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A MILD AND CONVENIENT ONE-POT SYNTHESIS OF 4-ARYL-*N*-OH-HANTZSCH ESTERS

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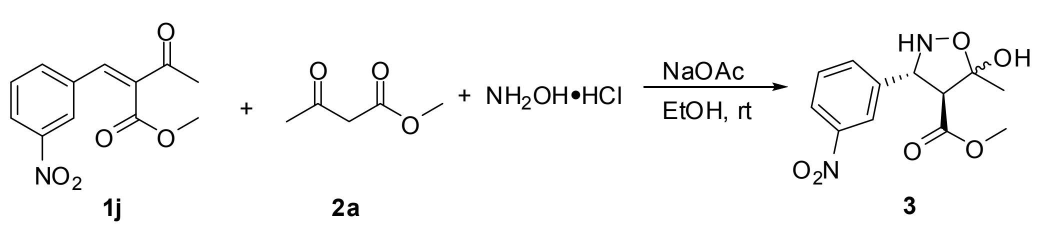
Abstract –A general methodology to prepare a series of 4-Aryl-*N*-OH Hantzsch esters was developed. The key factor is to control the first-step of Michael addition at 0 °C. The method was practical to produce symmetrical and unsymmetric *N*-OH-Hantzsch esters in moderate yield. This class of compounds might have use in medicinal and material science.

1,4-Dihydropyridines (1,4-DHPs) are an important class of biologically active heterocycles, as a well-known class of calcium channel antagonist and potent calcium channel agonist,[1,2] and as such commercialized in for instance nifedipine, amlodipine or nimodipine. Besides their overwhelming utilization in the cardiovascular pharmacology as Ca^{2+} channel blockers (CCBs),[3] they have also been investigated for other pharmacological activities such as antitumor,[4] antiviral,[5] anticancer,[6] HIV-I protease inhibition,[7] anticonvulsant.[8] A large amount of information is available on their medicinal chemistry properties.[9] Among the numerous methods developed for the synthesis of 1,4-dihydropyridines,[10] the traditional Hantzsch reaction is one of the most efficient methods.[11] However, this methodology is not applicable for the synthesis of chiral, unsymmetrical 1,4-DHPs. In many cases, chiral and/or unsymmetrical DHPs exhibited better or in the case of enantiomers an opposite pharmacological properties.[12] The details of slight stereoelectronic requirements for interactions at various receptors are still being investigated. The knowledge of stereochemical/conformational requirements for any biological activity requires the investigation of other related analogues of the DHP ring.

To have a better insight into the molecular interaction at the receptor level, an expansion investigation on the structure-activity relationship was needed. The design, synthesis, and evaluation of novel 1,4-DHPs with a varied pattern of substitution assumes a lot of significance. Most modification on 1,4-DHPs is focused on the five carbon atoms. As a result, our recent interest in the 1,4-dihydropyridines chemistry has been concentrated on the introduction a hetero atom on the nitrogen atom, which has rarely been investigated. Tu had synthesyzed a series of symmetrical acridinediones with *N*-OH-1,4-DHPs nucleus whose nitrogen atom was introdued a amino or hydroxyl group.[13] Sharma also reported a similar route to construct *N*-OH-1,4-DHPs from barbituric acid.[14] In continuation of our interest in heterocyclic chemistry.[15] Herein, we reported a convenient and efficient method for the synthesis of various symmetrical or unsymmetrical Hantzsch esters whose nitrogen atoms were introduced a hydroxyl group.

The preparation of *N*-OH-Hantzsch esters has only been reported in one patent.[16] However, we could not reduplicate the one-pot synthesis of symmetrical product and obtained complex mixture directly using aldehydes and β-keto esters in the first-step reaction using zinc(II) chloride ($ZnCl_2$) at 60 °C. What's more, the unsymmetrical Michael addition could not be well realized by using other reported catalysts such as potassium fluoride (KF) or cesium fluoride (CsF).

