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Oxidative aromatization of Hantzsch 1,4-dihydropyridines using $NaBrO_3/NaHSO_3$

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ABSTRACT

The oxidation of 1,4-dihydropyridines (DHPs) to the corresponding pyridine derivatives constitutes the principle metabolic route in biological systems, as well as a facile access to the corresponding pyridine derivatives. Herein, we report a new method for the oxidative aromatization of 1,4-DHPs using the combination of $NaBrO_3$ and $NaHSO_3$. Again the *in situ* generated HOBr from the reaction of $NaBrO_3$ and $NaHSO_3$ is expected to induce the dehydrogenation of 1,4-DHPs.

INTRODUCTION

Hantzsch 1,4-dihydropyridine (DHP) structural subunit is contained in a growing number of synthetic and natural products with a wide range of biological properties[1]. For example, the 1,4-DHP derived drugs such as nifedipine **(1)**, amlodipine **(1)**, felodipine **(3)**, nicardipine **(4)**, nimodipine **(5)** and nitrendipine **(6)** are frequently used as cardiovascular agents (Ca^{2+} channel blockers) for the treatment of hypertension and angina pectoris diseases[2]. The metabolism of these drugs involves an oxidative aromatization of 1,4-DHP nucleus to corresponding pyridine derivatives, which is catalyzed in the liver by cytochrome P-450[3]. The pyridine derivatives are then further metabolized leading to the cleavage of the ester groups[4]. In this respect, a convenient preparation of pyridines from 1,4-DHPs is important for the identification of metabolites[5].

RESULTS AND DISCUSSION

Owing to the great biological and synthetic importance of 1,4-DHP, a plethora of protocols are available in the literature for the oxidative aromatization of 1,4-DHP derivatives. There oxidants are broadly classified into three categories: (a) transition metal based oxidants, (b) halogen derived oxidants, (c) other oxidants. Various transition metal based oxidants[6] reported in the literature includes CrO_3, CrO_2, Pyridinium chlorochromate (PCC), $KMnO_4$, $Mn(OAC)_3$, MnO_2, Mn(TPP)Cl/$NaIO_4$, Mn (III)- salophen/ $NaIO_4$, $Fe(ClO_4)_3$/AcOH, $RuCl_3/O_2$, $Zr(NO_3)_4$, $(NH_4)_2$ $Ce(NO_3)_6$, $Cu(NO_3)_2$, $Bi(NO_3)_3.5H_2O$, $Pb(OAc)_2$, $Co(OAc)_2/H_2O_2$, Pd/C/AcOH. The halogen derived oxidants for the oxidative aromatization of 1,4-DHP are hypervalent iodine (III) reagents and I_2/MeOH[7]. The other oxidants are elemental sulfur under microware conditions[8], HNO_3[9], nitric oxide, SeO_2[10], N_2O_4[11], and DDQ[12].

Present work

Oxidative aromatization of Hantzsch 1,4-dihydropyridine to the corresponding pyridine derivative is relevant to the biological NADH redox processes. This fact prompted us to examine this interesting oxidative aromatization of 1,4-DHP. Herein, we wish to report a novel combination of $NaBrO_3$ with $NaHSO_3$ for an efficient oxidative aromatization of Hantzsch 1,4-DHP (SCHEME 1)

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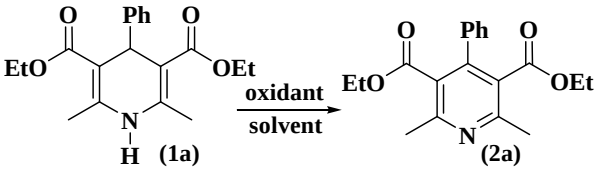
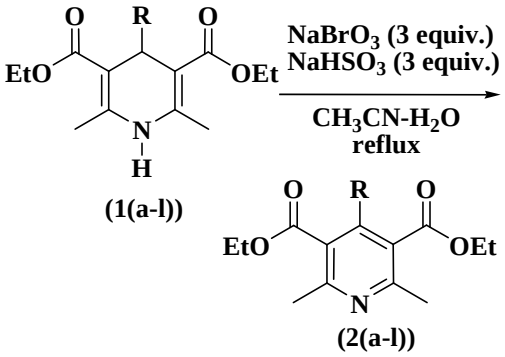
TABLE 1: Optimizing the reaction conditions



