ZEOBIS, A VERSATILE REAGENT FOR THE FAST AROMATIZATION OF HANTZSCH 1,4-DIHYDROPYRIDINES

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Abstract: Bismuth nitrate supported onto HZSM-5 zeolite (zeobis) has been found to be an efficient and selective reagent for the oxidation of Hantzsch 1,4-Dihydropyridines to the corresponding pyridine derivatives in excellent yields.

Key words: HZSM-5, Hantzsch 1,4- DHP, Bismuth nitrate, zeobis, aromatization.

There has been considerable growth in interest in the development of mild methods for the aromatization of 1,4-Dihydropyridines. This is because such derivatives serve as vital drugs in treatment of angina and hypertension. Some of them such as Amlodipine, Felodipine, Isradipine have been commercialized and it has been proven that their therapeutic success is related to their efficiency to bind to calcium channels and consequently to decrease the passage of transmembrane calcium current, associated in smooth muscle with a long lasting relaxation and cardiac muscle with a reaction of contractility throughout the heart.[1-3]

Aromatization of Hantzsch1,4-Dihydropyridines has also attracted considerable attention in recent years as Bocker[4] has demonstrated that metabolism of those drugs involves a cytochrom P-450 catalyzed oxidation in the liver. Due to the biochemical importance of the oxidation step of 1,4-DHP, this reaction has been the subject of a large number of studies and a plethora of reagents has been utilized to mimic the in vivo transformation.[5]

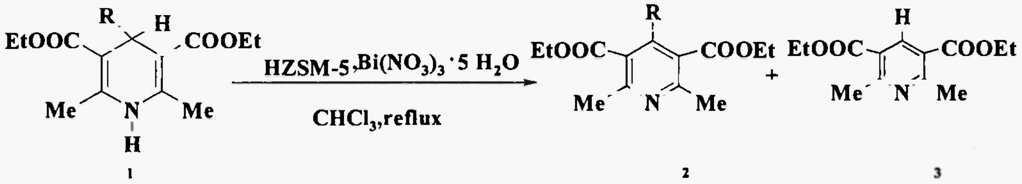
Several methods for the oxidation of 4- substituted Hantzsch 1,4-Dihydropyridines to the corresponding pyridine derivatives have been reported.[6-17] Although some of these methods are carried out under milder reaction conditions most of them require a strong or toxic oxidant, severe conditions[18,19] and tedious work-up procedures or sometimes long reaction times. For instance $Bi(NO_3)_3.5H_2O$ oxidizes several Hantzsch 1,4-DHP in acetic acid medium at room temperature in moderate to good yields but the reaction times are very prolonged.[20]

The use of solid supported reagents in synthetic chemistry has become popular due to the altered reactivity, none-aqueous conditions and convenient isolation they provide.[21] Furthermore, the combination of homogeneous catalysis and microwave heating is not only a hot topic but also a research area that is likely to have an impact on several fields on modern chemistry.[22,23]

Recently we reported on the oxidation of Hantzsch 1,4-DHPs using $Bi(NO_3)_3.5H_2O$ supported onto silica gel[24], manganese dioxide[25], bismuth chloride[26] under microwave irradiation and ferric perchlorate in acetic acid[27]. Now we wish to report Bismuth nitrate supported onto HZSM-5 zeolite as an efficient reagent for the oxidation of Hantzsch 1,4-DHPs in refluxing chloroform. In fact refluxing the mixture of 1,4- DHP (1 mmol), Bismuth nitrate (1 mmol) and HZSM-5 zeolite (1 g) gave after simple filtration, desired pyridine derivatives in excellent yields. (Scheme 1)

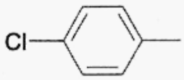
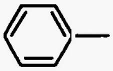
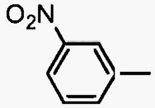
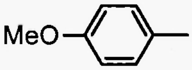
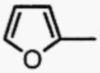
It is noteworthy to mention that the oxidation of Hantzsch 1,4-DHPs with secondary alkyl (entry **3**) at 4-position was accompained by explusion of this group to efford a mixture of **2** (68%) and **3** (32%) while in other case the substituted groups at 4-position were remained in the pyridine ring to give **2**.

