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Ionic Liquid Based Vilsmeier Reagent as Dehydrating Reagent for Generation of Ketenes and Their *in situ* Cycloaddition Reactions

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ABSTRACT

The ionic liquid version of Vilsmeier reagent has been used as an efficient activating reagent for intramolecular dehydration of various carboxylic acids for generation of ketenes intermediates. Variety of different ketenes, thus prepared, was treated with appropriate Schiff bases and alkyl azide and aryl azide to give β -lactams and triazolones respectively. The excellent yields obtained under this green protocol with minimal work up. The present system offers a competitive and better alternative to routine procedures.

KEYWORDS

Dehydration agent, Ionic liquid, Vilsmeier reagent, Ketenes, Cycloaddition reactions, β -Lactams, Triazolones.

INTRODUCTION

The ionic liquid is composed of special type of cations and anions which exist in liquid state at room temperature. This special liquid has found wide spectra of applications in various fields of chemistry due to interesting combination of their physical properties [1]. An ionic liquid containing some active functional group attached to cationic part is called Task specific ionic liquid and is used as organocatalyst for certain chemical reactions. This class of ionic liquid has revolutionized the field of organocatalyzed reactions by removing major drawbacks associated with routine organocatalysis *i.e.* toxicity, high cost, impurity of product, low yields and laborious work up procedure. Large number of organocatalyzed reactions have been tested with task specific ionic liquids with best yields, recycling of catalyst, non-toxic green procedure and easy recovery of pure products [2].

N,N-Dimethyl formamide is used as nucleophilic polar aprotic solvent for certain reactions which depend on it *i.e.* nucleophilic substitution reactions. Our group developed its ionic liquid version and named it DMF-like ionic liquid. It has been shown to be superior than normal DMF for all DMF-dependent reactions and reagents [3].

N,N-Dimethyl formamide can be used as a precursor of certain useful organo-reagents like *N,N*-dimethylchloro sulfite-methaniminium chloride called Vilsmeier reagent. It is normally prepared from dimethyl formamide and thionyl chloride quite

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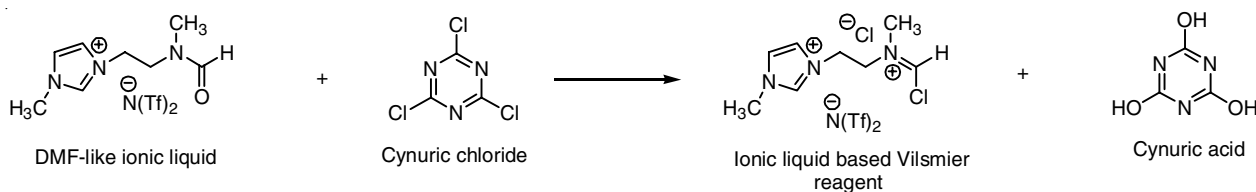
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Scheme-I: Preparation of ionic liquid based Vilsmeier reagent from DMF-like ionic liquid

conveniently. Most interestingly we synthesized ionic liquid based Vilsmeier reagent from it using 2,4,6-trichloro-1,3,5-triazine or cynuric chloride using 3:1 ratio (**Scheme-I**) and found it most efficient and easy-to-use than normal Vilsmeier reagent and achieved many Vilsmeier reagent dependent reactions with best results and procedural convenience [4].

Vilsmeier reagent is a highly electrophilic reagent used for catalyzing certain reactions. It has also been reported as an efficient dehydrating agent for various reactions [5-7]. However it is extremely water-sensitive and reverts to original DMF after hydrolysis even with moisture. Its ionic liquid version being hydrophobic resists hydrolysis and can be used conveniently under normal conditions. Due to oxophilic nature, Vilsmeier reagent has been used to activate the molecules containing hydroxyl as well as carboxyl group for some reactions such as dehydration. Therefore it can act as dehydrating agent for carboxylic acids leading to their esterification as well as ketene formation under appropriate conditions [8].

