Solvent-free synthesis of unsaturated ketones by the Saucy–Marbet reaction using simple ammonium ionic liquid as a catalyst

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Simple ammonium ionic liquids are efficient catalysts in promoting Saucy–Marbet reactions of unsaturated alcohols with unsaturated ethers to afford the corresponding unsaturated ketones, eliminating the need for volatile organic solvents. The effect of the anions and the cations of ionic liquids, quantity of ionic liquid, temperature, and chain-length of unsaturated alcohols on the reaction was investigated. The results showed that the Saucy–Marbet reaction was heavily influenced by the acidity of ionic liquid and $[Et_3NH][HSO_4]$ had the best catalytic activity. The conversion and selectivity obtained with this method are significantly increased in comparison to those catalyzed by traditional acid. Furthermore, the ionic liquid could be easily separated and reused with a slight loss of its activity. It provided a good alternative way for the industrial synthesis of unsaturated ketones.

Introduction

There is a growing need for greener and more sustainable processes in the chemical industry. Replacement or elimination of some toxic reagents or volatile organic solvents in chemical processes is one of the main goals of green chemistry. It is well known that unsaturated ketones such as 2-methyl-2-hepten-6-one, pseudoionone, and farnesylactone, are important substances and intermediates of flavors, fragrances, pharmaceuticals, and other fine chemicals.[1] The conventional method for the production of these unsaturated ketones is the Carroll reaction of unsaturated alcohols with alkyl acetoacetates in the presence of organic aluminium compounds.[2] The drawback of this method is a large amount of carbon dioxide—an atmospheric greenhouse gas that contributes to global warming—would be produced as a byproduct. An alternative method is the Saucy–Marbet reaction of unsaturated alcohols with unsaturated ethers.[3] For example, 6,10-dimethyl-4,5,9-undecatrien-2-one, a key intermediate of Vitamin E and Vitamin A, could be produced from 3,7-dimethyloct-6-en-1-yn-3-ol (dehydrolinalool) and 2-ethoxypropene by using the Saucy–Marbet reaction.[4] This reaction can be carried out in the presence of various acids used as catalysts, such as sulfuric acid, phosphoric acid, *p*-toluene sulfonic acid, trichloroacetic acid, and so on. The separation and recycling of catalysts are difficult. Furthermore, this reaction usually calls for volatile organic solvents such as halohydrocarbon, toluene, and petroleum ether,[5] otherwise the selectivity would obviously reduce. Despite numerous attempts to overcome these drawbacks, no benign methods with the advantages of easy separation, convenient recycling, and eliminating the need for volatile organic solvents have so far appeared for the synthesis of unsaturated ketones.

In recent years, ionic liquids have attracted more and more attention due to their special properties, such as an almost undetectable vapor pressure, high thermal stability, non-explosive properties, and strong solvent power for a wide range of organic, inorganic, and polymeric molecules.[6] Some ionic liquids have been successfully used as environmentally benign solvents or catalysts in a number of reactions,[7] such as the Diels–Alder reaction,[8] the Friedel–Crafts reaction,[9] esterification,[10] cracking reactions,[11] and so on. Among these ionic liquids reported in the past several years, a great deal of attention has been given to imidazolium ionic liquids. However, the industrial application of these imidazolium ionic liquids is limiting because of the difficult preparation, expensive cost and high toxicity.[12] Recently, some non-imidazolium ionic liquids such as phosphonium and ammonium ionic liquids have drawn much attention. For example, Bradaric *et al.* reported the industrial preparation of some representative phosphonium ionic liquids and discussed the comparisons with relevant imidazolium ionic liquids.[10] Han *et al.* presented the synthesis of guanidinium ionic liquids and an application for the desulfurization of flue gas.[14] Dai *et al.* reported a new family of cost-effective, highly proton conductive room temperature ionic liquids based on *N*,*N*-dimethylformamide and its potential application in the fuel cell industry.[15] Furthermore, we have succeeded in the industrial preparations of series of simple ammonium ionic liquids and the industrial application in the production of cinnamic acid using these ionic liquids as solvents and catalysts.[16] In special cases, these simple ammonium ionic liquids have attracted considerable interest in industry because of their advantages which include easy preparation, cheap cost, and low toxicity.

