



Regioselective Mononitration of Aromatic Compounds with N_2O_5 by Acidic Ionic Liquids *via* Continuous Flow Microreactor

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We employed N_2O_5 as highly active nitrating reagents and a host of acidic ionic liquid as catalysts in these reactions which were conducted in a continuous flow microreactor. When we utilized PEG₄₀₀-DAIL as catalysts, the conversion of toluene was increased to 95.5 % and the yield of mononitration product (*o/p* ratio reached 1.10) significantly improved to 99 %, meanwhile the reaction time was drastically shortened to 1/120 of the conventional reactor. Nitration in ionic liquids was surveyed using a host of aromatic substrates with similar reactivity. The ionic liquid recycling procedures had also been devised.

Keywords: Aromatic nitration, Microreactor, N_2O_5 , Ionic liquid.

INTRODUCTION

Nitration of aromatic compound is widely used in organic syntheses and industrial application. Many nitro-aromatic compounds are important intermediates during the synthesis of dyes, plastics and pharmaceuticals [1,2]. Despite this, the traditional method for aromatic nitration involving a mixture of nitric acid and sulfuric acid is still adopted by industry. The obvious disadvantages of the commercial manufacturing process, such as safety and environmental problems caused by wastewater containing organic acid, low selectivity and side reaction [3-7], have led to unremitting efforts to develop viable alternatives.

Compared with the above shortcomings in traditional nitration using mixed acid (the mixture of nitric acid and sulfuric acid), we employed a better way to greatly reduce the potential hazard of highly exothermic nitrations by using microreactors [8-10]. Microreactors (Fig. 1) have been shown to have very high heat transfer rate due to the high surface area to volume ratio, which enables the microreactors to control highly exothermic reactions efficiently. The continuous flow microreactor can provide more smaller reaction volume which improve much better heat exchange and mass transport and both temperature and residence time can be precisely controlled which may improve selectivity by suppression of side reactions [11].

With the purpose to overcome the disadvantages of conventional nitration such as environmental pollution and low selectivity, we used dinitrogen pentoxide (N_2O_5) as an eco-

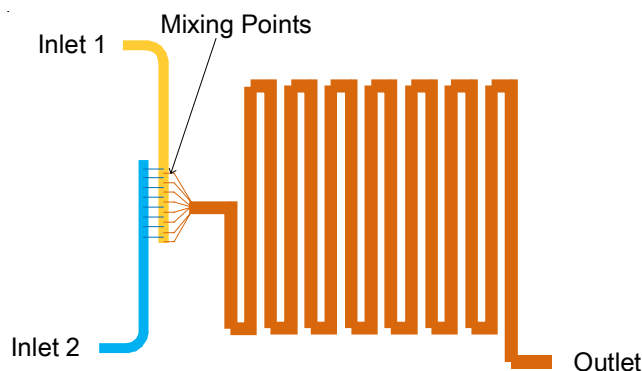


Fig. 1. Structure of the microreactor

friendly and highly selective nitrating agent which has many advantages. Millar and Philbin introduced N_2O_5 in a solvent into syntheses of nitramines and nitrate esters [12]. Radoslaw and Andrew [13] have developed a simple, fast and mild method for the nitration of aromatic rings, by using N_2O_5 catalyzed with $Fe(acac)_3$. The reaction is tolerant of a range of functional groups and gives almost quantitative yields.

In the past few years, a growing interest had been witnessed in ionic liquids as solvents or catalysts for aromatic nitration. Qiao *et al.* [14,15] and others [16,17] immobilized ionic liquids to modified silica gel and got an excellent *ortho/para* ratio. Fang *et al.* [18] reported that halogen-free SO_3H -functional Brønsted-acidic ionic liquids that bear an alkane. Sulfonic acid group in an acyclic trialkanylammonium cation could efficiently catalyze the nitration of aromatic compounds.

Nevertheless, there are many defects using ionic liquids as homogeneous catalyst for aromatic nitration in a conventional batch reactor, such as long reaction time, inconvenient post treatment and side reaction. We aim to overcome these disadvantages by introducing ionic liquids as homogeneous catalyst into microreactor system. It is found that the nitration of toluene in a microreactor reaction time was shortened to 1/120, as the catalyst, the recovery of the ionic liquid is relatively simple. We only need to extract the aqueous phase after reaction and drying it, then it can be used for reaction again.

