Tetrahedron 66 (2010) 9145–9150

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of thermoregulated phase-separable triazolium ionic liquids catalysts and application for Stetter reaction

Feng-li Yu[a], Rui-li Zhang[a], Cong-xia Xie[a,*], Shi-tao Yu[b]

[a] State Key Laboratory Base of Eco-chemical Engineering, College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, China
[b] College of Chemical Engineering, Qingdao University of Science and Technology, Qingdao 266042, China

ARTICLE INFO

Article history:
Received 6 April 2010
Received in revised form 26 September 2010
Accepted 29 September 2010
Available online 15 October 2010

Keywords:
Thermoregulated phase-separable catalysis (TPSC)
Stetter reaction
Triazolium ionic liquids
Catalyst recycle

ABSTRACT

A series of polyether-substituted triazolium ionic liquids catalysts have been first synthesized for resolving the problem of separation and reuse of Stetter catalysts. The catalysts possess the properties of critical solution temperature (CST) and inverse temperature-dependent solubility in toluene/heptane solvents. Based on these properties, the catalysts can achieve the catalytic process named as thermoregulated phase-separable catalysis (TPSC) with the characteristic of homogeneous reaction at higher temperature and phase-separation at lower temperature. The novel TPSC system has been successfully applied for Stetter reaction of furfural or butanal with ethyl acrylate. The experimental results have showed that the novel catalysts exhibit excellent TPSC with high recycling efficiency.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

Aromatic or aliphatic aldehydes through the polarity reversal add to α,β-unsaturated ketones, esters, and nitriles to form γ-diketones, 4-oxo carboxylic esters, and 4-oxo nitriles, respectively. Such a type of reaction named after Hermann Stetter was first found in 1973.[1] Stetter reaction is ideal atom-economic reaction (100% yield in theory), and the study on this reaction has achieved great progress in about thirty years. In 1979, Trost first used intramolecular Stetter reaction for synthesis of the natural product of (±)-Hirsutic acid C.[2] The first example of stereoselective Stetter reaction was reported by Enders in 1996.[3] In 2004, Grée and his group first used imidazolium-type room temperature ionic liquids (RTILs) as Stetter reaction media with good yields.[4] The Stetter reaction of *p*-fluorobenzaldehyde with methyl acrylate in RTILs as a key step was applied for the synthesis of haloperidol, an antipsychotic drug. Currently, Stetter reaction is one of the most important reactions in organic synthesis. It is widely used in total synthesis of natural products,[5] stereoselective synthesis,[6] heterocyclic synthesis,[7] and electrochemical materials synthesis.[8]

The catalyst is the key of Stetter reaction smoothly proceeding. The currently developed catalysts have cyanide ions,[9] thiazolium salts,[10] triazolium salts,[11] and tributylphosphine.[12] The catalytic mechanisms of these catalysts are analogous. The addition of the catalyst to the aldehyde affords a stabilized carbanion, which then reacts with the electrophilic olefin to give the expected 1,4-adduct. At present, Stetter reaction has some problems, which have not been well resolved. One of main difficulties is the separation of the catalyst from products, and therefore it is difficult to recycle the catalyst. Furthermore, most Stetter reactions with low reaction rates need relatively long reaction time. In 2006, Yang reported the first example of a microwave-assisted intramolecular Stetter reaction in RTILs.[13] The reaction time was shorted to 5–20 min in excellent yield. Importantly, the thiazolium catalyst in RTILs was proved to be recyclable and reusable. In 2007, Zeitler and Mager synthesized immobilized thiazolium and triazolium catalysts by introducing MeOPEG-supported azide to the different heterazoles for Stetter catalysts reuse.[14] Recently, Li et al. have reported a novel and convenient strategy to separate, recover, and reuse *N*-heterocyclic carbene catalysts in transesterification reactions.[15] In this strategy, the catalyst can achieve a rapid precipitation from the solution by adding hydrogen chloride after reaction.

Though homogeneous catalysis has high catalytic activity, it has the main difficulty of separating the catalyst from the reaction mixture. To resolve this difficulty, fluorous biphase system (FBS)[16] and some liquid/liquid biphasic systems[17] both with the characteristic of 'homogeneous reaction, two-phase separation', which can achieve high catalytic activity as well as facile catalyst/product separation have been well developed. The concept of 'thermoregulated phase transfer catalysis (TRPTC)' based on the cloud point of nonionic phosphine ligand, in which the catalyst transfers into the organic

---

[*] Corresponding author. Tel./fax: +86 532 84023927; e-mail address: xiecongxia@126.com (C.-x. Xie).

