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Old Reagents, New Results: Aromatization of Hantzsch 1,4-Dihydropyridines with Manganese Dioxide and 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.

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Abstract: Hantzsch 1,4-dihydropyridines are readily oxidized by manganese dioxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dichloromethane at room temperature. With manganese dioxide loss of the 4-substituent, in addition to aromatization, occurs when it is a secondary alkyl or a benzylic group and sonication significantly reduces the reaction times. In contrast, loss of the 4-substituent is never observed when DDQ is the oxidative species.

Aromatization of Hantzsch 1,4-dihydropyridines (1,4-DHP) has attracted considerable attention in recent years, essentially since the discovery that the metabolism of those drugs involves an oxidation step that is catalyzed, in the liver, by cytochrome P-450.[1-4] Consequently, that reaction has been the subject of a large number of studies and a plethora[5-9] of reagents, including clay-supported[10-16] oxidants, has been utilized to provide high-yield methods for the preparation of the corresponding pyridines.

As part of our research[11,14,16] in this field, we examined the possibility of using manganese dioxide and quinones to effect the aromatization of Hantzsch 1,4-DHP.

The reactions were performed in dichloromethane and were monitored by ^{1}H NMR spectroscopy (variation of the intensity of the peaks due to the protons of the 2- and 6-methyl groups; those peaks appear around δ = 2.2, 2.6, and 3.0 ppm for a Hantzsch 1,4-DHP, a 4-substituted Hantzsch pyridine, and the 4-unsubstituted Hantzsch pyridine **13**, respectively[14]).

Aromatization with Manganese Dioxide

Manganese dioxide, well known for its oxidizing[17-19] properties, was often underestimated by organic chemists but it takes actually advantage of a renewal of popularity.[12,13,20-22] In particular, it has recently been employed to aromatize Hantzsch 1,4-DHP under microwave irradiation.[12,13]

We wish to report that the reaction can be performed in dichloromethane at room temperature using a fivefold to tenfold excess (w/w) of manganese dioxide (Oxidation Grade; M.M.M. Sedema s.a.).

Thus, we observed (^{1}H NMR) that conversion of the dihydropyridine derivatives into the corresponding pyridines occurs when the 4-substitutent is a linear alkyl group, an aryl group, or an heteroaryl group. Loss of

the 4-substituent, in addition of aromatization, was noticed when it is a secondary alkyl group or a benzylic group. This is an expected [5,6] behavior during the oxidation of Hantzsch 1,4-DHP that can be avoided when the reactions are carried out with sulfur [23] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (*vide infra*) only.

Yields exceed 80 % within optimized reaction times varying from 5 to 200 minutes. The 1,4-dihydropyridines bearing a nitrophenyl group (**9** and **10**) or a thienyl group (**11**) in the 4-position are the most resistant derivatives, a result that parallels our previous findings [14] when pyridinium chlorochromate was used as the oxidant.

Improvement of the intimate mixing between the reactants can be achieved by irradiation of the heterogeneous media with sonic waves. [24,25] This enables to reduce the length of all the experiments to 5 minutes but this does not modify the course of the oxidations: we isolated the same final products as in the method using a magnetic stirrer and in comparable yields. Sonication caused the formation of extremely small particules of inorganic materials. They could be readily separated by a filtration through a cake of alumina, a technique that afforded the pyridine derivatives in a very pure form and in good to excellent yields as shown in Table 1.

Aromatization with Quinones

Quinones were rarely [26-28] reacted with 1,4-DHP and the reported results are poorly encouraging, especially when the heterocycle bears a substituent in the 4-position.

Preliminary experiments involving the 4-propyl- and the 4-phenyl-1,4-dihydropyridines (**3** and **6**) indicated that 1,4-benzoquinone is effectively a bad reagent for the aromatization of those heterocycles: no reaction was detected at room temperature (24 hours) and 40% only of the dihydropyridines were converted after 8 hours in refluxing dichloromethane. Better results were obtained with 2,3,5,6-tetrachloro-1,4-benzoquinone: the aromatization was complete within 12 hours in refluxing dichloromethane. But the reactions remained slow at room temperature: yields did not exceed 30 % after 8 hours.