We employed N_2O_5 as highly active nitrating reagents and a host of acidic ionic liquid (polyethylene glycol PEG-400-based dicationic acidic ionic liquid (PEG₄₀₀-DAIL) [19]) as catalysts in these reactions which were conducted in a continuous flow microreactor. Nitration in ionic liquids was surveyed using a host of aromatic substrates with similar reactivity. And ionic liquid recycling procedures had also been devised. The easily recovered ionic liquid opened up the possibility of a more economic process.

EXPERIMENTAL

We used a interdigital triangular-single channel-pillar microglass reactor in reactions ($V = 1.326 \text{ mL}$; mixed zone dimensions: height $150 \mu\text{m}$, width $50 \mu\text{m}$, reaction channel dimensions: depth 0.5 mm , width 4.5 mm , length 800 mm ; heat exchange area 3600 mm^2). As shown in Fig. 2, a sketch of aromatics nitration process-flow diagram controlled by microfluidic chip. The whole system consists of reactants, pumps, microreactor, thermostatic water bath and separating unit. The solvent was first added in ionic liquids and heated at 30°C in vacuum thus achieving fully mixing. Then a certain amount of N_2O_5 was added in the mixture. Reactants and nitrating reagents flow into the microchip and reaction channel controlled by constant pressure pump, reaction temperature adjusts by thermostatic water bath (Fig. 3).

The organic phase was washed with a few portions of saturated NaHCO_3 solution, then several times with water, dried with MgSO_4 and the sample of the organic layer was analyzed by gas chromatography (GC) using the internal standard method. The aqueous phase was composed of nitric acid of remaining and ionic liquid which could be readily recycled by simple evaporation.

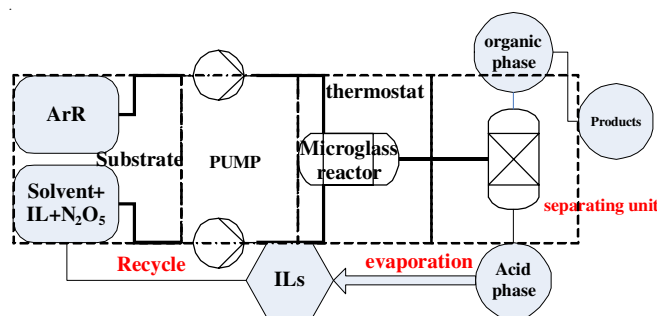


Fig. 2. Micro reaction process-flow diagram

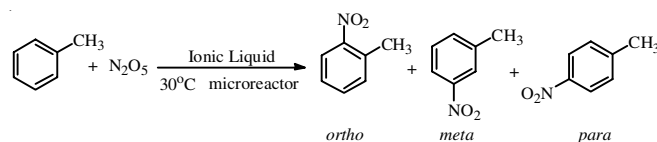


Fig. 3. Nitration of toluene catalyzed by ionic liquids in the microreactor system

RESULTS AND DISCUSSION

We found that the microreactor can not only increased the yields of nitroaromatic compounds, but also improved the selectivity of mononitration. Due to the improvement of heat transfer performance, it reduced oxidizing reaction and dinitration reaction controlled by temperature fluctuation, especially the lively aromatic like ethylbenzene, isopropylbenzene. More interestingly, we detected that the isomeric distribution using microreactor was differ from conventional batch reactor. For alkyl aromatics, the microreactor system can improve the *para*-selectivity of mononitration to some extent, oppositely, for not lively halogenated aromatics, the microreactor system can improve *ortho*-selectivity of mononitration.

The whole system is found to be a mild, efficient and safe process for the electrophilic nitration and mechanism for aromatics nitration in the microreactor catalyzed by PEG₄₀₀-DAIL (Fig. 4).

