

SILVER SALTS/ IODINE MONOCHLORIDE AS A NEW OXIDATION SYSTEM FOR THE OXIDATIVE AROMATIZATION OF 1, 4- DIHYDROPYRIDINES

**Morteza Montazerozohori*, Bahador Karami, Masoud Nasr-Esfahani and
Sayed Alireza Musavi**

Chemistry Department, Yasouj University, Yasouj 75918-74831, P.O.Box353, Iran
e-mail: mmzohori@mail.yu.ac.ir; mmzohory@yahoo.com

Abstract: Silver salts such as silver nitrate and silver oxide have been found to promote oxidative aromatization of various 1, 4-dihydropyridines to their corresponding pyridine derivatives by iodine monochloride under heterogeneous conditions in dichloromethane at room temperature. Silver oxide in comparison to silver nitrate promoted the oxidation to completion without any by-products in shorter reaction times and cleaner conditions. The products were separated by simple filtration of reaction mixture and evaporating of solvent and identified by physical and spectral data.

Introduction

Dihydropyridine derivatives first synthesized almost at 1882 when Arthur Hantzsch via a three-component reaction of a β -ketoester with an aldehyde and ammonia (1). Much attention and research activities have been devoted recently to the chemistry and biology of the Hantzsch dihydropyridine derivatives because of their wide utilities in different scientific branches such as synthesis of pyridine derivatives (2), serving as effective redox catalysts, as NADH coenzyme mimics and effective calcium channel antagonist with as exemplified by therapeutic agents such as Nifedipine, Nitrendipine, Nimoldipine Amoldipine (2c). The 1, 4-dihydropyridine based drugs are oxidatively transformed into the related pyridines by the action of cythochrome P-450 in the liver (3). Furthermore the aromatization of readily accessible 1, 4 –dihydropyridines is known as the easiest method to obtain pyridine derivatives. It is evident that the aromatization of 1,4-dihydropyridines has been obtained by using various oxidants such as bismuth nitrate pentahydrate(4-7), tetrakis-pyridine cobalt (II) dichromate (TPCD) (5-8), S-nitrosoglutathione(6-9), N_2O_4 complex of 18-crown-6 (7-10) , diphenylpicryl- hydrazyl and benzoyl peroxide as free radical oxidizing agents (8-11), CrO_3 (9-12), HNO_3 (10-13), silica gel supported ferric nitrate (silfen)(11-14), N_2O_3 (12-15), photochemical oxidation(13-16), inorganic acidic salts/ sodium nitrite or nitrate and catalytic oxidation (14-16-17-19), Dess-Martin periodinane(17-20), silver carbonate on silica gel and celite(18-21), microwave-assisted with $FeCl_3.SiO_2$ (19-22), bismuth(III) chloride supported onto wet HZSM-5 zeolite(20-23), selenium dioxide(21-24), iodobenzene diacetate(22-25), iodoxy benzoic acid (IBA)(23-26), iodine/alkali hydroxide(24-27), the one-pot synthesis and

aromatization in refluxing water(25-28), Co(II) catalyzed auto oxidation(2c) and biomimetic catalyzed oxidation(26-30).

However many of these methods suffer from disadvantages such as long reaction times, strong oxidant like CrO_3 and HNO_3 and require drastic reaction condition or the need of excess oxidant. Therefore this type of aromatization continues to attract the attention of researcher for the introducing of milder conditions applicable to a wide variety of 1, 4-dihydropyridines. In the course of our studies on the oxidation process (27), we planned to investigate the oxidation of 1, 4-dihydropyridines imploing silver salts/ ICl. Iodine monochloride that is a good iodinating reagent, have two crystalline forms α and β . In both structure, there are non-planner chains of ICl molecules in zig-zag formation[] Herein, we would like to report a mild, facile and efficient method for the aromatization of various types of 4- substituted 1,4- dihydropyridines with ICl in the presence of silver salts as promoting agent.

