267. Aromatization of 1,4-Dihydropyridines by Clay-Supported Metal Nitrates[1])

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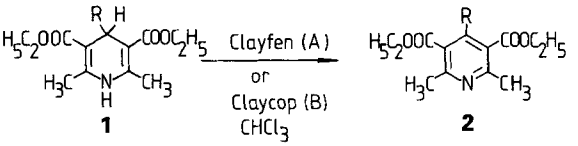
Summary

1,4-Dihydropyridines can be aromatized under very mild conditions by *K 10* clay-supported ferric and cupric nitrates.

1. Introduction. – Diethyl 4-substituted-2,6-dimethyl-3,5-pyridinedicarboxylates **2** are useful as antihypoxics and antiischemics [2] [3], and some representatives have acaricidal, insecticidal, bactericidal and herbicidal activity [4]. On the other hand these compounds are starting materials for the synthesis of antibacterial 1,6-naphthyridines [5] and 1,2-benzisoazalenes [6].

Scheme



Several methods are reported for aromatization of dihydropyridines **1**, *e.g.* using HNO_3 at 60°C [6] [7], S at 200°C [6] [7], $NaNO_2$ in acidic media [8] [9], chromic anhydride in AcOH [6], chloranil in benzene at reflux temperature [10], $K_2Cr_2O_7$ in H_2SO_4 [10], 5% Pd/C catalyst in a mixture of toluene and AcOH at reflux temperature [11], and $KMnO_4$ in AcOH [11].

Studying the utilization of clay-supported $Fe(NO_3)_3$ ('clayfen'), this reagent was proven to be efficient for oxidation of alcohols to aldehydes or ketones [12–14], nitration of phenols [14] and estrone [15]. Thioacetals can be cleaved into aldehydes and ketones by 'clayfen' and clay-supported $Cu(NO_3)_2$ ('claycop') [16].

A study on the mechanism of the oxidation process has revealed that nitrosonium cation (NO^+) releasing reagents are efficient oxidants for 1,4-dihydropyridines [9]. 'Clayfen' and 'claycop' can serve as a source of nitrosonium ion [13–16].

[1]) 'Clay-supported Reagent'; previous publication in this series: [1].

2. Experimental. – 1,4-Dihydropyridines **1** can be aromatized smoothly by 'clayfen' or 'claycop' at r.t. 'Clayfen' was prepared as previously described [12] from a mixture of 45 g of $Fe(NO_3)_3 \cdot 9H_2O$, 60 g of *K 10* bentonite clay (*Süd-Chemie*, Munich) and 750 ml of acetone. 'Claycop' [16] was prepared from a mixture of 40 g of $Cu(NO_3)_2 \cdot 3H_2O$, 60 g of *K 10* bentonite clay and 750 ml of acetone. In both cases, the solvent was evaporated under reduced pressure at 50° in a rotary vacuum evaporator.

'Clayfen' (5 g, *i.e.* 0.005 mol of $Fe(NO_3)_3$) or 'claycop' (3 g, *i.e.* 0.005 mol of $Cu(NO_3)_2$) was added to a soln. of diethyl 4-(un)-substituted-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate **1** (0.005 mol) in $CHCl_3$ (50 ml). The resulting suspension was stirred at r.t. for several hours (see the *Table*). The clay was then filtered off, washed with $CHCl_3$ (3 × 15 ml). The combined org. layer was washed with 50 ml of 5% aq. NH_3, then with H_2O (3 × 50 ml). After solvent evaporation diethyl 4-(un)-substituted-2,6-dimethyl-3,5-pyridinedicarboxylates **2** were obtained and identified by comparison (m.p., mixed m.p., TLC on silica gel, UV, IR and ^{1}H-NMR spectra) with authentic samples.

'Clayfen' and 'claycop' are efficient reagents for aromatization of 1,4-dihydropyridines and show advantages over the existing methods. These cheap and non-corrosive reagents can be used under mild experimental conditions. The yields obtained are comparable to those of reported procedures. Generally 'claycop' gives higher yield than 'clayfen', but it requires a little longer reaction period.

Table. *Aromatization of 1,4-Dihydropyridines*

Dihydro-pyridines **1**	R	Reaction time [h]	Conditions Methods[c])	Aromatic compds. **2**		Lit. m.p. [°C] and ref.
				Yield [%]	M.p. [°C]	
a [17]	H	1	A	27.8	72–73	70–2 [17]
		11	B	39.7	71–73	17 [7]
b [9]	C_6H_5	1	A	91.4	63–64	63–64.5 [9]
		1.5	B	91.5	61–62	
c [18]	4-ClC_6H_4	1	A	71.8	67–68	68 [18]
		1.5	B	85.6	66–68	
d [19]	3,4-$(MeO)_2C_6H_3$	1	A	61.9	100–102	101–102 [20]
		1.5	B	88.7	100–101	
e [21]	2-$NO_2C_6H_4$	1	A	59.1	75–76	75 [21]
		1.5	B	92.5	75–76	
f [21]	3-$NO_2C_6H_4$	1	A	87.4	oil[a])	63 [23]
		6	B	92.8	oil[a])	
g [21]	4-$NO_2C_6H_4$	1	A	86.0	112–113	115 [23]
		7	B	78.0	111–113	
h [24]	3-pyridyl	6	A	85.4	84–85	86–87 [24]
		12.5	B	91.5	85–86	
i [25]	5-nitro-2-furil	6	A	74.6	76–77[b])	–
		8	B	80.1	75–76	

[a]) This compound was prepared as the nitrate salt, m.p. 124–125° ([23]: 129–130°).

[b]) UV (EtOH; λ_{max} (log ε)): 317 (4.03), 218 (4.12). IR (KBr): 1735, 1570, 1380. ^{1}H-NMR ($CDCl_3$): 1.29 (*t*, *J* = 7, 6H); 2.63 (*s*, 6H); 4.35 (*q*, *J* = 7, 4H); 6.76 (*d*, *J* = 4, 1H); 7.32 (*d*, *J* = 4, 1H). Anal. calc.: C 56.35, H 5.01, N 7.73; found: C 56.28, H 4.90, N 7.64.

[c]) A = 'clayfen'; B = 'claycop'.

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