Thiazolium Salt Immobilized on Ionic Liquid: An Efficient Catalyst and Solvent for Preparation of α-Hydroxyketones

Farajollah Mohanazadeh[a]; Majid Aghvami[b]

[a] Institute of Industrial Chemistry, Iranian Research Organization for Science and Technologies, Tehran, Iran [b] Department of Chemistry, Tarbiat Moallem University, Tehran, Iran

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis
Taylor & Francis Group

Thiazolium Salt Immobilized on Ionic Liquid: An Efficient Catalyst and Solvent for Preparation of α-Hydroxyketones

Farajollah Mohanazadeh
Institute of Industrial Chemistry, Iranian Research Organization for Science and Technologies, Tehran, Iran

Majid Aghvami
Department of Chemistry, Tarbiat Moallem University, Tehran, Iran

*Aldehydes were efficiently converted to acyloins and benzoins using a new ionic liquid, 3-[2-(1-butyl-1H-imidazol-1,3-ium-3-yl)ethyl]-4,5-dimethyl-1,3-thiazol-3-ium dibromide **1**. This ionic liquid is introduced as a catalyst and a solvent. Acyloins and benzoins were easily isolated from the reaction mixture via simple extraction, and the ionic liquid could be recycled for further use. Also, α-hydroxy ketones with an aromatic and aliphatic substituent were prepared starting from aromatic and aliphatic aldehydes in the presence of ionic liquid **1**.*

INTRODUCTION

Ionic liquids have been utilized at ambient temperature as clean solvents and catalysts for green chemistry[1–3] and as electrolytes for batteries,[2] photochemistry,[4] and electrosynthesis.[5] Their vapor pressure is not significant. As such, no volatile organic components will be created.[6] They can easily be separated from organic molecules by distillation without loss of their catalytic property. Ionic liquids can tolerate up to 300°C allowing large kinetic control reactions. This behavior coupled with their good solvent properties, allows utilization of small reactor volumes. Because of the poor nucleophilic properties of the anions,[7,8] such as $[BF_4]^-$, $[PF_6]^-$, $[CF_3CO_2]^-$, $[CF_3SO_3]^-$, they do not interfere with the organic reactions. Also, they are water and

air insensitive and possess remarkably high thermal stability.[9] Many of these materials are derived from the 1-alkyl-3-methylimidazolium cation. By changing the anion or the alkyl chain at the cation, a wide variation in properties such as hydrophobicity,[10,11] viscosity, density, and solvation can be obtained. Although ionic liquids were initially introduced as alternative green reaction media, today they have marched far beyond this border, showing their significant role in controlling the reaction as catalyst.[12,13] Herein, we report the dramatic influence of a new tailor-made, task-specific, and stable ionic liquid, 3-[2-(1-butyl-1*H*-imidazol-3-ium-3-yl)ethyl]-4,5-dimethyl-1,3-thiazol-3-ium bromide **1** (Scheme 1), in benzoin condensations.

3 R = CH$_3$
4 R = CH$_2$CH$_2$OH

1 R = CH$_3$
2 R = CH$_2$CH$_2$OH
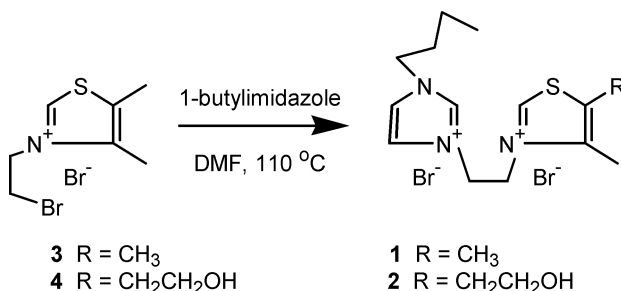
SCHEME 1

Benzoin condensation was traditionally catalyzed by cyanide anion and thiazolium salts. Also, a number of heterocyclic systems such as immobilized imidazole,[14] triazoles,[15,16] and thiazoles were used for benzoin condensation.[17] However; we have found that a specific ionic liquid efficiently promotes the benzoin condensation. By use of this ionic liquid, 3-[2-(1*H*-imidazol-3-ium-3-yl) ethyl]4,5-dimethyl-1,3-thiazol-3-ium dibromide **1**, we were successful in catalysing benzoin type condensations within a reasonable period of time (Table I) with high to moderate yields.

