Preparation of Cross-linked Poly{styrene-[4-vinylpyridinium dichloroiodate (I)]}: A New Polymeric Reagent for Regioselective Iodination of Aromatic and Heteroaromatic Molecules

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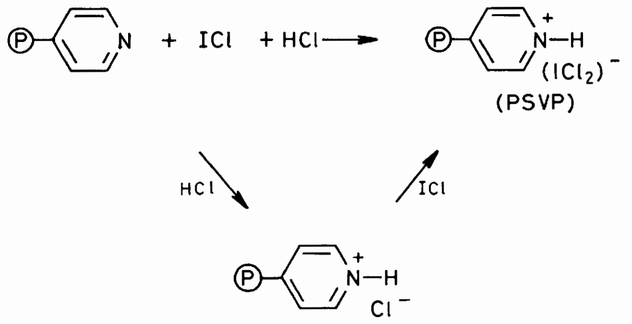
The reaction of crosslinked poly(styrene-4-vinylpyridine), containing 42—44% of pyridine rings, in chloroform suspension with a mixture of hydrogen chloride and iodine chloride formed the cross-linked poly{styrene-[4-vinyl pyridinium dichloroiodate (I)]}(PSVP). Better results were obtained when cross-linked poly[styrene-(4-vinylpyridinium chloride)] was prepared first, followed by the reaction with an equivalent amount of iodine chloride. Benzene and naphthalene derivatives were quantitatively converted with cross-linked PSVP into monoiodo substituted products of very high purity, while reaction of greater amounts of polymeric reagents with 3-amino- and 3,5-diamino-benzoic acid gave the tri-iodo derivatives. On the other hand, reaction with dimethyluracil led to the 5-iodo derivative, while in the reaction with 8-hydroxyquinoline the 5,7-di-iodo derivative was formed. In the case of 5-chloro-8-hydroxyquinoline, iodination occurred at the 7-position, while on reaction with 4-pyridone 3,5-di-iodo-4-pyridone was formed.

Introduction of fluorine and bromine into organic molecules with polymer-supported reagents, has many advantages.[1] In contrast, iodination with polymer-supported reagents has received less attention, the few reported reactions leading to crude mixtures whose purification is difficult.[2] Recently Manescalchi and co-workers[3] found that Amberlyst A-26 in the iodine form reacted with chlorine, to give a reagent which chlorinated aldehydes and ketones, and, in four-fold excess, converted alkenes into vicinal dichloroalkanes. Equimolar amounts of reagent and substrate led to a mixture of dichloro and chloroiodo compounds.

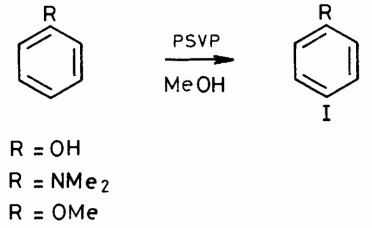
Iodine chloride is known to be the source of electrophilic iodine in various organic reactions; it forms a complex[4] with hydrogen chloride, and in the presence of pyridine gives pyridinium dichloroiodate(I).[5]

Since we had already found that the cross-linked copolymer of styrene and 4-vinylpyridine formed stable complexes with bromine and chlorine,[6] we were interested in the preparation of the iodine chloride complex. Reaction of cross-linked poly(styrene-4-vinylpyridine) prepared by emulsion polymerization,[6] containing 42—44% of pyridine rings, in chloroform suspension with a mixture of hydrogen chloride and iodine chloride formed the cross-linked poly{styrene-[4-vinylpyridinium dichloroiodate (I)]} PSVP) (Scheme 1), which after purification with chloroform gave a reagent containing 30% of iodine and 16.6% of chlorine; this indicated >95% functionalization of the pyridine rings. The changes in the i.r. spectra of the resins showed that for PSVP the signal for v(C=N) is shifted from 1580 to 1650 cm^{-1}, an important difference for characterization of the ionic nature of the complex.

