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Synthesis of Pyridines by Anodic Oxidation of 1,4-Dihydropyridines

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SYNTHESIS OF PYRIDINES BY ANODIC OXIDATION OF 1,4-DIHYDROPYRIDINES

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ABSTRACT: Anodic oxidation of a series 1,4-dihydropyridines were performed in acetonitrile-tetrabutylammonium perchlorate electrolyte solution at platinum electrode using controlled potential electrolysis. On the bases of electroanalytical results the electrochemical oxidation mechanism of 1,4-dihydropyridines could be designed ECEC process. As a result of two-electron oxidation corresponding pyridines were obtained in yields ranging from 85%-92%. The advantages of electrochemical synthesis of pyridine derivatives are simple reaction condition, low cost and of high purity products.

Pyridine derivatives are important heterocyclic compounds in chemical industry and pharmacutical industry. Since the discovery that the metabolism of those drugs involves an oxidation step that is catalyzed in the liver by cytochrome P-450[1,2,3,4], aromatization of Hantzsch 1,4-dihyropyridines(1,4-DHP) has attracted considerable attention in recent years, for example by oxidation with chromic acid,

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nitric acid, active manganese dioxide[5,6,7]. These reagents are either expensive or in large scale conversion create waste disposal problem. By now, numerous and systematic studies have been reported on the anodic oxidation of organic compounds containing nitrogen[8], therefore, we have examined the anodic oxidation of 1,4-DHP, without chemical oxidant. This report describes the results together with the electrochemical reaction mechanism.

Results and Discussion

Electrochemical Studies

The oxidation of 1,4-DHP were studied in some details. All electrochemical studies were conducted by using acetonitrile-tetrabutylammonium perchlorate solution. A single compartment cell fitted a saturated calomel electrode was used, the counter electrode was platinum sheet, and the working electrode was a polished disk of platinum(diameter = 2mm).

Typical cyclic voltammograms for oxidation of compound(**5a**) is shown in figure 1. Only an anodic peak was observed. The anodic peak potential(E_{Pa}) shifted in positive direction with the increase in scan rate(υ), and a linear relationship for E_{pa} against lgv, the current function($i_{Pa} / \upsilon^{1/2}$) remained constant with scan rate in the range from 10mV/S to 1500mV/S and the slope of lgi_{Pa} with lgυ curve was 0.50, all these indicate that the electrode process of compound(**5a**) is an irreversible one[9]. By calculation of related electrochemical kinetic parameters, heterogeneous rate constant 4.17×10^{-5}cm/s was obtained, indicating the electrode reaction is totally

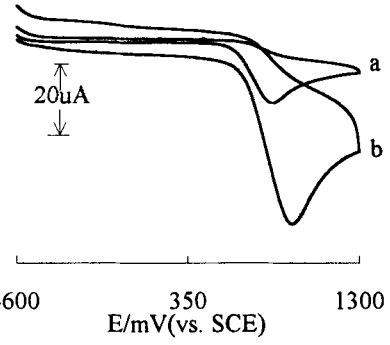


FIG. 1 Cyclic voltammogram of compound(**5a**)

Solution: compound(**5a**) 1 × 10^{-3} mol/L and 0.1 mol/L TBAP in MeCN

Working electrode: Platinum Scan rate: a 10mV/S, b 100mV/S

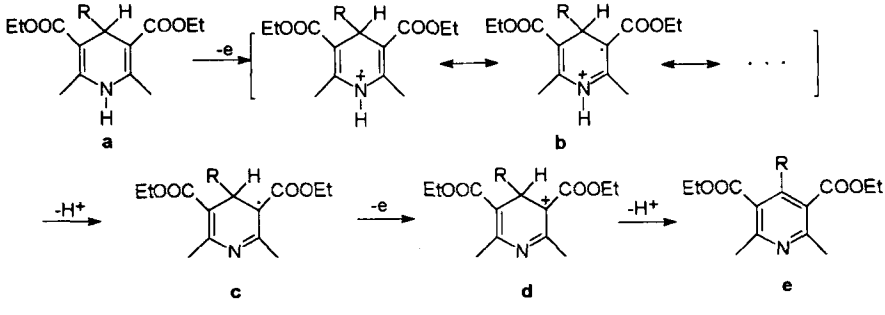
irreversible. Therefore, the exhaustive electrolysis at the applied potential of 1,4-dihydropyridines would be carried out completely and high yields would be expected. Similar CV experimental results of other compounds examined have been obtained also.

