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TMSCl Promoted Acylation of Amines with 5-(α-amino- α'-hydroxy)methylene Meldrum's Acids – Elucidation of Mechanism.

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Abstract:

Recently we have observed accelerating influence of trimethyl silyl chloride addition on the rate of the reactions of 5-(α-amino- α'-hydroxy)methylene Meldrum's Acids with amines, particularly in the case of highly basic amines. However the nature of the aforementioned process remain unexplained. In proposed communication we wish to report insightful elucidation of this mechanism. The reaction under investigation involves simply addition of the trimethyl silyl chloride to the mixture of amine and carbamoyl Meldrum's acid derivative. We considered three potentially possible ways for the TMSCl action. The first possibility is formation of the O-silylated Meldrum's acid, which would exclude formation of salt Meldrum's acid with amine, what undoubtedly hindered this reaction. The next way for the acceleration of the process is silylation of amine and subsequent reaction of silylated amine with carbamoyl Meldrum's acid. The last possibility is connected with the formation of equimolar amount of HCl during the reaction of TMSCl with carbamoyl Meldrum's acid or amine, which should speed up the rate of decomposition of the Meldrum's acid derivative. The NMR monitored experiments as well classical experiments in which predicted intermediate were added to the reaction mixtures excluded formation of O-silylated Meldrum's acid as well as influence of formed HCl as a reason of the acceleration investigated reaction. Our experiments revealed that silylated amine is responsible for rate acceleration of the reaction amines with 5-(α-amino- α'-hydroxy)methylene Meldrum's Acids in the presence of TMSCl.

