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HgO/I_2 as an Efficient Reagent for the Oxidative Aromatization of Hantzsch 1-NH, 4-Dihydropyridines under Mild and Heterogeneous Conditions

Morteza Montazerozohori [1]*, Bahador Karami [1] and Mohammad H. Habibi [2]

[1]*Department of Chemistry, Yasouj University, Yasouj 75914-353, Iran.*

[2]*Department of Chemistry, Isfahan University, Isfahan 81745-117, Iran.*

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ABSTRACT

A variety of Hantzsch 1-NH, 4-dihydropyridines were efficiently aromatized to the corresponding pyridine derivatives by treatment with HgO/I_2 reagent in dichloromethane under mild and heterogeneous conditions in good to excellent yields at room temperature. The products were separated by simple filtration and evaporation of the solvent.

KEYWORDS

HgO/I_2, Hantzsch 1,4-dihydropyridine, aromatization, heterogeneous.

1. Introduction

It has been recognized Hantzsch 1,4-dihydropyridines act as the vital drugs in the treatment of angina and hypertension. Some of these compounds such as Amlodipine, Felodipine, Isradipine, Lacidipine, Nicardipine and Nimodipine are commercially available. Therapeutic success of these compounds is related to their efficiency to bind to calcium channels and consequently to decrease the passage of the transmembrane calcium current for the treatment of the cardiovascular diseases.[1–3] In addition to the biological application of 1,4-dihydropyridines, in organic synthesis, these compounds are used for the preparation of the pyridine derivatives. 1,4-Dihydropyridines are synthesized under various conditions.[4] Several reagents have been reported for the aromatization of them, such as bismuth nitrate pentahydrate,[5] tetrakis-pyridine cobalt (II) dichromate (TPCD),[6] S-nitrosoglutathione,[7] N_2O_4 complex of 18-crown-6,[8] diphenyl picryl-hydrazyl and benzoyl peroxide as free radical oxidizing agents,[9] CrO_3,[10] HNO_3,[11] silica gel-supported ferric nitrate (silfen),[12] N_2O_3,[13] photochemical oxidation, [14] inorganic acidic salts/sodium nitrite or nitrate and catalytic oxidation,[15–17] Dess-Martin periodinane,[18] silver carbonate on silica gel and celite,[19] microwave-assisted with $FeCl_3.SiO_2$,[20] bismuth(III) chloride supported onto wet HZSM-5 zeolite,[21] selenium dioxide,[22] iodobenzene diacetate,[23] iodoxy benzoic acid (IBA),[24] iodine/alkali hydroxide,[25] the one-pot synthesis and aromatization in refluxing water,[26] Co(II)-catalysed auto oxidation[27] and biomimetic-catalysed oxidation.[28]

Most of the currently used reagents suffer from the requirement of the acidic or alkaline additives affecting the susceptible substituents of reactants and or the need of excessively strong oxidants. Mercury and mercury compounds play a crucial role in organic synthesis and transformation in thermal and photochemical conditions. HgO/I_2 has been reported to be an efficient reagent for several reactions such as iodination of alkoxy-substituted benzenes[29–30] and substituted anilines[31], selective oxidation of sulfide to sulfoxides[32] and dimerization of anilines and benzylamines.[33] This reagent acts in an electrophilic manner under heterogeneous conditions without addition of any acidic or basic reagents. In continuation of our recent studies on the aromatization of Hantzsch 1,4-dihydropyridines and the use of mercury compounds in organic reactions,[34–38] we report herein a new oxidative method for the aromatization of a variety of Hantzsch 1,4-dihydropyridines using HgO/I_2 reagent at room temperature.

2. Results and Discussion

We found that a variety of 1,4-dihydropyridines were oxidatively aromatized by HgO/I_2 reagent under mild and heterogeneous conditions in dichloromethane at room temperature (Scheme 1).

The yields and reaction times of the studied compounds are presented in Table 1.