On the other hand, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) appeared to be an excellent reagent to aromatize Hantzsch 1,4-DHP. With that highly reactive [29] quinone, we could oxidize 1,4-DHP bearing an alkyl group, an aryl group, or an heteroaryl group in the 4-position under very mild conditions (dichloromethane at r.t.), within short reaction times (60 minutes), and with excellent yields (70-90 % after purification by column chromatography). Among our results, let us emphasize the particular behavior of the dihydropyridines **4** (R=iso-propyl) and **5** (R=benzyl) as aromatization with DDQ is not accompained by the "classical" dealkylative process.

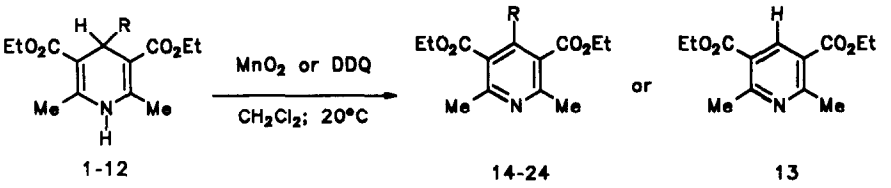
Conclusion

Our results demonstrate that aromatization of Hantzsch 1,4-dihydropyridines with manganese dioxide (optionally assisted by sonication) constitutes a simple, general, and rapid method that is characterized by high yields and by its low cost.

By comparison, oxidation of the same series of heterocycles by pyridinium chlorochromate supported on an inorganic solid [14] requires longer reaction times and montmorillonite K10 clay-supported cupric nitrate ("Claycop" [10,11,30]) is unable [10,11] to aromatize the Hantzsch 1,4-dihydropyridine substituted by an alkyl group in position 4, even under sonochemical conditions. [11]

The method involving DDQ is rapid and general too. It is very attractive starting from Hantzsch 1,4-DHP substituted in 4-position by a secondary alkyl group or a benzylic group, especially. In contrast to most procedures of oxidation of 1,4-DHP, use of DDQ enables to prevent the loss of the 4-substituent.

Table 1. Oxidation of Hantzsch 1,4-Dihydropyridines in the Presence of Manganese Dioxide and DDQ



1-12 14-24 13

R	Reaction	oxidation with MnO_2			oxidation with DDQ
		Ratio DHP/MnO_2 (w/w)	Magnetic stirring t (Yield)	Ultrasound [24] t (Yield)	t (Yield)
H	**1** ---> **13**	1/5	5 min (85 %)	5 min (81 %)	60 min (80 %)
C_2H_5	**2** ---> **14**	1/5	60 min (94 %)	5 min (95 %)	60 min (75 %)
C_3H_7	**3** ---> **15**	1/5	5 min (93 %)	5 min (95 %)	60 min (78 %)
$(CH_3)_2CH$	**4** ---> **13**	1/5	30 min (87 %)	5 min (83 %)	
	4 ---> **16**				60 min (84 %)
C_6H_5-CH_2	**5** ---> **13**	1/5	30 min (86 %)	5 min (80 %)	
	5 ---> **17**				60 min (75 %)
C_6H_5	**6** ---> **18**	1/5	30 min (87 %)	5 min (91 %)	60 min (90 %)
4-Cl-C_6H_4	**7** ---> **19**	1/5	5 min (90 %)	5 min (92 %)	60 min (85 %)
4-(OCH_3)-C_6H_4	**8** ---> **20**	1/5	5 min (92 %)	5 min (90 %)	60 min (70 %)
4-(NO_2)-C_6H_4	**9** ---> **21**	1/5	200 min (81 %)		
		1/10	5 min (85 %)	5 min (84 %)	60 min (73 %)
3-(NO_2)-C_6H_4	**10** ---> **22**	1/10	5 min (87 %)	5 min (85 %)	60 min (87 %)
2-Thienyl	**11** ---> **23**	1/5	60 min (92 %)		
		1/7	10 min (91 %)	5 min (91 %)	60 min (83 %)
2-Furyl	**12** ---> **24**	1/5	5 min (82 %)	5 min (86 %)	60 min (78 %)

EXPERIMENTAL

All compounds have been described in the literature and were identified on the basis of their spectral data and, eventually, their melting points.

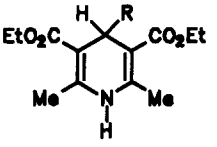
Aromatization with Manganese Dioxide

A mixture of the Hantzsch 1,4-DHP (5 mmol) and manganes dioxide (see Table 1) in dichloromethane (25 mL) at room temperature was stirred or sonicated [24] for an appropriate period (see Table 1). The mixture was filtered through a cake of alumina (20 g) and the inorganic solids were washed with dichloromethane (3 X 50 mL). Concentration of the solvent under reduced pressure yielded the pyridine in good purity.