Carboxylic acids and their derivatives with α -hydrogens in presence of suitable dehydrating agent undergo intramolecular dehydration to give ketenes. Ketenes are highly useful reactive intermediates which can undergo cycloaddition reactions with variety of reagents such as alkenes, imines, aldehydes or ketones to give cyclic ketones, amides, esters respectively. Similarly ketenes can undergo dimerization to form cyclic diketones and esters. In addition to this, they can react with 1,3-dipole compounds to form corresponding cyclic products.

The use of Vilsmeier reagent for generation of ketene from carboxylic acid by Vilsmeier reagent as a dehydrating agent is well known. Satyendra *et al.* [5] reported the use of Vilsmeier reagent an efficient and mild dehydrating agent for the *in situ* generation of monophenyl- diphenyl- and monochloroketenes directly from the corresponding carboxylic acids. These ketenes undergo cycloaddition reactions with 1,3-diaza compounds and 1,3-butadienes to afford 4(3*H*)-pyrimidinones and azetidones. In addition to these reactions, there are many other synthetic reactions which involve dehydration achieved by using *N,N*-dimethylchlorosulfitemethaniminium chloride (Vilsmeier reagent) as an organo-catalyst.

Cremonesi *et al.* [9] have reported the synthesis of new C_3 -spirofused 2-azetidones (β -lactams) by means of the Staudinger reaction between heterocyclic asymmetric ketenes and imines. They achieved the synthesis of ketenes from norbornane-2-carboxylic acid using Vilsmeier reagent as a dehydrating reagent. Arrieta *et al.* [6] reported the application of Vilsmeier reagent as a dehydrating agent for an efficient one-pot synthesis of some β -lactams like 1,3,4-oxadiazoles and 4*H*-3,1-benzoxazin-4-ones. Gorbyleva *et al.* [7] reported the Vilsmeier complex as a dehydrating agent in the synthesis of 2,6-dicyanopyridine.

In continuation of our ongoing projects on exploration of the applications of ionic liquid based Vilsmeier reagent, we have now investigated its potential for intramolecular dehydration of various carboxylic acids to form corresponding ketenes and their *in situ* cycloaddition reaction with suitable nucleophilic reagents.

EXPERIMENTAL

All the chemicals were purchased from Sigma-Aldrich. Reagents and solvents are commercial grade and were used as supplied, except when specified in the experimental procedure. CH_2Cl_2 was distilled from calcium hydride. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin Layer plates. Flash column chromatography was performed on Acros silica gel 60, 0.040-0.063 mm.

GC-MS parameters: Agilent 6890 N Network System equipped with capillary column HP-5MS (30 m \times 0.25 mm i.d., 0.25 μ m film thickness). The electron ionization (EI) mode at 70 eV was used for MS detection. The temperature of oven was held at 90 $^\circ$ C for 1 min, raised to 200 $^\circ$ C at 5 $^\circ$ C/min (2 min hold) and then to 280 $^\circ$ C at 20 $^\circ$ C/min (12 min hold). 1 μ L sample was injected in hexane (HPLC grade), using splitless mode. The carrier gas helium was used at a flow rate of 1.5 mL/min. The injector and MS transfer line temperature was set at 220 and 290 $^\circ$ C, respectively. To calculate retention indices, solution of standard alkanes (C_8 - C_{32}) was analyzed using same conditions.

General procedure

Ketene synthesis: The solutions of 1 mmol (449.37 mg) of IL-based Vilsmeier reagent and 1 mmol diphenylacetic acid (212.23 mg) were prepared in 3 mL and 2 mL of dichloromethane, respectively. Then both mixtures are mixed dropwise at 20 $^\circ$ C. After completion of addition, the reaction mixture was stirred magnetically and the progress of reaction was monitored by GC-MS. The reactive intermediate (**2c**) was formed almost instantaneously. Then we added slowly the slight excess of 1 mmol of Na_2CO_3 (84.5 mg) to the stirring mixture and progress of the reaction was traced. The reaction was found to be complete after 5 h.

