# The synthesis of 4-tosyloxy-2-substituted phenols using new solid pyridinium salt supported [hydroxyl(tosyloxy)iodo]benzene reagents

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Two new solid pyridinium salt supported HTIB reagents (*N*-{4-[hydroxyl(tosyloxy)iodo]benzyl}pyridinium tetrafluoroborate and *N*-{4-[hydroxyl(tosyloxy)iodo]phenylcarbamoylmethyl}pyridinium tetrafluoroborate) were synthesised using a pyridinium salt as a cationic support. Although the former was hygroscopic the latter was stable in air and in a highly humid atmosphere over a few weeks. The latter has an extra amide linkage. The structures of both compounds were established by IR, $^1$H NMR, $^{13}$C NMR, MS and elemental analysis. Then, two 4-tosyloxy-2-substituted phenols were successfully prepared using the new reagents. Both reagents were easily regenerated in high yields.

**Keywords**: [hydroxyl(tosyloxy)iodo]benzene, task-specific pyridinium salts, 4-tosyloxy-2-substituted phenols, synthesis

[Hydroxyl(tosyloxy)iodo]benzene (HTIB) is well known as a very useful synthetic reagent,[1] due to its moderate electrophilicity and its ability to bring about oxytosylation. The presence of the hypervalent iodine in the molecule, HTIB facilitates many oxidative transformations.[2–4] However, the reaction of HTIB usually generates an equimolar amount of iodobenzene as a byproduct, which requires extra effort to remove from the desired product. Although this can be accomplished by chromatography, it is usually not cost-effective in larger scale chemical synthesis or manufacture.

Traditionally, polymer-supported reagents have provided a possible approach to the separation problem.[5] However, they are limited in application due to their loading capacity and reactivity.[6] Recently, attention has been focused on the use of organic salts (such as room-temperature ionic liquids, RTILs) as a novel support. The exploration of task-specific organic salts has become an attractive research topic. Compared with traditional polymer-supported reagents, organic salt supported reagents have remarkable advantages, including high stability, favourable solubility, high loading capacity, non-toxicity and low vapor pressure. More importantly, organic salt supported reagents can be easily regenerated and reused.

1-(4-Diacetoxyiodobenzyl)-3-methylimidazalium tetrafluoroborate, an ion-supported phenyliodine diacetate (PIDA) reagent, has been prepared previously.[7] The RTIL-supported HTIB reagents {3–butyl-4(5)-[4-hydroxy(tosyloxy)iodobenzoyloxymethyl]-1-methyl-3*H*-imidazol-1-ium triflimide and 3–butyl-4(5)-[4-hydroxy(tosyloxy)iodobenzoyloxymethyl]-1-methyl-3*H*-imidazol-1-ium 4-methylbenzenesulfonate} have also been reported, which are viscous liquids with ester linkages.[8] We previously reported a new RTIL-supported HTIB reagent {1-[4-hydroxy(tosyloxy)iodobenzyl]-3-methylimidazalium tetrafluoroborate}[9] which is also a liquid. The reactivity of the RTIL-supported HTIB was exemplified by the $\alpha$-tosyloxylation of ketones in an ionic liquid [emim]$BF_4$ or acetonitrile under microwave irradiation. The ion-supported iodobenzene as a solid could be readily isolated and the HTIB regenerated.[9]

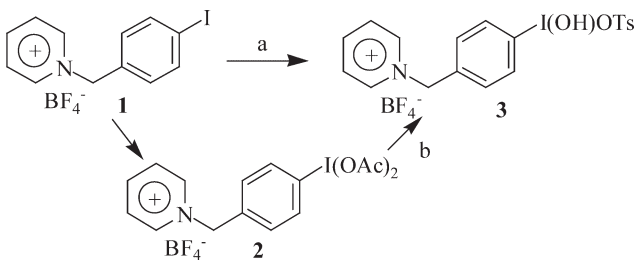
The RTIL-supported HTIB reagents which have been reported are usually viscous liquids, which are inconvenient to purify. Therefore, we are interested in exploring the solid ion-supported HTIB reagents. The properties of organic salts are changed by varying the structure of anions or/and cations. In designing the novel solid organic salt supported HTIB reagents, we considered the following facts: (1) it was found that the melting points of organic salt supported reagents is increased by using symmetric cations. The symmetric pyridine cation was found to be a good candidate to form solid organic salt supported HTIB reagents; (2) it was thought that the new organic salt supported HTIB reagent may be converted to a solid at room temperature by introducing an amide linkage between the cation and HTIB. We now report the efficient synthesis of two new solid pyridinium salt supported HTIB reagents.

