The Reaction Mechanism of Amines with 5-[Hydroxy(1-aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones in the Presence of TMSCl

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Abstract: Addition of trimethylsilyl chloride to the reaction mixture composed of 5-[hydroxy(1-arylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones and secondary amines strongly accelerate the rate of reaction. This phenomenon we have observed during our previous research, however, the reason for this phenomenon remained unclear. Currently, in order to elucidate the mechanism of this reaction we assumed and verified three possible pathways for the action of TMSCl in the reaction mixture. We took into account the following possibilities: acceleration of the reaction is caused by formation of O-trimethylsilylated Meldrum's acid or by silylated amine or is just induced by the presence of HCl liberated from TMSCl. The performed experiment allowed us to conclude that faster course of reaction is caused by the formation of N-trimethylsilylated amines.

Keywords: Acylation, Ketenes, Meldrum's Acid, Trimethylsilyl chloride

Introduction

Meldrum's acid derivatives have a broad scope of application in organic synthesis [1]. The most explored feature of these compounds is the ability to form ketenes in the course of thermal decomposition, which can be trapped with various nucleophiles (Scheme 1). Depending on the type of Meldrum's substrate, pyrolysis can led to formation of oxo-ketenes [2], carbamoylo-ketenes [3], thiocarbamoylo-ketenes [4], iminopropadienones [5] or even nitroso ketenes [6]. Practical use of formed ketenes allow the preparation of various useful compounds as for example: 3-substituted-β-lactams [3, 7], isooxazolols [8], pilicides [9], 1,3-oxazinones [10], or derivatives of tetramic acid [11].

In our laboratory we have focused on the reactivity and synthetic application of carbamoyl ketenes generated from 5-[hydroxy(1-aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones. In contrary to acyl Meldrum's acids, which became the subject of many publications including detailed mechanistic studies [12] the reactivity of carbamoyl Melrum's acid is poorly described in chemical literature. Excluding our own papers, there is only one example of systematical study of reactivity of carbamoyl Meldrum's acids with nucleophiles presented by Pak [13] and co-workers. However, this paper deals only with thermolytic reaction of carbamoyl Meldrum's acids with weakly basic nitrogen nucleophiles such as aromatic amines with electronwithdrawing groups or even amides. During our experiments [14] with 5-[hydroxy(1-aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones we have found that use of stronger basic secondary amines caused some problems such as low yield or too much time is required for completion of the reaction. We have found that the use of trimethylsilyl chloride allow to bypass these difficulties. Adition of 1,5 eq of TMSCl to the reaction mixture of an amine with 5-[hydroxy(1-aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione allow to obtain the acylation product with nearly quantative yield concomitantly reduction of temperature of the reaction by over fifty degrees [14]. At this moment, we used trimethylsilylchloride intuitively, treating this reagent, as at least good a source of HCl, which could catalyze the reaction. Although the actual effect of the addition

or TMSCl to reaction mixture remained unclear to us. In this paper, we wish to report on the elucidation of the reaction mechanism of amines with carbamoyl Meldrum's acids accelerated by TMSCl.

Results and Discusion

At the beginning of our research, we assumed three threaded hypotheses that would explain the observed phenomenon (Scheme 2), accelerating of the reaction of 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1**) with a secondary amine in the presence of TMSCl. Addition of TMSCl to the reaction mixture, containing **1** and the secondary amine, may cause formation of two silylated species, namely 5-[trimethylsilyloxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (path a) or trimethylsilyl amine (path b). Moreover a stepwise addition of TMSCl to only one reagent, for example **1**, does not exclude the formation of silylated amine in a subsequent trans-silylation process after addition of amine. Hence, we had to propose a set of intelligent experiments, which waned allow to separate the reciprocal influence of each reagents.

In the first probing of our hypothesis we assumed that for the acceleration of the reaction can be responsible initially formed 5-[trimethylsilyloxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**2**) (Scheme 2, path a). Such a course of process seems very likely, since it is well known that a greater affinity of silylating agents towards a hydroxy group rather than to a nitrogen nucleophiles exist. However from the other hand such a O-silylated Meldrum's acids should rather slow down than to speed up the reaction rate taking into account experiments, where Meldrum's acid derivatives which do not contain hydroxy or sulfhydryl groups were stable up to 130° for 4-5h [17].

