An efficient combination of Dess-Martin periodinane with molecular iodine or KBr for the facile oxidative aromatization of Hantzsch 1, 4-dihydropyridines

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Abstract

A highly efficient, mild, and simple protocol is presented for the oxidative aromatization of Hantzsch 1, 4-dihydropyridines using the combination of Dess-Martin periodinane with molecular iodine or KBr. The *in situ* generated acetyl hypoiodite or bromite formed due to the reaction between Dess-Martin periodinane and molecular iodine or KBr respectively is supposed to be the responsible species for bringing about the oxidative aromatization of 1, 4-dihydropyridines.

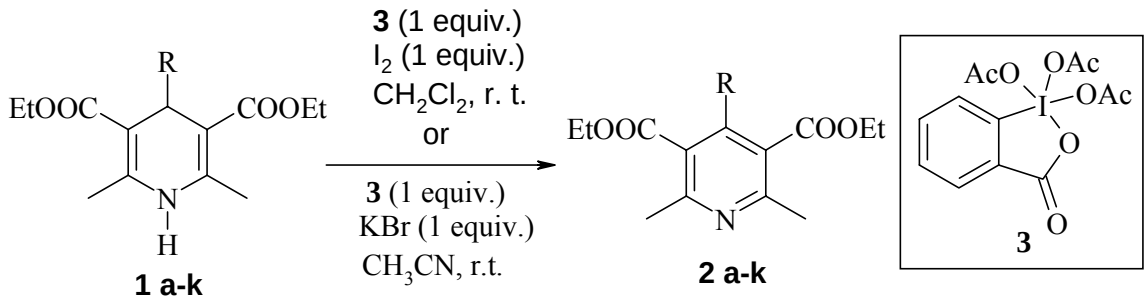
Keywords: 1,4-Dihydropyridines, hypervalent iodine, Dess-Martin periodinane, oxidation, molecular iodine, potassium bromide, acetyl hypoiodite

Introduction

Hantzsch 1,4-dihydropyridine (DHP) structural subunit is contained in a growing number of both natural products and synthetic compounds with wide range of biological properties.[1] For example, the 1,4-DHP derived drugs such as nefidine, nitrendipine, and nimodipine are frequently used as cardiovascular agents (Ca^{2+} channel blockers) for the treatment of hypertension and angina pectoris diseases.[2] This important class of calcium channel antagonists relaxes the cardiac muscle by decreasing the transmembrane calcium current on binding.[3] The metabolism of these drugs involves an oxidative aromatization of 1, 4-DHP nucleus to the corresponding pyridine derivatives, which is catalyzed in the liver by cytochrome P-450.[4] The pyridine derivatives are then further metabolized leading to the cleavage of the ester groups. In this respect, a convenient preparation of pyridines from 1, 4-DHPs is important for the identification of metabolites.[5] Furthermore, the oxidation of Hantzsch 1, 4-DHPs provides an easy access to the symmetrically substituted pyridine derivatives.[6]

The oxidative aromatization of 1, 4-DHP is usually accomplished by the transition metal based oxidants such as $KMnO_4$, MnO_2, PCC, CrO_3, ferric nitrate, cupric nitrate, $Zr(NO_3)_4$, $Bi(NO_3)_3$, $Co(OAc)_2$, $Pb(OAc)_4$, $RuCl_3$, Pd/C, ceric ammonium nitrate (CAN) and $Mn(OAc)_3$.[7] The other oxidants such as DDQ[8], heteropolyacid/$NaNO_2$/SiO_2[9], I_2/MeOH[10], nitric oxide[11], HNO_3[12] and SeO_2[13] are also reported for the oxidative aromatization of 1, 4-DHP. Although a plethora of reagents are known for the oxidative aromatization of 1,4-DHPs, many of them suffer from drawbacks such as strong oxidative conditions, prolonged reaction time, unsatisfactory yields, difficult work-up procedure, and toxicity of various transition metals. Some of the reported protocols for oxidative aromatization are also associated with side reactions such as solvent-dependent oxidation of a 2-methyl group,[7l] ring nitration byproducts in case of metallic nitrates[7m] and dealkylation at the 4-position in the cases of ethyl, isopropyl and benzyl substituted dihydropyridine derivatives.[7n-q] Thus, the development of an efficient and versatile method for the oxidative aromatization of 1, 4-DHP provides scope for further improvement towards mild reaction conditions and improved yields.