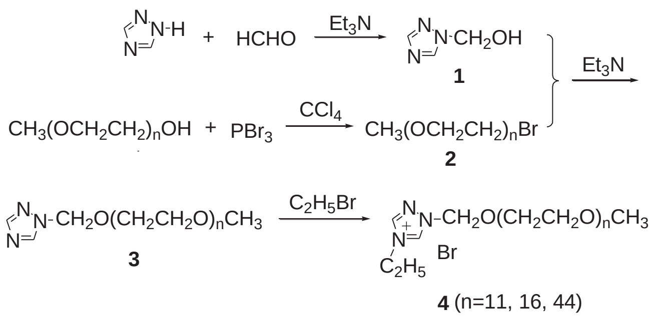
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.09.094

phase to catalyze the reaction at higher temperature and returns to the aqueous phase to be separated from the product at lower temperature, has widened the application scope of biphasic catalysis.[18] Based on the critical solution temperature (CST) of nonionic tensioactive phosphine ligand, a novel concept termed as thermoregulated phase-separable catalysis (TPSC), in which the catalyst itself becomes one-phase at room temperature and entirely dissolves in organic phase at higher reaction temperature, has been developed by Jin and Wang.[19] By simple decantation, the catalyst can be easily separated from products upon cooling of the reaction solution.

However, the catalysts in currently well developed systems mentioned above cannot apply for Stetter reaction. Therefore, we have designed and synthesized a series of novel thermoregulated triazolium ionic liquids catalysts for Stetter reaction by introducing a polyether chain to the triazole compound. It's proved that the new catalysts can achieve the process of TPSC in toluene/heptane solvents. Thus, the problem associated with the separation and reuse of Stetter catalysts can be well resolved. The novel TPSC system has been successfully applied for intermolecular Stetter reaction. The reactions of furfural and butanal with ethyl acrylate as two models have been investigated in detail. The results have showed that the novel catalysts exhibit excellent TPSC with high recycling efficiency.

2. Results and discussion

A series of novel thermoregulated triazolium ionic liquids catalysts were synthesized by introducing different lengths of polyether chain to the triazole compound. The total process of synthesis was shown in Scheme 1. 1*H*-1,2,4-Triazole reacted with paraformaldehyde in the presence of Et_3N to give 1-hydroxymethyl-1,2,4-triazole **1**. Poly(ethylene glycol) monomethyl ether with different number of polymerized ethylene oxide unit n ($n=11$, 16, 42) reacted with PBr_3 to afford bromine-substituted poly(ethylene glycol) monomethyl ether **2**. Then, compound **1** reacted with compound **2** to give polyether-substituted triazole compound **3**, which further reacted with bromoethane to obtain thermoregulated triazolium ionic liquids catalyst **4**. The total yield was about 50%. The structures of new compounds were confirmed by NMR. The catalysts **4** ($n=11$, 16, 42) newly synthesized are pale yellow and viscous liquids at room temperature. The viscosity increases with the length of polyether chain. In ^1H NMR spectrum of catalysts **4**, there is clearly the resonance of the CH-acidic triazolium proton at about $\delta=8.8$, which shows the existence of the precursor of active carbene species.



Scheme 1. The process of synthesis of thermoregulated triazolium ionic liquids catalysts.

2.1. Thermoregulated solubility of catalysts 4

The thermoregulated solubility of polyether-substituted nonionic phosphine ligands and their critical solution temperatures (CSTs) in nonpolar aprotic solvents have been reported.[20] The CST is the temperature from which the solubility increases markedly. The solubility of the novel triazolium ionic liquids catalysts **4** ($n=11$, 16, 42) on temperature has been, respectively, studied in toluene/heptane mixture solvents with different ratio. The results have showed that the catalysts **4** ($n=11$, 16, 42) exist at the CST and thermoregulated solubility in toluene/heptane (v/v)=1:1.5, toluene/heptane (v/v)=7:18 and toluene/heptane (v/v)=1:3, respectively. The corresponding solubility-temperature curves have been showed in Fig. 1. According to Fig. 1, when $n=11$, 16, 42, the CST of catalyst **4** appears at 40 °C, 60 °C, 65 °C, respectively. At room temperature, the catalyst **4** is hardly soluble. However, the solubility increases markedly when the temperature raises over the CST. One can see that the CST increases with the length of polyether chain. In addition, the reversibility of solubility is also observed. When the temperature decreases under the CST, the catalyst dissolved in solvents precipitates again.