Better results were obtained when cross-linked poly[styrene-(4-vinylpyridinium chloride)] was prepared first, followed by the reaction with an equivalent amount of iodine chloride. The reactivity of PSVP was studied in reactions with aromatic molecules: in the reaction of benzene with the polymeric reagent in methanolic or acetic acid solution, there was only a 10% conversion into iodobenzene. This led us to choose activated aromatic molecules as substrates. Phenol, dimethylaniline, and methoxybenzene reacted regioselectively in methanolic or acetic acid solution to give 4-iodo substituted products with complete conversion of the starting material (Scheme 2, Table). The structures of the products were determined by comparison of spectroscopic data with those of authentic samples. Since the purity of the products was very high, the isolation procedure was simple: the polymer beads were filtered off and the solvent evaporated under reduced pressure. No washing of the solution was needed, as in the case of other reagents for electrophilic iodination, where removal of impurities and iodine liberated during the reaction course is necessary.



Scheme 1.



Scheme 2.

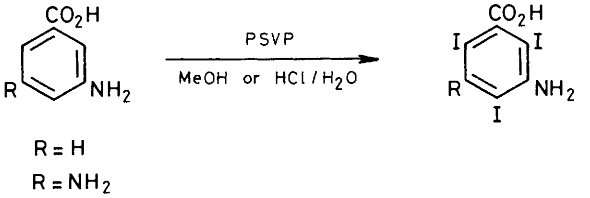
We have further studied the regioselectivity of iodination of activated 1- and 2-substituted naphthalene derivatives (1-naphthol, 2-naphthol, 1-methoxynaphthalene, 2-methoxynaphthalene). Substrates substituted at position 1 reacted with the polymeric reagent exclusively to give 4-iodo derivatives, while reaction with 2-substituted naphthalenes resulted in 1-iodo products (Table). Mono iodination was also established in

Table. Iodination by crosslinked PSVP

	Reaction conditions				
Compound	Solvent	React. Temp. (°C)	React. Time (min)	Yield (%)	Product
N,N,-Dimethylaniline	MeOH	25	240	80	4-Iodo-*N*,*N*-dimethylaniline[7]
Phenol	AcOH	50	270	60	4-Iodophenol[8]
Anisole	MeOH	Reflux	120	85	4-Iodoanisole[9]
1-Methoxynaphthalene	AcOH	50	300	85	4-Iodo-1-methoxynaphthalene[10]
2-Methoxynaphthalene	MeOH	50	210	77	1-Iodo-2-methoxynaphthalene[11]
1-Naphthol	AcOH	50	270	68	4-Iodo-1-naphthol
2-Naphthol	MeOH	Reflux	120	73	1-Iodo-2-naphthol
1,3,5-Trimethylbenzene	AcOH	50	270	76	2-Iodo-1,3,5-trimethylbenzene[13]
3-Aminobenzoic acid	$HCl-H_2O$	50	300	75	3-Amino-2,4,6-tri-iodobenzoic acid[14]
3,5-Diaminobenzoic acid	$HCl-H_2O$	25	180	77	3,5-Diamino-2,4,6-tri-iodobenzoic acid[15]
1,3-Dimethyluracil	AcOH	60	480	90	5-Iodo-1-3-dimethyluracil[16]
5-Chloro-8-hydroxyquinoline	MeOH	50	360	82	5-Chloro-8-hydroxy-7-iodoquinoline[17]
8-Hydroxyquinoline	MeOH	50	540	81	8-Hydroxy-5,7-di-iodoquinoline[17]
4-Pyridone	MeOH	Reflux	360	81	3,5-Di-iodo-4-pyridone[18]

the reaction with 1,3,5-trimethylbenzene, leading to the 2-iodo derivative as the only product (Table).

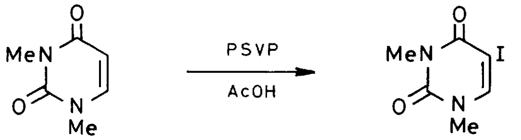
Since several polyiodo substituted aromatic molecules are important intermediates in the synthesis of pharmaceutically used iodo-contrast media, we were interested in the possibility of introduction of more than one iodo atom into aromatic molecules with our polymeric reagent. We found that reactions of 3-aminobenzoic acid and 3,5-diaminobenzoic acid with greater amounts of polymeric reagent in 15% aqueous hydrogen chloride solution resulted in tri-iodo substituted derivatives in high yields (Scheme 3). The purity of the crude products was high, and after one purification stage their quality was satisfactory according to pharmaceutical standards.



Scheme 3.

The selectivity of iodination of activated aromatic molecules with PSVP leading to high yields of products of high purity, motivated us to further study of the iodination of some heterocyclic molecules.