Being a part of our systematic research into ammonium ionic liquids and continuing our investigations into industrial applications, herein we reported a benign approach to

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Table 1 The effect of ionic liquids on the Saucy–Marbet reaction[a]

Entry	Catalyst	$T/°C$	Conv.(%)	Select.(%)
1	$[Et_2NH_2]HSO_4$	95	81	91
2	$[Et_3NH]HSO_4$	95	88	97
3	$[Pr_3NH]HSO_4$	95	85	95
4	$[Bu_3NH]HSO_4$	95	83	92
5	$[Et_3NH]H_2PO_4$	95	70	96
6	$[Hmim]HSO_4$	95	85	94
7	$[Bmim]H_2PO_4$	95	68	95
8	$[Bmim]PF_6$	Reflux	Trace	—
9	$[Bmim]BF_4$	Reflux	2	85
10	[Bmim]Cl	Reflux	Trace	—
11	[Bmim]Tfa	Reflux	8	97
12[b]	PTSA	95	89	72
13[c]	PTSA + Toluene	95	86	96

[a] Dehydrolinalool (0.05 mol), 2-ethoxypropene (0.15 mol), catalyst (0.25 mmol). [b] *p*-Toluene sulfonic acid was used. [c] *p*-Toluene sulfonic acid was used catalyst, and 20 ml toluene was used as solvent.

unsaturated ketones *via* Saucy–Marbet reactions catalyzed by simple ammonium ionic liquids under solvent-free conditions. High conversion and good selectivity could be obtained with these ammonium ionic liquids, eliminating the need for a volatile organic solvent and additional catalyst. In particular, these ionic liquids are very easy to be separate and reuse.

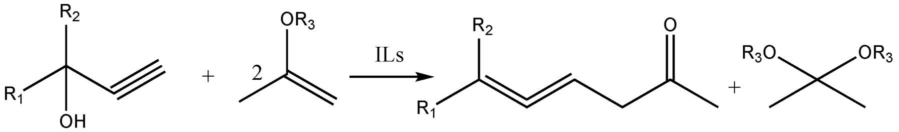
Results and discussion

The reaction of dehydrolinalool with 2-ethoxypropene was firstly used as an example to investigate the effect of ionic liquid on the Saucy–Marbet reaction (Scheme 1). Table 1 lists the effects of different ionic liquids on the reaction without any volatile solvent. It was clear that both conversion and selectivity of the reaction were heavily influenced by the anions of ionic liquids. The high conversion and good selectivity could be obtained when the strongly acidic HSO_4^- anion was used (Table 1, entries 1–5). For example, the conversion of 88% and selectivity of 97% were achieved when $[Et_3NH]HSO_4$ was used. However, the reaction was very slow, and therefore the conversion was lower than 10%, when neutral ionic liquids (Table 1, entries 9, 11) such as $[Bmim]BF_4$ were used. Furthermore, the reaction did not proceed at all in the presence of the $[Bmim]PF_6$ and [Bmim]Cl ionic liquids. When the $H_2PO_4^-$ anion was used (Table 1, entry 5), although the selectivity of the reaction was higher than 95%, the conversion of dehydrolinalool was clearly lower than those obtained with $[Et_3NH]HSO_4$ due to the weaker acidity of the dihydrogen phosphate ionic liquid. Above all, the results showed that the Saucy–Marbet reaction was heavily influenced by the acidity of ionic liquid.

