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α-Iodination of Ketones and Enol Acetates with Poly[styrene-*co*-(4-vinylpyridinium dichloroiodate(1−))]

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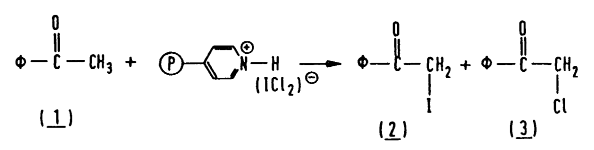
Synopsis. Crosslinked poly[styrene-*co*-(4-vinylpyridinium dichloroiodate(1−))] can be used as a very efficient polymeric reagent for α-iodination of ketones, diketones, and corresponding enol acetates.

Halo ketones represent synthetically useful materials and several general methods for their synthesis have been established.[1] In contrast to the chloro and bromo derivatives, α-iodo ketones received much less attention because of their relative instability. Most of the known methods of preparing α-iodo carbonyl compounds proceed from enol derivatives[2–5] or α-bromo ketone,[6] while for the direct iodination of ketones only a few methods have been described using the copper(II) acetate/iodine[7] or mercury(II) chloride/iodine system.[8] On the other hand, the treatment of alkenes with silver chromate and iodine[9] also led to the formation of α-iodo ketones.

Recently, we have found that crosslinked poly[styrene-*co*-(4-vinylpyridinium dichloroiodate(1−))] can be used as a very efficient polymeric reagent for selective electrophilic iodination of activated benzene and naphthalene derivatives,[10] as well as for iodination of heterocyclic systems[10] where electrophilic substitutions can take place.

We now wish to report that our polymeric reagent can be used for the direct α-iodination of ketones and also for iodination of the corresponding enol acetates.

A 5-hour reaction of 1 mmol of acetophenone with 1 g of polymeric reagent in methanol under reflux led to complete conversion of the starting material. ^{1}H NMR spectrum of the crude reaction mixture showed the signal at δ 4.65 corresponding to the α-chloro derivative[11] (Scheme 1).



Scheme 1.

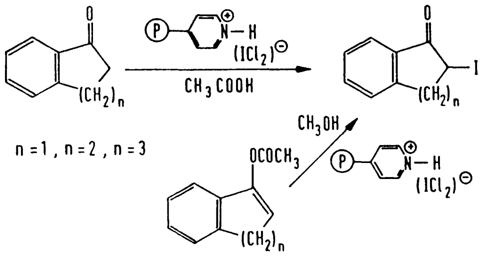
When the reaction was carried out in acetic acid solution at 50 °C, besides α-chloroacetophenone, the α-iodo derivative[11] was also formed (Scheme 1). The use of a lower reaction temperature decreased the conversion of the starting material, but increased the formation of iodinated product.

Table 1. The Effect of the Reaction Conditions on the Course of the Reaction with Acetophenone

Solvent	**1** /mmol	Polym. reag. /g	T/°C	Relative yields %**1**	%**2**	%**3**
CH_3OH	1	1	Reflux	—	—	100
CH_3COOH	1	1	50 °C	20	27	53
CH_3COOH	1	1	25 °C	25	56	19
CH_2Cl_2	1	1	25 °C	71	16	13

The results presented in the table suggest the initial formation of the iodinated product, while the degree of further substitution of iodine with chlorine depends on the reaction time.

Further, we studied the iodination of cyclic ketones, and 1-indanone, 1-tetralone, and 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one were chosen as substrates. A 4.5-hour reaction of 1 mmol of 1-indanone with 1 g of polymeric reagent in acetic acid solution at 50 °C led to complete conversion of the starting ketone. The mass spectrum and ^{1}H NMR of the product (see Experimental) showed that only iodinated product was obtained. On the basis of the spectroscopic data we concluded that 2-iodo-1-indanone was formed (Scheme 2).



Scheme 2.