Experimental

Chemicals and Apparatus

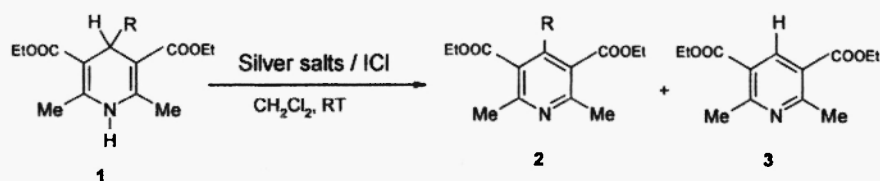
Chemicals were purchased from Merck, Fluka, and Aldrich. The reactions were monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data with those reported in the literature [14-16]. All 1,4- dihydropyridines **1** were synthesized by the reported procedure.⁴ IR spectra were recorded on FT-IR JASCO- 680 and the ^1H -NMR spectra were obtained on a Bruker-instrument DPX-300 MHz model.

Typical experimental procedure

To a solution of 1 mmol (0.359 g) **1i** in 8 mL dichloromethane, 1.5 mmol Ag_2O (0.324 g) and 1.5 mmol ICl (0.381 g) were added. The heterogeneous reaction mixture was stirred at room temperature. The reaction completed as monitored by TLC (n-hexane: ethyl acetate 15:5) after 30min. The reaction mixture containing AgCl and AgI as precipitates was filtered. To the filtrate, diluted aq. 5% $\text{Na}_2\text{S}_2\text{O}_3$, 5mL water and dried Na_2SO_4 were added and after 10 min the mixture was filtered. Dichloromethane removed by water bath (40-50°C) and **2i** as a pale yellow solid 0.32 g (90%) was obtained, mp 70-72 °C [Lit.²² mp 71-72°C]. ^1H NMR (CDCl_3), δ (ppm): 0.94–0.05 (t, 6H), 4.00–4.06 (q, 4H), 2.71 (s, 6H), 2.39 (s, 3H), 7.15–7.19 (m, 4H); IR(KBr): 2980, 1726, 1557, 1446, 1239, 1033, 821, 856, 775 cm^{-1} .

Results and Discussion

Several 1, 4-dihydropyridines were aromatized to the corresponding pyridine derivatives in good to excellent yields by treatment with silver salts/ ICl in dichloromethane at room temperature (Scheme 1).



Scheme-1

For the optimization of the reaction conditions, the several control experiments were designed based on 1, 4-dihydropyridine **3a** and **8a** as a typical substrate. Firstly the oxidation reaction was done by using of ICl in dichloromethane with ratio of 1:2 of substrate: ICl. The conversion was completed within 4-5 h to obtain corresponding pyridines (60-70%) as well as two or more unidentified by-products (30-40%). Secondly the oxidation reactions were performed in the presence of silver salts such as AgNO₃ and Ag₂O with ratio of 1:2 of substrate: silver salts. A very little progress of the aromatization was observed after 10 h. Finally the aromatization reactions were done in the presence of silver salts (AgNO₃ or Ag₂O)/ ICl with ratio 2(1): 2: 1 of AgNO₃ (Ag₂O): ICl: substrate. It was of interest to observe that the reaction rates and yields are dramatically increased while by-products decreased. Both silver nitrate and silver oxide were effective in accelerating the oxidation by iodine monochloride. Among the two silver salts studied, silver oxide was found to be more efficient as well as less by-products in this formation. It seems with using silver nitrate, after conversion of 1, 4- dihydropyridines to pyridine derivatives, the nitrated side products are generally formed that it is not observed when silver oxide is used. Therefore all of the reactions were done with Ag₂O/ Iodine monochloride. The results were summarized in the Table 1.

Table-1: Oxidative aromatization of 1, 4-dihydropyridines (1) to their corresponding pyridine derivatives (2 or 3) with Ag₂O/ Iodine monochloride in dichloromethane at room temperature.