To obtain the higher conversion and selectivity, five different bisulfate ionic liquids were used in the reaction, also listed in Table 1. It was found that the conversion of dehydrolinalool would decrease when the chain-length of the ionic liquids increased due to its higher lipophilic character.[17] Compared with the effect of the anions, the effect of chain-length of the cations was weak. $[Et_3NH]HSO_4$ might be the best catalyst for the Saucy–Marbet reaction in all the ionic liquids, due to its cheap cost, low toxicity and convenient preparation.

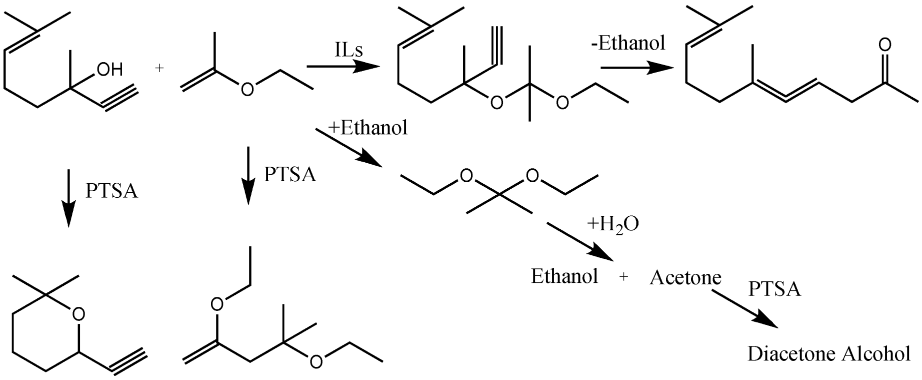
An important feature of the reaction catalyzed by bisulfate ionic liquids is that there is no evidence for significant formation of a side reaction, which may be related to the mild acidity of the ionic liquid.[18] During the reaction, the intermediate 3-(1-ethoxy-1-methylethoxy)-3,7-dimethyl-6-octen-1-yne could transform gradually to the desired product 6,10-dimethyl-4,5,9-undecatrien-2-one, and diethoxypropane would be formed by reaction of 2-ethoxypropene and ethanol, which were identified by GC-MS. However, the volatile organic solvent such as toluene was necessary when this reaction was carried out using *p*-toluenesulfonic acid (PTSA) as a catalyst. Otherwise, the selectivity would decrease significantly to 72%. The side products such as 2,6,6-trimethyl-2-ethynyltetrahydro-2*H*-pyran and a 2-ethoxypropene dimer would form because of the strong acidity of *p*-toluentesulfonic acid (Table 1, entry 12). On the other hand, some other side products such as acetone and diacetone alcohol would also be produced due to the presence of water, which was formed by the reaction of *p*-toluene sulfonic acid and ethanol. Furthermore, the separation and recycling of *p*-toluene sulfonic acid are difficult because of the formation of *p*-toluenesulfonic acid ethyl ester. Based on previous reports[3–5] and the observed reaction products, the reaction pathways under solvent-free conditions could be postulated, which is shown in Scheme 2.

It should be noted that the influence of the concentration of the ionic liquid on the reaction was strong. As can be seen in Table 2, the conversion of the reaction was low when the concentration of the ionic liquid was lower than 0.2%. And the selectivity would decrease when the quantity of the ionic liquid was higher than 5.0% because of the formation of side products such as 2-ethoxypropene dimers, acetone, diacetone alcohol, 2,6,6-trimethyl-2-ethynyltetrahydro-2*H*-pyran, and so on. Therefore, the optimal concentration of the ionic liquid to use as a catalyst is about 0.5%. In addition, the reaction seemed to be heavily influenced by the temperature (Table 2, entries 2, 5, 6). The conversion would reduce from 88% to 52% when the temperature of the reaction decreased from 95 °C to 75 °C. At the same time, the selectivity would decrease remarkably from 98% to 45% due to the fact that the thermal cracking



R_1=CH_3
R_2=H or $(CH_3)_2CCH(CH_2)_2$ or $(CH_3)_2CCH(CH_2)_2(CH_3)CCH(CH_2)_2$
R_3=CH_3 or CH_2CH_3

Scheme 1 Saucy–Marbet reaction catalyzed by ionic liquids.



