Poly{[4-(hydroxy)(tosyloxy)iodo]styrene}-promoted aromatisation of Hantzsch 1,4-dihydropyridines

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Hantzsch 1,4-dihydropyridines undergo smooth aromatisation on oxidation by poly{[4-(hydroxy)(tosyloxy)iodo] styrene} (PS-HTIB) in CH_2Cl_2 at room temperature to afford the corresponding pyridine derivatives in good yields. The polymeric reagent can be recycled and reused with no obvious loss of activity.

Keywords: poly{[4-(hydroxy)(tosyloxy)iodo]styrene} (PS-HTIB), aromatisation, Hantzsh 1,4-dihydropyridines, pyridine derivatives

Polymer-supported organic reagents have been applied to the preparation of the organic molecules.[1] Regeneration and reuse of the recovered polymer-supported reagent is possible thus providing an environmentally benign system.[2] Recently polymer-supported trivalent iodine reagents have been synthesised and used in organic synthesis.[3] Among them, poly{[4-(hydroxy)(tosyloxy)iodo]-styrene} (PS-HTIB) is an important reagent for the synthesis of α-tosyloxyketones.[4]

Hantzsch 1,4-dihydropyridines (**1**, Hantzsch 1,4-DHPs) are widely used as calcium channel blockers for the treatment of cardiovascular disorders.[5] These compounds are oxidised to pyridine derivatives by the action of cytochrome P-450 in the liver.[6] Consequently a convenient preparation of pyridines from 1,4-DHPs is important for the identification of metabolites. The oxidation of Hantzsch 1,4-DHPs provides easy access to pyridine derivatives. [Hydroxy(tosyloxy)-iodo]benzene (HTIB, PhI(OH)OTs, Koser's reagent) had been used[7] for the oxidation of 1,4-DHPs under mild conditions, but the by-product, iodobenzene could not be reused. On the basis of our study of PS-HTIB,[8] we now report a simple and efficient aromatisation reaction of 1,4-DHPs for the preparation of pyridine derivatives (Scheme 1). The present method has the advantage of mild reaction conditions, convenient manipulation and good yields. The polymeric reagent could be regenerated and reused.

Reaction of Hantzsch 1,4-DHPs **1** with poly{[4-(hydroxyl) (tosyloxy)iodo]- styrene} (PS-HTIB) in CH_2Cl_2 at room temperature in 30 min gave the corresponding pyridine derivatives **2** in good yield. The recovered poly(4-iodostyrene) (PS-IB) was dissolved in CH_2Cl_2 and precipitated by the addition of diethyl ether to purify the resin. The recovered resin was converted to PS-HTIB according to the literature method.[7] We used the regenerated PS-HTIB in the aromatisation reaction of **1a** and found that it had the same reactivity as the freshly prepared resin.

In summary, PS-HTIB is an efficient oxidant for the aromatisation of Hantzsch 1,4-dihydropyridines. This method offers significant advantages. It has good compatibility with a variety of substituents present in the dihydropyridine skeleton. The results extend its potential application in organic synthesis.

Experimental

Melting points were uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ with TMS as the internal standard. ^{13}C NMR spectra were recorded on a Bruker AC-400 (100 MHz) spectrometer in $CDCl_3$. IR spectra were recorded on a Shimidazu IR-408 spectrometer. 1,4-Dihydropyridines were prepared according to the literature procedures.[11] Poly{[4-(hydroxy)(tosyloxy) iodo]styrene} (PS-HTIB) was prepared by the literature method[8] and the functional group loading was 1.90 mmol/g determined by sulfur elemental analysis. The physical and spectroscopic data of the products were compared with those reported in the literature.[9,10]

General procedure

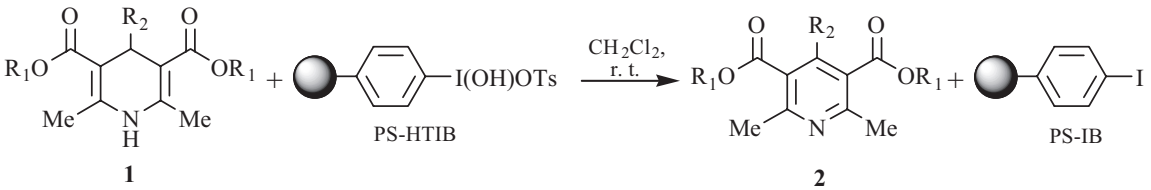
A mixture of Hantzsch 1,4-dihydropyridine (**1a**, 330 mg, 1.0 mmol) and poly{[4-(hydroxy)(tosyloxy)iodo]styrene} (PS-HTIB) (632 mg, 1.2 mmol) in dichloromethane (10 ml) was stirred at room temperature for 30 min. After complete conversion, as indicated by TLC, the reaction mixture was washed with water (15 ml), extracted with CH_2Cl_2 (2 × 10 ml). The combined CH_2Cl_2 layers were dried over anhydrous Na_2SO_4 and concentrated to about 5 ml under reduced pressure. Then Et_2O was added to precipitate, the poly (4-iodostyrene) (PS-IB) which was collected to be recycled. The filtrate was evaporated under reduced pressure to obtain the crude product **2a,** which was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to give 302 mg (92% yield) of **2a** as a pale yellow solid.

