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SHORT COMMUNICATIONS

Clinofen—A User-Friendly Oxidizing Agent for Very Fast Oxidation of Hantzsch 1,4-Dihydropyridines*

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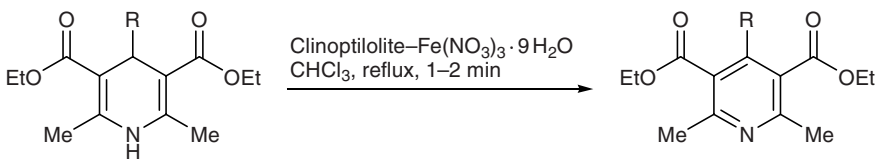
Hantzsch 1,4-dihydropyridines have been extensively utilized as analogs of NAD(P)H coenzymes to study the mechanism and synthetic potential of various redox processes [1, 2]. In addition, 1,4-dihydropyridine-based drugs such as Nifedipine and Niguldipine are widely used as calcium channel blockers for the treatment of cardiovascular disorders, including stenocardia, hypertension, and cardiac arrhythmia [3]. 1,4-Dihydropyridines are transformed into the corresponding pyridines in the course of both redox processes [2] and metabolism [4]. Therefore, aromatization of 1,4-dihydropyridines continues to attract attention of researchers from the viewpoint of searching for milder and general procedures applicable to a wide range of substrates. A number of methods and reagents have been reported recently for this purpose. They generally involve the use of strong inorganic oxidants such as nitric acid [5], ceric ammonium nitrate (CAN) [6], iron(III) and copper(II) nitrates [7], potassium permanganate [8], chromium(VI) oxide [9], pyridinium chlorochromate (PCC) [10], bentonite clay-supported manganese(IV) oxide [11], bismuth nitrate pentahydrate [12], clay-supported copper(II) nitrate under microwave activation [13], iron(III) nitrate on silica gel (silfen) [14], etc. [15–18]. Disadvantages of these procedures include the use of strong and toxic oxidants, severe conditions, long reaction times, necessity of excess reagent, formation of by-products, laborious work-up, and poor yields of the target products.

In this communication we report a very convenient, clean, and efficient procedure for the oxidation of Hantzsch 1,4-dihydropyridines with clinoptilolite–iron(III) nitrate (clinofen) [19]. Minerals of the clinoptilolite series are the most common rock-forming minerals of sedimentary rocks of volcanic origin, the latter being a source of natural zeolites. To the best of our knowledge, this is the first report on the use of clinoptilolite in organic synthesis. The reactions were carried out by heating a mixture of 1 mmol of 1,4-dihydropyridine **I**, 1 g of clinoptilolite, and 1 mmol of iron(III) nitrate in boiling chloroform for a very short time. As a result, the corresponding pyridines were formed in excellent yields. The products were isolated by simple filtration of the reaction mixture, followed by removal of the solvent. In the absence of clinoptilolite, the reaction was sluggish and (what is more important) molten iron(III) nitrat nonahydrate adhered to the wall of the reaction vessel. As followed from spectroscopic data, the oxidation did not involve substituent in the 4-position of the pyridine ring.

Thus we have proposed a readily accessible reagent for highly effective oxidation of Hantzsch 1,4-dihydropyridines to the corresponding pyridine derivatives. It



Ia–Ig **IIa–IIg**

R = H (**a**), 4-ClC_6H_4 (**b**), Et (**c**), Ph (**d**), 3-$O_2NC_6H_4$ (**e**), 4-$MeOC_6H_4$ (**f**), 2-furyl (**g**).

* The text was submitted by the authors in English.

is advantageous due to very short reaction time, easy and clean work-up, and excellent yields. As far as we know, Clinofen is the fastest among known oxidants for 1,4-dihydropyridines, and the proposed procedure considerably improves their oxidation.

1,4-Dihydropyridines **Ia–Ig** were synthesized according to the procedure described in [20] from the corresponding aldehydes, ammonia, and ethyl acetoacetate. All products were reported previously; their physical constants and spectral parameters coincided with those of authentic samples.

General procedure for the oxidation of 1,4-dihydropyridines Ia–Ig with iron(III) nitrate–clinoptilolite. Iron(III) nitrate nonahydrate, 0.4 g (1 mmol), was mixed with 1 g of clinoptilolite in 10 ml of chloroform, 1 mmol of 1,4-dihydropyridine **Ia–Ig** was added, and the mixture was heated for 1–2 min under reflux. The progress of reactions was monitored by TLC using petroleum ether–ethyl acetate as eluent. When the reaction was complete, the mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was the corresponding pure pyridine **IIa–IIg**.

Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (IIa). Reaction time 1 min. Yield 99%, mp 70°C; published data [21]: mp 69–70°C. IR spectrum (KBr), ν, cm^{-1}: 755, 1553, 1600, 1730, 2923, 2965. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.1 t (6H, CH_3), 3.0 s (6H, CH_3), 4.2 q (4H, CH_2), 8.6 s (1H, 4-H).

Diethyl 4-(4-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (IIb). Reaction time 2 min. Yield 99%, mp 66–67°C; published data [21]: mp 66–60°C. IR spectrum (film), ν, cm^{-1}: 2976, 1730, 1561, 1238, 1107. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.2–7.3 d (4H, H_{arom}).

Diethyl 4-ethyl-2,6-dimethylpyridine-3,5-dicarboxylate (IIc). Reaction time 1 min. Yield 99%, oily substance (cf. [5]). IR spectrum (film), ν, cm^{-1}: 1238, 1453, 1569, 1730, 2976. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.8–1.2 t (3H), 1.1 t (6H, CH_3), 2.4 s (6H, CH_3), 2.8 q (2H, CH_2), 4.2 q (4H, OCH_2).

Diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (IId). Reaction time 1 min. Yield 98%, mp 61°C; published data [5]: mp 61–62°C. IR spectrum (KBr), ν, cm^{-1}: 1107, 1561, 1730, 2976, 3015. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.1 t (6H, CH_3), 2.4 s (6H, CH_3), 4.2 q (4H, CH_2), 7.3 s (5H, H_{arom}).

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (IIe). Reaction time 1.5 min. Yield 99%, mp 62–63°C; published data [21]: mp 61–63°C. IR spectrum (KBr), ν, cm^{-1}: 1535–1538, 1560, 1623, 1730, 2965, 3050. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.1 t (6H, CH_3), 2.4 s (6H, CH_3), 4.2 q (4H, CH_2), 7.7 d (2H, H_{arom}), 8.2 s (1H, H_{arom}), 8.3 m (2H, H_{arom}).

Diethyl 4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (IIf). Reaction time 2 min. Yield 98%, mp 50°C [22]. IR spectrum (KBr), ν, cm^{-1}: 1115, 1292, 1515, 1615, 1730, 2970. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.1 t (6H, CH_3), 2.4 s (6H, CH_3), 3.8 s (3H, CH_3O), 4.2 q (4H, CH_2), 6.7 d (2H, H_{arom}), 7.2 d (2H, H_{arom}).

Diethyl 4-(2-furyl)-2,6-dimethylpyridine-3,5-dicarboxylate (IIg). Reaction time 2 min. Yield 99%, oily substance (cf. [23]). IR spectrum (KBr), ν, cm^{-1}: 1046, 1107, 1561, 1575, 1730, 2984, 3075. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.1 t (6H, CH_3), 2.4 s (6H, CH_3), 4.2 q (4H, CH_2), 6.2–6.5 m (2H, furyl), 7.4 s (1H, furyl).

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