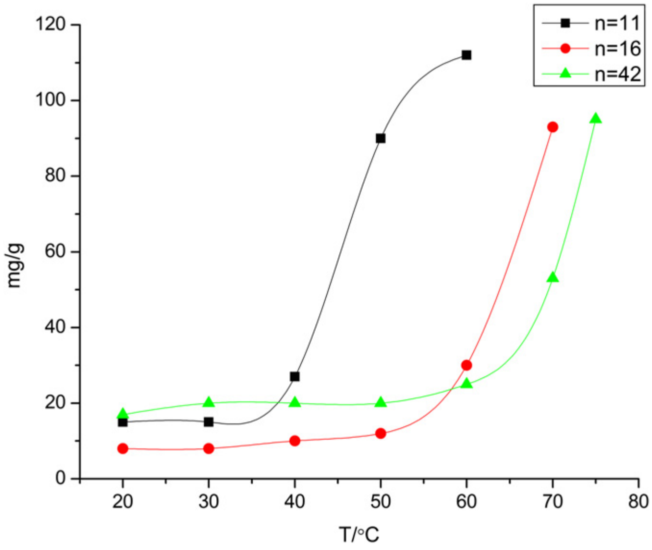
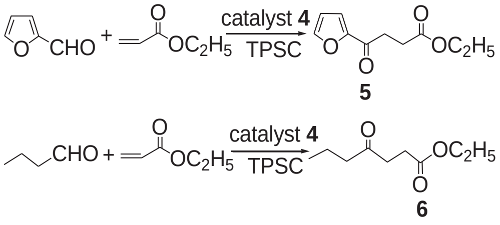


Fig. 1. Solubility-temperature curves of the triazolium ionic liquids catalysts **4** ($n=11$, toluene/heptane (v/v)=1:1.5; $n=16$, toluene/heptane (v/v)=7:18; $n=42$, toluene/heptane (v/v)=1:3).

2.2. TPSC for Stetter reaction of furfural or butanal with ethyl acrylate

The CST and inverse temperature-dependent solubility in toluene/heptane solvents enable the polyether-substituted triazolium ionic liquids catalysts **4** to achieve the catalytic process of TPSC. At room temperature, the viscous ionic liquids catalyst is at the bottom and insoluble in toluene/heptane solvents with the reagents. When heated to $T>$CST, the ionic liquids catalyst is completely soluble in organic solvents to homogeneously catalyze the reaction. After completion of the reaction, on cooling to room temperature ($T<$CST), the ionic liquids catalyst precipitates from the organic solvents accompanying the separation with the products. TPSC of the catalysts **4** ($n=11$, 16, 42) have been first applied for intermolecular Stetter reaction of aldehydes with α,β-unsaturated ester. The reactions of furfural and butanal with ethyl acrylate chosen as two models have been investigated in detail (Scheme 2).



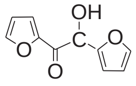
Scheme 2. Stetter reaction of furfural or butanal with ethyl acrylate.

Table 1
Stetter reaction of furfural or butanal with ethyl acrylate in the novel TPSC system

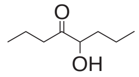
Entry	Aldeyde	n	Catalyst (mol %)	Time (h)	Temperature (°C)	Conversion (%)	Yield (%)
1	Furfural	11	20	12	40	92.3	40.2
2	Furfural	11	20	12	50	98.0	45.6
3	Furfural	11	20	12	60	98.5	45.8
4	Furfural	11	20	16	60	98.6	45.0
5	Furfural	11	15	12	60	96.5	43.4
6	Furfural	16	20	12	60	94.0	41.7
7	Furfural	16	20	12	70	99.1	48.5
8	Furfural	16	20	12	75	99.1	48.6
9	Furfural	16	15	12	70	99.0	48.3
10	Furfural	16	15	10	70	97.4	44.9
11	Furfural	16	10	12	70	87.6	38.9
12	Furfural	42	20	12	60	90.8	38.8
13	Furfural	42	20	12	70	94.0	40.6
14	Furfural	42	20	12	75	96.1	40.9
15	Furfural	42	25	12	75	96.5	41.8
16	Butanal	11	20	12	60	99.0	42.6
17	Butanal	16	20	12	70	99.0	44.9
18	Butanal	42	20	12	75	97.8	40.7

