

ANODIC OXIDATION OF HANTZSCH ESTERS IN ACETONITRILE

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ABSTRACT: Anodic oxidation of Hantzsch esters using electrochemical conditions, Pt electrode with acetonitrile as the solvent and ammonium tetraethyl fluoroborate as support, were carried out. The yields obtained are excellent in comparison to those previously reported, this new option requires less reaction time and generally no by-products are present.

INTRODUCTION

The Hantzsch esters have emerged as an important class of drugs for the treatment of cardiovascular disease (1). These class of molecules, generally undergo oxidative first pass metabolism in the liver in order to generate the corresponding pyridine; consequently such metabolites are interesting reference standards. Thus, the promotion of easy and high-yield methods for the oxidation of 1,4-dihydropyridines would be of great interest.

In addition, Hantzsch pyridines can be prepared in several ways already reported in the literature (2), in this regard some earlier methods have employed an oxidation with nitrous vapour or nitrogen trioxide among others (3, 4) and more recently by means of metallic nitrates supported on TAF (5). The assumption that oxidation-reduction processes might be easily obtained by electrochemical methods was confirmed by the results obtained using cyclic voltammetry which was employed to determine the voltages required to oxidize the corresponding dihydropyridines on a preparative scale.

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EXPERIMENTAL

1,4-Dihydropyridines were obtained by a previously reported method (*vide supra*), these molecules and the corresponding products were identified by physical and spectral procedures: melting points were obtained on a Fisher-Johns apparatus; ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 MHz and 75 MHz respectively employing the system CDCl_3/TMS ; infrared spectra were carried out on a Perkin-Elmer 283 B spectrophotometer using KBr; the mass spectrometric analysis (EIMS, FABMS and HRMS) were performed in JEOL JMS-SX 102 and JEOL JMS-AX 505 HA mass spectrometers, using positive ion mode technics, on FAB the target was bombarded with 10 Kev Xe atoms using nitrobenzyl alcohol as the matrix; for the electrosynthesis and cyclic voltammetry a Potentiostat/Galvanostat PARC model 173 was employed.

Typical example. A mixture of 100 mg (0.32 mmol) of 4-(2-thienyl)-3,4-diethoxycarbonyl- 2,5-dimethyl- 1,4-dihydropyridine and 2.5 ml. of ammonium tetraethylfluoroborate solution as support electrolyte were used for obtaining the oxidation potentials. The electrosynthesis products were obtained at these potentials. The reaction was monitored by *tlc* (*n*-Hexane/ EtOAc 1:1), filtered over celite and washed with water (3x20 ml) and dried over anh. 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, H_α and H_γ -thienyl), 7.4 (mc, 1H, H_β -thienyl); EIMS (70 eV) m/z (% ra): 335 (45) M^+ , 306 (45) $[\text{M}-29]^+$, 290 (15) $[\text{M}-45]^+$, 262 (100) $[\text{M}-73]^+$, 252 (52), 192 (56),

DISCUSSION

The results of several experiments performed to obtain in first place the oxidation potentials and then the promotion of the anodic oxidation under a preparative scale under a fixed potential, are shown in the Table 1.

Table 1. Anodic oxidation of 1, 4-dihydropyridines.

Experiment	4 Substituents	Eox vs CSE (Volts) ^a	Yield ^b (%)	Time ^c (h.)		mp. (°C)
				Theo.	Exp.	
1	H	1.050	97	3:30	3:45	79-80
2	Me	1.270	95	5:02	5:25	oil
3	<i>n</i> -Bu	1-225	95	4:05	4:20	oil
4	2-Furfuryl	1.300	94	3:40	3:55	oil
5	2-Thienyl	1.410	94	4:20	4:37	43-45
6	Cinnamyl	1.320	89	5:11	5:28	oil
7	α -Nap	1.300	94	3:30	3:50	oil

a) Obtained from cyclic voltammetry; b) Yields are of pure isolated product;

c) Theoretical reaction time calculated from Faraday's law.

The cyclic voltammetry method was performed with each Hantzsch esters in order to determine the corresponding oxidation potentials. The oxidation potentials are referred to the saturated calomel electrode (SCE). The potential scan rate (PSR) was 100 mV/s for all samples; in this sense it is worth to mention that the cyclic voltammograms show only one oxidation peak (pyridine), while the cathodic peak is absent, showing that an irreversible oxidation reaction is present.

Previously, seven dihydropyridines were prepared after the methods reported in the literature; then anodic oxidations on Hantzsch esters under controlled potentials with Pt electrodes using anhydrous acetonitrile as the solvent and ammonium tetraethylfluoroborate as support electrolyte under a preparative scale were performed. The oxidation experiments were carried out and the yields obtained are excellent and competitive to those previously reported. Additionally, this method requires less reaction time and generally no by-products are present. Finally, it is worth mentioning that the higher oxidation voltage (1.410 v) was obtained with the substituent containing sulphur, while the milder oxidation voltage (1.050 v) was obtained with the hydrogen substituent, it seems

that the influence of the substituent is affecting the oxidation potential in these compounds; further studies are in progress in order to obtain more information on this phenomena.

CONCLUSIONS.

The results showed that an electrochemical method can be used to oxidize the Hantzsch esters in order to obtain the corresponding pyridines on a preparative scale. The yields are almost quantitative and no by-products were detected in this method.

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