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Investigation on the Formation and Hydrolysis of *N,N*-Dimethylcarbamoyl Chloride (DMCC) in Vilsmeier Reactions Using GC/MS as the Analytical Detection Method

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Abstract:

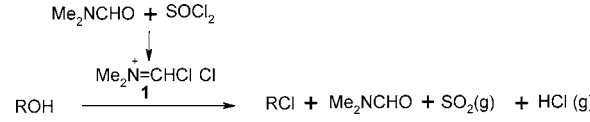
The formation of *N,N*-dimethylcarbamoyl chloride (DMCC) in Vilsmeier reactions (VRs) and the hydrolysis of DMCC during aqueous workup were investigated. The amount of DMCC formed was dependent on the chlorination reagent. The activity order was found to be: thionyl chloride > oxalyl chloride > phosphorus oxychloride. The concentrations of DMCC found in the tested reactions were normally at a level of 0−20 ppm. In the presence of a base the level was higher. DMCC hydrolyzed quickly under aqueous workup conditions. No more than 3 ppm of DMCC could be detected in the product after aqueous workup of the tested VR. Our results clearly indicate that by following the described procedure for VR it is perfectly safe from the health risk point of view to operate this chemistry when preparing compounds for pharmaceutical use. A very useful analytical procedure for detection and quantification of trace amounts of DMCC formed in the VR was developed. The method was based on derivatization of DMCC with ethanol to form ethyl *N,N*-dimethylcarbamate and analysis by GC coupled to a mass spectrometer in selected ion monitoring mode. The analytical method was selective and showed very good linearity. The limit of detection (LOD) and limit of quantification (LOQ) of DMCC using standard addition analysis with real Vilsmeier reaction matrices were determined to be LOD = 0.2 ppm and LOQ = 0.7 ppm.

Introduction

The Vilsmeier reaction (VR), or Vilsmeier−Haack reaction, has a large range of applications in organic synthesis.[1,2] One of the most important applications is the chlorination of an alcohol as is shown in Scheme 1. The actual chlorination reactant is the *in situ* generated Vilsmeier reagent **1**, which is formed by reaction of the chlorination agent and *N,N*-dimethylformamide (DMF), the latter normally present in catalytic amounts.[3]

N,N-dimethylcarbamoyl chloride, also called DMCC, is an active alkylating agent and has been used as an intermediate in the manufacture of a number of pharmaceuticals and pesticides.The formation of DMCC under VR conditions was reported as early as the 1960s.[4,5] The health safety concerns regarding the application of VR in organic synthesis was raised by D. Levin[6] in light of the fact that DMCC is a potential carcinogen according to the International Agency for Research on Cancer (IARC) evaluations.[7,8] During the last five years an increased interest regarding potential genotoxic impurities (PGIs) has emerged from health authorities and the phamaceutical industry. PGIs have had such an impact that process chemists must consider changing the reagent(s), choosing another route or applying a control strategy to eliminate any PGIs. At the moment there is inadequate evidence for carcinogenicity of DMCC in humans, although there is sufficient evidence for carcinogenicity in animals. Thus, DMCC generated in an organic process for the manufacturing of an API can be defined as a PGI. The permitted level is dependent on the daily dose, but DMCC is normally only allowed in ppm levels,[9,10] which puts challenges into the analytical methods.

Scheme 1. **Chlorine replacement of a hydroxyl group by Vilsmeier reagent 1**



The concerns around the formation of DMCC under the VR conditions have resulted in restricted application of the VR in the process development of pharmaceuticals even though little is reported as to how much or about how much DMCC is really generated during the reactions. In an ongoing project, we decided to apply the VR in the penultimate step, the chlorination of **2** for the synthesis of **5** (Scheme 2). In the process, DMF is utilized both as a protecting agent for the formation of the hydroxyl amidine **3** and as a catalyst for the Vilsmeier chlorination of **3** to generate the chlorinated amidine **4** (Scheme 2). In order to assess the health safety risk of the process before scaling it up into the pilot scale we decided to determine the amount of DMCC generated under the reaction conditions employed.

