Synthesis of a New Polymer-supported Reagent——Poly {[4-hydroxy(tosyloxy)iodo]styrene} and Its Application to the Synthesis of 2-Amino-4-arylthiazoles†

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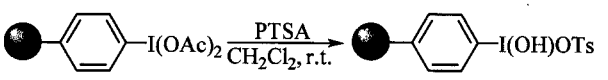
A new polymer-supported reagent——poly{[4-hydroxy(tosyloxy)iodo]styrene} has good reactivity in the formation of 2-amino-4-arylthiazoles, and the procedure of regeneration and cycle are also described.

Keywords 2-amino-4-arylthiazoles, polymer supported reagents, poly{[4-hydroxy(tosyloxy)iodo]styrene}

It is well known that polymer-supported reagents have the advantage of allowing the application of a larger excess of the reagent without additional purification steps. The most important point is that the polymer-supported reagents could be easily regenerated and reused,[1] which meets the requirement of green chemistry. In recent years, trivalent iodine compounds have been widely used in organic synthesis.[2] The advantages of using trivalent iodine compounds are simplicity in experimental operation and low toxicity of the reagents. Some polymer supported trivalent iodine reagents have been synthesized, such as poly[styrene(iodoso diacetate)], phenyl polystyryliodonium bisulfate,[3] and poly[styrene(iodoso difluoro acetate)],[4] and their application in organic synthesis has been reported.[5] [Hydroxy(tosyloxy)iodo]benzene is a very important reagent for the synthesis of various heterocyclic compounds.[6] We report here that the preparation of poly{[4-hydroxy(tosyloxy)iodo]styrene} and its utility in the synthesis of 2-amino-4-arylthiazole derivatives.

We first prepared the poly[styrene(iodoso diacetate)] from the commercial polystyrene ($M.\ W.$ = 45000) by the reported method.[7] Then the poly[styrene(iodoso diacetate)] was added to a solution of *p*-toluenesulfonic acid (PTSA) in CH_2Cl_2 at room temperature. In a few minutes, poly{[4-hydroxy(tosyloxy)iodo]styrene} was precipitated and collected by filtration (Scheme 1).

Scheme 1



IR spectrum proved the above conversion. The disappearance of 1645 cm^{-1}(C=O), 1290 cm^{-1}(O—C) and the emergence of 1200, 1020 cm^{-1}(O=S=O) showed that poly[styrene(iodoso diacetate)] had been converted to poly{[4-hydroxy(tosyloxy)iodo]styrene} completely. The exact loading was determined by element analysis, which revealed the resin contained 1.91 mmol/g of the functional group.

Thiazoles and its derivatives have bioactivity and pharmaceutical interest.[8] They are also important starting material for the synthesis of biologically active compounds.[9] Compared with the others, the method using [hydroxy(tosyloxy)iodo]benzene has the advantage of simple experimentation and avoids the use of highly lachrymatory and not readily available α-halogeno

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ketones.[10] In this paper, we synthesized 2-amino-4-arylthiazoles by employing immobilized [hydroxy(tosyloxy)iodo]-benzene.

Acetophenone (**1**) and poly{[4-hydroxy(tosyloxy)-iodo]styrene} were refluxed in CH_3CN for 6 h to form α-tosyloxy acetophenone. Then α-tosyloxy acetophenone and thiourea were added to ethanol and the solution was further refluxed for 6 h. After the evaporation of solvent, the resulting mixture was treated with a saturated solution of sodium hydrogen carbonate to give the product **2** (Scheme 2). The results are shown in Table 1.

Scheme 2

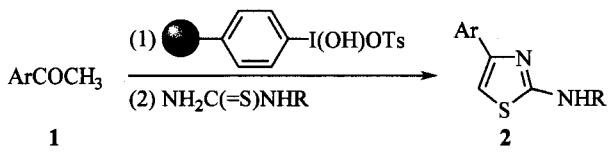


Table 1 Formation of 2-amino-4-arylthiazoles (**2**) by applying immoblized [hydroxy(tosyloxy)iodo]benzene