The second possibility for the acceleration of the reaction (path b), enclosed in our hypothesis, concerns the influence of HCl liberated in the reaction of TMSCl with the residual water present in the reaction mixture. Grabowski [12] and co-workers have shown the influence of the acidity on the rate of the

decomposition of **1.** Hence, we could not *ad hoc* exclude such a possibility in the examined reaction mechanism.

The third assumption for the acceleration of the discussed reaction (path c) means that secondary amine is converted into its silylated derivative, since silylated amines are well known for their strong nucleophilic properties and in this manner may speed up the reaction.

The key issue, which needed resolution in the course of determining the reaction mechanism, was to explain, which silylated sepcies is formed at the beginning of the reaction, O-silylated Meldrum's acid, N-silylated amine or neither of them.

In a first experiment, we questioned path (a) of the proposed mechanism, i.e., can **1** be O-silylated [18]. To answer this question, we prepared a reaction mixture containing **1**, triethyl amine, and TMSCl. After 17 h at room temperature, we analyzed the mixture by ^{1}H-NMR in benzene. Taking into account that carbamoyl Meldrum acid has only three types of H-atoms, we had to focus our observations on the Me groups of the acylal part. The spectra showed the presence of only one signal at δ 1.24. Substitution on the O-atom, for example, with alkyl groups has weak, however, noticeable influence on the chemical shift of Me H-atoms with Δδ ca. 0.06 [16, 19]. Hence, we added to a NMR tube **1** with the aim to demonstrate difference between silylated carbamoyl Meldrum's acid and **1**. However, the ^{1}H-NMR spectrum still showed only one signal at δ 1.24. This fact strongly suggest that compound **2** was not formed. The second diagnostic signal in the Meldrum's acid, which presence or disappearance may exclude or confirm the formation of **2**, is the signal of the acidic H-atom at δ 16.4. However, in the presence of triethyl amine this signal obviously disappear baceause of salt formation. Therefore, we performed another NMR experiment, in which we used *N,N*'-bis(trimethylsilyl)urea as a silylating agent which allows for silylation of carboxylic acids without the presence of a tertiary amine. As a result, we obtained again only one signal at δ 1.20. However, what is more important, even after conducting this reaction for 5 h, we still observed in the ^{1}H-NMR spectra unchanged signals of OH and NH groups, respectively, at δ 16.4 and δ 11.3.

These results clearly exclude path (a) as a route for the acceleration of the reaction of carbamoyl Medrum's acid with amines.

In order to obtain additional arguments, confirming or excluding formation of **2**, we performed large scale experiment in which 0.1 mol of **1** was dissolved in DCE and 1.1 eq of TEA and 1.5 eq TMSCl was added. The reaction mixture was left for 24 h. Thereafter, DCE and all volatile products was removed under reduced pressure. The residue was dissolved in dry Et_2O and treated with an excess of piperidine and stirred for additional 12 h. Then, the piperidinium salt of **1** was filtered and Et_2O destilled off. We should clarify the intention of our experiments, namely if **2** would be formed, it should react with piperidine under formation of *N*-trimethylsilylated piperidine **3** or **2** would react under piperidine at the elevated temperature with formation of malonoamide **4**. However, distillation of the Et_2O residue did not result even in traces of **3**, and malonoamide **4** also was not formed. These results also exclude path (a).

We also performed two additional experiments: **1** was treated in boiling DCE without and with addition of 1.5 eq of TMSCl. In both experiments, the time required for decomposition of **1** was as long as 24 h, whereas as previously reported [14] in boilig DCE **1** disappeared in the presence of TMSCl and amine within 2.5 h. This clearly indicates that TMSCl has no influence on the decomposition of **1** by accelerating his decomposition to ketene or by any other way. Taking into account the experiments already done, we can with certainty exclude path (a).