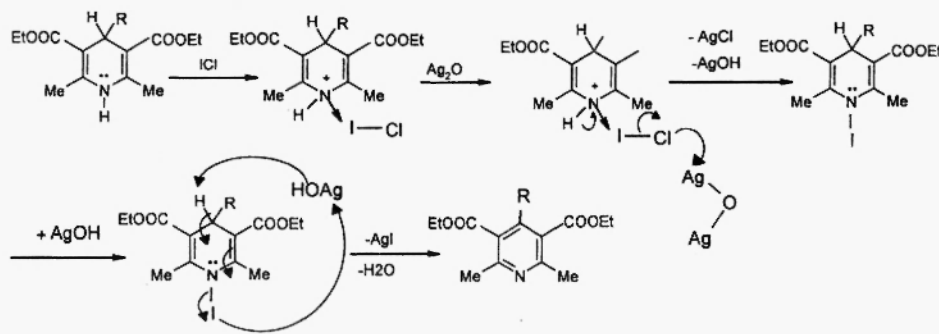
Entry	Substrate (R)	Product ^a	Time (Min)	Yield ^{b,c} (%)	M.p.(°C)[Lit.]
1	1a (H)	3	30	92	70-72[71-72] ^{14, 16, 22}
2	1b (Me)	2b	40	90	Oil [Oil] ^{14, 16}
3	1c (n-Pr)	2c	50	91	Oil [Oil] ^{14, 16}
4	1d (Ph)	2d	40	88	61-63[63-65] ^{14, 16, 22}
5	1e (i-Pr)	3	35	91	68-70[68-69] ^{14, 16, 22}
6	1f (Ph-CH ₂)	4	45	93	67-69[67-68] ^{14, 16, 22}
7	1g (3-NO ₂ -C ₆ H ₄)	2g	50	86	62-64[61-62] ^{14, 16, 22}
8	1h (2-MeO-C ₆ H ₄)	2h	35	90	57-59[57-58] ¹³
9	1i (4-MeO-C ₆ H ₄)	2i	45	92	49-52[50-51] ^{14, 16, 22}
10	1j (4-Cl-C ₆ H ₄)	2j	60	90	65-66[63-65] ^{14, 16, 22}
11	1k (2-Furyl)	2k	20	92	Oil [Oil] ^{14, 16}
12	1l (2-Cl-C ₆ H ₄)	2l	40	85	58-60[61-62] ^{14, 16, 22}
13	1m (Me-CH=CH)	2m	60	90	160-161[159-160] ^{14, 16, 22}
14	1n (4-F-C ₆ H ₄)	2n	50	85	87-88[88-90] ^{14, 16, 22}
15	1o (4-HO-C ₆ H ₄)	2o	40	80	170-172[172-173] ^{14, 16, 22}

^a The product were identified by comparison with those reported in the literatures.

^b Isolated yields. ^c 1.5 mmol Ag₂O(I): 1.5 mmol Iodine monochloride : 1 mmol substrate.

Also it was observed that the oxidation of **1**, the Entries 5, 6 bearing alkyl substituents at the 4-position leads only to dealkylated pyridine derivatives (**3**). This is in agreement with the observation made by the others employing different oxidative conditions (4-26). This fact can be related to alkyl moiety that may be responsible for generating stable carbocations during the progress of the reaction via aromatization. However, aryl substituted-1, 4-dihydropyridines **1** (Entries 4, 7-12 and 14-15) and vinyl substituted (Entry 13) furnished the corresponding pyridine derivatives **2** (Table 1). It is to say that many reported oxidative reagents for the aromatization of 1, 4-dihydropyridines **1** need acidic media that it may lead to hydrolysis of the susceptible functional groups. Since this system acts in neutral medium, hydrolysis of any group in the case of 1, 4-dihydropyridines **1** bearing susceptible substituent (COOEt) did not occur. Also Silver salt /ICl has been reported to be used for the iodination but in this reaction iodinated pyridine derivatives were not observed. Therefore this system behaves chemo selectively only on the nitrogen site of 1, 4-dihydropyridines to oxidize it to the pyridine derivatives under controlled condition. It is to be noted in all of the reactions black silver (I) oxide or silver nitrate were converted to yellowish-white precipitate containing mixture of AgCl and AgI.

