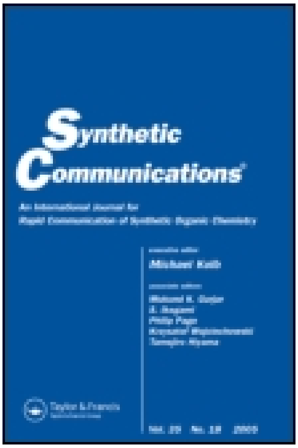

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Organic Reactions in Ionic Liquids: Ionic Liquid Promoted Knoevenagel Condensation of Aromatic Aldehydes with (2-Thio)Barbituric Acid

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ABSTRACT

The Knoevenagel condensation of aromatic aldehydes with (2-thio)barbituric acid proceeded efficiently in reusable ionic liquids, EAN, $BmimBF_4$,

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and $BmimPF_6$ at room temperature in the absence of any catalyst with high yields.

Key Words: Aromatic aldehyde; Ionic liquids; Knoevenagel condensation; (2-thio)barbituric acid.

The derivatives of the barbituric acid have been widely used as a sedative, hypnotic, anesthetic, anticonvulsant, antiosteoporosis, as well as an antitumor agent.[1] Arylidene (2-thio)barbituric acids are useful intermediates in synthesis of benzylbarbituric derivatives,[2] heterocyclic compounds,[1a] oxadeazaflavines,[3] and unsymmetrical disulfides.[4] Additionally, some of them have been recently studied as nonlinear optical materials[5] and dyes.[6]

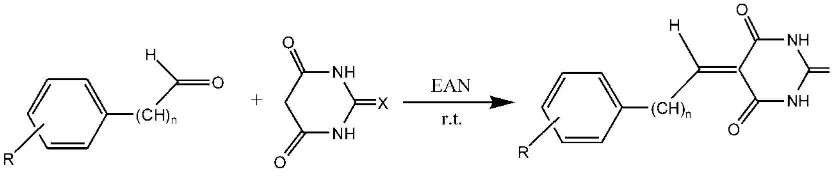
Generally, arylidene (2-thio)barbituric acids were synthesized by the Knoevenagel condensation of (2-thio)barbituric acids with aromatic aldehydes using various acid or base as catalyst in organic solvents.[1,7] Usually, the yields obtained are not satisfactory due to the formation of disubstituted condensation products accompanying the desired monosubstituted condensation products.[1,8] To achieve formation of only one (mono) condensation product, various efficient methods have been developed, such as adsorption on Al_2O_3-KF,[9] microwave irradiation,[10] infrared irradiation,[11] phase transfer catalysis.[12] However, these methods usually need to use catalysts, volatile organic solvents for product extraction from the solid reaction mixture, and sometimes long reaction times are needed and only modest yields obtained. Additionally, Jursic reported this condensation reaction could be performed in the absence of catalyst in methanol, but a large volume of environmentally unfriendly methanol was used and long reaction times were required when applied to the less reactive aromatic aldehydes.[1b] Therefore, preparation of arylidene (2-thio)barbituric acids using a facile and efficient method with environmentally benign technologies is still very interesting in organic synthesis.

In recent years, ionic liquids (ILs) have emerged as potential "greener" alternatives to volatile organic solvents[13] and they have been used as environmentally benign media for many important organic reactions.[14] Recently, we have reported an effective Knoevenagel condensation catalyzed by ethylenediammonium diacetate in ionic liquids $[Bmim]BF_4$ and $[Bmim]PF_6$ ([Bmim] = 1-butyl-3-methyl imidazolium).[15] In continuation of our interest in using ionic liquids as a recyclable, eco-friendly reaction medium in the Knoevenagel condensation, we found that the Knoevenagel reaction of aromatic aldehydes with (2-thio)barbituric acid could occur in ionic liquid [Bmim]BF_4, [Bmim]PF_6, and ethylammonium nitrate (EAN) in the absence of catalyst.[16] In fact, simple stirring of a mixture of aromatic aldehyde **1** and (2-thio)barbituric acid **2** in ionic liquid for an appropriate time at room temperature gave, after directly filtering, the desired arylidene (2-thio)barbituric acid **3** in high yield with practical purity (Sch. 1). The results are summarized in Table 1. The products were characterized by ^1H NMR and IR, consistent with the literature data. It should be noted that none of the products could be melted without decomposition.

As can be seen from the Table 1, the tested ionic liquids, [Bmim]BF_4, [Bmim]PF_6, and EAN, were all efficient for this reaction, which proceeded relatively slowly when performed in [Bmim]PF_6. The reaction was found to be general and applicable to the aromatic aldehydes bearing various substituents such as nitro, chloro, methyl, methoxyl, hydroxyl, N,N′-dimethylamino. Aromatic aldehydes bearing electron-donating groups reacted much more easily compared with those containing electron-withdrawing groups, the same as described in the literature.[1b] The reaction of 2-furancarboxaldehyde (Entry 13,14) and the aromatic α,β-unsaturated aldehyde, cinnamic aldehyde (Entry 16,29) with (2-thio)barbituric acid also could be completed in short times. Disappointedly, as simple as this reaction is, we can't obtain satisfactory results when applied to aliphatic aldehydes and ketones under the same reaction conditions. In addition, the ionic liquid could be typically recovered and reused with no appreciable decrease in yields and reaction rates (Entry 4-5, 25–26).

In order to compare with previous reported procedures, some literature data[1b,10–12] are summarized in Table 2.

In conclusion, we have demonstrated that the Knoevenagel condensation between aromatic aldehydes with (2-thio)barbituric acid could be effectively performed at room temperature in the ionic liquids [Bmim]BF_4, [Bmim]PF_6, and EAN. The present method has many obvious advantages compared to previous methods, including no need for the use of any catalyst, being



1 2 (X=O,S) 3

Scheme 1.

