Mechanism of the Reaction of Amines with 5-[(Aryl- or Alkylamino)hydroxymethylene]-2,2-dimethyl-1,3-dioxane-4,6-diones in the Presence of Chlorotrimethylsilane (Me_3SiCl)

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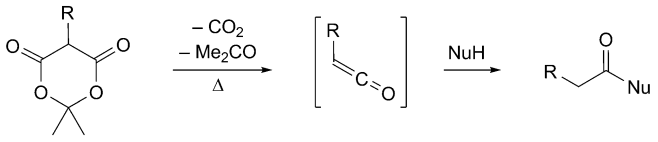
Addition of chlorotrimethylsilane (Me_3SiCl) to the mixture of a carbamoyl-substituted *Meldrum*'s acid, *i.e.*, a 5-[(arylamino)hydroxymethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione of type **1** and a secondary amine as nucleophile strongly accelerated the rate of their reaction. The reason for this phenomenon observed, during our previous research, remained, however, unclear. To elucidate the mechanism of this reaction, we assumed and verified three possible pathways for the action of Me_3SiCl (*cf. Scheme 2*): The acceleration of the reaction is caused *i*) by formation of a *O*-trimethylsilylated *Meldrum*'s acid of type **2**, *ii*) by the silylated amine **3**, or *iii*) by the presence of HCl liberated from Me_3SiCl. The performed experiments revealed that the faster course of reaction is caused by the formation of *N*-trimethylsilylated amines of type **3**.

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 lead to formation of oxo ketenes [2], carbamoyl ketenes [3], thiocarbamoyl ketenes [4], iminopropadienones [5], or even nitroso ketenes [6]. Practical application of the thus formed ketenes allow the preparation of various useful compounds, as *e.g.*, 3-substituted β-lactams [3][7], isoxazolols [8], pilicides [9], 1,3-oxazinones [10], or derivatives of tetramic acid [11].

Scheme 1



R = alkyl, aryl, acyl, carbamoyl, thiocarbamoyl, nitrosyl
NuH = ROH, RSH, R_2NH, imines

In our laboratory, we have focused on the reactivity and synthetic application of carbamoyl ketenes generated from 5-[hydroxy(aryl- or alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones. In contrast to acyl-substituted *Meldrum*'s acids, which became the subject of many publications including detailed mechanistic studies [12],

the reactivity of carbamoyl-substituted *Meldrum*'s acid is poorly described in the literature. Excluding our own papers, there is only one example of a systematic study of reactivity of carbamoyl-substituted *Meldrum*'s acids with nucleophiles presented by *Pak* and co-workers [13]. However, this article dealt only with thermolytic reaction of carbamoyl-substituted *Meldrum*'s acids with weakly basic *N*-nucleophiles such as aromatic amines with electron-withdrawing groups or even amides. During our experiments [14] with 5-[(aryl- or alkylamino)hydroxymethylene]-2,2-dimethyl-1,3-dioxane-4,6-diones, we found that the use of stronger basic secondary amines caused some problems such as low yield or a too long reaction time, difficulties that could be bypassed in the presence of chlorotrimethylsilane (Me_3SiCl). Thus, addition of 1.5 equiv. of Me_3SiCl to the mixture of an amine and 5-[(aryl- or alkylamino)hydroxymethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione led to the acylation product in nearly quantative yield, concomitantly with a reduction of the reaction temperature by over fifty degrees [14]. Initially, we used Me_3SiCl intuitively as catalyst, treating this reagent as an at least as good source of HCl as HCl itself. However, the actual effect of Me_3SiCl on the reaction remained unclear. We now wish to report on the elucidation of the mechanism of the reaction of amines with carbamoyl-substituted *Meldrum*'s acids promoted by Me_3SiCl.