Two competitive oxidative reactions were performed on 1,4-dihydropyridines of entry 4 (**1d**) with the same amount of iodine, the one in the absence of HgO and another in the presence of HgO. Without HgO the reaction took longer than 6 h and in the precence of HgO the reaction was completed in about 1.8 h. These results revealed the important role of the HgO in the progress of the reaction.

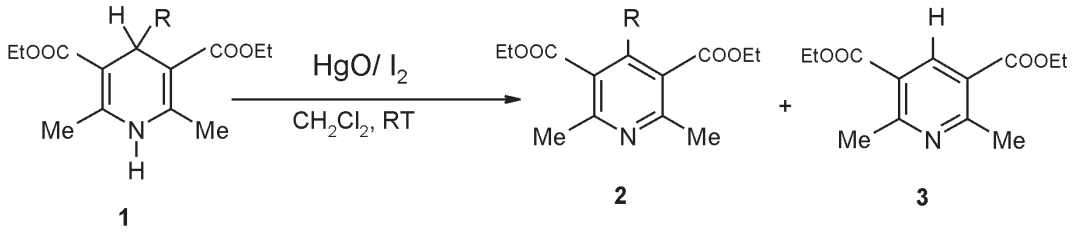
It was observed that the oxidation of (**1**) for entries 5, 6 (see Table 1) bearing alkyl substituents at the 4-position leads only to dealkylated pyridine derivatives (**3**). This is in agreement with the observation made by the others employing different oxidative conditions.[5–28] This fact can be related to the 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**) (see Table 1). It should be noted that many of the reported oxidative reagents for the aromatization of 1,4-dihydropyridines (**1**) need acidic media, which may lead to hydrolysis of the susceptible functional groups. Since the HgO/I_2 system acts in neutral medium, hydrolysis of any group in the case of 1,4-dihydropyridines (**1**) bearing susceptible substituents (COOEt) did not occur. Also HgO/I_2 has been reported to be used for iodination of alkoxy-substituted benzenes and substituted

* To whom correspondence should be addressed. E-mail: mmzohori@mail.yu.ac.ir; mmzohory@yahoo.com

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

Entry	Substrate (R)	Product [a]	Time/h	Yield [b,c]/%	M.p./°C [Lit.]
1	1a (H)	3	0.5	90	70-72[71-72] [15,17]
2	1b (Me)	2b	1.8	91	Oil [Oil] [15,17]
3	*1c* (*n*-Pr)	2c	1.3	89	Oil [Oil] [15,17]
4	1d (Ph)	2d	1.8	88	61-63[63-65] [15,17]
5	*1e*(*i*-Pr)	3	1.5	90	68-70[68-69] [15,17]
6	1f(Ph-CH_2)	3	0.6	92	67-69[67-68] [15,17]
7	1g (3-NO_2-C_6H_4)	2g	2.5	88	62-64[61-62] [15,17]
8	1h (2-MeO-C_6H_4)	2h	1.5	90	57-59[57-58] [14]
9	1i (4-MeO-C_6H_4)	2i	2	90	49-52[50-51] [15,17]
10	1j (4-Cl-C_6H_4)	2j	1.4	91	65-66[63-65] [15,17]
11	1k (2-Furyl)	2k	1.5	93	Oil [Oil] [15,17]
12	1l (2-Cl-C_6H_4)	2l	1.5	89	58-60[61-62] [15,17]
13	1m (Me-CH=CH)	2m	1.4	90	160-161[159-160] [15,17]
14	1n (4-F-C_6H_4)	2n	1.9	85	87-88[88-90] [15,17]
15	1o (4-HO-C_6H_4)	2o	1.8	85	170-172[172-173] [15,17]

[a] The products were compared to the spectral data reported in literature.
[b] Isolated yields.
[c] 1.5 mmol HgO(**I**): 1.5 mmol iodine : 1 mmol substrate.



