

O-alkylation of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate with 1,2-dichloroethane catalyzed by ionic type phase transfer catalyst and potassium iodide

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Abstract—Diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate was efficiently synthesized *via* the O-alkylation of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate with 1,2-dichloroethane over ionic type phase transfer catalysts, such as tetrabutyl ammonium bromide and benzyltriethyl ammonium chloride. The ionic type phase transfer catalysts showed higher catalytic activities than the nonionic type phase transfer catalysts, such as triethylamine, pyridine, 18-crown-6, and polyethylene glycol 400/600, in the O-alkylation reaction. The conversion of the disodium salt of more than 97% and the selectivity of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate of more than 98% were achieved when the O-alkylation reaction was synergistically catalyzed by tetrabutyl ammonium bromide and potassium iodide.

Keywords: O-alkylation, Phase Transfer Catalysis, Tetrabutyl Ammonium Bromide, Potassium Iodide, Diethyl 3,4-Ethylenedioxythiophene-2,5-dicarboxylate

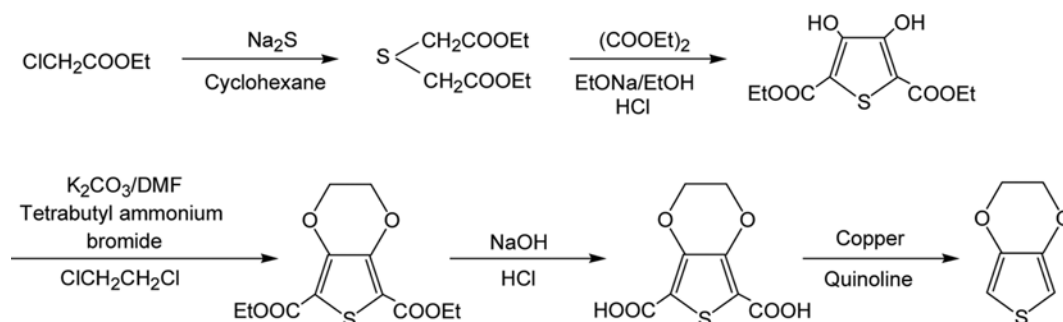
INTRODUCTION

Poly(3,4-ethylenedioxythiophene), as a new type of conjugated conducting polymer, is widely used in the preparation of organic light emitting diodes (OLED), solid electrolyte capacitors, antistatic coatings, organic solar cells, electrode coatings, and transparent electromagnetic interference shields due to its high electrical conductivity, good environmental stability, and facile preparation of transparent film [1-7]. 3,4-Ethylenedioxythiophene, as the monomer of poly(3,4-ethylenedioxythiophene), can be synthesized through a five-step route [8,9], including nucleophilic substitution, condensation, O-alkylation, hydrolyzation, and decarboxylation reactions (Scheme 1). However, in the O-alkylation step, the yield of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate is low when the alkylation reaction between diethyl 3,4-dioxythiophene-2,5-dicarboxylate and 1,2-dichloroethane is conventionally carried out with potassium carbonate as a base agent and *N,N*-dimethylformamide as a solvent.

To improve the O-alkylation rate, two types of catalysts, alky-

lamine and quaternary onium salt, have been investigated with *N,N*-dimethylformamide as a solvent and potassium carbonate as a base agent [10,11]. The O-alkylation reactions catalyzed by triethylamine and tetrabutyl ammonium bromide are illustrated in Scheme 2.