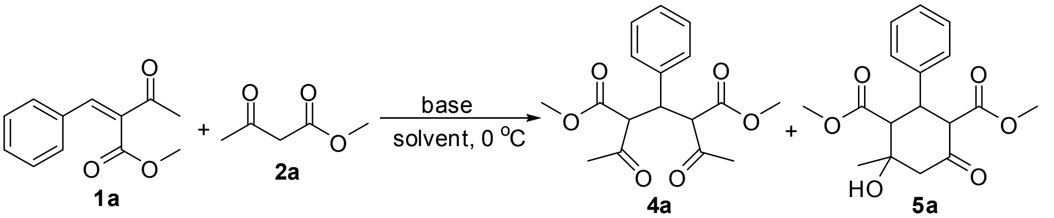
Two strategies were applied in the synthesis of *N*-OH-Hantzsch esters. Firstly, the classical Hantzsch esters synthetic method was tried through the three component reaction of *m*-nitrobenzaldhyde, methyl acetoacetate and hydroxylamine hydrochloride in the presence of sodium acetate (NaOAc) (Scheme 1). No any of the anticipated products were obtained. Then the second route was employed through the reaction of condensation product **1j**, methyl acetoacetate and hydroxylamine hydrochloride in the presence of NaOAc at room temperature. To our disappointment, the undesired product **3** (mixture of two isomers, 6:1) was generated in nearly quantitive yield. It revealed that reaction speed of addition between **1j** and hydroxylamine is by far faster than that of Michael addition between **1j** and methyl acetoacetate. Therefore, the key factor to produce *N*-OH-Hantzsch esters is the first-step of Michael addition. Then the two step strategy through Michael addition-condensation to generate the *N*-OH-Hantzsch esters was employed. Although secondary amine-catalyzed the consendation of two molecular acetoacetate and one molecular aldehyde is the classical method to generate the arylbisacetoacetate **4**,[17] it has few shortcomings such as long reaction time and only generation of the symmetric condensation product.



Scheme 1

The Michael reaction is generally regarded as one of the most efficient carbon-carbon bond forming reactions, which can be catalyzed by various bases.[18] Therefore, the influence of different bases and solvents on the Michael addition of **1a** with **2a** was studied (Table 1). At first, the reaction of **1a** with **2a** was performed with various bases (0.1 equiv) in EtOH at 0 °C. The results showed that cyclic product **5a** was the main competitive byproduct and the inorganic bases such as sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3) and sodium hydroxide (NaOH) was the relatively efficient base. Using NaOH as the base, intermediate 1,5-diketone compound **4a** could be obtained in the highest yield of 84%. While using other solvents such as THF, DMF, aceetonitrile (MeCN), acetone or dichloromethane (CH_2Cl_2), the yield or the selectivity was not good as EtOH. Herein, sodium hrdroxide/EtOH system was the optimal system to realize the Michael addition. In similar condition, prolonging the time or raising temperature was both favorable to the generation of byproduct **5a**. Reducing the amount of NaOH to 5 mol % still resulted in similar yield in a little longer time.

Table 1. Screening of the reaction condition.[a]