Keywords: acylation, ketene, Meldrum's acid,

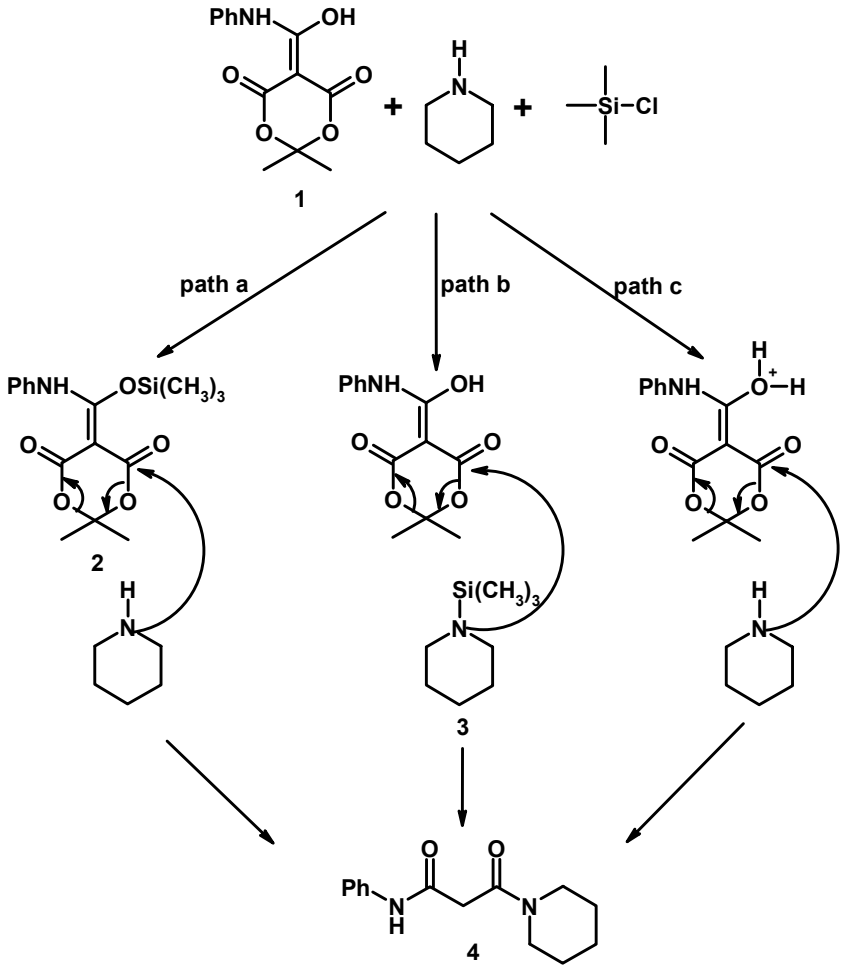
Introduction

Derivatives of Meldrum's acid have found broad scope of application in organic synthesis[1]. Synthetic usefulness of 3-substituted-1,3-dioxadiones is due to the fact that they are a potential source of ketene in the course of thermolysis[2]. Among others acyl derivatives of Meldrum's were used as a starting materials for synthesis lots of valuable compounds as: 3-substituted-β-lactams[3], isooxazolols[4], pilicides[5], 1,3-oxazinones[6], and pyrones[7].

Our recent researches we focused on the reactivity of carbamoyl Meldrum's acids with various nucleophilic reagents as amines, alcohols, thiols or imines under thermolytic condition in which carbamoyl ketenes colud be formed as a electrophilic reagents. Here sholud be stresed that reactivity of carbamoyl Meldrum's acids with nuclephiles was also investigated by group of Pak[8]. However for the reaction with arylcarbamoyl Meldrum's acid they used only weakly basic nitrogen nucleophiles as aromatic amines, amides or even sulfonamides. When we reinvesigate this reaction with wider scope of nucleophiles we found that use of highly basic secondary amines cause a problem with low yields and too prolonged reaction time. As a solution these problems we have proposed use of trimethyl silyl chloride, which used in amount of 1,5 eq allow to leave reaction time as short as only 2 h with subsequent reduction of reaction temperature for thirty degree, what we described in our recent publication[9]. However the nature of the aforementioned process was unexplained. In this communication we wish to report elucidation of the reaction mechanism.

Results and discussion

The acceleration of the reaction of carbamoyl Meldrum's acid with secondary amine can occur at several potential ways (Scheme 1). For the faster course of reaction colud be responsible O-silylated carbamoyl Meldrum's acid **2** (path a) as well as silylated amine **3** (path b) or even only HCl formed after addition of TMSCl to the reaction mixture (path c).
The addition of trimethyl silyl chloride to a mixture of Meldrum's acid with secondary amines may cause formation one of two silylated species or both, also stepwise addition of TMSCl to one only reagent for example amine and following by addition of carbamoyl Meldrum's acid doesn't exclude possibility of trans-silylation and formation of silylated carbamoyl Meldrum's acid. Hence the first issue was determination which silylated compounds is formed in investigated reaction.



Scheme 1

At the beginning we decided to check if carbamoyl Meldrum's acid **1** could be silylated by TMSCl in the presence of tertiary amine, we prepared reaction mixture composed from **1,** triethyl amine and TMSCl after 24 h we took sample of this reaction mixture and done NMR spectra without and with addition of starting carbamoyl Meldrum's acid **1**. Performed spectra not confirmed presence of silylated carbamoyl Meldrum's acid **2**, after addition of **1** the most diagnostic signal of this compound in ^{1}H NMR methyl groups at 1.2 ppm in benzene remain only one. However the spectra before addition of **1** showed disappearance of acidic proton of OH group at 16.4 ppm what may suggest formation of carbamoyl Meldrum's acid salt with triethyl amine. Above fact revealed that observation of only one signal of methyl groups at 1.2 ppm in the mixture after reaction with TMSCl might be inconclusive and can not completely exclude presence of silylated derivative of carbamoyl Meldrum's acid **2**. In the next NMR experiment we used N,N'-bis(trimethylsilyl)urea as a silylating agent which allow to perform reaction with out tertiary amine[10]. NMR spectra of the reaction mixture in benzene after addition of N,N'-bis(trimethylsilyl)urea to solution of **1**

again showed the presence only one signal of methyl groups at 1.2 ppm, and what is more important, even after 5 h there was still unchanged signal of OH group at 16.4 ppm as well as NH group at 11.3 ppm what clearly exclude formation of silylated derivative of carbamoyl Meldrum's acid.