In conclusion, we have developed a general and practical route for the aromatization of 1,4-Dihydropyridines to the corresponding pyridine derivatives in excellent yields using $Bi(NO_3)_3.5H_2O$,a commercially available, inexpensive, crystalline solid, supported onto HZSM-5 zeolite. This method is much faster than using bismuth nitrate without using supported. We believe this method is a nice development to the exicting methods.



Scheme-1

Table-1: Oxidation of 1, 4-DHPs using zeofen

Entry	R	Time(min)	Yield (%)^{b}	Observed m.p(°C)^{a}	Reported m.p(°C)
1	H—	3	99	70	69-70[28]
2		6	99	66-67	66-67[28]
3	Et—	8	68	oil	oil[5]
4		5	99	61	61-62[5]
5		12	98.5	62-63	61-63[28]
6		3	99	50	50[29]
7		5	98	oil	Oil[30]

a) Products exhibited physical properties in accordance with the assigned structures.
b) Yields refer to the isolated products.

Selected data for 1: Yield: 99%; mp: 70, (lit[28]. 69-70); IR $\bar{\nu}$ (KBr): 755, 1553, 1600, 1730, 2923, 2965cm^{-1}; ^{1}HNMRδ (CDCl$_3$):1.1 (t, 6H, 2CH$_3$); 3.0(s, 6H, 2CH$_3$); 4.2 (q, 4H, 2CH$_2$); 8.6 (s, 1H).

Selected data for 2: Yield: 99%, mp: 66-67(lit[28]. 66-67); IR $\bar{\nu}$ (film): 2976, 1730, 1561, 1238, 1107cm^{-1}; ^{1}HNMRδ (CDCl$_3$): 7.2-7.3 (d, 4H).

Selected data for 3: Yield: 68%, oil, (lit[5]. oil); IR $\bar{\nu}$ (film): 1238, 1453, 1569, 1730, 2976 cm^{-1}; ^{1}HNMRδ (CDCl$_3$): 0.8-1.2(t, 3H); 1.1 (t, 6H, 2CH$_3$); 2.4(s, 6H, 2CH$_3$); 2.8(q, 2H); 4.2(q, 4H, 2CH$_2$).

Selected data for 4: Yield: 99%, mp: 61, (lit[5]. 61-62); IR $\bar{\nu}$ (KBr): 1107, 1561, 1730, 2976, 3015 cm^{-1}; ^{1}HNMRδ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.4(s, 6H, $2CH_3$); 4.2(q, 4H, $2CH_2$); 7.3(s, 5H).

Selected data for 5: Yield: 98.5%, mp: 61-62, (lit[28]. 61-63); IR $\bar{\nu}$ (KBr): 1535-1538, 1560, 1623, 1730, 2965, 3050 cm^{-1}; ^{1}HNMRδ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.4(s, 6H, $2CH_3$); 4.2(q, 4H, $2CH_2$); 7.7(d, 2H); 8.2(s, 1H); 8.3(m,2H).

Selected data for 6: Yield: 99%, mp: 50, (lit[29]. 50); IR $\bar{\nu}$ (KBr): 1115, 1292, 1515, 1615, 1730, 2970 cm^{-1}; ^{1}HNMRδ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.4(s, 6H, $2CH_3$); 3.8(s, 3H, CH_3); 4.2(q, 4H, $2CH_2$); 6.7(d, 2H); 7.2(d,2H).

Selected data for 7: Yield: 98%, oil, (lit[30]); IR $\bar{\nu}$ (KBr): 1046, 1107, 1561, 1575, 1730, 2984, 3075 cm^{-1}; ^{1}HNMRδ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.4(s, 6H, $2CH_3$); 4.2(q, 4H, $2CH_2$); 6.2-6.5(c, 2H); 7.4(c, 1H).

Experimental

All the dihydropyridines were prepared according to the literature procedure, using the appropriate aldehydes, ammonia and ethyl acetoacetate[31]. All products were known; their physical and spectroscopic data were compared with those of authentic samples and found to be identical.

General procedure

A solution of the substrate (1mmol) in chloroform (5ml) was treated with $Bi(NO_3)_3.5H_2O$ (1 mmol) supported onto HZSM-5 zeolite (1g) and the reaction was magnetically stirred under reflux condition for the specified time (table 1). The reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the soild residue was washed with chloroform (10 ml). After evaporation of the solvent the corresponding pyridine derivatives were obtained in excellent yields.

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