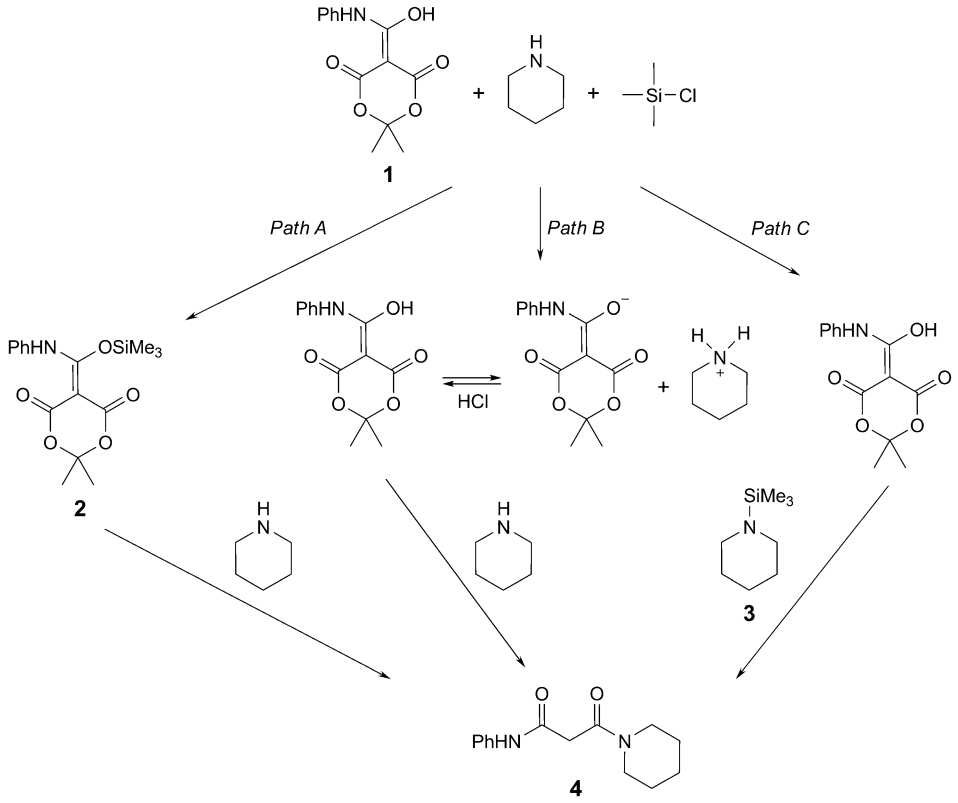
Results and Discussion. – At the beginning of this study, we assumed three hypotheses that would explain the observed phenomenon (*Scheme 2*), *i.e.*, the acceleration of the reaction of 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1**) with a secondary amine such as piperidine in the presence of Me_3SiCl to give the amide **4**. Addition of Me_3SiCl to **1** and the secondary amine may cause the formation of two silylated species, namely 2,2-dimethyl-5-{(phenylamino)-[(trimethylsilyl)oxy]methylene}-1,3-dioxane-4,6-dione (**2**) or (trimethylsilyl)amine **3**. Moreover, a stepwise addition of Me_3SiCl to only one species, for example **1**, does not exclude the formation of the silylated amine **3** in a subsequent transsilylation process after addition of the amine. Hence, we had to conceive a set of intelligent experiments allowing to separate the reciprocal influence of all involved species.

In the first probing of our hypothesis, we assumed that initially formed 2,2-dimethyl-5-{(phenylamino)[(trimethylsilyl)oxy]methylene}-1,3-dioxane-4,6-dione (**2**) promotes the acceleration of the reaction (*Scheme 2*, *Path A*). This seems very likely in view of the well known greater affinity of silylating agents towards an OH group rather than to a N-nucleophile. However, such an *O*-silylated *Meldrum*'s acid should rather slow down than speed up the reaction rate taking into account experiments, where *Meldrum*'s acid derivatives which do not contain OH or SH groups were stable up to 130° for 4–5 h [15].

The second possibility for the acceleration of the reaction (*Path B*) might be the presence of HCl liberated in the reaction of Me_3SiCl with the residual water present in the mixture. *Grabowski* and co-workers [12] have shown the influence of the acidity on the decomposition rate of **1**. Hence, we could not *ad hoc* exclude such a possibility for the examined reaction mechanism.

The third assumption for the acceleration of the discussed reaction (*Path C*) implies silylation of the secondary amine since silylated amines such as **3** are well known for their strong nucleophilic properties which may speed up the reaction.