*N*-[4-Hydroxyl(tosyloxy)iodobenzyl]pyridinium tetrafluoroborate **3** was obtained in high yield via two methods (Scheme 1), while *N*-{[4- hydroxyl(tosyloxy)iodo]phenylcarbamoylmethyl} pyridinium tetrafluoroborate **7** was synthesised by a one-pot procedure (Scheme 2). We made one attempt to prepare the ion-supported PIDA reagent from **6** with an amide linkage in the structure, but the yield of this reaction was very low (<30%). Since compound **6** could be easily transformed into **7**, the one-pot method was used to give a high yield.

We found that compound **5** was not stable in air due to its hygroscopicity. On the other hand, compound **5** was highly soluble in water. 1-(4-Iodobenzyl)-3- methylimidazolium tetrafluoroborate was prepared using 1-(4-iodobenzyl)-3-methylimidazolium chloride by anion exchange in acetone.[7] Because of the low solubility of the reactants in acetone, the reaction was very slow (60 h). However, 1,1-dimethylpyrrolidinium bis(trifluoromethanesulfonyl)imide salt was obtained in distilled water in 3 h.[10] Since **6** is insoluble in water, the transformation from compound **5** to **6** was completed in water in a few minutes in high yield.

Pyridinium based organic salts appear to absorb moisture, and compound **3**, was found to completely liquefy in air. However, **7** was stable under atmospheric conditions. In our view, the introduction of the amide linkage changed its properties.

Because of the asymmetry of the imidazole structure, these imidazolium salt supported reagents have a lower melting point and exist in a liquid phase.[9] This study demonstrates that solid pyridinium salt supported HTIB reagents can be successfully prepared by the introduction of the amide linkage or by the application of the symmetry of pyridinium cation. Introducing the amide linkage confers a high stability to the




**Scheme 1** (a) *m*-CPMA/p-TsOH; (b) *p*-TsOH.

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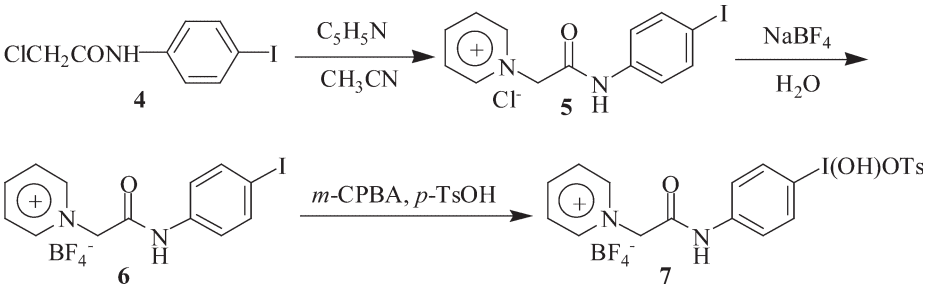



**Scheme 2**

new solid reagent in air, which had previously restricted the application to other syntheses.

Monohydric phenols, which contain some electron-withdrawing substituents at the *ortho* position, on treatment with HTIB in dichloromethane underwent tosyloxylation to the corresponding 4-tosyloxy-2-substituted phenols.[11] We now reported the syntheses of two 4-tosyloxy-2-substituted phenols using new solid pyridinium salt supported HTIB reagents **3** and **7** (Scheme **3**).

The most important feature is that **3** and **7** can be regenerated and reused for the same reaction, and consequently they have several advantages over the conventional HTIB reagents in their ability to be recycled.

