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Protic guanidinium ionic liquid as a green and highly efficient catalyst for the synthesis of functionalized spirochromenes under solvent-free conditions

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ABSTRACT

A simple and efficient method for the synthesis of functionalized spirochromenes is explained using protic guanidinium ionic liquid as a catalyst under solvent-free conditions at room temperature. This procedure is simple, clean, and excellent yields are obtained in short reaction times.

1. Introduction

The spirooxindole system is the core structure of many pharmacological agents and natural products [1], for example, cytostatic alkaloids such as spirotryprostatins A, B, pteropodine, strychnofoline, (−)-horsfiline and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors [2].

Among the heterocyclic spirooxindole ring system, these ones, together with substituted fused 4*H*-chromenes, have gained great importance due to their spasmolitic, anticoagulant, diuretic, anticancer, and antinaphylactic activities [3]. There have been several reports available in the literature on the synthesis of spirooxindoles with fused 4*H*-chromenes via multicomponent condensation reactions. The general procedure for the synthesis of these compounds involves the condensation of isatin, active methylene component, and 1,3-dicarbonyl compound in the presence of different catalysts, such as $InCl_3$ or $InCl_3$/SiO_2 [4], triethylbenzyl ammonium chloride (TEBA) [5], NH_4Cl [6], NEt_3 [7], ethylenediamine diacetate [8], β-cyclodextrin [9], L-proline [10], $HAuCl_4{\cdot}3H_2O$ [11], MgO [12], $[BMIm]BF_4$ [13], and sodium stearate [14]. Although all of these methods are effective, some of them have drawbacks such as long reaction times [5,9], high cost of the catalyst [6], harsh reaction conditions [4] and unreusability of the catalyst [5–8]. Therefore, there is still a demand for simple and facile methodologies for the preparation of spirochromene compounds with more efficiency and shorter reaction times.

Ionic liquids (ILs), considered as being a relatively recent magical chemical due their unique properties, have a large variety of applications in all areas of chemical synthesis. The unique properties of ILs, such as a negligible vapor pressure, good thermal stability, tunable viscosity, miscibility with water and with organic solvents, as well as good extractability for various organic compounds and metal ions, mainly depend on their special structures [15]. Protic ionic liquids (PILs) are a subclass of ILs family formed by an equimolar combination of a Brønsted acid and a Brønsted base and have an additional tunable feature as a result of proton transfer, proton activity. Environmentally

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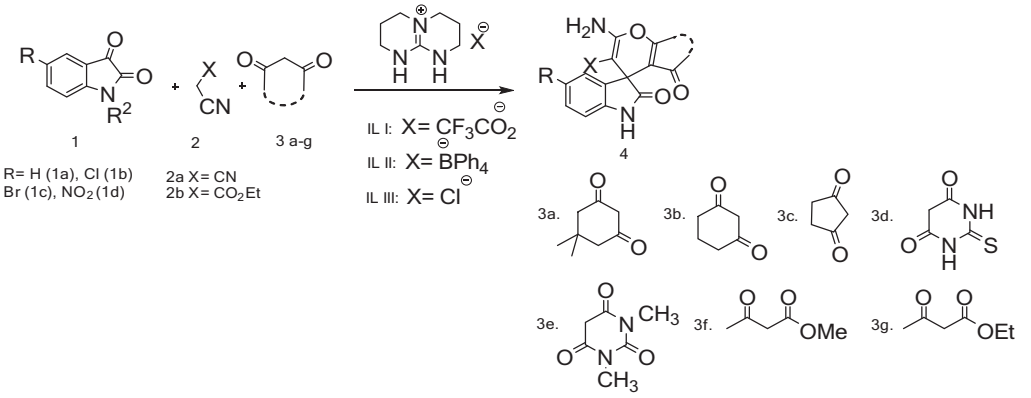

Scheme 1. Synthesis of spirochromenes catalyzed by [TBD]-based ionic liquids.

considerable properties of PILs motivated chemists to investigate their application to other fields such as catalysis [16–21]. However, there are some limitations associated with the use of ILs as catalysts, such as a lack of potential activation sites on the substrates and their sensitivity to air and moisture, leading to the inactivation of the reaction. Therefore, the design of more active PILs that can also be employed as catalysts has been an important topic in this research field.

