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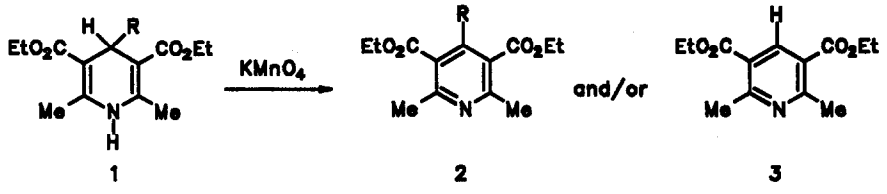
Potassium Permanganate, a Versatile Reagent for the Aromatization of Hantzsch 1,4-Dihydropyridines

Jean-Jacques Vanden Eynde,* Rita D'Orazio, and Yves Van Haverbeke

University of Mons-Hainaut, Organic Chemistry Laboratory, B-7000 Mons (Belgium)

Abstract: A variety of Hantzsch esters have been oxidized with potassium permanganate. The structure of the final products dramatically depends on the nature of the 4-substituent and on the experimental conditions.

Oxidation of Hantzsch esters (1) usually yields the corresponding pyridine derivatives (2) but expulsion of the substituent in the 4-position (to afford 3) has been observed if this substituent is a benzylic group or a secondary alkyl group.[1,2] This reaction of aromatization is well documented.[2-4] However, there is still a need to widen its scope as the metabolism of Hantzsch esters, utilized in the treatment[5-7] of hypertension, proceeds through the oxidation of the 1,4-dihydropyridine system.[8-11] Recently, it was reported [12] that several 4-*n*-alkyl-1,4-dihydropyridines can be dealkylated by treatment with clay-supported manganese dioxide but in the absence of solvent and under microwave irradiation. This unusual result prompted us to describe our findings on the chemical behavior of various Hantzsch esters in the presence of potassium permanganate, all the more since, to our knowledge, there is only one paper on this particular topic.[13]



1 2 3

Fig. Oxidation of Hantzsch 1,4-Dihydropyridines

In order to provide optimized reaction times, we controlled most of our experiments by ^{1}H NMR spectroscopy[14] (Varian EM 360-L).

In this way, we observed that, starting from a 4-*n*-alkyl-1,4-dihydropyridine, the course of the reactions is independent on the length of the 4-*n*-alkyl group (R^4 = C_2H_5, C_4H_9, C_9H_{19}) but it is highly dependent on the experimental conditions. This is illustrated in Table 1 in the case of the 4-propyl derivative.

When the reactions are carried out in one-phase systems, *i.e.* in solvents in which both the heterocycle and the oxidant are soluble (acetic acid, acetone - entries 1 and 2), the (expected[1]) 4-propylpyridine **2** is obtained selectively.

When potassium permanganate is only partially soluble in the solvent or in the medium containing the heterocycle (entries 3 - 12), another competitive process occurs and, beside **2**, the dealkylated pyridine **3** is formed. The ratio [**2**]/[**3**] increases as the reaction temperature decreases (*cfr.* entries 7 and 8-10; entries 11 and 12).

Finally, when the oxidant is insoluble in the reaction medium (entries 13 - 15), the sole dealkylated pyridine **3** is isolated and this even in the presence of catalytic amounts of potassium permanganate (entry 15).

We also noticed that, under given conditions of temperature and solvent(s), yields and/or reaction times can be improved (without significant modification of the ratio [**2**]/[**3**]) by supporting the oxidant on an inorganic solid[15-18] (*cfr.* entries 3 and 5 - 10; entries 13 and 14 - 15) and by irradiating the reaction mixture with ultrasonic waves[19] (*cfr.* entries 8 and 9 - 10).