## Experimental

Melting points were determined using a WBS-1B digital thermometer, and were uncorrected. $^1$H NMR and $^{13}$C NMR were recorded on a Bruker DRX-500AVANCE spectrometer using TMS as the internal standard. IR spectra were recorded on a Nicolet Protege 460 IR spectrometer. Mass spectra were obtained on a HP5989B and an Agilent 5975I instrument. Elemental analyses were performed using an EA2400 II instrument.

*N*-(4-Iodobenzyl)pyridinium tetrafluoroborate **1** and *N*-[4–bis (diacetoxy)iodobenzyl] pyridinium tetrafluoroborate **2** were prepared according to literature methods.[12] All other reagents were of analytical or chemical grade purchased commercially and used as received unless noted otherwise.

*4-Iodochloroacetanilide* (**4**): $Et_3N$ (2 mL) was added to a chloroform solution (10 mL) of 4-iodoaniline (2.62 g, 12.0 mmol). Then the solution was cooled to 0 °C, and 2-chloroacetyl chloride (1.34 g, 12.0 mmol) was added dropwise to this solution. The resulting solution was warmed to room temperature and stirred for 2 h. The precipitated product was collected by vacuum filtration, washed with distilled water and dried under reduced pressure to afford an off-white solid (2.90 g, 82%). M.p. 192–194 °C (194.0–195.0 °C).[13] IR (KBr): *v* 3307, 3076, 2949, 2852, 1672, 1611, 1586, 1484, 818, 495 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 4.19 (s, 2 H, $CH_2$), 7.34 (d, *J* = 8.7 Hz, 2 H, ArH), 7.67 (d, *J* = 8.7 Hz, 2 H, ArH), 8.20 (s, 1 H, NH). (Ar = benzene).

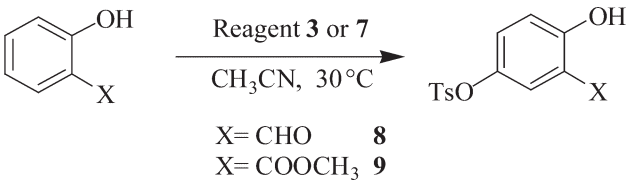
*N-(4-Iodophenylcarbamoylmethyl) pyridinium tetrafluoroborate* (**6**): Compound **4** (3.32 g, 18.0 mmol) was dissolved in anhydrous acetonitrile (20 mL), and anhydrous pyridine (3.56 g, 45.0 mmol) was added to this solution. The resulting mixture was heated at reflux for 5 h with magnetic stirring and protected from moisture by using an anhydrous $CaCl_2$ drying tube. The solvent and excess pyridine were then evaporated and the residue was cooled to room temperature. Water (10 mL) was added to the reaction and the residual solid was dissolved. $NaBF_4$ (1.98 g, 18 mmol) was dissolved in water (10 mL), and then this solution was added to flask. A white precipitate appeared after 10 min by stirring with increasing amounts of $NaBF_4$ solution. The precipitate was filtered, washed with a little water, and then dried under vacuum to afford a white solid (4.40 g, 92%). M.p. 176.0–178.0 °C. IR (KBr): *v* 3365, 3098, 3076, 3057, 2927, 2853, 1705, 1605, 1587, 1488, 815, 496 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ (ppm) 2.29 (s, 3 H, $CH_3$), 5.63 (s, 2 H, $CH_2$), 7.42 (d, *J* = 8.7 Hz, 2 H, ArH), 7.70 (d, *J* = 8.7 Hz, 2 H, ArH), 8.23 (t, *J* = 7.4 Hz, 2 H, PyH), 8.70 (t, *J* = 7.8 Hz, 1 H, PyH), 9.03 (d, *J* = 5.6 Hz, 2 H, PyH), 10.79 (s, 1 H, NH). (Py = pyridinium) $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ (ppm) 62.1, 87.6, 121.3, 127.4, 137.8, 137.9, 146.2, 146.4, 163.6. MS (Agilent 5975I) (EI, 70eV): *m/z* (%) 339.0 (9) [$M^+$–$BF_4^-$], 261.0 (19) [$M^+$–$BF_4^-$–$C_5H_4N$], 246.0 (17) [*p*-$IC_6H_4NHC{\equiv}O^+$], 245.0 (100) [*p*-$IC_6H_4N{=}C{=}O^{\cdot+}$], 219.0 (100) [*p*-$IC_6H_4NH_2]^+$, 79.1 (94) $[C_5H_5N]^+$. Anal. Calcd for $C_{13}H_{12}BF_4IN_2O$: C, 36.64; H, 2.84; N 6.58. Found: C, 36.68; H, 2.85; N, 6.57%.

