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ORGANIC SYNTHESIS USING PTC-5: NUCLEOPHILIC AROMATIC SUBSTITUTION UNDER LIQUID-LIQUID AND SOLID-LIQUID PHASE TRANSFER CONDITIONS[1].

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Abstract - The reaction of 1-chloro-4-nitrobenzene(1) with dithiols generated in situ from thiouronium salts(2) under PT conditions, which in turn have been procured by the reaction of appropriate α,ω-dibromoalkanes with thiourea have been investigated. The reactions of (1) with various diols have also been investigated and their reaction mechanism is discussed.

INTRODUCTION

Nucleophilic aromatic substitution reactions have been studied relatively to a lesser extent than aliphatic nucleophilic substitution reactions under phase transfer conditions (PTC)[2-4]. Earlier these reactions have been performed using quaternary ammonium salts[5,6] or crown ethers[7,8] as PT catalysts. But recently nucleophilic aromatic substitution reactions of dihalobenzene derivatives have been performed under PT conditions using polyethlene glycols as catalysts[9]. Previously we have reported the synthesis of alkyl aryl thioethers from thioiminium salts and organic halides under PT conditions[10]. Here we report the results of our studies on the reaction of (1) with dithiols and diols under liquid-liquid and solid-liquid PT conditions.

RESULTS AND DISCUSSION

On refluxing a mixture of equivalent amounts of appropriate dithiouronium salt(2, n = 2) and (1) under solid-liquid PT conditions using pulverized potassium hydroxide as base, benzene as organic phase and triethylbenzylammonium chloride(TEBA) as catalyst, a product mixture consisting of four components is obtained after the usual work up. The first component, Rf 0.58 (benzene) has been found to be 4,4'-dinitrodiphenyl sulphide(3)(mmp; ir)[11]. The second component 1,2-bis(4-nitrophenylthio) ethane (4,n=2), M^+ m/z 336 and ^1H nmr δ 3.5(s,4H,2x-CH_2-), 7.35-8.5(q,8H,due to 1,4-disubstituted benzene). IR ν_{max} 1570, 1510, 1330, 1080, 840 cm^{-1}. The third component Rf 0.34 (benzene) has been found to be 4,4'-dinitrodiphenyl disulphide(5)[12].

The fourth component Rf 0.2($CHCl_3$) could not be isolated in amounts sufficient for structure elucidation. In order to see the synthetic utility of this technique the reactions of (1) have been performed with 2(n = 5,6) and the results of these investigations are tabulated in table-I.

The reaction here may be thought to proceed either through simple aromatic nucleophilic displacement reaction[13], or it may follow free radical chain mechanism(SRN') as depicted below[14,15,16].

$$\begin{array}{lcl} \mathrm{ArX} & \xrightarrow{e} & \mathrm{ArX}^- \\ \mathrm{ArX}^- & \longrightarrow & \mathrm{Ar} + \mathrm{X}^- \\ \mathrm{Ar} + \mathrm{Y}^- & \longrightarrow & \mathrm{ArY}^- \\ \mathrm{ArY}^- + \mathrm{ArX} & \longrightarrow & \mathrm{ArY} + \mathrm{ArX}^- \end{array}$$

Scheme - I

Table 1 Reactions of (1) with dithiouronium salts under solid-liquid and liquid-liquid PTC.

Sr No	Dithiouronium salt	Time in[c,d] hrs	% yields[a] of 3	4	5
1.	2a	10	6(10)	25(20)[b]	20
2.	2c	12	5(15)	35(25)	20
3.	2d	12	5(12)	35(25)	25

(a) In all these reactions unreacted (1) has been isolated in small amounts.