In order to determine the influence of the ring size of the cycloketone on the reaction pathway with poly[styrene-*co*-(4-vinylpyridinium dichloroiodate(1−))], we studied the reaction with 1-tetralone and 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one. The reactions were carried out in methanol at room temperature or at 50 °C, and in both cases complete conversion of the starting material was observed. The product formed in the reaction with 1-tetralone was established to be 2-iodo-1-tetralone[12] by its ^{1}H NMR and mass spectrum. On the basis of the spectroscopic data of the product formed with 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one we concluded that iodination took place at position six and 6-iodo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one was obtained as the only product.

Further, we studied the reaction of two diketones: 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and 1,3-indandione with the polymeric reagent. A 5-hour reaction of 1 mmol of dimedone and 1 g of polymeric reagent at 50 °C in acetic acid solution gave a mixture with two singlet signals in its ^{1}H NMR spectrum at δ=5.16 and 4.50 with 1 : 2 relative ratio of the integrals. The mass spectrum of the crude reaction mixture, besides other fragmentations, also showed signals at m/z=266 and 174. On the basis of the above mentioned spectroscopic data, we determined that 2-chloro and 2-iodo derivatives were formed in the ratio of 1 : 2. We tried to separate the reaction mixture using several types of chromatographic methods, but we were unsuccessful because of the high instability of 2-halo dimedones.

The reaction of 1,3-indandione with the polymeric reagent under the same reaction conditions led to the formation of only the 2-chloro derivative,[13] as determined by ^{1}H NMR spectroscopy and the mass spectrum. When a lower reaction temperature (25 °C) was used, the conversion of the starting diketone decreased, but besides the 2-chloro derivative, the 2-iodo product was also formed, in the ratio of 65 : 35, respectively. From the results we concluded that initially formation of the iodinated product took place, followed by substitution of iodine by chlorine, which depended on the reaction temperature and reaction time.

As in many known methods for the preparation of α-iodo carbonyl compounds enol derivatives are used as substrates, we decided to study the reactions of poly[styrene-*co*-(4-vinylpyridinium dichloroiodate(1−))] with some enol acetates. A 3.5-hour reaction of 1 mmol of 1-phenylethenyl acetate[14] with 0.5 g of polymeric reagent in methanol at 0 °C gave a crude reaction mixture which, besides a singlet signal at δ=2.6 corresponding to acetophenone, showed two singlet signals in its ^{1}H NMR spectrum at δ=4.4 and 4.7. The signal at the lower field corresponded to the chlorinated product, while the signal at δ=4.4 corresponded to iodinated product (iodinated and chlorinated product were in the ratio of 56 : 44). The formation of acetophenone can be explained by the reaction of the enol acetate with the HCl liberated in small quantity during the course of the reaction. The reaction of 1-cyclohexenyl acetate[14] with the polymeric reagent led to complete conversion of the starting material, 2-iodocyclohexanone[15] being formed as the only product. We also studied the reaction of enol acetates of 1-indanone,[16] 1-tetralone,[17] and 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one.[17] In all cases, α-iodo ketones were formed and the yields of pure products were also satisfactory (Scheme 2).

From the experimental observations we concluded that poly[styrene-*co*-(4-vinylpyridinium dichloroiodate(1−))] can be used as a polymeric reagent for α-iodination of ketones and the corresponding enol acetates.

Experimental

IR spectra were recorded using a Perkin-Elmer 727B instrument, and ^{1}H NMR spectra on a JEOL JNM-PS-100 with Me_4Si as internal reference. Mass spectra were taken on a CEC-21-110 spectrometer. Analytical and preparative TLC were carried out on Merck-PSC-Fertigplatten Kieselgel F 254. Melting points were determined on a Kofler apparatus and are uncorrected.

1-Phenylethenyl acetate,[14] 1-cyclohexenyl acetate,[14] 1*H*-inden-3-yl acetate,[16] 1,2-dihydro-4-naphthyl acetate,[17] and 6,7-dihydro-5*H*-benzocyclohepten-9-yl acetate[17] were prepared by known procedures.

