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Aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines with HIO_3 and I_2O_5 in water

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Abstract—Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines were converted to the corresponding pyridines and pyrazoles efficiently by the treatment of a catalytic amount of HIO_3 or I_2O_5 in water.

Five- and six-membered heterocyclic compounds often play important roles in biologically active natural products and synthetic compounds of medicines.[1] Among them, Hantzsch 1,4-dihydropyridines (1,4-DHPs) have attracted considerable attention as calcium channel blockers for the treatment of cardiovascular diseases[2] and are oxidatively transformed into the corresponding pyridine derivatives by the action of cytochrome p-450 in the liver.[3] Aromatization of 1,4-DHPs has been extensively explored by using various oxidants.[4] However, most of the oxidative processes suffer from the use of strong oxidants such as HNO_3,[4b] $KMnO_4$,[4c] or CAN[4d] and I_2–CH_3OH.[4e] Recently, attention has been paid to more efficient and environmentally benign processes, such as electrochemical oxidation[5] and catalytic aerobic oxidation using Pd/C,[6] $RuCl_3$,[7] activated carbon,[8] $Fe(ClO_4)_3$[9] or NHPI[10] as the catalyst.

1,3,5-Trisubstituted pyrazolines are important five-membered heterocyclic compounds, which can be easily prepared from phenylhydrazine and chalcone derivatives. The processes of oxidative aromatization of these dihydroheteroaromatics provide the corresponding pyrazoles, which are known to possess diverse biological activities, including antiinflammatory, antidiabetic, antiarrhythmic, and antibacterial activities.[11] For this conversion of pyrazolines, a number of processes have been reported, which employed reagents such as $AgNO_3$,[12] $KMnO_4$,[13] HgO,[14] MnO_2,[15] $Pb(OAc)_4$,[16] iodobenzene diacetate.[17] However, many of these systems suffer from expensive transition metal oxidants, relatively high oxidant loading and use of organic solvents.

We wish to report herein an efficient aqueous room temperature aromatization with a number of economic, environmental benign, and safe iodine(V) agents (Tables 1 and 2). To the best of our knowledge, this is the first example of HIO_3 (iodic acid, IA) and its anhydride I_2O_5 (iodine pentoxide, IP)-mediated metal-free aromatization of dihydropyridines and pyrazolines in water.

Despite their extensive use in industry,[18] IA and IP have rarely been employed in organic synthesis. It is seen from Table 1 that a variety of 1,4-DHPs are aromatized to the corresponding pyridines in excellent isolated yields by using 20 mol % of IP at room temperature in water. Among them, the deisopropyl aromatic pyridine is produced in the case of 4-isopropyl-HEH (**1d**). It is seen from Table 2, various 1,3,5-trisubstituted pyrazolines are aromatized to the corresponding pyrazoles in almost quantitative yields by using 20 mol % of IP catalyzed by 5 mol % of KBr at room temperature in water. In general, the reactions are very clean, efficient, and are completed within 5 h.[19]

In order to study the possible mechanism of the aromatization, a series of experiments were carried out. We presume iodine(V) reagents should be the terminal oxidants as I_2 observed in the procedure. The quantitative ratio of I_2O_5/HEH may be about 1/5 according to the stoichoimetric calculation. In fact, it accords commendably with the following experimental results (Table 3). However, about 40 mol % of HIO_3 was required in the

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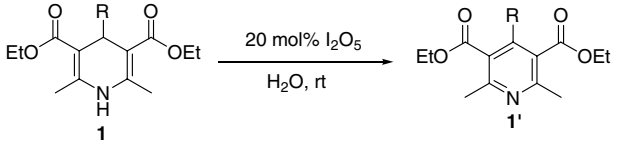
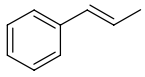
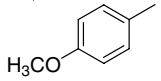
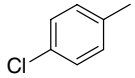
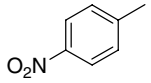
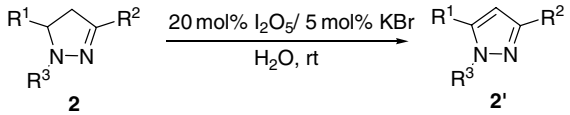
Table 1. Conversion of 1,4-DHPs to pyridines mediated by HIO_3 and I_2O_5[a]