Entry	(1a)	$NaBrO_3$	$NaHSO_3$	Solvent	Reaction time (h)[a]	Yield of (2a) (%)[b]
1	1 mmol	1 mmol	-	CH_3CN	10	00
2	1 mmol	1 mmol	-	CH_3CN-H_2O (3:2)	10	00
3	1 mmol	3 mmol	-	CH_3CN-H_2O (3:2)	10	23
4	1 mmol	1 mmol	1 mmol	CH_3CN-H_2O (3:2)	8	57
5	1 mmol	3 mmol	3 mmol	CH_3CN-H_2O (3:2)	7	84

[a]Refluxing conditions, [b]Isolated yields

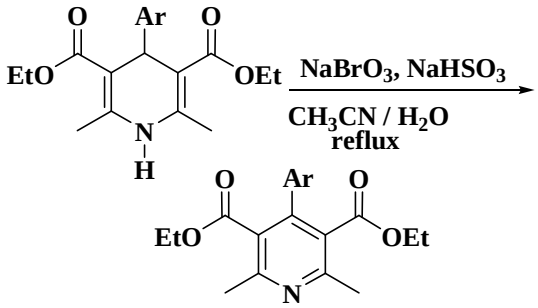
TABLE 2: Oxidative aromatization of 1,4-dihydropyridines using $NaBrO_3$/ $NaHSO_3$ combination in CH_3CN-H_2O system



Entry	R	Product	Reaction time (h)	Yield (%)[a]	M. p.(°C) observed	M. p.(°C) literature
a	C_6H_5	2a	8	83	60-62	63-64[13]
b	4-$MeOC_6H_4$	2b	11	81	51-53	51-53[13]
c	4-MeC_6H_4	2c	10	74	72-73	72-73[13]
d	3,4-$(MeO)_2C_6H_3$	2d	13	78	89-91	-
e	4-ClC_6H_4	2e	10	83	66-68	65-67[13]
f	3-$NO_2C_6H_4$	2f	12	80	61-63	62-64[13]
g	4-$NO_2C_6H_4$	2g	13	76	112-114	114-115[13]
h	2- furyl	2h	09	79	40-43	40-42[13]
i	H	2i	12	71	69-70	69-70[13]
j	$C_6H_5CH_2$	2j	10	75	70-71	70-71[8]
k	n-C_3H_7	2k	11	72	Oil	Oil[8]
l	n-C_6H_{13}	2l	13	77	Oil	Oil[13]

[a]Isolated yields after chromatography

The oxidative aromatization of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate **(1a)** was chosen as a model substrate. The optimized reaction conditions were investigated by varying the quantity of oxidants as well as the solvents and the results

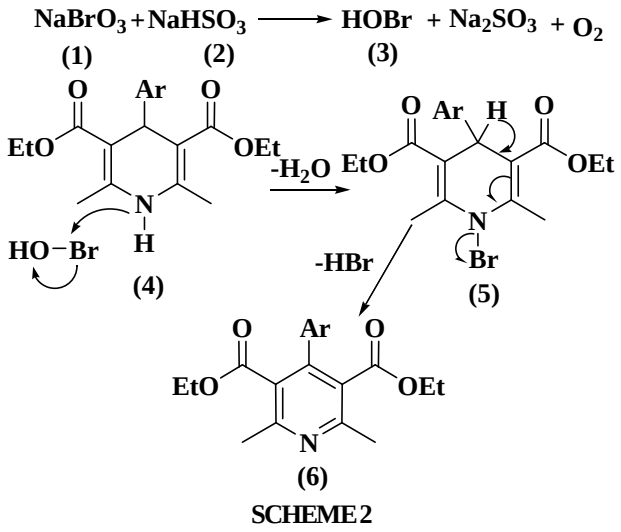


SCHEME 1

are summarized in TABLE 1.