The next possibilty for the acceleration of the reaction may be associated with the acidity of the reaction mixture. As was aforementioned, Grabowski et al.[12] demonstrated that rate of formation of ketenes from acyl Meldrum's acids directly depends on the concentration of free acid form of Meldrum's acid derivative. Therefore, taking into account that the highest difference we have observed for the reaction with strong basic secondary amines (meaning very slow reaction without TMSCl and very fast ones with 1.5eq of TMSCl) [14] led us to suppose that addition of controlled amounts of a strong acid to the reaction mixture through hydrolysis of TMSCl with residual water may have a decisive influence on the rate of the reaction, just by change the acid-base equilibrium.

However, we should cite our own experiment, where we run the reaction of **1** with piperidine in ethylbenzene saturated with HCl, in which the rate of decomposition of **1** was slightly faster, but the yield of malonoamide still remained unsatisfactory [14]. Nevertheless, this result can't exclude path (b), because during saturation with excess of HCl all amine is converted into its hydrochloride, so that the rate of decomposition **1** to ketene is obviosuly higher, but there is a too low concentration of free amine to efficiently react with the formed ketene. The addition of 1.5 eq of TMSCl to the reaction mixture containing 2 eq of amine may produce only up to 1.5 eq amine hydrochloride and thus leaving still free amine. Therefore, we performed an experiment taking 1 eq of **1**, 1.5 eq of piperidine hydrochloride, and 0.5 eq of free piperidine in boiling DCE. Under these conditions, we observed that total decomposition of **1** took as long as 24 h instead 2.5 h as in the presence of TMSCl and the obtained yield of malonoamide **4** was lower than 70% in comparision with 96% in the presence of TMSCl. Ten times longer reaction time clearly exclude path (b) – simply acid catalysis of the decomposition **1** to ketene.

The last possibility for the acceleration of the reaction is the intervention of *N*-silylated amine - path (c). To confirm this route, we performed the following experiment: 1eq of **1** and 1.5 eq of trimethylsilyl piperidine was heated in boiling DCE. After 2.5 h all starting **1**was consumed and the yield was as high as 96%. This experiment shows that the use of presilylated amine or use the of TMSCl results in the same yield and time required for decomposition of **1**. This finding finally confirm path (c).

Knowing that the acceleration of the reaction between **1** and amine is caused by the formation of silylated amines in the first step of the reaction, we focused on the interaction of silylated amines with **1**. Some observed facts can be summarized as follows: after addition of TMSCl acceleration of the reaction is enormous – in some cases ten times faster reaction in over fity degrees lower temperature. The influence of TMSCl is more remarkable in the cases of *N*-aryl derivatives of **1** than in the cases of *N*-alkyl derivatives **1** and finally reaction of **1** with secondary amine without TMSCl in low boiling solvents is extremely slow (as we checked in a separate experiment: complete decomposition of **1** in the reaction with diethylamine in DCE requires ca. 100 h). These facts strongly

suggests that in the case of the use of TMSCl/amine or just *N*-silylated amine,we indeed observe a change of the reaction mechamism, from formation of ketene and addition of nucleophile to the addition-elimination type of reaction. This idea is opposite to views presented by Grabowski et al. [12],which showed no dependence of the reaction rate on nucleophilicity and pointed ketene as a undoubtedly existing intermediate. However, they examined acyl Meldrum acid, which are more prone to thermal decomposition to ketenes, whereas carbamoyl Meldrum's acid are more resistant. Although Wentrup and Shtaiwi [5] have observed the formation iminopropanediones, formed from **1,** but under harsh conditions of FVT (flash vacuum thermolysis) at 350-550°.

Therefore we postulate that at low temperatures when the formation of ketenes from **1** is virtually put off (100 h in boiling DCE) *N*-silyl amine acts as a strong nucleophile and reacts directly with the dioxadione system through addition-elimination mechanism (Scheme 3) whereas in high boiling solvent such as ethylbenzene in the absence of TMSCl **1** may react through the established mechanism of decomposition to ketene. The addition of *N*-silyl amine to the 1,3-dioxadione system is facilitated when an *N*-aryl substitutent is present, because in the case of *N*-alkyl derivatives of **1** we did not observe such a significant acceleration.

