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Ionic liquid catalyzed one-pot synthesis of spiropyran derivatives via three-component reaction in water

Abstract: The ionic liquid $[H_3N^+CH_2CH_2OH][CH_3COO^-]$ (HEAA) catalyzes a three-component, one-pot condensation of malononitrile/ethyl cyanoacetate, 1,3-dicarbonyl compound/enol, and quinone or ninhydrin in water to afford a spiropyran derivative. This method has advantages of mild reaction conditions, short reaction time, and environmental friendliness.

Keywords: basic ionic liquid; environmental friendliness; $[H_3N^+CH_2CH_2OH][CH_3COO^-]$; one-pot.

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Introduction

Development of environmentally benign and clean synthetic procedures has become the goal of present day organic synthesis. Water plays an essential role in life processes and is also an environmentally friendly medium for organic reactions [1]. As multicomponent reactions (MCRs) are flexible, show good atom economy, and are eco-friendly, they have gained great importance in synthetic organic chemistry [2–4].

Ionic liquids are salts with melting points below 100°C, typically having broad liquid ranges, low vapor pressures, and high polarity. They are receiving considerable attention because they offer a unique environment for synthetic chemistry, biocatalysis, separation science, and electrochemistry [5]. The implementation of task-specific ionic liquids further enhances the versatility of classical ionic liquids where both reagent and medium are coupled [6–8].

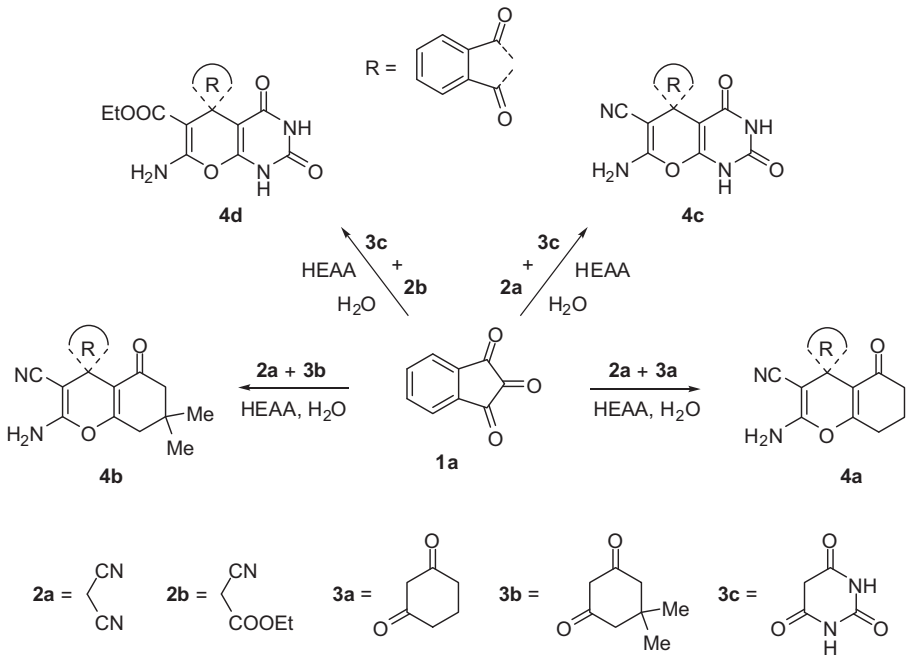
Spiro compounds are important pharmacophores with analgesic, fungicidal, antidepressant, antitumor, and antibiotic activities [9, 10]. Likewise, polysubstituted spiropyran derivatives, important spiro heterocyclic molecules, have been reported for use in the pharmaceutical industry because they possess a broad spectrum of biological potency including antimicrobial, antiproliferative, antitumor, and antiviral activities [11, 12].

Currently, several methods have been reported for the preparation of spiropyran-fused heterocycles [13–16]. Although each of the known procedures for the synthesis of spiropyran systems has its merits, further studies are still necessary to develop facile, environmental, and economical multicomponent methodology. We now report a clean and efficient method for the preparation of spiropyran-fused heterocycles in water using the ionic liquid $[H_3N^+CH_2CH_2OH][CH_3COO^-]$, abbreviated as HEAA, as a catalyst. The method is based on a three-component reaction of malononitrile or ethyl cyanoacetate, 1,3-dicarbonyl compound, and quinone or ninhydrin.