When triethylamine was used as the catalyst for the O-alkylation of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate with alkyl dibromides in *N,N*-dimethylformamide, 3,4-cycloalkoxy-2,5-diethoxy carbonylthiophene derivatives were more rapidly produced than those produced in the conventional potassium carbonate and *N,N*-dimethylformamide reaction system [10]. When tetrabutyl ammonium bromide was used as the catalyst for the O-alkylation of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate with 1,2-dichloroethane in the presence of *N,N*-dimethylformamide as a solvent and potassium carbonate as a base agent at 130-135 °C, the yield of 3,4-ethylenedioxythiophene-2,5-dicarboxylic acid reached 76.9% after sodium hydroxide and following hydrochloric acid treatment [11]. In the above mentioned catalytic systems, trialkylamine and tetrabutyl ammonium bromide enhanced the O-alkylation reac-

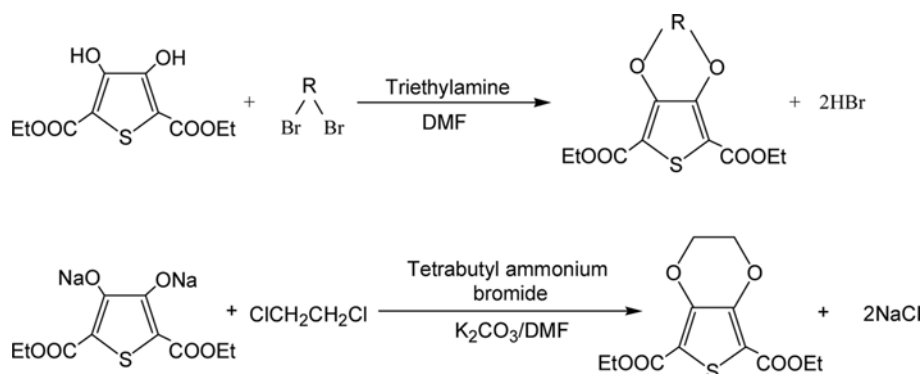


Scheme 1. Five-step synthesis of 3,4-ethylenedioxythiophene.

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Scheme 2. O-alkylation reactions catalyzed by triethylamine and tetrabutyl ammonium bromide [10,11].

tion. However, the yields of 3,4-cycloalkoxy-2,5-diethoxy carbonylthiophene derivatives are not satisfactory. Since potassium carbonate and *N,N*-dimethylformamide are also used in quantity, the O-alkylation reaction is worthy of further investigation.

Recently, it has been reported that potassium iodide can be used as an effective catalyst in organic reactions [12–14]. For example, potassium iodide, 18-crown-6, and TBHP effectively co-catalyzed the arylsulfonylation of alkenes with sulfonylhydrazides [12]. Potassium iodide and tetrabutyl ammonium bromide co-catalyzed the reaction between sodium cyanide and *p*-chlorobenzyl chloride to *p*-chlorophenyl acetonitrile [13]. The reaction involved in situ formation of *p*-chlorobenzyl iodide, which led to the increase in reaction rate. In the reduction of α -haloketone to ketone, potassium iodide catalyzed the reduction reaction [14]. First, α -haloketone reacted with I^- to form α -iodoacetophenone because I^- served as both a good nucleophile and a good leaving group. Then, α -iodoacetophenone was easily reduced to ketone, giving I^- ion. The resultant I^- ion could directly go into the next catalytic cycle. Since potassium iodide can effectively activate halohydrocarbons, it could be a potential catalyst in the O-alkylation reaction using 1,2-dichloroethane as an alkylation reagent.

We report here the synthesis of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate *via* the O-alkylation of solid phase disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate with 1,2-dichloroethane using tetrabutyl ammonium bromide (or benzyltriethyl ammonium chloride) as an ionic type phase transfer catalyst and potassium iodide as a co-catalyst. The reaction rate and product yield were significantly improved by using tetrabutyl ammonium bromide and potassium iodide catalysts. The present reaction system avoided the utility of both potassium carbonate and *N,N*-dimethylformamide, which is different from the conventional O-alkylation process. Furthermore, using solid phase disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate as the starting material avoided the acidification of the disodium salt to diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate. The effect of types of phase transfer catalysts and reaction parameters on the O-alkylation reaction was investigated in detail, and the catalytic reaction routes were also suggested.

