Scientia Iranica C (2015) 22(6), 2326–2331

SCIENTIA
IRANICA

Sharif University of Technology
Scientia Iranica
Transactions C: Chemistry and Chemical Engineering
www.scientiairanica.com

Research Note

A novel bi-SO$_3$H functional DABCO derived ionic liquid based on nitrate ion as a versatile reagent for rapid mono-nitration of phenols and naphthols

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Received 17 November 2013; received in revised form 25 December 2014; accepted 26 January 2015

KEYWORDS
Task specific ionic liquid;
Green chemistry;
Sultone.

Abstract. The mono nitration of phenols and naphthols has been reported at high yields and short reaction times using a task specific ionic liquid based on nitrate ion, 1,4-bis(4-sulfobuthyl)-1,4-diazabicyclo[2.2.2]octane di nitrate, as the reagent, without an acid co-catalyst, under mild conditions. The reagent could be recovered and reused several times without significant loss of reactivity.

1. Introduction

Nitration of phenols and naphthols creates an industrially important reaction, and the resultant product is a versatile intermediate for the manufacture of drugs and pharmaceuticals [1]. Also, these compounds are useful materials for fine chemicals [2]. Conventionally, nitration requires the use of a mixture of concentrated sulfuric acid with nitric acid, which is not environmentally benign to treat. Furthermore, their use always leads to the formation of dinitro compounds, oxidized products and undesirable tarry materials resulting from over-oxidation of the reactive substrate. Because of these disadvantages, the development of a new class of catalyst or reagent for the nitration of phenols and naphthols is of great significance in organic synthesis. Therefore, various methods have been reported in which, for nitration, the competitive oxidation of substrate, greener reagents and regioselectivity have been subjects of investigation [3-7].

In recent years, ionic liquids have been extensively used as versatile reagents in organic transformations, mainly as the catalyst or the dual catalyst-solvent in synthetic organic chemistry.

Recently, the nitration of aromatic compounds in the presence of task specific ionic liquids has been reported in which both an acidic catalyst and a nitro group source are present and are simultaneously employed [8]. However, synthesis of a new nitrating agent that is highly efficient, experimentally simple and economically convenient still remains a challenge.

2. Material and methods

Chemicals were purchased from the Fluka, Merck, and Aldrich chemical companies. Melting points were determined by an Electrothermal 9100 and were not corrected. TLC on commercial aluminum-backed plates of silica gel 60 F254 was used to monitor the progress of reactions. NMR spectra were recorded on Bruker Avance3 400 MHz spectrometers, with 7-10 mM solutions in D$_2$O or DMSO in the presence of tetramethyl silan as an internal standard.

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Table 1. Nitration of phenols and naphthols using 1,4-bis(4-sulfobuthyl)-1,4-diazabicyclo[2.2.2]octane di nitrate[a].

Entry	Substrates	Products	Yield (%)[b]	Time (min)	M.p (Lit.)°C
1	Phenol	o-nitro phenol	81	10	44 [8]
2	Naphthalene-1-ol	2-nitronaphthalen-1-ol	86	10	123 [12]
3	Naphthalene-2-ol	1-nitronaphthalen-2-ol	89	10	103 [13]
4	Resorcinol	4-nitrobenzene-1,3-diol	67	5	81-83 [14]
5	m-Cresol	5-methyl-2-nitrophenol	80	7	35 [14]
6	p-Cresol	4-methyl-2-nitrophenol	84	7	31 [15]
7	2-Chlorophenol	2-chloro-6-nitrophenol	85	20	67 [14]
8	4-Chlorophenol	4-chloro-2-nitrophenol	91	20	89 [12]
9	2-Hydroxybenzaldehyde[c]	2-hydroxy-3-nitrobenzaldehyde	78	30	105 [14]
10	4-Hydroxybenzaldehyde	4-hydroxy-3-nitrobenzaldehyde	86	25	139-144 [16]
11	Vanillin	4-hydroxy-3-methoxy-5-nitrobenzaldehyde	90	10	175-178 [14]

[a]: Reaction condition: phenols or naphthols (1 mmol);
1,4-bis(4-sulfobuthyl)-1,4-diazabicyclo[2.2.2]octane di nitrate (0.5 mmol), CH_2Cl_2 (1 mL), at room temperature.

[b]: Isolated yield by flash chromatography;
The known products were characterized by comparison of spectral data or MP with those authentic samples.

[c]: This reaction progressed in 55°C.

