# AROMATIZATION OF HANTZSCH 1,4-DIHYDROPYRIDINES WITH DESS-MARTIN PERIODINANE UNDER CLASSICAL HEATING AND MICROWAVE IRRADIATION IN SOLVENTLESS SYSTEM

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Hantzsch dihydropyridines were readily oxidized by Dess-Martin periodinane supported onto $HNO_3$/ silica gel under classical heating in dichloromethane and microwave irradiation in solventless system.

Oxidation of Hantzsch 1,4-dihydropyridines is generally the key step in their numerous reactions of biological importance (1-3). Some of them are calcium channel blockers for the treatment of cardiavascular diseases (4) and oxidatively transformed into the corresponding pyridine derivatives by the action of cytochrom P-450 in the liver (5).

Aromatization of 1,4-DHP has been achieved using various oxidants (6). However, many of the reported oxidation procedures either suffer from the use of strong oxidant, require severe conditions, or need excess of the oxidants.
The Dess-Martin periodinane (DMP), 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxal-3(1H)-one (7), is one of the mildest and most convenient reagents available for oxidation of alcohols. DMP enjoys increasing use despite suggestion that its behavior can be capricious (8).

The reagent impregnated on solid supports (9), especially that are efficient in dry media (10) have gained popularity in organic synthesis because of their selectivity and ease of manipulation. The microwave enhanced chemical reactions in general and on inorganic solid supports in particular, have gained popularity over the usual homogeneous and heterogeneous reactions (11).

During the course our ongoing program to develop environmentally benign solvent-free methods, using microwave irradiation (12) and armed with the experiences concerning manipulation of Dess-Martin periodinane (13) and oxidation of Hantzsch 1,4-dihydropyridine (14), herein, we report a facile method for the oxidation of Hantzsch 1,4-dihydropyridine using Dess-Martin periodinane supported onto $HNO_3$/ silica gel under classical heating and microwave irradiation in solventless system.

First we investigated the oxidizing ability of Dess-Martin periodinane in dichloromethane under reflux. Under this condition the reaction was sluggish and after long period of time, a considerable amount of starting material was recovered unchanged. The supported Dess-Martin periodinane was explored on various inorganic solid supports such as alumina, zeolite, clay and silica gel etc. and found that among these materials, $HNO_3$/ silica gel afforded the best results to aromatize Hantzsch 1,4-dihydropyridine. Probably silica gel not only behaves as an acid but also provides water from its inter-layers that is responsible for the acceleration of oxidizing ability of Dess-Martin periodinane. The phenomenon of acceleration of the Dess-Martin oxidation by water has been noticed previously (15). The supported Dess-Martin periodinane was prepared by grinding the reagent (1.2 mmol) with $HNO_3$/ silica gel (1 g). This supported reagent was refluxed with a Hantzsch 1,4-dihydropyridine (**1**, R = H, Scheme 1) for 90 min to obtain the corresponding aromatic compound (**2**, R = H) in 92% yield.

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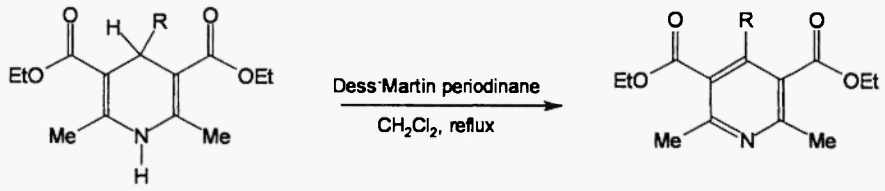



**1a-i** **2a-i**

**SCHEME -1**

To establish the generality of the method various Hantzsch 1,4-dihydropyridines were oxidized similarly to obtain the corresponding substituted pyridine in high yields and relatively long time (Table-1). The important role of $HNO_3$/ silica gel is apparent from the fact that only poor yield (~ 25%) was obtained without support and longer reaction time was required. A drop of $HNO_3$ as a co-catalyst seemed to be necessary since without it in spite of using silica gel the yield is still poor. Although these reactions are very convenient, yet the efficiency may be further enhanced by conducting the reaction under microwave irradiation in solventless system.