Diethyl 2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate (**2a**): Pale yellow solid; m.p. 63–64°C (Lit.[9] m.p. 62–63°C). IR (KBr): 3131, 1739, 1715, 1574, 1239, 1106, 1020 cm^{-1}. ^{1}H NMR: δ = 7.24–7.44 (m, 5 H), 4.00 (q, *J* = 7.2 Hz, 4 H), 2.60 (s, 6 H), 0.98 (t, *J* = 7.2 Hz, 6 H).

Diethyl 4-(2-furyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (**2b**): Pale yellow oil (Lit.[9] oil). IR (KBr): 3069, 1740, 1735, 1539, 1242, 1112, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1. 22 (t, 6H, *J* = 7.2 Hz), 2.57 (s, 6H), 4.24 (q, 4H, *J* = 7.2 Hz), 6.47–6.48 (m, 1H), 6.53–6.62 (m, 1H), 7.48–7.49 (m, 1H).

Diethyl 4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**2c**): Colourless solid; m.p. 48–49°C (Lit.[10] m.p. 49°C). IR (KBr): 1738, 1615, 1558, 1515, 1292, 1254, 1182, 1109, 1028 cm^{-1}. ^{1}H NMR: δ = 7.18 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 3.99 (q, *J* = 7.2 Hz, 4 H), 3.78 (s, 3 H), 2.59 (s, 6 H), 0.99 (t, *J* = 7.2 Hz, 6 H).

Diethyl4-(4-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**2d**): Pale yellow solid; m.p. 64–65°C (Lit.[10] m.p. 64–65°C). IR (KBr): 1737, 1559, 1231, 1108, 1044 cm^{-1}. ^{1}H NMR: δ = 7.31 (d, *J* = 8.8 Hz, 2 H), 7.19 (d, *J* = 8.8 Hz, 2 H), 4.02 (q, *J* = 7.2 Hz, 4 H), 2.54 (s, 6 H), 0.97 (t, *J* = 7.2 Hz, 6 H).



1 **2**

Scheme 1

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Dimethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (**2e**): Colourless solid; m.p. 136–137°C (Lit.[10] m.p. 137°C). IR (KBr): 1730, 1555, 1286, 1114, 1036 cm^{-1}. ^1H NMR: δ = 7.53–7.17 (m, 5 H), 3.60 (s, 6 H), 2.61 (s, 6 H).

Dimethyl 4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**2f**): Pale yellow solid; m.p. 115–116°C (Lit.[10] m.p. 115–117°C). IR (KBr): 1737, 1609, 1565, 1517, 1296, 1245, 1184, 1111, 1030 cm^{-1}. ^1H NMR: δ = 7.19 (d, *J* = 8.4 Hz, 2 H), 6.93 (d, *J* = 8.4 Hz, 2 H), 3.87 (s, 3 H), 3.61 (s, 6 H), 2.62 (s, 6 H).

Dimethyl 4-(4-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**2g**): Colourless solid; m.p. 138–139°C (Lit.[10] 138–140°C). IR (KBr): 1737, 1556, 1241, 1217, 1098, 1045, 1017 cm^{-1}. ^1H NMR: δ = 7.29 (d, *J* = 8.8 Hz, 2 H), 7.14 (d, *J* = 8.8 Hz, 2 H), 3.55 (s, 6 H), 2.56 (s, 6 H).

Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**2h**): Colourless solid; m.p. 71–72°C (Lit.[10] m.p. 72–73°C). IR (KBr): 1723, 1590, 1554, 1299, 1254, 1224, 1107, 1046 cm^{-1}. ^1H NMR: δ = 8.67 (s, 1 H), 4.39 (q, *J* = 7.2 Hz, 4 H), 2.85 (s, 6 H), 1.41 (t, *J* = 7.2 Hz, 6 H).

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