RESULTS AND DISCUSSION

At first, 4-methyl-5-(2-hydroxyethyl) thiazole was selected for the preparation of the ionic liquid. It is easily obtained from the sulfite cleavage of thiamine.[19] The ionic liquid, 3-[2-(1-butyl-1*H*-imidazol-3-ium-3-yl)ethyl]-5-(hydroxyethyl)-4-methyl-1,3-thiazol-3-ium dibromide **2** (Scheme 1), was obtained by reaction of 1-butylimidazole with 3-(2-bromoethyl)-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium bromide **4**. Compound **4** is prepared by reaction of 4-methyl-5-(2-hydroxyethyl) thiazole with 1,2-dibromoethane. Benzoin is obtained

from the reaction of benzaldehyde in the ionic liquid **2** in the presence of triethylamine (2 equiv.) and ethanol (2 equiv.). We have found, however, that the presence of the 5-(2-hydroxyethyl) group decreases the activity of the catalyst, possibly by providing an alternate and competing route (Scheme 2b), which leads to the formation of a fused perhydrofurothiazoline ring system (**12**). This has been shown for 2-(1-hydroxyalkyl) and 2-(1′-hydroxyaryl) derivatives of thiamine in protic[20] and aprotic[21] media under the influence of a variety of bases. It should be noted that the presence of the 4,5 double bond of the thiazolium nucleus is of crucial importance in restoring the aromatic character of the thiazolium ring in the transition state of the reaction. This, in fact, is equivalent to the conversion of enamine **10** to imine **11**, whose formation is essential for the production of acyloin and benzoin (Scheme 2a).
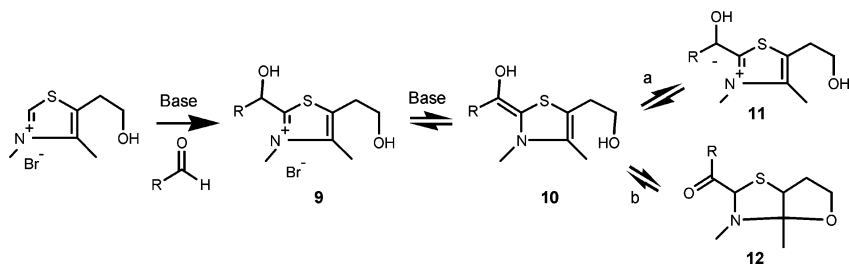
SCHEME 2

4,5-Dimethylthiazole is the better choice for the preparation of the catalyst. 4,5-Dimethylthiazole was mixed with 1,2-dibromoethane at 110°C for 6 h. The resulting thiazolinium bromide **3** was reacted with 1-butylimidazole in DMF, which afforded the ionic liquid **1**. The new ionic liquid **1** is used as the catalyst and solvent for the preparation of benzoins and acyloins. The major advantage of this method is the simple recovery of catalyst and solvent, thus providing a convenient economical synthesis of these classes of compounds. Furthermore, the present approach is superior, not only with respect to the yields, but also in its range of applicability as compared to the cyanide catalyzed benzoin condensation. For example, whereas our method results in 90 % yield of furoin (Table I), the benzoin condensation of 2-furaldehyde affords furoin in low yield. Also, by use of this new ionic liquid **1** we obtained 4,4′-dinitrobenzoin (Table I) in 85% yield; its preparation is not possible by the classical benzoin condensation method.