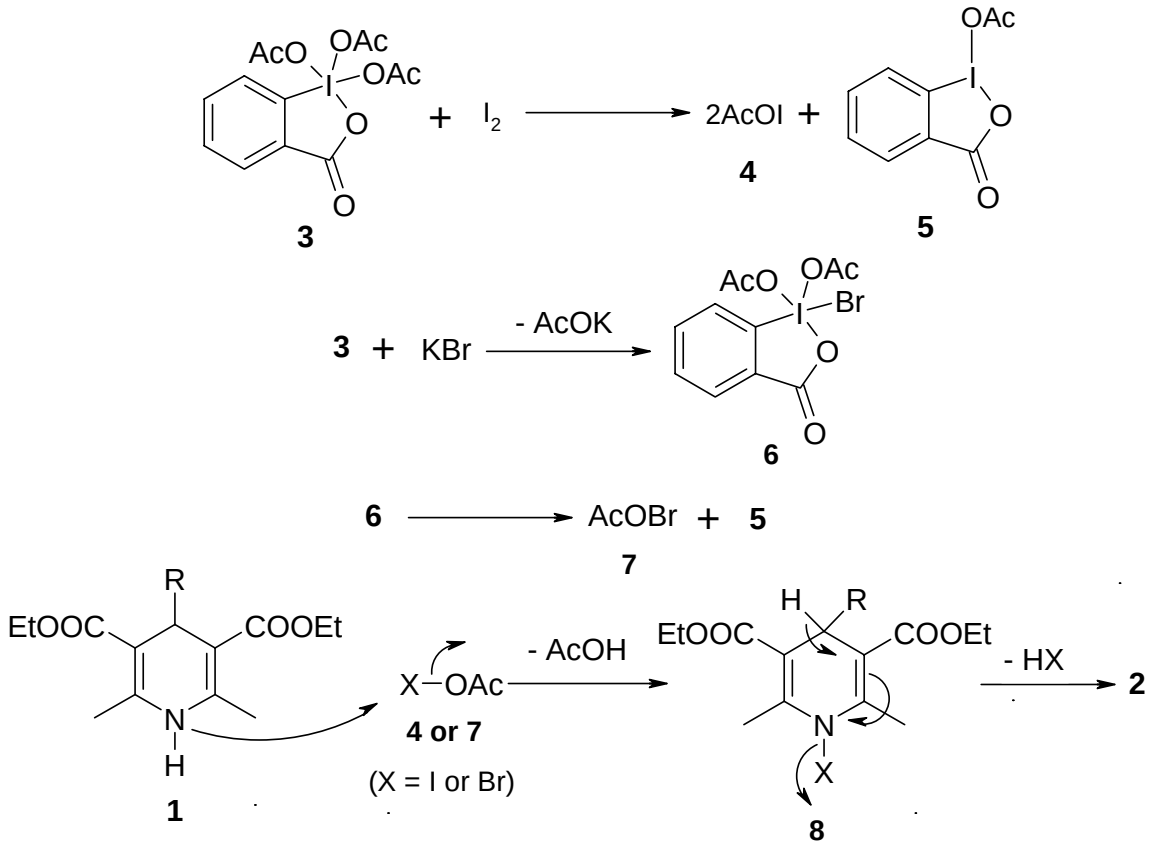
In recent decades, there is a considerable growth in the applications of hypervalent iodine reagents in organic synthesis.[14] The trivalent iodine reagents such iodosobenzene diacetate, bis(trifluoroacetoxyiodo)benzene, and [hydroxy(tosyloxy)iodo]benzene have been previously utilized for the oxidative aromatization of 1, 4-DHPs.[15] However, the oxidative dealkylation of aliphatic alkyl group at 4-position was observed in all the cases. Dess-Martin periodinane [DMP; 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one] is a versatile pentavalent iodine reagent which is extensively utilized as a reagent of choice for the oxidation of primary and secondary alcohols.[16] The mild reaction conditions (room temperature and neutral pH), high chemoselectivity, and convenience of use have made this reagent especially suitable in various natural product synthesis.[17] This versatility of DMP prompted us to examine its potential as an oxidant for the Hantzsch 1, 4-DHPs. In continuation of our interest in hypervalent iodine reagents[18], herein we report that DMP in combination with molecular iodine or KBr can serve as mild oxidant for the oxidative aromatization of the Hantzsch 1, 4-DHPs in high yields (Scheme 1).