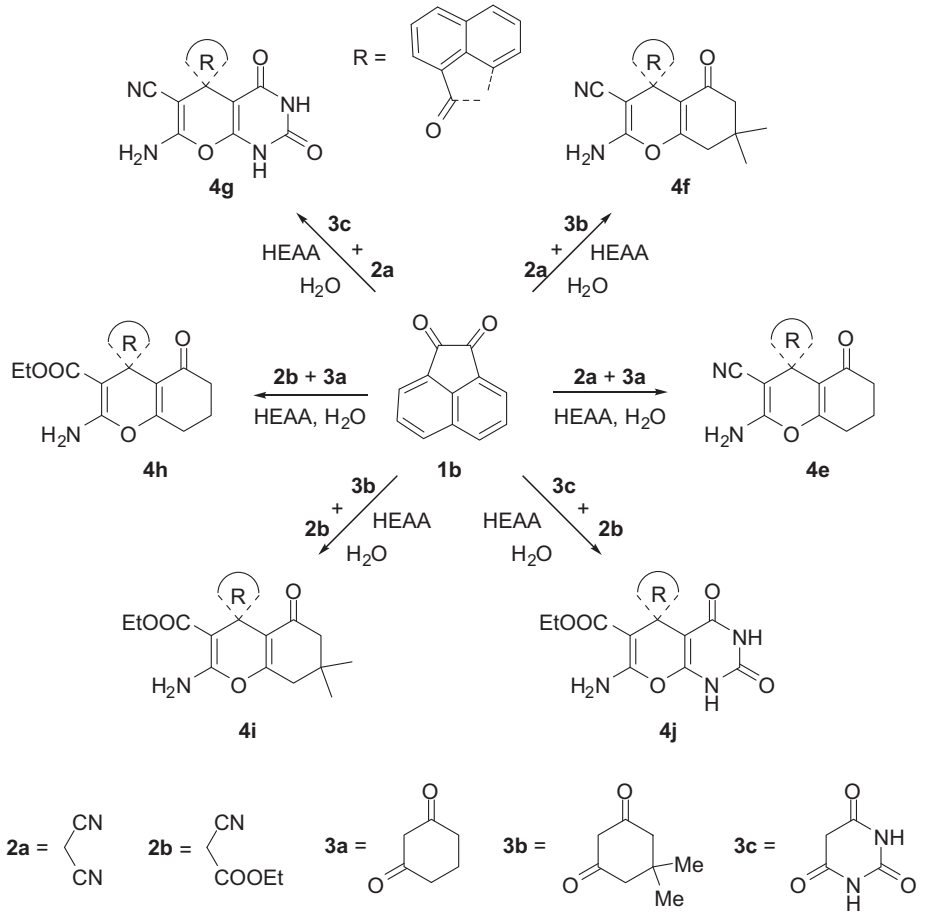
Results and discussion

In the initial research, we tested the reaction of ninhydrin (**1a**), malononitrile (**2a**), and 5,5-dimethylcyclohexane-1,3-dione (**3b**) as model substrates in the presence of HEAA in water (Scheme 1). Compounds **1a**, **2a**, and **3b** (1 mmol each) were allowed to react in water (5 mL) in the presence of HEAA (0.01 mmol) at 90°C for 1 h. A single product **4b** was obtained in 89% isolated yield. Encouraged by this result, we examined the effects of different solvents on the reaction. It was observed that pure water or in a mixture with ethanol was the most efficient medium to promote this reaction, and the spiropyran product was obtained with 88% to 94% yields. The use of other solvents, such as MeCN, DMSO, DMF, CH_3COCH_3, and $CHCl_3$, led to lower yields. The reaction hardly proceeded in THF. In water, the best yield of the desired product was obtained at 90°C.

