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A convenient and efficient protocol for oxidative aromatization of Hantzsch 1,4-dihydropyridines using benzyltriphenylphosphonium peroxymonosulfate under almost neutral reaction conditions

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Abstract—Oxidative aromatization of 4-alkyl or aryl and heterocyclic-substituted derivatives of Hantzsch 1,4-dihydropyridines to the corresponding pyridine derivatives has been studied using benzyltriphenylphosphonium peroxymonosulfate as an oxidant in the presence of $BiCl_3$ under nearly neutral reaction conditions at ambient temperature.

The chemistry of 1,4-dihydropyridines (DHPs) was reviewed in 1972 by Eisner and Kuthan,[1] and in 1988 by Stout and co-workers.[2] DHP drugs such as nifedipine, nicardipine, amlodipine, and others are effective cardiovascular agents for the treatment of hypertension.[3] Also, DHPs play a vital role for their antioxidant effect that may contribute to their pharmacological activities.[4] This effect is not due to the Ca^{2+} antagonist effect, but is related to the reactivity of these compounds toward radical species.[4a] The oxidative aromatization of DHPs to the corresponding pyridine derivatives constitutes the principal metabolic route in particular in biologically significant NADH redox processes,[5] as well as a facile access to the corresponding pyridine derivatives, which show antihypoxic and antiischemic activities,[6] from the easily available DHPs.[7] Consequently, this aromatization reaction continues to attract the attention of organic and medicinal chemists for the discovery of a plethora of protocols applicable to a wide range of DHPs. Many of the reported procedures involve the use of ferric or cupric nitrates on a solid support,[8] ceric ammonium nitrate,[9] clay-supported cupric nitrate accompanied by ultrasound promotion,[10] manganese dioxide or DDQ,[11] nitric oxide,[12] bismuth nitrate penahydrate,[13] PCC,[14] tetrakis-(pyridine) cobalt(II) dichromate,[15] nicotinum dichromate,[16] *S*-nitrosoglutathione,[17] N_2O_4 complex of 18-crown-6,[18] 3-carboxypyridinium chlorochromate (CPCC),[19] $KMnO_4$,[20] MnO_2/bentonite/microwave irradiation,[21] HNO_3,[22] HNO_2,[23] *tert*-butylhydroperoxide,[24] silica gel-supported ferric nitrate,[6] phenyliodine (III) bis(trifluoroacetate) or elemental sulfur,[25] photochemical oxidation,[26] inorganic acidic salts/sodium nitrite or nitrate,[27] polystyrene-bound Mn(TPP)Cl/$NaIO_4$,[28] Mn(TPP)Cl/$(n\text{-Bu})_4NIO_4$,[29] triazolinediones,[30] $Zr(NO_3)_4$,[31] H_2O_2/$Co(OAc)_2$, [32] urea nitrate and peroxydisulfate-Co(II),[33] hypervalent iodine reagents,[34] I_2-MeOH,[35] selenium dioxide,[36] heteropoly-acid/$NaNO_2$/wet SiO_2,[37] cytochrome P-450,[38] electrochemical catalysis,[39] manganese triacetate,[40] *N*-hydroxyphthalimide/O_2/$Co(OAc)_2$,[41] catalytic amount of $Fe(ClO_4)_3$/HOAc,[42] Mn(III)-salophen/$NaIO_4$,[43] and catalytic amount of Pd/C in acetic acid.[44]

However, most of the reported oxidation protocols require an extended period of time for completion, utilize strong oxidants in large excess and afford only modest yields of the products, produce by-products which are difficult to remove, and utilize oxidizing reagents and catalysts which are either highly toxic and expensive or present serious disposal problems. Therefore, we decide

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to introduce a new reagent to overcome these limitations.

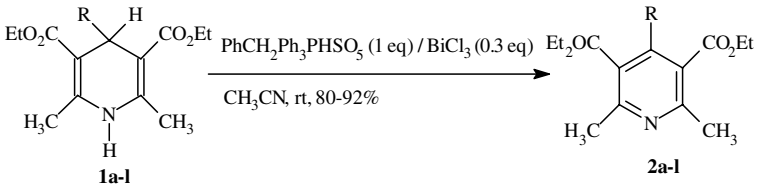
Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is an inexpensive, water-soluble, and stable oxidizing reagent that is commercially available, but this reagent is insoluble in organic solvents and buffering is needed due to its acidity.[45] Recently, we have reported benzyltriphenylphosphonium peroxymonosulfate **BTPPMS** as a mild, inexpensive, and efficient oxidizing reagent for oxidation of alcohols to aldehydes and ketones under aprotic[46a] or solvent-free conditions,[46b] oxidative-deprotection of trimethylsilyl and tetrahydropyranyl ethers and of ethylene acetals under non-aqueous conditions[46c] or microwave irradiation,[46d] conversion of oximes, phenylhydrazones, 2,4-dinitrophenylhydrazones, and semicarbazones to carbonyl compounds in aprotic solvent[46e] or accelerated using microwave,[46f] oxidation of urazoles to triazolinediones in a solventless system,[46g] selective and efficient oxidation of sulfides and thiols under solvent-free[46h] or aprotic conditions,[46i] solid-state deprotection of acetals and thioacetals,[46j] dethioacetalization of 1,3-dithiolanes and 1,3-dithianes,[46k] and highly selective iodination of phenols.[46l] Following our continued interest in exploring **BTPPMS** as a powerful oxidizing reagent,[46] herein we report efficient and convenient oxidative aromatization of DHPs to the corresponding pyridine derivatives employing **BTPPMS** as an oxidant in the presence of bismuth chloride under non-aqueous conditions. Thus, a series of 4-alkyl or aryl and heterocyclic substituted derivatives of DHPs was subjected to oxidation in acetonitrile at ambient temperature to furnish the corresponding pyridine derivatives.

