Polymer-Supported Ionic-Liquid-Catalyzed Synthesis of 1,2,3,4-Tetrahydro-2-oxopyrimidine-5-carboxylates *via Biginelli* Reaction

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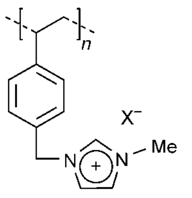
The *Biginelli* reaction between an aromatic aldehyde, ethyl acetoacetate, and urea – catalyzed by polymer-supported, re-usable, room-temperature ionic liquids (RTIL) such as **1b** – was shown to efficiently proceed in glacial AcOH at 100° to afford the corresponding pyrimidine-5-carboxylates **3** in yields up to 99% within 2 h (*Table 2*). The catalyst(s) could be reused at least five times, basically without loss of activity, which makes this transformation not only straight-forward, but also considerably less expensive compared to methods involving classical RTIL catalysts.

Introduction. – Recently, the classical *Biginelli* reaction [1] has found great interest because partly hydrated pyrimidinones have shown pharmacological activities. These compounds may act as antihypertensives, calcium channel blockers, α-1a antagonists [2], and neuropeptide Y (NPY) antagonists [3]. Furthermore, several marine alkaloids with interesting biological activities containing the dihydropyrimidine-5-carboxylate skeleton were isolated recently [4].

The main drawback of the *Biginelli* reaction is the low yield for extended reaction times in the case of substituted aromatic and aliphatic aldehydes [5]. So, the development of alternative synthetic methodologies is of great importance. This has led to the development of several new synthetic strategies involving combinations of *Lewis* acids [6], *e.g.*, $BF_3 \cdot OEt_2$, KSF, PPE (=polyphosphate ester), $B(OH)_3$, onium salts, and (transition) metal salts [7] such as $InCl_3$, LiBr, $LaCl_3 \cdot 7\ H_2O$, $CeCl_3 \cdot 7\ H_2O$, $Mn(OAc)_3 \cdot 2\ H_2O$, $Cu(OTf)_2$ ($Tf = F_3CSO_2$), or $FeCl_3 \cdot 6\ H_2O$.

Room-temperature ionic liquids (RTIL) have attracted much interest among organic chemists. Typically, RTIL used for organic reactions are *Lewis* acids that can catalyze acid/base reactions. Some RTIL-catalyzed *Biginelli* reactions have been reported [8], *e.g.*, with 1-butyl-3-methyl-1*H*-imidazol-3-ium tetrafluoroborate ($BMimBF_4$) or the corresponding hexafluorophosphate ($BMImPF_6$). Unfortunately, these and other compounds are generally very expensive and difficult to remove from the products. Thus, we immobilized the catalyst on *Merrifield* resin to obtain polystyrene–methylimidazolium (PsMim)-based, re-usable ionic liquids of type **1** [9]. These compounds were found to efficiently catalyze *Biginelli* reactions, giving rise to very good yields in short reaction times.

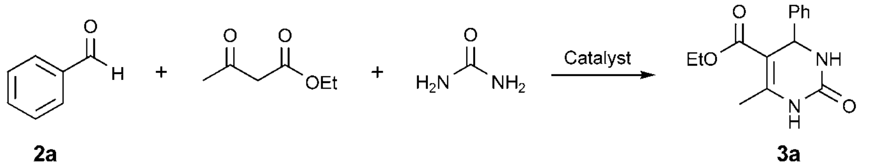
In this paper, we describe the application of catalysts **1** for the synthesis of a variety of substituted tetrahydropyrimidine-5-carboxylates **3**.



1a X = BF_4^- ($PsMimBF_4$)
1b X = PF_6^- ($PsMimPF_6$)

Results and Discussion. – To optimize the conditions for the RTIL-catalyzed *Biginelli* reaction, we investigated the condensation between benzaldehyde (**2a**), ethyl acetoacetate (=ethyl 3-oxobutanoate), and urea, which gave rise to ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (**3a**; *Table 1*). First, we determined the efficiency of the two polymer-supported catalysts Ps-$MimBF_4$ (**1a**) and $PsMimPF_6$ (**1b**) as a function of solvent. Both were found to readily catalyze the reaction. However, $PsMimBF_4$ produced more insoluble byproducts in EtOH and $CHCl_3$ compared to $PsMimPF_6$. Also, the solvent (and temperature) remarkably affected the yield, glacial AcOH being better than MeCN or EtOH, with isolated yields of **3a** of 98%, 85%, and 71%, respectively (*Table 1*). Thereby, the same catalyst (**1b**) could be used at least five times without significant loss in activity (*Entry 6*), and no precipitation was observed during reaction, which is a prerequisite for high yields.

Table 1. *Polymer-Supported, Ionic-Liquid-Catalyzed* Biginelli *Reaction with Benzaldhyde.* Conditions: catalyst, 3.5 mol-%; aldehyde and ethyl acetoacetate, 10 mmol each; urea, 15 mmol.