A survey of the literature revealed that there was neither a suitable analytical method nor data available for the detection

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Scheme 2. **Chlorination of compound 2 using a Vilsmeier reaction, with in situ protection of the amino group by using DMF**

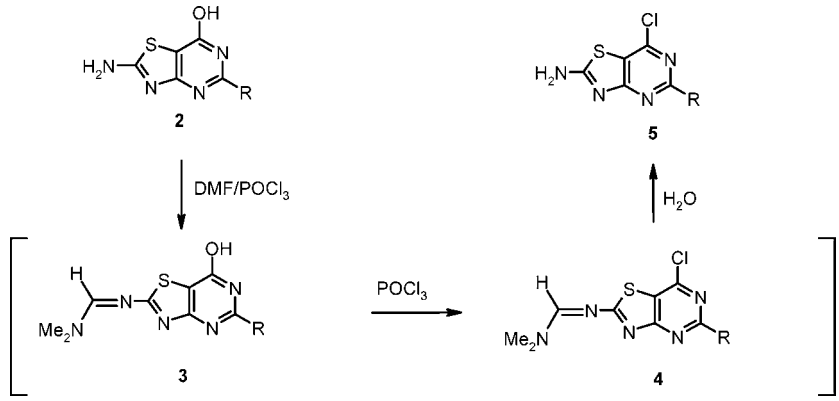


Table 1. **Detection of DMCC in the reaction of different chlorinating agents with DMF**

entry	chlorinating agent	solvent	molar ratio (DMF: mhlorinating agent)	temp. (°C)	time (min)	DMCC detected (ppm)
1	$SOCl_2$	neat	1:0.4	23	30	11
2	$SOCl_2$	neat	1:1.1	23	30	6
3	$SOCl_2$	neat	1:2.4	23	30	13
4	$POCl_3$	neat	1:0.4	23	30	1.1
5	$POCl_3$	neat	1:1.1	23	30	0.8
6	$POCl_3$	neat	1:2.4	23	30	1.0
7	$SOCl_2$	dioxane	1:2.4	23	30	2.4
8	$POCl_3$	dioxane	1:2.7	23	30	1.9[b]
9	$POCl_3$	dioxane	1:2.7	65	180	~7
10	$SOCl_2$:pyridine	dioxane	1:1:2.4	23	30	2400[a]
11	$POCl_3$:pyridine	dioxane	1:1:2.7	70	30	17[b]
12	$POCl_3$:**2**	dioxane	1:0.8:2.7	65	180	104
13	$(COCl)_2$	dioxane	1:2.6	23	120	Detected but not quantified due to poor solubility
14	$(COCl)_2$	CH_2Cl_2	1:2.6	23	30	2
15	$POCl_3$	CH_2Cl_2	1:2.6	23	30	0.2
16	$SOCl_2$	CH_2Cl_2	1:2.6	23	30	5.0

[a] The amount of DMCC is estimated. It exceeded the linear range of this method. [b] Some emulsion was observed.

of DMCC in a VR matrix. Matienzo and co-workers[11] reported a direct analysis by GC for the determination of DMCC in air for as low as ppb levels by concentrating the sample on an absorbing polymer before analysis. Rusch and co-workers[12] reported a quantitative analytical method for determination of DMCC in air by derivatization of the sample with 4-(*p*-nitrobenzyl)pyridine and spectrophotometric analysis of the derivative. Alternative analytical techniques such as LC/MS and GC/MS, without derivatization, had been investigated but suffered from corrosion problems.[13]

Results and Discussions

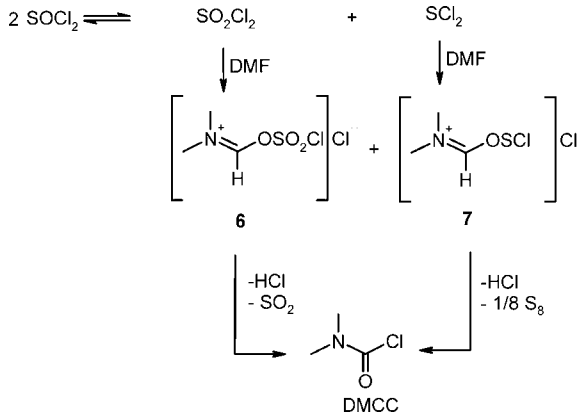
Quantitative Determination of DMCC under Various Conditions. With the development of GC/MS in selected ion monitoring (SIM) method we determined the amounts of DMCC generated in the VR under different conditions. Reactions of DMF with the three most commonly used chlorination agents, thionyl chloride ($SOCl_2$), phosphorus oxychloride ($POCl_3$), and oxalyl chloride [$(COCl)_2$], were investigated. The results are summarized in Table 1. A neat mixture of DMF and thionyl chloride (ratio 1:0.4; 1:1.1, and 1:2.4) at room temperature after 30 min generated levels of DMCC at 11 ppm, 6 ppm, and 13 ppm (entries 1−3). Under similar reaction conditions using similar equivalents of $POCl_3$the reactions yielded 1.1 ppm, 0.8 ppm, and 1.0 ppm of DMCC, respectively (entries 4−6). The results from these experiments show that increasing the equivalents of the chlorinating reagent does not increase the amount of DMCC proportionally. Another important observation is that $POCl_3$ gave a considerable reduction of the amount of DMCC obtained.