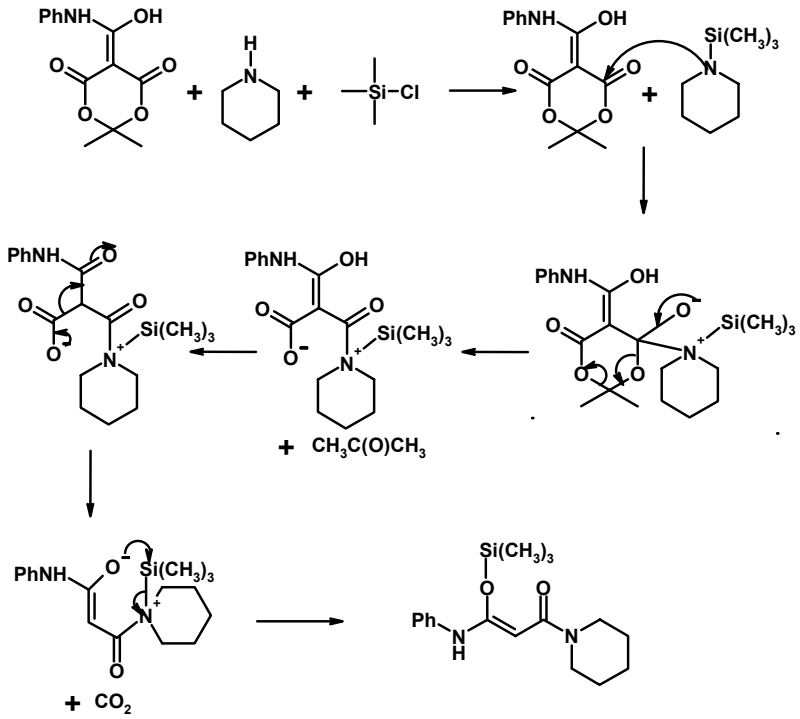
Additionaly to exclude formation of **2** we perform following experiment: in a large scale; 100 mmol of **1** was dissolved in dichloromethane and treated with 1.1 eq of triethylamine followed by addition of 1.5 eq of TMSCl. After 24 h methylen chloride was removed and residue was dissolved in ethyl ether and treated with excess of piperidine and stirred for 12 h, after which crystaline solid of carbamoyl Meldrum's acid salt with piperidine was filtred and etheral residue was distiled. Possibly formed **2**, may undergouse two reactions: first is reaction with piperidine at room temperature to yield trimethylsilyl amine **3** or the second is reaction with amine at the elevated temperature to form malonamide **4**. However after vaccum distilation of the etheral residue we did not obtain even traces of **3,** and also we did not isolated malonamide **4,** what strongly sugest that **2** is not formed.

To check if the reaction may follow by path **c**, we performed experiment between 1 eq of carbamoyl Melddrum's acid, 1,5eq of piperidine hydrochloride and 0,5 eq of free piperidine in dichloroethane what should simulate action of HCl liberated after addition of TMSCl. We did not observe accleration of the reaction, complete decomposition of carbamoyl Meldrum's acid took 24 h instead 2,5 h as in the presence of TMSCl and the yield was lower – 70% instead 96%.

Exclusion of path a and c, indicate that for the acceleration of the reaction must be responsible formation of silylated amine and its reaction with carbamoyl Meldrum's acid faster than reaction of free amine. To confirm our suposition we run the reaction of **1** with trimethylsilylated piperidine, the yield of malonoamide and rate was identical as during reaction with TMSCl means 96% within 2.5 h in dichloroethane as a solvent.

Our observations led as to conclusion that following mechanism take place during the reaction of the carbamoyl Meldrum's acid **1** with secondary amines in the presence of TMSCl (Scheme 2): after addition of TMSCl to the reaction mixture trimethylsilylated amine is formed. Trimethylsilylated amine as a good nucleophilic species react quickly with **1** to form malonamide **4**. At this point we sholud stress that our observation of the reactivity of various nucleophiles (for example aromatic amines versus alcohols) toward carbamoyl Meldrum's acid derivatives prompted us to adopt the view that this reaction proceeds via nucleophilic addition – elimination. This view is oposite to results presented by Grabowski[11], where in the

case of acyl Meldrum's acids influence of nucleophilicity on the rate of decomposition of acyl Meldrum's acid was excluded.