When 1 equivalent of **(1a)** was refluxed with 1 equivalent $NaBrO_3$ in CH_3CN (15 mL), the oxidation of **(1a)** did not occur and all the starting material was quantitatively recovered. This result is in contrast with the well known oxidizing capacity of $NaBrO_3$ in various oxidation reactions. The above failure was partially attributed to the complete insolubility of $NaBrO_3$ in CH_3CN. Therefore, we again examined the oxidation of **(1a)** (1 mmol) with $NaBrO_3$ (1 mmol) in CH_3CN-H_2O system in 3:2 v/v proportion. However, the oxidation of **(1a)** was again failed to produce **(2a)** in any appreciable yield. Excess of $NaBrO_3$ (3 equiv. with respect to **(1a)** also did not influence the out come of oxidative aromatization of **(1a)**. Thus, $NaBrO_3$ alone does not induce oxidative aromatization of 1,4-DHP. Based upon the literature report of $NaBrO_3$ in combination with $NaHSO_3$ for a variety of oxidative transformations, we then examined the same for oxidation of **(1a)**. It was observed that the addition of $NaHSO_3$ (1 mmol) to the solution of **(1a)** (1 mmol) and $NaBrO_3$ (1 mmol) in CH_3CN- H_2O (3:2 v/v proportion) resulted in the formation of **(2a)** in 57% yield. However, the addition of excess of $NaBrO_3$ (3 mmol) and $NaHSO_3$ (3 mmol) to **(1a)** (1 mmol) in CH_3CN-H_2O increased the oxidation yield of **(1a)** to 84%. These experiments proved that $NaBrO_3$ in combination with $NaHSO_3$ in CH_3CN-H_2O solvent system transforms 1,4-DHP to the corresponding pyridine derivatives in excellent yields.

The potential scope of this method was investigated by subjecting various alkyl, aryl and heterocyclic Hantzsch 1,4-DHP under the above reaction conditions and the results are summarized in TABLE 2. 1,4-DHP with both aliphatic and aromatic substituents at 4-position underwent smooth oxidative aromatization. The aryl moiety at 4-position having different groups at dif-



SCHEME 2

ferent positions did not show much differences in the yields of the products. Heterocyclic moiety such as furan at 4-position of 1,4-DHP also underwent the facile transformation.

Reaction mechanism

The tentative mechanism of the reaction is depicted in SCHEME 2. The reaction of $NaBrO_3$ with $NaHSO_3$ will generate hypobromous acid (HOBr) **(3)** which is an active source of electrophilic bromine. Hantzsch 1, 4-DHP **(4)** will then react with electrophilic hypobromous acid to form the intermediate **(5)** involving N-Br bond formation. Finally, the concomitant oxidative aromatization of **(5)** will take place by the elimination of hydrogen at 4-position to form the product **(6)**.

Spectral analysis

IR spectra were recorded on a Shimadzu FTIR-1710 spectrophotometer.

The ^{1}H NMR spectra were recorded on 400 MHz instrument and the chemical shifts were reported with TMS as an internal standard. The representative spectral analysis for few of the products is given below:

(i) Diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (2a)

Yellow solid, M. p. 60-62^{0}C (Lit.[12b] M. p. 63-64^{0}C); IR (KBr, cm^{-1}): 3026, 2983, 2937, 1735, 1701, 1685, 1556, 1290, 862, 754, 700; ^{1}H NMR ($CDCl_3$): δ = 0.82 (t, J =7.12 Hz, 6H, $2CH_3$), 2.53 (s, 6H, $2CH_3$), 3.92 (q, J = 7.16 Hz, 4H, $2OCH_2$), 7.18 (m, 2H, ArH), 7.29 (m, 3H, ArH); LCMS (M + 1): m/z = 328.

(ii) Diethyl 2,6-dimethyl-4-(3,4-dimethoxyphenyl) pyridine-3,5-dicarboxylate (2d)

Yellow solid, M. p. 89-91°C; IR (KBr, cm^{-1}) : 3004, 2985, 2902, 2833, 1721, 1560, 1508, 1255, 1143, 1028, 862, 755, 669; ^{1}H NMR ($CDCl_3$): δ = 1.02 (t, J = 7.16 Hz, 6H, $2CH_3$), 2.61 (s, 6H, $2CH_3$), 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.05 (q, J = 7.12 Hz, 4H, $2OCH_2$), 6.81-6.87 (m, 3H, ArH); LCMS (M + 1): m/z = 388.