Scheme 1

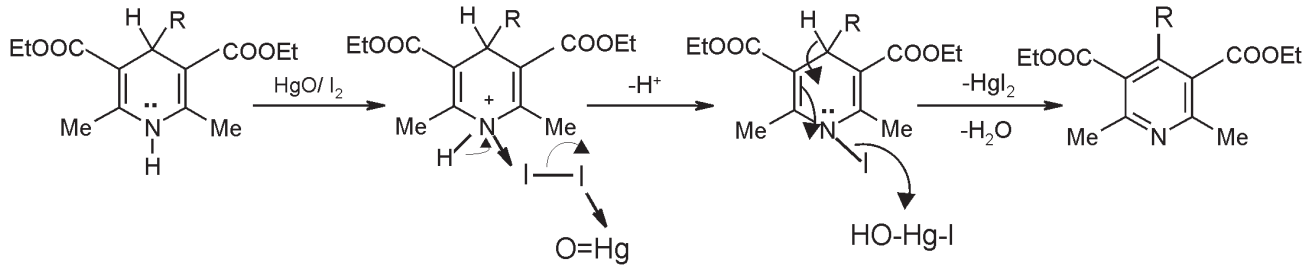
anilines[29–33] but in this reaction iodinated pyridine derivatives were not observed (Entries 8, 9 and 15). Therefore this system behaves regioselectively on the nitrogen site of 1,4-dihydropyridines oxidizing it to the corresponding pyridine derivatives.

As mentioned above, iodine in the absence of HgO did not complete the reaction in suitable time, which means that HgO accelerates the oxidative function of iodine. Based on this evidence and previous suggestions[33] about the mechanism of the system as shown in Scheme 2, our rationale of the reaction mechanism includes coordination interaction of HgO with iodine that polarizes the I-I bond when bound to attack to N-H moiety of 1,4-dihydropyridines and leads to heterolytic cleavage of the I-I bond. The Hg-centre continues to interact with bounded-iodine (N-I) followed by deprotonation or dealkylation at the 4-position of 1,4-dihydropyridines to generate the pyridine derivatives (**2** or **3**).

Other iodine compounds, especially hypervalent iodine such as iodobenzene diacetate,[23] iodoxy benzoic acid (IBA),[24] have been reported for the aromatization of the titled compounds with comparative reaction times with similar yields. However, it must be considered that these iodo species are stronger oxidizing agents in comparison to iodine due to the higher oxidation number of iodine therein. Therefore the HgO/I_2 reaction is a milder alternative. The reaction also proceeds under heterogeneous and neutral conditions that lead to facile work-up. Compared to some alternative catalytic methods,[27] HgO/I_2 oxidizes the titled compounds in shorter reaction times and in comparable or better yields.

3. Conclusion

HgO/I_2 is a valuable neutral reagent due to efficiency, convenient work-up of products, available, clean reactions, suitable times and high yields. 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.



Scheme 2

4. Experimental

4.1. 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.[15–17] All 1,4-dihydropyridines (**1**) were synthesized according to the reported procedure.[4] IR spectra were recorded on a FT-IR JASCO-680 and the ^{1}H-NMR spectra were obtained on a Brucker-instrument 300 MHz model.

4.2. Typical Experimental Procedure

To a solution of 1 mmol (0.359 g) **1h** in 8 mL dichloromethane, 1.5 mmol HgO (0.324 g) and 1.5 mmol I_2 (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 7:3) after 1.5 h. The reaction mixture containing HgI_2 as precipitates was filtered. To the filtrate, diluted aq. 5% $Na_2S_2O_3$, 5 mL water and dried Na_2SO_4 were added and after 10 min the mixture was filtered. The product was extracted with dichloromethane, and the solvent was evaporated on a water bath (40–50°C) to obtain **2h** as a pale yellow solid 0.32 g (90%), mp 57–59 °C [Lit.[14] mp 57–58°C].

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