Efficient Coupling Reactions of Arylalkynes and Aldehydes Leading to the Synthesis of Enones

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Ionic liquids such as 1-butyl-3-methyl-1*H*-imidazolium 4-methylbenzenesulfonate (BmimOTs) and its 1-ethyl analogue EmimOTs are novel effective and recyclable media for acid-catalyzed coupling reactions of aromatic alkynes with aldehydes affording (*E*)-enones (*Scheme 1*, *Table*) with simple recovery and easy workup due to the absence of volatile organic solvents. This transformation avoids the use of moisture-sensitive and heavy-metal *Lewis* acids.

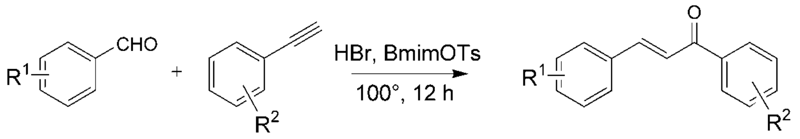
Introduction. – In past decades, the addition of alkynylmetal or alkyne reagents to aldehydes and ketones resulting in the formation of propargyl alcohols (= prop-2-yn-1-ols) has been extensively studied [1][2]. However, the novel reaction between alkynes and carbonyl compounds to give conjugated enones has received less attention. To the best of our knowledge, few descriptions of coupling of alkynes and aldehydes to enones have been reported [3]. Unfortunately, the reported methodology for the coupling reaction was found to be unsatisfactory and needed improvement.

During the last decade, the increasing environmental consciousness of the chemical community has led to the search for more efficient and environmentally friendly methods for organic synthesis [4]. One of the related significant progresses has been made by the application of ionic liquids in catalytic processes due to their very low vapor pressure and their capacity to dissolve easily many organic and inorganic substances [5]. Application of ionic liquids as novel media for catalytic hydrogenation, *Suzuki*-type and other cross-coupling reactions, oxidation reactions, *etc.*, has rapidly expanded [6]. Recently, the use of ionic liquids as *Lewis* acid catalysts and reaction media has developed into a very important field [7]. Recent work has demonstrated unique catalytic properties of ionic liquids in alkylation reactions, *Friedel–Crafts* reactions, and other reactions [8]. Compared to transition metal salts *Lewis* acid catalysts, ionic liquids have not been extensively explored as *Lewis* acid catalysts.

Herein, we report the first use of ionic liquids, such as 1-butyl-3-methyl-1*H*-imidazolium 4-methylbenzenesulfonate (BmimOTs), as a novel medium to promote the coupling reaction of alkyne and aldehydes.

Results and Discussion. – The ionic liquid BmimOTs was synthesized by using procedures similar to those used to prepare $BmimBF_4$ [9]. We first investigated the miscibility of BmimOTs with other chemicals (solvents). Thus, BmimOTs is miscible with H_2O, EtOH, amines, and aldehydes but immiscible with Et_2O, AcOEt, and toluene. The coupling of phenylacetylene and benzaldehyde in BmimOTs at 100° for 12 h was used as test reaction (*Scheme 1*; $R^1 = R^2 = H$). The results showed that the use of 1.2 equiv. of alkyne and 1.0 equiv. of aldehyde led in good yields to the (*E*)-enone. The (*E*)-configuration of the enone was determined by comparison of NMR and GCMS data with reported ones [3]. The 1-ethyl-3-methyl-1*H*-imidazolium 4-methylbenzenesulfonate (EmimOTs) is also an effective ionic liquid in this coupling reaction. However, when the reaction was run in H_2O (or DMF) and TsOH or HBr was used as a catalyst (20 mol-%) under reflux (100°), only minimal reaction took place, even after longer reaction periods. Similarly, no coupling product was obtained when the reaction was performed in other ionic liquids, such as $BmimBF_4$ or $BmimPF_6$. According to the above findings and the analysis of by-products, we propose that traces of HBr were probably responsible for the catalytic effect because BmimOTs was difficult to obtain free of HBr.

Scheme 1



Upon completion of the reaction, addition of H_2O to the reaction mixture precipitated the product, which was recovered in high yield by simple filtration. After evaporation of the residual H_2O, the ionic liquid was recycled and reused for the next run. The recycled ionic liquid BmimOTs with a drop of HBr per 1 mmol of benzaldehyde substrate could be reused five times without appreciable loss of activity for the coupling reaction of benzaldehyde and phenylacetylene. However, the ionic liquid without additional HBr led to only moderate yields after five runs.

A variety of aldehydes and alkynes were then examined for this ionic-liquid-promoted coupling reaction (see *Scheme 1* and the *Table*). Most of the obtained enones are interesting in organic synthesis and pharmacological industries [10]. Aromatic aldehydes with electron-donating and electron-withdrawing groups, including those bearing an alkoxy, chloro, bromo, or nitro substituent, were able to undergo the corresponding coupling reaction and displayed high conversions to the thermodynamically favored (*E*)-enones (*Entries 4–10*). The decreased yields for aliphatic aldehydes are due to the oxidation of the aliphatic aldehydes and resulted in the formation of the corresponding acids (*Entry 11*). With aliphatic alkynes or diphenylacetylene as the starting material, no reaction occurred, even after prolonged reaction periods (*Entries 2* and *3*).

