

Communications

Aromatization of Hantzsch 1,4-Dihydropyridines with a Polymer-supported Hypervalent Iodine Reagent

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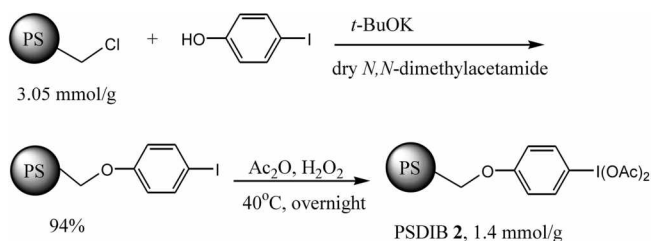
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Hantzsch 1,4-dihydropyridines (**1**, Hantzsch 1,4-DHPs), which can be prepared by a three-component coupling of ethyl acetoacetate, an aldehyde and ammonia, are widely used as calcium channel blockers for the treatment of cardiovascular disorders.¹ Hantzsch 1,4-DHPs are oxidized to pyridine derivatives by the action of cytochrome P-450 in the liver.² In this respect, a convenient preparation of pyridines from 1,4-DHPs is important for the identification of metabolites. Furthermore, the oxidation of Hantzsch 1,4-DHPs provides an easy access to pyridine derivatives. Oxidation of 1,4-DHPs has been achieved using various oxidants.³ A recent method includes the use of $\text{SiCl}_4/\text{NaNO}_2$ as a heterogeneous oxidant.⁴

Recently we reported that 1,4-DHPs can be aromatized to pyridines within a few minutes by [hydroxy(tosyloxy)iodo]benzene (HTIB, $\text{PhI}(\text{OH})\text{OTs}$).^{3a} In continuing our efforts to find a new oxidant for the 1,4-DHPs, herein we wish to report that a polymer-supported hypervalent iodine(III) reagent can serve as a new oxidant for the aromatization of the 1,4-DHPs.

Hypervalent iodine(III) compounds such as (diacetoxyiodo)benzene ($\text{PhI}(\text{OAc})_2$), [bis(trifluoroacetoxy)iodo]benzene ($\text{PhI}(\text{OCOCF}_3)_2$), and HTIB⁵ have been widely used as green oxidants in organic synthesis due to their ready availability, high efficiency, stability to air and moisture, and low toxicity.⁶ Preparation and use of polymeric version of iodine(III) reagent as a form of polymer-supported (diacetoxyiodo)benzene (PSDIB) was reported by several research groups. For example, Ley *et al.*⁷ and Togo *et al.*⁸ showed that PSDIB could be prepared by iodination of polystyrene followed by peracetic acid oxidation. Similarly, Giannis *et*



Scheme 1

*et al.*⁹ reported a preparation of aminomethylpolystyrene-supported (diacetoxyiodo)benzene reagents.

Our preparation of PSDIB **2** starts from Merrifield's peptide resin (Aldrich 45,696-9, 3.05 mmol Cl/g), as shown in Scheme 1.¹⁰

Williamson reaction of Merrifield's resin (loading at 3.05 mmol/g) with *p*-iodophenol in the presence of $\text{KOBu-}t$ gave the coupled product in good yield. Subsequent oxidation was carried out using freshly prepared peracetic acid at 25 °C overnight.^{7,8} The resin was collected in a glass filter, rinsed with methanol and dried *in vacuo* to a constant weight. Activity of resin **2** thus prepared was determined by the following way: a known amount of benzyl alcohol was treated with a defined amount of PSDIB **2** in CDCl_3 and this oxidation reaction was followed by ¹H-NMR spectroscopy until the ratio of benzaldehyde and alcohol was constant (for one day). Based on this ratio and the known amount of starting material, the activity was found to be 1.4 mmol/g.

Next, we turned our effort to the oxidation of Hantzsch 1,4-DHPs **1** with resin **2**. The oxidation was performed by treating 1,4-DHPs (0.5 mmol) with 2 equivalents of **2** (0.71

