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Facile and efficient aromatization of 1,4-dihydropyridines with $M(NO_3)_2{\cdot}XH_2O$, TNCB, TBAP and HMTAI and preparation of deuterium labeled dehydronifedipine from nifedipine-d_3

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ABSTRACT

The easy and efficient aromatization of various 1,4-dihydropyridines was investigated using various metal nitrates, trinitratocerium(IV) bromate (TNCB), and tetrabutyl ammonium periodate (TBAP) as oxidant in acetic acid at 100 °C, as well as hexamethylenetetramine-iodine (HMTAI) reflux in methanol. The efficient conversion of nifedipine-d_3 to dehydronifedipine-d_3 as an internal standard can be used in the measurement of nifedipine concentration in a body.

The oxidation of Hantzsch's 1,4-dihydropyridines (1,4-DHPs) to the corresponding pyridines has been extensively studied.[1] The relevance of this reaction to the metabolism of Hantzsch's esters as calcium channel blocking drugs is exploited to treat various cardiovascular disorders.[2] For example, 1,4-DHP-derived drugs such as nifedipine, nitrendipine, and nimodipine are frequently used as cardiovascular agents (Ca^{2+} channel blockers) in the treatment of hypertension and angina pectoris diseases.[3] The metabolism of these drugs involves the oxidative aromatization of 1,4-DHP nucleus to the corresponding pyridine derivatives, which are catalyzed in the liver by cytochrome P-450.[4] Therefore, numerous studies have been performed on the mimicking of this enzyme.[5,6]

To investigate the mode of action, pharmacokinetics and drug metabolism of dihyropyridine drugs derived from it, such as nifedipine, nilvadipine and amlodipine, the stable isotope-labeled drugs are necessary.[7] In particular, tritium, carbon-14, iodine-125 and labeled dihydropyridine drugs have been used in metabolic investigations, and to determine the affinity as well as binding to receptors in various tissues.[8] However, standard samples for analyzing drugs are very difficult to obtain, and many researchers are interested in the preparation of labeled drugs as internal standards for GC–MS analysis. To fulfill the demand for highly pure standards, including isotope-labeled dihydropyridines, the authors initiated a study of the synthesis of such standards. However, our expertise in the synthesis of internal standards for various controlled drugs motivated us to synthesize nifedipine-d_3.[9]

Numerous reagents have been recommended for the oxidative aromatization of 1,4-DHPs to the pyridines, such as I_2,[10] $KMnO_4$,[11] SeO_2,[12] $KBrO_3/SnCl_4{\cdot}5H_2O$,[13] magtrieve,[14] $Pb(OAc)_4$,[15] chloranil,[16] $H_2O_2/Co(OAc)_2$,[17] Co-naphthenate/O_2,[18] nicotinium dichromate,[19] clay or wet-SiO_2 supported oxidants,[20] *S*-nitrosoglutathione,[21] NO,[22] palladium catalyst,[23] peroxydisulfate–cobalt(II),[24] hypervalent iodine reagents,[25] inorganic acidic salts, and sodium nitrite or nitrate,[26] solid acids,[27] sodium periodate catalyzed by manganese(III) Schiff's base,[28] *N*,*N*′-ethylene-bis(benzoylacetoniminato) copper(II),[29] cytochrome P-450,[30] electrochemical methods,[31] K_2FeO_4 by microwave promoted[32] and photooxidation.[33] Although some of these reactions are performed under mild conditions, most of them require a long period for completion, strong oxidants, freshly prepared reagents, tedious work-up, dealkylation, the formation of side products and only modest yields of the products (Table 1). Therefore, a convenient, rapid and efficient method for oxidizing 1,4-DHPs is still sought.

Metal nitrates are widely known inorganic salts, and have been used in various organic transformations, such as the tetrahydropyranylation of alcohols and phenols,[34] selective and solvent-free oxidation using microwave,[35] the nitration of thiophene derivatives, the highly regioselective conversion of epoxides to bromohydrins,[36] aldol condensation,[37] Fischer–Tropsch synthesis,[38] the preparation of vitamin B12,[39] and the chemoselective and regioselective reduction of nitroarenes, carbonyls and azo dyes.[40]

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Table 1
Various reagents for the oxidative aromatization of 1,4-DHP (**1b**) to the pyridine (**2b**)