When enolizable ketones and aromatic aldehydes in a 1:1 ratio were used as substrates in BmimOTs under the same conditions, high yields of enones were also achieved, as exemplified in *Scheme 2*. It is of interest to note that enones were also formed in high yields on coupling aromatic imines and phenylacetylene under the same conditions; no imine was detected in the final reaction mixture because of the poor stablility of imines in BmimOTs due to trace amounts of HBr, which might convert the imine to the aldehyde. The similarity of the alkyne and ketone coupling with aromatic

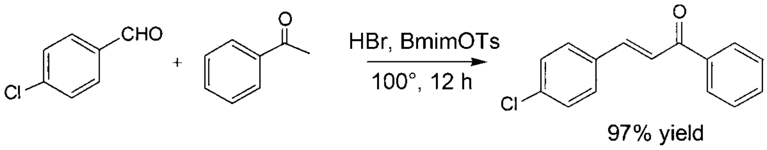
Table. *BmimOTs-Promoted Coupling Reaction of Alkynes and Aldehydes* (*cf. Scheme 1*)[a])

Entry	Aldehyde	Alkyne	Yield [%][b])
1	PhCHO	PhC≡CH	90
2	PhCHO	PhC≡CPh	trace
3	PhCHO	$Me(CH_2)_3C≡CH$	trace
4	$4-MeC_6H_4CHO$	PhC≡CH	84
5	$4-ClC_6H_4CHO$	PhC≡CH	95
6	$4-NO_2C_6H_4CHO$	PhC≡CH	94
7	$2-ClC_6H_4CHO$	PhC≡CH	78
8	$2-MeOC_6H_4CHO$	PhC≡CH	60
9	$3-MeOC_6H_4CHO$	PhC≡CH	78
10	$4-BrC_6H_4CHO$	PhC≡CH	89
11	$PhCH_2CH_2CHO$	PhC≡CH	65

[a]) Reaction conditions: aldehyde (2 mmol) and alkyne (2.4 mmol) in BmimOTs (3 ml) at 100° for 12 h.
[b]) Yield of isolated material.

aldehydes showed that hydrolysis of the alkyne might be a reasonable mechanism under the acidic conditions.

Scheme 2



It is known that the addition of HBr to acetylene is difficult and requires a catalyst [11]. However, we found that acetophenone (**3**) was formed on hydrolysis of phenylacetylene (**1**) alone under the coupling conditions described above (*Scheme 3*). On the basis of these results, we suggest that in the coupling reaction, the enone was not formed by isomerization of the 1,3-di-arylpropargyl alcohol (=1,3-diaryprop-1-yn-1-ol), an intermediate that was not observed under the coupling conditions. Instead, we propose a reasonable mechanism involving as the first step the addition HBr to the alkyne, promoted by the ionic liquid (*Scheme 3*). The intermediate **2** could then be hydrated by H_2O to form the corresponding acetophenone (**3**), which reacts with the aldehyde to give the corresponding enone. Thus, acetophenones could be the crucial intermediates. The proposed mechanism is supported by the formation of trace amounts of intermediate **2** and ketone **3** as detected by GCMS.

In conclusion, we showed that ionic liquids such as BmimOTs and EmimOTs are good recyclable media in promoting the acid-catalyzed coupling reaction between an arylalkyne and an aromatic aldehyde affording the thermodynamically favored (*E*)-enone. This interesting process compares favorably with earlier reported methodologies, especially in terms of simple recovery, easy workup, absence of volatile organic solvents, and avoidance of moisture-sensitive and heavy metal *Lewis* acids.

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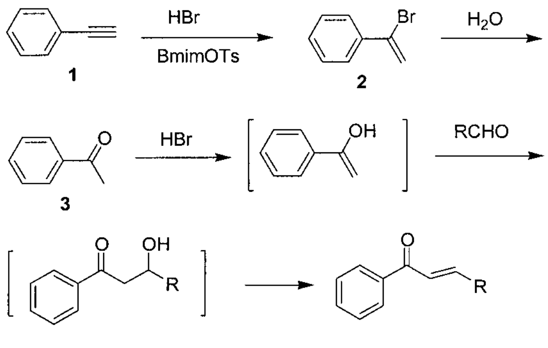
Scheme 3



Experimental Part

General. All solvents and reagents were used without purification. All the products were fully characterized by GC/MS (*Agilent-6890N-GC/5973N* and *HP-5* spectrometers) and usual spectral methods. TLC: silica gel F_{254} plates; visualization under ultraviolet light. Flash column chromatography (FC): silica gel (100–200 mesh). IR spectra: FT-IR apparatus. ^1H- and ^{13}C-NMR spectra: 400 and 100 MHz, resp., referenced to the internal solvent signals.

*1-Butyl-3-methyl-1*H*-imidazolium 4-Methylbenzenesulfonate (*BmimOTs*).* To BmimBr at r.t., a small amount of H_2O was added with stirring, and then TsOH (1 equiv.) was added slowly. The mixture was stirred for an additional period of 4 h. Then the H_2O was evaporated at 70° to give BmimOTs.

Coupling Reaction of Alkynes with Aldehydes, General Procedure. To a mixture of aldehyde (2.0 mmol) and arylalkyne (2.4 mmol), the ionic liquid BmimOTs (3 ml) was added, and strirring was continued at 100° for 12 h. After completion of the reaction, H_2O (10 ml) was added at r.t., and the precipitated product filtrated. The crude product was purified by FC (silica gel, petroleum ether/AcOEt 15:1).

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