The reaction conditions of two Stetter reactions have been first optimized. The experimental results are listed in Table 1. The effect of reaction temperature on the Stetter reaction is studied. According to the entries 1–3, when the reaction temperature (T=50 °C) is higher than the CST (n=11, CST=40 °C), the conversion of furfural and the isolated yield of product obviously increase. Further increase of reaction temperature (T=60 °C) only results in slight increase of yield. The homogeneously reaction system can be observed when T>CST, and the result provides further proof for TPSC. When the reaction time prolongs from 12 to 16 h, the conversion varies slightly (entries 3 and 4). It shows that the reaction completes on the whole in 12 h. When the quantity of ionic liquids catalyst **4** decreases from 20 to 15 mol %, the conversion and the yield decrease accordingly (entries 3 and 5). According to Table 1, the selected optimum reaction conditions for the Stetter reaction of furfural with ethyl acrylate are as follows: n=11, the quantity of catalyst 20 mol %, toluene/heptane (v/v)=1:1.5, the reaction temperature 50 °C, the reaction time 12 h (entry 2); n=16, the quantity of catalyst 15 mol %, toluene/heptane (v/v)=7:18, the reaction temperature 70 °C, the reaction time 12 h (entry 9); n=42, the quantity of catalyst 20 mol %, toluene/heptane (v/v)=1:3, the reaction temperature 75 °C, the reaction time 12 h (entry 14). However, n=16 seems to be the best result, because the conversion and the selectivity of Stetter product are relatively higher. It shows that the total length of polyether chain of catalyst **4** could affect its catalytic activity. There is little difference when n=11 or 16. The weaker catalytic activity of catalyst **4** (n=42) possibly results from large spatial effect, which makes it not well contact with reaction substrates. For the Stetter reaction of butanal with ethyl acrylate, the conversion of butanal can reach up to 97% and the isolated yield is higher than 40% under the optimum conditions (entries 16–18).

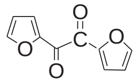
According to Table 1, the yield of Stetter reaction is relatively low, though higher than that of the corresponding Stetter reaction catalyzed by the thiazolium salt catalyst.[1] The lower selectivity of Stetter product is mainly due to that the reaction of catalytic carbanion with a second aldehyde molecule, which affords condensation byproduct is badly in competition with the Stetter reaction.[21] In addition, the polymerization of ethyl acrylate could occur at higher temperature. The main byproducts are determined by GC–MS in the Stetter reaction of ethyl acrylate with furfural or butanal. Molecular ion peak of 192 or 144 is obtained in two reactions. The self-condensation product of furfural or butanal, compound **7** or compound **8**, is distinguished according to the corresponding molecular ion and fragment ions. In the reaction of furfural with ethyl acrylate, another self-condensation product of compound **9** is also obtained with molecular ion peak of 190. Additionally, two reactions both have molecular ion peak of 200. It showed that two reactions both brought out the polymerization product of ethyl acrylate, and compound **10** is distinguished. Acrylic acid derived from ethyl acrylate hydrolysis reacts with another ethyl acrylate by Diels–Alder reaction to afford compound **10**. To our best knowledge, the best result is about 60% in imidazolium-type RTILs media.[4] Therefore, it is still a great challenge to improve the selectivity of Stetter product. Besides, the ethoxy chain of the catalyst **4** has a certain impact on the selectivity of Stetter product in our catalytic system. From Table 1, the longer ethoxy chain (n=42) makes the selectivity of Stetter product decrease. Therefore, the cation and the anion might have effects on catalytic activity for Stetter reaction.[22] It is possible that the selectivity of Stetter product could get further increase by changing triazole substrates as well as anions, such as BF_4^-, PF_6^- in thermoregulated triazolium ionic liquids catalysts, which will be investigated in further study.



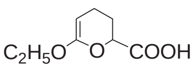
7



8



9



10

2.3. Catalyst recycle

TPSC has combined the advantages of a one-phase homogeneous catalysis with an easy way of catalyst separation. After the reaction, the reaction mixture is cooled to room temperature. The upper organic phase with the product is separated from the lower ionic liquids catalyst by simple decantation. So, the lower ionic liquids catalyst can be recycled by adding fresh solvents and reaction substrates. Moreover, the lower ionic liquids catalyst is extracted with the organic solvent. The analysis result for the extract liquor has showed there is negligible Stetter product. Therefore, the solubility of Stetter product in the ionic liquids is very low, and the yield in recycle is reliable. Fig. 2 shows the recycling efficiency of the catalyst **4** (n=16) for the Stetter reaction of furfural with ethyl acrylate under the optimum reaction conditions. The conversion of furfural and yield primarily keep constant at the first five cycles. However, a slight decrease of the conversion and yield is observed from the sixth recycle. The results have indicated that the ionic liquids catalyst can be efficiently recycled five times without any significant loss of catalytic activity. In the Stetter reaction of butanal with ethyl acrylate, the conversion of butanal still can reach over 95% after the catalyst **4** (n=16) is recycled seven times.