Scheme 2. *Hypothetical Paths for the Acceleration of the Reaction of* **1** *with Amines by* Me_3SiCl



The key issue to be elucidated was to determine which silylated species was 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 [16]. To answer this question, the mixture of **1**, Et_3N, and Me_3SiCl in (D_6)benzene was analyzed by ^{1}H-NMR spectroscopy after 17 h at room temperature. Taking into account that a carbamoyl-substituted *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 only one Me signal at δ(H) 1.24. Substitution at the O-atom, *e.g.*, with alkyl groups, has a weak, however, noticeable influence on the chemical shift of these Me groups with a $\Delta\delta$ of *ca.* 0.06 [17][18]. Hence, we recorded the ^{1}H-NMR spectrum of **1** in (D_6)benzene with the aim to reveal a difference between silylated carbamoyl-substituted *Meldrum*'s acid **2** and **1**. However, the ^{1}H-NMR spectrum still showed only one signal at δ(H) 1.24. This fact strongly suggests that compound **2** was not formed. The second diagnostic signal of *Meldrum*'s acid, which may exclude or confirm the formation of **2**, is the presence or disappearance of the signal of the acidic H-atom at δ(H) 16.4. However, in the presence of Et_3N, this signal obviously disappears because

of salt formation. Therefore, we performed another NMR experiment, in (D_6)benzene with a mixture of **1** and *N*,*N*′-bis(trimethylsilyl)urea, a silylating agent which allows for silylation of carboxylic acids without the presence of a tertiary amine [19]. But again, in the ^{1}H-NMR spectrum only one Me signal was observed at δ(H) 1.20, and even after conducting this silylation reaction for 5 h, the unchanged signals of the OH and NH groups were still present at δ(H) 16.4 and 11.3, respectively. These results clearly exclude *Path A* as a route for the acceleration of the reaction of carbamoyl-substituted *Meldrum*'s acid with amines.

To obtain additional arguments, confirming or excluding the formation of **2** (*Path A*), we performed a large-scale experiment with 0.1 mol of **1** in $ClCH_2CH_2Cl$, 1.1 equiv. of Et_3N, and 1.5 equiv. of Me_3SiCl. After 24 h, $ClCH_2CH_2Cl$ and all volatile products were evaporated, and the residue was dissolved in dry Et_2O and treated with an excess of piperidine for additional 12 h. Then, the piperidinium salt of **1** was filtered, and Et_2O destilled off. The intention of this experiments is the following: if **2** was formed, it should react with piperidine under formation of *N*-trimethylsilylated piperidine **3**, or **2** would react with piperidine at elevated temperature by formation of malonamide **4**. However, distillation of the Et_2O residue did not result even in traces of **3**, and malonamide **4** also was not formed. These results also exclude *Path A*.

The following two additional experiments also exclude *Path A:* When **1** was treated in boiling $ClCH_2CH_2Cl$ without and with addition of 1.5 equiv. of Me_3SiCl, the time required for decomposition of **1** was as long as 24 h, whereas, as previously reported [14], in boilig $ClCH_2CH_2Cl$, **1** disappeared in the presence of Me_3SiCl and amine within 2.5 h. This clearly indicates that Me_3SiCl has no influence on the decomposition of **1** by accelerating its decomposition to ketene or by any other way.

The next possibilty for the acceleration of the reaction may be associated with the acidity of the mixture (*Path B*). As aforementioned, *Grabowski* and co-workers [12] demonstrated that the rate of formation of ketenes from acyl-substituted *Meldrum*'s acids directly depends on the concentration of the free acid form of the *Meldrum*'s acid derivative. Therefore, taking into account that the highest observed difference for the reaction with strong basic secondary amines, *i.e.*, a very slow reaction without Me_3SiCl and a very fast one with 1.5 equiv. of Me_3SiCl [14], led us to suppose that addition of controlled amounts of a strong acid to the mixture through hydrolysis of Me_3SiCl with residual water may have a decisive influence on the rate of the reaction, just by changing the acid–base equilibrium. However, as previously reported [14], the reaction of **1** with piperidine in ethylbenzene saturated with HCl was slightly faster, but the yield of malonamide **4** still remained unsatisfactory. Nevertheless, this result cannot exclude *Path B*, because during saturation with excess of HCl, all amine is converted into its hydrochloride so that the rate of decomposition of **1** to ketene is obviously higher, but there is a too low concentration of free amine to efficiently react with the formed ketene. The addition of 1.5 equiv. of Me_3SiCl to the mixture containing 2 equiv. of amine may produce only up to 1.5 equiv. of amine hydrochloride and thus leave still free amine. Therefore, we performed an experiment with 1 equiv. of **1**, 1.5 equiv. of piperidine hydrochloride, and 0.5 equiv. of free piperidine in boiling $ClCH_2CH_2Cl$. Under these conditions, we observed that total decomposition of **1** took as long as 24 h instead of 2.5 h as in the presence of Me_3SiCl, and the obtained yield of malonamide **4** was lower than 70% in comparision with 96% in the presence of Me_3SiCl. A ten times

longer reaction time clearly excludes *Path B*, *i.e.*, a simple acid catalysis of the decomposition of **1** to ketene.