Preparation of β -lactam: To the solution of diphenylketene, we added the equimolar amount (1 mmol, 133.20 mg) of propylidene aniline as a solution in 2 mL dichloromethane solution dropwise at 20 $^\circ$ C. The reaction mixture was further allowed to stir and its progress was traced by GC-MS. The reaction was found to complete after 13 h. After completion of reaction, dichloromethane was removed under *in vacuo*. The β -lactam product 1-phenyl-3,3-diphenyl-4-ethyl-azetidone-2-one was isolated from regenerated DMF-like ionic liquid by extraction with 3 \times 3 mL of diethyl ether. After removal of ether the product was dried in oven and yield was determined to be 98 %. The product was then characterized by 1H NMR.

Preparation of triazolone: To the solution of diphenylketene, we added the equimolar amount of phenylazide (142.12 mg, 1 mmol) as a solution in 3 mL dichloromethane by slow dropwise with constant stirring at 30-35 °C. The progress of reaction was monitored by TLC analysis. Then complete formation of triazolone was achieved within 12 h. After the similar work up, as given above, the required triazolone product 2,5,5-triphenyltriazolone was obtained in 94 % yield. It was identified by GC-MS and confirmed by ¹H NMR.

RESULTS AND DISCUSSION

The methodology consists of generation of ketenes by intramolecular dehydration of suitable carboxylic acid to give corresponding ketene by using ionic liquid-based Vilsmeier reagent as a dehydrating reagent, then *in situ* treatment of ketene with suitable nucleophilic species to give corresponding products. In present study, we will treat the ketene with imines and alkyl azides to form β-lactams and triazolones respectively. The first case is an example of [2+2] cycloaddition in which all five types of ketenes were treated with same imine *i.e.* propylidene-aniline to give variety of β-lactams. The second example includes the [3+2] cycloaddition reaction of phenyl azide with ketenes to form corresponding triazolones. In every reaction ketene was *in situ* treated with equimolar amount of desired reagent for a required cycloaddition reaction. The reactions went smoothly with stirring the reaction mixture at 0-20 °C. All of the reactions provided best yields of β-lactams and triazolones. All of the ketenes prepared under present protocol were stable and no dimerization side reaction was observed.

Optimization of reaction conditions

Generation of ketenes: We will generate the ketene from carboxylic acid by its dehydration with ionic liquid based Vilsmeier reagent. The preparation of ketene by intramolecular dehydration of carboxylic acid (**1a**) by reaction with ionic liquid based Vilsmeier reagent (**1b**) suggests that carboxylic acid should be treated with equimolar amount of Vilsmeier reagent leading to the formation of intermediate (**1c**) (Scheme-II). The intermediate on reaction with non-nucleophilic base *i.e.*, Na₂CO₃ undergoes removal of α-hydrogen to give desired ketene (**1d**) and regenerate DMF-like ionic liquid (**1e**) 1 mmol (449.37 mg) of ionic liquid based Vilsmeier reagent (**2b**) was mixed dropwise to 3 mL of dichloromethane at 0 °C under constant stirring. Then we added dropwise the equimolar amount (212.23 mg) of diphenylacetic acid (**2a**) as a solution in 2 mL dichloromethane. After completion of addition, the reaction mixture was stirred with magnetic stirrer and the progress of reaction was monitored by GC-MS. The intermediate (**2c**) was formed almost instantaneously. The consumption of **2a** revealed the completion of formation of compound **2c**. Then

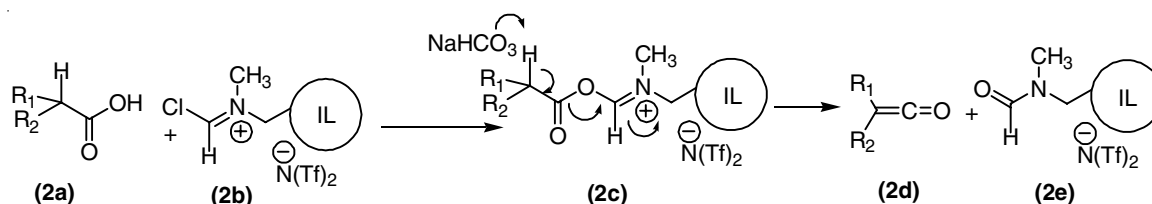
we added slowly the slight excess of sodium bicarbonate (84.5 mg) to the stirring mixture and progress of the reaction was traced. The reaction was found to be completed after 5 h. In order to reduce the time duration of this step, we repeated the second step at various temperatures with 5 °C rise in temperature in each step. We obtained maximum yield at 20 °C (Table-1).