(iii) Diethyl 2,6-dimethyl-4-p-tolylpyridine-3,5-dicarboxylate (2c)

Yellow solid, M. p. 72-73^{0}C (Lit.[12b] M. p. 72-73^{0}C); IR (KBr, cm^{-1}) : 3022, 2982, 2872, 1732, 1560, 1236, 1107, 1043, 756, 667; ^{1}H NMR ($CDCl_3$): δ= 0.96 (t, J =7.12 Hz, 6H, $2CH_3$), 2.17 (s, 3H, $ArCH_3$), 2.60 (s, 6H, $2CH_3$), 4.03 (q, J =7.16 Hz, 4H, $2CH_2$), 7.13 (d, J = 8.44 Hz, 2H, ArH), 7.17 (d, J = 8.24 Hz, 2H, ArH); LCMS (M + 1): m/z = 342

(iv) Diethyl 2,6-dimethyl-4-(4-chlorophenyl) pyridine-3,5-dicarboxylate (2e)

Yellow solid, M. p. 66-68^{0}C (Lit.[12b] M. p. 65-67^{0}C); IR (KBr, cm^{-1}) : 3007, 2983, 2938, 1732, 1643, 1561, 1236, 1107, 758, 669; ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, J =7.12 Hz, 6H, $2CH_3$), 2.60 (s, 6H, $2CH_3$), 4.04 (q, J = 7.12 Hz, 4H, $2CH_2$) 7.20 (d, J = 8.44 Hz, 2H, ArH), 7.31(d, J=8.52Hz, 2H, ArH); LCMS(M +1): m/z = 364

(v) Diethyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (2f)

Yellow solid, M. p. 61-63^{0}C (Lit.[12b] M. p. 62-64^{0}C); IR (KBr, cm^{-1}): 3084, 2985, 2935, 1734, 1716, 1558, 1236, 1047, 860, 738; ^{1}H NMR ($CDCl_3$): δ = 1.01 (t, J = 8 Hz, 6H, $2CH_3$), 2.63 (s, 6H, $2CH_3$), 4.07 (q, J = 7.04 Hz, 4H, $2CH_2$), 7.61 (m, 2H, ArH), 8.19 (s, 1H, ArH), 8.26 (m, 1H, ArH); LCMS (M + 1): m/z = 373

EXPERIMENTAL

General procedure for the oxidative aromatization of 1,4-DHP using $NaBrO_3$/$NaHSO_3$ reagent:

To a solution of $NaBrO_3$ (6 mmol) in water (12 mL) was added the 1,4-DHP (2 mmol) in acetonitrile (20 mL) followed by the drop wise addition of a solution of $NaHSO_3$ (6 mmol) over a period of about 15-30 min. The mixture was then refluxed for 7-20 hours. The reaction mixture was poured in to 40 mL of CH_2Cl_2.

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After separation of the organic phase, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was washed with anhydrous $Na_2S_2O_3$ solution and dried over anhydrous sodium sulphate. After filtration, the dichloromethane was removed in vacuum and the residue was purified by column chromatography (silica gel, petroleum ether: ethyl acetate =10:1) to give aromatized pyridine product.

CONCLUSION

The oxidative aromatization of 1,4-dihydropyridines using $NaBrO_3$/$NaHSO_3$ reagent offers following notable advantages: (a) a transition-metal free protocol, (b) utilization of aqueous medium in combination with CH_3CN, (c) less toxic effect, (d) no dealkylation at 4-position of 1,4-DHP in case of alkyl substituents, (e) good yields of the products, (f) an added entry in the novel applications of $NaBrO_3$/$NaHSO_3$ reagent. In conclusion, a transition metal free oxidative aromatization of Hantzsch 1, 4-DHPs was achieved efficiently under almost neutral conditions, by using $NaBrO_3$ in combination with $NaHSO_3$.

REFERENCES

[1] **(a)** U.sner, J.Kuthan; Chem.Rev., **72**, 1 **(1992)**.
(b) M.David, A.Stout, I.Meyers; Chem. Rev., **82**, 223 **(1982)**.
(c) M.Kawase, A.Shah, H.Gaveriya, N.Motohashi, H.Sakagami, A.Varga, Molnar; J.Bioorg.Med. Chem., **10**, 1051 **(2002)**.
(d) J.J.Vanden Eynde, A.Mayence; Molecules, **8**, 381 **(2003)**.

[2] **(a)** S.F.Flaim, R.Zelis; Fed.Proc., **40**, 2877 **(1981)**.
(b) J.L.Reid, P.A.Meredith, F.J.Pasanisi; Cardiovasc. Pharmacol., **S18**, 7 **(1985)**.
(c) F.R.Buhler, W.J.Kiowski; Hypertens, **S3**, 5 **(1987)**.
(d) D.J.Triggle, D.D.Lango, R.A.Janis; Med.Res. Rev., **9**, 123 **(1989)**.
(e) B.B.Ana, M.A.Rosa, M.J.Rosa, W.Wolfgang; Forensic Sci.Int., **156**, 23 **(2006)**.