**TABLE-1:** Aromatization of Hantzsch 1,4-dihyropyridine with Dess-Martin periodinane in $CH_2Cl_2$

| Entry | Substrate | Reaction time min | Mp ( C) | | Yield[a](%) |
|---|---|---|---|---|---|
| | | | Found | Lit. | |
| **2a** | H | 65 | 70 | 70-1 (17) | 80 |
| **2b** | $CH_3$ | 80 | Liquid (17) | | 80 |
| **2c** | $C_2H_5$ | 70 | Liquid (18) | | 82 |
| **2d** | $C_3H_7$ | 65 | 61-3 | 61-3 | 82 |
| **2e** | $C_6H_5$ | 65 | 61-3 | 62-4 (6b) | 80 |
| **2f** | 4-$(CH_3O)C_6H_4$ | 80 | 50-2 | 50 (6b) | 78 |
| **2g** | 3-$(O_2N)C_6H_4$ | 65 | 62 | 61-3 (6a) | 82 |
| **2h** | 4-$(Cl)C_6H_4$ | 80 | 66-8 | 66-8 | 78 |
| **2i** | 2-Furyl | 75 | Liquid (6a) | | 82 |

[a]Yields refer to isolated products.

Several 1,4-dihydropyridines were aromatized to the corresponding pyridines in very short time and high yields with Dess-Martin periodinane under microwave irradiation in solvent-free condition. The results are summarized in the Table-2 indicate the scope of reaction with respect to various 1,4-dihyropyridines.

The salient features of this reaction are mild reaction conditions, very short time, eco-friendly conditions and excellent yields. No dealkylation was observed under the present reaction conditions which is normally happened during aromatization by other oxidants (16). In addition, Dess-Martin periodinane supported onto $HNO_3$/silica gel does not show the disadvantage of giving nitrated side product observed in the aromatization of 1,4-dihydropyridines with metallic nitrates (17). The spectroscopic and physical data for the products are given in Table-3.

In conclusion, from a practical point of view, aromatization of 1,4-dihydropyridines with Dess-Martin periodinane either under reflux or under microwave irradiation is a valuable and excellent synthetic method. Indeed, under microwave irradiation and solvent-free condition, reactions are extremely fast and yields are high (Table II). Lack of solvent in this method gives additional eco-friendly condition. Contrary to

most methods, our procedure causes aromatization of Hantzsch 1,4-dihydropyridines without damage to substituent at 4-position. We believe this methodology will find its uses in organic synthesis.

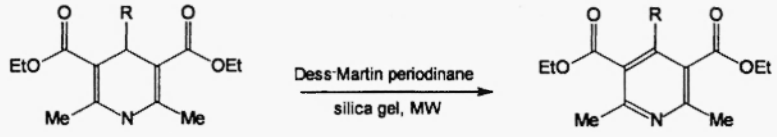
**TABLE-2:** Aromatization of Hantzsch 1,4-dihyropyridine with Dess-Martin periodinane under microwave irradiation in solventless system

| Entry | Substrate R | Reaction time min | Mp(°C) | | Yield[a] (%) |
|---|---|---|---|---|---|
| | | | Found | Lit. | |
| **2a** | H | 5 | 70-1 | 70-1 (17) | 90 |
| **2e** | $C_6H_5$ | 7 | 61-3 | 62-4 (6b) | 85 |
| **2f** | 4-$(CH_3O)C_6H_4$ | 5 | 51 | 50 (6b) | 82 |
| **2g** | 3-$(O_2N)C_6H_4$ | 5 | 62-4 | 61-3 (6a) | 85 |
| **2h** | 4-$(Cl)C_6H_4$ | 5 | 67 | 66-8 | 80 |
| **2i** | 2-Furyl | 5 | Liquid (6a) | | 78 |