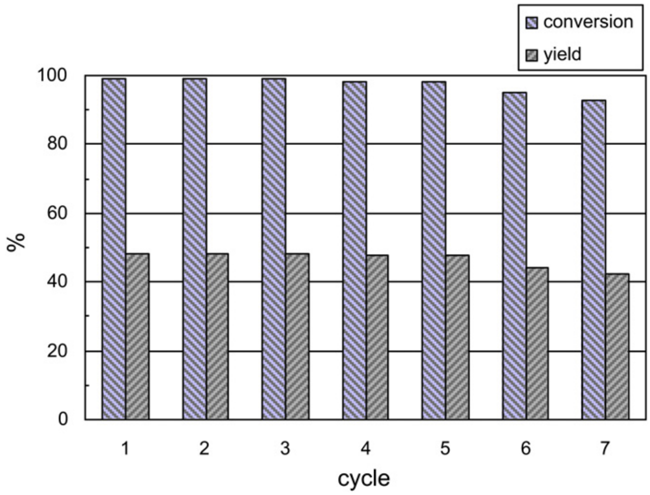


Fig. 2. Recycling efficiency of the catalyst **4** (n=16) in the Stetter reaction of furfural with ethyl acrylate.

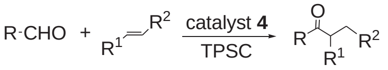
After seven cycles, the catalyst **4** (n=16) is recovered and weighed in the Stetter reaction of furfural with ethyl acrylate. The loss of 7.2% is found, which is agree with the calculated amount according to Fig. 1 (the solubility of ionic liquids, 7.0 mg/g at 20 °C) and the used solvents amount (20 mL) each cycle. If the temperature is reduced to 0–4 °C after the reaction each cycle, the loss of the ionic liquids catalyst can reduce to 4–5% accordingly. When the equivalent amount of lost catalyst is added, the conversion can restore to 99%. The recovered catalyst is determined by ^{1}H NMR. It's found that the structure of the catalyst doesn't change after recycle. Therefore, the catalyst has high stabilization and excellent recycling efficiency.

2.4. TPSC for Stetter reaction with different substrates

The above experiments results have showed the new developed TPSC system of thermoregulated triazolium ionic liquids catalysts can be successfully used for Stetter reaction of furfural or butanal with ethyl acrylate. To widen the application of the new TPSC system, different substrates of Stetter reaction are employed. The additions of different aldehydes to benzylideneacetophenone or acrylonitrile catalyzed by the catalyst **4** (n=16) have also been investigated under the selected reaction conditions, and the compared results are listed in Table 2.

The experiments results have showed the thermoregulated triazolium ionic liquids catalyst in the new developed TPSC system also has a certain catalytic activity for Stetter reaction of furfural or benzaldehyde with benzylideneacetophenone (entries 3 and 4), and the corresponding Stetter product is afforded. In these reaction systems, the self-condensation of aldehyde is in competition with Stetter reaction by the analysis of GC–MS. The lower Stetter selectivity may be increased by optimizing reaction conditions. More importantly, the above described process of TPSC is observed in these reactions. The ionic liquids catalyst can be recovered and reused. According to entries 5–7, the reaction of furfural with acrylonitrile only affords the corresponding Stetter product of 7.6%, and the reaction of benzaldehyde or butanal with acrylonitrile gives no Stetter product, though the conversions of aldehydes in these reactions are high. It shows the new catalytic system exhibits very low or even no catalytic activity for Stetter reaction of selected aldehydes with acrylonitrile under the experimental conditions. In these reaction systems, self-condensation of aldehyde and polymerization of acrylonitrile are mainly proceeded by the analysis of GC–MS. This agrees with the previous reports.[1] Stetter reaction of aldehydes to acrylonitrile catalyzed by thiazolium salt also gives low yield for the above reason. From Table 2, heteroaromatic furfural exhibits higher reactivity than benzaldehyde and butanal in all these Stetter reactions. Detailed research will be made in further work.

Table 2
Stetter reaction with different substrates in the new TPSC system[a]



5, 6, 11-13

Entry	R	R^1	R^2	Product	Conversion[b] (%)	Yield (%)
1	2-Furyl	H	$CO_2C_2H_5$	**5**	99.0	48.3
2	n-C_3H_7	H	$CO_2C_2H_5$	**6**	95.2	37.4
3	2-Furyl	C_6H_5	COC_6H_5	**11**	100.0	32.7
4	C_6H_5	C_6H_5	COC_6H_5	**12**	90.8	25.4
5	2-Furyl	H	CN	**13**	91.8	7.6
6	C_6H_5	H	CN	—	85.6	—
7	n-C_3H_7	H	CN	—	98.5	—

[a] Reactions conditions: the catalyst **4** (n=16), the quantity of catalyst 15 mol %, toluene/heptane (v/v)=7:18, the reaction temperature 70 °C, the reaction time 12 h.
[b] Conversion of aldehyde.