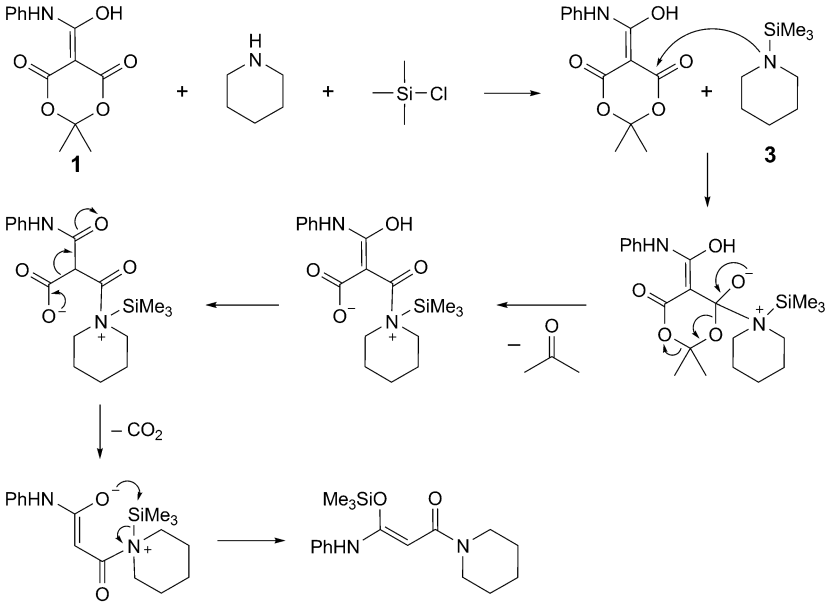
The last possibility for the acceleration of the reaction is the intervention of *N*-silylated amine **3** (*Path C*). To confirm this route, we performed the following experiment: 1 equiv. of **1** and 1.5 equiv. of 1-(trimethylsilyl)piperidine (**3**) were heated in boiling $ClCH_2CH_2Cl$. After 2.5 h, all starting **1** was consumed, and the yield of **4** was as high as 96%. This experiment shows that the use of pre-silylated amine or the use of Me_3SiCl results in the same yield and time required for the decomposition of **1**. This finding finally confirms *Path C*.

Having established that the acceleration of the reaction between **1** and an amine is caused by the formation of a silylated amine in the first step, we focused on the interaction of silylated amines with **1**. Some observed facts can be summarized as follows: after addition of Me_3SiCl, the acceleration of the reaction was enormous – in some cases, the conversion was ten times faster and, occurred at temperatures more than 50° lower than in the absence of Me_3SiCl. The influence of Me_3SiCl was more pronounced in the cases of *N*-aryl derivatives such as **1** than in the cases of *N*-alkyl derivatives of type **1** and, finally, reaction of **1** with a secondary amine in the absence of Me_3SiCl in low-boiling solvents was extremely slow, as established, *e.g.*, by the complete decomposition of **1** requiring *ca.* 100 h in the reaction with Et_2NH in $ClCH_2CH_2Cl$. These facts strongly suggest that in case of the use of Me_3SiCl/amine or just *N*-silylated amine, we indeed observe a change of the reaction mechanism, from formation of ketene and addition of a nucleophile to the addition–elimination-type of reaction. This idea is opposite to views presented by *Grabowski* and co-workers [12], which showed no dependence of the reaction rate on nucleophilicity and pointed to ketene as an undoubtedly existing intermediate. However, they examined acyl-substituted *Meldrum* acids, which are more prone to thermal decomposition to ketenes, whereas carbamoyl-substituted *Meldrum* acids are more resistant. Although *Shtaiwi* and *Wentrup* [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 $ClCH_2CH_2Cl$), an *N*-silylamine acts as a strong nucleophile and reacts directly with the 1,3-dioxane-4,6-dione system through an addition–elimination mechanism (*Scheme 3*), whereas in high-boiling solvents such as ethylbenzene in the absence of Me_3SiCl, **1** may react through the established mechanism of decomposition to ketene. The addition of *N*-silylamine to the 1,3-dioxane-4,6-dione system is facilitated when an *N*-aryl substituent is present, because in the case of *N*-alkyl derivatives of type **1**, we did not observe such a significant acceleration.

