

SPECIFIC “IONIC LIQUIDS” AS NEW ORGANOCATALYSTS OF BIGINELLI REACTION

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Abstract: New ionic liquids bearing an imidazolium core with a carboxy group have been prepared in an attempt to design new organocatalysts of Biginelli reaction. Trends in the properties of these compounds are discussed. The synthesized compounds represented a novel class of molten salts and may be considered as new organocatalysts for chemical reaction.

Keywords: ionic liquids, organocatalyst, Biginelli reaction.

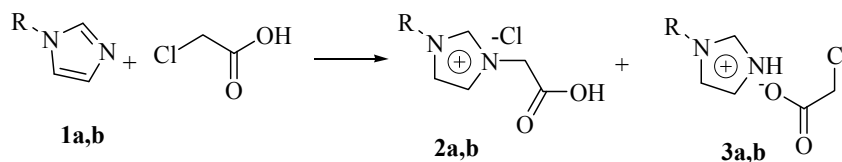
Introduction

The knowledge about the three-component condensation reaction between an aldehyde, a urea or thiourea, and an easily enolizable carbonyl compound, is quite extensive, and has been described by the Italian chemist Pietro Biginelli in 1893. This reaction offers a straightforward approach to 3,4-dihydropyrimidin-2-(1*H*)-ones(thiones) and others bioactive heterocyclic compounds [1,2]. The discussed reaction has catalyzed mineral, organic or Lewis acids and microwave irradiation as well [1-4].

Herein, we describe the specific synthesis of the carboxy group containing imidazolium ionic liquids with hydrogensulphate as well as bromide as anions and their catalytic properties.

Results and discussion

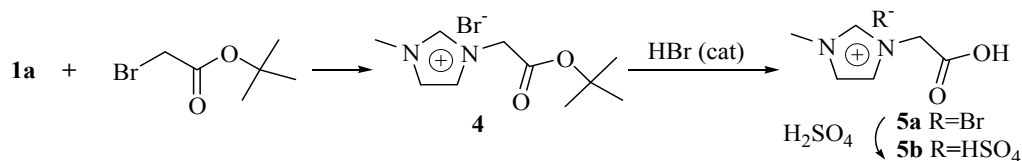
A short time ago we reported about the synthesis of the mixture **2a,3a** or **2b,3b** from monochloroacetic acid and N-substituted imidazoles **1a,b**, and their application as catalysts of Biginelli reaction [5].



Scheme 1

In continuation of this approach, we are looking for ionic liquids composed of imidazolium cations with “free” carboxyl group. Wang Z. *et al* [6] proposed synthesis of compound **2a** via alkylation of 1-methylimidazole **1a** with chloroacetic acid under basic condition. We repeated the published procedure, but obtained the mixture of products.

We therefore decided to develop the new route to such compounds. The most logical protocol for the synthesis comprises the use the protected carboxyl group α -monohalogenated acetic acid followed by removal of protecting group.

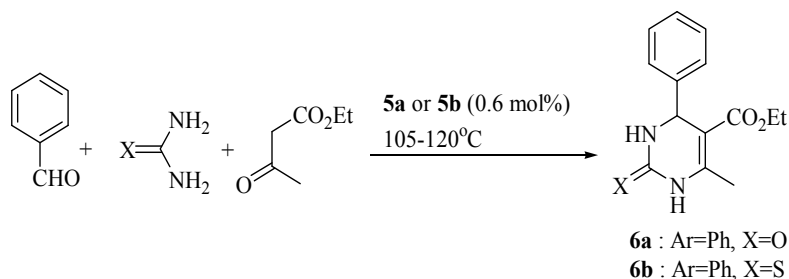


Scheme 2

In this respect, imidazolium bromide **4** has been prepared by reaction of the appropriate imidazole **1a** with *tert*-butyl bromoacetate, which was subsequently treated with catalytic amount of water solution of HBr to afford the

3-carboxymethyl-1-methyl-1*H*-imidazolium bromide **5a** according to Scheme 2. Oily salt **5b** was obtained by addition of one equivalent of 98% H₂SO₄ to product **5a**.

We examined the Biginelli reaction of ethyl acetoacetate with benzaldehyde and urea (or thiourea) in the presence of **5a** and **5b** (0.6 mol%) at elevated temperatures (scheme 3).



Scheme 3

Both reactions gave rise to the corresponding 3,4-dihydropyrimidin-2-(1*H*)-ones(thiones) **6a,b** which were formed in variable yield. The yield, as well as the time of the reaction, was significantly improved by the nature of the catalyst (see Table 1).

Table 1

Physical and analytical data of synthesized compounds

No Compound	Mol. Formula	M.p. °C Registered / Ref.	Catalyst	Time (min) Registered / Ref.	Yield (%) Registered/ Ref.
6a	C ₁₄ H ₁₆ N ₂ O ₃	213-214/ 233-236 [4] 213-214 [5] 235-236 [7]	2a,b	90 [5]	56 [5]
			3a,b	60 [5]	61 [5]
			5a	30	72
			5b	10	67
6b	C ₁₄ H ₁₆ N ₂ O ₂ S	212-213/ 220-224 [4] 212-213 [5]	2a,b	90 [5]	55 [5]
			3a,b	80 [5]	67 [5]
			5a	60	65
			5b	10	65

It is worth noting, that our synthesized “ionic liquids” are more effective catalysts in comparison with other early published ones [4-6].