One of the main feature of the previous results is a discrepancy in the n value(n=2) determined by exhaustive electrolysis at the applied potential and the phenomena that the cyclic voltammogram exhibits only one anodic peak. It is suggested that the electrochemical oxidation process of 1,4-DHP include two one-electron oxidation steps, but the standard potential for two oxidation steps($E_1°$ and $E_2°$) are exceedingly close each other, even though the second oxidation might take place more easily than the first one[10]. This conclusion is reasonable for the reaction mechanism of organic compounds, too[8]. At first, with one electron loss, 1,4-DHP

transformed into a radical cation (**b**). Then, the radical cation lost a proton to form a radical(**c**) on the third (or fifth) carbon atom. Nevertheless, the radical(**c**) was unstable compared to starting substance, so as to lose another electron more easily, giving rise to cation(**d**). The cation(**d**) underwent chemical reaction, involving cleavage of C-H bond, deprotonation and aromatization, as a possible intermediate, leading to corresponding pyridine(**e**) at last.

In previous studies[11], we have examined 12 1,4-DHP with different 4-substituents and found that the potentials of anodic peak(E_{pa}) of 4-substituent-1,4-DHP are more positive than that of parent 1,4-DHP, also the E_{pa} of aryl-substituent-1,4-DHP are positive than that of aliphytic-substituent-1,4-DHP, but there is no order between the E_{pa} values related to the electro-withdrawing or electro-donating ability of 4-substituents. These results revealed that the E_{pa} of 1,4-DHP are mainly affected by the steric-effect from 4-substituent, instead of the ability of electro-withdrawing or electro-donating from 4-substituent. Therefore, we suggest that the first electron loss must happen on nitrogen atom.

In view of above results, the mostly likely mechanism for the oxidation of 1,4-DHP which would fit the obtained electrochemical results, can be illustrated in following scheme:



Anodic oxidation of 1,4-DHP

Anodic oxidation of 1,4-DHP were performed in acetonitrile solution containing tetrabutylammonium perchlorate(0.1mol/L). Controlled potential electrolysis was used at applied potential corresponding to the value which was positive than the peak potential given in voltammogram by ~ 0.5V. All electrochemical synthesis was carried out in a undivided cell at reticulated platinum anode(1 × $2cm^2$) in good yields(85%-92%).

The oxidation products of **1e** ~ **5e** were isolated after the electrochemical reaction, and after purification, their IR 、 NMR and MS are in agreement with the assigned structure.

Conclusion

The advantages of the electrochemical synthesis of pyridine derivatives are simple reaction condition(low electrolysis cell voltage, undivided cell), low cost, almost no waste problem and products of high purity .

Experimental Section

Materials: The 1,4-DHP and its derivatives were synthesized according to the literature[14]. The melting points 、 mass spectra 、 IR spectra and 'HNMR spectra of the products were in accord with the literature. Acetonitrile(CH_3CN,AR) was dried with 4A molecular sieves and distilled. Tetrabutylammonium perchlorate(TBAP) was prepared according to [15]. All reagents, unless noted otherwise, are commercial products.

