

## 267. Aromatization of 1,4-Dihydropyridines by Clay-Supported Metal Nitrates<sup>1)</sup>

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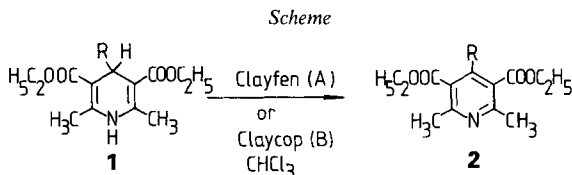
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### Summary

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].



Several methods are reported for aromatization of dihydropyridines **1**, e.g. using  $\text{HNO}_3$  at  $60^\circ\text{C}$  [6] [7],  $\text{S}$  at  $200^\circ\text{C}$  [6] [7],  $\text{NaNO}_2$  in acidic media [8] [9], chromic anhydride in  $\text{AcOH}$  [6], chloranil in benzene at reflux temperature [10],  $\text{K}_2\text{Cr}_2\text{O}_7$  in  $\text{H}_2\text{SO}_4$  [10], 5%  $\text{Pd/C}$  catalyst in a mixture of toluene and  $\text{AcOH}$  at reflux temperature [11], and  $\text{KMnO}_4$  in  $\text{AcOH}$  [11].

Studying the utilization of clay-supported  $\text{Fe}(\text{NO}_3)_3$  ('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  $\text{Cu}(\text{NO}_3)_2$  ('claycop') [16].

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

<sup>1)</sup> '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  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ , 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  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ , 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  $\text{Fe}(\text{NO}_3)_3$ ) or 'claycop' (3 g, *i.e.* 0.005 mol of  $\text{Cu}(\text{NO}_3)_2$ ) was added to a soln. of diethyl 4-(un)-substituted-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate **1** (0.005 mol) in  $\text{CHCl}_3$  (50 ml). The resulting suspension was stirred at r.t. for several hours (see the *Table*). The clay was then filtered off, washed with  $\text{CHCl}_3$  (3 × 15 ml). The combined org. layer was washed with 50 ml of 5% aq.  $\text{NH}_3$ , then with  $\text{H}_2\text{O}$  (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  $^1\text{H-NMR}$  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 <b>1</b>	R	Reaction time [h]	Conditions Methods <sup>c)</sup>	Aromatic compds. <b>2</b>		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]	$\text{C}_6\text{H}_5$	1	A	91.4	63–64	63–64.5 [9]
		1.5	B	91.5	61–62	
c [18]	4- $\text{ClC}_6\text{H}_4$	1	A	71.8	67–68	68 [18]
		1.5	B	85.6	66–68	
d [19]	3,4-(MeO) $_2\text{C}_6\text{H}_3$	1	A	61.9	100–102	101–102 [20]
		1.5	B	88.7	100–101	
e [21]	2- $\text{NO}_2\text{C}_6\text{H}_4$	1	A	59.1	75–76	75 [21]
		1.5	B	92.5	75–76	
f [21]	3- $\text{NO}_2\text{C}_6\text{H}_4$	1	A	87.4	oil <sup>a)</sup>	63 [23]
		6	B	92.8	oil <sup>a)</sup>	
g [21]	4- $\text{NO}_2\text{C}_6\text{H}_4$	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 <sup>b)</sup>	–
		8	B	80.1	75–76	

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

<sup>b)</sup> UV (EtOH;  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 317 (4.03), 218 (4.12). IR (KBr): 1735, 1570, 1380.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 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.

<sup>c)</sup> A = 'clayfen'; B = 'claycop'.

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## REFERENCES

- [1] *P. Laszlo & E. Polla*, *Tetrahedron Lett.* 25, 4651 (1984).
- [2] *E. Wehinger, H. Meyer & U. Benz*, Ger. Offen DE. 3.209.276, Chem. Abstr. 100, 22580 (1984).
- [3] *E. Wehinger, H. Meyer & U. Benz*, Ger. Offen DE. 3.209.274, Chem. Abstr. 100, 51454 (1984).
- [4] *Ciba Ltd.*, Neth. Appl. 6.414.307; Chem. Abstr. 64, 714 (1966).
- [5] *M. Balogh, I. Hermecz, G. Kulcsár, Z. Mészáros, S. Virág, T. Szutz & G. Sebestyén*, Belg. Patent 889, 340; Chem. Abstr. 96, 85541 (1982).
- [6] *W. Treibs & J. Beger*, Ann. 652, 192 (1962).
- [7] *E. E. Ayling*, J. Chem. Soc. 1938, 1014.
- [8] *K. Goerlitzer & D. Buss*, Arch. Pharm. (Weinheim) 314, 949 (1981).
- [9] *B. Loev & K. M. Snader*, J. Org. Chem. 30, 1914 (1965).
- [10] *J. A. Berson & E. Brown*, J. Am. Chem. Soc. 77, 444 (1955).
- [11] *A. Kamal, M. Ahmad, N. Mohd & A. M. Hamid*, Bull. Chem. Soc. Jpn. 37, 610 (1964).
- [12] *A. Cornélis & P. Laszlo*, *Synthesis* 1980, 849.
- [13] *A. Cornélis, P. Y. Herzé & P. Laszlo*, *Tetrahedron Lett.* 23, 5035 (1982).
- [14] *A. Cornélis, P. Laszlo & P. Penmetreau*, *Clay Minerals* 18, 437 (1983).
- [15] *A. Cornélis, P. Laszlo & P. Penmetreau*, J. Org. Chem. 48, 4771 (1983).
- [16] *M. Balogh, A. Cornélis & P. Laszlo*, *Tetrahedron Lett.* 25, 3313 (1984).
- [17] *S. Checchi*, *Gazz. Chim. Ital.* 89, 2151 (1959).
- [18] *L. E. Hinkel & W. R. Madel*, J. Chem. Soc. 1929, 750.
- [19] *L. E. Hinkel, E. E. Ayling & W. H. Morgan*, J. Chem. Soc. 1935, 816.
- [20] *H. J. Kahn, V. Petrow, E. L. Rewald & B. Sturgeon*, J. Chem. Soc. 1949, 2128.
- [21] *L. E. Hinkel, E. E. Ayling & W. H. Morgan*, J. Chem. Soc. 1931, 1835.
- [22] *R. Lepetit*, Ber. 20, 1340 (1887).
- [23] *A. H. Cook, J. M. Heilbron & L. Steger*, J. Chem. Soc. 1943, 413.
- [24] *R. H. Wiley & J. S. Ridgway*, J. Org. Chem. 26, 595 (1961).
- [25] *V. Kastron, G. Duburs, R. Vitolins & A. Kimenis*, *Khim. Farm. Zh.* 13, 57 (1979); Chem. Abstr. 91, 91468 (1979).