In conclusion, the formation of *N*-trimethylsilylated amines is directly responsible for the acceleration of the reaction of 5-[(aryl- or alkylamino)hydroxymethylene]-2,2-dimethyl-1,3-dioxane-4,6-diones with amines. Me_3SiCl 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.

Scheme 3. *Reaction Mechanism of* **1** *with 1-(Trimethylsilyl)piperidine* (**3**)



This work was financially supported by the *Founds for Science* in 2010 – 2011 (research project N N204 088338).

Experimental Part

1. *General.* All solvents used in this study were dried over appropiate drying agents and distilled prior to use. Commercially available reagents were purchased from *Sigma–Aldrich*. Commercially unavailable reagents were prepared by literature procedures: 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1**) [17] and 1-(trimethylsilyl)piperidine [20]. TLC: *Merck* silica gel *60 F_{254}*. Flash column chromatography (FC): *Zeochem ZEOprep 60/40-63*. M.p.: *Warsztat Elektromechaniczny* (Warszawa); uncorrected. NMR Spectra ($CDCl_3$): *Varian Unity Plus 500*; at 500 (^{1}H): 500 and 125 MHz (^{13}C); δ in ppm rel. to Me_4Si as internal standard, J in Hz. HR-ESI-MS: *Micromass-Quattro-LCT* mass spectrometer; in *m*/*z*.

2. *Attempts of Silylation of 5-[Hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione* (**1**). To a stirred soln. of **1** (26.3 g, 0.1 mol) in CH_2Cl_2 under Ar and cooled to 0°, Et_3N (15.29 ml, 0.11 mol) was added. After 15 min, Me_3SiCl (16.27 g, 0.15 mol) was added dropwise. After additional 15 min, the cooling bath was removed, and the mixture was stirred for 24 h. Then CH_2Cl_2 was evaporated and the residue dissolved in dry Et_2O. Piperidine (9.86 ml, 0.1 mol) was added to this soln. and the mixture stirred at r.t. for 12 h. Thereafter, the crystalline precipitate of the carbamoyl-substituted *Meldrum*'s acid salt with piperidine was filtered off. The Et_2O soln. was concentrated without appearance of any residue. The precipitate of *Meldrum*'s acid salt with piperidine was suspended in 2M HCl (200 ml), and filtered, the solid washed with H_2O and then dissolved in AcOEt, and the soln. dried ($MgSO_4$) and concentrated. Crystallization from AcOEt gave 10.73 g of recovered **1**. M.p. 104 – 106°. Spectral data: in agreement with [17].

3. *3-Oxo*-N-*phenyl-3-(piperidin-1-yl)propanamide* (= *β-Oxo*-N-*phenylpiperidine-1-propanamide*; **4**) *from Piperidine Hydrochloride.* To a stirred soln. of **1** (263 mg, 1 mmol) in $ClCH_2CH_2Cl$, piperidine (43 mg, 0.5 mmol) and piperidine hydrochloride (183 mg, 1.5 mmol) were added. The mixture was stirred

and heated under reflux for 24 h. After decomposition of **1**, the $ClCH_2CH_2Cl$ was evaporated and the residue purified by FC (AcOEt/hexane 5:2): 172 mg (70%) of **4**. M.p. 115–117°. ^{1}H-NMR: 1.61–1.70 (*m*, 3 CH_2); 3.49 (*s*, CH_2); 3.52–3.65 (*m*, 2 CH_2); 7.12 (*t*, *J* = 7.3, 1 arom. H); 7.34 (*t*, *J* = 7.8, 2 arom. H); 7.60 (*d*, *J* = 7.8, 2 arom. H); 10.18 (*s*, NH). ^{13}C-NMR: 24.5; 25.8; 26.7; 40.1; 43.6; 47.5; 120.3; 124.5; 129.2; 138.1; 164.6; 167.0. HR-ESI-MS: 246.1381 ($[M+Na]^+$, $C_{14}H_{18}N_2NaO_2^+$; calc. 246.1368).

4. *Propanamide* **4** *from 1-(Trimethylsilyl)piperidine* (**3**). As described in *Exper. 3*, with **1** (263 mg, 1 mmol), $ClCH_2CH_2Cl$, piperidine (43 mg, 0.5 mmol), and 1-(trimethylsilyl)piperidine (**3**; 235 mg, 1.5 mmol). The mixture was stirred and heated under reflux for 2.5 h. Workup as described in *Exper. 3:* 240 mg (96%) of **4**. Data: identical to those of **4** from *Exper. 3*.

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Received June 26, 2012