Table 1 Selected data for the electrochemical synthetic pyridines

Compd.	R	Anode potential (V vs. sce)	yield(%)	m.p.(C°) experiment	lit.
1e	H-	1.3	90*	74 ~ 75	75 ~ 76[12]
2e	C_6H_5-	1.5	92*	60 ~ 62	62 ~ 63[7]
3e	4-Cl-C_6H_4-	1.5	85*	66 ~ 67	65 ~ 67[7]
4e	3-4-2(Cl)-C_6H_3-	1.5	85*	66 ~ 68	66 ~ 68[13]
5e	CH_3-	1.3	87	168 ~ 170**	170 ~ 173[12]

*after recrystallization ** examined as picrate

Apparatus and Procedures: Melting points are uncorrected. The IR spectra(KBr pellet) were recorded on a Nicolet FT-IR 5DX spectrophotometer and the 'HNMR spectra were recorded on Bruker ACF 300 spectrometer using tetramethysilane as an internal standard. Mass spectra were recorded on ZAV-HS GC-MS organic mass spectrometer.

The cyclic voltammetric experiment was performed by BAS100B anlyzer. The 10-cm^3 electrolysis cell was fitted with a platinum disk electrode, 2mm in diameter, a platinum sheet as a counter electrode and a saturated calomel reference electrode terminating a double salt bridge(full of CH_3CN-0.1mol/L TBAP).

Preparative controlled potential electrolysis was carried out by means of a potentiostat.

General procedure for preparation of products**1e,2e,3e,4e** :

The 1,4-DHP(1mmol) was added into the electrolysis cell filled with CH_3CN-TBAP(0.1mol/L) solution(40ml). The potential was maintained at 1.3 ~ 1.5v by means of potentiostat with initial current of about 12mA. Electrolysis was discontinued when the current drops to 1mA. Then the electrolysis was completed,

the solvent was evaporated and 40ml water was added. The solid formed was collected on a Buchuer funnel and purified by flash column chromatography on silica gel using petrol ether(60-90C°)-ethyl acetate(v:v = 4:1) as eluent, After recrystallization of them from the appropriate solvent, pure compounds(**1e-4e**) were obtained which were identified with m.p.、 IR 、 ^{1}HNMR and MS.

Diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate:

IR(KBr) υ 2980, 2931, 1722, 1588, 1553, 1300, 1222 ,1124, 1046, 772cm^{-1}; MS *m/e*(%) 251(43.1), 223(9.6),206(100) ,178(46.0), 150(23.4), 106(20.0), 91(5.2), 77(15.2), 57(12.8); ^{1}HNMR($CDCl_3$) δ 1.41(t,J=7.1Hz,6H,2CH_3), 2.85(s,6H,2ArCH_3), 4.40(q,J=7.1Hz,4H,2OCH_2), 8.67(s,1H,ArH).

Diethyl 2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate:

IR(KBr) υ 3064, 2980, 1714, 1553, 1285, 1222, 1053, 758, 702cm^{-1}; MS *m/e*(%.) 327(100), 282(66.2), 254(48.3), 236(87.5), 210(27.7), 139(34.9), 105(20.9), 71(38.3), 57(82.9); ^{1}HNMR($CDCl_3$) δ 0.90(t,J=7.1Hz,6H,2CH_3), 2.60(s,6H,2ArCH_3), 4.00(q,J=7.1Hz,4H,2OCH_2), 7.03-7.27(m,5H,Ph-H).

Diethyl 2,6-dimethyl-4-(4-chlorophenyl)-3,5-pyridinedicarboxylate:

IR(KBr) υ 3050, 2987, 1728, 1560, 1293, 1236, 1011, 857, 793cm^{-1}; MS *m/e*(%.) 361(100), 316(78.4), 288(50.3), 270(53.8), 244(22.0), 173(9.6), 139(41.4), 77(9.6), 57(71.4); ^{1}HNMR($CDCl_3$) δ 0.95(t,J=7.1Hz,,6H,2CH_3), 2.60(s,6H,2CH_3), 4.00(q,J=7.1Hz,4H,2OCH_2), 7.20(d,J=8.4Hz,2H,Ph-H),7.36(d,J=8.4Hz,2H,Ph-H).