As dealkylative aromatization of a 4-*n*-alkyl-1,4-dihydropyridine is an unexpected[1,2] result, it was of interest to elucidate its mechanism. For that purpose, we oxidized the 4-nonyl derivative in refluxing benzene in the presence of a catalytic amount of potassium permanganate supported on montmorillonite KSF (*cfr.* entry 15). The reaction medium was analyzed by GC-MS and ^{1}H NMR spectroscopy. In this way, we detected, beside **3**, alkanes (C_9H_{20}, $C_{18}H_{38}$, and higher) and alkylbenzenes (C_6H_5-C_9H_{19} and higher). To interprete this observation, we suggest that the *n*-dealkylative process is initiated by a homolytic breakdown of the N-H bond (with transfer of one electron to the oxidizing species and elimination of a proton) to yield a 1,4-dihydropyridine radical.[20-25] This should be followed by the homolytic cleavage of the alkyl-heterocycle bond to yield the pyridine product **3** and an alkyl radical. The latter can undergo different coupling reactions or it can also reinitiate the radical process, thus justifiyng the fact that, under particular conditions, catalytic amounts of potassium permanganate are sufficient to observe the dealkylative aromatization.

Table 1. Aromatization of Diethyl 1,4-Dihydro-2,6-dimethyl-4-propyl-3,5-pyridinedicarboxylate by Potassium Permanganate under Various Experimental Conditions[a]

Entry	Solvent	Support or catalyst	T°	t	Final product(s)	Yield[b] (%)
1	CH_3CO_2H	-	80 °C	6h	2	45[c,d]
2	$(CH_3)_2CO$	-	20 °C	1h	2	40[c,d]
3	C_6H_6/H_2O (2/1)	-	reflux	1h	2 + 3	15 + 25[d]
4		$(BzNEt_3)^{(+)}Cl^{(-)}$	reflux	1h	2 + 3	20 + 30[d]
5		Al_2O_3	reflux	6h	2 + 3	30 + 50
6		Montmorillonite K10	reflux	6h	2 + 3	30 + 50
7		Montmorillonite KSF	reflux	1h	2 + 3	40 + 60
8		Montmorillonite KSF	20 °C	1h	2 + 3	60 + 40
9[e]		Montmorillonite KSF	20 °C	150s	2 + 3	60 + 40
10[e]	CH_2Cl_2/H_2O (2/1)	Montmorillonite KSF	20 °C	150s	2 + 3	60 + 40
11	C_6H_6	15-crown-5	reflux	6h	2 + 3	30 + 70
12		15-crown-5	20 °C	6h	2 + 3	80 + 20
13		-	reflux	6h	3	35
14		Montmorillonite KSF	reflux	6h	3	>95
15[f]		Montmorillonite KSF	reflux	12h	3	>95

[a]: 60 ml of solvent(s) for 10 mmol of dihydropyridine and 10 mmol (1.58 g) of $KMnO_4$, the latter is eventually mixed with 3.42 g of the inorganic support before starting the reaction.

[b]: determined by ^1H NMR, except otherwise specified.

[c]: isolated.

[d]: longer reaction times do not improve the yield probably because[26] of an autocatalytic process of decomposition .

[e]: under ultrasonic irradiation (VCR 375, Sonics and Material Inc., Danbury, CT, U.S.A.).

[f]: 1 mmol (0.16 g) of $KMnO_4$ and 4.84 g of clay were used in that experiment.

To extend our study, we oxidized 4-aryl-1,4-dihydropyridines under the experimental conditions described in Table 1 and we observed that all reactions yielded the corresponding 4-arylpyridines (**2**). On the other hand, reactions involving the 4-benzyl and the 4-isopropyl Hantzsch esters yielded the dealkylated pyridine **3**. From the 4-benzyl dihydropyridine, formation of benzyl alcohol and benzaldehyde (beside **3**) was ascertained on the basis of ^{1}H NMR spectra recorded on crude samples of the reaction mixtures. From the 4-isopropyl derivative, acetone was identified, in the same way, as (one of) the by-product(s).