Most VRs will be run in a solvent, and the solvent of interest to us was dioxane. When repeating the experiments above with dioxane present, $SOCl_2$/DMF gave 2.4 ppm, and $POCl_3$/DMF gave 1.9 ppm of DMCC. The analytical results showed that a very low level of DMCC was found, and the difference between $SOCl_2$ and $POCl_3$ is now very small (entries 7−8).

An emulsion was observed in the mixture of $POCl_3$, DMF, and dioxane at room temperature. To minimize the formation of emulsion an experiment at increased temperature (65 °C instead of 23 °C) was performed. The amount of DMCC was then increased up to approx 7 ppm (entry 9).

(11) Matienzo, L. J.; Hensler, C. J. *Am. Ind. Hyg. Assoc. J.* **1982**, *43* (11), 838–844.
(12) Rusch, G. M.; LaMendola, S. L.; Kats, G. V.; Laskin, S. *Anal. Chem.* **1976**, *48* (14), 2259–2261.
(13) When GC/MS was employed for the analysis of DMCC in the mixture of thionyl chloride and DMF, the injector was severely corroded. When LC/MS was used, the injector syringe was corroded.

Scheme 3. **Formation of DMCC in the reaction of DMF with SCl_2 and SO_2Cl_2**



A base is often employed in VRs to neutralize the HCl generated during the reaction. Pyridine is one of the most commonly used bases in this regard. Our interest then turned to investigating the effect that addition of a base, such as pyridine, could have. The results show that it had a great impact on the formation of DMCC when $SOCl_2$ and DMF were used in dioxane. The amount of DMCC formed in this case was as high as 2400 ppm (compare entries 7 and 10). An enhancement of the amount of DMCC could be detected also when $POCl_3$ was used, but not to the same extent (compare entries 9 and 11). When the pyridine was replaced by the substrate **2** that is also a base, the amount of DMCC increased from 2.7 ppm to 104 ppm (compare entries 7 and 12), which indicates that the presence of a base increases the formation of DMCC. The mechanism of the formation of DMCC under VR conditions has not been thoroughly investigated. We believe that in the case when thionyl chloride is used as the chlorinating reagent two possible routes can lead to the formation of DMCC: one involving sulfuryl chloride and one involving sulfur dichloride as shown in Scheme 3. The reversible reduction−oxidation of thionyl chloride can generate sulfuryl chloride and sulfur dichloride.[14] The sulfuryl chloride reacts with DMF to form complex **6** that on elimination of SO_2 and HCl yields DMCC as suggested by Kühle.[4] The sulfur dichloride forms complex **7** with DMF, which on elimination of S(s) and HCl yields DMCC.[5] The formation of DMCC is an irreversible process due to the formation of gaseous sulfur dioxide and solid sulfur. This process is apparently base promoted by capture of the proton generated during the reaction. This explains why there was a significant amount of DMCC formed with sulfur precipitation in entry 10. This is in line with the observation by Hasserodt[5] where a reaction of SCl_2 and DMF gave as much as 25% of DMCC.

DMCC was detected in the reaction mixture of DMF and oxalyl chloride in dioxane but not quantified due to the poor solubility of the mixture in dioxane (entry 13). In order to determine the amount of DMCC formed we replaced dioxane with CH_2Cl_2 and found 2 ppm of DMCC in the solution (entry 14). Since the reaction mixtures of DMF with both $POCl_3$ and $SOCl_2$ are soluble in dichloromethane we determined the amount of DMCC in these systems as well (entries 15 and 16).

(14) Evans, A. G.; Meadows, G. W. *Trans. Faraday Soc.* **1947**, *43*, 667–674.

