these methods have their own disadvantages yet, such as using unamiable organic solvent, added catalyst required, difficult to prepare in large scale, etc. Considering the importance of 5-arylidene-thiazolidine-2,4-diones, we think it is still significant to develop more facile and practical

Recently, the interest in room temperature ionic liquids is increasing as green reaction media for synthetic organic chemistry,^{13,14} and some reports have shown the Knoevenagel condensation could be performed efficiently in task specific ionic liquids.¹⁵⁻¹⁷ In continuation of our interest in using ionic liquids as eco-friendly medium and catalyst for the condensation reactions,^{18,19} we report herein 5-arylidene-thiazolidine-2,4-diones could be synthesized conveniently by the condensation of thiazolidine-2,4-dione with aromatic aldehydes catalyzed by alkaline ionic liquid 1-butyl-3-methylimidazolium hydroxide ([bmim]OH). (**Scheme 1**).



Scheme 1

For this study, the functional ionic liquid [bmim]OH was synthesized as lit.²⁰ The results were summarized in Table 1, all the products were characterized by NMR, IR spectrum and melting points that were consistent with the literature data. As can be seen from the Table 1 that this procedure was found to be general and applicable to the aromatic aldehydes bearing various substituents such as methoxyl, *N,N'*-dimethylamino, hydroxyl, chloro, bromo, nitro, etc. It is noteworthy that aromatic aldehydes bearing electron-withdrawing groups reacted more easily compared with those containing electron-donating groups the same as described in the literature,⁸ and only *Z*-isomers were obtained as literatures described.^{4,9,11} Besides, the reaction of the hindered aldehyde 2,6-dichlorobenzaldehyde (Entry 8), the heteroaromatic aldehyde 2-furancarboxaldehyde (Entry 13) and α,β -unsaturated Cinnamic aldehyde (Entry 14) with thiazolidine-2,4-dione also could be completed efficiently with high yields obtained. Moreover, the functional alkaline ionic liquid [bmim]OH could be typically recovered and reused with no appreciable decrease in yields and reaction rates (Entries 15-16).

In conclusion, we have demonstrated that 5-arylidene-thiazolidine-2,4-diones could be conveniently synthesized by the condensation of thiazolidine-2,4-dione with aromatic aldehydes in task specific ionic liquid [bmim]OH for the first time, which play a dual role as solvent and base catalyst in this reaction. The present method has many obvious advantages compared to the previous methods, including no need for the use of any added catalyst, being environmentally more benign, simple work-up, high yield, potential for recycling of ionic liquid, and the generality.

Table 1. Synthesis of 5-arylidene-thiazolidine-2,4-diones catalyzed by [bmim]OH

Entry	Product	Ar	Time (h)	Yield ^a (%)	Mp ^b ()	Lit.mp()
1	3a	<i>p</i> -MeOC ₆ H ₄	6	91	218-219	218 ¹²
2	3b	<i>p</i> -Me ₂ NC ₆ H ₄	6	85	296-297	296 ²¹
3	3c	<i>p</i> -HOC ₆ H ₄	6	81	>300	>300 ^{4,11}
4	3d	<i>o</i> -HOC ₆ H ₄	6	71	226-227	225-226 ¹²
5	3e	C ₆ H ₅	2	74	247-248	247-249 ⁴
6	3f	<i>p</i> -ClC ₆ H ₄	3	82	230-231	231-232 ²²
7	3g	<i>o</i> - ClC ₆ H ₄	4	86	183-184	172 ²³
8	3h	2,6- Cl ₂ C ₆ H ₃	4	87	153-154	152-154 ²⁴
9	3i	3,4-Cl ₂ C ₆ H ₃	4	90	212-213	-----
10	3j	<i>p</i> -Br C ₆ H ₄	4	91	241-242	242-244 ⁴
11	3k	<i>m</i> -NO ₂ C ₆ H ₄	2	89	208-209	245 ⁶ 185-190 ¹²
12	3l	<i>p</i> -NO ₂ C ₆ H ₄	2	87	265-267	267-270 ¹²
13	3m	2-furyl	2	81	228-230	230-233 ¹²
14	3n	C ₆ H ₅ CH=CH	3	92	219-221	218-220 ¹²
15	3a	<i>p</i> -MeOC ₆ H ₄	6	88 ^c	218-219	218 ¹²
16	3a	<i>p</i> -MeOC ₆ H ₄	6	89 ^d	218-219	218 ¹²