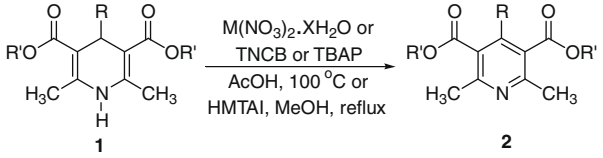
Oxidant	Temp (°C)	Solvent	Time (min)	Yield (%)
$PhCH_2Ph_3PHSO_5/BiCl_3$	rt	CH_3CN	120	89[24a]
$KBrO_3/SnCl_4$	82	CH_3CN	40	90[13]
$Cu(C_{22}H_{22}N_2O_2)$	118	AcOH	60	90[29]
$PhI(OAc)_2$	rt	CH_2Cl_2	60	87[25b]
DMP/I_2	rt	CH_2Cl_2	25	89[25d]
DMP/KBr	rt	CH_3CN	180	82[25d]
$Oxone/NaNO_2$, wet-SiO_2	rt	CH_2Cl_2	75	91[27]
hv	rt	CCl_4	180	100[33b]
Ag_2CO_3/SiO_2	82	CH_3CN	105	94[20h]
Ag_2CO_3/Celite	82	CH_3CN	210	90[20h]
Mn(III)–Salophen/Oxone	rt	Aq CH_3CN	30	94[24b]

Cerium(IV) compounds are the most important oxidants among lanthanide reagents; specifically, ceric ammonium nitrate (CAN) is the most versatile oxidizing lanthanide reagents. Sodium bromate is also well documented as an oxidizing agent in various organic transformations, but both have their limits. A synergistic effect between CAN and sodium bromate in trinitratocerium(IV) bromate, $(NO_3)_3CeBrO_3$ (TNCB), which is quite stable and capable of the oxidation of benzyl alcohols and acyloins,[41] the solvent-free oxidation of alcohols and deprotection, the oxidative deprotection of trimethylsilyl ethers,[42] and the coupling of thiols,[43] makes CAN and sodium bromate synthetically valuable reagents.

Tetra-*n*-butylammoinum periodate was reported to be used in the oxidation of sulfides to sulfoxides, the decarboxylation of α-hydroxy carboxylic acids, the transformation of phenyl bromides to benzoic acids,[44] the oxidation of olefins to oxiranes,[45] the decarboxylation of arylacetic acids,[46] and oxidative cleavage of covalent stannylene derivatives.[47] Along with these reports, it was also been documented that the oxidation of 1,4-DHP's was performed with tetra-*n*-butylammonium periodate in the presence of catalytic amount of tetraphenylporphyrinatomanganese(III) chloride [Mn(TPP)Cl] and imidazole as a co-catalyst.[286] Hexamethylenetetraamine bromide has been well documented for various transformations,[48] but it is congener hexamethylenetetramine iodide is some what ignored by scientific fraternity. So we decided to explore its utility in organic transformations.

The ease of handling, environmental friendliness, and extensive availability of these reagents motivated the development of an efficient and mild protocol for the aromatization of 1,4-DHPs to corresponding pyridines using metal nitrates, TNCB, TBAP and HMTAI (Scheme 1).

To determine the optimal reaction conditions and the efficiency of various solvents for the oxidation of 1,4-DHP (**1b**), the representative of reactions were studied using $Ni(NO_3)\cdot 6H_2O$, and TNCB as oxidants. In the initial experiment, **1b** was subjected to oxidize to study the effect of solvent on the reaction. Solvents from benzene to the polar acetonitrile were used,[49] and poor to moderate yields were obtained at room temperature. The results obtained using acetic acid[50] as a solvent in the effective aromatization of 1,4-DHPs motivated its use in the following reactions. Surprisingly, the oxidative transformation of **1b** to **2b** was completed in a short time with good yield (Table 2). The dependence of molar ratio on the oxidant in the oxidative transformation to the corresponding substrate was studied. 0.5 equiv of the oxidant gave a very poor yield with a longer reaction time, but increasing the loading of the oxidant not only increased the yield of the reaction but also considerably reduced the reaction time. Two equivalents of the oxidant were sufficient for the complete conversion of 1,4-DHP to pyridine in a short reaction time at 100 °C (Table 3). Temperature is crucial to efficient conversion. Therefore, the model reaction was performed at an elevated temperature, and reveled that 100 °C is optimal. Because of these results, several 1,4-DHPs were oxidized to corresponding pyridines in high yields and short reaction times using various metal nitrates, and TNCB, under the aforementioned conditions, as indicated in Table 4.