Table 2. **Determination of the amount of DMCC formed in the chlorination of compound 2**

entry	sampling stage	temperature (°C)	time (h)	DMCC (ppm)
1	amidine **3, 4**	60	3.0	87
2	**5**	70	0.5	0.9
3	**5** (isolated)	23	na	2.8

Table 3. **Experimental data from the hydrolysis of DMCC in the presence of $POCl_3$**

t [s]	C_t [mol/L] × 10^{-3}	ln C_t
0	11.4100	−4.47
240	10.1100	−4.59
360	8.7700	−4.74
480	7.4900	−4.89
600	6.1990	−5.08
720	5.3670	−5.23
840	4.5160	−5.40
960	3.7548	−5.59
1080	3.2324	−5.74
1200	2.5160	−5.98
1500	1.2733	−6.67
1800	0.8104	−7.12
2400	0.2569	−8.27
3000	0.0764	−9.45
3600	0.0316	−10.36

Comparing the data in entries 14 to 16 we could find that the reactivity of the three chlorination reagents for the formation of DMCC on reaction with DMF is: $SOCl_2$ (5 ppm) > $(COCl)_2$ (2 ppm) > $POCl_3$ (0.5 ppm).

The formation of DMCC in the chlorination of compound **2** using $POCl_3$ was investigated, and the results are found in Table 2. The reaction was performed in dioxane and was complete within 3 h at 60 °C. The analysis of the reaction mixture gave 87 ppm of DMCC (entry 1). On completion, the reaction mixture was quenched with water and hydrolyzed for 30 min to remove the amino protection group. After the hydrolysis the concentration of DMCC in the reaction mixture was 0.9 ppm (entry 2), and the isolated product **5** (yield 90%) contained only 2.8 ppm of DMCC (entry 3).

Hydrolysis of DMCC in Dioxane/Water under Acidic Conditions. VRs are often followed by an aqueous workup in an organic process. This offers an opportunity to reduce the amount of DMCC once it is formed because of its fast hydrolysis. Solvolysis of DMCC in pure water has been carefully investigated over a wide ranges of temperature by Queen.[15] The rate constant for the hydrolysis in H_2O is >0.0025/s, and its half-life in moist air (50% relative humidity) is approximately 3 h, both of which indicate a fairly rapid hydrolysis.[16]

To get a better understanding of the hydrolysis of DMCC under our process conditions, we performed a reaction at our standard conditions without the substrate compound **2**. Thus, a mixture of DMCC, dioxane, and $POCl_3$ was heated to 80 °C and then quenched with water. Samples were taken from the quenched reaction mixture and analyzed with the GC/MS method. The concentration of DMCC found at each time (C_t) and the ln C_t data are listed in the Table 3. The plot of ln C_t against the reaction time is shown in Figure 1. The good linear

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(16) *Dangerous Properties of Industrial Materials Report*; Van Nostrand Reinhold: New York, 1987; Vol. 7 (1), pp 51−54.

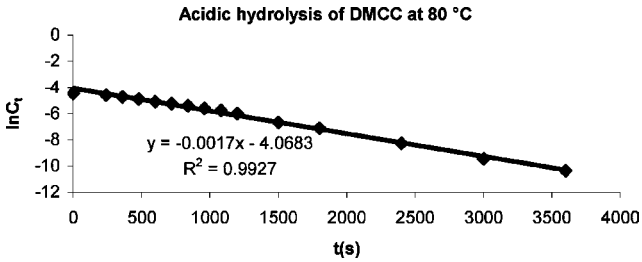
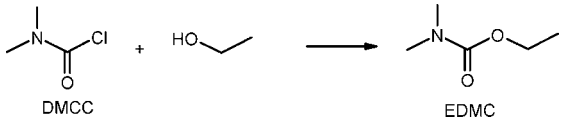


Figure 1. **Hydrolysis of DMCC in the presence of $POCl_3$: ln C_t plotted against time.**

Table 4. **Hydrolysis rate constant and half-life time of DMCC under different conditions**

entry	temperature (°C)	reaction conditions	rate constant k (s^{-1})	half-life τ (min)
1	80	dioxane/ $POCl_3$/ H_2O	0.0017	6.80
2	80	dioxane/ $POCl_3$/ H_2O (In the presence of **2**)	0.0028	4.13
3	50	dioxane/ $POCl_3/D_2O$	0.0010	11.55

Scheme 4. **Derivatization of DMCC with ethanol for the detection and determination of DMCC formed in the Vilsmeier reaction**



relationship between ln C_t and t indicates that the hydrolysis of DMCC exhibits the expected first-order reaction: ln $C_t = -kt + \ln C_0$. From this equation we could determine the hydrolysis rate constant as $k = 0.0017$ s^{-1}. Similar experiments were carried out in the presence of compound **2**, and the hydrolysis rate constant was found to be $k = 0.0028$ s^{-1}. The half-life (τ) of DMCC under these conditions was 6.80 and 4.13 min, respectively, based on the equation $\tau = \ln 2/k$. We have also investigated the hydrolysis in the presence of $POCl_3$ by ^1H NMR and found the half-life of DMCC to be 11.55 min at 50 °C (entry 3, Table 4).