a Isolated yield. b Melting points were uncorrected. c-d Second and third recycling of [bmim]OH.

EXPERIMENTAL

Melting points were determined on a digital melting point apparatus and were not corrected. Infrared spectra were recorded on an AVATAR-360 Infrared Spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a BRUKER-300 MHz spectrometer using DMSO-*d*₆ as the solvent with tetramethylsilane (TMS) as an internal standard. Elemental analysis was performed on an Elementar Vario MICRO analyzer. TLC was accomplished on Merck silica gel 60 F₂₅₄ on aluminium sheets.

General Procedure for the Preparation of 3a~3n

Aromatic aldehyde **1** (2 mmol), thiazolidine-2,4-dione **2** (2 mmol), were added in ionic liquid [bmim]OH (1 mL). The reaction mixture was stirred at 80 °C for an appropriate time, reaction was monitored by thin layer chromatography (TLC). Upon completion of the reaction, after adding 1 mL water and filtering the solid directly from the reaction mixture, gave the desired product **3** in high yield, which was purified by recrystallization from EtOH. After isolation of the product, the remainder of the ionic liquid was dried for 4 h under vacuum at 70 °C. The next run was performed under identical reaction conditions.

Spectroscopic data for **3g**, **3i** and **3k**:

3g: IR (KBr): 3421, 3145, 3052, 1743, 1735, 1604, 1462, 1431, 1318, 1162 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 7.50-7.54 (m, 2H), 7.55-7.60 (m, 1H), 7.64-7.67 (m, 1H), 7.93(s, 1H), 12.76(brs, 1H). ¹³C NMR (DMSO-*d*₆): δ = 168.08, 167.43, 134.95, 132.28, 131.47, 130.80, 129.33, 128.54, 127.69, 127.17. Anal. Calcd for C₁₀H₆ClNO₂S: C, 50.11; H, 2.52; N, 5.84. Found: C, 50.01; H, 2.43; N, 5.61.

3i: IR (KBr): 3417, 3172, 1754, 1705, 1578, 1466, 1321, 1108cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 7.59(s, 1H), 7.61(d, 1H, *J* = 2.1 Hz), 7.85-7.86(m, 2H), 12.81(brs, 1H). ¹³C NMR (DMSO-*d*₆): 167.88, 167.69, 137.02, 134.32, 133.15, 132.52, 132.49, 129.43, 129.38, 126.77.

Anal. Calcd for C₁₀H₅Cl₂NO₂S: C, 43.81; H, 1.84; N, 5.11. Found: C, 43.64; H, 1.95; N, 4.98.

3k: IR (KBr): 3420, 3163, 1745, 1690, 1605, 1532, 1352, 1326, 1152 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 7.83(t, 1H, *J* = 8.1 Hz), 7.96(s, 1H), 8.03(d, 1H, *J* = 7.8 Hz), 8.28-8.32(m, 1H), 8.46(t, 1H, *J* = 1.8 Hz), 12.80(brs, 1H). ¹³C NMR (DMSO-*d*₆): 167.79, 167.49, 148.74, 135.88, 135.26, 131.37, 129.87, 127.14, 124.94, 124.84. Anal. Calcd for C₁₀H₆N₂O₄S: C, 48.00; H, 2.42; N, 11.20. Found: C, 47.97; H, 2.61; N, 10.89.

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