[3] **(a)** R.Bocker, E.P.Guengerich; J.Med.Chem., **29**, 1596 **(1986)**.
(b) F.P.Guengerich, W.R.Brian, M.Iwasaki, M.A. Sari, C.Baarnhielm, P.Berntsson; J.Med.Chem., **34**, 1838 **(1991)**.

[4] **(a)** D.M.Stout, A.I.Meyers; Chem.Rev., **82**, 223 **(1982)**.
(b) X.Y.Wei, A.Rutledge, D.J.Triggle; J.Mol. Pharmacol., **35**, 541 **(1989)**.

[5] T.Itoh, K.Nagata, Y.Matsuya, M.Miyazaki, A. Ohsawa; J.Org.Chem., **62**, 3582 **(1997)**.

[6] **(a)** J.J.Vanden Eynde, R.D'orazio, Y.Van Haverbeke; Tetrahedron, **50**, 2479 **(1994)**.
(b) F.Delgado, C.Alvarez, O.Garcia, G.Penieres, C.Marquez; Synth.Commun., **21**, 2137 **(1991)**.
(c) M.C.Bagley, M.C.Lubinu; Synthesis, **8**, 1283 **(2006)**.
(d) PCC: J.Eynde, A.Mayence, A.Maquestiau; Tetrahedron, **48**, 463 **(1992)**.
(e) A.Sausins, G.Duburs; Heterocycles, **27**, 291 **(1988)**.
(f) M.Balogh, I.Hermecz, Z.Meszaros, P.Laszlo; Helv.Chim.Acta, **67**, 2270 **(1984)**.
(g) A.Maquestiau, A.Mayence, J.Eynde; Tetrahedron Lett., **32**, 3839 **(1991)**.
(h) G.Sabitha, G.S.K.K.Reddy, C.S.Reddy, N. Fatima, J.S.Yadav; Synthesis, 1267 **(2003)**.
(i) S.H.Mashraqui, M.A.Karnik; Synthesis, 713 **(1998)**.
(j) M.Anniyappan, D.Muralidharan, P.T.Perumal; Tetrahedron, **58**, 5069 **(2002)**.
(k) M.M.Hashemi, Y.Ahmadibeni, H.Ghafuri; Monatsh.Chem., **134**, 107 **(2003)**.
(l) B.Han, Z.Liu, Q.Liu, L.Yang, Z.L.Liu, W.Yu; Tetrahedron, **62**, 2492 **(2006)**.
(m) W.A.F.Gladstone, R.O.Norman; J.Chem.Soc., Chem.Commun., 1536 **(1966)**.
(n) H.Mashraqui, Madhavi, A.Karnik; Tetrahedron Lett., **39**, 4895 **(1998)**.
(o) N.Nakamichi, Y.Kawashita, M.Hayashi; Org. Lett., **4**, 3955 **(2002)**.
(p) J.R.Pfister; Synthesis, 689 **(1990)**.
(q) R.S.Varma, D.Kumar; Tetrahedron Lett., **40**, 21 **(1999)**.

[7] J.S.Yadav, B.V.Subba Reddy, G.Sabitha, G.S.Kiran Kumar Reddy; Synthesis, **11**, 1532 **(2000)**.

[8] R.S.Varma, Kumar, Dalip; J.Chem.Soc., Perkin Trans., **1**, 1755 **(1999)**.

[9] O.Garcia, F.Delgado, A.C.Cano, C.Alvarez; Tetrahedron Lett., **34**, 623 **(1993)**.

[10] X.Cai, H.Yang, G.Zhang; Can.J.Chem., **83**, 273 **(2005)**.

[11] M.A.Zolfigol; M.H.zebarjadian, M.M.Sadeghi; I.Mohammadpoor-Baltork, H.R.Memarian, M.Shamsipur; Synth.Commun., **31**, 929 **(2001)**.

[12] J.J.Vanden Eynde, F.Delfosse, A.Mayence, Y.Van Haverbeke; Tetrahedron, **51**, 6511 **(1995)**.

[13] H.Adibi, A.R.Hajipour; Bioorg.Med.Chem.Lett., **17**, 1008 **(2007)**.