Aromatization with Quinones

A suspension of the Hantzsch 1,4-DHP (10 mmmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.27 g; 10 mmol) in dichloromethane (20 mL) was stirred at room temperature for 60 min. The precipitate was filtered, washed with dichloromethane (2 X 20 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (alumina-CH_2Cl_2).

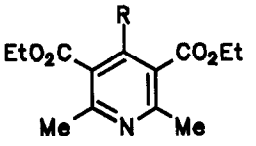
Table 2. Selected Data for the Diethyl 1,4-Dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates **1-12**



N°	R	NMR ($CDCl_3$ - δ: ppm) δ R	δ C⁴-**H**	M.p. (°C)
1 [31]	H	3.2	3.2	183-185
2 [32]	C_2H_5-	1.2-0.8 (5H)[a]	4.1[a]	111-113
3 [33]	C_3H_7-	1.2-0.8 (7H)[a]	4.1[a]	125-127
4 [32]	$(CH_3)_2$-CH-	1.3 (1H)[a]; 0.8 (d-6H)	4.1[a]	97-99
5 [34]	C_6H_5-CH_2-	7.4-6.9 (c-5H); 2.6 (d-2H)	4.1[a]	114-116
6 [35]	C_6H_5-	7.3-7.0 (c-5H)	5.0 (s)	158-160
7 [36]	4-Cl-C_6H_4-	7.2 (s-4H)	4.9 (s)	144-146
8 [37]	4-(OCH_3)-C_6H_4-	7.3 (d-2H); 6.7 (d-2H); 3.7 (s-3H)	5.0 (s)	158-160
9 [38]	4-(NO_2)-C_6H_4-	8.2 (d-2H); 7.5 (d-2H)	5.1 (s)	128-130
10 [36]	3-(NO_2)-C_6H_4-	8.0-7.2 (c-4H)	5.0 (s)	162-164
11 [37]	2-Thienyl-	7.1-6.4 (c-3H)	5.1 (s)	171-173
12 [35]	2-Furyl-	7.1 (s); 6.1 (c-1H); 5.85 (c-1H)	5.1 (s)	160-161

δ CH_3 (pos 2 and 6): 2.2 (s-6H); CO_2-C_2H_5: 4.0(q-4H); 1.1 (t-6H); **NH**: between 5.2 and 8.9 ppm.
a: overlapping with other signals

Table 3. Selected Data for the Diethyl 2,6-dimethyl-3,5-pyridinedicarboxylates **13-24**



N°	R	NMR ($CDCl_3$ - δ: ppm) δ R	M.p. (°C)
13 [32]	H-	9.4 (s-1H)	69-70
14 [32]	C_2H_5-	2.6 (2H)[a]; 1.2 (3H)[a]	oil
15 [33]	C_3H_7-	2.6 (2H)[a]; 1.6-0.8 (5H)[a]	oil
16 [23]	$(CH_3)_2$-CH	2.8 (m-1H); 1.2 (d-6H)[a]	oil
17 [23]	C_6H_5-CH_2	7.2 (s-5H); 4.3 (s-1H)[a]	oil
18 [39]	C_6H_5-	7.1 (s-5H)	62-63
19 [40]	4-Cl-C_6H_4-	7.1 (c-4H)	65-67
20 [37]	4-(OCH_3)-C_6H_4-	7.2 (d-2H); 6.9 (d-2H); 3.3 (s-3H)	51-52
21 [41]	4-(NO_2)-C_6H_4-	8.2 (d-2H); 7.4 (d-2H)	114-116
22 [41]	3-(NO_2)-C_6H_4-	8.2 (c-2H); 7.5 (c-2H)	61-63
23 [42]	2-Thienyl-	7.3-6.7 (c-3H)	76-79
24 [43]	2-Furyl-	7.5 (c-1H); 6.6-6.3 (c-2H)	38-41

δ CH_3 (pos 2 and 6): 2.6 (s-6H), but 3.0 (s-6H) for **13**; $CO_2C_2H_5$: 4.3 (q-4H); 1.2 (t-6H) ppm.
a: overlapping with other signals

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