Diethyl 2,6-dimethyl-4-(3,4-dichlorophenyl)-3,5-pyridinedicarboxylate:

IR(KBr) υ 3040, 2980, 1721, 1533, 1285, 1236, 913, 871, 828cm^{-1}; MS *m/e*(%)

395(100), 350(96.4), 323(26.9),304(51.8), 278(25.0), 242(6.6), 207(9.1), 173(38.8), 139(15.1), 57(11.1); ^{1}HNMR($CDCl_3$) δ 1.05(t,J=7.1Hz,6H,$2CH_3$), 2.61(s,6H,$2ArCH_3$), 4.10(q,J=7.1Hz,4H,$2OCH_2$), 7.10~7.48(m,3H,Ph-H).

Procedure for the preparation of **diethyl 2,4,6 — trimethyl — 3,5 — pyridine dicarboxylate:**

Anodic oxidation of compd.(**5a**)(260mg,1mmol) and the isolation of the product was performed by the same way as described above. The oily product obtained(226mg, 87%) was crystallized in ethanol solution saturated with picric acid, leading to the corresponding picrate. The precipitate was isolated by filtration being analytically pure sample.

IR(KBr) υ 2994, 2650, 1736,1547,1370, 1236, 1046, 995, 709cm^{-1}; MS *m/e*(%) 265(36.9), 236(27.5), 220(100), 192(25.4), 164(16.6), 120(9.8), 77(18.9), 57(7.3); ^{1}HNMR($CDCl_3$) δ 1.40(t,J=7.1HZ,6H,$2CH_3$), 2.49(s,3H,$ArCH_3$), 2.72(s,6H,$2ArCH_3$),4.49(q,J=7.1Hz,4H,$2OCH_2$),7.61(br,1H,OH),8.95(s,2H,Ph-H)

References and Notes

1. Bossert, Von F.; Meyer, H. and Wehinger,E. *Angew. Chem. Int. Ed. Engl.* **1981**,20, 762

2. de Matteis, F.; Hollands, C.; Gibbs, A.F,; De Sa, N. and Rizzardini, M. *FEBS Let.* **1982**, 145, 87

3. Bocker, R. H. And Guengerich, F. P. *J. Med. Chem.* **1986**, 29, 1596

4. Mc Cluskey, S. A.; Riddick, D. S.; Mackie, J. E.; Kimmet, S. M.; Whitney, R. A. and Marks, G. S. *Can. J. Physiol. Pharmcol.* **1992**, 70, 1069

5. Siddiqui, J. *India. Chem. Soc.* **1939**, 16, 410

6. Loev, B.and Snader, K.M. *J. Org. Chem.* **1965**, 30(6), 1914

7. Eynde, J. J. V.; Pelfosse, F.; Mayence, A. and Haverveke, Y. V. *Tetrahedron,* **1995**, 51(23), 11

8. Baizer, M. M. and Lund, H. "Organic Electrochemistry," Marcel Dekker, Inc., New York,**1983**, pp463,pp411

9. Bard, A. J. and Faulkner, L. F. "Electrochemical Methods," John Wiley and Sons, New York, **1985**, pp223

10. Polcyn, K. S. and Shain, I. *Anal. Chem.* **1966**, 36(3),370

11. Lixin Zhang, Bingxiang Wang, Shimin Zhu, Hongyuan Chen, *Chem. J. Chinese Universities.* **1997**,18(11),1779

12. Oliveto, E. P. "Heterocyclic Compounds Pyridine and Derivatives," Part III pp300

13. Eisner, V. And Kathan, J. *J. Chem. Review.* **1972**, 72, 1

14. Hinkel, L. E. And Cremer, H. W. *J. Chem. Soc.* **1920**, 117, 137

15. Kolthoff, I. M. And Coetsee, J. F. *J. Am. Chem. Soc.* **1957**, 79, 870

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