3. Conclusions

In summary, a series of novel thermoregulated triazolium ionic liquids catalysts for Stetter reaction by introducing a polyether chain to the triazole compound have been synthesized, and a novel TPSC system has been developed for resolving the problem associated with the separation and reuse of Stetter catalysts. The novel TPSC system has been successfully applied for intermolecular Stetter reaction. The reactions of furfural and butanal with ethyl acrylate as two models have been fully investigated. The reaction conditions are, respectively, optimized. The recycling efficiency of the catalyst is also studied. The results have showed the novel ionic liquids catalysts have exhibited not only excellent property of TPSC but also good recycling efficiency. Under the optimum reaction conditions, the catalyst can be reused five times without obvious loss of catalytic activity. The novel TPSC system has widened the application scope of liquid/liquid biphasic catalysis and provided a much potential route for environmentally benign synthesis.

4. Experimental

4.1. General

All chemicals were used as purchased and of chemically pure or reagent grade. The solvents were dried by known procedures and used freshly distilled. All the glass vessels were dried before use. The reaction products were analyzed by a Thermo Finnigan GC–MS. ^{1}H and ^{13}C NMR spectra were recorded with a Brucker AV 500 MHz spectrometer. The melting point was determined on a RY-1 microscopic melting apparatus and uncorrected.

*4.1.1. 1-Hydroxymethyl-1,2,4-triazole (**1**).* 1*H*-1,2,4-triazole (98%, 0.1 mol, 7.04 g), 96% paraformaldehyde (0.1 mol, 3.13 g), and catalytic amount of triethylamine were put into a 100 mL three-neck flask with a magnetic stirrer, a thermometer, and a reflux condenser. The resulted mixture was stirred and heated to melt. The reaction was kept for 0.5 h at the molten temperature. After that, the mixture was cooled to room temperature. Acetone was added to recrystallize. The product was desiccated under infrared lamp to give compound **1** (9.12 g, 92.1%) as a white solid: mp 68–69 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.73 (s, 2H), 7.48 (s, 1H), 8.13 (s, 1H), 8.65 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 71.2, 145.2, 157.4.

*4.1.2. Bromine-substituted poly(ethylene glycol) monomethyl ether (**2**).* Poly(ethylene glycol) monomethyl ether (10 mmol, *n*=11, 16, 42) and 20 mL CCl$_4$ were put into a 100 mL four-neck flask equipped with a thermometer, a reflux condenser, and a dropping funnel. Under the stirring, fresh distilled PBr$_3$ (15 mmol, 4.05 g) in 30 mL CCl$_4$ was slowly added dropwise to the poly(ethylene glycol) monomethyl ether solution. During the dropwise process, the temperature of the reaction solutions was kept at 30–40 °C. After finishing the addition, the temperature was elevated to 65–70 °C and the reaction solution was stirred for 5 h. After completion of the reaction, the product was separated from the reaction mixture with a separatory funnel. The upper light yellow liquid was washed twice with CCl$_4$ to afford compound **2** (*n*=11, 16, 42) as a pale yellow oil that was used without further purification.

*4.1.3. Polyether-substituted triazole (**3**).* 1-Hydroxymethyl-1,2,4-triazole **1** (5 mmol, 0.495 g) was first dissolved in 20 mL toluene. Then, 5 mmol of bromine-substituted poly(ethylene glycol) monomethyl ether **2** (*n*=11, 16, 42), and Et$_3$N (5 mmol, 0.505 g) were added. The resulted mixture was stirred and heated under reflux for 6 h. After completion of the reaction, the mixture was cooled to room temperature. Et$_3$N salt was separated from the solution by filtration, and the solvent was removed under atmospheric distillation to afford compound **3** (*n*=11, 16, 42) as a yellow oil. Yield: 75%–80%. Compound **3** (*n*=16): ^{1}H NMR (D$_2$O, 500 MHz) δ 3.12 (s, 3H), 3.30–3.80 (m, 64H), 5.56 (s, 2H), 8.25 (s, 1H), 8.86 (s, 1H); ^{13}C NMR (D$_2$O, 125 MHz) δ 30.5, 67.1–73.2, 145.0, 158.1.