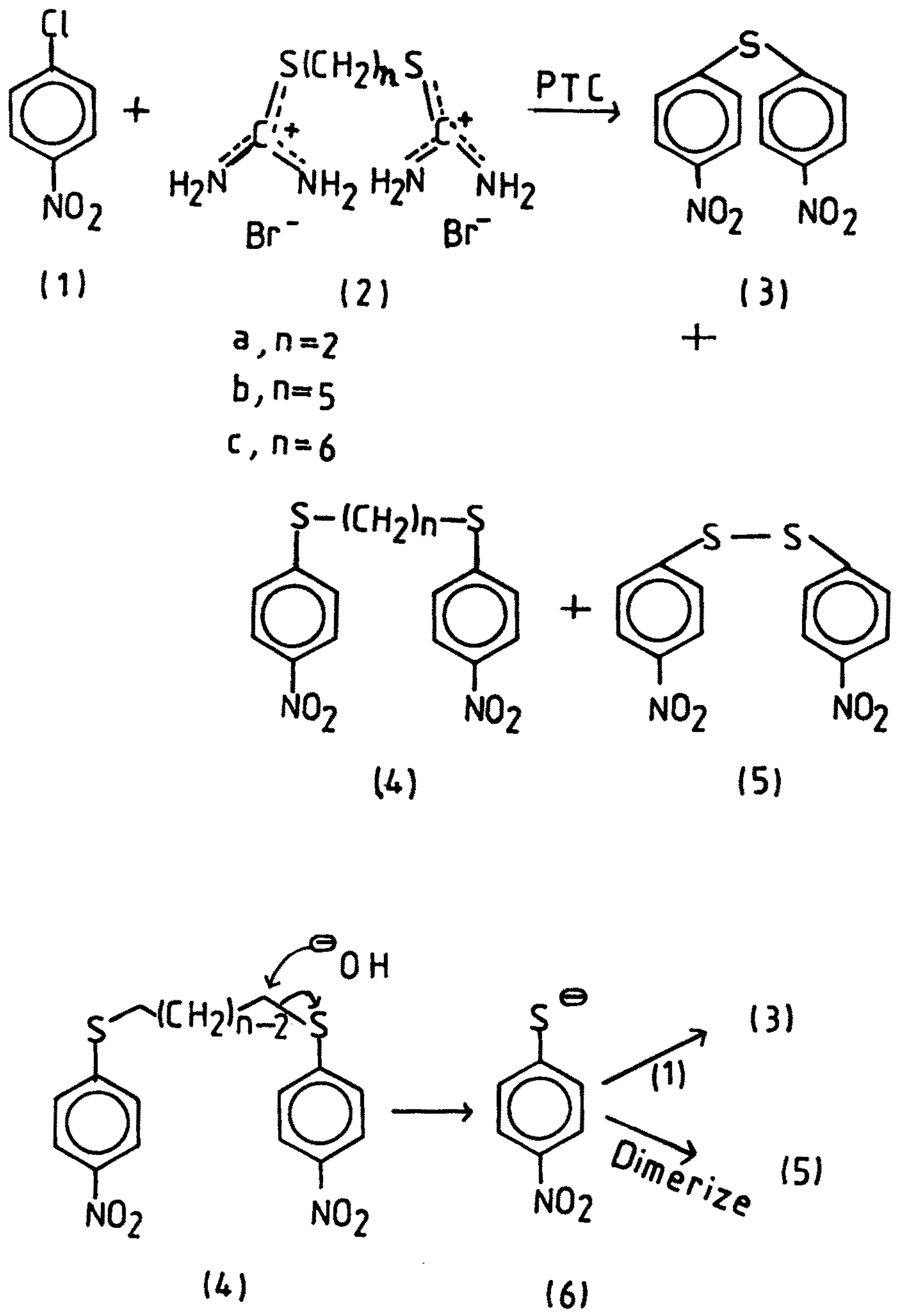
(b) Figures in paranthesis refer to the yields under liquid-liquid PTC.

(c) Addition of p-benzoquinone retards the rate of reaction.

(d) In the absence of the catalyst (TEBA) the rate of reaction is very slow indicating that the thiouronium salts under these conditions do not act as PT catalysts.

The support for the latter mechanism comes from esr measurements which shows at 3350 gauss (g = -2.00). But when an electron trap (p-benzoquinone) is added to the reaction mixture, the rate of the reaction is retarded and the reaction does not stop. This indicates that reaction does not follow free radical chain mechanism exclusively, rather, both the mechanisms viz free radical chain and aromatic nucleophilic diplacement reaction are operative. Under the latter mechanism the formation of products may be explained as depicted in Scheme-II.

