RESEARCH PAPER MARCH, 168–169 JOURNAL OF CHEMICAL RESEARCH 2006

Zeofen: a user friendly agent for oxidation of the Hantzsch 1, 4-dihydropyridines

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Hantzsch 1, 4-dihydropyridines (DHPs) were readily oxidised by zeofen (ferric nitrate and HZSM-5 zeolite) to the corresponding pyridines in good yields.

Keywords: Hantzsch 1, 4-dihydropyridine, zeofen, ferric nitrate, aromatisation

Oxidation of Hantzsch 1, 4-DHPs to the corresponding pyridines has been extensively studied in view of the pertinence of this reaction to the metabolism of Hantzsch esters and calcium channel blocking drugs used in treatment of various cardiovascular disorders.[1] The reaction has been used to study the biologically significant NADH redox processes.[2]

Numerous reagent and procedures have been recommended for this purpose, such as: $KMnO_4$,[3] CrO_3,[4] HNO_3,[5] pyridinum chlorochromate (PCC),[6] inorganic acidic salts and sodium nitrite or nitrate.[7-10] Most of them have their own merits and disadvantages.

In addition this aromatisation reaction with most of these reagents leads to dealkylation at the 4-position or formation of side products.[3] In some other instances only moderate to poor yields are obtained.[3-6] Another disadvantage is that most of these reagents are corrosive, irritants and toxic.

The introduction of supported reagents for bringing about various chemical transformations has provided an attractive option for organic syntheses.[11-15] Such reagents not only modify the reactivity but also may impart product selectivity, enhanced reaction rates, cleaner reaction products, and operational simplicity, and are eco-friendly.[16-19] Metal nitrates supported on various inorganic materials have been used as oxidising agents. Ferric nitrate on silicagel,[17,18] and ferric nitrate supported on K-10 montmorillonite clay[16-19] are some of the reagents employed for the oxidation process. However, these reagents face some problems. Preparation of these reagents involves tedious solvent removal, and prolonged activation under special conditions such as reduced pressure, and a specific temperature range.[17,19] Thus, there seems to be still scope for developing a supported metal nitrate oxidant.

In view of these limitations and in continuation of our program to extend Hantzsch oxidation[20] we decided to develop a practical and general approach for oxidation of 1, 4-dihydropyridines. We have developed and used zeofen (short for zeolite HZSM-5 supported ferric nitrate) as a green oxidant for various oxidation reactions (oxidation of alcohols,[21] deprotection of THP and trimethylsilyl ethers,[22] oxidative deoximation[23]). In continuation of our program we report the oxidation of 1, 4-dihydropyridines with this eco-friendly reagent. The aromatisations of Hantzsch 1, 4-DHPs were conducted by refluxing of the mixture of 1, 4-DHPs and zeofen in dichloromethane. Upon completion of the reaction (monitored by TLC) and simple filtration, the desired pyridine derivatives were obtained in excellent yields.

In conclusion, a readily prepared reagent can be used as a highly effective oxidant in aromatization of Hantzsch 1, 4-DHPs to pyridine derivatives. The advantages of this reagent are very short reaction times, easy and clean work-up and excellent yields. We believe this eco-friendly reagent is an efficient reagent and will find uses in synthetic methodology.

In terms of reaction time, to our best knowledge, this reagent seems to be one of the most efficient oxidant for the 1, 4-DHPs among known oxidants

Experimental

Chemicals were purchased from Fluka, Merck, Riedel de Haen AG and Aldrich chemical companies. Yields refer to isolated products. All Hantzsch 1, 4-DHPs were synthesised by the reported procedures.[24] The oxidation products were characterised by comparison of their spectral (IR, ^{1}H NMR) data with reported physical data in the literature.

General procedure: preparation of zeofen

To prepare zeofen, $Fe\ NO_3.9H_2O$ (0.8 gr, 2 mmol) and an equivalent weight of Hantzsch-5 zeolite were crushed together so as to form an intimate mixture (zeofen).

Aromatisation of Hantzsch 1,4-dihydropyridines: typical procedure

Zeofen (1–1.2 equiv) was added a stirring solution of dihydropyridine in dichloromethane. The reaction was refluxed for 3–7 min. After the completion of the reaction (monitored by TLC) the reagent was filtered off and washed with dichloromethane. Evaporation of the solvent gave the corresponding pyridines. The results are summarised in Table 1.

Selected data for **1**: Yield: 100%; m.p. 70 °C, (lit.[25] 69–70); IRν (KBr): 755, 1553, 1600, 1730, 2923, 2965cm^{-1}; ^{1}H NMR δ ($CDCl_3$):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: 95%, liq, (lit.[26] liq); IRν (film): 1064, 1560, 1730, 2930, 2984cm^{-1}; ^{1}H NMR δ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.3 (s, 3H), 2.4(s, 6H, $2CH_3$); 4.2(q, 4H, $2CH_2$).

Selected data for **3**: Yield: 76%, liq, (lit.[26] liq); IRν (film):1238, 1453, 1569, 1730, 2976 cm^{-1}; ^{1}H NMR δ ($CDCl_3$): 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: 100%, m.p. 61 °C, (lit.[26] 61–62); IRν (KBr): 1107, 1561, 1730, 2976, 3015 cm^{-1}; ^{1}H NMR δ ($CDCl_3$):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: 100%, m.p. 61–62 °C, (lit.[25] 61–63); IRν (KBr): 1535–1538, 1560, 1623, 1730, 2965, 3050 cm^{-1}; ^{1}H NMR δ ($CDCl_3$): 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,1H).

Selected data for **6**: Yield: 100%, m.p. 50 °C, (lit.[25] 50); IRν (KBr): 1115, 1292, 1515, 1615, 1730, 2970 cm^{-1}; ^{1}H NMR δ ($CDCl_3$): 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: 100%, m.p. 66–67 °C, (lit.[25] 66–67); IRν (KBr): 2976, 1730, 1561, 1238, 1107cm^{-1}; ^{1}H NMR δ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.4(s, 6H, $2CH_3$); 4.2(q, 4H, $2CH_2$); 7.2–7.3 (d, 4H).

Received 4 September 2005; accepted 23 October 2005
Paper 05/3477

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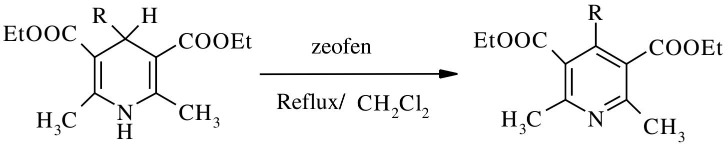
Table 1 Oxidation of 1, 4-DHPs using zeofen



Entry	R	Reaction times/min	Yield/%[a]	M.p./°C[b]	
				Observed	Reported
1	H-	7	100	70	69–70[25]
2	Me-	7	95	Liq	Liq[26]
3	Et-	3	76	Liq	Liq[26]
4	Ph-	3	100	61	61–62[26]
5	3-NO_2 ph	3	100	62–63	61–63[25]
6	4-MeO ph	120	100	50	50[25]
7	4-Cl ph	5	100	66–67	66–67[25]

[a] Yields refer to the isolated pure products.

[b] Products exhibited physical properties in accordance with the assigned structures.

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