EXPERIMENTAL

1. Chemicals

Disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxy-

late (>99%) was synthesized from diethyl thiodiglycolate and diethyl oxalate according to the previously reported method [8,9]. 1,2-Dichloroethane, potassium iodide, triethylamine, pyridine, 18-crown-6, polyethylene glycol 400/600, benzyltriethyl ammonium chloride, and tetrabutyl ammonium bromide were purchased from Sinopharm Chemical Reagent Co., Ltd. All the chemicals were of analytical grade and used as received without further purification.

2. Synthesis of Diethyl 3,4-Ethylenedioxythiophene-2,5-dicarboxylate

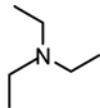

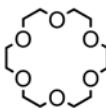
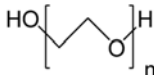
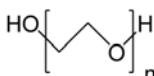
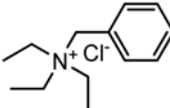
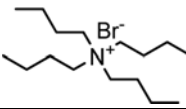
0.02 mole of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and given amounts of phase transfer catalyst and potassium iodide were added into 60 mL of 1,2-dichloroethane in a 250 mL three-necked flask equipped with a condenser under stirring at 300 rpm. The reaction was carried out at different reaction temperatures in a water bath. At different reaction intervals, the reaction mixture was analyzed on a Varian HPLC system equipped with a reverse-phase column (ChromSpher 5 C18, 4.6 mm×250 mm) and a UV detector ($\lambda=295$ nm) at 30 °C. The mobile phase consisted of methanol and 1% acetic acid aqueous solution (70 : 30, v/v) with a flow rate of 0.6 mL/min. The concentrations of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate were calculated by the external standard method.

RESULTS AND DISCUSSION

1. Effect of Phase Transfer Catalyst

The conversions of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and the selectivities of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate in the O-alkylation reaction between the disodium salt and 1,2-dichloroethane catalyzed by various phase transfer catalysts are listed in Table 1. The controlled experiment showed that the O-alkylation reaction could not be carried out without phase transfer catalyst. Potassium iodide itself had no catalytic activity for the O-alkylation reaction. When triethylamine, pyridine, 18-crown-6, polyethylene glycol 400, and polyethylene glycol 600 were used as phase transfer catalysts, the conversion of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate was less than 26% and the selectivity of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate was less than 64% after reacting at 83 °C (refluxing temperature) for 8 h. When the O-alkylation reaction was catalyzed by benzyltriethyl ammonium chloride and tetrabu-

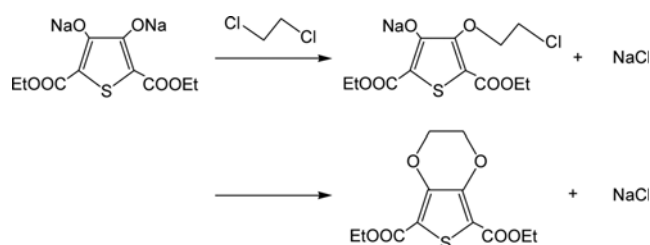
Table 1. The conversion of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and the selectivity of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate^a

Phase transfer catalysts	Chemical structures of catalysts	Catalyst loadings (mole)	Conversions (%)	Selectivities (%)
Controlled	/	/	0	0
Potassium iodide	KI	0.003	0	0
Triethylamine		0.003	14.7	47.8
Pyridine		0.003	19.2	12.0
18-Crown-6		0.003	20.5	63.8
Polyethylene glycol 400		0.003	21.8	9.0
Polyethylene glycol 600		0.003	25.1	62.4
Benzyltriethylammonium chloride		0.003	94.6	99.2
Tetrabutyl ammonium bromide		0.003	96.0	98.7

^aThe O-alkylation reaction was carried out by using 0.02 mole of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and 60 mL of 1,2-dichloroethane over different phase transfer catalysts at 83 °C (reflux temperature) for 8 h

tyl ammonium bromide at 83 °C for 8 h, the conversion of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate was 94.6% and 96.0%, respectively. And the selectivity of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate was 99.2% and 98.7%.