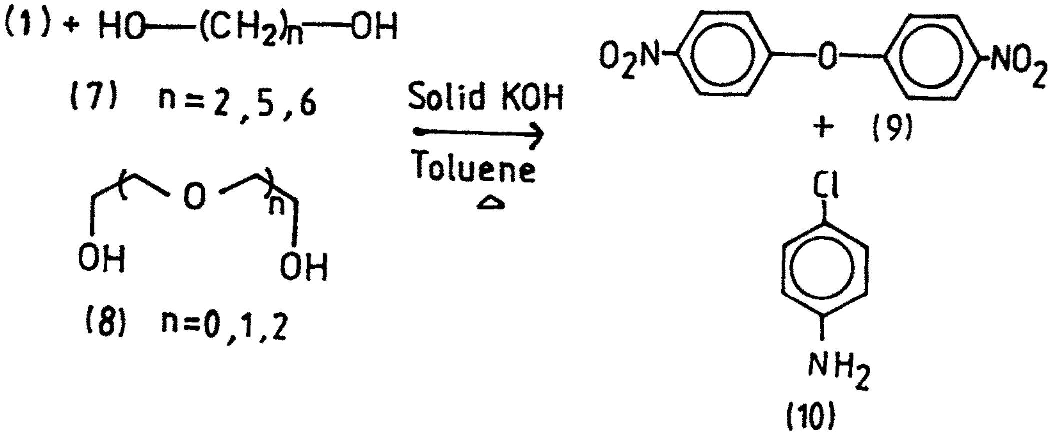
A hydroxide ion acts as a nucleophile and attacks the sp^3 carbon atom adjacent to the sulphur atom in (4) and p-nitrothiophenolate ion being a better leaving group is eliminated. p-Nitrothiophenolate ion thus formed would act as a nucleophile and may react either with (1) to give (3) or it may dimerize to (5). In order to establish this 4(n=5) has been refluxed under the same PT reaction conditions. On monitoring the progress of the reaction (tlc) it has been found that after 0.5 hr the formation of (3) and (5) started (tlc) and the solution turned dark red. Thus, it has been confirmed that (4) does decompose under the reaction conditions to give (3) and (5) through the intermediacy of (6) which also accounts for the lower yield of(4).


Cl
NO2
+
S(CH2)nS
C+
H2N
NH2
Br−
PTC
S
(1)
(2)
(3)
a, n=2
b, n=5
c, n=6
+
S−(CH2)n−S
S — S
(4)
(5)
⊖OH
S⌒(CH2)n−2⌒S
S⊖
(1)
Dimerize
(6)

SCHEME -II

These results promoted us to further exploit the synthetic utility of these reaction conditions and we planned to investigate the reaction of (1) with other binucleophiles. For this purpose the reactions of some easily available diols have been investigated under the conditions.

On refluxing a solution of equivalent amounts of (1) and (7, n = 2) in toluene containing solid KOH as base and TEBA as catalyst, a product mixture consisting of three components is obtained. On addition of methanol to the semi-solid residue a crystalline product separated out which has been found to be 4,4'-dinitrodiphenyl ether (9)[17]. The mother liquor consisted of one major component which after purification has been found to be 4-chloroaniline (10)[18]. The third component could not be isolated in amounts sufficient for structure elucidation. This reaction has been found to be very fast in the absence of TEBA which indicates that ethyleneglycol itself acts as a PT catalyst[9]. This promted us to investigate the catalytic role of some simple diols in these reactions.



$$(1) \xrightarrow[\text{TEBA}, \Delta]{\text{S-L PTC}} \text{No Reaction}$$

Thus the above reaction has been performed using various glycols viz trimethylene, tetramethylene, hexamethylene, diethylene, triethylene and tetraethylene glycols in catalytic amounts under solid-liquid PT conditions with KOH as base and toluene as solvent at reflux temperature. With all these glycols the reaction has been found to be very fast and is complete in 30 minutes (tlc). The results of these investigations are tabulated in Table-II.

But under liquid-liquid PT conditions using 50% aqueous KOH, these diols fails to catalyse the reaction owing to higher solubility of diols in aqueous phase. Further, the reaction does not proceed in the absence of a diol which again supports its catalytic role.

Table II Reactions of (1) with various glycols

Sr No	Catalyst	Time in hrs	% yield of (9)	(10)
1.	None	6	0	0
2.	TEBA + 7, n = 2	1	10	5
3.	7, n = 2	0.5	15	4
4.	7, n = 3	"	15	3
5.	7, n = 4	"	15	5
6.	7, n = 6	"	15	5
7.	8, n = 0	"	20	5
8.	8, n = 1	"	25	5
9.	8, n = 2	"	25	5

Here the reaction may be thought to proceed through either of the two mechanisms (i) a simple nucleophilic aromatic substitution (SNAr) or (ii) a free radical chain mechanism (SRN).

On performing these reactions in the presence of an electron trap, (p-benzoquinone) in an equivalent amount the rate of the reaction is considerably retarded and on using two equivalents of the electron trap, the reaction does not proceed at all even on prolonged heating, unlike in the case of the reactions with dithiols. This is further supported by the esr studies of the reaction which shows a signal at H_s=3350 gauss (g = 1.99).