*4.1.4. Thermoregulated triazolium ionic liquids catalyst (**4**).* Polyether-substituted triazole **3** (*n*=11, 16, 42) (10 mmol), bromoethane (10 mmol, 1.09 g), and 30 mL dried acetonitrile were mixed in a 100 mL round-bottomed flask with a reflux condenser (potassium hydroxide drying tube) and heated under reflux for 24 h. After cooling, the acetonitrile was removed under atmospheric distillation. The residue was washed twice with heptane to afford the product **4** (*n*=11, 16, 42) as a yellow and viscous liquid. Yield: 80%–83%. Compound **4** (*n*=16): ^{1}H NMR (D$_2$O, 500 MHz) δ 1.30 (t, *J*=7.2 Hz, 3H), 3.08 (s, 3H), 3.20–3.84 (m, 64H), 4.52 (q, *J*=7.2 Hz, 2H), 5.68 (s, 2H), 8.01 (s, 1H), 8.83 (s, 1H); ^{13}C NMR (D$_2$O, 125 MHz) δ 15.8, 32.2, 55.4, 69.2–77.8, 147.6, 160.3.

4.2. General procedure for Stetter reaction

Freshly distilled aldehyde (50 mmol) and α,β-unsaturated ester, ketone or nitrile (50 mmol), a certain amount of thermoregulated triazolium ionic liquids catalyst **4**, and the same amount of Et$_3$N, and the selected solvents were mixed together in a 100 mL round-bottomed flask with a reflux condenser. Under the stirring, the temperature raised to determinate temperature and kept for determinate time. After that, the reaction mixture was cooled to room temperature. By simple decantation, the upper organic phase containing products was separated from the ionic liquids catalyst, which was at the bottom of the flask. Subsequently, the organic phase was washed with water and then dried over MgSO$_4$. The solvents were removed by atmospheric distillation and the residue was purified by fractional distillation, recrystallization or flash chromatography on silica gel to afford corresponding Stetter product.

*4.2.1. 4-Oxo-4-(2-furyl)-butyric acid ethyl ester (**5**).* The residue was recrystallized from acetone to afford compound **5** as a white needle-shaped crystal: mp 52–53 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.24 (t, *J*=7.0 Hz, 3H), 2.73 (t, *J*=6.8 Hz, 2H), 3.16 (t, *J*=7.0 Hz, 2H), 4.15 (q, *J*=7.0 Hz, 2H), 6.55 (t, *J*=7.1 Hz, 1H), 7.24 (d, *J*=6.9 Hz, 1H), 7.60 (d, *J*=6.9 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 14.19, 27.90, 33.07, 60.72, 112.26, 117.07, 146.38, 152.43, 172.70, 187.39; MS *m*/*z* (relative intensity, %) 197 (0.85, M^{+}+1), 196 (8.62, M^{+}), 151 (15.08), 95 (100), 67 (9.87), 55 (11.67).

*4.2.2. 4-Oxo-heptanoic acid ethyl ester (**6**).* The residue was vacuum distilled to afford compound **6** as a colorless oil: 88–90 °C/13 mmHg; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 0.82 (t, *J*=7.2 Hz, 3H), 1.14 (t, *J*=7.1 Hz, 3H), 1.50 (m, 2H), 2.32 (t, *J*=7.1 Hz, 2H), 2.46 (t, *J*=7.0 Hz, 2H), 2.61 (t, *J*=7.0 Hz, 2H), 4.01 (q, *J*=7.1 Hz, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 13.62, 14.08, 17.20, 28.86, 36.98, 44.61, 60.52, 172.82, 209.09; MS *m*/*z* (relative intensity, %) 145 (0.55, M^{+}+1), 144 (7.87, M^{+}), 127 (19.23), 101 (45.78), 71 (58.87), 43 (100).

*4.2.3. 2,4-Diphenyl-1-(2-furyl)-1,4-butanedione (**11**).* The residue was chromatographed on silica gel using 9:1 hexane/EtOAc to afford compound **11** as a pale yellow solid: mp 120–122 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 3.32 (dd, *J*=18.0, 4.0 Hz, 1H), 4.17 (dd, *J*=18.0, 10.0 Hz, 1H), 5.12 (dd, *J*=10.0, 4.0 Hz, 1H), 6.53 (m, 1H), 7.24–7.57 (m, 10H), 7.97(m, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 42.74, 48.67, 112.28, 118.18, 127.45–129.00, 133.26, 136.36, 138.24, 146.50, 152.16, 187.70, 197.82; MS *m*/*z* (relative intensity, %) 305 (7.46, M^{+}+1), 304 (7.87, M^{+}), 199 (68.13), 105 (100), 95 (87.91), 77 (87.04).

