A CONVENIENT HANTZSCH SYNTHESIS OF 1,4-DIHYDROPYRIDINES USING TETRAETHYL ORTHOSILICATE

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Abstract: Hantzsch dihydropyridine synthesis using tetraethyl orthosilicate as a water scavenger is described. With this method reaction time was drastically shortened in comparison with conventional methods. Generally, the obtained yields were good or excellent. Steric and electronic effect of different substituents on the yield and reaction time is studied. From the obtained results the plausible reaction mechanisms is proposed.

INTRODUCTION

1,4-Dihydropyridines (1,4-DHPs) are very important class of compounds because of their pharmacological activity as a calcium antagonist (1) or agonist. The 1,4-DHPs antagonists cause vasorelaxation by blocking voltage-operated calcium channel in smooth muscle cells and also by increasing NO release from the intact endothelium (2). Nifedipine 1 (3) as a first representative of these drugs was marketed in 1975. by Bayer AG. Since then a lot of new biologically active substances from 1,4-DHPs class appeared (4). Some of these compounds are characterized by larger bioavailability or greater tissue selectivity. To this day, 1,4-DHPs are still the most potent group of calcium channel blocker and their best seller members are nicardipine 2 (5), amlodipine 3 (6) and still nifedipine.



Brought to you by | University of Arizona Authenticated Download Date | 5/28/15 11:16 PM The traditional methods for preparation of 1,4-DHPs by Hantzsch synthesis (7) includes reaction of one mole aldehydes, one mole ammonia and two moles of β -ketoesters. Usually the reaction is carried out in alcoholic solvent at reflux temperature. When sterically hindered benzaldehydes are used (8a-c), this method gives low yield and need long reaction time. Because of that a lot of improvements were reported that includes using sealed tube (8b, 9a-c) or autoclav (10a-b).

RESULTS AND DISCUSSION

The aim of our work is to study the influence of different dehydrating agents in Hantzsch reaction which chemically react with water produced in cyclization. When chlorinated agents like POCl₃, PCl₃, PCl₅ etc. were used the polymeric materials are the main product. Tetraethyl orthosilicate, Si(OEt)₄, as dehydrating agent was chosen because it was successfully used in preparation of sterically hindered enamines (11), which belongs to the class of compounds similar to 1,4-DHPs. Since the first results using Si(OEt)₄ was promising we decided to examine this reaction in details.

Here we report on new method of Hantzsch 1,4-DHPs synthesis using Si(OEt)₄ as water scavenger. This method was used for preparation of several 1,4-DHPs according to Scheme 1 and results are summarized in Table 1. Steric and electronic effects of substituents on the starting benzaldehydes were systematically studied. As a donor of ammonia was used ammonium acetate and acetic acid serves as an acid catalyst. The amount of tetraethyl orthosilicate in reaction was equivalent to amount of benzaldehyde since that was found optimal due to its transformation to amorphous silicium dioxide. The reaction temperature was 90 °C at beginning and latter spontaneously decrease to 78 °C, what is boiling temperature of ethanol produced in reaction.

Results from Table 1 reveals that reaction times in comparison with known literature methods for Hantzsch synthesis was substantially shortened from several hours or days to 30-100 minutes. Results for different substituted benzaldehydes (*o*-, *m*- and *p*-) show that yield and reaction time are dependent on steric and electronic effect of substituents, but not so expressive. Generally, the yields were good or excellent and increased if electron withdrawing substituents (NO₂ and halogen) is used. On the other hand, reaction time is preferably dependent on steric effect, particularly of *para*-substituents; compounds **22** and **24**. In the case of compound **18** the reaction parameters are highly affected by the influence of *ortho*-ethoxy substituent what caused lower yield and prolonged reaction time.



Table 1. 1,4-Dihy	dropyridines :	synthesized	using S	Si(OEt)₄
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Comp.	R	R ₂	R ₃	Yield ^a	Reaction	mp ^b [°C]	mp [°C] (ref. reported)
		1.0		[%]	time [min]		
15	Н	Η	H	58	60	156-158	157-159 (8c)
16	NO_2	н	н	57.5	75	124.5-125.5	125 (8b)
17	Cl	н	н	55	75	125-126	122.5-123 (10a)
18	OEt	н	н	48	100	127-128	121.5-122 (10a)
19	Н	NO_2	н	85.5	45	168.7-169.7	103 (12), 164 (8b),
							164-165 (13), 168 (14),
							168-169 (15)
20	Н	Cl	Н	85.5	30	143-144	142 (8a)
21	Н	Η	C1	85.5	30	145-147	149 (8a)
22	Н	Н	NO_2	85.5	30	133-134	136 (12)
23	Н	Η	F	78.5	40	151-152	-
24	Н	Н	OCH ₂ Ph	60	35	170-171.5	-

^a Isolated yield after column chromatography

^b Compounds recrystallized from MeOH

The question, which is place oneself, is how tetraethyl orthosilicate decrease reaction time, by reacting with water formed in the reaction mixture or by direct reacting with intermediates? In the case of the latter mechanism will be different from classical Hantzsch reaction. Katritzky et. al (16) using ¹⁵N and ¹³C NMR techniques explained the mechanism of Hantzsch cyclization which includes Michael addition of amino crotonic ester **25** to Knoevenagel product **26** as a rate determining step, Scheme 2. Knoevenagel product is produced by condensation of appropriate ketoester and aldehyde. They also showed that steps where water is produced are much faster than Michael addition.



