J. Sci. I. R. Iran

Vol.8 No.3
Summer1997

AROMATIZATION OF HANTZSCH 1,4-DIHYDROPYRIDINES WITH ZINC CHLOROCHROMATE NONAHYDRATE

M.M. Hashemi* and S. Balalaie

Department of Chemistry, Sharif University of Technology, P.O. Box 11365-9516, Tehran, Islamic Republic of Iran

Abstract

Hantzsch 1,4-dihydropyridines are rapidly oxidized to the corresponding pyridine derivatives using zinc chlorochromate nonahydrate [$Zn(ClCrO_3)_2.9H_2O$] in dichloromethane at room temperature. In addition to aromatization, no loss of the 4-substituent is observed.

Introduction

The 4-substituted 1,4-dihydropyridines are valued not only for their pharmacological effects but also as a tool for investigation of the calcium channel blockers [1], particularly since the discovery of the metabolism of these drugs which involves an oxidation step catalyzed by cytochrome P-450 in the liver [2]. In this regard, aromatization of Hantzsch 1,4-dihydropyridines has attracted considerable attention and reagents have been developed for this purpose, e.g. HNO_3 [2], HNO_2 [3], $NaNO_3$/AcOH [4], and claycop [5]. Several reviews are available on this subject [6-8]. In recent years, other methods have been used such as: CAN [9], MnO_2/Bentonite [10,11], HNO_3/Bentonite using microwave irradiation [12], ultrasound and claycop [13], supported PCC [14], supported $KMnO_4$ [15], nitric oxide [16] and MnO_2 [17].

In this report, we introduce zinc chlorochromate as a mild reagent for aromatization of 4-alkyl, 4-aryl and 4-heteroaryl 1,4-dihydropyridines in dichloromethane at room temperature with good yields.

In some methods, long reaction periods and low yields have been reported [3-5]. Some dihydropyridines may undergo decarboxylation and loss of substituent on the 4-position can also occur when heated [15].

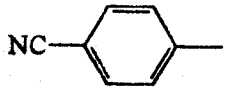
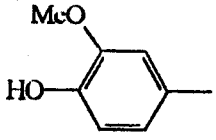
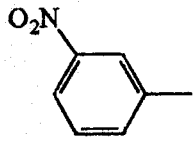
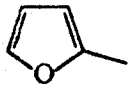
Keywords: Aromatization; Dihydropyridines; Zinc chlorochromate

Results and Discussions

Diethyl 1,4-dihydro-2,6-dimethyl pyridine-3,5-dicarboxylate **1** in CH_2Cl_2 at room temperature with ZCC for 5 min. gives pyridine derivative **10** with 85% yield. IR spectrum indicated the absence of N-H group and the presence of C=N group at 1600 cm^{-1}. The ^{1}H-NMR spectrum ($CDCl_3$, δ ppm) reveals a signal at 8.6 ppm due to H-4 which is in accordance with the aromatic character of the product. When 4-substituted 1,4-dihydropyridines are aromatized, no loss of alkyl group is observed. The protons of the methyl groups in positions 2 and 6 of the ring in **1** are characterized by an intense singlet at 2.2 ppm, whereas in the oxidized form the methyl protons appeared at δ 2.6 ppm. This procedure has been applied to other 4-alkyl, 4-aryl and 4-heteroaryl-1,4-dihydropyridines and the results are shown in Table 1. The reactions are completed within 5-30 min. After aromatization, as a general trend, the signal at δ 4.1 ppm disappeared for all compounds studied and only the alkyl protons could be observed for the 4-alkyl substituted compounds. In 4-aryl and 4-heteroaryl, the same trend was observed in which the H-4 was lost during aromatization.

In conclusion, ZCC is a reagent of choice for aromatization of 1,4-dihydropyridine derivatives, and dealkylation reactions and dearylation are not observed. Mild reaction condition, good yields of the products, ease of the work-up and stability of the reagent are the most significant aspects of this method.

Table 1. Selected data for the diethyl-2,6-dimethyl-3,5-pyridine carboxylate

1,4-DHP	R	Product	Time (min.)	Yield (%)[a]	δ(R)ppm
1	H	10	5	85	8.6 (s, 1H)
2	CH_3-	11	5	80	2.3 (s, 3H)
3	$CH_3CH_2CH_2$-	12	5	78	2.6 (2H), 0.8-1.6 (5H)
4	$(CH_3)_2CHCH_2$-	13	5	74	1.0 (d, 6H), 1.5 (m, 1H), 2.6 (d, 2H)
5	C_6H_5-	14	5	82	7.3 (s, 5H)
6		15	5	72	7.4 (d, 2H), 7.7 (d, 2H)
7		16	5	82	6.9-7 (3H)
8		17[b]	30	65	7.5 (m, 2H), 8.2 (m, 2H)
9		18[b]	30	65	6.3-6.6 (2H), 7.5 (m, 1H)

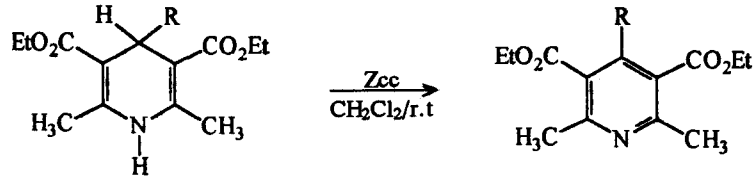
δ CH_3 (position 2 and 6) 2.6 (s, 6H) and $CO_2C_2H_5$ 4.3 (q, 4H), 1.2 (t, 6H)
[a] All yields correspond to isolated pure compounds.
[b] Ratio of oxidant:reactant is 3: 1.