Table 1. Knoevenagel condensation of aromatic aldehydes with (2-thio)barbituric acids.

Entry[a]	Product	R	n	X	Ionic liquids	Time (min)	Yield (%)[b]	Mp/(lit.) (°C)
1	**3a**	H	0	O	[Bmim]BF_4	30	96	272–273 (271–272)[11]
2	**3a**	H	0	O	[Bmim]PF_6	60	95	272–273
3	**3a**	H	0	O	EAN	30	96	272–273
4	**3a**	H	0	O	EAN	30	94[c]	
5	**3a**	H	0	O	EAN	30	95[d]	
6	**3b**	*p*-CH_3	0	O	EAN	10	97	298–299 (297–298)[11]
7	**3c**	*p*-OCH_3	0	O	EAN	10	96	276–277 (276–277)[11]
8	**3d**	*p*-$(CH_3)_2N$	0	O	[Bmim]BF_4	10	98	275–276 (277)[1b]
9	**3d**	*p*-$(CH_3)_2N$	0	O	[Bmim]PF_6	20	96	275–276
11	**3d**	*p*-$(CH_3)_2N$	0	O	EAN	10	98	275–276
12	**3e**	3,4-OCH_2O	0	O	EAN	10	94	>300 (320)[11]
13	**3f**	2-furfuraly	0	O	[Bmim]BF_4	20	95	261–262 (264)[1b]
14	**3f**	2-furfuraly	0	O	EAN	20	96	261–262
15	**3g**	*p*-OH	0	O	EAN	10	95	>300 (275)[10b]

16	**3h**	H	2	O	EAN	20	94	265–266 (270)[10b]
17	**3i**	*o*-NO_2	0	O	EAN	240	85	258–259 (260)[10b]
18	**3j**	*p*-Cl	0	O	EAN	180	83	278–280 (280–281)[11]
19	**3k**	H	0	S	EAN	30	94	271–272 (274.7)[18]
20	**3l**	*p*-OCH_3	0	S	EAN	10	98	>300 (>300)[12b]
21	**3m**	*p*-CH_3	0	S	EAN	10	97	>300 (>300)[12b]
22	**3n**	3,4-OCH_2O	0	S	EAN	10	98	>300 (>300)[12b]
23	**3o**	*p*-$(CH_3)_2N$	0	S	EAN	10	98	>300 (254.4)[18]
24	**3p**	*p*-Cl	0	S	[Bmim]BF_4	180	87	290–291 (291–292)[11]
25	**3p**	*p*-Cl	0	S	[Bmim]BF_4	180	85[c]	
26	**3p**	*p*-Cl	0	S	[Bmim]BF_4	180	86[d]	
27	**3p**	*p*-Cl	0	S	[Bmim]PF_6	300	85	290–291
28	**3p**	*p*-Cl	0	S	EAN	180	86	290–291
29	**3q**	H	2	S	EAN	20	98	>300 (220–300)[7a]

[a] All reactions were run with aromatic aldehyde (1 mmol) and (2-thio)barbituric acid (1 mmol) in 2 mL ionic liquid.

[b] Isolated yields.

[c-d] Second and third recycling of EAN or [Bmim]BF_4.

Table 2. Knoevenagel condensation of aromatic aldehydes with (2-thio)barbituric acids under different reaction conditions.

	Yields (%)			Yields (%)	
Product	This work	Literature	Product	This work	Literature
3d	98	73,[10a] 81,[11] 79[12a]	**3f**	96	86,[10a] 81[1b]
3j	83	68,[10a] 62,[11] 84,[12b] 75[10b]	**3l**	98	98[12b]

[1b] Yield for reaction in methanol at r.t. for 5 days.

[10a] Yield for reaction under microwave irradiation catalyzed by Montmorillonite KSF.

[10b] Yield for reaction under microwave irradiation catalyzed by Montmorillonite KSF and NaCl.

[11] Yield for reaction under infrared irradiation for 45 min.

[12a] Yield for reaction catalyzed by CTMAB at r.t. for 0.5 h in water.

[12b] Yield for reaction catalyzed by TEBA at 70°C for 2 h in water.

environmentally more benign, ease of product isolation, simplicity of methodology, high yield, and generality. We have shown that ionic liquids play a dual role as solvent and promoter in this reaction, resulting in a simpler system—a good example of green chemistry.

EXPERIMENTAL

Melting points were determined on digital melting point apparatus and were not corrected. Infrared spectra were recorded on a VECTOR-22 Infrared Spectrophotometer. ^{1}H NMR spectra were recorded on a BRUKER-400 MHz spectrometer using DMSO-d_6 as the solvent with TMS as an internal standard. The ionic liquid [Bmim]PF_6 and [Bmim]BF_4 was synthesized as lit;[18] ethylammonium nitrate (EAN) was synthesized according to the literature.[19] All other materials are commercially available and were used without further purification.

General Procedure for the Preparation of 3a–3q

Aromatic aldehyde **1** (1 mmol), (2-thio)barbituric acid **2** (1 mmol) were added in ionic liquid [Bmim]BF_4, [Bmim]PF_6, or EAN (2 mL). The reaction mixture was stirred at room temperature for an appropriate time; reaction was monitored by TLC. Upon completion of the reaction, after filtering the solid directly from the reaction mixture and washing with water, gave the desired product **3** in high yields with essential purity. After isolation of the product, the remainder of the ionic liquids ENA was dried for 4 h under vacuum at 50°C. The next run was performed under identical reaction conditions.

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