A COMPARATIVE STUDY OF THE OXIDATION OF HANTZSCH ESTERS INDUCED BY TAFF-METALLIC NITRATES.

R. Miranda*(1), J. M. Aceves(1), C. Gutierrez(1), R. Martínez(1) F. Delgado(2) A. Cabrera(3) and M. Salmón(3).
(1) Facultad de Estudios Superiores Cuautitián, Universidad Nacional Autónoma de México, Campo 1, Av. 1o. de Mayo s/n, Cuautitlán Izcalli, Estado de México, CP 54740.
(2) Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Departamento de Quimica Orgánica, Prolongación Carpio y Plan de Ayala, Casco de Santo Tomás, México, D. F., CP 11340.
(3) Instituto de Quimica, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, México, D.F., CP 04510.

Abstract: Several 4-(substituted) -Hantzsch esters upon oxidation with bentonite supported metallic nitrates (Ag^{+}, Fe^{+3}, Cu^{+2}, Co^{+2}) under mild conditions, afforded the corresponding pyridines. As result of a comparative study, a synergism between the nitrate and the metallic ions with the TAFF support is suggested.

INTRODUCTION.

Several 4-(substituted)-Hantzsch esters have been studied in great detail as cardiovascular drugs (1-3), also several Hantzsch pyridines are useful as antihypoxies (4,5), others exhibit acricidal, insecticidal, bactericidal and herbicidal activities (6).

As it is well known, the Hantzsch synthesis is a widely used general procedure to obtain considerable structural modifications of pyridine; in this method the intermediate (1,4-dihydropyridine) is commonly aromatized by a set of different ways of oxidation. Several methods are available for the oxidative aromatization (7, 8); however most of them employ rather severe conditions.

---

*Author for correspondence.

In addition, there is an increased interest in the use of supported reagents, particularly with montmorillonites ***K10*** and ***KSF*** (8).

As a part of our research program we are interested in the employment of TAFF, a Mexican bentonite(9), which has been successfully applied by our group either as a support or as a catalyst (10). Here we report the results of several experiments performed with four metallic nitrates (Fe^{3+}, Co^{2+}, Cu^{2+}, Ag^{1+}) adsorbed on TAFF, using anhydrous methylene chloride as the solvent in order to promote the oxidation of the target Hantzsch esters.

EXPERIMENTAL

All reaction products were characterized by ^{1}H NMR, EIMS and IR spectral data; the melting points reported are uncorrected; the TAFF-supported metallic nitrates were prepared after Laszlo's procedure (8); the corresponding substrates were obtained by previously reported methods (11).

Typical example: 100 mg of 4-(2-thienyl)-3,4-diethoxycarbonyl- 2,5-dimethyl- 1,4-dihydropyridine and 3 g of $Co(NO_3)_2$/ bentonite in 50 ml of CH_2Cl_2 were gently refluxed for 3 h. The reaction was monitored by *tlc* (*n*-Hexane/ EtOAc 1:1), filtered over celite and washed with water (3x20 ml) and dried over Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography and crystallized from EtOH. Yield 50 % of pure compound was obtained (Hantzsch Pyridine). Yellow crystals; mp 63-64 °C; IR (KBr) ν cm^{-1}: 1730, 1570, 1580; PMR($CDCl_3$/TMS) δ ppm: 1.1 (t, 6H), 2.6 (s, 6H), 4.15(q,4H), 7.05 (m, 2H, Hα and Hγ-thienyl), 7.4 (mc, 1H, Hβ-thienyl); EIMS (70 eV) m/z (% ra): 335 (45) $M^{+\cdot}$, 306 (45) $[M-29]^+$, 290 (15) $[M-45]^+$, 262 (100) $[M-73]^+$, 252 (52), 192 (56).

RESULTS

Table 1. Oxidation of Hantzsch esters induced by TAFF-supported nitrates.

	$AgNO_3$		$Cu(NO_3)_2$		$Fe(NO_3)_3$		$Co(NO_3)_2$		Substituent	mp
Exp.	t(h)	%	t(h)	%	t(h)	%	t(h)	%	R	(°C)
1	0.25	90	2.5	71	2.5	65	6.0	40	H	79 80
2	1.50	70	3.0	60	3.0	60	6.0	32	Me	oil
3	1.50	72	3.0	63	3.5	65	6.0	38	Et	oil
4	0.5	60	1.75	50	1.3	70	3.0	50	*n*-Bu	oil
5	0.5	86	0.5	85	0.5	80	3.0	50	2-Thienyl	45 43
6	0.5	65	1.0	50	1.0	65	3.5	47	C_6H_5	33 35
7	0.25	--a--	0.5	--a--	0.5	--a--	5.0	---	*p*-OHC_6H_4	oil
8	0.25	67	0.75	80	0.5	70	3.0	36	Cinnamyl	oil

a) A mixture of the expected product and a quinoid derivative due to the *p*-hydroxyphenyl substituent is obtained. All yields reported are of pure isolated product.