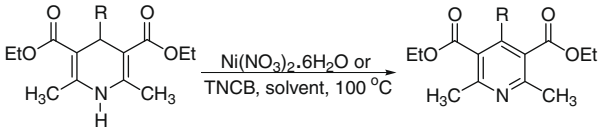
Scheme 1. General scheme for the oxidation of 1,4-dihydropyridines using $M(NO_3)_2\cdot XH_2O$ or TNCB or TBAP in acetic acid at 100 °C or HMTAI reflux in methanol.

The oxidation of 1,4-DHPs using metal nitrates in acetic acid at 100 °C is usually a very clean and efficient method. Alkyl groups are incompatible at 4-position of 1,4-DHP under various oxidizing conditions, and readily undergo dealkylation. However, the proposed protocol leaves intact numerous substituents at the 4-position, such as alkyl, aryl and heterocyclic groups.

Aromatization by TNCB in acetic acid at 100 °C had a very short reaction time with moderate to good yield of the corresponding pyridines. The observed oxidation of 1,4-dihydropyridines with an alkyl group or a phenyl at the 4-position gave the usual product with retention of the group at 4-position but trace amount of dealkylated pyridine derivative was also observed. This is a general trend in the oxidation of 1,4-dihydropyridines. However, compounds **1g**, **1h**, **1j** and **1k** were subjected to the same reaction conditions to obtain corresponding pyridines with the retention of the substitution at the 4-position. Metal nitrates were found to be more effective than TNCB in aromatization.

In the light of the aforementioned conditions, several 1,4-DHPs were oxidized to corresponding pyridines using TBAP in acetic acid at 100 °C is very clean and efficient. Surprisingly, this method tolerates several substituents, such as alkyl, aryl and heterocyclic groups at the 4-position of 1,4-DHPs. One of the salient features of this protocol is the short reaction time. It is one of the best methods known for the oxidation of 1,4-DHPs to corresponding pyridines.

Table 2
Screening of solvent for converting **1b** to **2b** with 1 equiv of $Ni(NO_3)_2\cdot 6H_2O$ and TNCB at rt



1b **2b**

Solvent	$Ni(NO_3)_2\cdot 6H_2O$		TNCB	
	Time (h)	Yield (%)	Time (h)	Yield (%)
C_6H_6	12	—	12	—
CH_2Cl_2	12	—	12	—
CH_3CN	12	10	12	8
$AcOH/H_2O$ (1:1)	6	52	6	41
AcOH	1	63	1	48

Table 3
Screening of the amount of $Ni(NO_3)_2\cdot 6H_2O$ and TNCB in acetic acid at 100 °C for converting **1b** to **2b**

Equiv	$Ni(NO_3)_3\cdot 6H_2O$		TNCB	
	Time (h)	Yield (%)	Time (h)	Yield (%)
0.5	12	48	12	37
1	1	70	2	55
1.5	0.5	84	2	60
2	0.16	95	0.083	75

Table 4
Oxidation of 1,4-DHP's by different metal nitrates TNCB and TBAP in acetic acid at 100 °C, and HMTAI in methanol[55]

1,4-DHP	R	R′	Product	Time [min] (Yield)[%]							Mp (°C)	
				A	B	C	D	E	F	G	Literature	Found
1a	–H	$-C_2H_5$	**2a**	5 (97)	5 (93)	5 (91)	10 (92)	10 (85)	5 (94)	10 (93)	70–71[38]	70–71
1b	$-C_6H_5$	$-C_2H_5$	**2b**	5 (90)	10 (95)	5 (98)	10 (95)	5 (75)	5 (93)	10 (92)	63–64[9,51]	62–63
1c	$-CH_3$	$-C_2H_5$	**2c**	10 (91)	5 (90)	5 (92)	5 (94)	5 (65)	5 (95)	5 (93)	Oil[52]	Oil
1d	$-(CH_2)_2CH_3$	$-C_2H_5$	**2d**	5 (90)	10 (89)	5 (90)	5 (95)	10 (70)	5 (92)	10 (94)	Oil[52]	Oil
1e	$-(CH_2)_8CH_3$	$-C_2H_5$	**2e**	10 (93)	10 (88)	5 (87)	5 (90)	10 (68)	5 (92)	5 (90)	Oil[9,51]	Oil
1f	$-4-CH_3C_6H_4$	$-C_2H_5$	**2f**	10 (90)	5 (93)	10 (94)	5 (92)	5 (72)	10 (93)	5 (89)	72–73[9,51]	74–75
1g	$-4-(CH_3)_3CC_6H_4$	$-C_2H_5$	**2g**	5 (95)	5 (90)	5 (95)	5 (94)	5 (71)	5 (91)	5 (91)	—	97–98
1h	$-4-CH_3OC_6H_4$	$-C_2H_5$	**2h**	10 (96)	5 (90)	10 (89)	5 (90)	5 (76)	10 (90)	5 (92)	51–53[9,51]	52–53
1i	$-CH{=}CHC_6H_5$	$-C_2H_5$	**2i**	5 (90)	5 (92)	10 (88)	10 (91)	5 (69)	10 (90)	5 (94)	162–165[9,51]	162–163
1j	$-3-ClC_6H_4$	$-C_2H_5$	**2j**	10 (89)	5 (94)	5 (92)	10 (88)	5 (63)	5 (92)	10 (92)	41–44[7]	43–44
1k	$-4-NO_2C_6H_4$	$-C_2H_5$	**2k**	15 (90)	10 (90)	5 (91)	10 (94)	10 (68)	10 (93)	5 (92)	114–115[9,51]	115–116
1l	-2-Furyl	$-CH_3$	**2l**	10 (96)	5 (93)	5 (92)	5 (94)	5 (70)	5 (91)	5 (90)	Oil[16,51]	Oil