Scheme 2

Conclusion

The reaction of carbamoyl Meldrum's acid with secondary amines in the presence TMSCl take place in accordance with the mechanism in which trimethylsilylated amine is a key intermediate responsible for the faster rate of the process. Our experiments demonstrated that surprisingly N-silylated compound is formed instead of the O-silylated Meldrum's acid derivative which should be expected because of the well known higher stability of the O-Si than N-Si bond.

Experimental

Reagents were purchased from Sigma-Aldrich. Analytical TLC was performed on aluminum sheets of silica gel UV-254 Merck. Flash chromatography was performed using 40-63 microns of Zeochem silica gel. The ^{1}H, ^{13}C were recorded at Varian Gemini 200 and Varian Unity Plus 500. Melting points are uncorrected. Commercially unavailable reagents were prepared using literature procedures as follows: 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **1** [13], N-trimethylsilyl piperidine[12]

*Attempts to silylation of 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **1***

To the stired under argon and cooled to 0°C solution of 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (26.3 g, 0.1 mol) in dichloromethane, triethylamine (15.29 cm^3, 0.11 mol) was added. After 15 minutes TMSCl (16.27 g 0.15 mol) was added dropwise. After additional 15 minutes cooling bath was removed and reaction mixture was stireed for 24 h. Methylene chloride was removed under vaccum and residue was dissolved in dry ethyl ether and piperidine (9.86 cm^3 0.1 mol) was added and stirred at R.T for 12 h after which crystaline precipitate of carbamoyl Meldrum's acid salt with piperidine was filtred and etheral solution was removed under vaccum what did not left any residue. The precipitate of Meldrum's acid salt with piperidine was suspended in the 2 M HCl 200 cm^3, filtred washed with water, dissolved in ethylacetate and dried with $MgSO_4$. After crystalization from AcOEt 10.73 g of 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione was recovered, mp 104-106 °C. Spectral data in agreement with literature[13].

*N-Phenyl-3-oxo-3-piperidin-1-yl-propionamide **4** from piperidine hydrochloride.*

To a stirred solution of 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (263 mg, 1 mmol) in 1,2-dichloroethane, piperidine (43 mg, 0.5 mmol) and piperidine hydrochloride (183 mg, 1.5 mmol) was added. The reaction was stirred and heated to reflux for 24 h. After decomposition of **1**, solvents was removed under reduced presure and the residue was purified by flash column chromatography, (AcOEt/Hex, 5:2). Yield 172 mg 70% mp 115-117 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.61-1.70 (m, 6 H, CH_2), 3.49 (s, 2H, CH_2), 3.52-3.65 (m, 4H, CH_2), 7.12 (t, J= 7.32 Hz, $1H_{arom}$), 7.34 (t, J= 7.81 Hz, $2H_{arom}$), 7.60 (d, J= 7.81 Hz, $2H_{arom}$), 10.18 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.5, 25.8, 26.7, 40.1, 43.6, 47.5, 120.3, 124.5, 129.2, 138.1, 164.6, 167.0. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{18}N_2O_2$: 246.1368; found: 246.1381.

*N-Phenyl-3-oxo-3-piperidin-1-yl-propionamide **4** from N-trimethylsilylpiperidine*

To a stirred solution of 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (263 mg, 1 mmol) in 1,2-dichloroethane, piperidine (43 mg, 0.5 mmol) and *N-trimethylsilylpiperidine* (235 mg, 1.5 mmol) was added. The reaction wasstirred and heated

to reflux for 2.5 h. After decomposition of **1**, solvents was removed under reduced presure and the residue was purified by flash column chromatography, (AcOEt/Hex, 5:2). Yield 240 mg, 96 %, mp 115-117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.61-1.70 (m, 6 H, CH_2), 3.49 (s, 2H, CH_2), 3.52-3.65 (m, 4H, CH_2), 7.12 (t, J= 7.32 Hz, $1H_{arom}$), 7.34 (t, J= 7.81 Hz, $2H_{arom}$), 7.60 (d, J= 7.81 Hz, $2H_{arom}$), 10.18 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.5, 25.8, 26.7, 40.1, 43.6, 47.5, 120.3, 124.5, 129.2, 138.1, 164.6, 167.0. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{18}N_2O_2$: 246.1368; found: 246.1381.

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