2.1. General procedure for preparation of novel ionic liquid based on nitrate ion

The zwitterion was prepared according to the reported procedure with slight modification [9]. A mixture of triethylenediamine (DABCO) (5.8 g, 0.05 mol) and 1,4-butane sulfonate (13.6 g, 0.1 mol) was added to toluene (50 ml) and stirred magnetically for 72 h at 80°C. A white solid zwitterion was formed. The white solid zwitterion was filtrated and washed repeatedly with ether. After being dried at 80°C, white solid zwitterion was obtained in good yield ($>$ 90%). HNO_3 100% (6.75 g, 0.1 mmol) was added to the obtained zwitterion and the mixture was stirred for 8h at 80°C. A yellow precipitate was formed that was washed with toluene (30 mL) and diethyl ether (2×30 mL) to remove non-ionic residue, and dried in a powerful vacuum. Viscous yellow oil was formed. The pH of the ionic liquid was determined to be between 2-2.2.

Spectroscopic data for IL: IR (Nujol, cm^{-1}): $\upsilon_{\max}$ 3400-3100, 1573, 1369, 1411, 1231; ^1H NMR (300 MHz, D_2O): δ 1.35 (m, 2H, CH_2), 1.48 (m, 2H, CH_2), 2.77 (t, J = 7.8 Hz, 2H, CH_2), 3.37 (t, J = 7.8 Hz, 2H, CH_2), 3.79 (s, 4H, $2CH_2$), 4.18 (HOD); ^{13}C NMR (75 MHz, D_2O): 21.2, 21.8, 51.9, 55.8, 59.3; Anal. calcd for $C_{14}H_{30}N_4S_2O_{12}$: C 32.94, H 5.88, N 10.98; found: C 32.88, H 6.01, N 10.88%. MS: m/z = 511 (M^++1), 510 (M^+), 448 (M^+ - NO_3), 386 (M^+-$2NO_3$), 311 (M^+-$C_4H_8SO_3HNO_3$), 112 (M^+-$C_8H_{16}S_2O_6H_2N_2O_6$).

2.2. General Experimental procedure for nitration of phenol

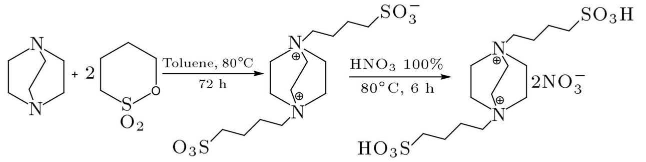
Phenol (0.094 g, 1 mmol) and IL reagent (0.25 g, 0.5 mmol) in 1 mL CH_2Cl_2 were magnetically stirred at room temperature. After the completion of the reaction (as monitored by TLC), water was added and the solid was precipitated. The separated solid was filtered and the crude product was purified by silica-gel in short column chromatography using petroleum ether-ethyl acetate (98:2) as eluent. The yield was (0.11 g) 81% mp 43°C ([8], mp 44°C).

The spectral data for 4-hydroxy-3-methoxy-5-nitrobenzaldehyde (Table 1, entry 11):

^1H NMR (400 MHz, DMSO-d_6) δ: 4.57 (s, 3H), 7.60 (s, 1H), 8.06 (s, 1H), 9.85 (s, 1H); ^{13}CNMR (100 MHz, DMSO-d_6) δ:58.39, 114.14, 122.48, 128.40, 138.67, 149.37, 151.66, 192.03; IR (KBr) ν: 3200-3400 9br), 2860, 2735, 1589, 1354 cm^{-1}; Anal. calcd for $C_8H_7NO_5$: C 48.33, H 3.55, N 7.10; found: C 48.22, H 3.68, N 6.99.

2.3. A procedure for recycling of zwitterionic

After completion of the reaction, water (15 mL) was added to the reaction mixture and stirred for 20 min. The crude nitrating product was precipitated (the zwitterionic salt is miscible with water). The solid product was separated and the water was evaporated in a rotary evaporator. The zwitterion remained as white solid. It was washed thoroughly with diethyl ether, chloroform and methanol and dried in a vacuum at 80°C. It can be reused as a nitrating agent after treating with an appropriate amount of nitric acid (experimental section). The recovered ionic liquid can be used repeatedly without significant loss of reactivity.



Scheme 1. The synthetic path of 1,4-bis(4-sulfobu-thyl)-1,4-diazabicyclo[2.2.2]octane di nitrate.