Scheme 2 Postulated reaction pathways under solvent-free conditions.

Table 2 The effect of temperature and concentration of ionic liquid on the Saucy–Marbet reaction[a]

Entry	Concentration	T (°C)	Conv. (%)	Select. (%)
1	0.2%	95	73	95
2	0.5%	95	88	97
3	1.0%	95	89	95
4	5.0%	95	92	84
5	0.5%	85	75	86
6	0.5%	75	52	45

[a] Dehydrolinalool (0.05 mol), 2-ethoxypropene (0.15 mol), $[Et_3NH]HSO_4$ (0.25 mmol).

Table 3 The effect of unsaturated alcohol and 2-alkoxypropene on the Saucy–Marbet reaction[a]

Entry	Unsaturated alcohol	2-alkoxypropene	Conv. (%)	Select. (%)
1	2-methyl-3-butyn-2-ol	2-ethoxypropene	91	98
2	Dehydronerolidol	2-ethoxypropene	80	93
3	Dehydrolinalool	2-methoxypropene	90	98
4	Dehydronerolidol	2-methoxypropene	84	95

[a] Unsaturated alcohol (0.05 mol), 2-alkoxypropene (0.15 mol), $[Et_3NH]HSO_4$ (0.25 mmol), 95 °C.

of the intermediate to the desired product is difficult at lower temperatures.

To test the influence of chain-length of unsaturated alcohols on the Saucy–Marbet reaction, 2-methyl-3-butyn-2-ol and dehydronerolidol were also investigated. It is shown in Table 3 that the conversion and selectivity of 2-methyl-3-butyn-2-ol would increase in comparison to dehydrolinalool. On the contrary, when the long chain unsaturated alcohol such as dehydronerolidol was used, the conversion in chain length of unsaturated alcohols. Furthermore, the effect of different 2-alkoxypropene on the reaction was investigated, which is also listed in Table 3. The results indicated that the conversion of 90% and selectivity of 98% were obtained owing to the higher activity of 2-methoxypropene (Table 3, entry 3), when 2-methoxypropene was used instead of 2-ethoxypropene.

Table 4 The recycling of ionic liquid $[Et_3NH][HSO_4]$[a]

Entry	Cycle no.	Conv. (%)	Select. (%)
1	0	88	97
2	1	85	93
3	2	87	95
4	3	84	94
5	4	86	95

[a] All reactions were carried out at 95 °C.

The separation of products and ionic liquid is very easy because the raw materials and products are immiscible with water, while the ionic liquid is hydrophilic. When the reaction was completed, after distilling off the low boiling mixtures, such as 2-ethoxypropene and formed diethoxypropane, in high vacuum, water was added. Then the aqueous phase was separated from the organic phase by phase separation, and the ionic liquid could be recycled by separating out water under reduced pressure from the aqueous phase. It was necessary to remove traces of water because even a small amount of water in the ionic liquid would affect the Saucy–Marbet reaction. The product with a purity of 98.5% was isolated using vacuum distillation, which showed that ionic liquids did not contaminate it, although some of these ionic liquids were volatile.[19] It is shown in Table 4 that the ionic liquid could be recycled with a slight loss of its activity. It seemed that $[Et_3NH]HSO_4$ could have the potential to be used more than five times.

Experimental

Materials

2-Methyl-3-butyn-2-ol (>99%), 3,7-dimethyl-oct-6-en-1-yn-3-ol (dehydrolinalool, >99%), and 3,7,11-trimethyl-dodec-10-en-1-yn-3-ol (dehydronerolidol, >98.5%) were provided by Zhejiang NHU Co., Ltd. 2-Methoxypropene (>99%) and 2-ethoxypropene (>99%) were provided by Zhejiang Jubang Hi-Tech Corporation. Sulfuric acid, phosphoric acid, trifluoroacetic acid, *p*-toluenesulfonic acid, diethylamine, triethylamine, *n*-tripropylamine, *n*-tributylamine, 1-methylimidazole, toluente, *n*-butyl bromide, *n*-butyl chloride, sodium bisulfate, sodium hexafluorophosphate, and sodium tetrafluoroborate were all used as received unless otherwise stated.