In continuation of our studies on the development of new catalysts and methods for organic synthesis [22], herein we report the highly efficient and simple methods for the synthesis of some spirochromene derivatives from isatin derivatives, alkyl-malonates and 1,3-dicarbonyl compounds in the presence of [TBD][TFA] ionic liquid as a catalyst at room temperature under solvent-free conditions (Scheme 1).

2. Results and discussion

Initially, three triazabicyclodecene-based ionic liquids (Fig. 1, I–III) were synthesized and used as catalysts for the synthesis of spirochromene compounds.

In order to determine optimum reaction conditions, the reaction of isatin **1** (1 mmol) as a model compound with malononitrile **2** (1 mmol) and dimedone (1 mmol) was examined under different reaction conditions and shown in Table 1. Different catalyst loadings were examined and, as it is clear from Table 1, when an amount of 20 mol% of IL **I** was used as a catalyst under solvent-free conditions at room temperature after 20 min, the expected spirochromene was obtained at a yield of 85% (Table 1, entry 1). Lowering the catalyst loading to 5 mol%, an excellent yield of the product was obtained in shorter reaction times (Table 1, entries 2–4). The model reaction was also studied in different organic solvent such as ethanol, acetonitrile,

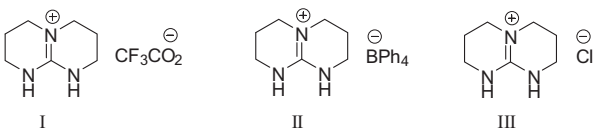

Fig. 1. Structurally related TBD based protic ionic liquids.

tetrahydrofuran, toluene, and dichloromethane. In all solvents, the reaction procedure afforded the product with a moderate yield in longer reaction times (Table 1, entries 5–9). Although ionic liquids **II** and **III** are effective in this reaction, they give lower yields than IL **I** (Table 1, entries 10 and 11). When the model reaction was carried out in the presence of TBD and CF_3CO_2H, only a moderate yield of spirochromene was obtained in longer reaction times (Table 1, entries 12 and 14). This clearly evidences the significant role of IL **I** in this reaction. From the above observations, the best yields were obtained under solvent-free reaction conditions at room temperature (Table 1, entry 4).

In order to evaluate the generality and applicability of this methodology, the reaction of isatin with 1,3-dicarbonyl and active methylene compounds were concentrated using [TBD][TFA] (5 mol%) at room temperature under solvent-free conditions for the synthesis of a series of tetrahydrospiro [chromene-4,3′-indoline] **4a–4t** derivatives, as shown in Table 2.

Several types of isatins, including either electron-withdrawing or electron-donating groups, malononitrile or cyanoacetic ester and cyclic 1,3-diketones were used in this reaction. It was observed that all these cyclic 1, 3-diketones as well as active methylene compounds were

Table 1
Optimization of reaction conditions for the synthesis of spirochromene **4a.**

Entry	Catalyst	Solvent	Time (min)	Yield (%)[a]
1	IL I, 20 mol%	–	20	85
2	IL I, 15 mol%	–	15	90
3	IL I, 10 mol%	–	10	95
4	IL I, 5 mol%	–	5	98
5	IL I, 5 mol%	EtOH	5	65
6	IL I, 5 mol%	CH_3CN	30	70
7	IL I, 5 mol%	THF	25	85
8	IL I, 5 mol%	Ph–CH_3	40	72
9	IL I, 5 mol%	CH_2Cl_2	35	65
10	IL II, 5 mol%	–	35	95
11	IL III, 5 mol%	–	5	88
12	TBD, 5 mol%	–	25	65
13	TBD, 10 mol%	–	30	75
14	CF_3CO_2H, 5 mol%	–	35	60

[a] Isolated yield.