In the case of acyloins, although the yields were lower relative to those of benzoins, from an economical point of view and because of

TABLE I Synthesis of Acyloins and Benzoins

| Acyloins, benzoins	Yield[a] (%)	Time (h)
Butyroin	80	96
Palmitoin	51	96
Benzoin	92	12
Furoin	90	12
4,4′-Dinitrobenzoin	85	12
4,4′-Dimethylbenzoin	83	12

[a]Comparison of spectral data (IR, NMR, UV) and thin layer chromatography with authentic sample also confirmed structure and purity of the reported acyloins and benzoins.

the ease of experimental procedure this approach is prefered over the standard acyloin condensation.

In the case of benzoins (Table I) additional stability of the imine α-carbanion (**11**, Scheme 2), is provided by the resonance contribution of the aromatic ring. This, in turn, results in good yields and short reaction times. For acyloins, longer reaction times are required due to the absence of such resonance stabilization (Table I). Furthermore, a low yield may be expected for palmitoin because of the hindrance in the approach of its large prerequisite aldehyde molecule to the thiazolium nucleus.

A variety of bases may be used to generate the catalytically active thiazolium ion.[21−23] The use of hydroxides was avoided since they are known to also cause opening of the thiazolium ring and render it inactive.[24] Alkoxides were also not considered since they are known to be excellent catalysts for aldol condensation of aliphatic aldehydes. Triethylamine, on the other hand, is a poor catalyst for aldol condensation and is incapable of opening the thiazolium ring. We have found that the use of two equivalents of triethylamine produces optimal yields.

The convenience of this experimental procedure encouraged us to evaluate the potential use of the ionic liquid **1** in the synthesis of compounds of the type R′COCHOHR″ where R′ = aryl and R″ = alkyl, or vice versa (Scheme 3).
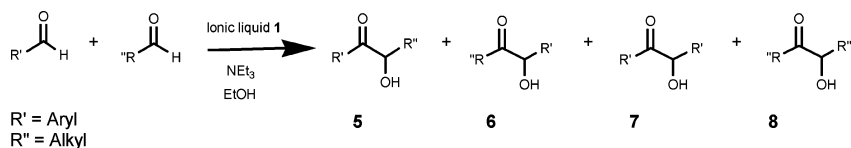
SCHEME 3
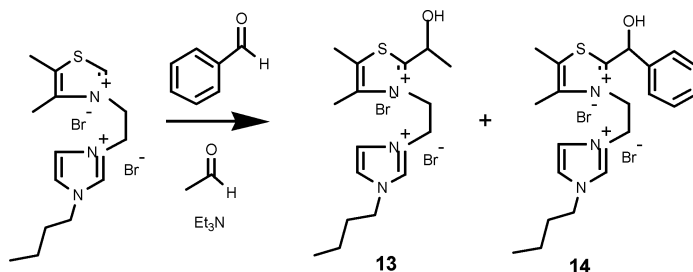
SCHEME 4

At first glance, the major shortcoming of such an approach would appear to be the equivalent possibility of concomitant formation of four different products. However, on further inspection it seems reasonable to assume that formation of **5** and **7** is favored over **6** and **8**. This is based on the fact that in the case of **5** and **7** the transition state of the reaction involves an imine α-carbanion which is further stabilized by resonance contribution of the aromatic ring (**14**, Scheme 4). Such a transition state is lower in energy and is therefore expected to be reached easier as compared to the transition state for the formation of **6** or **8** in which resonance stabilization is absent (**13**, Scheme 4). In fact, whereas benzoins are formed in 90% yields within a few hours with the ionic liquid **1**, acyloins could only be obtained in moderate to good yields after four days (see Table II).

It appears reasonable to assume that formation of benzoin (**7**, Scheme 3) may be suppressed by keeping the concentration of the aromatic aldehyde low during the course of the reaction, since most of the aromatic

TABLE II Synthesis of Compounds 5–8

Condition	5 + 6	7	8
(a)	73	6	n.d
(b)	62	10	n.d
(c)	57	14	n.d
(d)	43	20	n.d

(a) Both aldehydes added simultaneously.

(b) 1/2 Benzaldehyde added with acetaldehyde and 1/2 added after 24 h.

(c) 1/4 Benzaldehyde added with acetaldehyde and the rest added in 24 h intervals.