Preparation of Poly[styrene-*co*-(4-vinylpyridinium dichloroiodate(1−))]. a) Thirty-five grams of crosslinked poly(styrene-4-vinylpyridine),[18] containing 42—44% of pyridine rings, was suspended in 150 ml of chloroform, cooled to 0 °C and 50 g of a mixture of HCl-ICl 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, 65 g of polymeric reagent was obtained. Three hours of drying of 1 g of polymer at 100 °C gave 0.93 g of polymeric reagent, containing 30.0% of iodine and 16.6% of chlorine (calculation for poly[styrene-*co*-(4-vinylpyridinium dichloroiodate(1−))] 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) Thirty five grams of crosslinked poly(styrene-4-vinylpyridine),[18] containing 42—44% of pyridine rings, was suspended in 150 ml of chloroform, cooled to 0 °C and 30 g of 36% HCl was added. After stirring at 0 °C for 30 minutes, 30 g of ICl was slowly added. The suspension was stirred at 0 °C for another 60 minutes and at room temperature for 30 minutes. The polymer was filtered off, washed with methanol and chloroform, and after drying to constant weight at room temperature 70 g of polymeric reagent was obtained.

General Reaction Procedure: One mmol of substrate was dissolved in the appropriate solvent and a given amount of poly[styrene-*co*-(4-vinylpyridinium dichloroiodate(1−))] was added. The reaction mixture was stirred at a given temperature for a given time, the insoluble beads were filtered off, washed with 10 ml of the reaction solvent, the solvent evaporated in vacuo and the crude reaction mixture analysed by ^{1}H NMR spectroscopy.

Halogenation of Acetophenone: Polymeric reagent: 1 g; solvent: methanol, acetic acid, or CH_2Cl_2, 20 ml. The effect of the solvent and the reaction temperature on the course of the reaction is presented in Table 1. Products were isolated by preparative TLC (SiO_2, CH_2Cl_2 : petroleum ether 1 : 1) and identified on the basis of a comparison of the spectroscopic data with the literature ones.[11]

Iodination of 1-Indanone: Polymeric reagent: 0.5 g; solvent: acetic acid, 20 ml; reaction conditions: 50 °C, 4.5 hours. The crude reaction product was crystallized from ethanol and 193 mg (75%) of 2-iodo-1-indanone were obtained; IR 710, 1260, 1600, 1710 cm^{-1}, ^{1}H NMR (CCl_4) δ=3.45 (1H, dd, $J_{A,B}$=18 Hz, $J_{2,3A}$=3 Hz, H-3A), 3.90 (1H, dd, $J_{A,B}$=18 Hz, $J_{2,3B}$=7.5 Hz, H-3B), 4.92 (1H, dd, $J_{2,3B}$=7.5 Hz, $J_{2,3A}$=3 Hz, H-2), 7.50 (4H, m, aromatic H's), mass spectra m/z (relative intensity): M$^+$ 258(100), 131(88), 127(23), 103(84), 102(35), 77(61). Found: m/z 257.9550, Calcd for C_9H_7IO: M, 257.9544, mp 68—70 °C (from ethanol).

Iodination of 1-Tetralone: Polymeric reagent: 0.5 g; solvent: methanol, 20 ml; reaction conditions: 25 °C, 5 hours. The crude reaction mixture was crystallized from ethanol and 218 mg (80%) of 2-iodo-1-tetralone[12] were isolated: ^{1}H NMR ($CDCl_3$) δ=2.22 (2H, m, H-4), 3.05 (2H, m, H-3), 5.0 (1H, t, $J_{2,3}$=4.5 Hz, H-2), 7.3 (3H, m, aromatic H's), 8.05 (1H, dd, J=7.5 Hz, 3 Hz, H-8), mass spectra m/z (relative intensity): M$^+$ 272(77%), 146(17), 145(68), 144(14), 128(17), 127(28), 118(46), 117(86), 116(28), 115(100), 91(40), 90(46), 89(43). Found: m/z 271.9705, Calcd for $C_{10}H_9IO$: M, 271.9700, mp 76—78 °C (lit, 76—77 °C).[12]