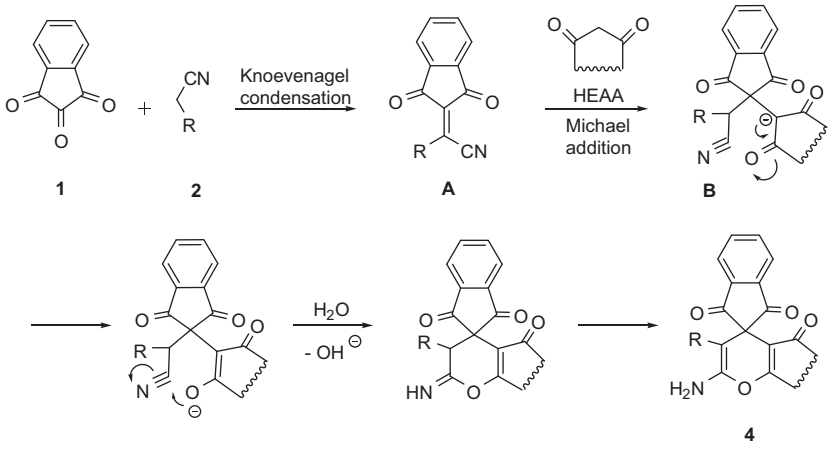
Additional products **4a**, **4c,d** derived from ninhidrin are shown in Scheme 1. The best yields were obtained for the reactions of malononitrile (**2a**) producing **4a–c**, whereas the reaction of ethyl cyanoacetate (**2b**) leading to **4d** was less efficient.



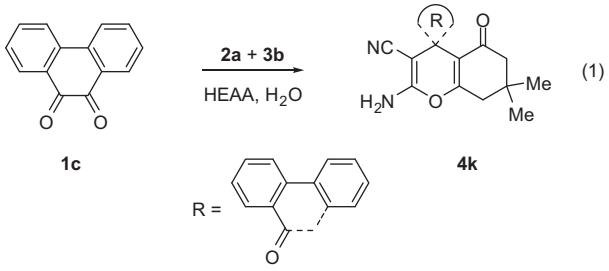
Scheme 1 Three-component synthesis of spiropyran derivatives **4a–d.**



Scheme 2 Three-component synthesis of spiroacenaphthylene derivatives **4e–j.**



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



To further explore the generality and scope of this reaction, we utilized acenaphthenequinone (**1b**) (Scheme 2) and 9,10-phenanthroquinone (**1c**) (Equation 1) as starting materials. The reactions of **1b** in water were efficient producing the corresponding products **4e–j** in yields greater than 85%. However, the reaction of **1c**, **2a**, and **3b** in water furnished the desired product **4k** in low yield. By contrast, the use of a mixture EtOH-H_2O (1:1) as the reaction medium resulted in an increase of the yield of **4k** to above 60%. Unfortunately, all attempted three-component reactions of 9,10-phenanthroquinone (**1c**) with ethyl cyanoacetate failed to yield the expected products.

A suggested mechanism by using the reactions of ninhidrin (**1a**) for illustration is given in Scheme 3. Compound **1** first undergoes Knoevenagel condensation with malononitrile or ethyl cyanoacetate **2** to generate the intermediate **A**. Then, compound **A** is involved in Michael addition with an anion derived from a 1,3-dicarbonyl compound **3** to give another intermediate product **B**. The catalyst HEAA may facilitate enolization of the substrate **3**. It is suggested that the final product **4** is formed in the intramolecular cyclization of **B** (Scheme 3).

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 unreacted starting materials and other organic contaminations. Water was then removed under reduced pressure and the residue of HEAA was dried before subsequent use. The results are presented in Table 1.

Known products were characterized by melting point, IR, and ^{1}H NMR for comparison with the literature data. All new products were characterized by melting point, IR, ^{1}H NMR, ^{13}C NMR, and HR-MS.

Table 1 Recyclability of the catalyst HEAA[a].

Entry	Cycle	Yield (%)
1	Fresh	94
2	First recycle	93
3	Second recycle	91
4	Third recycle	90
5	Fourth recycle	90

[a]Isolated yields.

Conclusion

We herein report the HEAA-catalyzed one-pot reaction for the synthesis of spiropyran derivatives in the presence of water. This reaction can be carried out under mild conditions and covers a range of substrates with excellent yields of spiropyran products. This protocol provides an efficient, environmentally friendly synthetic route to spiropyran derivatives.