(d) Benzaldehyde added dropwise to the reaction mixture during 3 days.

n.d = not determined.

aldehyde would be presented in the form of "active aldehyde"[25−27] (**14**, Scheme 4) and little free aldehyde would be available for benzoin formation. It should be noted, however, that a low concentration of aromatic aldehyde and a very high concentration of aliphatic aldehyde would have two undesirable consequences. First, most of the catalyst would be tied up in the form of "active aliphatic aldehyde," leading mainly to the formation of acetoin and a very small amount of **6** (Scheme 3). Second, with diminishing availability of aliphatic aldehyde (due to acetoin formation), production of **5** and **6** will decrease, and the aromatic aldehyde will have no choice but to self condense (benzoin formation, see Table II).

It is, therefore, clear that to obtain good yields of **5** (or **6**), there should be an excess of aliphatic aldehyde available to the "active aromatic aldehyde." The use of an of excess aliphatic aldehyde and the reversibility of the formation of the "active aliphatic aldehyde" (*vide supra*) would fulfill such a requirement.

To test these hypotheses, we used a 2 : 2 : 2 : 10 : 20 molar ratio of ionic liquid **1** : triethyl amine : ethanol : benzaldehyde : acetaldehyde in a set of experiments. All reactions were run for four days with the only variable parameter being the mode of addition of the aromatic aldehyde to the reaction mixture. As shown in Table II, the best yield was obtained under condition **a** (Table II).

It is evident that due to the presence of triethylamine in the reaction medium, equilibrium may be established between **5** and **6** by simple keto-enol tautomerism. In most cases we observed a ca. 2 : 1 ratio of **5** : **6** by ^{1}H NMR. This, however, presents no difficulty since **6** may be quantitatively converted to **5** in ethanol using trace amounts of potassium carbonate (see Experimental). Furthermore, the conversion of **5** to **6** have also been reported to proceed in quantitative yields in both acidic and basic media.[28−30] Conversion of **5** to **6** under the influence of carboligase has also been reported.[29−32]

It should be noted that the synthesis of **5** or **6** by conventional means of C-C bond formation involves multi-step reaction sequences, leading to very poor yields of the hydroxy ketones.[28,30,33−36] Biochemical synthesis of these compounds involving thiamine-containing enzymes, also results in very poor yields.[32] In the present approach—due to the nature and conditions of the reaction—formation of acetoin and some benzoin is unavoidable. Nevertheless, these compounds, which are valuable in their own rights, may be easily separated from **5** and **6** by distillation because of the large differences in their boiling points.

It should be mentioned that, the presence of ethanol or isopropanol is necessary for the promotion of the reaction. For example, benzoin is obtained in 92% yield in the presence of ethanol. Under the same

conditions in the absence of ethanol the yield of the reaction was found to be 40%.

The solvent-catalyst is regenerated by heating at 70°C for 30 min under reduced pressure, mixing with ether containing 1% HCl, decanting, and heating at 80°C under vacuum for 30 min. It is advisable to devote a batch of the solvent-catalyst to one type of reaction. In this manner, after 5 cycles the same batch of ionic liquid was found to catalyze the benzion condensation of benzaldehyde in 90% yield.

EXPERIMENTAL

The ^{1}H NMR spectra were measured with a Jeol JNM-PMX60 spectrometer. Infrared spectra were obtain with a Perkin-Elmer 267 spectrophotometer. Thin layer chromatography was performed on silica gel (Macerey-Nagel Co., Plygram Sil G/uv 254). All chemicals were purchased from Aldrich.

3-(2-Bromoethyl)-4,5- dimethyl-1,3-thiazol-3-ium Bromide (3)

4,5-Dimethylthiazole (45.2 g, 0.4 mol) and 1,2-dibromoethane (75.2 g, 0.4 mol) were heated together in an oil bath (110°C) for 6 h. After cooling acetone (200 mL) was added and the crude solid product was filtered off and washed with acetone (2 × 50 mL). The precipitate was collected and recrystallized from ethanol / ether (2 : 1), mp = 185–186°C. ^{1}H NMR (DMSO-d6): δ = 10.3 (s, 1H), 5.1 (t, J = 6.2 Hz, 3H), 4.1 (t, J = 6.2 Hz, 3H), 2.6 (s, 6H).