| Temperature (°C) | Time duration (h) |
|------------------|-------------------|
| 0 | 15.0 |
| 5 | 13.5 |
| 10 | 9.0 |
| 15 | 7.0 |
| 20 | 5.0 |

1,3-Cycloaddition reaction of ketenes with imines: After confirming the completion of preparation of diphenylketene by GC-MS, we added the equimolar amount of propylidene aniline (1 mmol, 133.20 mg) as a solution in 2 mL dichloromethane solution dropwise at 20 °C. The reaction mixture was further allowed to stir and its progress was traced by GC-MS. The reaction was found to complete after 13 h. After completion of reaction, the dichloromethane was removed under *vacuo*. The β-lactam product 1-phenyl-3,3-diphenyl-4-ethyl-azetidione-2-one was isolated from regenerated DMF-like ionic liquid by extraction with 3 × 3 mL of diethyl ether. After removal of ether, the product was dried in oven and yield was determined to be 98 %. The product then characterized by ¹H NMR. The remaining reaction mixture was extracted with 2 × 2 mL water to remove soluble sodium chloride; both dichloromethane and DMF-like ionic liquid are immiscible with water. The dichloromethane was separated from DMF-like ionic liquid by rotary evaporator and ionic liquid was dried in oven for further use.

Following the same procedure variety of ketenes were prepared from corresponding carboxylic acids and were treated with same Schiff base to form of β-lactams. The details of results are shown in (Table-2, entry 5-10).

1,3-Cycloaddition reaction of ketenes with azides: Initially the required diphenyl ketene was prepared according to above procedure. The solution of phenyl azide (142.12 mg, 1 mmol) in 3 mL dichloromethane was added to it by slow dropwise with constant stirring at 20 °C. The progress of reaction was monitored by TLC analysis. After 5 h we found only 15 % of the product. In order to speed up the reaction we raised the temperature of reaction mixture to 30 and then to 35 °C. Then complete formation of triazolone was achieved within 12 h. After the similar work up, as given above, the required triazolone product *i.e.*, 2,5,5-triphenyltriazolone was obtained in 94 % yield. It was identified by GC-MS and confirmed by ¹H NMR.



Scheme-II: Ionic liquid-based Vilsmeier reagent catalyzed ketene preparation

TABLE-2
 PREPARATION OF KETENES BY IONIC LIQUID BASED VILSMEIER
 REAGENT CATALYZED DEHYDRATION OF CARBOXYLIC ACID

| Entry | Carboxylic acid | Ketenes | Imine | Product | Yield (%) (GC) |
|-------|-----------------|---------|-----------|---------|----------------|
| 1 | | | | | 98 |
| 2 | | | | | 95 |
| 3 | | | | | 90 |
| 4 | | | | | 94 |
| 5 | | | | | 77 |
| 6 | | | Ph-N=N=N: | | 94 |
| 7 | | | Ph-N=N=N: | | 83 |
| 8 | | | Ph-N=N=N: | | 80 |
| 9 | | | Ph-N=N=N: | | 89 |
| 10 | | | Ph-N=N=N: | | 67 |

Different kinds of ketenes were synthesized according to the developed optimized conditions. The prepared ketenes include methyl, dimethyl, phenyl methyl, diphenyl and *t*-butyl methyl ketenes. They were *in situ* treated with propylidene aniline to give corresponding β -lactams (Table-2, entry 1-5). In another phase of investigation, same ketenes were also treated with phenylazide to give corresponding 2,5,5-triphenyltriazolone (Table-2, entry 5-10). The excellent yields of the required products have been obtained under green conditions with low cost and easy work up.

Conclusion

We have covered only introductory scope of our methodology for ketene generation and its reactions. More ketenes can be generated and further reactions can be examined and present studies hint towards the bright prospects of the results.

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