These results show that even though DMCC might be formed during the Vilsmeier reaction, an aqueous workup can eliminate it down to a very low level. It should also be possible to capture and hydrolyse DMCC in a scrubber from the process ventilation system to prevent air contamination.

Development of the Analytical Method. The analyses of standard samples of the ethanol adduct of DMCC, i.e. ethyl *N*,*N*-dimethyl carbamate (EDMC), using GC with flame ionisation detection (FID) showed that this analytical technique could be used for detection and quantification of DMCC. However, when authentic samples from the Vilsmeier synthesis were analysed, interferences from the sample matrix were observed. Therefore, an analytical procedure involving derivatization of DMCC with ethanol to form EDMC (Scheme 4) and a subsequent analysis by GC/MS-SIM using an internal standard (IS) was developed. A number of compounds were tested as the IS with respect to peak shape and retention time. Naphthalene was chosen as the most suitable compound. Using GC/MS in SIM mode only few chosen ions were recorded, and the interference from compounds eluting at the same time range could be minimised or avoided. Moreover, the sensitivity of the analysis was improved.

GC/MS analyses in full scan mode of standard solutions of EDMC and naphthalene were carried out to decide which ions should be selected for SIM analysis. For each compound three ions were selected. One ion was used for quantifications, and the other two were chosen as qualifiers (see Experimental Section for detailed information regarding the selected ions). Figure 2 shows mass spectra of both EDMC and naphthalene. Figure 3 shows the chromatograms from GC/MS-SIM analysis of a sample obtained after one of the VRs.

The concentration of DMCC in the analyzed samples was determined by standard addition analysis at four levels. This analytical approach is used when sample matrix can cause incorrect readings from a calibration curve based on pure standards. For all four samples the area ratio of EDMC to IS detected by GC/MS-SIM vs the amount of the sample were plotted against the amount of added standard of DMCC. The quantity of DMCC was calculated by extrapolating the calibration curve to a point at a zero signal, and the absolute value of the *x*-intercept was the amount of the DMCC in the analysed sample.

Qualification of the Analytical Method. *Selectivity.* Since the SIM mode with three characteristic ions recorded for the analysed substance was used, the method was considered to be selective, when the inspection of the intensity of the ions showed consistency with the expected abundance ratio between them, and the retention time was the same for the monitored ions. Fulfilling these required conditions assured that the desired compound was detected and quantified.

Linearity. The results from standard addition analysis showed a very good linear correlation between the amount of DMCC added and the area ratio of the detected EDMC and IS. The correlation coefficient for all analysed samples was $R^2 > 0.9$. Figure 4 presents an example of this linear response from the GC/MS-SIM analysis of one sample from a VR studied during the method development.

Limit of Detection and Limit of Quantification. Limit of detection (LOD) and limit of quantification (LOQ) of DMCC with the Vilsmeier reaction matrices were determined to be LOD = 0.2 ppm, and LOQ = 0.7 ppm. These values of LOD and LOQ were determined with the sample matrix at signal-to-noise ratios (S/N) of $S/N = 3$ for LOD and $S/N = 10$ for LOQ.

Conclusions

In the presented investigation a robust analytical procedure for measuring DMCC, using derivatisation with ethanol and GC/MS analysis in selected ion monitoring mode has been developed. The performance of the analytical method shows that it can accurately measure DMCC in Vilsmeier reaction mixtures down to single digit ppm levels.

The analytical method enabled us to investigate the impact of some common chlorinating agents on the formation of DMCC in the Vilsmeier reaction. In all cases the amount of DMCC was low (<15 ppm), and the established order was thionyl chloride > oxalyl chloride > phosphorus oxychloride, with the latter yielding the lowest amount of DMCC. It was also found that, when an organic base was present in the reaction mixture, it profoundly increased the amount of DMCC formed.