**TABLE-3:** Spectroscopic data for products **2a-i**

| Entry | Molecular formula | $^1$HNMR, δ ($CDCl_3$, ppm) | IR, $\tilde{\upsilon}$ (KBr disc, $cm^{-1}$) |
|---|---|---|---|
| **2a** | $C_{13}H_{17}NO_4$ | 8.6 (s, 1H, CH) | 2956, 2923, 1730, 1600, 1553, 155 |
| **2b** | $C_{14}H_{19}NO_4$ | 2.3(s, 3H, Me) | 2984, 2930, 1730, 1560, 1046 |
| **2c** | $C_{15}H_{21}NO_4$ | 1.2(d, 3H, Me)<br>2.8(t, 2H, $CH_2$) | 2976, 1730, 1569, 1453, 1238 |
| **2d** | $C_{16}H_{23}NO_4$ | 0.8-1.6 (m, 5H, $CH_3$, $CH_2$)<br>7.6(t, 2H, $CH_2$) | 2969, 1730, 1569, 1453, 1375, 1261, 1040 |
| **2e** | $C_{19}H_{21}NO_4$ | 7.3(s, 5H, Ph) | 3015, 2976, 1730, 1561, 1107 |
| **2f** | $C_{20}H_{23}NO_5$ | 3.8(s, 3H, $OCH_3$)<br>6.7(d, 2H, aromatic)<br>7.2(d, 2H, aromatic) | 2970, 1730, 1615, 1515, 1292, 1115 |
| **2g** | $C_{19}H_{20}N_2O_6$ | 7.7(d, 2H, aromatic)<br>8.2(s, 1H, aromatic)<br>8.3(m, 2H, aromatic) | 3050, 2965, 2930, 1730, 1650, 1623, 1538, 1635 |
| **2h** | $C_{19}H_{20}NO_4Cl$ | 7.2-7.3(d, 4H, aromatic) | 2976, 1730, 1561, 1230, 1107 |
| **2i** | $C_{19}H_{23}NO_5$ | 6.2-6.5(dd, 2H, aromatic)<br>7.4(dd, 1H, aromatic) | 3075, 2984, 1730, 1575, 1561, 1107, 1046 |

$CH_3$ at 2 and 6 positions in all compounds appeared at δ = 2.4, but for 2a appeared at δ = 3. $CH_3CH_2COO$ appeared at 1,1 (t, 6H, 2 Me) and 4.02 (q, 4H, 2 $CH_2$).




**SCHEME 2**

## EXPERIMENTAL

All products are known compounds and are identified by comparison of their physical and spectroscopic data with those of reported in literature. 1,4-Dihydropyridines were synthesized according to reported procedure. Ir spectra were recorded (KBr disc) on Philips, PU 9800 FT-IR spectrometer. $^1$HNMR spectra were recorded on FT-NMR, Bruker 500 MHz spectrometer in $CDCl_3$ and chemical shifts

are indicated in δ ppm. Melting points (uncorrected) were measured by electrothermal 9100.

**Preparation of Dess-Martin periodinane supported onto silica gel.**

Dess-Martin periodinane (1.05 g, 1.2 mmol) was grinded thoroughly with silica gel (1 g)/$HNO_3$(one drop) using a spatula.

**Pyridines 2a-l: General procedure**

A mixture of Hantzsch pyridine (1 mmole) and supported Dess-Martin periodinane (1.2 mmole) in $CH_2Cl_2$ (15 mL) was refluxed for the specified time (Table I). After complete conversion as indicated by TLC, the reaction mixture was filtered off. The filtrate was washed with the solution of sodium thiosulfate (10%) and saturated solution of sodium bicarbonate. The organic layer was separated and dried over $MgSO_4$, filtered off and evaporated to dryness. Final purification performed by column chromatography.

**Pyridines 2a, e, f, g, h, i; General procedure.**

Hantzsch 1,4 dihydropyridine (1 mmole) was thoroughly mixed and grinded with supported Dess-Martin periodinane (1.2 mmole) in a beaker using a spatula. The beaker was placed in a household microwave oven in specified time (Table II). The progress of reaction was monitored by TLC. After the completion of reaction, to the crude, $CH_2Cl_2$ was added. The mixture was filtered off and filtrate was washed with 10% solution of sodium thiosulfate and saturated solution of sodium bicarbonate. The organic layer was separated and evaporated to dryness. The crude was purified by column chromatography.

**CAUTION**

Although we did not have any accident using Dess-Martin periodinane, the use of microwave oven in an efficient hood is highly recommended.

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