

Aromatization of Hantzsch 1,4-Dihydropyridines with Urea-Hydrogen Peroxide/Maleic Anhydride

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A simple method for the oxidative aromatization of Hantzsch 1,4-dihydropyridines to the corresponding pyridines is reported using urea-hydrogen peroxide/maleic anhydride in acetonitrile.

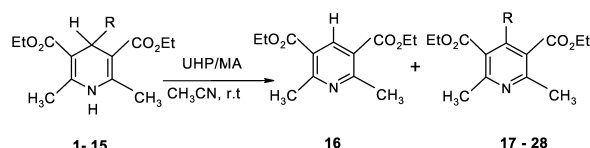
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Introduction

Hantzsch 1,4-dihydropyridines (Hantzsch 1,4-DHPs) are widely used as calcium channel blockers for the treatment of cardiovascular disorder including hypertension [1]. These compounds are oxidized to pyridine derivatives by the action of cytochrome P-450 in the liver [2]. Furthermore, the oxidation of Hantzsch 1,4-DHPs provides an easy access to pyridine derivatives.

Significant research has been carried out and many approaches have appeared for the aromatization of Hantzsch 1,4-dihydropyridines, such as oxidation with $\text{Ti}(\text{NO}_3)_3 \cdot 3 \text{H}_2\text{O}$ [3], BaMnO_4 [4], photochemical reactions [5], KMnO_4 [6], solid supported pyridinium chlorochromate (PCC) [7], silica gel supported ferric nitrate [8], nitric oxide [9], MnO_2 [10], ceric ammonium nitrate (CAN) [11], *tert*-butylhydroperoxide [12], clay supported cupric nitrate [13], $\text{Bi}(\text{NO}_3)_3$ [14], I_2/MeOH [15], $\text{Zr}(\text{NO}_3)_4$ [16], tetakis-pyridine cobalt(II) dichromate (TPCD) [17], iodo-benzene diacetate [18], $\text{NaNO}_2/\text{NaHSO}_4/\text{SiO}_2$ [19], $\text{NaNO}_2/\text{C}_2\text{H}_2\text{O}_4$ [20], 3-carboxypyridinium chlorochromate (CPCC) [21], $\text{K}_2\text{S}_2\text{O}_8/\text{Co}(\text{NO}_3)_2$ [22] and RuCl_3/O_2 [23]. In continuing our effort to find a milder and high-yielding oxidant for the Hantzsch 1,4-DHPs, herein we wish to report that urea-hydrogen peroxide (UHP) in combination with maleic anhydride (MA) can serve as a powerful oxidant for the aromatization of the Hantzsch 1,4-DHPs.

Urea-hydrogen peroxide alone or in combination with carboxylic anhydrides has proved to serve as



Scheme 1.

a valuable alternative to anhydrous hydrogen peroxide. The range of substrates oxidized includes, alkenes (epoxidation), ketones (Baeyer-Villiger reaction), aromatic hydrocarbons (to phenols) [24], sulfides (to sulfoxides and sulfones) and nitriles (to amides) [25], nitrogen heterocycles (to N-oxides) [24–27].

Results and Discussion

A series of 1,4-DHP derivatives (**1–15**, Scheme 1) were synthesized to investigate their conversion to the corresponding pyridines. The combination of UHP/MA, which is readily available and inexpensive serves as an excellent oxidant for a variety of Hantzsch 1,4-dihydropyridines. The results are reported in Table 1. Initially dihydropyridine **8** has been used as a substrate to test the feasibility of UHP/MA used as an oxidant for DHP's. The results are summarized in Table 2. Treatment of **8** with UHP in acetonitrile at ambient temperature or at reflux condition (ratio 1:15) indicated that it was unreactive towards UHP. A better activity of UHP was obtained when combined with MA. Subsequent experiments revealed that at r. t. a ratio of UHP:MA=15:3 was most effective. Acetic anhydride and trifluoroacetic anhydride have also

Table 1. Oxidation of 1,4-dihydropyridines with UHP/MA.