The formation of 4-chloroaniline in these reactions indicates that $-NO_2$ group has been reduced to $-NH_2$. In order to establish this the reaction of O- and p-nitroaniline has been performed under the same reaction condition and 2,2'-diamine azobenzene and 4,4'-diaminoazo benzene have been isolated respectively as the major products. But mechanims of their formation could not be established.

Conclusion :

Thus with dithiols the reaction follow simple nucleophilic aromatic substitution as well as free radical chain mechanism, whereas with diols, it is free radical chain process only. The former observation is contrary to the one proposed by Bunnet that when electron withdrawing groups are present, aromatic nucleophilic substitution SNAr mechanism prevails[16]. Secondly, like polyethylene glycols these simple diols can also act as efficient PT catalysts under solid-liquid PTC in nucleophilic aromatic substitution reactions, whereas dithiols do not act as catalysts but as nucleophiles.

EXPERIMENTAL

Melting points were determined in capillaries and are uncorrected. ^1H NMR were recorded on EM-390, 90MHz instrument, Mass spectram were run on Jeol JMS D-300 spectrometer instrument and IR spectra were recorded on 2000 spectromom spectrophotometer. ESR spectra were recorded in capillaries, on JES-FE 3X6 instrument.

Preparation of Dithiouronium salts :

To a solution of thiourea (0.02 mole) in alcohol was added , -dibromoalkane(0.01 mole) and reaction mixture was refluxed. The progress of the reaction was monitored by tlc and the reaction was complete after 18 hours (tlc). The solvent was removed under reduced pressure and the salt was dried in vacuum. These salts were used as such for further reaction. Analysis : 2,n = 2 Found: C,13.90; H, 3.34; N, 16.15. $C_4H_{12}N_4S_2Br_2$ C, 14.12; H, 3.53; N, 16.47 % , 2, n = 3 Found: C, 22.69; H, 4.77; N, 14.78. $C_5H_{12}N_4S_2Br_2$ requires C, 22.50; H, 4.84; N, 15.05% . 2, n = 4 Found : C, 24.59; H, 5.17; N, 14.24; $C_6H_{12}N_2S_2Br_2$ requires C, 24.87; H, 5.18; N,14.51 % .

General Procedure

Reactions of dithiouronium salts with (1) under solid-liquid PTC :

To a solution of (1) (3.1g, 0.02 mole) in benzene was added dithiouronium salt 2, n = 2(3. 16g, 0.01 mole), triethylbenzylammonium chloride as catalyst and pulverized potassium hydroxide (2g) as base. The reaction mixture was refluxed and the progress of the reaction was monitored by tlc. The organic layer was separated, washed with water and dried (Na_2SO_4). The residue was found to consist of four components which were separated through column chromatography over silica gel using benzene as eluent. The first component (4,4'-Dinitrodiphenylsulphide) and component (4,4'-Dinitrodiphenyl disulphide) were found common in all cases and were identical with authentic samples.

Similarly the reaction of various 2 were performed and their m.p., mass, analysis, ^1H NMR and ir spectral data respectively are given below..

Reaction of (2), n = 2 with (1) M.p. 120-21°C $M^{+\cdot}$ m/z 336, ^1H NMR($CDCl_3$) δ3.5(s,4H,2xCH_2-), 7.3-8.35(q,8H,aromatic); ν_{max}($CHCl_3$) 1570, 1510, 1330, 1080, 840 cm^{-1},[Found: C, 50.21; H, 3.76; N, 8.35; $C_{14}H_{12}N_2O_4S_2$ requires C,50.00, H,3.57; N,8.33%].

Reaction of (2), n = 5 with (1): M.p. (92°C), $M^{+\cdot}$ m/z 378, ^1H nmr($CDCl_3$) δ 1.48 (m,6H;S-CH_2-($\underline{CH}_2$)$_3$-CH_2-S-), 3.0(t,4H,-S-$\underline{CH}_2$-S), 7.24-8.2(q,8H,aromatic H). ν_{max}($CHCl_3$) 3200, 1585, 1500, 1340, 1090, 840 cm^{-1}.
ESR : H_s = 3375 Gauss, g_s = 2.08,[Found: c, 53.81; H, 4.71; N, 7.31; $C_{17}H_{18}N_2O_4S_2$ requires C, 53.97; H, 4.76; N, 7.41%].