3-[2-(1-Butyl-1*H*-imidazol-3-ium-3-yl)ethyl]-4,5-dimethyl-1,3-thiazol-3-ium Dibromide (1)

1-Butylimidazole (12.4 g, 0.1 mol) and 3-(2-bromoethyl)-4,5-dimethyl-1,3-thiazol-3-ium bromide (30.1 g, 0.1 mol) were allowed to react in DMF (100 mL) for 60 min at 110°C. The mixture was then diluted with diethyl ether (300 mL). The ether was decanted and fresh ether was added; this step was repeated twice. After the third decanting of ether, any remaining ether was removed by heating the mixture to 60°C and stirring while on a vacuum line. The pure oily product was obtained in quantitative yield. ^{1}H NMR (DMSO-d6): δ = 10.3 (s, 1H), 9.6 (s, 1H), 8.1 (s, 1H), 8.0 (s, 1H), 4.9 (br. s, 4H), 4.3 (t, J = 7.2 Hz, 2H), 2.6 (s, 6H), 1.6 (q, J = 7.2 Hz, 2H), 1.2 (m, 2H), 0.8 (t-like, 3H).

General Procedure for Preparation of Acyloins and Benzoins

A three-neck flask equipped with nitrogen inlet and outlet tubes and reflux condenser was charged with ionic liquid (85 g, 0.2 mol), ethanol (9.2 g, 0.2 mol), and triethylamine (20.2 g, 0.2 mol). To the stirring mixture—under nitrogen atmosphere—we added 1 mole of freshly distilled aldehyde. The mixture was heated at 80°C for the time specified in Table I and then allowed to cool to room temperature. The mixture was extracted with ethyl acetate (2 × 50 mL). The ethyl acetate was removed under reduced pressure. Palmitoin, benzoin, furoin, 4,4′-dinitrobenzaldehyde, and 4,4'-dimethylbenzaldehyde were recrystallized from ethanol. Bytyroin was purified by vacuum distillation.

Preparation of Compounds 5–8

Ionic liquid **1** (85 g, 0.2 mol), ethanol (9.2 g, 0.2 mol), and triethylamine (20.2 g, 0.2 mol) were mixed at room temperature. Under nitrogen atmosphere, a mixture of acetaldehyde (88 g, 2 mol) and benzaldehyde (106 g, 1 mol) were added dropwise to the suspension. After 4 days at room temperature, the reaction mixture was extracted with ethyl acetate. Ethyl acetate, ethanol and acetoin were removed from the mixture by distillation at atmospheric pressure. The residue, distilled under reduced pressure, gave a mixture of **5** and **6** (bp[13]: 130–135°C). Benzoin (m.p.: 136–137°C) was separated from the residue by crystallization from ethanol.

Conversion 1-Hydroxy-1-phenylpropane-2-one (6) to 2-Hydroxy-1-phenylpropane-1-one (5)

A mixture of **5** and **6** (3 g, 0.02 mol) in ethanol (40 mL) was added to a solution of sodium potassium carbonate (0.276 g, 0.002 mol) in water (15 mL). After 8 days at room temperature, the mixture was extracted with ether. The ethereal layer was dried and evaporated to dryness. The product was obtained as a pure oil (100%).

REFERENCES

[1] J. D. Holbrey and K. R. Seddon, *Clean Products and Process,* **1,** 223 (1991).

[2] T. Welton, *Chem. Rev*., **99,** 2071 (1999).

[3] R. D. Rogers and K. R. Seddon, *Ionic Liquids: Industrial Application to Green Chemistry*, (ACS, Washington DC, 2002). ACS Symposium Series 818.

[4] C. M. Gordon, A. J. McLean, M. J. Muldoon, and I. R. Dunkin, *Photochemistry in Ionic Liquids*, (ACS, Washington DC, 2002) ACS Symposium Series 818.