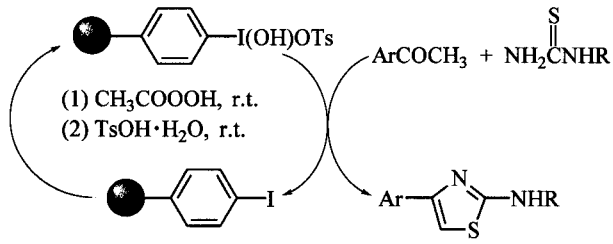
Entry	Product **2**		Yield (%)[a]
	Ar	R	
1	Ph	H (**2a**)	64
2	*p*-BrC_6H_4	H (**2b**)	60
3	*p*-$CH_3C_6H_4$	H (**2c**)	63
4	*p*-$CH_3OC_6H_4$	H (**2d**)	55
5	*m*-$NO_2C_6H_4$	H (**2e**)	70
6	*p*-ClC_6H_4	H (**2f**)	71
7	Ph	C_6H_5 (**2g**)	52
8	*p*-$CH_3C_6H_4$	C_6H_5 (**2h**)	51
9	Ph	H (**2a**[b])	60

[a] Isolated yield; [b] by applying poly{[4-hydroxy(tosyloxy) iodo]-styrene} recycled for 4 times.

After the reaction, poly(iodostyrene), which was collected by simple filtration, was converted to poly{[4-hydroxy(tosyloxy)iodo]styrene} according to above described method. The elemental analysis revealed that the loading of the resin was 1.89 mmol/g. This result showed the resin had almost the same ammount of functional group as the one prepared initially. We used the regenerated resin, which was recycled for 4 times, to the synthesis of 2-amino-4-arylthiazoles and got good results (Table 1, Scheme 3).

In conclusion, in the presence of poly{[4-hydroxy-(tosyloxy)iodo]styrene} acetophenone can react readily with thiourea to produce thiazoles in moderate yields. After the reaction, poly{[4-hydroxy(tosyloxy)iodo]styrene} can be recovered by the reaction of poly(iodostyrene) with peracetic acid and then treated with *p*-toluenesulfonic acid.

Scheme 3



Experimental

Polystyrene (*M. W.* = 45000) was purchased from Aldrich. ^1H NMR spectra were recorded on a Bruker (400 MHz) spectrometer, using CD_3COCD_3 as solvent and TMS as the internal standard. Infrared spectra were recorded on a Perkin Elmer 683 spectrophoto meter in KBr. Mass spectra were obtained on an HP 5989B specterometer. Melting points were uncorrected. The poly[styrene(iodoso diacetate)] was prepared according to the reported method.[7]

Synthesis of poly{[4-hydroxy(tosyloxy)iodo]styrene}

To a solution of 2.0 g of poly[styrene(iodoso diacetate)] in 20 mL of CH_2Cl_2, was added 2.4 g of *p*-toluenesulfonic acid. After several minutes, the yellow solid formed was isolated by vacuum filtration. The solid was washed with acetone (2 × 10 mL) and ether (2 × 10 mL) to give 1.8 g of poly{[4-hydroxy(tosyloxy)iodo]-styrene}. Elemental analysis, S%: 6.10%. The loading of the resin was 1.91 mmol/g. IR ν_{max}: 3400, 1200, 1020, 817, 760, 700 cm^{-1}.

Synthesis of 2-amino-4-arylthiazoles (**2a—2g**)

Acetophenone **1** (1 mmol) was added to a solution of poly{[4-hydroxy(tosyloxy)iodo]styrene} (1.2 mmol) in CH_3CN (10 mL). The resulting solution was then re-

fluxed for 6 h. After filtration to remove the resin and evaporation, ethanol was added to the residue. The solid formed upon cooling was collected by filtration. To a solution of thiourea or substituted thiourea (1 mmol) in 20 mL of ethanol, was added the obtained solid. The mixture was further refluxed for 6 h. The solution was evaporated *in vacuo* and the resulting mixture was treated with a saturated solution of sodium hydrogen carbonate. It was extracted with chloroform (4 × 10 mL) and dried over Na_2SO_4. Chloroform was distilled off to give the products.

2-Amino-4-phenylthiazole (**2a**) A white solid; m. p. 145—146 ℃ (lit.[11] 147 ℃); ^{1}H NMR (CD_3COCD_3) δ: 7.81 (s, 5H), 6.78 (s, 1H); IR (KBr) ν: 3440, 1560, 1530, 1485, 1445, 1340, 770, 715 cm^{-1}; MS (70 eV) *m/z* (%): 176 (M^+, 100), 134 (57), 89 (15).

2-Amino-4-(p-bromophenyl) thiazole (**2b**) A pale yellow solid; m.p. 180—182 ℃ (lit.[11] 180—181 ℃); ^{1}H NMR (CD_3COCD_3) δ: 7.84—7.87 (m, 2H), 7.38—7.41 (m, 2H), 6.91 (s, 1H); IR (KBr) ν: 3440, 1630, 1530, 1487, 1338, 820 cm^{-1}; MS (70 eV) *m/z* (%): 256 ($M+2^+$, 98), 254 (M^+, 100), 214 (27), 212 (28), 175 (10).