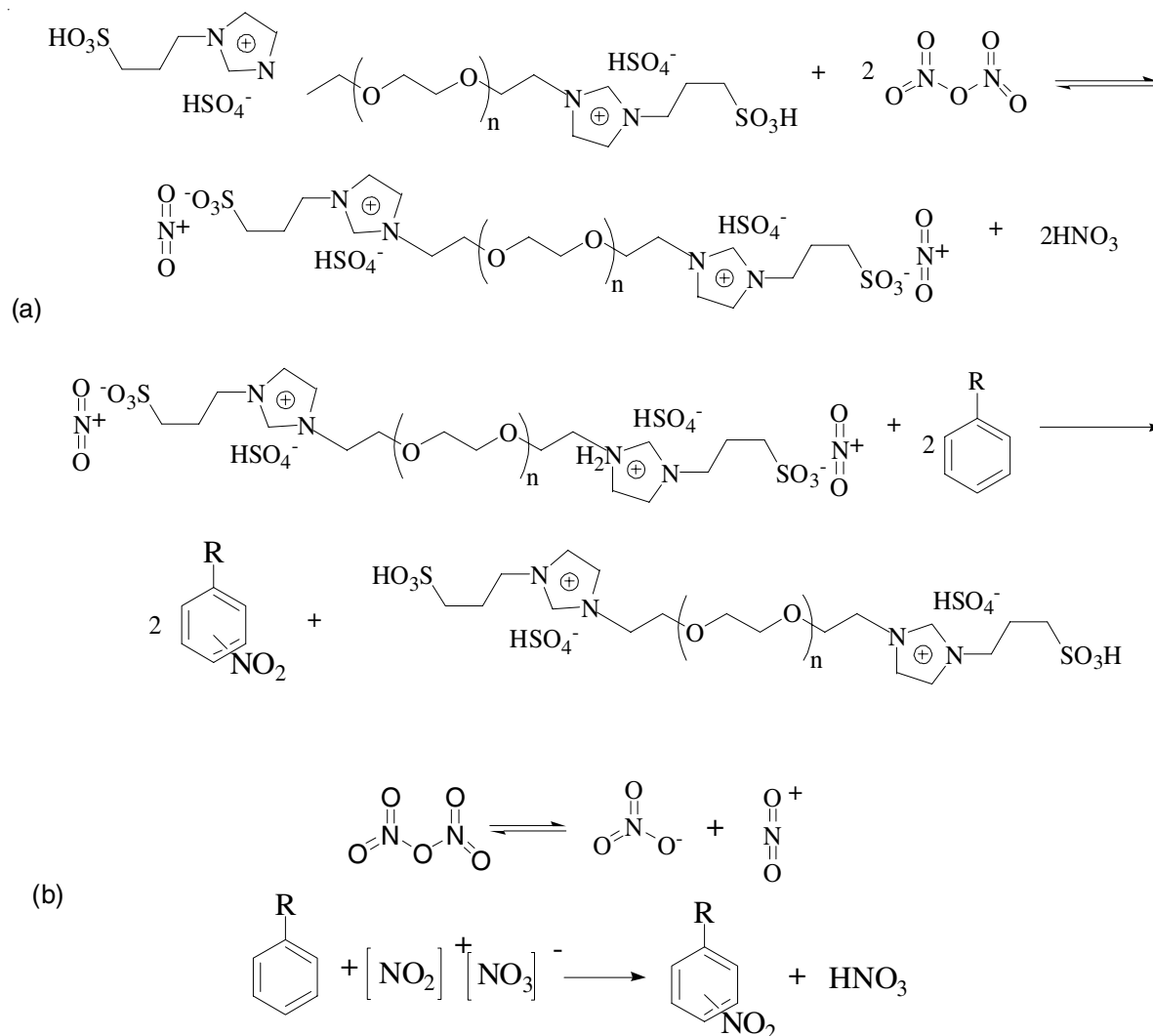
Influence regioselective nitration of toluene in different ionic liquid via microreactor: Taking the nitration of toluene for example, the reaction was compared with several reported ionic liquid systems [20] and the results are summarized in Table-1. As can be seen from Table-1, compared with the blank

