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Ionic liquid catalyzed one-pot synthesis of novel spiro-2-amino-3-phenylsulfonyl-4*H*-pyran derivatives

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ABSTRACT

A series of novel spiro-2-amino-3-phenylsulfonyl-4*H*-pyran derivatives were synthesized via the three component, one pot reaction of phenylsulfonylacetonitrile and 1,3-dicarbonyl compounds with isatins or acenaphthenequinone in ethanol with a novel basic ionic liquid 2-hydroxyethyl ammonium acetate [$H_3N^+CH_2CH_2OH$][CH_3COO^-] (HEAA) as catalyst. HEAA was found to be a suitable and efficient catalyst for this condensation. This method has some distinct advantages such as mild reaction conditions, short reaction time, and environmental friendliness.

Introduction

Sulfones and sulfoxides are important intermediates in organic synthesis[1] and additionally have a wide applicability in diverse fields including agrochemicals,[2] pharmaceuticals,[3] and polymers.[4] Especially, sulfones and sulfoxides are important intermediates in the synthesis of many interesting biologically active compounds.[5,1,6–8] Omeprazole and Fipronil pesticide are two typical examples of extensive application of these intermediates in pharmaceutical and fine chemical industries.[9] Sulfones are notable as 'chemical chameleons'[10] due to the ability of the sulfonyl group to serve as a temporary transformer of chemical reactivity. The group RSO_2 can function as a nucleofuge producing a sulfinate anion[11] and powerfully stabilize adjacent carbanions.[12,13] Although lacking inherent asymmetry, the sulfonyl group can also function as a potential stereoinducer.[14]

Poly-functionalized oxindole derivatives are also a very important class of heterocyclic compounds and are the core structure of many pharmacological agents and natural alkaloids.[15–17] Several spiroheterocycles, containing both indole and pyran heterocycles, possess anticonvulsant and analgesic,[18] herbicidal,[19] and antibacterial activities.[20] Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives, highly enhances biological activity.[21,22] The derivatives of spirooxindole ring systems are useful as antimicrobial and antitumor agents, and as inhibitors of the human NKI receptor, besides being found in a number of alkaloids like horsifiline, spirotryprostatin, and (+)-elacomine.[23]

Recently, ionic liquids (ILs) are receiving considerable attention because they offer a unique medium for chemistry, biocatalysis, separation science, material synthesis, and electrochemistry.[24] The implementation of task specific ionic liquids (TSILs) further enhances the versatility of classical ionic liquids where both reagent and medium are coupled.[25] Their dual organic and ionic nature allows them to establish nearly all kinds of interactions with the reacting species including transition states, and hence sometimes give rise to improved yields and rate increase.[26] Structural variation of ionic liquids gives more flexibility to their applications due to the possibility of fine tuning their miscibility to merit phase-separation from products.[27] Moreover, functionalized ionic liquids offer specific types for catalysis applications and served as solution phase supports in combinatorial syntheses.[28]

Due to the potential biological and pharmacological activities of fused spiro-2-amino-3-phenylsulfonyl-4*H*-pyran derivatives, and our interest in the synthesis of heterocyclic compounds,[29] we report a simple and efficient method for the preparation of pyrimidine-fused heterocycles in ethanol using HEAA as the catalyst in the multi-component reaction of phenylsulfonylacetonitrile and 1,3-dicarbonyl compounds with acenaphthenequinone or isatins.

Results and discussion

First, phenylsulfonylacetonitrile **2** was synthesized according to previous work[30] by means of reaction between sodium benzenesulfinate and 2-chloroacetonitrile (Scheme 1).

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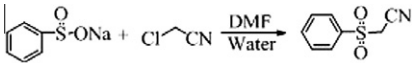


Scheme 1. Preparation of phenylsulfonylacetonitrile **2**.

Then, the three-component reaction of isatins **1** (1 mmol), phenylsulfonylacetonitrile **2** (1 mmol), and 5,5-dimethyl-cyclohexane-1,3-dione **3b** (1 mmol) was carried out as the model reaction to optimize the reaction condition. Different catalysts such as [Bmim]PTSA, [Bmim]Cl, Et_3N, HEAA and the loading of the HEAA were investigated. The results were summarized in Table 1. We found that without catalyst or acidic ionic liquid this reaction cannot be catalyzed, and the neutral ionic liquids can promote the reaction but the yield is lower than 50% (Table 1, entries 1–4). In contrast, we found that basic catalyst can catalyze this reaction, and the basic ionic liquid (HEAA) gave the highest yield (90%) with 10% loading (Table 1, entries 6–10). And the outcomes displayed that 10% mmol catalyst was sufficient to complete this reaction. Larger amounts of the catalyst did not improve the yields. And we also found that this reaction was completed in 2 h, and reflux temperature is the most suitable temperature for this reaction.