Experimental

Melting points were determined with an X-4 microscopic melting point apparatus and are uncorrected. IR spectra were recorded on a NEXUS 670 spectrometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were

measured in DMSO-d_6 on a Bruker Avance II instrument at 500 MHz and 125 MHz, respectively. Synthesis of the ionic liquid has been previously reported [17]. 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 compound 4

A mixture of compounds **1** (1 mmol), **2** (1 mmol), and **3** (1 mmol), the ionic liquid $[H_3N^+CH_2CH_2OH][CH_3COO^-]$ (0.1 mmol) in water (5 mL) was stirred at 90°C for 30 min [monitored by thin-layer chromatography (TLC)]. After completion of the reaction, the mixture was cooled to room temperature and poured into water (10 mL). The solid product was collected by filtration and crystallized from ethanol to give pure compound **4**.

2-Amino-1′,3′,5-trioxo-1′,3′,5,6,7,8-hexahydrospiro[chromene-4,2′-indene]-3-carbonitrile (4a) This compound was obtained from **1a**, **2a**, and **3a** as a yellow solid; yield 91% (0.29 g); mp >300°C (reported mp >300°C [18]); ^{1}H NMR: δ 1.96 (m, 2H, CH_2), 2.29 (m, 2H, CH_2), 2.72 (m, 2H, CH_2), 7.64 (s, 2H, NH_2), 7.99–8.05 (m, 4H, ArH).

2-Amino-7,7-dimethyl-1′,3′,5-trioxo-1′,3′,5,6,7,8-hexahydrospiro[chromene-4,2′-indene]-3-carbonitrile (4b) This compound was obtained from **1a**, **2a**, and **3b** as a yellow solid; yield 94% (0.33 g), mp >300°C (reported mp >300°C, [18]); ^{1}H NMR: δ 1.04 (s, 6H, $2CH_3$), 2.19 (s, 2H, CH_2), 2.62 (s, 2H, CH_2), 7.64 (s, 2H, NH_2), 7.99–8.05 (m, 4H, ArH).

7′-Amino-1,2′,3,4′-tetraoxo-1,1′,2′,3,3′,4′-hexahydrospiro[indene-2,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (4c) This compound was obtained from **1a**, **2a**, and **3c** as a yellow solid; yield 90% (0.29 g); mp >300°C (reported mp >300°C, [18]); ^{1}H NMR: δ 7.77 (s, 2H, NH_2), 8.04 (m, 4H, ArH), 11.30 (s, 1H, NH), 12.75 (s, 1H, NH).

Ethyl 7′-amino-1,2′,3,4′-tetraoxo-1,1′,2′,3,3′,4′-hexahydrospiro[indene-2,5′-pyrano[2,3-*d*]pyrimidine]-6′-carboxylate (4d) This compound was obtained from 1a, 2b, and 3c as a yellow solid; yield 81% (0.30 g); mp >300°C; IR: ν 3380, 3281, 1703, 1671, 1507, 1403, 1330 cm^{-1}; ^{1}H NMR: δ 0.30 (m, 3H, CH_3), 3.57 (m, 2H, CH_2), 8.18 (s, 2H, NH_2), 7.90 (m, 4H, ArH), 11.17 (s, 1H, NH); 12.49 (s, 2H, NH_2); ^{13}C NMR: δ 202.4, 166.6, 162.3, 159.7, 153.6, 149.0, 141.8, 135.0, 121.7, 87.7, 73.6, 59.4, 51.2, 30.7, 12.3; MS (ESI): m/z 384.1 $(M+H)^+$. HR-MS (ESI, m/z): Calcd for $[C_{18}H_{14}N_3O_7+H]^+$ 384.0832, found 384.0814.

2′-Amino-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro-[acenaphthylene-1,4′-chromene]-3′-carbonitrile (4e) This compound was obtained from **1b**, **2a**, and **3a** as a white solid; yield 94% (0.32 g); mp 247–248°C; (reported mp 245–247°C, [19]); ^{1}H NMR: δ 1.94 (m, 2H, CH_2), 2.16 (m, 2H, CH_2), 2.71–2.72 (d, 2H, J = 5 Hz, CH_2), 7.30 (s, 2H, NH_2), 7.40–8.27 (m, 6H, ArH).