Table 1. Aromatization of Hantzsch 1,4-Dihydropyridines **1** with PSDIB **2**

| Entry | 1,4-DHPs | R | Time | Pyridines ^b | Yield % ^c | mp (°C) | Lit. mp (°C) |
|-----------------|-----------|---|-------|------------------------|----------------------|---------|----------------------|
| 1 | 1a | C ₆ H ₅ | 2.5 h | 3a | 73 | 60-61 | 61-62 ^{2a} |
| 2 ^a | 1a | C ₆ H ₅ | 2.5 h | 3a | 72 | | |
| 3 | 1b | 3-NO ₂ C ₆ H ₄ | 12 h | 3b | 68 | 61-62 | 61-63 ^d |
| 4 | 1c | 4-NO ₂ C ₆ H ₄ | 12 h | 3c | 62 | 114-115 | 114-116 ^e |
| 5 | 1d | 2-ClC ₆ H ₄ | 7 h | 3d | 63 | 61-62 | 62 ^f |
| 6 | 1e | 4-MeOC ₆ H ₄ | 2.5 h | 3e | 47 | 50-51 | 50 ^g |
| 7 | 1f | C ₆ H ₅ CH ₂ | 6 h | 4 | 60 | 67-68 | 70-71 ^e |
| 8 | 1g | C ₆ H ₅ CH=CH | 24 h | 3g | 43 | 159-160 | 162-163 ^e |
| 9 | 1h | CH ₃ CH=CH | 12 h | 3h | 53 | 159-160 | 162-163 ^d |
| 10 | 1i | CH ₃ | 2 h | 3i | 73 | oil | oil ^h |
| 11 ^a | 1i | CH ₃ | 2 h | 3i | 72 | | |
| 12 | 1k | <i>n</i> -C ₃ H ₇ | 2 h | 3k | 61 | oil | oil ^h |
| 13 | 1l | (CH ₃) ₂ CH | 1 h | 4 | 80 | 68-69 | 70-71 ^e |
| 14 ^a | 1l | (CH ₃) ₂ CH | 1 h | 4 | 96 | | |

^arecycled resin was used. ^ball products are known compounds and were characterized by their mps and NMR spectra. ^cyield refers to the isolated pure product. ^dVanden Eynde, J.-J.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. *Tetrahedron* **1995**, *51*, 6511. ^eMashraqui, S. H.; Kamik, M. A. *Tetrahedron Lett.* **1998**, *39*, 4895. ^fBeilstein E II **22**, 127.

g) in CH₂Cl₂ (5 mL) at 25 °C until the oxidation was complete.¹¹ Our results are summarized in Table 1. Surprisingly, our polymer-supported reagent **2** was found to be more active than PhI(OAc)₂, the corresponding monomeric reagent under a similar reaction condition: the oxidation of **1a** with PhI(OAc)₂ was not completed within 5 h, giving a 3 : 1 mixture of **3a** and **1a**, as reported before.^{3a} However, **1a** could be cleanly oxidized to pyridine **3a** by PSDIB **2** within 2.5 h (entry 1). As expected, the presence of electron-withdrawing group such as nitro group retarded the oxidation (entries 3, 4, 5). Hantzsch 1,4-DHPs **1f** and **1l** bearing a benzyl group or an isopropyl group at the 4-position underwent simultaneous dealkylation to give **4** as a sole product, as observed in the oxidation with HTIB.^{3a}

We also studied the regeneration and recycling of the used PSDIB. After the first run the polymer was recovered by filtration followed by washing with MeOH. The recovered polymer was then reoxidized with peracetic acid in the usual manner. The activity of regenerated **2** was almost same as before, as evidenced by the similar reaction time and chemical yields (entries 1 vs. 2, 10 vs. 11 and 13 vs. 14).

In conclusion, polymer-supported (diacetoxyiodo)benzene (PSDIB) of the structure **2**, which is easily prepared from Merrifield's peptide resin, can serve as a new and recyclable oxidant for the aromatization of Hantzsch 1,4-dihydropyridines.

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- Preparation of a polymer-supported hypervalent iodine(V) reagent from Merrifield's resin has been reported in the literature: see, Sorg, G.; Mengel, A.; Jung, G.; Rademann, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4395.
- In a typical experiment, a solution of 1,4-DHP (**1a**, 165 mg, 0.5 mmol) in CH₂Cl₂ (5 mL) was allowed to react with PSDIB **2** (710 mg, 1.0 mmol) and the mixture was stirred at 25 °C. The progress of the reaction was monitored by TLC (for **1a**, R_f = 0.20; for **3a**, R_f = 0.36 in hexanes:EtOAc = 5:1). After 2.5 h, the reaction was found to be complete. The reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous NaHCO₃ solution. The organic phase was separated, dried and concentrated under reduced pressure. Finally, the purification by silica gel column chromatography gave 240 mg (73% yield) of **3a** as a pale yellow solid, mp 60-61 °C (Lit.^{2a} mp 61-62 °C).