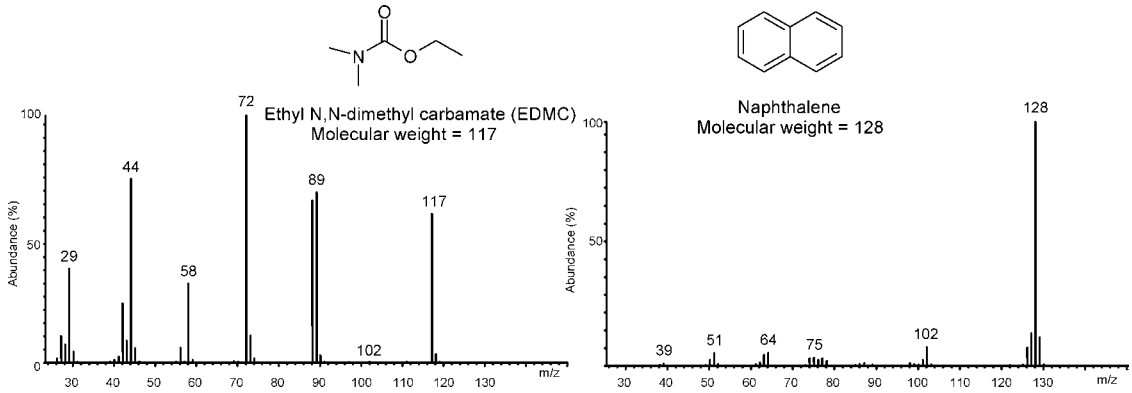


Figure 2. **Mass spectra of EDMC (the derivative of DMCC) and naphthalene (chosen as the internal standard), respectively, acquired by GC/MS analysis in full scan mode of pure standard samples. Characteristic ions selected for EDMC to be analysed in SIM mode were *m*/*z* 117, 89, and 72, and for naphthalene the following three ions were chosen: *m*/*z* 128, 102, and 64; *m*/*z* depicts mass-to-charge ratio.**

