

Aromatization of Hantzsch 1,4-Dihydropyridines with [Hydroxy(tosyloxy)iodo]benzene

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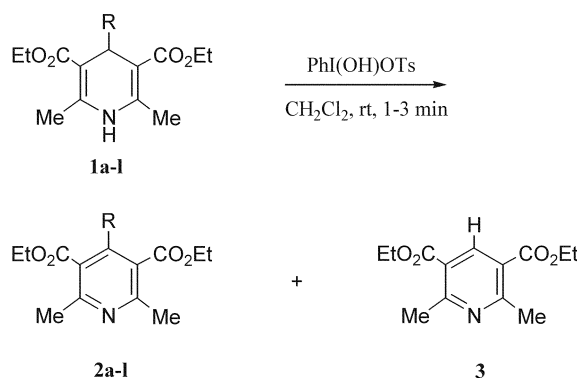
Key Words : 1,4-Dihydropyridines, Aromatization, Hypervalent iodine

Hantzsch 1,4-dihydropyridines (**1**, Hantzsch 1,4-DHPs) are widely used as calcium channel blockers for the treatment of cardiovascular disorder including angina, hypertension and cardiac arrhythmias.¹ These compounds 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 However, some methods suffer from low chemical yields,^{3j-k} strong oxidative conditions,^{3a-b,h} cumbersome workup,^{3j-k} side-product formation^{3j} or long reaction time.^{3j} We reported that Hantzsch 1,4-DHPs can be aromatized to pyridines by MagtrieveTM, a magnetically retrievable and environmentally safe oxidant (CrO₂).⁴ In continuing our efforts to find a milder and high-yielding oxidant for the Hantzsch 1,4-DHPs, herein we wish to report that [hydroxy(tosyloxy)iodo]benzene (HTIB, PhI(OH)OTs, Koser's reagent)⁵ can serve as a powerful oxidant for the aromatization of the Hantzsch 1,4-DHPs.

Hypervalent iodine(III) and iodine(V) reagents have been used as green-oxidants for a variety of substrates.⁶ Literature survey showed that phenyliodine(III) bis(trifluoroacetate) (PhI(OCOCF₃)₂, PIFA) was already used for the solid state oxidation of 1,4-DHPs under microwave irradiation conditions.⁷ One drawback of this reagent is that dealkylation occurs even in the case of 4-ethyl-1,4-DHP.⁷ When we attempted the oxidation of **1a** (R = phenyl) with iodobenzene diacetate (PhI(OAc)₂), a non-fluorinated analog of PIFA in CH₂Cl₂ at room temperature, the oxidation was not completed within 5 h, giving a 3 : 1 mixture of **2a** and **1a**. Further search for the efficient hypervalent iodine oxidants led to the finding that HTIB⁸ is an extremely efficient reagent for the aromatization of 1,4-DHPs, as shown in Scheme 1.

As shown in Table 1, the oxidation of 1,4-DHPs with HTIB was completed within just a few minutes in CH₂Cl₂ at room temperature, requiring no activation such as microwave irradiation⁷ or ultrasound.^{3c} HTIB was found to be equally effective for the aromatization of 1,4-DHPs bearing an alkyl group or an aryl group in the 4-position.^{3c} Also, dealkylation of 4-ethyl derivative **1j**, which was observed during PIFA oxidation⁷ did not occur in the present case. However, as observed in the oxidation with Cr(VI)^{3c-d} or

Cr(IV) reagents,⁴ 1,4-DHPs **1f** and **1h** bearing a benzyl group or an isopropyl group at the 4-position underwent simultaneous dealkylation to give **3** as a sole product. This dealkylation probably may proceed *via* a radical cation intermediate **4** that is formed by single electron transfer (SET) from 1,4-DHP to HTIB, as suggested in Scheme 2.^{7,10} When 4-alkyl group is benzyl or isopropyl group, the 4-alkyl group rather than proton is expelled from **4** as a stable carbocation, resulting in the formation of dealkylated radical **5**. Further oxidation of **5** ultimately gives the observed product **3**.