Substrate	R	Product	Time (min)	Yield (%) ^a
1	H	16	30	84
2	CH ₃	17	25	95
3	CH ₃ (CH ₂) ₃ CH ₂	18	25	88
4	(CH ₃) ₂ CH	16	60	78
5	C ₆ H ₅ CH=CH	19	10	82
6	C ₆ H ₅ CHCH ₃	16	40	90
7	C ₆ H ₅ CH ₂ CH ₂	20	45	85
8	C ₆ H ₅	21	25	93
9	CH ₃ C ₆ H ₄	22	25	90
10	2-CH ₃ O-C ₆ H ₄	23	40	92
11	4-CH ₃ O-C ₆ H ₄	24	45	85
12	3-NO ₂ -C ₆ H ₄	25	80	93
13	4-NO ₂ -C ₆ H ₄	26	35	96
14	4-Cl-C ₆ H ₄	27	30	87
15	2-Furyl	28	20	79

^a Isolated yields.

Table 2. Oxidation of 1,4-dihydropyridines in acetonitrile.

Entry	Reagents (mmol)	Time (min)	Completion (%)
1	UHP (15), MA (0), DHP (1)	240	no reaction
2	UHP (15), MA (1), DHP (1)	120	no reaction
3	UHP (15), MA (2), DHP (1)	45	quant.
4	UHP (10), MA (3), DHP (1)	35	quant.
5	UHP (10), MA (2), DHP (1)	45	quant.
6	UHP (15), MA (3), DHP (1)	25	quant.
7	UHP (15), TFAA (3), DHP (1)	120	no reaction
		120 ^a	40
8	UHP (15), Ac ₂ O (3), DHP (1)	120	no reaction
		120 ^a	20

^a Reflux condition.

been tested; unfortunately, oxidation of **8** did not proceed effectively. The effect of different solvents, such as acetonitrile, chloroform, dichloromethane, carbon tetrachloride, acetone and hexane on the oxidation reaction of **8** by UHP/MA at ambient temperature was investigated. In contrast to nonpolar organic solvents, high reaction rate and yield are the features obtained in polar organic solvent. For example, the treatment of **8** with oxidant in acetonitrile afforded pyridine **21** with complete conversion whereas the same reaction in hexane gave starting material.

To establish the generality of this method, 1,4-dihydropyridines bearing various alkyl, aryl and heterocyclic substituents at C-4 were oxidized under

afore-mentioned conditions. As shown in Table 1, 1,4-DHPs bearing a benzyl group or an isopropyl group at 4-position afforded exclusively dealkylated pyridine. This is in agreement with the observation made by others [3, 4, 16, 21] employing different oxidative conditions. Dealkylation of 4-alkyl-dihydropyridines containing normal alkyl substituents, which was observed during oxidation by reported methods, such as with iodobenzene diacetate [18] or *tert*-butylhydroperoxide [12], did not occur under our conditions. 1,4-DHPs bearing alkenyl- or aryl substituents at C-4 furnished the corresponding pyridine derivatives (Table 1).

Conclusion

In summary, we have described a general, simple and practical route for the oxidative aromatization of Hantzsch 1,4-dihydropyridines to the corresponding pyridines in excellent yields using relatively safe and commercially available reagents urea-hydrogen peroxide/maleic anhydride.

Experimental Section

1,4-Dihydropyridines were synthesized by the reported procedures [5, 28]. The oxidation products were characterized by comparison of (¹H-NMR, IR) and their physical data with the authentic samples.

Oxidation of Hantzsch 1,4-dihydropyridines with UHP/MA.

General procedure: A mixture of 1,4-Dihydropyridine (1 mmol), UHP (15 mmol) and MA (3 mmol) in acetonitrile (10 ml) was stirred at room temperature for the time given in Table 1. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was filtrated. The filtrate quenched with aq. Na₂S₂O₈ (10 ml, 0.5 M) and then aq. NaHCO₃ solution and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated under reduced pressure.

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