*N-{[4-Hydroxyl(tosyloxy)iodo]phenylcarbamoylmethyl}pyridinium tetrafluoroborate* (**7**): Compound **6** (3.83 g, 9.0 mmol) and *p*-TsOH•$H_2O$ (1.71 g, 9.0 mmol) were dissolved in acetonitrile (25 mL), and then *m*-CPBA (2.16 g, 80%, 10.0 mmol) was added and the mixture was stirred under a nitrogen atmosphere. After the reaction, $Et_2O$ was added, and a yellow solid was filtered out from the resulting mixture. The solid was washed with $Et_2O$ to provide **7** (4.36 g, 79%). M.p. 136.0–138.0 °C. IR (KBr): *v* 3276, 3060, 1696, 1607, 1587, 1543, 1488, 1197, 1034, 810, 501 cm$^{-1}$. $^1$H NMR(500 MHz, DMSO-$d_6$): $\delta$ (ppm) 2.29 (s, 3 H, $CH_3$), 5.64 (s, 2 H, $CH_2$), 7.11 (d, *J* = 8.0 Hz, 2 H, ArH), 7.42 (d, *J* = 8.8 Hz, 2 H, ArH), 7.49 (d, *J* = 8.0 Hz, 2 H, ArH), 7.69 (d, *J* = 8.8 Hz, 2 H, ArH), 8.20–8.25 (m, 2 H, PyH), 8.69 (t, *J* = 7.8 Hz, 1 H, PyH), 9.03 (d, *J* = 5.5 Hz, 2 H, PyH), 10.78 (s, 1 H, NH). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ (ppm) 20.9, 62.2, 87.9, 121.4, 121.5, 125.6, 127.6, 127.9, 137.8, 137.9, 145.4, 146.4, 146.5, 163.4. MS (HP 5989B) (EI, 70eV): *m/z* (%) 261 (25) [$M^+$–$BF_4^-$-$C_5H_4N$–OH–OTs], 245 (14) [*p*-$IC_6H_4N{=}C{=}O^{\cdot+}$], 219 (80) [*p*-$IC_6H_4NH_2]^+$, 93 (37) $[PhNH_2]^+$, 79 (60) $[C_5H_5N]^+$. Anal. Calcd for $C_{20}H_{20}BF_4IN_2O_5S$: C, 39.09; H, 3.28; N 4.56. Found: C, 39.06; H, 3.29; N, 4.57%.

*N-[4-Hydroxyl(tosyloxy)iodobenzyl]pyridinium tetrafluoroborate (***3***)*

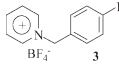
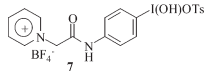
*Method a*: Compound **3** was prepared under the similar condition of compound **7**.

*Method b*: A mixture of **2** (3.0 g, 6.0 mmol) and *p*-TsOH•$H_2O$ (1.14 g, 6.0 mmol) in acetonitrile (20 mL) was stirred at room temperature. After the reaction, the solvent was then evaporated and the residue was washed with $Et_2O$. The residual solid was further dried vacuum at 50 °C to afford **3** as a yellow solid (3.25 g, 95%). M.p. 52.0–54.0 °C. IR (KBr): *v* 3428, 3072, 1570, 1486, 1449, 1182, 1043, 816, 522 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ (ppm) 2.28 (s, 3 H, $CH_3$), 5.80




**Scheme 3**

**Table 1** Syntheses of two 4-tosyloxy-2-substituted phenols with pyridinium salt supported HTIB reagents in acetonitrile and regeneration of new reagents

| Reagent |  3 |  7 |
|---|---|---|
| Yield (**8**,%) | 64 | 62 |
| Yield (**9**,%) | 61 | 60 |
| Yield (**3** or **7**,%)[a] | 91 | 78 |

[a]The yields of regenerated reagents after a single reaction.