Brought to you by | University of Arizona Authenticated Download Date | 5/28/15 11:16 PM If Hantzsch reaction with $Si(OEt)_4$ goes according to the mechanism reported by Katritzky et. al. shortening of reaction time would not be observed. In this case $Si(OEt)_4$ would react with intermediates, which were previously formed in the slowest step of reaction. So, Katritzky's mechanism is not completely in accordance with our experimental data. By the Scheme 3 it was proposed the plausible mechanisms for the Hantzsch synthesis using $Si(OEt)_4$.

First step in the Hantzsch synthesis is producing amino crotonic ester 29, which can be detected by TLC at the beginning of reaction. The second molecule of ethylacetoacetate in Knoevenagel condensation with appropriate benzaldehyde gives chalcone 30. The next step, condensation of compound 29 and 30 was promoted with tetraethyl orthosilicate. The silicate intermediate 31 eliminates triethyl orthosilicate and give Schiff base 32, the same intermediate as theoretically proposed by Katritzky et. al (16). The key step in the synthesis is the intramolecular Michael cyclization in intermediate because the C-C bond forming is much faster than bimolecular addition, Scheme 2. At the end, the intermediate 33 isomerize to 1,4-dihydropyridine 34. The possible variant of reaction mechanism goes *via* bisenamine 35 produced by condensation of enamine 29 with second molecule of ethylacetoacetate 14. This intermediate is also proposed by Katritzky et. al (16) but only as a metastable side-product.



Brought to you by | University of Arizona Authenticated Download Date | 5/28/15 11:16 PM The tetraethyl orthosilicate, present in reaction, help nucleophilic addition of bisenamine 30 to benzaldehyde 36 by reacting with intermediate and producing 37. From this intermediate two possible paths can occur; via intermediate 32 after elimination of triethyl orthosilicate, or via intermediate 38 after isomerization. Intramolecular S_N^2 cyclization in silicate intermediate 38 afforded intermediate 39 that lose proton and isomerize to 1,4-dihydropyridine 34. All the proposed mechanisms for formation of C-C bond include cyclic intermediate that is much faster step than Michael addition in classical Hantzsch cyclization.

As conclusion we can state that Hantzsch 1,4-dihydropyridine synthesis using Si(OEt)₄ as water scavenger was very useful since it offer good yields and low reaction times. The plausible mechanism for this reaction was proposed.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer Spectrum One spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on a Varian XL-GEM 300 and shifts are given in ppm downfield from TMS as an internal standard. Elemental analyses were done in Central Analytical Service (CAS) at Ruder Boskovic Institute. HPLC analyses were performed with a Thermo Separation Products (San Jose, USA) instrument equipped with vacuum degasser SCM 1000, quaternary gradient pump P 4000, autosampler AS 3000, scanning UV/VIS detector UV 3000 HR and ChromQuest 251 software.

General procedure of investigated reaction: The mixture of appropriate benzaldehydes (4-13, 10.0 mmol), ethylacetoacetate (14, 10.0 mmol, 2.53 ml), ammonium acetate (10.0 mmol, 0.77 g) and tetraethyl orthosilicate (10.0 mmol, 2.23 ml) was heated at 90 °C for the time showed in Table 1. After cooling to room temperature reaction mixture was purified by chromatography on silica gel column (200 g) using dichloromethane /ethylacetate 9:1 as eluent. 4-(4-Fluoro-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5dicarboxylic acid diethyl ester (23) and 4-(4-benzyloxy-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5dicarboxylic acid diethyl ester (24) are the new compounds. 23: mp 151-152 °C; IR (KBr) v 3340, 3070, 2180, 2930, 2900, 1900, 1690, 1660, 1640, 1605, 1490, 1385, 1300, 1020 and 635 cm⁻¹; ¹H NMR (CDCl₃) § 1.16-1.21 (6H, m), 2.30 (6H, s), 4.01-4.17 (4H, m), 4.97 (1H, s), 6.13 (1H, s), 6.85-6.91 (2H, m), and 7.21-7.26 (2H, m) ppm; ¹³C NMR (CDCl₃) δ 13.93, 19.10, 38.75, 59.55, 103.77, 114.21, 114.48, 129.25, 129.35, 143.64, 143.69, 144.09, 159.66, 162.89, and 167.64 ppm. 24: mp 170-171.5 °C; IR (KBr) v 3370, 2990, 2940, 1700, 1650, 1630, 1610, 1590, 1510, 1460, 1310, 1240, 1100, and 850 cm⁻¹; ¹H NMR (CDCl₃) δ 1.19-1.24 (6H, m), 2.30 (6H, s), 4.03-4.14 (4H, m), 4.93 (1H, s), 4.99 (2H, s), 5.77 (1H, s), 6.82 (2H, d, J = 8.6 Hz), 7.19 (2H, d, J = 8.6 Hz), and 7.30-7.42 (5H, m) ppm; ^{13}C NMR (CDCl₃) δ 13.99, 19.26, 38.52, 59.51, 69.77, 104.17, 113.99, 127.45, 127.77, 128.43, 128.91, 137.21, 140.56, 143.62, 157.16, and 167.72 ppm.

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