Scheme 1

Results and Discussion

A set of experiments was carried out first to define a standard procedure for this oxidation using the 1, 4-DHP **1a** (R = C_6H_5-) as a model substrate. The reaction of **1a** (1 mmol) with DMP (1 mmol) in CH_2Cl_2 (10 mL) at room temperature stirring as well as under reflux conditions for 12 hrs did not produce the oxidation product **2a** in appreciable yield. Thus in contrast to trivalent iodine reagents[15], DMP as such alone is insufficient to produce oxidative aromatization of 1, 4-DHP. Therefore, we decided to examine its activation with molecular iodine or KBr for the oxidative aromatization of 1,4-DHPs[19]. When DMP (1 mmol) was added to a stirred solution of **1a** (1 mmol) and molecular iodine (1 mmol) in CH_2Cl_2 (10 mL), the brown color of iodine immediately disappeared and after the usual work-up procedure, the formation of oxidation product **2a** took place in 91 % yield. Having succeeded with the combination of DMP and molecular iodine, we then examined the reaction of **1a** (1 mmol) with DMP (1 mmol) and KBr (1 mmol) in CH_3CN (10 mL) at room temperature stirring for 4 hrs. KBr is insoluble in CH_2Cl_2 and therefore, we attempted the reaction of **1a** with DMP/KBr in CH_3CN. To our delight, oxidation of **1a** to **2a** again occurred smoothly in 81 % yield. Thus, DMP in combination with I_2 or KBr smoothly oxidizes 1, 4-DHP to the corresponding pyridine derivatives under almost neutral conditions.



Scheme 2

The tentative mechanism of the reaction is depicted in Scheme 2. The reaction of molecular iodine with DMP will generate acetyl hypoiodite **4**. Similarly, the ligand exchange reaction of DMP with one equivalent of KBr will form the putative intermediate **6** involving I-Br bond formation. The overwhelming tendency of the intermediate **6** for the reductive elimination around coordination sphere of iodine will generate acetyl hypobromite **7** which is an active source of electrophilic bromine.[19] Hantzsch 1, 4-DHP **1** will then react with electrophilic acetyl hypoiodite or hypobromite to form the intermediate **8** involving N-X (X = I or Br) bond formation. Finally, the concomitant oxidative aromatization of **8** will take place by the elimination of hydrogen at 4-position to form the product **2**.

Table 1. Oxidative aromatization of 1,4-dihydropyridines 1 to the corresponding pyridine derivatives 2

1,4-DHPs 1	R	Product 2	DMP/I_2		DMP/KBr		Mp (^{o}C) (Reported)[lit]
			Time (min)	Yield[a] (%)	Time (hr)	Yield[a] (%)	
1a	C_6H_5-	2a	25	89	3	82	62-63 (62-64)[7k]
1b	*4*-$MeOC_6H_4$-	2b	30	91	4	78	52-53 (51-53)[7k]
1c	*3,4*-$(MeO)_2C_6H_3$-	2c	35	88	5	71	75-77
1d	*4*-MeC_6H_4-	2d	35	87	5	74	72-73 (72-73)[7k]
1e	*4*-ClC_6H_4-	2e	30	89	4	77	66-67 (66-67)[7r]
1f	*3*-$O_2NC_6H_4$-	2f	25	92	4	81	61-63 (62-64)[7r]
1g	*4*-$O_2NC_6H_4$-	2g	30	90	4	84	115(114-115)[7k]
1h	*2*-furyl	2h	25	88	5	85	40-43 (40-42)[7r]
1i	H	2i	30	93	3	84	68-70 (69-70)[7r]
1j	*n*-C_4H_9-	2j	40	80	4	73	Oil[7r]
1k	$(CH_3)_2CH$-	2k	50	76	6	69	Oil[7r]
1l	$C_6H_5CH_2$-	2l	30	81	5	77	69-70 (70-71)[7r]

[a]Yields refer to isolated pure products.

To establish the generality of this method, various alkyl, aryl, and heterocyclic Hantzsch 1, 4-DHP were oxidized under the above reaction conditions and the results are summarized in Table 1. It follows from Table 1 that both electron donating and electron withdrawing substituents on the 1, 4-DHPs afforded the corresponding pyridine derivatives in good to excellent yields. The structures of all the products were confirmed from melting points and spectroscopic data. In the cases of alkyl substituents such as n-butyl and benzyl (Table 1, entries 1i and 1j) at the 4-position of 1, 4-DHP, the oxidative aromatization smoothly took place without the formation of any 4-dealkylated product. In general, the combination of DMP with molecular iodine was found to be

better than with KBr in terms of the higher yields and lesser reaction time for the oxidative aromatization of 1, 4-DHP. This is attributed to the more oxidation potential of iodonium ion compared to bromonium ion. The reaction time for oxidative aromatization of all 1, 4-DHPs with DMP / I_2 is, therefore, typically less than one hour.

Conclusions

In conclusion, a transition metal free oxidative aromatization of Hantzsch 1,4-DHPs was achieved efficiently under almost neutral conditions, by using DMP in combination with molecular iodine or KBr. The mild reaction conditions, no dealkylation at the 4-position of 1,4-DHPs, short reaction time, and easy work-up procedure are some of the important features of the reaction. Extension of this method to the preparation of other heterocyclic compounds is under way in this laboratory.

Experimental Section

General Procedures. Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer. ^{1}HNMR spectra were recorded at 400 MHz in $CDCl_3$ using TMS as internal standard. Dess-Martin periodinane was purchased from was purchased from Spectrochem.