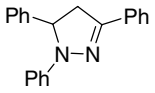
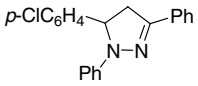
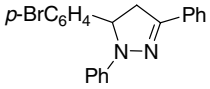
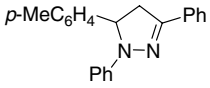
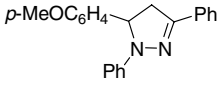
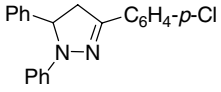


Entry	R	*T* (h)	Yield[b] (%)
1a	H	2 (min)	100
1b	CH_3	4	95
1c	$CH_2CH_2CH_3$	1.5	98
1d[c]	CH_3CHCH_3	24	94
1e		1	96
1f		3.5	92
1g		2	98
1h		2.5	96
1i		1	95
1j		12	95

[a] The products were identified by comparing their ^1H NMR and EI-MS spectral data with those reported in the cited references.
[b] Isolated yield.
[c] The oxidative product is same to the substrate **1a**.

Table 2. Conversion of 1,3,5-trisubstituted pyrazolines to pyrazoles by using HIO_3 and I_2O_5 catalyzed by KBr[a]



Entry	Substrate	*T* (h)	Yield[b] (%)
2a		3.5	98
2b		3	96
2c		4.5	96
2d		5	97
2e		8	96
2f		4	96

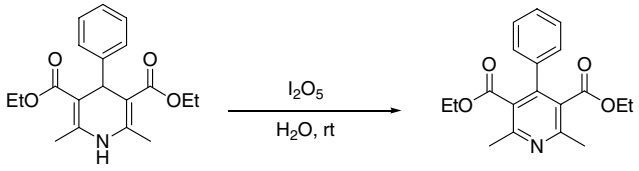
[a] The products were identified by comparing their ^1H NMR and EI-MS spectral data with those reported in the cited references.
[b] Isolated yield.

oxidation. Therefore, we prefer to I_2O_5 as the oxidant considering the cost. Additionally, the aromatization reaction can be smoothly carried out without oxygen by protection of nitrogen (Scheme 1).

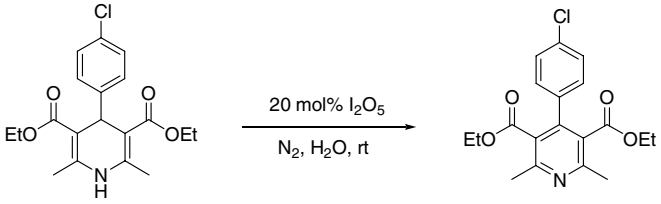
It is believed to be a free radical procedure of the aromatization. Detailed mechanistic studies on the oxidation are undertaken.

In conclusion, this work demonstrated a novel and mild method for the aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines by using catalytic, low-cost, and environmentally friendly iodine(V) reagents in water. Extension of this procedure to other substrates is underway in our laboratory.

Table 3. Conversion of **1g** to pyridine by using I_2O_5



Entry	Quantity of I_2O_5 (mol %)	*T* (h)	Yield (%)
1	1	15	<5
2a	10	4	50
2b	10	7	70
2c	10	15	75
3	20	2	98



Scheme 1.

Acknowledgement

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19. Typical procedure: the starting materials were put into water, and 20 mol % I_2O_5 or 20 mol % I_2O_5/5 mol % KBr were added in potions, detected by TLC, when completed, abstracted by ethyl acetate, washed by Na_2SO_3, dried with anhydrous $MgSO_4$, isolated through column chromatography. Characteristic identify of representative products: compounds **1′a**: diethyl 4-(4-chlorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate,[4e] pale yellow solid; mp 65–66 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.95$ (t, 6H, $J = 7.2$ Hz), 2.59 (s, 6H), 4.02 (q, 4H, $J = 7.2$ Hz), 7.18 (d, 2H, $J = 8.4$ Hz), 7.34 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.5, 22.8, 61.4, 126.7, 128.2, 129.5, 134.6, 134.9, 144.7, 155.5, 167.5$; EI-MS: $m/z = 363, 361, 316, 288, 270, 139, 43$. Compound **2′a**: 1,3,5-triphenylpyrazole:[10] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.83$ (s, 1H), 7.4 (m, 13H), 7.92 (d, 2H, $J = 7.6$Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 105.2, 125.3, 125.8, 127.4, 128.0, 128.3, 128.4, 128.6, 128.7, 128.9, 130.5, 133.0, 140.0, 144.3, 151.9$; EI-MS: $m/z = 296, 86, 84, 77$.