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Phase-Transfer Catalyzed Reactions on Polymers

4. The Reaction of Crosslinked Poly(chloromethylstyrene) with Phthalimide

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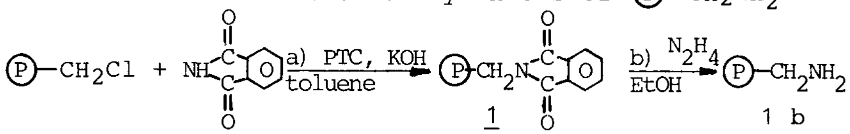
SUMMARY

The reaction of crosslinked chloromethylated polystyrene with phthalimide and solid KOH in organic aprotic solvents in the presence of phase-transfer catalysts leads to polymeric N-alkyl derivative of phthalimide, which is a convenient starting material for the synthesis of poly(aminomethylstyrene).

INTRODUCTION

Crosslinked poly(aminomethylstyrene) Ⓟ—CH_2NH_2) is widely used in the solid-phase synthesis of peptides (MERRIFIELD 1969, SPARROW 1976, SARIN et al. 1980), as a weak-base anion-exchange resin (HELFFERICH 1962), and as a polymeric reagent (TAM et al. 1980, REBEK et al. 1975). Usually, Ⓟ—CH_2NH_2 is prepared in the reaction of crosslinked poly(chloromethylstyrene) (Ⓟ—CH_2Cl) with ammonia under elevated pressure (RICH and GURWARA 1975, ORŁOWSKA and DRABAREK 1980), with potassium phthalimide in anhydrous dimethylformamide followed by hydrazinolysis (WEINSHENKER and SHEN 1972), or with hexamethylenetetramine followed by alkaline hydrolysis (TROSTYANSKAYA and TEVLINA 1957, RICARD et al. 1981). These reactions are time-consuming and the last two ones proceed only in polar aprotic solvents at temperatures up to 140°.

Recently, SANTANIELLO and PONTI (1980) have reported a convenient synthesis of N-alkyl phthalimides via phase-transfer(PT) catalyzed reactions of phthalimide with alkyl halides in toluene in the presence of solid potassium hydroxide. We thought that a similar procedure might be used to obtain compound 1 which is an intermediate in the Gabriel synthesis of Ⓟ—CH_2NH_2



The second step of this procedure (reaction 1b), as a known process, will not be discussed in the present communication.

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EXPERIMENTAL

Chloromethylated polystyrene crosslinked with 1% of divinylbenzene (Ⓟ—CH_2Cl) and containing 22,5% of chlorine was obtained as reported previously (GÓŹDŹ and KOLARZ 1980). The product of the reaction of Ⓟ—CH_2Cl with phthalimide in the presence of solid, powdered potassium hydroxide and phase-transfer catalysts was analyzed for chlorine content by combustion in an oxygen-filled flask and automatic potentiometric titration with a 0,01 M silver nitrate solution. Phase-transfer catalysts used, i.e., 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) and tetrabutylammonium bromide (TBAB) were those reported earlier (GÓŹDŹ and RAPAK 1981).

A 300 mg sample of Ⓟ—CH_2Cl containing 1,9 mmol of chlorine was weighed into a 5-ml glass vial, together with 355 mg of phthalimide (2,41 mmol, 27% excess to Cl), 130 mg of solid, powdered potassium hydroxide (2,3 mmol, 20% excess to Cl), a given amount of the catalyst (Tab. 1) and 4 ml of the solvent(s). The vial was sealed under nitrogen and shaken continuously in an oil bath at 100° for the desired time. Next, the sample was separated on a filter, washed with methanol, methanol-water (vol. ratio 1:1), water, acetone, finally with methanol, and dried i.vac. at 50° overnight.

RESULTS AND DISCUSSION

The data shown in Tab. 1 indicate that the reaction of Ⓟ—CH_2Cl with phthalimide in the presence of solid potassium hydroxide and phase-transfer catalysts proceeds in excellent yields in aprotic hydrocarbon medium, in this case in toluene. The degree of functionalization was higher than 97% after 4h at 100° when TBAB was used as a catalyst. Runs 2 and 8 show that the amount of TBAB has no critical influence on the degree of functionalization under comparable reaction conditions, but its presence is necessary for this reaction to proceed (run 9).