A—$Cu(NO_3)_2{\cdot}3H_2O$ in acetic acid at 100 °C; B—$Ni(NO_3)_2{\cdot}6H_2O$ in acetic acid at 100 °C; C—$Co(NO_3)_2{\cdot}6H_2O$ in acetic acid at 100 °C; D—$Mg(NO_3)_2{\cdot}6H_2O$ in acetic acid at 100 °C; E—TNCB in acetic acid at 100 °C; F—TBAP in acetic acid at 100 C; G—HMTAI in methanol, reflux.

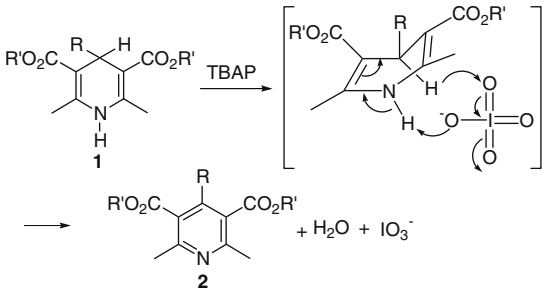


Figure 1. Mechanism of oxidation of 1,4-DHPs by TBAP.

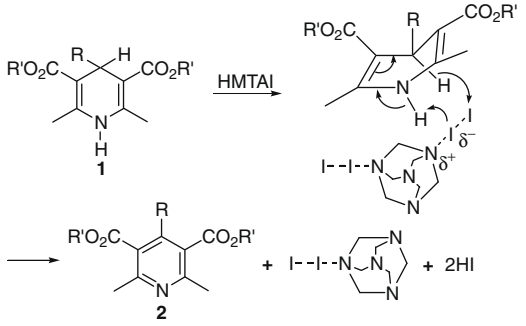


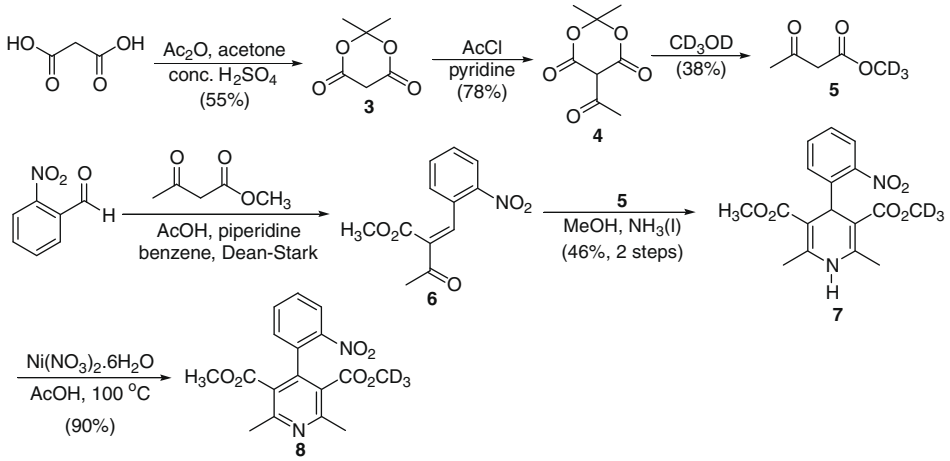
Figure 2. Mechanism of oxidation of 1,4-DHPs by HMTAI.