In conclusion, formation of *N*-trimethylsilylated amines is directly responsible for the acceleration of the reaction of 5-[hydroxy(1-aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones with amines. TMSCl has no influence on the rate of the decompostion of **1.** All facts strongly suggest that *N*-trimethylsilylated amines react with **1** according to an addition-elimination mechanism rather that by formation of free ketenes.

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Experimental Part

General. All solvents used in this study were dried over appropiate drying agents and destilled prior to use. Commercially available reagents were purchased from Sigma-Aldrich. Commercially unavailable reagents were prepared using literature procedures: 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-

dione (**1)** [16], *N*-trimethylsilyl piperidine [15]. TLC: *Merck Kieselgel 60 F_{254}*. Flash column chromatography (CC): *Zeochem ZEOprep 60/40-63*. M.p: *Warsztat Elektromechaniczny W-wa*; uncorrected. NMR Spectra: *Varian Unity Plus 500* (^{1}H: 500 and ^{13}C: 125 MHz) Varian Gemini 200 (^{1}H: 200 and ^{13}C: 50; chemical shifts (δ) in ppm rel. to internal Me_4Si; coupling constants in Hz. HR-ESI-MS: *MicroMas Quattro LCT* mass spectrometter.

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

To a stirred under argon and cooled to 0° solution of **1** (26.3 g, 0.1 mol) in dichloromethane triethylamine (15.29 mL, 0.11 mol) was added. After 15 min 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 [16].

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

To a stirred solution of **1** (263 mg, 1 mmol) in 1,2-dichloroethane (DCE), piperidine (43 mg, 0.5 mmol) and piperidine hydrochloride (183 mg, 1.5 mmol) were added. The mixture was stirred and heated at reflux for 24 h. After decomposition of **1**, DCE was removed under reduced presure and the residue was purified by CC, (AcOEt/hexane, 5:2). Yield 172 mg (70%), m.p. 115-117°, ^{1}H-

NMR (500 MHz, $CDCl_3$): 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* = 7.3, $1H_{arom}$), 7.34 (*t*, *J* = 7.8, $2H_{arom}$), 7.60 (*d*, *J* = 7.8, $2H_{arom}$), 10.18 (*s*, 1H, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 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* $[M + Na]^+$ calc. 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 **1** (263 mg, 1 mmol) in DCE, piperidine (43 mg, 0.5 mmol) and *N*-trimethylsilylpiperidine (235 mg, 1.5 mmol) was added. The mixture was stirred and heated at reflux for 2.5 h. After decomposition of **1**, DCE was removed under reduced presure and the residue was purified by CC (AcOEt/hexane 5:2). Yield 240 mg, (96 %), m.p. 115-117°. ^{1}H-NMR (500 MHz, $CDCl_3$): 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* = 7.3, $1H_{arom}$), 7.34 (*t*, *J* = 7.8, $2H_{arom}$), 7.60 (*d*, *J* = 7.8, $2H_{arom}$), 10.18 (*s*, 1H, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 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* $[M + Na]^+$ calc. for $C_{14}H_{18}N_2O_2$: 246.1368; found: 246.1381.