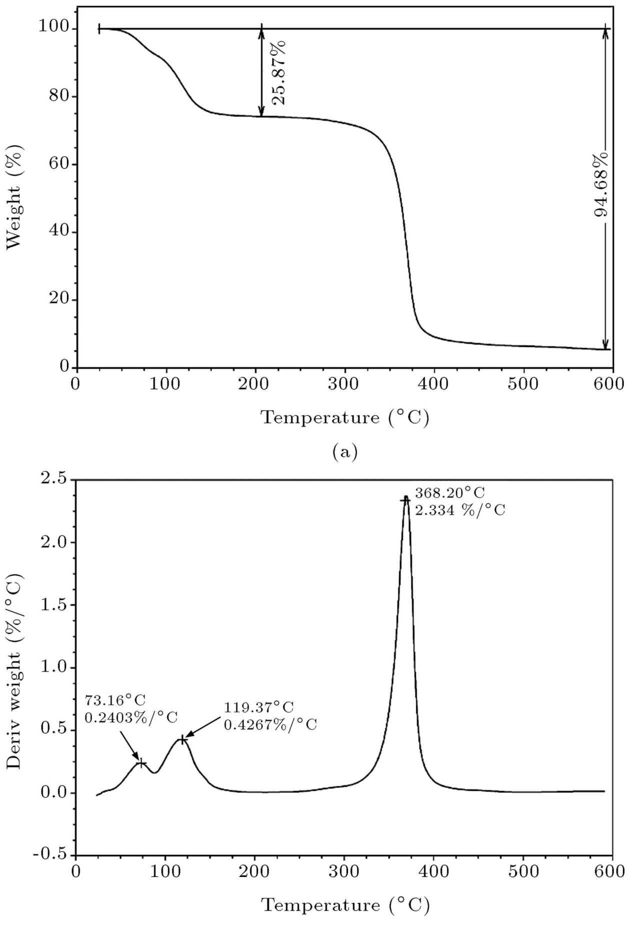
3. Results and discussion

As part of our research, in continuation of our studies on the nitration of phenolic compounds [10,11], we designed and synthesized a new task specific ionic liquid based on DABCO, consisting of nitrate anion, 1,4-bis(4-sulfobuthyl)-1,4-diazabicyclo[2.2.2]octane di nitrate, as a convenient reagent, without the need of an acid catalyst, for facile nitration of phenols and naphthols under very mild conditions. The operation was simple and IL could be recovered and reused several times.

Firstly, the ionic liquid was synthesized by the reaction of DABCO with 1,4-butane sultone in toluene. The formed solid zwitterion then treated with HNO_3 100% to give a viscous yellow oil (Scheme 1). The structure of IL was confirmed by TGA, FTIR, ^{1}HNMR, mass spectroscopy and a CHN analyzer, as reported in the experimental section.

A thermogravimetric analysis (TGA) was used to study the thermal stability of the nitrating reagent (Figure 1). As seen in Figure 1, three weight loss stages were observed in the TGA/DTG curves. The peak at 73°C (nearly 8%) indicated the loss of residual solvent and water molecules present in the ionic liquid reagent. The next peak, at 120°C, corresponding to weight loss, is about 19%, which can be attributed to the loss of NO_2. Weight loss occurring at 370°C is related to further molecular decomposition. These results suggest the synthesized reagent is stable up to 120°C and it is safe to carry out the nitration of phenolic compounds under mild reaction conditions. Such stability is crucial from the view point of green chemistry, because the strong acids used in traditional nitration reactions at elevated temperatures continue to emit toxic vapors and harm the environment.

After characterization of the 1,4-bis(4-sulfobuthyl)-1,4-diazabicyclo[2.2.2] octane di nitrate, its role was evaluated as a reagent for the mono-nitration of phenols and naphthols without the co-catalyst. To standardize the reaction conditions, a series of experiments were performed with a variation of temperature and solvents. The best results, in terms of yield and time, were achieved by carrying out the reaction of 2-naphthol (1 mmol) and 1,4-bis(4-sulfobuthyl)-1,4-diazabicyclo[2.2.2]octane di nitrate (0.5 mmol) in 1 mL CH_2Cl_2 at room temperature. Thus, in a typical reaction procedure, several diversity substituted phenols (1 mmol) and 1,4-bis(4-sulfobuthyl)-1,4-diazabicyclo[2.2.2]octane di nitrate (0.5 mmol) were stirred in dichloromethane at room temperature. All the reactions went smoothly at ambient temperature within several minutes. The results are summarized in Table 1.



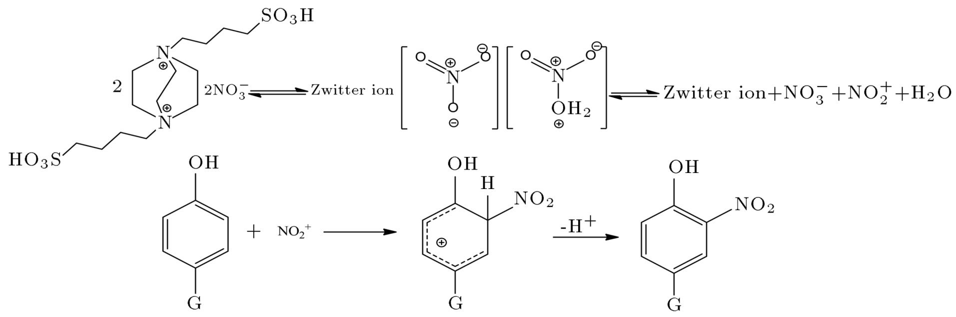
(a)

(b)

Figure 1. (a) TG and (b) DTG of 1,4-bis(4-sulfobuthyl)-1,4-diazabicyclo [2.2.2]octane di nitrate at range of 25-500°C, with a temperature increase rate at 10°C in argon.