Less satisfactory results were obtained when 18-crown-6 was used as a catalyst (runs 3-5); a similar observation has been reported in the case of reaction of some alkyl halides with phthalimide under comparable conditions(SANTANIELLO and PONTI 1980). We found, however, that the reaction yield may be increased,in this case by using a medium having a higher dielectric constant, i.e., a 2:1 vol/vol mixture of toluene with acetonitrile (run 7). This effect seems to be brought about by an increased solubility of the reactants in the reaction medium.

As regards the mechanism of this reaction, it is belived that in the first stage the catalyst partly solubilizes potassium hydroxide in the organic phase:

$$Q^+Br^-(l) + KOH(s) \rightleftharpoons Q^+OH^-(l) + KBr(s) \tag{2a}$$

where: Q^+ - tetrabutylammonium cation
l and s denote liquid and solid phase, resp.,

TABLE 1
The reaction of Ⓟ—CH_2Cl with phthalimide and solid KOH under phase-transfer conditions[a]

Run	Solvent	Catalyst[b]	Reaction time, h	Chlorine content, wt.-%	D.F.[c], %
1	Toluene	TBAB(25)	2	2.81	80.5
2			4	0.33	97.5
3		18-CR-6(25)	2	13.2	29.4
4			4	12.4	32.3
5			10	9.39	45.1
6	Toluene/ CH_3CN[d]	TBAB (25)	4	0.44	96.7
7		18-CR-6(25)	4	4.22	71.8
8	Toluene	TBAB (10)	4	1.82	87.0
9		None	10	20.4	5.8
10	DMF		2	2.48	82.6
11			4	2.66	81.4

[a] The reaction conditions are given in EXPTL. PART
[b] TBAB - tetrabutylammonium bromide (mole-% in relation to Cl in Ⓟ-CH_2Cl); 18-CR-6 - 18-crown-6.
[c] D.F.: degree of functionalization, in mole-% of the chlorine atoms substituted by the N-phthalimide moiety.
[d] Volume ratio of benzene:acetonitrile = 2:1.

or, in the case of 18-crown-6:

$$\text{⬡}(l) + KOH(s) \rightleftharpoons \text{⬡}K^+\; OH^-(l) \tag{2b}$$

where: ⬡ - 18-crown-6.
Next, quaternary ammonium hydroxide or the complexed potassium hydroxide react with phthalimide dissolved in small amounts in the organic phase, to give quaternary ammonium phthalimide:

$$Q^+OH^-(l) + HN\supset Z(l) \rightleftharpoons Q^+\bar{N}\supset Z(l) + H_2O \tag{3a}$$

where: $-N\supset Z$ denotes the N-phthalimide moiety, or potassium phthalimide:

$$\text{⬡}K^+\; OH^-(l) + HN\supset Z(l) \rightleftharpoons \text{⬡}K^+\; {}^-N\supset Z(l) + H_2O \tag{3b}$$

Only then the products of reactions 3a and 3b diffuse into the gel phase of Ⓟ—CH_2Cl and react with it to give the desired product 1. The formed salts Q^+Cl^- or ⬡K^+ Cl^- are markedly less lipophilic than their phthalimide counterparts, thus they diffuse back into the organic phase and are regenerated into their hydroxide forms according to reaction 2a and:

$$K^+ Cl^-(1) + KOH(s) \rightleftharpoons K^+ OH^-(1) + KCl(s) \qquad 4$$

It seems quite unlikely that phthalimide could react with solid KOH to any meaningful degree in toluene in the absence of the catalyst, since the solubility of these species in it, particularly that of KOH, is extremely low. This situation may change to some degree in later stages of the process, since water evolved in reactions 3a and 3b can dissolve partly potassium hydroxide, thus making the transfer of the hydroxide anion into the organic phase more hindered by the water of hydration.

The above-proposed scheme may explain the observed higher efficiency of TBAB as compared to 18-crown-6 in the process studied, since: i) the solubility of $Q^{+}{}^{-}N{\subset}Z$ can be expected to be higher than that of $K^+ {}^{-}N{\subset}Z$ due to a more lipophilic structure of the former, and ii) there is a possibility of the decomposition of $K^+ {}^{-}N{\subset}Z$ into potassium phthalimide which is insoluble in toluene,and the free crown ether.

In conclusion, it may be stated that the proposed method for the preparation of Ⓟ$-CH_2-N{\subset}Z$ offers considerable advantages over those used thus-far because of its simplicity and markedly lower costs of the reagents needed.

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