[5] W. Lu, A. G. Fadeev, B. Qi, and B. R. Mattes, *Synth. Met.*, **139,** 136 (2003).

[6] C. L. Hussey, *Pure Appl. Chem.*, **60,** 1763 (1988).

[7] S. T. Handy, M. Okello, and G. Dickenson, *Org. Lett.*, **5,** 2513 (2003).

[8] L. C. Branco and C. A. M. Afonso, *J. Org. Chem.*,**69,** 4381 (2004).

[9] H. L. Ngo, K. LeCompt, L. Hargens, and A. B. McEwen, *Thermochim. Acta*, **357,** 97 (2000).

[10] J. G. Huddleston, A. E. Visser, W. M. Reichert, H. D. Willauer, G. A. Broker, and R. D. Rogers, *Green Chem.*, **3,** 156 (2001).

[11] D. Bonhote, A. P. Dias, N. Papageogiou, K. Kalyanasundaram, and M.Gratzel, *Inorg. Chem.*, **35,** 1168 (1996).

[12] G. Yanlong, S. Feng, and D. Yoiquan, *Catal. Commun.*,**4,** 597 (2003).

[13] B. C. Ranu and S. Banerjee, *Org. Lett.*,**7,** 3049 (2005).

[14] J. M. D. Storey and C. Williamson, *Tetrahedron Lett.*,**64,** 7337 (2005).

[15] D. Enders and U. Kallfass, *Angew. Chem. Int. Ed.*,**41,** 1743 (2002).

[16] D. Enders, K. Breuer, U. Kallfass, and T. Balensiefer, *Synthesis*, **8,** 1292 (2003).

[17] R. L. Knight and F. J. Leeper, *Tetrahedron Lett.*, **38,** 3611 (1997).

[18] C. A. Dvorak and H. V. Rawal, *Tetrahedron Lett.*, **39,** 2925 (1998).

[19] R. R. Williams, R. E. Waterman, and E. R. Buchman, *J. Am. Chem. Soc.*, **57,** 536 (1935).

[20] K. Karimian, M. Askari, M. Farahani, and N. Sachinvala, *Synthesis*, 48 (1981).

[21] A. Takamizawa, K. Hiari, K. Hamushima, and S. Mitsumoto, *Tetrahedron Lett.*, 5071 (1967).

[22] K. Karimian, F. Mohtarami, and M. Askari, *J. Chem. Soc. Perkin Trans. II*, 1538 (1981).

[23] H. Stetter and G. Dambkes, *Synthesis,* 403 (1977).

[24] T. C. Bruice and S. Benkovic, *Bioorganic Mechanisms* (W. A. Benjamin Inc., New York, 1966) Vol. 2.

[25] J. P. Kuebrich and R. L. Schowen, *J. Am. Chem. Soc.*, **93,** 1220 (1971).

[26] J. P. Kuebrich, R. L. Schowen, S. M. Wang, and M. E. Lupes, *J. Am. Chem. Soc.*, **93,** 1241 (1971).

[27] J. Correia, *J. Org. Chem.*, **48,** 3343 (1983).

[28] T. I. Teminkova, *J. Gen Chem.*, USSR, **10,** 468 (1940).

[29] E. M. Kotchergine, *Bull. Soc. Chim.*, **43,** 573 (1928).

[30] A. Favorskii, *Bull. Soc. Chim.*, **39,** 216 (1926).

[31] K. V. Auwers and H. Mauss, *Biochem. Z.*, **192,** 200 (1928).

[32] K. V. Auwers, *Biochem. Z.*, **289,** 390 (1937).

[33] G. Richard, *Compt. Rend.*, **214,** 673 (1942).

[34] P. L. Jullian and J. Oliver, *J. Org. Synth. Coll.*, **II,** 391 (1943).

[35] K. Kaji and H. Nagshima,*J. Pharm. Soc. Japan*, **76,** 1247 (1956).

[36] M. Tsuruga, *Japanese Patent 5624*, Chem. Abstr., **51,** 1557i (1955).