Benzyltriphenylphosphonium peroxymonosulfate **BTPPMS**, a mild, efficient, stable, and cheap reagent, is a white powder which is quite soluble in dichloromethane, chloroform, acetone, and acetonitrile and insoluble in non-polar solvents such as carbon tetrachloride, *n*-hexane, and diethyl ether. This reagent is readily prepared by the dropwise addition of an aqueous solution of Oxone® to an aqueous solution of benzyltriphenylphosphonium chloride in quantitative yield at room temperature and could be stored for months without losing its potency.[46] The amounts of HSO_5^- in this reagent have been determined by an iodometric titration method[47] and the measurements are consistent with almost 99% by weight of active oxidizing agent.

We have reported a convenient method for aromatization of DHPs, affording pyridine derivatives in high yields within short reaction periods. Simply by adding oxidant **BTPPMS** to a solution of DHP derivative and bismuth chloride in acetonitrile, rapid and convenient oxidation is achieved at room temperature. The products can be separated by straightforward workup. The method has been applied successfully to a variety of substituents like alkyl, aryl, cinnamyl, and heterocyclic groups in the 4-position of DHPs (Scheme 1 and Table 1).

To choose the most appropriate medium in order to be able to carry out such a aromatization reaction in a more efficient way minimizing the time, solvent, and amount of catalyst and oxidant, the oxidation of diethyl 1,4-dihydro-2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate **1a** as the model compound using bismuth chloride and **BTPPMS** in various solvents was examined. The solvents examined were tetrahydrofuran, diethyl ether, dichloromethane, chloroform, and acetonitrile. The reactions were carried out by stirring model compound **1a** with **BTPPMS** and $BiCl_3$ (1:0.3) at room temperature. Dichloromethane and other solvents were inferior to acetonitrile, because the reaction stopped at lower conversions in these solvents than that in acetonitrile (TLC analysis). When the reaction was carried out in CH_3CN, the reaction took place rapidly and the corresponding pyridine derivative **2a** was obtained in 100% conversion, it turned out to be one of the best choices, in view of its relatively solubility characteristics. Then, we decided to explore the role of **BTPPMS** in the presence of hydrated and anhydrous metal salts such as $ZnCl_2$, $FeCl_3.6H_2O$, $AlCl_3$, and $BiCl_3$ in dry aprotic solvent for the oxidation of **1a**. It was found that $BiCl_3$ was effective metal salt for the promotion of the reaction in dry acetonitrile (conversion 100%). As we mentioned in our previously reported procedures,[46] this could be the effect of softness of $BiCl_3$ in comparison to the other Lewis acids used in these experiments. Other investigation on the oxidation efficiency of **BTPPMS** alone at ambient temperature indicated that in the absence of bismuth chloride, oxidation process into aromatized product **2a** by the peroxymonosulfate anion is less effective. Finally, the optimum molar ratio of **1a**, to $BiCl_3$ to **BTPPMS** (1:0.3:1) is found to be ideal for complete aromatization of **1a–l** to pyridine derivatives **2a–l** while the reaction remains incomplete with lesser amounts, e.g. 1:0.1 or 1:0.2 (TLC analysis). An increase in the molar ratio of Lewis acid and time did not improve the yields significantly. The products **2a–l** were isolated by filtering the reaction mixture and extracting with dichloromethane and concentrating in vacuo. The residue was purified by column chromatography over silica gel or recrystallization in an appropriate solvent and confirmed by elemental analysis, MS, melting point, ^1H NMR, ^{13}C NMR, and IR spectral data with those of authentic samples and reported in the literature.[48] This method offers a simple, general, efficient route for converting DHPs to the corresponding pyridine derivatives. To evaluate the utility of this procedure for large scale, a tenfold scale oxidation was carried out successfully with **BTPPMS** for the aromatization of **1a**, and the corresponding product **2a** was obtained in 88% yield as revealed from ^1H NMR and TLC analysis within 2 h. The reagent **BTPPMS** was prepared according to our previously reported procedures.[46] Hantzsch DHPs were synthesized according to the reported procedure.[7]