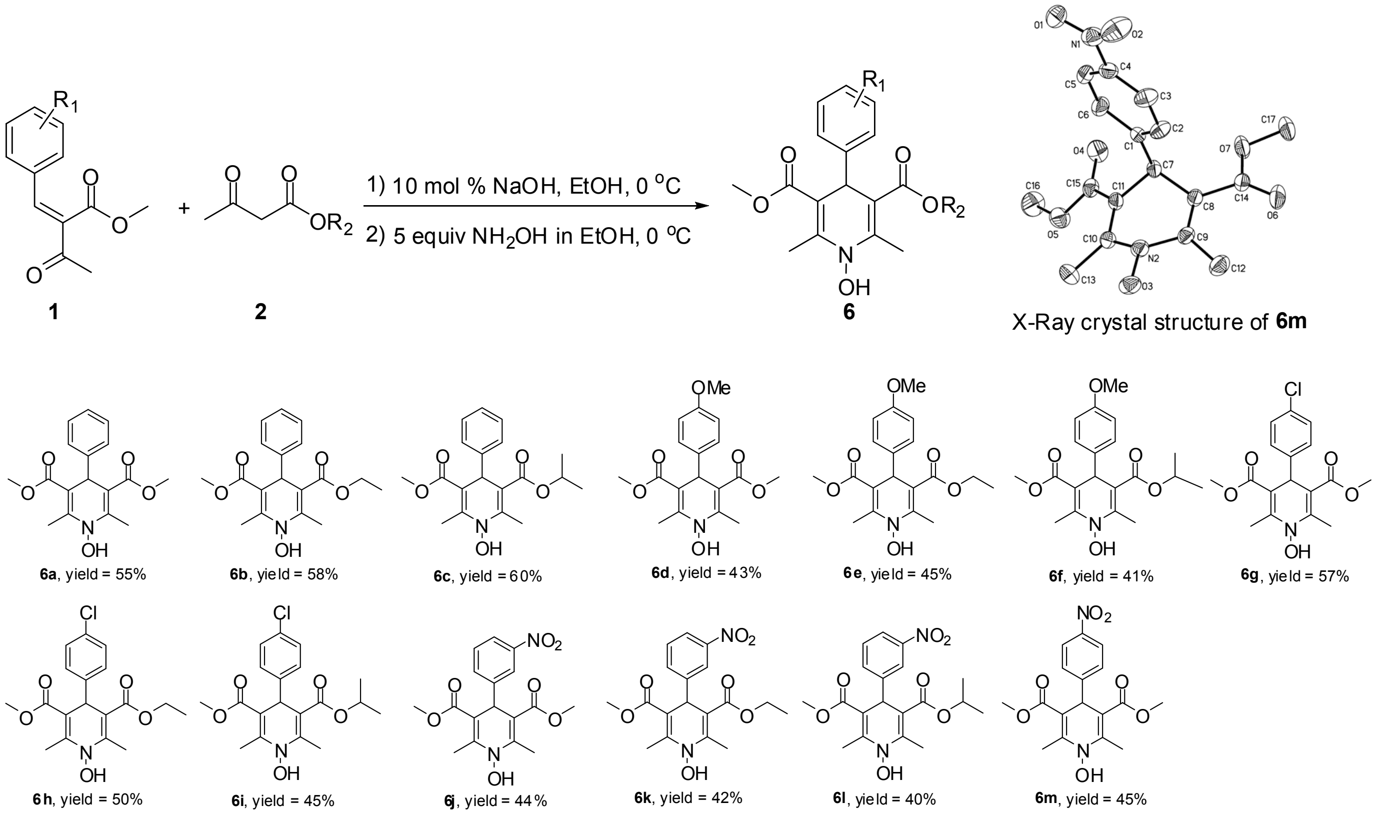


entry	solvent	base	time (h)	yield of **4a** (%)[b]	yield of **5a** (%)[b]	entry	solvent	base	time (h)	yield of **4a** (%)[b]	yield of **5a** (%)[b]
1	EtOH	KF	24	20	2	8	EtOH	piperidine	5	17	20
2	EtOH	NaOAc	24	29	4	9	EtOH	$(Et)_3N$	24	27	2
3	EtOH	Na_2CO_3	4	78	9	10	THF	NaOH	24	25	19
4	EtOH	K_2CO_3	4	60	15	11	DMF	NaOH	3.5	82	9
5	**EtOH**	**NaOH**	**1**	**84**	**6**	12	MeCN	NaOH	3.5	73	10
6	EtOH	NaOH[c]	2	82	8	13	acetone	NaOH	3.5	77	11
7	EtOH	DBU	3.5	67	9	14	CH_2Cl_2	NaOH	24	37	3

[a] 1 mmol of **1a**, 1.2 mmol of **2a**, and 10 mol % of base was stirred in 10 mL solvent at 0 °C. [b] All the yields were determined by HPLC analysis. [c] 5 mol % of NaOH was used.

Next, the one-pot reaction was tried by adding solution of 5 equiv of hydroxylamine in EtOH to the first-step reaction mixture at 0 °C, the desired *N*-OH-Hantzsch ester **6a** was obtained as a yellow solid in 55% yield after stirring for 1 h (Scheme 2). Increasing the temperature leads to more byproducts. Under these optimized conditions, the reaction scope was evaluated by using various condensation products **1** and *β*-keto esters **2**. Symmetrical and unsymmetric *N*-OH-Hantzsch esters **6** could be obtained in moderate to good yields of 40-60% at 0 °C. The slight electronic effects were observed. **1** with strong electron-withdrawing groups or strong electron-rich groups resulted in little lower yields.