Thus, our results reveal that aromatization of a 4-*n*-alkyl-1,4-dihydropyridine in the prsence of potassium permanganate can occur following two competitive mechanisms depending on the experimental conditions: the expected ionic pathway[1,2] yields **2** whereas a radical pathway yields **3**. For the other derivatives (R^4 = benzyl, secondary alkyl, aryl), the competition is not apparent. This can be rationalized as follows: the ionic pathway proceeds through expulsion of the 4-substituent only when it is a benzylic or a secondary alkyl group (because of the stability of the correspondig carbonium ions[1]); the radical pathway proceeds through expulsion of the 4-substituent except when it is an aryl group (because, in this case, expulsion of the hydrogen radical is more favourable). The importance of each mechanism is closely related to the solubility of the oxidant in the solvant containing the heterocycle: the radical mechanism is favoured as the solubility of potassium permanganate decreases in the reaction medium (*cfr.* Table 1).

In conclusion, from a practical point of view, aromatization of Hantzsch 1,4-dihydropyridines by potassium permanganate is a valuable synthetic method starting from 4-aryl and 4-unsubstituted derivatives essentially. Indeed, under suitable conditions (triphasic system under ultrasonic irradiation), reactions are extremely fast and yields are excellent as reported in Table 2 (dichloromethane was preferred as the solvent for reasons of solubility). In the other cases, the reagent is less useful since it often yields mixtures of products or the sole pyridine **3**. However, as catalytic amounts of potassium permanganate are sufficient to induce an aromatization process, the method could be employed to synthesize pyridines bearing groups that are sensitive to oxidants.

From a mechanistic point of view, we should like to emphasize that there is a parallelism between the chemical behavior of 1,4-dihydropyridines in the presence of potassium permanganate and their metabolism in the presence of cytochrome P-450. Indeed, the latter is known to proceed in one-electron steps and gives rise also to radical dealkylations of the 4-*n*-alkyl derivatives.[8-11]

Table 2. Optimized Results for the Aromatization of Hantzsch 1,4-Dihydropyridines by Potassium Permanganate Supported on Montmorillonite KSF

Starting product R	Method A[a] Reaction time[c] (s)	Method A[a] Final product(s)	Method B[b] Reaction time[c] (h)	Method B[b] Final product
H	150	2 = 3	3	2 = 3
C_2H_5	150	2 + 3[d]	5	3
C_3H_7	150	2 + 3[d]	5	3
C_4H_9	150	2 + 3[d]	5	3
C_9H_{19}	150	2 + 3[d]	4	3
C_6H_5-CH_2	150	3	3	3
$(CH_3)_2$-CH	150	3	3	3
C_6H_5	300	2	5	2
4-(NO_2)-C_6H_4	300	2	6	2
4-(OCH_3)-C_6H_4	300	2	5	2
4-Cl-C_6H_4	300	2	5	2

[a]: A mixture of the dihydropyridine (10 mmol) and potassium permanganate (1.58 g; 10 mmol) on montmorillonite KSF (3.42 g) in dichloromethane (40 ml) and water (20 ml) was irradiated, at room temperature, by ultrasonic waves (VCR 350, Sonics and Materials Inc., Danbury, CT, U.S.A.). The suspension was filtered. The organic layer was separated, dried, and concentrated under reduced pressure to yield the crude pyridine derivative (>80 %).

[b]: A mixture of the dihydropyridine (10 mmol) and potassium permanganate (1.58 g; 10 mmol) on montmorillonite KSF (3.42 g) in benzene (60 ml) was heated under reflux. The suspension was filtered. The filtrate was concentrated under reduced pressure to yield the crude pyridine derivative (>80 %).

[c]: required to observe, by ^{1}H NMR, the complete conversion of the 1,4-dihydropyridine.

[d]: determined by ^{1}H NMR; the products were not isolated; [2]/[3] ≈ 1.5.

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