Reaction of dimethyluracil with the polymeric reagent in acetic acid solution led to complete conversion into the 5-iodo derivative (Scheme 4), while reaction with 8-hydroxyquinoline gave 5- and 7-iodo derivatives, transforming to the 5,7-di-iodo derivative when greater amounts of polymeric reagent were used. In the case of 5-chloro-8-hydroxyquinoline, iodination occurred at the 7-position, while the reaction with 4-pyridone resulted in the formation of 3,5-di-iodo-4-pyridone (Table).



Scheme 4.

From the experimental observations we concluded that PSVP can be used as a very efficient polymeric reagent for selective electrophilic iodination of activated benzene and naphthalene derivatives, as well as for iodination of heterocyclic systems where electrophilic substitutions can take place.

Experimental

I.r. spectra were recorded using a Perkin-Elmer 727 B instrument, and ^1H n.m.r. spectra on a JEOL JNM-PS-100 spectrometer with Me_4Si as internal reference. Mass spectra were taken on a CEC-21-110 spectrometer. Analytical t.l.c. was carried out on Merck-PSC-Fertigplatten Kieselgel F 254. M.p.s were determined on a Kofler apparatus and are uncorrected.

Cross-linked Poly(styrene-4-vinylpyridine).[6]—The microporous polymer (effective size 0.4—0.8 mm) containing 42—44% of pyridine rings and 2% of DVB, was prepared by emulsion polymerization of styrene, 4-vinylpyridine, and divinylbenzene, using a 1% solution of W 28/20 poly(vinyl alcohol).

Preparation of Poly{styrene-[4-vinylpyridinium dichloroiodate (I)]} *PSVP.*—(a) Cross-linked poly(styrene-4-vinylpyridine) (35 g), containing 42—44% of pyridine rings, was suspended in chloroform (150 ml), the solution cooled to 0 °C and a mixture of HCl—ICl (50 g) was added. The suspension was stirred at 0 °C for 60 min and at room temperature for a further 30 min. The polymer was filtered off and extracted with chloroform in a Soxhlet apparatus. After drying *in vacuo* for 24 h, the polymeric reagent was obtained (65 g). Drying of the polymer (1 g) for 3 h at 100 °C gave polymeric reagent (0.93 g), containing 30.0% of iodine and 16.6% of chlorine (calculation for PSVP containing 43% of pyridine rings: 29% of iodine and 16.2% of chlorine), which means that the polymeric reagent contained 2.2 mequiv. of $(ICl_2)^-$ per gram of resin.

(b) Cross-linked poly(styrene-4-vinylpyridine) (35 g), containing 42—44% of pyridine rings, was suspended in chloroform (150 ml), the solution cooled to 0 °C and 36% HCl (30 g) was added. The mixture was stirred at 0 °C for 30 min after which ICI (30 g) was slowly added. The suspension was stirred at 0 °C for a further 60 min and at room temperature for 30 min. The polymer was filtered off, washed with methanol and chloroform, and dried to constant weight at room temperature to give the polymeric reagent (70 g).

Iodination of Aromatic and Heteroaromatic Molecules: General Procedure—To a stirred solution of substrate (1 mmol) in an appropriate solvent (20 ml), the polymeric reagent (0.5 g) was added. The mixture was stirred either at room temperature or a higher temperature for the times recorded in the Table. The polymer was filtered off and washed twice with solvent (5 ml), and the combined solutions were evaporated under reduced pressure. Unless otherwise indicated the spectroscopic data for the compounds prepared were in agreement with those for authentic samples.

4-*Iodo*-N,N-*dimethylaniline*.[7] The title compound was crystallized from ethanol (197 mg, 80%), m.p. 75—77 °C (lit.,[7] m.p. 79 °C).

4-*Iodophenol*.[8] The title compound was crystallized from water (132 mg, 60%), m.p. 89—91 °C (lit.[8] m.p. 92 °C).

4-*Iodoanisole*.[9] The title compound was crystallized from methanol (199 mg, 85%), m.p. 49—51 °C (lit.[9] m.p. 50—51 °C).

4-*Iodo*-1-*methoxynaphthalene*.[10] Light petroleum was added to the crude product and the mixture cooled to 0 °C to give the title compound (241 mg, 85%), m.p. 52—53 °C (lit.[10] m.p. 54—56 °C).