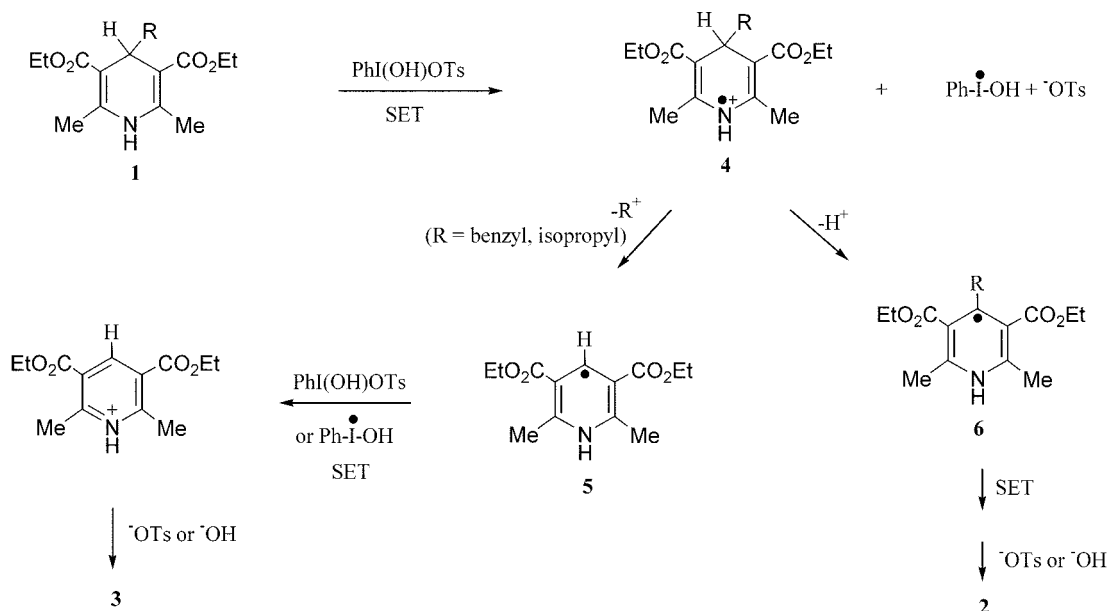


Scheme 1

Table 1. Aromatization of Hantzsch 1,4-Dihydropyridines with PhIOH(OTs)

1,4-DHPs	R	Time	Pyridines ^a	Yield % ^b	mp (°C)	Lit. mp (°C)
1a	C ₆ H ₅	1 min	2a	92	60-61	61-62 ^{2a}
1b	3-NO ₂ C ₆ H ₄	1 min	2b	91	61-62	61-63 ^{3g}
1c	4-NO ₂ C ₆ H ₄	1 min	2c	93	114-115	114-116 ^{3k}
1d	2-ClC ₆ H ₄	2 min	2d	94	61-62	62 ^c
1e	4-MeOC ₆ H ₄	2 min	2e	91	50-51	50 ^{3k}
1f	C ₆ H ₅ CH ₂	3 min	3	95	67-68	70-71 ^{3k}
1g	C ₆ H ₅ CH=CH	1 min	2g	93	159-160	162-163 ^{3k}
1h	MeCH=CH	1 min	2h	93	159-160	162-163 ^{3k}
1i	CH ₃	2 min	2i	92	oil	oil ^{3g}
1j	C ₂ H ₅	2 min	2j	92	oil	oil ^{3g}
1k	<i>n</i> -C ₃ H ₇	2 min	2k	95	oil	oil ^{3g}
1l	(CH ₃) ₂ CH	2 min	3	98	68-69	70-71 ^{3k}

^a all products are known compounds and were characterized by their mps and NMR spectra. ^b yield refers to the isolated pure product. ^c Beilstein E II 22, 127.



Scheme 2. Proposed mechanism of oxidation of 1,4-DHPs with PhI(OH)OTs.

In summary, we have found that HTIB can serve as a mild, fast and efficient oxidant for the aromatization of Hantzsch 1,4-dihydropyridines to pyridines.¹² In terms of reaction time, HTIB seems to be the most efficient oxidant for the 1,4-DHPs among known oxidants, to our best knowledge.

References and Notes

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- HTIB is available from Aldrich Chemical Company, Inc.
- In a typical experiment, a solution of Hantzsch 1,4-DHP (**1a**, 330 mg, 1.0 mmol) in dichloromethane (5 mL) was allowed to react with PhI(OH)OTs (470 mg, 1.2 mmol) and the mixture was stirred at rt. The progress of the reaction was monitored by thin layer chromatography (for **1a**, R_f = 0.20; for **2a**, R_f = 0.36 in hexanes/EtOAc = 5/1). After 1 min, the reaction was found to be complete. The reaction mixture was diluted with EtOAc (20 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 (hexanes/EtOAc = 5/1) gave 320 mg (97% yield) of **2a** as a pale yellow solid, mp 60-61 °C (Lit.^{2a} mp 61-62 °C).
- A mechanism involving single electron transfer (SET) steps has been proposed for the oxidation by *o*-iodoxybenzoic acid (IBX), a hypervalent iodine(V) reagent.¹¹ Dealkylation observed in the present study suggests the involvement of similar SET process.
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- Greater reactivity of PhI(OH)OTs compared to PhI(OAc)₂ may be ascribed to the more ionic nature of I-OTs bond in PhI(OH)OTs, rendering the iodine atom more electrophilic.⁵