The reaction medium has been recognized to be one of the most important factors influencing the reaction. Several solvents were tested for the reaction, the results are shown in Table 2. It can be observed ethanol was the most efficient medium to promote this reaction. (Table 2, entry 1) Other solvents, such as THF, MeCN, DMSO, DMF, CH_3COCH_3, and $CHCl_3$ led to lower yields (Table 2, entry 2–8). The reaction hardly proceeded in THF. Therefore, ethanol was selected as the reaction solvent in the following investigation.

With the optimal conditions in hand, the multicomponent reaction was carried out by stirring a mixture of isatins **1**, phenylsulfonylacetonitrile **2**, and 1,3-dicarbonyl compounds **3** in the presence of HEAA in refluxing ethanol for 2 h, afforded spiro-2-amino-3-phenylsulfonyl-4*H*-pyrans derivatives **4** in good yields (Scheme 2). The results were good in terms of yields and product purity in the presence of HEAA, while without HEAA the reaction cannot proceed. Using this method, twelve new compounds **4** were selectively synthesized by the three-component condensation of two different isatins **1** (isatin and 5-chloroisatin), phenylsulfonylacetonitrile **2**, and 1,3-dicarbonyl compounds **3** (**3a**–**3h**) in good yields. However, we found that the three-component reaction of phenylsulfonylacetonitrile **2** and ethyl 3-oxobutanoate **3h** with isatins **1** cannot proceed, which is probably due to the lower reactivity of ethyl 3-oxobutanoate (Table 3, entry 8). The results are summarized in Table 3.

To the best of our knowledge, this new procedure provides the first example of a three-component reaction for the synthesis of spiro-2-amino-3-phenylsulfonyl-4*H*-pyran derivatives. This method, based on a three-component HEAA-catalyzed reaction in EtOH, is simple and convenient and would be applicable for the synthesis of different types of spiro-2-amino-3-phenylsulfonyl-4*H*-pyrans. In addition, we have proposed the mechanism which is shown in Scheme 3.

To further explore the potential of this protocol for spiro-heterocycle synthesis, we investigated the reaction of acenaphthylene-1,2-dione **5** instead of isatin **2** and obtained spiroacenaphthylene derivatives. Using this protocol, another five new compounds **4** were synthesized by the one-pot, three-component condensation of acenaphthylene-1,2-dione **5**, phenylsulfonylacetonitrile **2**, and 1,3-dicarbonyl compound **3**, in good yields (Scheme 4). The results are summarized in Table 4.

In the next phase of study the viability of catalysis by the recycled ionic liquid was evaluated. In this regard preparation of **4b** was chosen as the model. After completion of the reaction the filtrate was extracted with diethyl ether several times to remove

Table 1
Optimization of the reaction conditions[a]

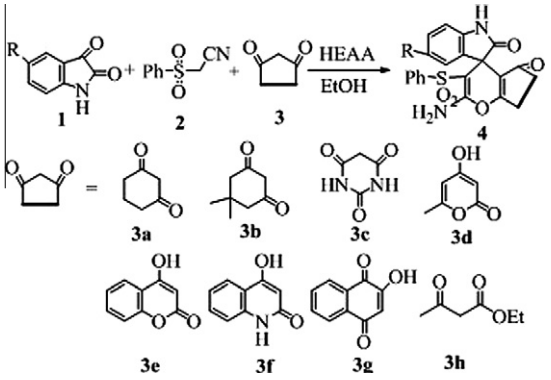
Entry	Catalyst	Catalyst (%)	Time (h)	Yield[b] (%)
1	—	—	5	Trace
2	[Bmim]PTSA	10	5	Trace
3	[Bmim]Cl	10	5	49
4	[Bmim]Br	10	5	46
5	Et_3N	10	2	72
6	$C_5H_{10}N$	10	2	67
7	HEAA	10	2	89
8	HEAA	5	2	81
9	HEAA	10	2	90
10	HEAA	15	2	88
11	HEAA	20	2	89

[a] Reaction conditions: isatins (1 mmol), phenylsulfonylacetonitrile (1 mmol), 5,5-dimethyl-cyclohexane-1,3-dione (1 mmol), EtOH (5 ml), HEAA (0.1 mmol), 80 °C.
[b] Yields refer to isolated products.

Table 2
HEAA-catalyzed reaction of isatins, phenylsul-fonylacetonitrile, and 5,5-dimethyl-cyclohexane-1,3-dione in different solvents

Entry	Solvent	Time (h)	Yield[a] (%)
1	EtOH	2	90
2	H_2O	2	30
3	CH_3CN	2	55
4	$CHCl_3$	2	34
5	DMF	2	35
6	THF	2	14
7	DMSO	2	21
8	CH_3COCH_3	2	38

[a] Yields refer to isolated products.