The O-alkylation reaction was enhanced by the phase transfer catalysts, but their effect on the O-alkylation reaction was dependent on their chemical structures. The ionic type phase transfer catalysts had higher catalytic activities than the nonionic type phase transfer catalysts for the O-alkylation reaction. It can be explained as being due to that the organic cation counterparts of the ionic type phase transfer catalysts effectively coordinated with the organic anion counterparts of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and transferred them from solid state into 1,2-dichloroethane phase for the O-alkylation reaction. The nonionic type phase transfer catalysts had weak coordination interaction with disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate, giving low disodium salt conversion. Otherwise, the selectivities of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate were low when nonionic type phase transfer catalysts were used. It can be explained as that the formation of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate was *via* two steps: mono-alkylation and O-alkylation (Scheme 3). The structures of the nonionic type phase transfer catalysts affected the conversion of mono-alkylation product to O-alkyla-

**Scheme 3. The process of O-alkylation reaction.**

tion product, giving different selectivities of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate.

Tetrabutyl ammonium bromide and benzyltriethyl ammonium chloride both had good catalytic activity for the O-alkylation reaction. Herein, tetrabutyl ammonium bromide was chosen as the phase transfer catalyst in the following studies.

2. Effect of Tetrabutyl Ammonium Bromide Loading

Fig. 1 shows the effect of tetrabutyl ammonium bromide loading on the O-alkylation reaction of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate with 1,2-dichloroethane. When the O-alkylation reaction was carried out at 83 °C with tetrabutyl ammonium bromide loadings of 0.0005, 0.001, and 0.002 mole,

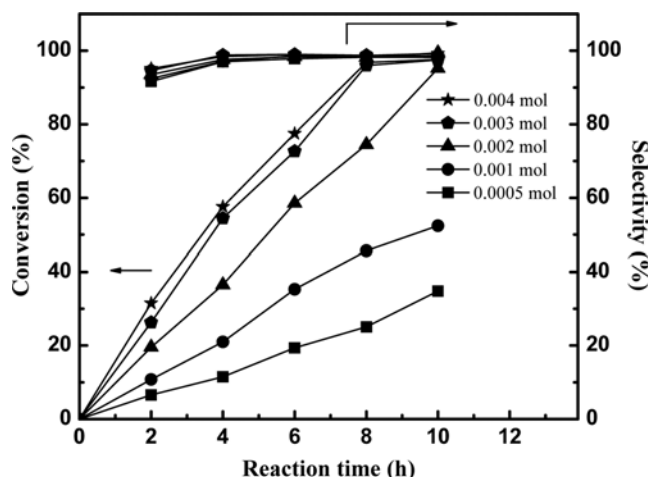


Fig. 1. Effect of tetrabutyl ammonium bromide loading on the O-alkylation reaction between disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and 1,2-dichloroethane. The O-alkylation reaction was carried out by using 0.02 mole of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and 60 mL of 1,2-dichloroethane with different loadings of tetrabutyl ammonium bromide at 83 °C.

the conversion of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate gradually increased to 34.8%, 52.4%, and 95.2%, respectively, with prolonging the reaction time to 10 h. When tetrabutyl ammonium bromide loadings were increased to 0.003 and 0.004 mole, the conversion of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate gradually increased to 96.0% and 96.8%, respectively, with prolonging the reaction time to 8 h. With further prolonging the reaction time to 10 h, the conversion slightly increased to 97.5% and 97.6%, respectively. The selectivity of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate was higher than 98% at different catalyst loading levels after reacting for 10 h. In-