TABLE-1
REGIOSELECTIVE NITRATION OF TOLUENE IN DIFFERENT IONIC LIQUID *via* MICROREACTOR^a

Ionic liquid ^a	Conversion (%) ^b	Selectivity (%) ^b	Product isomers (%) ^b			<i>o/p</i> ratio
			<i>ortho</i>	<i>meta</i>	<i>para</i>	
None	70.5	> 99.5	56.4	3.0	40.6	1.38
95 % HNO_3	92.7	98.9	53.5	4.9	41.6	1.29
$\text{HNO}_3/\text{H}_2\text{SO}_4$	94.4	97.1	61.4	4.6	34.0	1.80
[MIMPS][HSO_4]	91.1	99.2	54.0	5.3	40.7	1.33
[TEPSA][HSO_4]	93.8	99.4	53.4	5.5	41.1	1.30
PEG ₄₀₀ -DAIL	95.5	99.0	51.5	1.7	46.8	1.10
$[(\text{CH}_2)_4\text{SO}_3\text{HMim}][\text{NO}_3]$	94.7	99.3	56.9	4.8	38.3	1.49
[Emim][NO_3]	76.3	> 99.5	56.2	3.9	39.9	1.41
[BsPy][HSO_4]	84.7	> 99.5	54.2	3.3	42.5	1.27
[BMIM][HSO_4]	81.5	> 99.5	56.3	3.1	40.6	1.38

^aReaction conditions: toluene velocity 1 mL/min , reaction time = 48 s , $n(\text{toluene}):n(\text{N}_2\text{O}_5) = 1:2$, bath temperature 30°C continuous flow, catalyst's amount $5.0 \text{ \%mol}$ (mole ratio to toluene).added into acid phase, ignored the change of volume.

^bSelectivity refers to the percentage of three kinds of products listed in the table (ratio to all the reaction products), determined by original GC data.

Fig. 4. Possible mechanism of nitration of aromatics catalyzed by PEG₄₀₀-DAIL

experiment, the use of all kinds of different acidic ionic liquids had the effect of increasing conversion. Thereinto the 95 % HNO_3 , [MIMPS][HSO_4^-], [TEPSA][HSO_4^-], [BsPy][HSO_4^-] and PEG₄₀₀-DAIL have higher selectivity of *p*-nitrotoluene product. The PEG₄₀₀-DAIL could successfully decreased the ratio of *o/p* to 1.10, while the conversion was still kept at 95.5 %. But the traditional ionic liquids could not remain competitive both in terms of conversion and selectivity.

Effect of catalyst's amount in toluene nitration via the microreactor: The typical reaction with toluene was investigated to optimize the reaction conditions (Table-2). It was observed that the all these different amounts of PEG₄₀₀-DAIL had an effective influence. When the amount of catalyst was increased to 5 % mol, the conversion and the *para*-selectivity of the nitrotoluene got the best result. To further increase of catalyst's amount, the conversion reduced and the *para*-selectivity of the nitrotoluene had no further improved. With an increase in the amount of catalyst probably because the ionic liquid has high viscosity and is insoluble in the reactant so that it's reunion is obvious which resulted in lower and lower catalytic activity.

Effect of solvent in toluene nitration with PEG₄₀₀-DAIL in the microreactor: Selecting different solvents investigated

TABLE-2
EFFECT OF CATALYST'S AMOUNT IN TOLUENE NITRATION via THE MICROREACTOR^a

PEG ₄₀₀ -DAIL (% mol) ^b	Conversion (%)	Selectivity (%)	Product isomers (%)			<i>o/p</i> ratio
			<i>ortho</i>	<i>meta</i>	<i>para</i>	
0	70.5	> 99.5	56.4	3.0	40.6	1.38
2.5	82.6	> 99.5	53.6	1.9	44.5	1.20
5.0	95.5	99.4	51.5	1.7	46.8	1.10
7.5	94.6	99.3	53.2	2.0	44.8	1.19
10.0	92.1	99.1	53.9	2.1	44.0	1.22

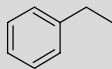
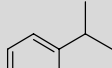
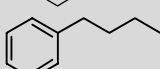
^aReaction conditions: toluene velocity 1 mL/min, reaction time = 48 s, $n(\text{toluene}):n(\text{N}_2\text{O}_5) = 1:2$, CH_2Cl_2 as solvent, bath temperature 30 °C, continuous flow, PEG₄₀₀-DAIL added into acid phase, ignored the change of volume. ^bMole ratio to toluene

the influence for the yield of the reaction (Table-3). The polarity of five kinds of solvent in the order is



We found that the polarity of the solvent influenced the conversion more rather than the selectivity of the reaction. The higher of the polarity, the yield was higher. Meanwhile only in the CCl_4 the selectivity and the *o/p* ratio had a little increase. On the contrary, in other solvents the influence of selectivity is negative.