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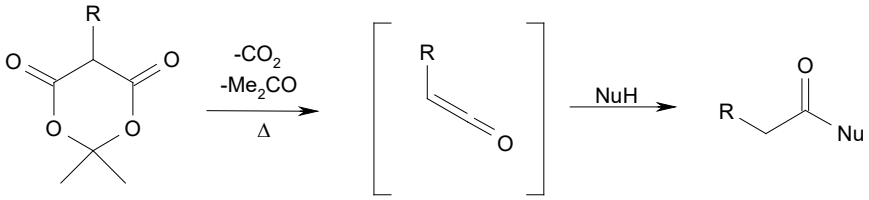
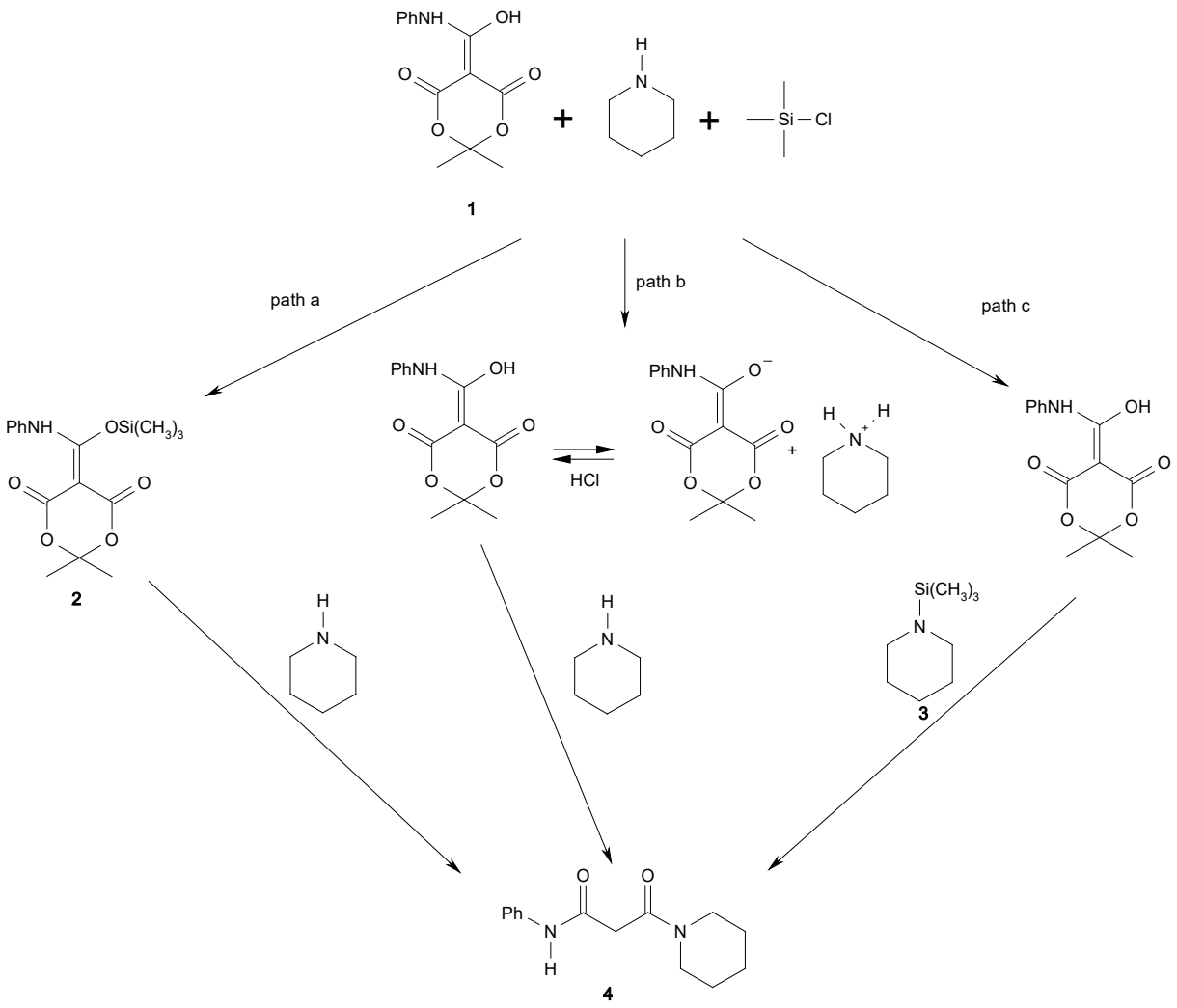
Scheme 1