Reaction of (2), n = 6 with (1) M.p. (120-23°C) $M^{+\cdot}$ m/z 392, ^1H nmr($CDCl_3$)δ 1.6(m,8H,-SCH_2($\underline{CH}_2$)$_4$$CH_2$S-), 3.0(t,4H,S$\underline{CH}_2$($CH_2$)$_4$$\underline{CH}_2$S-), 7.1-8.2(q,8H,aromatic H), ν_{max}($CHCl_3$) 3200, 1585, 1340, 1095, 850 cm^{-1}.
ESR : H_s = 3375 Gauss, g_s = 2.08,[Found C, 54.86; H, 5.27; N, 7.04; $C_{18}H_{20}N_2O_4S_2$ requires C,55.10; H,5.10; N,8.14%].

Reaction of dithiouronium salt with (1) under solid-liquid PTC in the presence of p-benzoquinone :

To a solution of (1) (0.02 mole) in benzene, was added thiouronium salt (0.01 mole), TEBA as catalyst, pulverized potassium hydroxide (2g) as base, and p-benzoquinone as an electron trap (0.01 mole) and the reaction mixture was refluxed on water bath. The progress of the reaction was monitored by tlc and the rate of reaction was decreased.

General procedure

Reactions of dithiouronium salts with (1) under liquid-liquid PTC using 60% aqueous potassium hydroxide solution :

To a solution of (1) (0.02 mole) in benzene, was added dithiouronium salt (0.01 mole), triethylbenzylammonium chloride (TEBA) as catalyst, and 60% aqueous potassium hydroxide (20 ml). The reaction mixture was refluxed on water bath. The progress of the reaction was monitored by tlc. After completion of the reaction (10 hrs), the organic layer was separated, washed with water and dried (Na_2SO_4). The residue obtained after work up was found to consist of four components in all cases, which were isolated through column chromatography over silica gel using benzene as eluent. The first component (4,4'-dinitrodiphenylsulphide) and third component (4,4'-dinitrophenyl disulphide) were found common in all cases and were comparable with authentic samples.

General procedure

Reactions of diols with (1) under solid-liquid PTC using solid KOH as base :

A mixture consisting of solid potassium hydroxide (2g) (1) (0.01 mole) and the appropriate diol, as catalyst in dry toluene (25 ml), was refluxed. The reaction started immediately and the reaction mixture turned red. The progress of the reaction was monitored by tlc. The reaction was complete [tlc, disappearance of (1)] after 30 minutes. The organic layer was washed with water, dried (Na_2SO_4) and the solvent distilled off. The residue was found to consist of three components. The component Rf 0.85(50:50 hexane:benzene) separated out on addition of methanol to the semi solid residue and was found to be identical with an authentic sample of 4,4'-dinitrodiphenyl ether. The mother liquor was concentrated and chromatographed to give the second component which was found to be identical with an authentic sample of 4-chloroaniline. The third component Rf 0.35(50:50 hexane:benzene) could not be isolated in sufficient amount for structure illucidation.

Alternately, the above reaction was performed using an excess of diol, but the same products were formed in the same ratio under identical conditions.

Reaction of diols with (1) under solid-liquid PTC using solid K_2CO_3 as base :

A mixture of solid potassium carbonate (5g), (0.01 mole) and diethyleneglycol in toluene was refluxed on a hot plate. But even after a long period the reaction did not show any progress and substrate(1) was isolated as such.

Reaction of diols with (1) under solid-liquid PTC using solid KOH in the presence of p-benzoquinone :

A mixture of solid KOH (2g), (1) (0.01 mole), diethyleneglycol as catalyst, in toluene (25 ml), containing p-benzoquinone as electron trap, was refluxed on a hot plate. The progress of the reaction was monitored by tlc. After 2 hours, component Rf 0.85 (hexane:benzene) started forming and the reaction did not proceed to completion.

Alternatively, the above reaction was performed using two equivalents of p-benzoquinone and the reaction did not show any progress even on prolonged heating.

Reactions of diols with (1) under solid-liquid PTC using solid KOH and TEBA as catalyst :

The reaction was performed as described above with the only difference that TEBA was used as catalyst. In this experiment the reaction took relatively longer time and was complete after 1.5 hours (tlc).

Reaction of (1) with KOH in the absence of diol :

A mixture of solid KOH, TEBA as catalyst, (1) in toluene was refluxed on a hot plate for a prolonged period, but it did not show any progress.

Reaction of diol with (1) under liquid-liquid PTC :

A mixture of 50% aqueous potassium hydroxide (5 ml), toluene (25 ml), (1), (0.01 mole) and diethyleneglycol as catalyst was refluxed. But the reaction did not show any progress even on prolonged heating.

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