DISCUSSION

The results of several experiments are summarized in Table 1, the corresponding Hantzsch pyridines are obtained in good yields. In general pure compounds were adquired, the work up procedure is very simple and the bentonite is accessible and inexpensive. It is also worth mentioning that all supported reagents showed the same reactivity without decomposition even after several months of storage.

In addition, the reaction using silver nitrate supported on bentonite, in general gave the better yields in shorter times, in comparison to the cobalt nitrate reagent which gave the poorer yields in longer times. There is a possible correlations with the electropositive potential used in electrochemistry and the effectiveness of these metallic elements in the present work. However, additional research is necessary in order to confirm this theory. Laszlo and coworkers (8), suggest that the nitrates ions are responsible of this kind of reaction, but our opinion is that the yield is also related to the type of metallic ion used on the bentonite support as can be observed in Table 1.

AKNOWLEDGEMENTS: R. Miranda to **DGAPA-UNAM DO104593** and F. Delgado to *CONACyT* **1555 P-E** for financial support

REFERENCES.

(1) S. M. Jain, K. Ravi, K. L. Dhar, S. Singh and G. B. Singh, Indian J. Chem., **29 B** 277 (1990).

(2) M. Iwahami, T. Shibanuna, M. Fuyimato, R. Kawi and M. Murakani, Chem. Pharm. Bull., 27, 1426 (1979).

(3) C. Kamei, K.. Kurokawa and K. Tasaka, Arzheim-forsch, **35-II**,1377 (1985).

(4) E. Wehinger, H. Meyer and U. Benz, Ger. Offen, de 320976, (1983); Chem. Abst., 100, 22580 (1984).

(5) E. Wehinger, H. Meyer and U. Benz, Ger. Offen, de 320974, (1983); Chem. Abst., **100,** 51454 (1984).

(6) Ciba LTD, Neth. Appl., (1965), 6414307; Chem Abst., **64**, 714 (1966).

(7) W. Treibs and J. Beger, Ann., **652**, 192 (1962).

(8) M. Balogh, I. Hermecz, Z. Meszaros and P. Laszlo, Helv. Chim. Acta, **67,** 2272 (1984), and included references.

(9) Tonsil Actisil FF(TAFF), a commercial Mexican bentonitic clay is available from Tonsil Mexicana S.A. Insurgentes Sur 1971; CP 01020, Mexico City at US 0.95/kg; examined with X-ray flourescence this clay proved to have the following composition (in percent): SiO_2,74.5; Al_2O_3, 9.3; MgO, 0.4; Fe_2O_3, 1.3; CaO, 0.4; K_2O, 0.4; TiO_2, 0.4; H_2O, 9.5 (110 °C). The clay showed a specific surface area of 55.30 m^2/g. Employing X-ray diffraction (powder) an interlayer distance typical of a montmorrillonite 15 Å ($2\theta = 7$) was obtained. When X-ray thermodiffractograms were obtained the laminar structure was shown to be unstable over 150 °C (T= 100, 200,.....800 °C). It is worth mentioning that quartz and cristobalite are also important components.

(10) M. Salmón, N. Zavala, M. Martinez, R. Miranda, R. Cruz, J. Cardenas, R. Gaviño and A. Cabrera, Tetrahedron Lett., **35,** 5727 (1994); R. Sanabria, R. Miranda, V. Lara and F. Delgado, Synth. Commun., **24,** 2805 (1994); F. Delgado, J. Tamariz, G. Zepeda, M. Lara, R. Miranda and J. Garcia, Synth. Commun., **25,** 759 (1995); M. Salmón, N. Zavala, A. Cabrera, J. Cardenas, R. Gaviño, R. Miranda and M. Martínez, J. Mol. Cat., **104** L 127 (1995); A. Cabrera, J. Peón, L. Velasco, M. Salmón, R. Miranda and M. Salmón, J. Mol., Cat. **104** L 5 (1995); G. Penieres, R. Miranda, J. Garcia, J.M. Aceves and F. Delgado, Heterocyclic Commun., (1996) In press.

(11) E Baer and A. L. Tonosi, J. Am. Chem. Soc., **78**, 2857 (1956).

Received on February 10, 1997