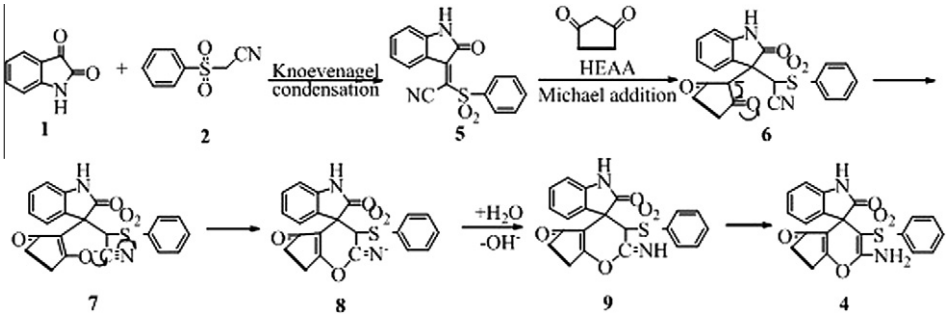


Scheme 2. Three-component synthesis of spiro-2-amino-3-phenylsulfonyl-4*H*-pyran derivatives **4**.

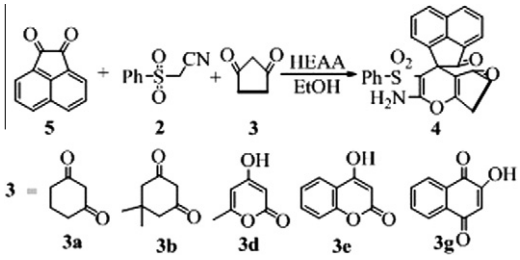
Table 3
Three-component synthesis of spiro-2-amino-3-phenylsulfonyl-4*H*-pyran derivatives **4**

Entry	R	Compound **3**	Products	Time (h)	Yield[a] (%)
1	H	**3a**	**4a**	2	93
2	H	**3b**	**4b**	2	92
3	H	**3c**	**4c**	3	86
4	H	**3d**	**4d**	2.5	91
5	H	**3e**	**4e**	2.5	90
6	H	**3f**	**4f**	3	87
7	H	**3g**	**4g**	3	83
8	H	**3h**	**4h**	5	Trace
9	Cl	**3a**	**4i**	2	91
10	Cl	**3b**	**4j**	2	90
11	Cl	**3d**	**4k**	3	89
12	Cl	**3e**	**4l**	3	85
13	Cl	**3g**	**4m**	3	89

[a] Yields refer to isolated products



Scheme 3. Possible mechanism for the formation of products **4**.



Scheme 4. Three-component synthesis of spiroacenaphthylene derivatives **4**.

Table 4
Three-component synthesis of spiroacenaphthylene derivatives **4**

Entry	Compound 3	Products	Time (h)	Yield[a] (%)
1	**3a**	**4n**	2	94
2	**3b**	**4o**	2	92
3	**3d**	**4p**	3	91
4	**3e**	**4q**	3	90
5	**3g**	**4r**	3	88

[a] Yields refer to isolated products.

Table 5
Recyclability of the HEAA[a]

Entry	Cycle	Yield (%)
1	Fresh	93
2	First recycle	92
3	Second recycle	90
4	Third recycle	89
5	Fourth recycle	89

[a] Yields refer to isolated products.

unreacted starting materials and other organic contaminations. Then the water was evaporated under reduced pressure and dried to recover the ionic liquid for subsequent use. Table 4 displays similar high conversions obtained after consecutive recycling of the ionic liquid (Table 5).

Conclusion

In conclusion, we herein report the HEAA-catalyzed one-pot reaction for the synthesis of novel spiro-2-amino-3-phenylsulfonyl-4*H*-pyran derivatives, which are compounds of major synthetic, biological, and medicinal importance. This reaction can be carried out under mild conditions and covers a great range of substrates with excellent yields of spirooxindole products. This novel protocol provides an efficient, easy to separate, environmental friendly synthetic route for synthesis of novel spiro-2-amino-3-phenylsulfonyl-4*H*-pyran derivatives.

Experimental

Melting points were determined with an X-4 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a NEXUS 670 spectrometer in KBr. ^{1}H NMR and ^{13}C NMR spectra were measured on a BRUKER AVANCE-II 500 and 125 MHz, respectively, spectrometer using TMS as internal standard and DMSO-d_6 as solvent. Mass spectra were documented on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV.

The synthesis of this task-specific ionic liquid has been carried out from a similar method in the literature.[31] The ionic liquid was formed quantitatively and in high purity as assessed by ^{1}H NMR. All other chemicals (AR grade) were commercially available and used without further purification.

General procedure for the synthesis of compounds 4

The mixture of aromatic isatins **1** (1 mmol), phenylsulfonylacetonitrile **2** (1 mmol), 1,3-dicarbonyl compounds **3** (1 mmol), and HEAA (0.1 mmol) in EtOH (5 ml) was stirred at 80 °C for about 2 h (monitored by thin-layer chromatography [TLC]). After completion of the reaction, the resulting mixture was cooled to room temperature and poured into water (10 ml). The solid product was collected by filtration and recrystallized from ethanol to give the pure compound **4**. The same reaction procedure was carried out by using other materials.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.073.

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