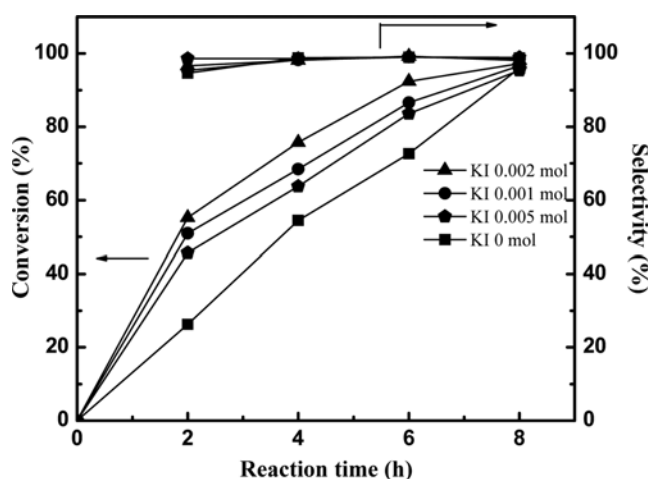


Fig. 2. Effect of KI loading on the O-alkylation reaction between disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and 1,2-dichloroethane. The O-alkylation reaction was carried out by using 0.02 mole of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate, 0.003 mole of tetrabutyl ammonium bromide, and 60 mL of 1,2-dichloroethane with different loadings of KI at 83 °C.

ing the phase transfer catalyst loading favored the O-alkylation of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate with 1,2-dichloroethane to diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate.

3. Effect of Potassium Iodide Loading

Fig. 2 shows the effect of potassium iodide loading on the O-alkylation reaction in the presence of tetrabutyl ammonium bromide as the phase transfer catalyst with a loading of 0.003 mole at 83 °C. When potassium iodide loading was 0, 0.001, 0.002, and 0.005 mole, with increasing the reaction time from 2 to 8 h, the conversion of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate increased from 26.3% to 96.0%, 51.0% to 96.7%, 55.2% to 97.2%, and 45.7% to 95.4%, respectively. The selectivity of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate was more than 98% after reacting for 8 h. The presence of potassium iodide obviously enhanced the O-alkylation reaction, indicating that potassium iodide and tetrabutyl ammonium bromide synergistically catalyzed the O-alkylation reaction. When the loading of potassium iodide was 0.002 mole, the maximum conversion of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate was achieved at different reaction times. With further increasing the loading of potassium iodide to 0.005 mole, the conversion of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate at different reaction times was less than those with potassium iodide loading of 0.002 mole. The reason is that I^- can replace the Cl^- of 1,2-dichloroethane, giving high alkylation rate. However, if the concentration of I^- is too high, excessive I^- anions could combine with the I^- of iodoethane, inhibiting the O-alkylation reaction.

4. Effect of Reaction Temperature

The effect of reaction temperature on the O-alkylation reaction is shown in Fig. 3. The conversion of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and the selectivities of diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate increased from 42.1%

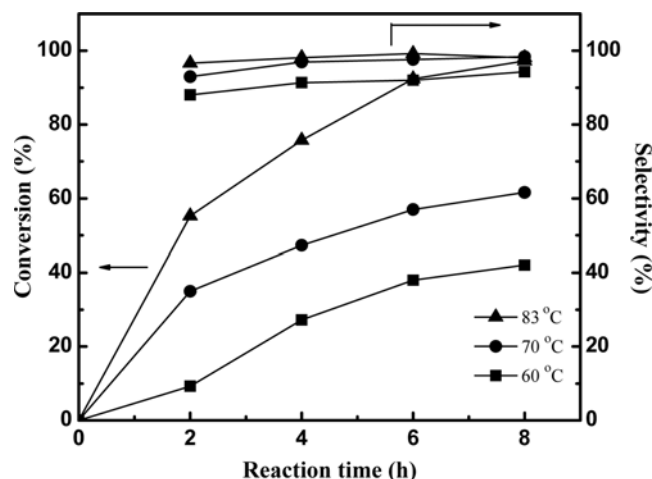
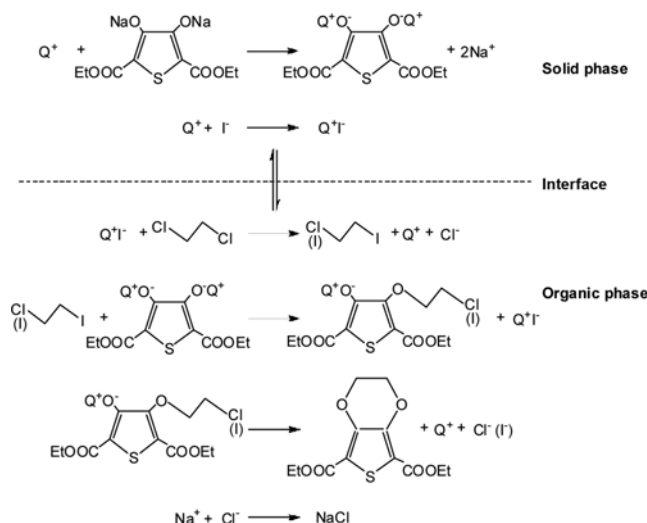