*4.2.4. 1,2,4-Triphenyl-1,4-butanedione (**12**).* The residue was chromatographed on silica gel using 15:1 hexanes/EtOAc to afford compound **12** as a white needle-shaped crystal: mp 124–126 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 3.32 (dd, *J*=21.0, 3.5 Hz, 1H), 4.23 (dd, *J*=21.0, 10.0 Hz, 1H), 5.34 (dd, *J*=10.0, 3.5 Hz, 1H), 6.53 (m, 1H), 7.22–7.59 (m, 11H), 7.97(m, 4H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 43.85, 48.69, 127.33–129.17, 132.85, 133.21, 136.45, 138.63, 198.04, 198.89; MS *m*/*z* (relative intensity, %) 314 (3.16, M^{+}), 209 (9.33), 105 (100), 77 (58.65).

*4.2.5. 4-Oxo-4-(2-furyl)-butyronitrile (**13**).* The residue was chromatographed on silica gel using 15:1 hexanes/EtOAc to afford compound **13** as a pale yellow needle-shaped crystal: mp 76–78 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.73 (t, *J*=7.5 Hz, 2H), 3.23 (t, *J*=7.5 Hz, 2H), 6.56 (t, *J*=6.8 Hz, 1H), 7.61 (d, *J*=6.5 Hz, 1H), 7.76 (d, *J*=6.5 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 11.29, 33.78, 112.61, 117.70, 118.88, 146.89, 151.71, 184.48; MS *m*/*z* (relative intensity, %) 150 (2.10, M^{+}+1), 149 (15.23, M^{+}), 95 (100), 67 (8.06).

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 21006055).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.094. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. (a) Stetter, H.; Schrechenberg, M. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 81; (b) Stetter, H.; Kuhlmann, H. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 539; (c) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639.
2. Trost, B.; Shuey, C. D.; DiNinno, F.; McElvain, C. D. *J. Am. Chem. Soc.* **1979**, *101*, 1284.
3. Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, l899.
4. Anjaiah, S.; Chandrasekhar, S.; Grée, R. *Adv. Synth. Catal.* **2004**, *346*, 1329.
5. Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509.
6. (a) Galopin, C. C. *Tetrahedron Lett.* **2001**, *42*, 5589; (b) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552.
7. (a) Raghavan, S.; Anuradha, K. *Tetrahedron Lett.* **2002**, *43*, 5181; (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876.
8. Parakka, P. J.; Cava, M. P. *Synth. Met.* **1995**, *68*, 275.
9. Phillip, R. B.; Herbert, S. A.; Robichaud, A. A. *Synth. Commun.* **1986**, *16*, 411.
10. Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534; (b) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, R. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696; (c) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, *9*, 2025; (d) Mennen, A. M. L.; Blank, J. T.; Tran-Dube, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195; (e) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, l654.
11. (a) Kerr, M. S.; Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298; (b) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314.
12. Gong, J. H.; Im, Y. J.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2002**, *43*, 1247.
13. Zhou, Z. Z.; Ji, F. Q.; Cao, M.; Yang, G. F. *Adv. Synth. Catal.* **2006**, *348*, 1826.
14. Zeitler, K.; Mager, I. *Adv. Synth. Catal.* **2007**, *349*, 1851.
15. Zeng, T. Q.; Song, G. H.; Li, C. J. *Chem. Commun.* **2009**, *41*, 6249.
16. Horvath, I. T.; Rabai, J. *Science* **1994**, *266*, 72.
17. (a) Bianchini, C.; Frediani, P.; Sernan, V. *Organometallics* **1995**, *14*, 5458; (b) Behr, A.; Toslu, N. *Chem. Eng. Technol.* **2000**, *23*, 122; (c) Bergbreiter, D. E.; Osbum, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 9058.
18. (a) Jin, Z. L.; Zheng, X. L.; Fell, B. *J. Mol. Catal. A: Chem.* **1997**, *116*, 51; (b) Jin, Z. L.; Zheng, X. L. In *Aqueous Phase Organometallic Catalysis*; Herrmann, W. A., Ed.; Wiley-VCH: Weinheim, 1998; pp 233–240.
19. Wang, Y. H.; Jiang, J. Y.; Wu, X. W.; Cheng, F.; Jin, Z. L. *Catal. Lett.* **2002**, *79*, 55.
20. Wang, Y. H.; Jiang, J. Y.; Zhang, R.; Liu, X. H.; Jin, Z. L. *J. Mol. Catal. A: Chem.* **2000**, *157*, 111.
21. White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124.
22. (a) Wu, C. T.; Marsh, K. N.; Deev, A. V.; Boxall, J. A. *J. Chem. Eng. Data* **2003**, *48*, 486; (b) Crosthwaite, J. M.; Muldoon, M. J.; Aki, S. N. V. K.; Maginn, E. J.; Brennecke, J. F. *J. Phys. Chem. B* **2006**, *110*, 9354.