It is reasonable to speculate that the reaction mechanism involves the condensation of urea with the aldehyde at high temperature to yield the corresponding iminium intermediate, which is then trapped by an aldol-type reaction with the enol derived from the ketoester. Such an effect may also be of significance in the action of “free” carboxy group of acetic acid and the enhancement of selectivity in the presence of imidazolium, as well as hydrogensulphate or bromine ions.

Conclusions

In conclusion, we have synthesized two new ionic liquids bearing an imidazolium core with a carboxy group, which can be easily used as organocatalysts of Biginelli reaction. These results open new possibilities in the construction of a new type of specific “catalysts” and could be used in the future for the production of pharmaceutically interesting products without any transition metal contamination. The studies of the enantiospecific variant of the Biginelli reaction are now being investigated in our laboratory.

Experimental

All the used solvents were of reagent quality, and all commercial reagents were used without additional purification. Removal of all solvents was carried out under reduced pressure. Analytical TLC plates were Silufol® UV-254 (Silpearl on aluminium foil, Czecho-Slovakia). IR spectra were recorded on a Specord 75 IR instrument. ¹H and ¹³C NMR spectra were recorded for d₆-DMSO 2-3% solution on a Bruker AC-80 (80 and 20 MHz).

N-methylimidazole 3 and **tert-butyl 2-bromoacetate** – reagents from Aldrich Chemical Company.

Preparation of 3-(tert-butyloxycarbonylmethyl)-1-methyl-1H-imidazolium bromide 4. Bromide **4** was prepared by mixing 0.82 g (0.001 mol) of N-methylimidazole **1a** and 1.94 g (0.001 mol) *tert*-butyl 2-bromoacetate in 5 ml of dry MeCN at room temperature for 24 hours. The solvent was removed and obtained 2.59 g of **4**. The yield was 94%. IR (ν/cm^{-1}): 1248 ((CH₃)₃C), 2854 (CH₃) 3153, 1577 (CH=C), 1743 (C=O), 623 (Br). ¹H NMR (δ , ppm): 1.37 s (9H, *tert*-butyl), 3.92 s (3H, Me-N), 5.29 s (2H, CH₂), 7.86 s, 7.90 s, 9.39 s (3H, imidazole). Mol. For. C₁₀H₁₇BrN₂O₂ Cal. C 43.34; H 6.18; N 10.11. Find C 43.24; H 6.00; N 9.87.

Preparation of 3-carboxymethyl-1-methyl-1H-imidazolium bromide 5a. Several drops of 45% solution of HBr in water were added to a solution of 2.77 g (0.001 mol) of **4** in MeCN (5 ml) at room temperature. The residue was stirred at room temperature for 3 hours, followed by distilling of the solvent and drying over P₂O₅ and we obtained 1.79 g of **5a**. The yield was 82%. M.p. 184-185°C from ethanol. IR (ν/cm^{-1}): 3450, 3091, 2906 (OH⁻), 2906 (CH₃), 2570, 2479 (N⁺), 3114, 1463, 1570 (CH=C), 1732 (C=O), 619 (Br⁻), ¹H NMR (δ , ppm): 3.88 s (3H, Me-N), 4.97 s (2H, CH₂), 4.97 s (1H, CO₂H), 7.68 s, 7.70 s, 9.10 s (3H, imidazole). Mol. For. C₆H₉BrN₂O₂ Cal. C 32.60; H 4.10; N 12.67. Find C 32.54; H 4.00; N 12.88.

Preparation of 3-carboxymethyl-1-methyl-1H-imidazolium hydrogensulphate 5b. Mixture of **5a** (1.97 g, 0.089 mol) and H₂SO₄ (0.87 g, 0.089 mol) in 5 ml MeCN was stirred for 30 min. Distilling of the solvent followed drying over P₂O₅ to give 2.34 g of yellow oil **5b**. The yield was 98%. IR (ν/cm^{-1}): 3417, 3158 (OH⁻), 2965, 2888 (CH₃), 2552 (N⁺), 3120, 1419 (CH=C), 1088 (HSO₄⁻), 1740 (C=O). ¹H NMR (δ , ppm): 3.84 (C, 3H, N-CH₃), 5.09 (C, 2H, CH₂-CO), 7.65 s 7.67 s 9.04 s (3H, imidazol), ¹³C NMR (δ , ppm): 36.21 (CH₃), 59.84 (CH₂), 123.54, 124.04, 135.96 (CH imidazole), 168.45 (C). Mol. For. C₆H₁₀N₂O₆S. Cal. C 30.25; H 4.23; N 11.76. Find C 30.29; H 4.11; N 11.56.

General procedure of preparation of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 6a and ethyl 6-methyl-2-thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 6b. To a mixture of 1.06 g (0.01 mol) of benzaldehyde, 1.3 g (0.01 mol) of ethyl acetoacetate and 0.01 mol of thiourea or urea were added 0.6 mol % of appropriate catalyst. The mixture was heated at 105-120°C. On completion of reaction, the mixture was dispersed in EtOH, the residue was filtered off, washed with H₂O and dried over P₂O₅. A sample was recrystallized for analysis from EtOH. Physical, analytical and catalytically data of synthesized compounds are presented in Table.

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