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Tetramethylguanidine-[*bmim*][BF_4]. An Efficient and Recyclable Catalytic System for One-Pot Synthesis of 4*H*-Pyrans

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Summary. A clean and efficient method for the synthesis of 4*H*-pyran derivatives through the one-pot condensation of aromatic aldehydes, malononitriles, and β-dicarbonyl compounds, using guanidine base tetramethylguanidine in [*bmim*][BF_4] ionic liquid as a recyclable catalytic system, was described.

Keywords. Ionic liquid; Catalysts; Guanidine; Cyclization; One-pot; 4*H*-Pyrans.

Introduction

In recent years one of the prime concerns of chemists is search for replacements of the toxic and/or flammable conventional organic solvents with environmentally benign ones [1]. In this context, room temperature ionic liquids have recently received recognition as an eco-friendly alternative to replace volatile organic solvents that are currently used as solvents in both academic and industrial processing [2].

Polyfunctionalized 4*H*-pyrans constitute a structural unit of a number of natural products [3] and because of the inherent reactivity of the pyran ring are versatile synthons [4]. In addition, polyfunctionalized 4*H*-pyrans are biologically interesting compounds which possess various pharmacological activities [5], *e.g.* antiallergic [6] and antitumor [7] activities. In the family of polyfunctionalized 4*H*-pyrans, apart from the biological activities of themselves, 4*H*-pyrans are also useful intermediates for the synthesis of various compounds, such as pyranopyridine derivatives [8], polyazanaphthalenes [9], pyrano[2,3-*d*]pyrazoles [9], pyrano[2]pyrimidines [10] and pyridin-2-ones [11], with potential biological activities. Moreover, 4*H*-pyrans can be transformed into corresponding pyridines related to important *DHP* type calcium antagonists [12].

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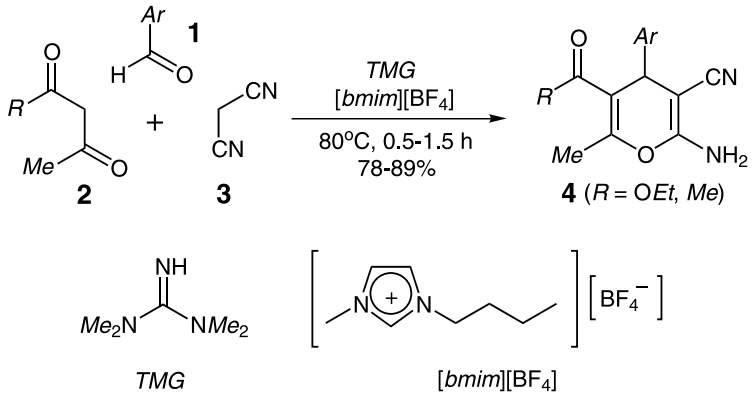

Scheme 1

Routinely, 5-substituted-2-amino-4-aryl-3-cyano-6-methyl-4*H*-pyrans were prepared through the cyclization of arylidenemalononitriles with 1,3-dicarbonyl compounds in the presence of an organic base such as piperidine, pyridine, or triethylamine [8–10, 13]. Recently, *Shestopalov* and co-workers [14] have developed a one-pot electrochemical synthesis of title compounds catalyzed by electrogenerated base. Most of these reactions were carried out in volatile and flammable organic solvents such as ethanol with the yields ranged from 60 to 80%. In addition, the recovery of catalysts is also a tedious and energy-consuming procedure.

In view of the emerging importance of ionic liquids as environmentally friendly and recyclable reaction media, we report herein an efficient one-pot preparation of title compounds promoted by a strong guanidine base [15], 1,1,3,3-tetramethylguanidine (*TMG*), using ionic liquid [*bmim*][BF_4] as the solvent (Scheme 1).

Results and Discussions

Initially, to investigate the influence of different solvents on the cyclization, the condensation between benzaldehyde, malononitrile, and ethyl acetoacetate was chosen as a model. In a blank experiment, the equimolar mixture of benzaldehyde (5 mmol), malononitrile (5 mmol), and ethyl acetoacetate (5 mmol) was heated in 3 cm^3 of ethanol at 80°C. After being stirred for 3 hours, it gave no product. Then 10 mol-% of *TMG* were added and the mixture was heated for 1.5 h at the same temperature. The desired product was obtained in 81% yield. It was found that ionic liquids had superiority over ethanol in view of higher isolated yields and reaction rates. There are no considerable differences in reaction rates and yields either with *TMG*-[*bmim*][BF_4] (83%, 50 min) or with the *TMG*-[*bmim*][PF_6] (84%, 50 min) catalytic system. These data point out an accelerating effect of the ionic solvents. Possibly, the ionic nature of the imidazolium ionic liquids could facilitate the reaction by providing stabilization of reactive charged intermediates [16]. It is worth mentioning that, if the ionic liquid was used in the absence of organic base, no reaction was observed after 3 h. In our procedure, [*bmim*][BF_4] was chosen due to its hydrophilicity, by which the final treatment was facilitated.