Experimental Section

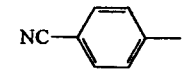
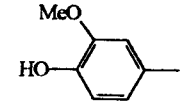
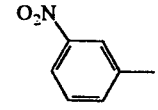
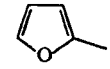
All products are known compounds. They are identified by comparison of their physical and spectral data with those reported in the literature. 1,4-Dihydropyridines were prepared by standard procedure [18]. IR spectra were recorded (film) on FT-IR Unicam Mattson 1000 Spectrophotometer. ^{1}H-NMR spectra were recorded on JEOL EX-90 (90 MHz) and Brucker AC-80 (80 MHz) spectrometers in $CDCl_3$ and chemical shifts are indicated in δ ppm. Zinc chlorochromate nonahydrate was prepared according to the reported method [19,20].

General Procedure for Oxidation of 1,4-Dihydropyridines

To a stirring solution of 1,4-dihydropyridine (1 mmol) in CH_2Cl_2 (20 ml) was added a solution of oxidant (1-1.5 g, 2-3 mmol) in CH_2Cl_2 (10 ml). The orange-red color of the reagent disappeared after 1 min.. Stirring was continued for an additional 5-30 min.. Progress of the reaction was monitored by TLC (CH_2Cl_2/EtOAc, 98:2). The mixture was filtered through a silica gel pad and was washed with CH_2Cl_2 (30 ml). The filtrate was evaporated and the residue was purified by preparative TLC on silica gel



1-9 10-18

No.	R	No.	R
1	H		
		6	
2	CH_3-		
		7	
3	$CH_3CH_2CH_2$-		
		8	
4	$(CH_3)_2CHCH_2$-		
		9	
5	C_6H_5-		

Scheme 1

(CH_2Cl_2/EtOAc, 98:2). The desired products are isolated in 65-85% yields.

References

1. Goldmann, S. and Stoltefuss, J. *Angew. Chem. Int. Ed. Engl.*, **30**, 1559-1578, (1991).
2. Bocker, R.H. and Guengerich, F.P. *J. Med. Chem.*, **29**, 1596-1603, (1986).
3. Loev, B. and Sander, K.M. *J. Org. Chem.*, **30**, 1914-1916, (1965).
4. Loev, B., Goodman, M.M., Snader, K.M., Tedeschi, R. and Macko, E. *J. Med. Chem.*, **17**, 956-965, (1974).
5. Laszlo, P. *Aldrichimica Acta*, **21**, 97-103, (1988).
6. Eisner, U. and Kuthan, J. *Chem. Rev.*, **72**, 1-72, (1972).
7. Stout, D.M. and Meyers, A.I. *Ibid.*, **82**, 223-243, (1982).
8. Sausins, A. and Duburs, G. *Heterocycles*, **27**, 291-314, (1988).
9. Pfister, J.R. *Synthesis*, 689-690, (1990).
10. Alvarez, C., Delgado, F., Garcia, O., Medina, S. and Marquez, C. *Synth. Commun.*, **21**, 619-624, (1991).
11. Delgado, F., Alvarez, C., Garcia, O., Penieres, G. and Marquez, C. *Ibid.*, **21**, 2137-2141, (1991).
12. Garcia, O., Delgado, F., Cano, F. and Alvarez, C. *Tetrahedron Lett.*, **34**, 623-625, (1993).
13. Maquestiau, A., Mayence, A. and Vanden Eyden, J.J. *Ibid.*, **32**, 3839-3840, (1991).
14. Vanden Eyden, J.J., Mayence, A. and Maquestiau, A. *Tetrahedron*, **48**, 463-468, (1992).
15. Vanden Eyden, J.J., D'Orazio, R. and Van Haverbeke, Y. *Ibid.*, **50**, 2479-2484, (1994).
16. Iton, T., Nagata, K., Okada, M. and Ohsawa, A. *Tetrahedron Lett.*, **36**, 2269-2272, (1995).
17. Vanden Eyden, J.J., Delfosse, F., Mayence, A. and Van Haverbeke, Y. *Tetrahedron*, **51**, 6511-6516, (1995).
18. a) Norcross, B.E., Clement, G. and Weinstein, M. *J. Chem. Educ.*, **46**, 694-695, (1969), b) Mann, F.G. and Saunders, K.J. *Practical organic chemistry*, pp. 295-296, Longman Scientific and Technical, (1975).
19. Firouzabadi, H. and Sharifi, A. *Synthesis*, 999-1002, (1992).
20. Firouzabadi, H., Sharifi, A. and Karimi, B. *Iranian J. Chem. & Chem. Eng.*, **12**, 32, (1993).