With a literature survey we found that HgO/ I₂ reagent (28) is similar to this system and has been used for the oxidation of various organic substrates under heterogeneous conditions. Based on the evidences from the reaction and previous suggestions on such a system as shown in Scheme 2, our rationale about of the proposed mechanism includes coordination interaction of iodine monochloride to 1-NH of 1,4- dihydropyridines. Then silver oxide enters into the reaction to accept chloride ion to produce AgCl and AgOH. Then continuation of interaction of Ag-center (AgOH) with bounded-iodine (N-I) or proton abstraction by it runs deprotonation or dealkylation at the 4- position of 1, 4- dihydropyridines to generate the pyridine derivatives (**2** or **3**).



Scheme-2

Although other iodine compounds specially hypervalent iodine such as iodobenzene diacetate (22), iodoxy benzoic acid (23), have been reported for the aromatization of the titled compounds with the same yields but it must be considered that they are more serious oxidant than iodine monochloride due to higher oxidation number of iodine therein. Therefore it seems that current reaction is milder and under heterogeneous neutral conditions that leads to easily work up.

Conclusion

We think that $\text{Ag}_2\text{O}/\text{ICl}$ is a good neutral reagent due to efficiency, convenient work-up of products, available, clean reactions, suitable times and high yields of reactions. In this paper we reported a convenient, efficient and practical method for the oxidative aromatization of 1, 4- dihydropyridines **1** to the pyridine derivatives **2** or **3**, under mild and heterogeneous conditions.

Acknowledgements

Financial support for this work by Yasouj University is acknowledged.

References

1. Hantzsch, A. *Ann.* 215 (1882).
2. (a) M. A. Zolfigol and M. Safaiee, *Synlett*, **5**, 827 (2004). (b) F. Aydin and R. Ozen, *J. Chem. Res.* 486(2) (2004), (c) S. P. Chavan, R. K. Kharul, U. R. Kalkote, and I. Shivakumar, *Synth. Commun.* **33**(8), 1333 (2003) and references therein.
3. Meyers, A. I.; Brown, J. D. *J. Am. Chem. Soc.* **109**, 3155 (1987).
4. S. H. Mashraqui and M. A. Karnik, *Synthesis*, 713 (1998).
5. B. Wang, Y. HU and H. Hu, *Synth. Commun.*, **29**, 4193 (1999).
6. Y. Z. Mao, M. Z. Jin, Z. L. Liu and L. M. Wu, *Org. Lett.*, **2**, 741 (2000).
7. M. A. Zolfigol, M. H. Zebarjadian, M. M. Sadeghi, I. Mohammadpoor-Baltork, H. R. Memarian and M. Shamsipur, *Synth. Commun.*, **31**, 929 (2001).
8. M. M. Sadeghi, H. R. Memarian and A. R. Momeni, *J. Sci. I. R. Iran*, **12**, 141 (2001).
9. E. Grinsteins, B. Stankevics and G. Duburs Kim, *Geterotsikl. Soedin.*, 1118 (1976).
10. (a) B. Loev, M. M. Goodman, K. M. Snader, R. Tedeschi and E. Macko, *J. Med. Chem.*, **29**, 1596 (1986). (b) O. Garcia, and F. Delgado, *Tetrahedron Lett.*, **34**, 623 (1993).
11. B. Khadikar and S. Borkat, *Synth. Commun.*, **28**, 207 (1998).
12. H. R. Memarian, M. M. Sadeghi, and H. Aliyan, *Indian J. Chem.*, **37B**, 219 (1998).
13. (a) M. A. Zolfigol, F. Shirini, A. Ghorbani Choghamarani and I. Mohammadpoor-Baltork, *Phosphorus, Sulfur, and Silicon*, **178**, 1709 (2003). (b) X.-H. Cai, H.-J. Yang, and G.-L. Zhang, *Can. J. Chem.*, **83**, 273 (2005). (c) J.-W. Lee and K.-Y. Ko, *Bull. Kor. Chem. Soc.*, **25**, 19 (2004).
14. K. Niknam, M. A. Zolfigol, S. M. Rezvani and I. Mohammadpoor-Baltork, *Heterocycles*, **65**, 657 (2005).
15. (a) M. A. Zolfigol, F. Shirin, A. Ghorbani Choghamarani and I. Mohammadpoor-Baltork, *Green Chem.*, **4**, 562(2002). (b) Sh. Mashraqui and M. Karnik, *Tetrahedron Lett.*, **39**, 4895 (1998). (c) N. Nakamichi, Y. Kawashita and M. Hayashi, *Org. Lett.*, **4**, 3955(2002).