1-*Iodo*-2-*methoxynaphthalene*.[11] The title compound was crystallized from ethanol (218 mg, 77%), m.p. 88—89 °C (lit.,[11] m.p. 88 °C); δ ($CDCl_3$) 4.0 (3 H, s, OCH_3), 7.15 (1 H, d, $J_{3,4}$ 9 Hz, 3–H), 7.42—7.72 (4 H, m, 5-, 6-, 7-, 8-H), and 8.14 (1 H, d, $J_{3,4}$ 9 Hz, 4–H); *m/z* (relative intensity) 284 (M^+, 8), 169 (13), 168 (100), 128 (11), 127 (8), 115 (89), and 63 (9) (Found: *m/z* 283.9699. Calc. for $C_{11}H_9IO$: *M*, 283.9699).

4-*Iodo*-1-*naphthol*. The title compound was crystallized from ethanol (183 mg, 68%), m.p. 104—105 °C; δ ($CDCl_3$) 6.75 (1 H, d, $J_{2,3}$ 9 Hz, 2—H), 7.9 (1 H, d, $J_{2,3}$ 9 Hz, 3-H), and 7.57—8.14 (4 H, m, 5-, 6-, 7-, 8-H); *m/z*: (relative intensity) 270 (M^+, 93), 144 (27), 143 (20), 115 (67), and 61 (100) (Found: *m/z* 269.9130. Calc. for $C_{10}H_7IO$: *M*, 269.9143).

1-*Iodo*-2-*naphthol*.[12] The title compound was crystallized from ethanol (197 mg, 73%), m.p. 87—89 °C (lit.,[12] m.p. 90 °C).

2-*Iodo*-1,3,5-*trimethylbenzene*.[13] The title compound was crystallized from dilute acetic acid (186 mg, 76%), m.p. 27—29 °C (lit.,[13] m.p. 30—31 °C).

3-*Amino*-2,4,6-*tri-iodobenzoic acid*.[14] 3-Aminobenzoic acid (1 mmol, 137 mg) was dissolved in 15% aqueous hydrogen chloride (20 ml) and polymeric reagent (2g) was added. The reaction mixture was then stirred at 50 °C for 5 h, neutralized with 15% aqueous ammonia (pH 8), and the polymer filtered off. After acidification to pH 1, the title compound was obtained (386 mg, 75%), m.p. 196 °C (lit.,[14] m.p. 196.5—197.5 °C).

3,5-*Diamino*-2,4,6-*tri-iodobenzoic acid*.[15] The same procedure as described for the preparation of 3-amino-2, 4, 6-tri-iodobenzoic acid was used to give the title compound (408 mg, 77%), m.p. 152—156 °C (decomp.) [lit.,[15] m.p. 154—158 °C (decomp.)].

5-*Iodo*-1,3-*dimethyluracil*.[16] The title compound was crystallized from methanol (293 mg, 90%), m.p. 230—231 °C (lit.,[16] m.p. 124—125 °C); $\nu_{max.}$ 745, 1 340, 1 450, 1 610, and 1 700 cm^{-1}; δ[$(CD_3)_2SO$] 3.33 (3 H, s, NCH_3), 3.45 (3 H, s, NCH_3), and 8.4 (1 H, s, 5-H); *m/z* (relative intensity) 265 (M^+, 96), 209 (19), 168 (39), 127 (9), 82 (13), 62 (13), 53 (24), 43 (16), and 42 (100).

5-*Chloro*-8-*hydroxy*-7-*iodoquinoline*.[17] The title compound was crystallized from dioxane (250 mg, 82%) m.p. 173—175 °C (lit.,[17] m.p. 178—179 °C).

8-*Hydroxy*-5,7-*di-iodoquinoline*.[17] Hydroxyquinoline (1 mmol, 145 mg) was dissolved in methanol (20 ml) and polymeric reagent (1 g) was added and the suspension stirred at 50 °C for 7 h. The polymer was filtered off and washed with methanol and the combined filtrate and washings were evaporated under reduced pressure. Crystallization of the residue from dioxane gave the title compound (321 mg, 81%), m.p. 221—223 °C, (lit.,[17] m.p. 214—215 °C).

3,5-*Di-iodo*-4-*pyridone*.[18] The same procedure as described for the preparation of 8-hydroxy-5, 7-di-iodoquinoline was used. The title compound crystallized from ethanol (280 mg, 81%), m.p. 320—322 °C (lit.,[18] m.p. 321 °C).

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