2-Amino-4-(p-methylphenyl) thiazole (**2c**) A white solid; m.p. 124—125 ℃ (lit.[11] 124—125 ℃); ^{1}H NMR (CD_3COCD_3) δ: 7.72—7.76 (m, 2H), 7.15—7.19 (m, 2H), 6.85 (s, 1H), 2.32 (s, 1H); IR (KBr) ν: 3445, 1635, 1530, 1520, 1335, 820 cm^{-1}; MS (70 eV) *m/z* (%): 190 (M^+, 100), 175 (3), 148 (29).

2-Amino-4-(methoxyphenyl) thiazole (**2d**) A pale brown solid; m.p. 203—204 ℃ (lit.[11] 204—205 ℃); ^{1}H NMR (CD_3COCD_3) δ: 7.77—7.80 (m, 2H), 6.91—6.94 (m, 2H), 6.76 (s, 1H), 3.81 (s, 3H); IR (KBr) ν: 3445, 1925, 1530, 1518, 1328, 832 cm^{-1}; MS (70 eV) *m/z* (%): 206 (M^+, 100), 191 (36), 175 (2).

2-Amino-4-(m-nitrophenyl) thiazole (**2e**) A yellow solid; m.p. 188—189 ℃ (lit.[11] 188—190 ℃); ^{1}H NMR (CD_3COCD_3) δ: 7.36—8.70 (m, 4H), 7.24 (s, 1H); IR (KBr) ν: 3440, 1630, 1510, 1470, 1345, 870, 800, 710 cm^{-1}; MS (70 eV): *m/z* (%): 221 (M^+, 100), 175 (38), 89 (37).

2-Amino-4-(p-chlorophenyl) thiazole (**2f**) A white solid; m.p. 163—164 ℃ (lit.[11] 163—164 ℃); ^{1}H NMR (CD_3COCD_3) δ: 7.86—7.89 (m, 2H), 7.38—7.42 (m, 2H), 7.00 (s, 1H); IR (KBr) ν: 3438, 1630, 1530, 1477, 1400, 1339, 820 cm^{-1}; MS (70 eV) *m/z* (%): 212 (M + 2, 38), 210 (M^+, 100), 170 (16), 168 (44), 175 (10).

2-Phenylamino-4-phenylthiazole (**2g**) A grayish solid; m.p. 135—136 ℃ (lit.[12] 136 ℃); ^{1}H NMR (CD_3COCD_3) δ: 7.30—7.99 (m, 10H), 7.17 (s, 1H); IR (KBr) ν: 3385, 1494, 1422, 1325, 821, 728, 690 cm^{-1}; MS (70 eV) *m/z* (%): 252 (M^+, 100), 175 (2), 34 (30).

2-(p-Methylphenyl) amino-4-phenylthiazole (**2h**) A grayish solid; m.p. 143—144 ℃ (lit.[12] 145 ℃); ^{1}H NMR (CD_3COCD_3) δ: 7.66—8.34 (m, 9H), 7.20 (s, 1H), 2.32 (s, 1H); IR (KBr) ν: 3390, 1630, 1490, 1420, 820, 720, 700 cm^{-1}; MS (70 eV) *m/z* (%): 266 (M^+, 100), 148 (14), 118 (12).

Purification of recovered poly(iodostyrene)

3 g of the recovered poly(iodostyrene) was dissolved in $CHCl_3$ (50 mL) at 60 ℃ and methanol was added to precipitate the poly(iodostyrene) (2.2 g).

Regeneration of poly{[4-hydroxy(tosyloxy) iodo] styrene}

The purified poly(iodostyrene) 2.2 g was dissolved in 15 mL of CH_2Cl_2 and 9 mL of peracetic acid was slowly added dropwise. The mixture was stirred for 10 h. Afier addition of ether to the solution, a white polymer was isolated. Then dried to obtain 3 g of poly[styrene(iodoso diacetate)]. To a solution of 3.0 g of poly[styrene(iodoso diacetate)] in 30 mL of CH_2Cl_2, was added 3.6 g of *p*-toluenesulfonic acid. After several minutes, the yellow solid formed was isolated by vacuum filtration. The solid was washed with acetone (3 × 10 mL) and ether (3 × 10 mL) giving 2.7 g of poly{[4-hydroxy(tosyloxy) iodo]-styrene} (S%: 6.06%). The loading of the resin: 1.89 mmol/g.

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