The aforementioned conditions for the oxidation of 1,4-DHP by hexamethylenetetramine-iodine (HMTAI), were performed, but gave some dealkylated product. The alternative condition was 2 equiv of HMTAI in methanol at reflux temperature effectively converted **1b** to the corresponding pyridine **2b** within 5 min. To establish the generality of this protocol, various 1,4-DHPs were subjected to the same conditions and the outcomes presented in Table 4. All substituents at the 4-position, such as alkyl, aryl and heterocyclic groups, were found to be intact, and the reaction time was short.

Figure 1 presents the mechanism of oxidation with tetrabutyl ammonium periodate (TBAP). The periodate ion removed a proton and a hydride from 1,4-DHP, and formed the corresponding pyridine, iodate ion and one H_2O. Little is known about the mechanism and structure of the HMTAI, but we strongly believe that active species must be formed between nitrogen and the I_2 molecule as a transition state.[53] Therefore, hydride transfer from the 1,4-DHP moiety to the active species may drive equilibrium to the right-side, causing aromatization of the 1,4-DHP.

Figure 2 proposes a mechanism. The electron-rich iodine may remove a proton from the amino group of 1,4-DHP to form an HI, and the bonding electron pair conjugates to eject a hydride from the 4-position of 1,4-DHP. The ejected hydride reacts with the other iodine to form HI. Two molecules of HI are neutralized by HMTAI to form an ammonium salt. This neutralization drives the reaction to the products.

Preparation of nifedipine-d_3 began with the synthesis of methyl acetoacetate-d_3 by Meldrum's acid (Scheme 2).[54] Acetylation of



Scheme 2. Synthesis of nifedipine-d_3 and dehydronifedepine-d_3.

Meldurm's acid (**3**), followed by refluxing with methanol-d_4, and yielded methyl acetoacetate-d_3 (**5**). Methyl acetoacetate was condensed with 2-nitrobenzaldehyde and then with methyl acetoacetate-d_3 (**5**) to yield nifedipine-d_3 (**7**). Efficient oxidation with $Ni(NO_3)_2{\cdot}6H_2O$ under the specified conditions gave the corresponding dehydronifedipine-d_3 (**8**) in quantitative yield.

In conclusion, metal nitrates, TNCB, TBAP and HMTAI are valuable for use with the methods currently available for the oxidation of Hantzsch's 1,4-DHPs. These reagents are very stable and can be taken in carrying out their reactions in general conditions. A short reaction time, easy work-up[55] and good to excellent yields of corresponding pyridines are obtained. Additionally, this protocol provides transformation to corresponding pyridines without any external activation such as microwave or ultrasound. Nifedipine-d_3 is easily and elegantly synthesized and ultimately converted to the corresponding dehydronifedipine-d_3, which can be exploited as an internal standard for the quantitative measurement of the consumption of nifedipine in the body. This synthesis may be useful in studying metabolic activity and pharmacokinetics and in the quantitative analysis of nifedipine.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.04.096.

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55. *General procedure of oxidation of Hantzsch's 1,4-dihydropyridines using $Cu(NO_3)_2{\cdot}3H_2O$, $Ni(NO_3)_2{\cdot}6H_2O$, $Co(NO_3)_2{\cdot}6H_2O$, $Mg(NO_3)_2{\cdot}6H_2O$, TNCB and TBAP in acetic acid at 100 °C:* Metal nitrate or TNCB (2 equiv) was added to the solution of 1,4-DHP (1 equiv) in acetic acid (3.0 mL) and it was heated at 100 °C for a given time. After completion of reaction, reaction mixture was cooled down to rt and acetic acid was neutralized by 2 M NaOH. Aqueous layer was extracted by dichloromethane, combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain crude product which was further purified by silica gel column chromatography using ethyl acetate–hexanes as mobile phase yielded corresponding pyridine.
General procedure for oxidation of Hantzsch's 1,4-DHPs (1g) by HMTAI in methanol: An HMTAI (167 mg, 0.26 mmol) was added to the solution of 1,4-DHP (**1g**) (50 mg, 0.13 mmol) in 7.0 mL methanol and it was heated at reflux for given time. After completion of reaction, reaction mixture was cooled down to rt and filtered through short Celite pad. Methanol was removed under reduced pressure to obtain crude product which was further purified by silica gel column using ethyl acetate–hexane as mobile phase yielded corresponding pyridine.