2a **3a**

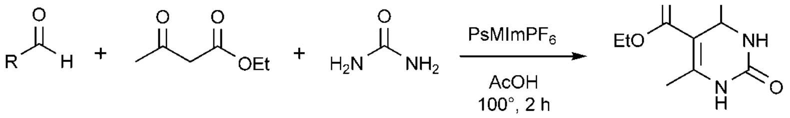
Entry	Catalyst	Solvent	*T*	Time	**3a** [%][a])	Turnover[b])
1	None	EtOH	78°	4 h	13	–
2	None	MeCN	82°	4 h	25	–
3	None	AcOH	100°	2 h	70	–
4	$PsMImPF_6$	EtOH	78°	4 h	71	20
5	$PsMImPF_6$	MeCN	78°	4 h	85	24
6	$PsMImPF_6$	AcOH	100°	2 h	98[c])	28
7	$PsMImBF_4$	MeCN	82°	4 h	84[d])	24

[a]) Isolated yield after recrystallization. [b]) Ratio of product (equiv.) rel. to catalyst. [c]) When the same catalyst was used five times, the yields were 98, 97, 94, 90, and 91%, resp., with basically constant turnovers of 28 to 26. [d]) Most by-products were insoluble in EtOH or $CHCl_3$.

Encouraged by the above results, other substrates, *i.e.*, several aromatic and aliphatic aldehydes **2**, were reacted under optimized conditions in the presence of $PsMImPF_6$ (**1b**) in AcOH at 100° for 2 h (*Table 2*).

Aromatic aldehydes with electron-donating groups R (**2a**, **g**) favored the *Biginelli* condensation under these conditions ($\geq$98% yield). In contrast, aromatic aldehydes with electron-withdrawing substituents (**2b**–**f**) gave rise to somewhat lower, but still good yields (74–91%). Steric effects due to *ortho*-substituents negatively affected the reactivity of the substrates (*Entry 2 vs. 3* in *Table 2*). The low yield of **3h** was most-likely due to protonation of the 4-Me_2N group of **2h**, thus becoming an electron-withdrawing 4-Me_2NH^+ group. Finally, the aliphatic aldehyde **2i** (butanal) was not suited for this kind of transformation under the conditions applied (*Entry 9*).

Table 2. *Polymer-Supported, Ionic-Liquid-Catalyzed Synthesis of Compounds* **3** *with PsMImPF6* (**1b**). Conditions: catalyst, 3.5 mol-%; aldehyde and ethyl acetoacetate, 10 mmol each; urea, 15 mmol.



2 **3**

Entry	No.	R	**3a**–**i** [%][a])	M.p. [°]	Turnover
1	**a**	Ph	98	200–202	28
2	**b**	2-Cl-C_6H_4	80	215–217	23
3	**c**	4-Cl-C_6H_4	91	212–213	26
4	**d**	2,4-Cl_2-C_6H_3	74	248–250	21
5	**e**	4-NO_2-C_6H_4	88	207–209	25
6	**f**	2-MeO-C_6H_4	87	201–202	25
7	**g**	4-Me-C_6H_4	99	171–173	28
8	**h**	4-Me_2N-C_6H_4	53	230–232	15
9	**i**	Pr	23	152–153	7

[a]) Isolated yield after recrystallization.

Conclusions. – The use of recoverable, polymer-supported room-temperature ionic liquids (RTIL) as catalysts provides a simple and effective method for the *Biginelli* reaction performed with *aromatic* aldehydes. The problem of separating expensive RTIL from the products, especially problematic for large-scale preparations, can be readily circumvented with the catalyst $PsMImPF_6$ (**1b**).

Experimental Part

General. All solvents and reagents were used without purification. Thin-layer chromatography (TLC) was performed on silica-gel *H 60* plates; visualization by UV and exposure to I_2. Melting points (m.p.) were measured on a *Rapido PHMK 79/2523* instrument (*VEB Wagetechnik*) and are uncorrected. IR Spectra were recorded on an FT-IR apparatus. ^1H-NMR Spectra were recorded at 400 MHz and referenced to internal solvent signal. GC/MS were recorded on *Agilent 6890N/5793N/HP-5*. All products (**3**) were fully characterized, and their anal. data were compared with those given in the literature. For m.p., see *Table 2*.

Catalyst Preparation. To a flask containing polystyrene-based chloromethyl resin (5.0 g; 200–400 mesh, 3.5 mmol Cl/g) was added DMF (15 ml), and the resin was stirred for 2 h. Then, 1-methyl 1-*H*-imidazole (20 mmol) was added, and the mixture was heated at 80° for 24 h. The resin was filtered under reduced pressure, washed with anh. EtOH, and stirred for 12 h in EtOH at 80°. Then, the beads were filtered off and dried *in vacuo* to afford yellowish PsMImCl resin, which was subjected to ion exchange with 20 weight-% $NaBF_4$ or NH_4PF_6 in

H_2O for 24 h. The beads were then filtered, washed neutral with H_2O, and dried *in vacuo* to afford $PsMImBF_4$ (**1a**) or $PsMImPF_6$ (**1b**), resp.

General Procedure for the $PsMImPF_6$ *Catalyzed Preparation of Compounds* **3**. A soln. of the aldehyde (10 mmol), ethyl acetoacetate (1.30 g, 10 mmol), urea (0.91 g, 15 mmol), and $PsMImPF_6$ (**1b**; 100 mg, 3.5 mol-%) in glacial AcOH (40 ml) was heated at 100° for 2 h in a single-neck flask. Then, the hot soln. was filtered through a sintered funnel to remove the catalyst for re-use. The filtrate was cooled to r.t., and then poured onto crushed ice (40 g). Stirring was continued for several minutes, and the solid product was filtered through another sintered funnel. The crude product was purified by recrystallization (EtOH).

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