Aromatization of DHP by **BTPPMS** proceeds according to the stoichiometry of Scheme 2. The possible mechanism is proposed according to a radical pathway upon homolytic cleavage of O–O bond in peroxymonosulfate anion (^-O_3S-O-OH) according to Scheme 2. It is believed that the presence of metal ion increases the rate of decomposition of peroxymonosulfate anion to form a hydroxyl radical and a sulfate radical anion. The

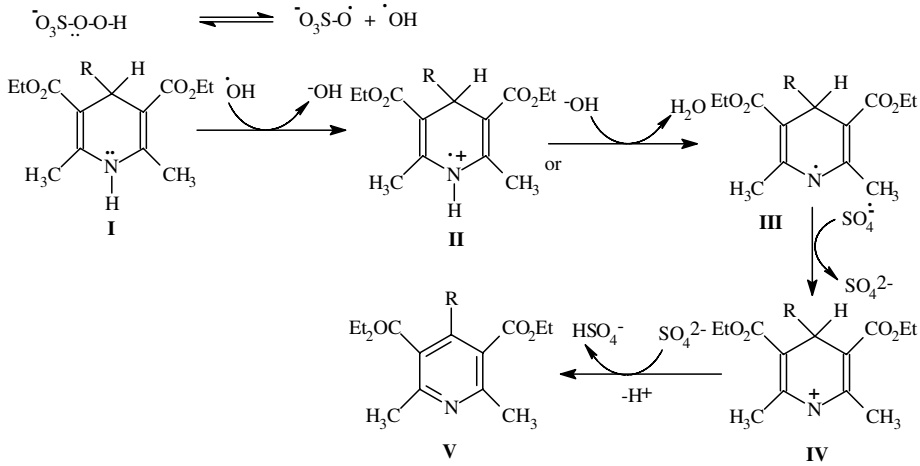


Scheme 1. Oxidative aromatization of Hantzsch 1,4-dihydropyridines using **BTPPMS** and bismuth chloride.

Table 1. Oxidative aromatization of DHPs using bismuth chloride as a catalyst in the presence of benzyltriphenylphosphonium peroxymonosulfate as an oxidant under nearly neutral reaction conditions[a]

Compound	R	Time (min)	Yield (%)[b]	Mp (°C)	
				Found	Reported
1a	C_6H_5	120	89	60–62	63–64[40]
1b	CH_3	90	92	Oil	Oil[40]
1c	H	90	89	69–70	71[40]
1d	*p*-$MeOC_6H_4$	80	85	50–52	51–53[40]
1e	*p*-ClC_6H_4	100	81	66–67	65–67[11]
1f	2-Furyl	90	80	40–43	40–42[32]
1g	*p*-$O_2NC_6H_4$	150	88	115–116	114–115[40]
1h	*m*-$O_2NC_6H_4$	150	90	61–63	62–64[32]
1i	*p*-MeC_6H_4	80	86	72–73	72–73[40]
1j	2-Thienyl	90	80	Oil	Oil[40]
1k	PhCH=CH	80	80	162–164	162–163[40]
1l	*n*-C_4H_9	90	84	Oil	Oil[33]

[a] Confirmed by comparison with authentic samples.
[b] Yield of isolated pure product after purification.



Scheme 2. Proposed mechanism for aromatization of 1,4-dihydropyridines through possible radical pathway.

hydroxyl radical initiates the oxidation reaction by abstracting an electron on the nitrogen of 1,4-dihydropyridine **I** to give the radical cation **II** and hydroxide anion. This radical cation **II** loses a proton to form an intermediate **III** and water, which transfers an electron to the sulfate radical anion to form the cation **IV** and sulfate anion, subsequently resulting in the aromatized product(s) **V** and hydrogen sulfate anion.

In conclusion, we have developed a novel system using **BTPPMS**-$BiCl_3$ as an interesting alternative to liquid, strong, and expensive oxidants and catalysts as mentioned in introduction in the oxidative aromatization of DHPs. Nearly neutral reaction conditions, moderate to high yields of products, and simple work-up are other advantages of the present methodology. It has also been demonstrated that the process is amenable to scale up.

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48. *Representative procedure for oxidative aromatization of diethyl 1,4-dihydro-2,6-dimethyl-4-phenyl-3,5-pyridinedi-*

carboxylate **1a** *to diethyl 2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate* **2a**. To a solution of **BTPPMS** (1 mmol, 0.466 g) and bismuth chloride (0.3 mmol, 0.094 g) in acetonitrile (5 mL) in a 250-mL round-bottomed flask, diethyl 1,4-dihydro-2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate **1a** (1 mmol, 0.329 g) was added. The reaction mixture was stirred at room temperature for 2 h. After disappearance of the starting DHP monitored by TLC using EtOAc/cyclohexane (2:8), the mixture was filtered off through a sintered glass funnel, and the pyridine derivative was extracted with dichloromethane (2× 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was recrystallized in ethanol to afford diethyl 2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate **2a** as a pale yellow solid in 89% yield as revealed from TLC and ^1H NMR analysis, mp 61–64 °C (Lit.[23a] mp 62–64 °C).