Fig. 3. Effect of reaction temperature on the O-alkylation reaction between disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and 1,2-dichloroethane. The O-alkylation reaction was carried out by using 0.02 mole of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate, 0.003 mole of tetrabutyl ammonium bromide, 60 mL of 1,2-dichloroethane, and 0.002 mole of KI at different reaction temperatures.



Scheme 4. Possible reaction routes in the O-alkylation reaction between disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and 1,2-dichloroethane catalyzed by tetrabutyl ammonium bromide and KI.

to 97.2% and 94.3% to 98.1%, respectively, when the reaction temperature was increased from 60 to 83 °C after reacting for 8 h. The results showed that increasing reaction temperature favored the O-alkylation reaction.

5. Reaction Routes

Possible reaction routes in the O-alkylation reaction catalyzed by both tetrabutyl ammonium bromide and potassium iodide are illustrated in Scheme 4. Tetrabutyl ammonium bromide played the role of the phase transfer catalyst in the O-alkylation reaction because it could be easily dissolved in 1,2-dichloroethane. Tetrabutyl ammonium cations (Q⁺) interacted with diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate anions and transferred them into 1,2-dichloroethane phase. At the same time, tetrabutyl ammonium cations interacted with potassium iodide and produced Q⁺I⁻. The resultant Q⁺I⁻ was transferred into 1,2-dichloroethane phase. Then, 1,2-dichloroethane interacted with Q⁺I⁻ to form iodide-substituted chloroethane by replacing Cl⁻ in 1,2-dichloroethane with I⁻. In the liquid organic phase, tetrabutyl ammonium cation-coordinated diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate anion reacted with iodide-substituted dichloroethane to form diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate. The recovered Q⁺I⁻ took part in the next catalytic cycle. The resultant Cl⁻ and Na⁺ reacted to form NaCl.

CONCLUSIONS

Ionic type phase transfer catalysts, such as tetrabutyl ammonium bromide and benzyltriethyl ammonium chloride, showed higher

catalytic activities than the nonionic type phase transfer catalysts, such as triethylamine, pyridine, 18-crown-6, polyethylene glycol 400, and polyethylene glycol 600, in the O-alkylation of disodium salt of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate with 1,2-dichloroethane to diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate.

Tetrabutyl ammonium bromide and potassium iodide efficiently co-catalyzed the O-alkylation reaction. Tetrabutyl ammonium bromide as the phase transfer catalyst transferred diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate anion and I⁻ into 1,2-dichloroethane phase. Cl⁻ in 1,2-dichloroethane was substituted with I⁻. The resultant iodide-substituted chloroethane easily reacted with diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate anion in organic phase to form diethyl 3,4-ethylenedioxythiophene-2,5-dicarboxylate with a high yield. The method probably has potential application in alkylation reaction between chloroalkane and solid organic reactant.

ACKNOWLEDGEMENT

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