Instruments

The NMR spectra of the ionic liquids and unsaturated ketones were recorded with a 500 MHz Bruker spectrometer in DMSO or $CDCl_3$ and calibrated with tetramethylsilane (TMS) as the internal reference. Samples of the reaction mixture were analyzed regularly to monitor the reaction by gas chromatography. The products and intermediates were identified by HP5973 GC-MS with a DP17 column (30 m × 0.25 mm × 0.25 μm) by comparing retention times and fragmentation patterns with authentic samples. The reaction conversion and selectivity were determined using GC112A equipped with an ATSE-30 column (30 m × 0.25 mm × 0.25 μm) and a flame ionization detector. Ethyl benzoate (99.9%) was applied as an internal standard for quantitative analysis.

Typical Saucy–Marbet reaction procedure

The simple ammonium ionic liquids of general type [amine][acid] were synthesized according to our former paper.[16] The NMR data and other physical properties of these simple ammonium ionic liquids in this paper are in good agreement with our early reports. Other ionic liquids used in this paper were synthesized according to standard literature methods.[20] A batch reactor, which composed of a four-neck flask connected with a reflux condenser, mechanical stirrer and an oil bath equipped with a thermostat, was used for this reaction. In a typical Saucy–Marbet procedure, the 2-ethoxypropene (12.9 g, 0.15 mol) was added slowly to the mixtures of dehydrolinalool (7.6 g, 0.05 mol) and triethylamine bisulfate ionic liquid (0.05 g, 0.25 mmol) at 90 °C and stirred for 2 h. Then the reaction mixture was stirred for an additional period of 24 h at 95 °C. After the reaction was completed, the low boiling mixtures were distilled off under reduced pressure, and water was added. The organic phase was separated and analysed by gas chromatography (typical data are listed in Table 1 and Table 2). The ionic liquids in the aqueous phase could be collected and reused by evaporating off water in high vacuum. The product of 8.0 g was obtained by using vacuum distillation with a purity of 98.5%. The main impurity was 2,6,6-trimethyl-2-ethynyltetrahydro-2*H*-pyran and dehydrolinalool. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.91 (s, 9H), 2.01–2.26 (m, 7H), 5.07 (m, 1H), 5.99 (d, 1H), 6.10 (d, 1H), 7.40 (m, 1H); IR (v cm^{-1}): 2966.6, 2925.4, 2856.5, 1684.5, 1667.3, 1628.5, 1445.3, 1360.7, 1316.0, 1252.9, 973.8, 825.5; GC-MS, m/z: 41, 43, 69, 81, 109, 124, 149, 177, 192.

Conclusion

In summary, simple ammonium ionic liquids are highly efficient catalysts for Saucy–Marbet reactions of unsaturated alcohols with unsaturated ethers, eliminating the need for volatile organic solvents. The effect of ionic liquid on the Saucy–Marbet reaction was investigated and the results showed that the Saucy–Marbet reaction was heavily influenced by the acidity of ionic liquid. The high selectivity of 97% and good conversion of 88% could be obtained using $[Et_3NH]HSO_4$ as the catalyst, which may be related to the mild acidity of ionic liquids. Furthermore, the separation and recycling of the ionic liquids were easy with only a slight loss of their activity. Considering the high conversion and good selectivity of this method, as well as the cheap cost, convenient preparation, and low toxicity of simple ammonium ionic liquid, it can provide a good alternative way for the industry synthesis of unsaturated ketones, which was also important to reduce carbon dioxide emissions from chemical industry.

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