16. M. M. Heravi, F. Dirkwand, H. A. Oskooie, M. Ghassemzadeh, *Heterocyclic Commun.*, **11** (1), 75 (2005).
17. A. R. Momeni, T. Sameh, H. Golmohammadi, H. Javaherian Naghash, H. Aliyan, A. R. Massah and S. Solati, *Bull. Korean Chem. Soc.*, **27**(3), 355 (2006).
18. A. Hosseini, M. R. Halvagar, M. A. Khalilzadeh, E. Alaei and M. Tajbakhsh, *J. Chem. Res.*, **1**, 48(2) (2005).
19. M. M. Heravi and M. Ghassemzadeh, Phosphorus, Sulfur, and Silicon and the Related Elements, **180**(2), 347(2005).
20. X. -H. Cai, H. -J. Yang and G. -L. Zhang, *Can. J. Chem.* **83**(3), 273 (2005).
21. D.-P. Cheng and Z.- C. Chen, *Synth. Commun.* **32**(5) 793 (2002).
22. J. S. Yadav, B. V. S. Reddy, A. K. Basak, G. Baishya and A. V. Narsaiah, *Synthesis*, 451 (2006).
23. J. S. Yadav, B.V. Subba Reddy, G. Sabitha and G. S. Kiran Kumar Reddy, *Synthesis* **11**, 1532 (2000).
24. J. -J. Xia and G. -W. Wang, *Synthesis* 2379 (2005).
25. S. P. Chavan, R. K. Kharul, U. R. Kalkote, and I. Shivakumar, *Synth. Commun.* **33**(8), 1333 (2003).
26. M. Nasr-Esfahani, M. Moghadam, S. Tangestaninejad and V. Mirkhani, *Bioorg. Med. Chem. Lett.*, **15**(13), 3276 (2005).
27. (a) B. Karami, M. Montazertozohori, Gh. Karimipour, M. H. Habibi, *Bull. Kor. Chem. Soc.*, **26**(9), 1431 (2005); (b) B. Karami, M. Montazertozohori, M. H. Habibi, M. A. Zolfigol, *Heterocyclic Commun.* **11**(6), 513 (2005); (c) B. Karami, M. Montazertozohori, M. H. Habibi, *Phosphorus, Sulfur, Silicon and related elements*, **181**, 2825-2831 (2006); (d) B. Karami, M. Montazertozohori, M. H. Habibi, *molecules*, **10**, 1358 (2005); (e) B. Karami, M. Montazertozohori, M. Nasr-Esfahani, *Heterocycles*, **65**, 2188 (2005).
28. K. Orito, T. Hatakeyama, M. Takeo, S. Uchiito, M. Tokuda and H. Sugimoto, *Tetrahedron*, **54**, 8403 (1998) and the references cited therein.

Received on March 07, 2007.