(s, 2 H, $CH_2$), 7.14 (d, $J$ = 8.0 Hz, 2 H, ArH), 7.33 (t, $J$ = 8.0 Hz, 2 H, ArH), 7.47 (d, $J$ = 8.0 Hz, 2 H, ArH), 7.82 (t, $J$ = 8.0 Hz, 2 H, ArH), 8.16–8.20 (m, 2 H, PyH), 8.63 (d, $J$ = 7.5 Hz, 1 H, PyH), 9.17 (d, $J$ = 5.5 Hz, 2 H, PyH). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ (ppm) 20.8, 62.7, 96.4, 125.5, 128.1, 128.6, 131.1, 133.9, 137.8, 138.0, 144.9, 145.5, 146.1. MS (HP 5989B) (EI, 70eV): $m/z$ (%) 296 (1) [$M^+$–$BF_4^-$–OH–OTs], 295 (1) [$M^+$–$BF_4^-$–OH–TsOH], 217 (35) [I–$C_6H_4CH_2^+$], 169 (5) [$M^+$–$BF_4^-$–OH–OTs–I], 91 (93) [$C_6H_5CH_2^+$], 79 (100) [$C_5H_5N]^{+\cdot}$. Anal. Calcd for $C_{19}H_{19}BF_4INO_4S$: C, 39.94; H, 3.35; N, 2.45. Found: C, 39.97; H, 3.34; N, 2.45%.

*Synthesis of 4-tosyloxy-2-substituted phenols using reagent* **3***; general procedure*

Substituted monohydric phenols (2 mmol) were added to a solution of reagent **3** (2.1 mmol) in acetonitrile (20 mL), the mixture was stirred in at 30 °C. After completion of reaction [as monitored by TLC(EtOAc–petroleum=1:10)], the product was purified as follows: the solvent was evaporated under reduced pressure to give a solid residue, which was washed with EtOAc or $CHCl_3$ (10 mL × 3) to afford the pyridinium salt supported iodobenzene **1** as a white solid. At the same time, the washings were combined and concentrated under reduced pressure to give a product which was further purified by preparative TLC on silica gel using 1:10 EtOAc-petroleum as developing solvent.

*Regeneration of reagent* **3***; general procedure*

After extraction with EtOAc, the pyridinium salt supported iodobenzene **1** was used to prepare reagent 3 under the similar condition of compound **7**.

The syntheses of 4-tosyloxy-2-substituted phenols using reagent **7** and the regeneration of reagent **7** were similar to reagent **3**. The results are listed in Table 1.

*2-Formyl-4-tosyloxyphenol* (**8**): Yellow crystals. M.p. 216.7–217.5 °C; lit.[11] 219–220 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 2.38 (s, 3 H, $CH_3$), 6.81 (d, $J$ = 9.0 Hz, 1 H), 6.98 (dd, $J$ = 9.0, 3.0 Hz, 1 H), 7.21 (d, $J$ = 3.0 Hz, 1 H), 7.27 (d, $J$ = 8.0 Hz, 2 H), 7.64 (d, $J$ = 8.0 Hz, 2 H), 9.72 (s, 1 H, –CHO), 10.90 (s, 1 H, OH).

*2-Methoxyformyl-4-tosyloxyphenol* (**9**): Yellow crystals. M.p. 88.3–90.2 °C; lit.[11] 91–92 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 2.38 (s, 3 H, $CH_3$), 3.85 (s, 3 H, –$OCH_3$), 6.77 (d, $J$ = 9.0 Hz, 1 H), 6.87 (dd, $J$ = 9.0, 3.0Hz, 1 H), 7.25 (d, $J$ = 8.0 Hz, 2 H), 7.50 (d, $J$ = 3.0 Hz, 1 H), 7.63 (d, $J$ = 8.0 Hz, 2 H), 10.65 (s, 1 H, OH).

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