The yields of mono-nitration slightly lessened with phenols having powerful electron-donating groups (Table 1, entry 4), due to the formation of dinitro compounds. *Ortho* and *meta*-substituted phenols afforded the *ortho* nitrated product as major products (Table 1, entries 1-3, 5, 7 and 9), whereas the *para*-substituted phenols produced selectively the *orhto*-isomer (Table 1, entries 6, 8, 10 and 11). The deactivated phenol required elevated temperatures (Table 1, entry 9). Using this methodology, the natural compound could be nitrated with high yield (Table 1, entry 11). Standard workup and purification by a short column chromatography provided the pure product.

Since the yield of the model reaction has no change in the presence of iodine as a radical scav-



Scheme 2. The proposed mechanism.

Table 2. Comparison of the results of using 1,4-bis(4-sulfobuthyl)-1,4-diazabicyclo[2.2.2]octane di nitrate with results of other works for mono nitration of phenol.

Entry	Condition	Time (min)	Yield (%)
1	Melamin trisulfonic acid/$NaNO_3$/solvent free/RT [21]	5	87
2	$WSSnO_2$/HNO_3/60°C [22]	60	80
3	Celloluse-$Ni(NO_3)_2$/TCT, CH_3CN/RT [11]	45	80
4	$Zn(NO_3)_2$/TCT, CH_3CN/RT [10]	90	80
5	NH_4NO_3/$KHSO_4$, CH_3CN/RT [23]	6 h	95
6	EAN/TFAA[a], -15 to -5°C [24]	10	94
7	$ZrO(NO_3)_2$/acetone/RT [25]	30	100
8	$Ni(NO_3)_2$/pTSA/acetone/RT [26]	30	85
9	NBS/$AgNO_3$/CH_3CN/Reflux [27]	2.5 h	87
10	[Msim]NO_3[b]/CH_2Cl_2/RT [8]	Immediately	93
11	$Fe(NO_3)_3$[bbim]BF_4[c]/30-60°C [28]	1.5 h	89
12	This work	10	81

[a]: Ethylenamonium nitrate/trifluoroacetic anhydride;

[b]: 3-methyl-1-sulfonic acid imidazolium nitrate;

[c]: 1,3-Di-n-buthyl imidazolium tetraflouroborat.

enger [8], the NO_2 radical is not involved in the mechanism, and it is an electrophilic substitution reaction. The SO_3H groups in IL as Brønsted acid sites are responsible for the generation of NO_2^+. Mishra et al. reported that Brønsted acid sites are responsible for the NO_2^+ formation, while Lewis sites favor the formation of a *para*-substituted product [17]. The suggested mechanism is depicted in Scheme 2.

The ionic liquid used in this work prompted the nitration reaction of phenols for two reasons:

1. The length of alkyl chain can increase the lipophilicity of ILs, so the solubility values of phenolic compounds would increase as the lipophilicity increases, and this would quicken the nitration reaction [18];
2. The strong interaction of the charged intermediate that formed in the rate determining step of the reaction with the ionic liquid.

If the aromatic nitration is accomplished by the nitronium ion, the rate determining step is the formation of the Wheland intermediate (σ complex) which once formed, undergoes rapid deportonation to give the nitro phenolic product. To enhance the rate of the reaction, the rate of formation of the Wheland intermediate must be increased. Therefore, the strong interaction between ionic liquid and the Wheland intermediate would increase the yield and reduce the time of the reaction [19].

In Table 2, the efficiency of our method for the mono-nitration of phenol is compared with some other published works. Each of these methods has its own advantages, but also suffer from some disadvantages, including expensive reagents or catalysts, use of corrosive reagents, long reaction times, and use of a non-recyclable catalyst. Entry 10 reported the fast nitration of phenol; this methodology would be restricted with the nitration of an imidazolium ring. Within the literature, the nitration of bases is well known, and Ridd has demonstrated the nitration of imidazolium salts [20].

4. Conclusion

In summary, we have provided a novel reagent for convenient and efficient mono-nitration of phenols and naphthols at room temperature. The significant advantages offered by this protocol are: simple operation, easy accessibility of reactants, no involvement of harmful acid catalysts, reactions at room temperature, and short reaction times. We believe that this methodology, with several green aspects, is an attractive alternative for the nitration of phenols and naphthols.

Acknowledgments

We thank the Department of Chemistry and the Office of Gifted Students at Semnan University for their financial support.

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