Iodination of 6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-one: Polymeric reagent: 0.5 g; solvent: methanol, 20 ml: reaction conditions: 50 °C, 5 hours. 257 mg (90%) of oily 6-iodo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one were obtained: ^{1}H NMR (CCl_4) δ=2.1 (4H, m, H-3, H-4), 3.06

(2H, t, J=6 Hz H-5), 5.25 (1H, t, $J_{2,3A}=J_{2,3B}=4.5$ Hz), 7.45 (4H, m, aromatic H's), mass spectra m/z (relative intensity): M^+ 286(41%), 160(10), 159(29), 132(13), 131(100), 129(20), 128(11), 127(16), 116(11), 115(17), 104(13), 103(14), 91(14), 89(14), 77(20), 63(15), 51(17). Found: m/z 285.9860, Calcd for $C_{11}H_{11}IO$: M, 285.9856.

Halogenation of 5,5-Dimethyl-1,3-cyclohexanedione: Polymeric reagent: 0.5 g; solvent: acetic acid, 20 ml; reaction conditions: 50 °C, 5 hours. On the basis of ^{1}H NMR and mass spectroscopic data we determined that 2-iodo and 2-chloro-5,5-dimethyl-1,3-cyclohexanedione were formed in the ratio of 2 : 1, and we were unable to separate them.

Halogenation of 1,3-Indandione: Polymeric reagent: 1 g; solvent: acetic acid, 20 ml; reaction conditions: 50 °C, 5 hours. The crude product formed was crystallized from ethanol and 150 mg (83%) of 2-chloro-1,3-indandione (mp 112—114 °C, lit,[13] 112—113 °C) were isolated: ^{1}H NMR ($CDCl_3$) δ=4.8 (1H, s, H-2), 8.05 (4H, m, aromatic H's), mass spectra m/z (relative intensity): M^++2 182(31%), M^+ 180(100), 124(26), 104(38), 89(63), 76(45), 50(33). Found: m/z 179.9980, Calcd for $C_9H_5ClO_2$: M, 179.9978.

Halogenation of 1-Phenylethenyl Acetate: Polymeric reagent: 0.5 g; solvent: methanol, 5 ml; reaction conditions: 0 °C, 3 hours. ^{1}H NMR analysis of the crude reaction mixture revealed that 38% of 2-iodoacetophenone, 30% of 2-chloroacetophenone, and 32% of acetophenone were formed, which were isolated by preparative TLC (SiO_2, petroleum ether 40—70 °C: CH_2Cl_2 1 : 1) and identified on the basis of a comparison of their spectroscopic data with the literature ones.[12]

Iodination of 1-Cyclohexenyl Acetate: Polymeric reagent: 0.7 g; solvent: methanol, 5 ml; reaction conditions: 25 °C, 2.5 hours. After purification of the crude product formed by SiO_2 column chromatography (elution by diethyl ether: hexane 1 : 2), 144 mg (64%) of oily 2-iodocyclohexanone[15] was obtained. The spectroscopic data were in agreement with literature.

Iodination of 1*H*-Inden-3-yl Acetate: Polymeric reagent: 0.75 g; solvent: methanol, 5 ml; reaction conditions: 25 °C, 6 hours. The crude product formed was purified by crystallization from ethanol, and 131 mg (52%) of 2-iodo-1-indanone (mp 65—67 °C) were isolated.

Iodination of 1,2-Dihydro-4-naphthyl Acetate: Polymeric reagent: 0.75 g; solvent: methanol, 5 ml; reaction conditions: 25 °C, 6 hours. The crude product formed was purified by crystallization from ethanol, and 205 mg (75%) of 2-iodo-1-tetralone (mp 77—78 °C, lit,[12] 76—78 °C) were isolated. Spectroscopic data were in agreement with those of the authentic sample.

Iodination of 6,7-Dihydro-5*H*-benzocyclohepten-9-yl Acetate: Polymeric reagent: 0.75 g; solvent: metanol, 5 ml; reaction conditions: 25 °C, 6 hours. The crude product formed was purified by SiO_2 column chromatography, and 226 mg (79%) of 6-iodo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one were obtained. The spectroscopic data were in agreement with those of the authentic sample.

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