TABLE-4
 COMPARISON OF THE OTHER AROMATICS NITRATION IN DIFFERENT REACTORS^a

Substrate	Reactor ^b	Reaction time	Conversion (%)	Selectivity (%)	Product distribution (%)			o/p ratio
					<i>ortho</i>	<i>meta</i>	<i>para</i>	
	A	7200 s	53.8	99.1	—	—	—	—
	B	48 s	60.1	> 99.5	—	—	—	—
	A	7200 s	72.2	98.9	45.8	4.9	49.3	0.93
	B	48 s	78	99.3	45.4	5.3	51.3	0.88
	A	7200 s	73.9	90.7	26.4	6.9	66.7	0.40
	B	42 s	91.4	94.6	24.8	6.8	68.4	0.36
	A	7200 s	74.5	98.7	15.3	10.1	74.6	0.20
	B	48 s	80.3	> 99.5	14.3	9.8	75.9	0.19
	A	7200 s	55.8	99.1	16.6	0.3	84.1	0.20
	B	48 s	59.6	> 99.5	17.1	—	82.9	0.21
	A	7200 s	51.9	99.1	33.8	0.4	65.8	0.51
	B	48 s	58.4	> 99.5	39.2	—	60.8	0.65
	A	7200 s	42.3	99.3	34.3	0.4	65.3	0.52
	B	48 s	48.5	> 99.5	38.9	—	61.1	0.64

^aReaction conditions: toluene velocity 1 mL/min, n(aromatics):n(N₂O₅)=1:1.2, CH₂Cl₂ as solvent, bath temperature 30 °C, continuous flow, no catalyst; ^bA = batch reactor, V= 100 mL; B = microglass reactor, V= 1.326 mL

 TABLE-3
 EFFECT OF SOLVENT IN TOLUENE NITRATION WITH PEG₄₀₀-DAIL IN THE MICROREACTOR

Solvent	Conversion (%)	Selectivity (%)	Product isomers (%)			o/p ratio
			<i>ortho</i>	<i>meta</i>	<i>para</i>	
CCl ₄	72.2	> 99.5	51.3	1.7	47.0	1.09
CH ₂ Cl ₂	95.5	> 99.5	51.5	1.7	46.8	1.10
CHCl ₃	95.8	99.4	51.6	2.0	46.4	1.11
CH ₃ CN	96.6	99.3	52.6	2.1	45.3	1.16
CH ₃ NO ₂	99.0	99.0	53.0	2.3	44.7	1.18

Reaction conditions: Toluene velocity 1 mL/min, reaction time = 48 s, n(toluene):n(N₂O₅) = 1:2, bath temperature 30 °C, continuous flow, PEG₄₀₀-DAIL (catalyst's amount 5.0 % mol (mole ratio to toluene)). added into acid phase, ignored the change of volume.

Comparison of the other aromatics nitration in different reactors: On the basis of toluene, with N₂O₅ for nitrating agent, we compared the other aromatics nitration results in different reactors in the same mole ratio and reaction temperature, as shown in Table-4.

The procedure was repeated six times and the results indicated that PEG₄₀₀-DAIL could be recycled without the apparent loss of catalytic activity after six times of recycling.

Conclusion

The PEG₄₀₀-DAIL was used as homogeneous, recyclable catalysts for continuous nitration in a special microglass reactor. Under the same conditions, the conversion of alkyl-benzenes and halogenated-benzenes were increased about 15 % and 10 % *versus* batch reactor and the yield of mononitration product significantly improved, meanwhile the reaction time was drastically shortened to 1/120 of the conventional reactor. Further systematic work towards nitrating *via* a continuous flow microreactor is in progress.

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