Table 1. One-pot synthesis of 5-acyl/alkoxycarbonyl-2-amino-4-aryl-3-cyano-6-methyl-4*H*-pyrans in [*bmim*][BF_4] catalyzed by *TMG*

Entry	*Ar*	*R*	Products	Time / min	Yield/%[a]
1	C_6H_5	O*Et*	**3a**	50	83
2	4-Cl–C_6H_4	O*Et*	**3b**	30	87
3	4-*Me*O–C_6H_4	O*Et*	**3c**	90	82
4	3-NO_2–C_6H_4	O*Et*	**3d**	30	81
5	4-CN–C_6H_4	O*Et*	**3e**	30	85
6	4-OH–C_6H_4	O*Et*	**3f**	70	80
7	3-*Me*O–4-OH–C_6H_3	O*Et*	**3g**	90	78
8	2,4-Cl_2–C_6H_3	O*Et*	**3h**	40	89
9	C_6H_5	*Me*	**3i**	60	82
10	4-*Me*O–C_6H_4	*Me*	**3j**	70	80
11	4-*Me*–C_6H_4	*Me*	**3k**	90	81
12	3-NO_2–C_6H_4	*Me*	**3l**	40	85

[a] isolated yields

The scope and generality of this process were next examined with a variety of other substrates (Table 1). In all the cases tested, the cyclization went smoothly with 10 mol-% of *TMG* under similar reaction conditions, giving the corresponding 4*H*-pyran derivatives in good yields. Condensations were carried out in [*bmim*] [BF_4] at 80°C for times ranging from 0.5 to 1 h. Yields, usually on the order of 78–89%, were obtained almost routinely (Table 1). The electronic effects of phenyl ring substituents were also explored. It is seen from Table 1 that electron-donating groups disfavor product formation as demonstrated for **3c**, **3f**, and **3g**, and electron-withdrawing groups favor the formation of product as shown for **3d** and **3e**, respectively. Additionally, that electron-withdrawing groups favor the formation of products is further supported with a sterically hindered substrate bearing electron-withdrawing groups (Table 1, Entry 8, **3h**).

As a second idea, we studied the extension of our procedure to the formation of 5-acetyl-2-amino-4-aryl-3-cyano-6-methyl-4*H*-pyrans using acetylacetone under similar conditions (Table 1, Entry 9–12). In accord with our expectation, these reactions proceeded smoothly and afforded corresponding products in good yields.

From the environmental and economic points of view, another advantage of this procedure is that the catalyst-containing solvent can be easily recovered and reused in subsequent reactions. Since the 4*H*-pyran products were weakly soluble in aqueous ionic phase, after reaction, the paste-like mixture thus obtained was diluted with a certain amount of water, the crude product precipitated was filtered off and the catalyst and solvent, [*bmim*][BF_4], were recovered easily by removing water under reduced pressure and drying at 100°C for several hours. The recovered *TMG*-IL could be reused in subsequent reactions, affording similar isolated yields of title compounds.

Investigations by using benzaldehyde, malononitrile, and ethyl acetoacetate as model substrates showed that successive reuse of the recovered ionic liquids and the catalyst gave the product with a yield similar to the first round. As shown in

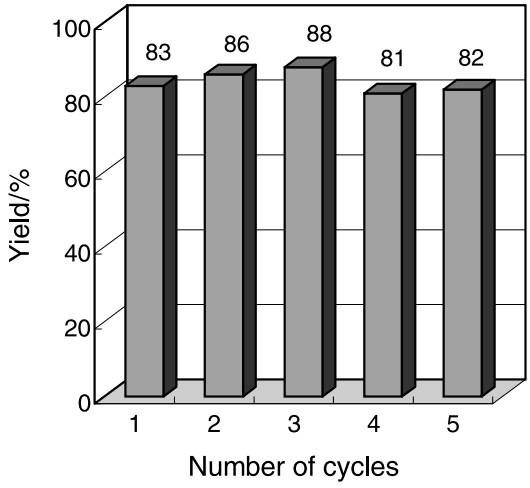

Fig. 1. Recycling studies of *TMG*-[*bmim*][BF_4] system

Fig. 1, catalyst-containing ionic liquid can be recycled at least five times with essentially no loss in catalytic activity. It is noteworthy that the product was isolated in 88% yield (Fig. 1, Run 3) even without any replenishment of the catalyst, indicating that both the ionic liquid and the catalyst were recyclable and reusable.

In conclusion, we have developed a *TMG*-catalyzed clean synthesis of biologically interesting 4*H*-pyrans in good isolated yields using a room temperature ionic liquid [*bmim*][BF_4] as recyclable medium. In comparison with the previously reported methods, the following advantages were achieved: (1) without any additional volatile solvent, (2) simple work-up, and (3) reusable catalyst-solvent system.

Experimental

All products are known compounds, their physical and spectroscopic data were compared with those reported in the literature and found to be identical. Melting points were determined on a X-4 micro-melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets with a Nicolet Nexus 470 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM 500 spectrometer in acetone-d_6 with *TMS* as an internal standard.

General Procedure

To a 25 cm^3 round bottomed flask containing aromatic aldehydes (5 mmol), malononitrile (5 mmol), and ethyl acetoacetate (or acetylacetone) (5 mmol) was added *TMG* (0.5 mmol) and [*bmim*][BF_4] (3 cm^3). The mixture was then heated at 80°C for the indicated time (Table 1). The product separated out from the homogeneous mixture subsequently as the reaction progressed. After completion of the reaction (monitored by TLC), 1 cm^3 of water was added to the mixture, and the crude product was collected by filtration, washed with water, air dried, and recrystallized from 95% *Et*OH to afford pure products.

The catalyst-containing ionic phase was recovered easily by removing water under reduced pressure and drying at 100°C for 2 h.

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