4-PHENYL-1,4-DIHYDROPYRIDINES BY AQUEOUS HANTZSCH REACTIONS

F. M. da Silva, M. Gonçalves, F. T. Ferre, J. D. Sena, R. B. Coelho and J. Jones Junior *

Dept. Química Orgânica - Instituto de Química – UFRJ - CP 68.584, CEP 21941-972, Rio de Janeiro, RJ, Brasil

Abstract: A family of biologically active 4-phenyl-1,4-dihydropyridines were synthesized in a two-step one-pot aqueous Hantzsch protocol. The yields ranged from 44% to 93%. This method provides a particular ecological advantage as it replaces the need for organic solvents with water.

Introduction

The first synthesis of a dihydropyridine is attributed to Arthur Hantzsch for work done in 1882. [1,2,3] In the 1930s, the discovery that the NADPH coenzyme contained a 1,4-dihydropyridine structure as its key reactive moiety motivated many related studies regarding its biological activity.[2,3] The recent literature reveals that these compounds have a variety of physiological properties.[4-8]

In the classical Hantzsch synthesis, the product is formed by the condensation of 2 mol of ethyl acetoacetate with 1 mol of an aldehyde in the presence of ammonia.[1] The current literature contains many modifications to these reaction conditions to make the methodology more efficient, including the use of microwaves[9-11], ionic liquids[12], molecular iodine[13], solid-phase organic synthesis techniques[10, 14] and solvent-free conditions.[15, 16]

Currently, the study of organic reactions, which use water as the solvent, are considered an important strategy in order to develop more environmentally friendly methodologies. Water is an innocuous solvent, besides being more abundant and less expensive than organic solvents.[17-22]

We present here an efficient methodology to generate a family of 1,4-dihydropyridines in water using the Hantzsch reaction.

Experimental

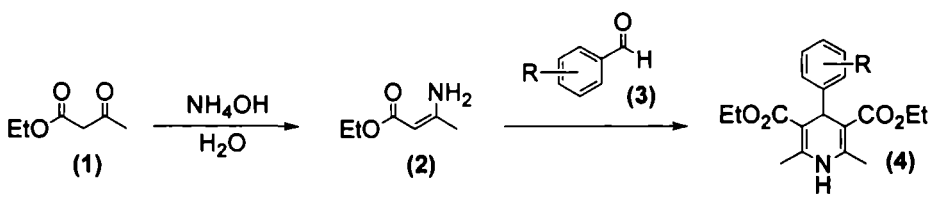
Typical procedure: To 10 mL of aqueous NH_4OH (conc.) solution was added 30 mmol of ethyl acetoacetate (1). The reaction mixture was refluxed for 1 h. Then 5 mmol of the aromatic aldehyde (3a-f) was added and refluxed, and the reaction mixture was refluxed for an additonal 5 h. The reaction mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was dried (anhydrous Na_2SO_4) and the solvent was evaporated under reduced pressure. The product was purified by column chromatography (hexane / ethyl acetate 2:1). All 1,4-dihydropyridines were characterized by ^1H and ^{13}C NMR, IR and mass spectra and compared with authentic samples.[23]

Results

The 1,4- dihydropyridines (4) were obtained via a two-step one-pot protocol in aqueous media. The first step is the reaction of ethyl acetoacetate (1) with ammonium

hydroxide, in order to form the intermediate, ethyl 3-aminocrotonate (2). Soon after, the reaction of two equivalents of this intermediate with an aromatic aldehyde (3) leads to the desired product (Scheme).

Scheme



3	a	b	c	d	e	f
R	4-OCH_3	4-Cl	4-NO_2	H	2-OCH_3	2-Cl

The table shows the results of this methodology for several aldehydes and comparison with the literature data for their synthesis.

Table

4	R	Yield (%)	(%) literature yield
a	4-OCH_3	70	11[15]
b	4-Cl	93	90[11]
c	4-NO_2	88	99[16]
d	H	90	93[16], 91[11]
e	2-OCH_3	44	92[16]
f	2-Cl	78	11[15]

In conclusion, we have developed a simple and efficient methodology for the synthesis of 1,4-dihydropyridines using the Hantzsch reaction in water.

References

1- A. Hantzsch, Justus Liebigs Ann. Chem. **215**, 1 (1882).
2- D.M. Stout, A.I. Meyers, Chem. Rev. **82**, 223 (1982).
3- U. Eisner, J. Kuthan, Chem. Rev. **72**, 1 (1972).
4- M. Kawase, A. Shah, H. Gaveriya, N. Motohashi, H. Sakagami, A. Varga J. Molnar, J. Bioorg. Med. Chem. **10**, 1051 (202).
5- M. Suarez, Y. Verdecia, B. Illescas, R. Martinez-Alvarez, A. Avarez, E. Ochoa, C. Seoane, N. Kayali, N. Martin, Tetrahedron **59**, 9179 (2003).
6- B. Jauk, T. Pernat, C.O. Kappe, Molecules **5**, 227 (2000).
7- S. Visentin, B. Rolando, A. Di Stilo, R. Fruttero, M. Novara, E. Carbone, C. Roussel, N. Vanthuyne, A. Gasco, J.Med. Chem. **47**, 2888 (2004).
8- R. Shan, C. Velazquez, E.E. Knaus, J. Med. Chem. **47**, 254 (2004).
9- B.M. Khadikar, V.G. Gaikar, A.A. Chitnavis, Tetrahedron Lett. **36**, 8083 (1995).
10- A. Agarwal, P.M.S. Chauhan, Tetrahedron Lett. **46**, 1345 (2005).
11- M. Anniyappan, D. Muralidharan, R.T. Perumal, T. Paramasivan, Synthetic Communications **32** (4), 659 (2002).

12- R. Sridhar, P.T. Perumal, Tetrahedron **61**, 2465 (2005).
13- S. Ko, M.N.V. Sastry, C. Lin, C.-F Yao, Tetrahedron Lett. **46**, 5771 (2005).
14- J.G. Breitenbucher, G. Figliozzi, Tetrahedron Lett. **41**, 4311 (2000).
15- R. Osnaya, A.G. Arroyo, L. Parada, F. Delgado, J. Trujillo, M. Salmón, R. Miranda, ARKIVOC **(xi)**, 112 (2003).
16- M.A. Zolfigol, M. Safaiee, Synlett **5**, 827 (2004).
17- F.M. da Silva, P.S.B. Lacerda, J. Jones Jr, Quim.Nova **28**, 103 (2005).
18- R. Breslow, Acc. Chem. Res. **24**, 6 (1991).
19- P.A. Grieco, Organic synthesis in water; Ed. Blacki Academic & Professional: London, 1998.
20- C.-H. Li, T.-H. Chan, Organic reaction in aqueous media, Ed. John Wiley & Sons, Inc.: New York, 1997.
21- A.R. Katritzky, S.M. Allin, Acc. Chem. Res. **29**, 399 (1996).
22- F.M. da Silva, J. Jones Jr, Quim. Nova **24**, 646 (2001).
23- B. Loev, K.M. Snader, J.Org. Chem. **30**, 1914 (1965).

Received on July 28, 2008