General procedure for oxidative aromatization of 1,4-DHP using DMP and molecular iodine

To a magnetically stirred mixture of 1, 4-dihydropyridine (1 mmol) and iodine (1 mmol) in 15 mL of CH_2Cl_2, DMP (1 mmol) was added. The resulting reaction mixture was stirred for the period of time as shown in Table 1. After ascertaining the completion of the reaction by TLC, the reaction mixture was treated with sodium thiosulphate and sodium bicarbonate (10 % each). The reaction mixture was then extracted with CH_2Cl_2 (15 mL x 2).The combined organic layer was dried using anhydrous sodium sulphate and the solvent was distilled. The product was purified by short silica gel column using the mixture of petroleum ether and ethyl acetate (9:1) to afford the corresponding pyridine derivatives.

General Procedure for oxidative aromatization of 1,4-DHP using DMP and KBr

To a magnetically stirred solution of the 1, 4-dihydropyridine (1 mmol) and KBr (1 mmol) in CH_3CN (10 mL), DMP (1 mmol) was added at room temperature. The reaction mixture was stirred for the time as indicated in Table 1. TLC monitored the progress of the reaction. After the completion of the reaction, water (10 mL) was added, extracted with CH_2Cl_2 (2 x 10 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the

residue was purified by column chromatography over silica gel to furnish the corresponding pyridine derivatives.

All the products are known in the literature and the corresponding reference of the same is mentioned in Table 1. However, the selected spectral data of few products are given below.

Spectral data of selected products

Diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (2a). ^{1}H NMR ($CDCl_3$): δ = 0.83 (t, 6H, *J* =7.12 Hz, $2CH_3$), 2.53 (s, 6H, $2CH_3$), 3.93 (q, 4H, *J* = 7.12 Hz, $2OCH_2$), 7.18 (m, 2H, ArH), 7.29 (m, 3H, ArH). IR (KBr): 3026, 2983, 2937, 1735, 1701, 1685, 1556, 1290, 862, 754, 700 cm^{-1}. LCMS (M + 1): m/z = 328

Diethyl 2,6-dimethyl-4-(3,4-dimethoxyphenyl)pyridine-3,5-dicarboxylate (2c). ^{1}H NMR ($CDCl_3$): δ = 0.99 (t, 6H, *J* = 7.12 Hz, $2CH_3$), 2.61 (s, 6H, $2CH_3$), 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.06 (q, 4H, *J* = 7.12 Hz, $2OCH_2$), 6.81-6.87 (m, 3H, ArH).
IR (KBr): 3004, 2985, 2902, 2833, 1721, 1560, 1508, 1255, 1143, 1028, 862, 755, 669 cm^{-1}. LCMS (M + 1): m/z = 388

Diethyl 2,6-dimethyl-4-*p*-tolylpyridine-3,5-dicarboxylate (2d). ^{1}H NMR ($CDCl_3$)**:** δ = 0.96 (t, 6H, *J* =7.12 Hz, $2CH_3$), 2.17 (s, 3H, $ArCH_3$), 2.60 (s, 6H, $2CH_3$), 4.05 (q, 4H, *J* =7.12 Hz, $2CH_2$), 7.13 (d, 2H, *J* = 8.24 Hz, ArH) 7.17 (d, 2H, *J* = 8.24 Hz, ArH). IR (KBr): 3022, 2982, 2872, 1732, 1560, 1236, 1107, 1043, 756, 667 cm^{-1}. LCMS (M + 1): m/z = 342

Diethyl 2,6-dimethyl-4-(4-chlorophenyl)pyridine-3,5-dicarboxylate (2e). ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, 6H, *J* =7.12 Hz, $2CH_3$), 2.60 (s, 6H, $2CH_3$), 4.04 (q, 4H, *J* = 7.12 Hz, $2CH_2$) 7.20 (d, 2H, *J* = 8.52 Hz, ArH), 7.35 (d, 2H, *J* = 8.52 Hz, ArH). IR (KBr) : 3007, 2983, 2938, 1732, 1643, 1561, 1236, 1107, 758, 669 cm^{-1}. LCMS (M + 1): m/z = 364.

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (2f). ^{1}H NMR ($CDCl_3$): δ = 1.01 (t, 6H, *J* = 7.12 Hz, $2CH_3$), 2.63 (s, 6H, $2CH_3$), 4.04 (q, 4H, *J* = 7.12 Hz, $2CH_2$), 7.61 (m, 2H, ArH), 8.19 (s, 1H, ArH), 8.26 (m, 1H, ArH). IR (KBr): 3084, 2985, 2935, 1734, 1716, 1558, 1236, 1047, 860, 738 cm^{-1}. LCMS (M + 1): m/z = 373.

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