2′-Amino-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carbonitrile (4f) This compound was obtained from **1b**, **2a**, and **3b** as a light yellow solid; yield 92% (0.34 g); mp 268–269°C (reported mp 268–270°C, [20]); ^{1}H NMR: δ 1.02 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.11 (1H, d, J = 16 Hz, CH_aCH_b), 2.06 (1H, d, J = 16 Hz, CH_aCH_b), 2.63 (s, 2H, CH_2), 7.32 (s, 2H, NH_2), 7.38–8.28 (m, 6H, ArH).

7′-Amino-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydro-2*H*-spiro-[acenaphthylene-1,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile (4g) This compound was obtained from 1b, 2a, and 3c as a yellow solid; yield 86% (0.31 g); mp >300°C (reported mp >300°C, [20]); ^{1}H NMR: δ 7.47 (s, 2H, NH_2), 7.55–8.31 (m, 6H, ArH); 11.07 (s, 1H, NH), 12.41 (s, 1H, NH).

Ethyl 2′-amino-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carboxylate (4h) This compound was obtained from **1b**, **2b**, and **3a** as a yellow solid; yield 90%, (0.35 g); mp 226–227°C (reported mp 225–227°C, [19]); ^{1}H NMR: δ -0.04 (m, 3H, CH_3), 1.88 (m, 2H, CH_2), 2.09 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), 7.93 (s, 2H, NH_2), 7.25–8.11 (m, 6H, ArH).

Ethyl 2′-amino-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carboxylate (4i) This compound was obtained from **1b**, **2b**, and **3b** as a white solid; yield 89% (0.42 g); mp 258–260°C (reported mp 259–262°C, [20]); ^{1}H NMR: δ 0.04 (m, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.92 (d, 1H, J = 16 Hz, CH_aCH_b), 2.07 (d, 1H, J = 16 Hz, CH_aCH_b), 2.55 (d, 1H, J = 17.5 Hz, $CH_{a2}CH_{b2}$), 2.65 (d, 1H, J = 17.5 Hz, CHa_2H_{b2}), 3.31 (m, 2H, CH_2), 7.23–8.10 (m, 6H, ArH), 7.93 (s, 2H, NH_2).

Ethyl 7′-amino-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydro-2*H*-spiro-[acenaphthylene-1,5′-pyrano[2,3-*d*]pyrimidine]-6′-carboxylate (4j) This compound was obtained from **1b**, **2b**, and **3c** as a white solid; yield 85% (0.42 g); mp >300°C (reported mp >300°C, [20]); ^{1}H NMR: δ -0.08 (m, 3H, CH_3), 3.21 (m, 2H, CH_2), 7.35–8.14 (m, 6H, ArH), 8.12 (s, 2H, NH_2), 10.89 (s, 1H, NH), 12.29 (s, 1H, NH).

2-Amino-7,7-dimethyl-5,10′-dioxo-5,6,7,8-tetrahydro-10′*H*-spiro[chromene-4,9′-phenanthrene]-3-carbonitrile (4k) This compound was obtained from **1c**, **2a**, and **3b** as a white solid; yield 67% (0.27 g); mp >300°C; IR: ν 3380, 3327, 3211, 2960, 2196, 1681, 1651, 1601, 1480, 1449, 1415, 1348, 1322 cm^{-1}; ^{1}H NMR: δ 7.19–8.39 (m, 8H, ArH), 7.21 (s, 2H, NH_2); 2.08 (1H, d, J = 16 Hz, CH_aCH_b), 2.19 (1H, d, J = 16 Hz, CH_aCH_b), 2.56 (1H, d, J = 17 Hz, CH_aCH_b), 2.80 (1H, d, J = 17 Hz, CH_aCH_b), 1.08 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR: δ 197.1, 194.9, 163.6, 157.9, 143.2, 137.0, 134.9, 129.1, 128.9, 128.5, 128.3, 128.2, 127.3, 127.2, 123.6, 123.3, 117.5, 115.2, 60.8, 59.7, 49.9, 47.5, 32.5, 28.1, 26.9; MS (ESI): m/z 397.2 $(M+H)^+$. HR-MS (ESI, m/z): Calcd for $[C_{25}H_{21}N_2O_3+H]^+$ 397.1552, found 397.1541.

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