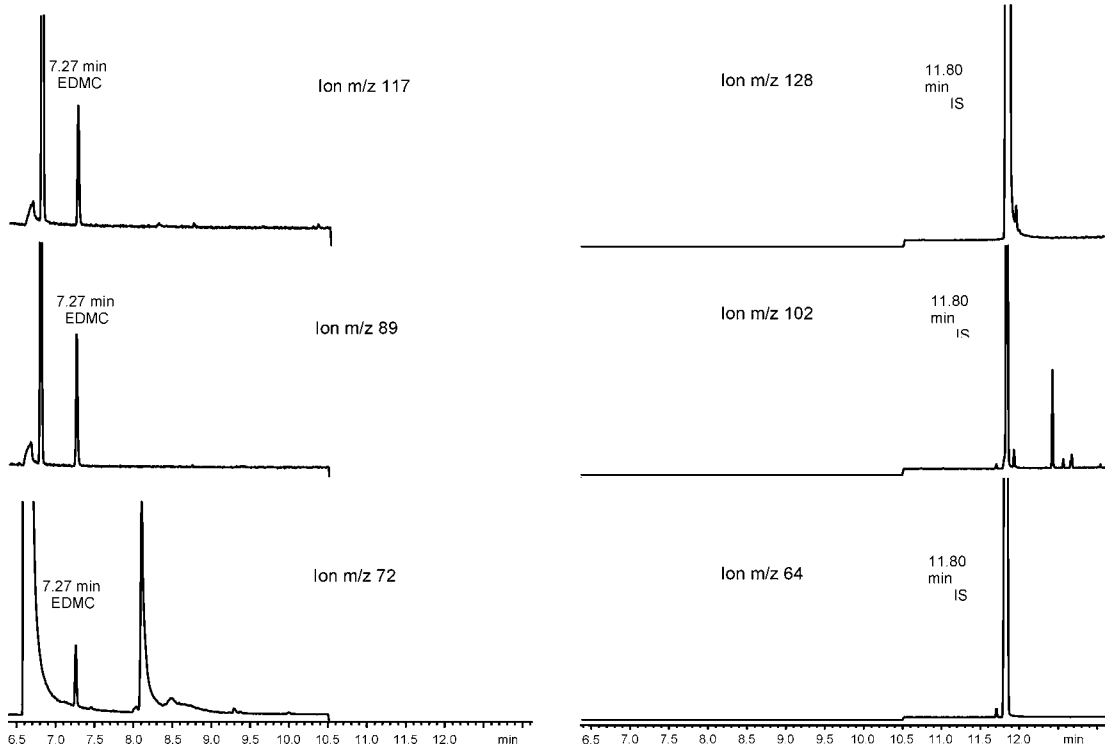


Figure 3. **GC/MS analyses in SIM mode of the sample from a Vilsmeier reaction with $POCl_3$ and DMF (1:1), at room temperature for 4.5 h. Six chromatograms showing the response to the six analysed ions are presented. The concentration of DMCC in the analysed sample was 4.4 ppm.**

It has been shown that DMCC hydrolyses rapidly under aqueous workup conditions. This provides an opportunity for process chemists to design their processes in such a way that the formed DMCC is decreased to acceptable levels during an aqueous workup. Therefore, processes for manufacturing pharmaceuticals based upon a Vilsmeier reaction can be developed without risking the health of process operators or patients.

Experimental Section

Materials. *N*,*N*-Dimethylcarbamoyl chloride (DMCC) and naphthalene were purchased from Sigma-Aldrich with 99+% purity. Other chemicals were obtained commercially with analytical purity. Compound **2** was synthesized according to the published method.[17]

Preparation of Ethyl *N*,*N*-Dimethylcarbamate (EDMC). This compound was prepared in a similar fashion to the one reported earlier[18] by reacting DMCC (1 equiv.) with C_2H_5OH (4 equiv) in the presence of pyridine (1 equiv) at 75 °C. On completion, the excess of C_2H_5OH was removed by vacuum distillation. The remaining product was partitioned between diluted HCl and CH_2Cl_2. Pure EDMC was obtained by distillation (139−142 °C/1 atm). Yield: 75%. Purity: 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, J = 7.3 Hz, 3H), 2.82 (s, 6H), 4.06 (q, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.84, 35.95, 38.61, 60.84, 156.68. High resolution mass spectrometry (HRMS): $C_5H_{11}NO_2$, $(M + H)^+$ calculated *m*/*z* 118.0854, found *m*/*z* 118.0846.

(17) Nordvall, G.; Ray, C.; Rein, T.; Sohn, D. PCT Int. Appl. WO 2006107258 A1, 2006.
(18) Valega, T. M. *J. Org. Chem.* **1966**, *31* (4), 1150–1153.

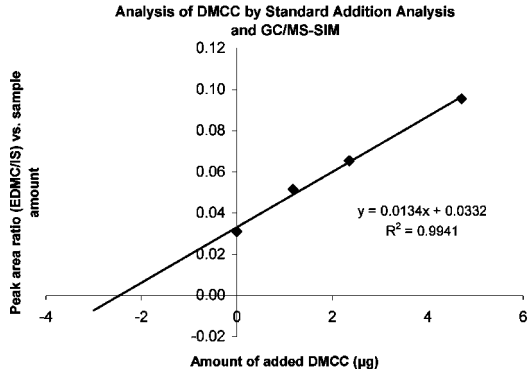


Figure 4. **Linearity of the analytical method for determination of DMCC using standard addition analysis and GC/MS-SIM technique. Data originate from a Vilsmeier reaction with $POCl_3$ and DMF (1:1), at room temperature for 4.5 h. The amount of DMCC detected in this sample (0.564 g) was 2.48 μg, which corresponded to a concentration of 4.4 ppm in the analysed sample.**

Conversion of Compound 2 to Compound 5.[17] A mixture of $POCl_3$ (1.34 g, 8.74 mmol), DMF (0.28 g, 3.8 mmol), and dioxane (8.26 g, 8.02 mL) was stirred for 30 min at room temperature. Compound **2** (1.0 g, 3.3 mmol) was added to this mixture. The whole mixture was then heated to 60 °C for 3 h by which time the intermediate **3** was fully converted to the intermediate **4** as confirmed by LC/MS. H_2O (2.0 mL) was then added to the solution and heated at 70 °C for 30 min. After the disappearance of the intermediate **4**, the reaction mixture was poured in cold H_2O (10 mL). Compound **5** was obtained by filtration with a typical yield of 80% from compound **2**.