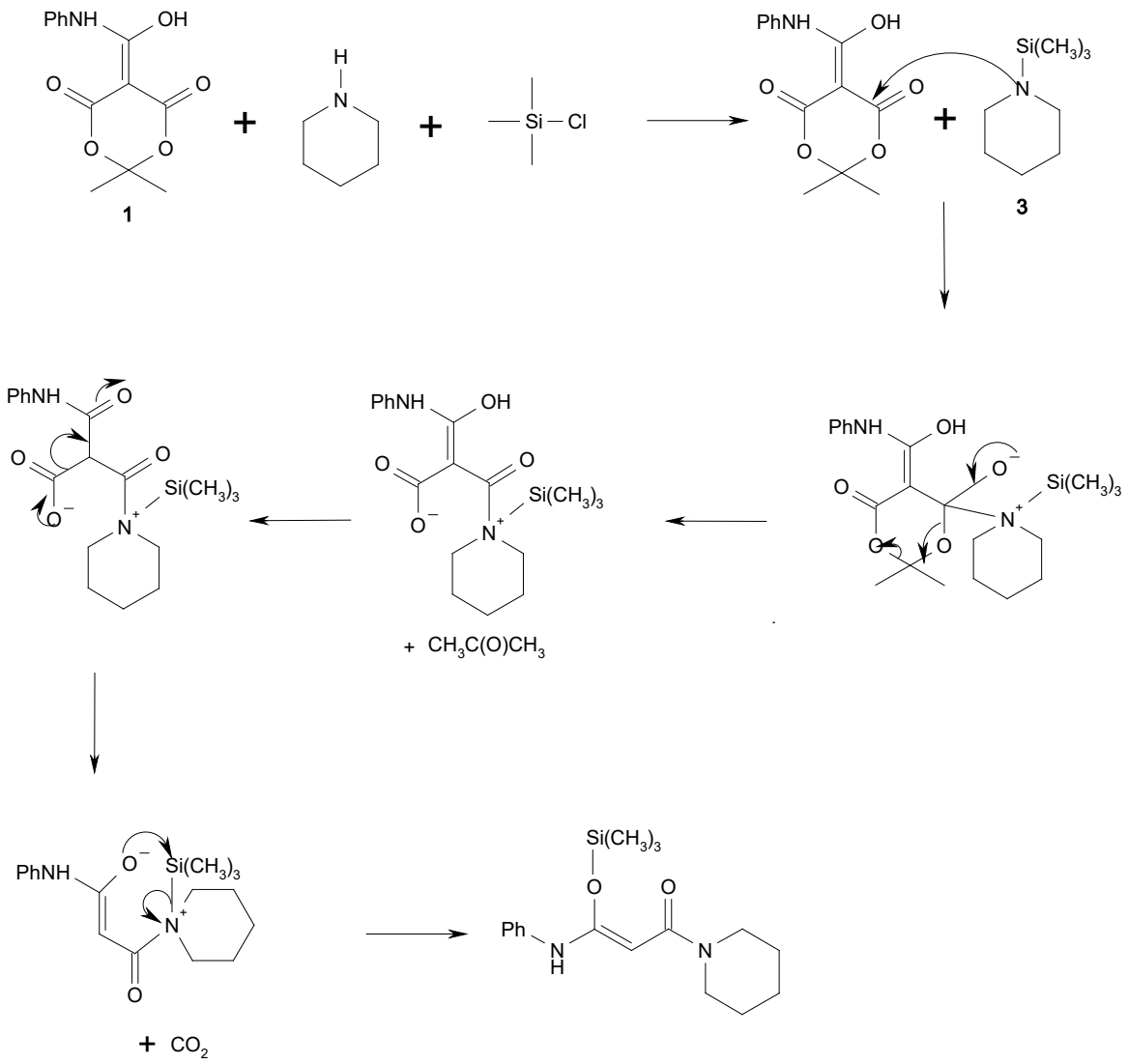
R= Alkyl, Aryl, Acyl, Carbamoyl, Thiocarbamoyl, Nitrosyl
NuH = ROH, RSH, R_2NH, imines

Scheme 2



*Hypothetical paths for acceleration of the reaction of **1** with amines by TMSCl*

Scheme 3



*Reaction mechanism of **1** with N-trimethylsilyl piperidine.*

Graphical Abstract