Given the easy access to *N*-OH-Hantzsch esters, the present method should be applied in the synthesis of libraries with high functional group diversity, which may find application in the field of DHP chemistry, diversity-oriented synthesis and drug discovery. In this study, all the products were characterized by their NMR, IR and MS spectra. The *N*-OH proton was appeared in the range of 10-11 ppm in DMSO-d_6. Sometimes, the signal of OH was very weak probably due to a fast exchange with water present in DMSO-d_6. The structure of the product **6m** was further established by the X-ray diffraction analysis.[19]



Scheme 2

In conclusion, we have developed a useful protocol for the synthesis of a series of *N*-OH-1,4-Hantzsch esters whose nitrogen atom was introduced a hydroxyl group. The key factor is to controll the Michael addition reaction to prevent the further cyclization. Particularly, the method shows several attractive characteristics, namely, one-pot, convenient, simple work-up procedure. *N*-OH-1,4-DHPs represent an interesting family of compounds for the development of effective drugs. The terminal hydroxyl group makes 1,4-DHP be further transformed or introduced to other molecule easily for further studies of the potential use in medicinal fields.

EXPERIMENTAL

General Methods: Flash chromatographic purification of products was performed on silica gel (200-300 mesh). Thin-layer chromatography was visualized with a UV light (254 and 365 nm). IR spectra were taken on a Bruker Vector-22 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}H NMR spectra were recorded at 500 MHz on a Bruker Avance-500 spectrometer in $CDCl_3$ with chemical shifts (δ) given in ppm relative to TMS as an internal standard. ^{13}C NMR spectra were recorded on a Bruker Avance-500 (125 MHz) spectrometer with complete proton decoupling, chemical shifts are reported in ppm relative to the solvent resonance as the internal standard ($CDCl_3$, δ = 77.16 ppm). All intensities in the ^{13}C NMR spectral data are 1C except where indicated.

Three component reaction of 1j, methyl acetoacetate and hydroxylamine: To a 25 mL of one neck flask was sequentially added **1j** (125 mg, 0.5 mmol), methyl acetoacetate (58 mg, 0.5 mmol), hydroxylamine hydrochloride (69 mg, 1.0 mmol), sodium acetate (82 mg, 0.1 mmol) and 10 mL of EtOH. The mixture was stirred at room temperature until the disappearance of **1j**. Most of the solvent was removed and then 15 mL of water was added. After extraction with CH_2Cl_2 (10 mL × 3) the combined organic layers were dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent followed by column chromatography on silica gel using petroleum ether/EtOAc (3:1) gave the corresponding product **3** (diastereo mixture, 6:1, 138 mg, 98%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.10 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.40 (d, J = 6.9 Hz, 1H), 6.56 (s, 1H), 5.07 (t, J = 6.4 Hz, 1H), 3.69 (s, 3H), 3.17 (d, J = 5.6 Hz, 1H), 1.58 (s, 3H); ^{1}H NMR (300 MHz, $CDCl_3$) 8.30 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 6.7 Hz, 1H, NH), 5.17 (t, J = 6.0 Hz, 1H), 3.84 (s, 3H), 3.20 (d, J = 5.1 Hz, 1H), 2.87 (s, 1H, OH), 1.75 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.0, 147.9, 133.1, 130.1, 121.8, 120.7, 106.1, 65.9, 62.3, 52.1, 23.2; IR(KBr) ν/cm^{-1}: 3228, 2950, 1696, 1662, 1587, 1429, 1378, 1357, 1298, 1243, 1206, 1193, 1155, 1042, 1028, 866, 831, 772, 764, 700; MS-ESI 305 $[M+Na]^+$.

General procedure for the synthesis of *N*-OH-1,4-Hantzsch esters 6: Sodium hydroxide (200 mg, 5 mmol) was added to a solution of hydroxylamine hydrochloride (348 mg, 5 mmol) in dry EtOH (10 mL), and the resulting mixture was stirred for 1 h and filtered. A mixture of **1** (1 mmol), acetoacetate **2** (1.2 mmol), and 10% NaOH (4 mg, 0.1 mmol) was stirred in 10 mL of EtOH in ice bath for 1-2 h. Upon completion as shown by TLC, NH_2OH solution in EtOH was added to the mixture and then the mixture was allowed to stir at 0 °C for 6-8 h. After completion of the reaction detected by TLC, the mixture was added 20 mL water, and then extracted with CH_2Cl_2 (15 mL × 3). The organic layer was dried over $MgSO_4$, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether) to provide *N*-OH-1,4-Hantzsch esters **6**. All the characteristic data and spectra could be found in the supporting information.

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