Hydrolysis Studies by the ^{1}H NMR Method. $POCl_3$ (0.4 mL, 4.30 mmol) was added to D_2O (1.2 mL, 66.1 mmol), and the mixture was stirred for 10 min. The hydrolyzed phosphorus oxychloride in D_2O was added to a solution of *N*,*N*-dimethylcarbamoyl chloride (DMCC) (0.4 g, 3.72 mmol) in dioxane, and the resulting mixture was stirred at 50 °C. Nine samples were removed from the reaction mixture during 26 min and analyzed quantitatively with ^{1}H NMR for the determination of the hydrolysis rate constant as well as the half-life time.

Hydrolysis Studies Using the GC/MS Method. A solution of DMCC (31 mg, 0.3 mmol) and $POCl_3$ (0.3 mL, 3.23 mmol) in dioxane (25 mL) was heated to 80 °C. A sample (0.4 mL) was removed from this hot solution and used as the zero samples. H_2O (2 mL) was added to the hot solution, and the whole mixture was stirred at this temperature for 60 min. The samples were removed from the mixture for quantitative determination of DMCC by the GC/MS method.

GC/MS-SIM Conditions. *GC.* The analyses were carried out on an HP 6890 GC system combined with an HP 5973 mass selective detector and equipped with an Agilent DB-1701 column (14% cyanopropyl-phenyl-methylpolysiloxane), 30 m × 0.25 mm, 0.25 μm film thickness.

Helium was used as carrier gas, at a constant flow rate of 1.0 mL/min.

Injection conditions: split injection; split ratio 50:1; injector temperature 250 °C.

GC oven temperature program: 40 °C for 2 min, raised at 10 °C/min to 130 °C, then 40 °C/min to 300 °C, and kept at 300 °C for 5 min.

MS. Temperatures: MS quadrupole 150 °C, MS source 230 °C.

Acquisition mode was set to Selected Ion Monitoring. Ions monitored for EDMC from 6.0 to 10.5 min were *m*/*z* 72.0, 89.0, and 117.0. Ion *m*/*z* 117.0 was used for quantifications, and *m*/*z* 72.0 and 89.0 were qualifiers. Ions monitored for naphthalene (IS) from 10.5 to 20.2 min were *m*/*z* 64.0, 102.0, and 128.0. For quantifications ion *m*/*z* 102.0 was chosen, and ions *m*/*z* 64.0 and 128.0 were selected as qualifiers.

Dwell time: 100 ms.

Vilsmeier Reactions. *Neat Reactions.* The reactions of chlorinating agents $SOCl_2$, $POCl_3$ and oxalyl chloride with DMF in different molar ratios were carried out in approx 3 mL scale in 7 mL glass test tubes.

Reactions in Dioxane. The chlorinating reagent (in excess) was added to a solution of DMF in approx 5 mL dioxane. The reactions were carried out in a 25 mL three-necked round-bottom flask equipped with a thermometer and a magnetic stirrer bar.

Reactions in the Presence of Base. The procedure was the same as the one mentioned above but with one equivalent pyridine added.

Reactions in Dichloromethane. The chlorinating reagent (in excess), was added to a solution of DMF in dichloromethane in three different 7 mL glass test tubes. The mixture was stirred using a magnetic stirrer bar at the desired temperature.

Reactions in the Presence of Compound 2. $POCl_3$ (1.34 g, 8.74 mmol) was added to a solution of DMF (0.28 g, 3.83 mmol) in dioxane (8 mL) in a three-necked round-bottom flask. After 30 min, compound **2** (1.0 g, 3.28 mmol) was added. The whole mixture was then stirred with a magnetic stirrer bar at 65 °C for 3 h.

Sample Preparation for GC/MS-SIM Analysis. Four samples (approximately 0.5 g) were taken simultaneously from the reaction mixture and weighed. The samples were added to four separate 5-mL test tubes with C_2H_5OH (1 mL) and then heated to 70 °C. The test tubes were equipped with a magnetic stirrer and septa penetrated with glass capillaries. The test tubes were placed in a heating block. Acetonitrile (0.5 mL) was added to one of the test tubes and standards of DMCC in acetonitrile (0.5 mL) were added to the other three tubes. After one hour, the mixture was cooled to room temperature. Saturated $NaHCO_3$ (1−2 mL) and H_2O (1−2 mL) were added to each tube to reach pH 8−9. Each sample was extracted with CH_2Cl_2 (2 mL) containing 50 ppm naphthalene (IS). The organic phase from each of the four samples was dried over anhydrous Na_2SO_4 before being submitted to the GC/MS analysis.

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