Tetrahedron 70 (2014) 6515–6521

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Methacryloyl chloride dimers: from structure elucidation to a manifold of chemical transformations

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ARTICLE INFO

Article history:
Received 4 April 2014
Received in revised form 30 June 2014
Accepted 5 July 2014
Available online 9 July 2014

Keywords:
Methacryloyl chloride
Diels–Alder reaction
Lewis acid
Cationic rearrangement
Carboxonium ions

ABSTRACT

We report the isolation and elucidation of structure, formation mechanisms, and reactivity of elusive methacryloyl chloride dimers. Upon standing of a sample of methacryloyl chloride (**1**) for prolonged periods of time dimer **3** forms via oxa-Diels–Alder reaction even at low temperatures. If traces of a Lewis acid are present, dimer **3** isomerizes into a mixture of 2-oxo-cyclopentanecarbonyl chlorides **4**, **14**, and traces of **5**, with a relative ratio that depends on the nature of the Lewis acid and reaction time. Dimer **3** can also be separated and isolated by vacuum distillation and selectively converted into derivatives of 2,5-dimethyl-2-hydroxyadipic acid, as well as into the compound **14** by treating with a catalytic amount of titanium tetrachloride. Additionally, based on the study, suggestions on purification and handling of methacryloyl chloride are proposed.

1. Introduction

In synthetic chemistry, a broad variety of simple and readily available commercial reagents serve as building blocks for assembly of diverse target structures of different complexity using common organic reactions. The chemistry of such reagents is usually very well explored and it is quite unexpected to discover previously unreported transformations of a simple organic compound that has been known and intensively employed in synthesis for more than a century. It is especially interesting, if a usual commercial reagent affords upon standing a previously overlooked relatively complex structure with multiple possibilities for further functionalization.

Recently we observed the formation of a white crystalline water soluble substance after a sample of commercial methacryloyl chloride[1,2] (MAACl) **1** with a reported purity of more than 97% was inadvertently exposed to air for several days. After detailed molecular structure analysis we were quite surprised to observe the formation of previously undescribed 2,5-dimethyl-2-hydroxyadipic acid[3] **2** (Fig. 1). This discovery attracted our attention not only due to its astounding nature, but also because of the importance of adipic acid in polymer chemistry[4] as well as possible usefulness of **2** as a molecular building block. However, it was impossible to postulate a simple reaction pathway leading directly from MAACl to the new substance **2**. It was clear that in a first step, a dimerization reaction with a bond formation between terminal alkene carbon atoms should occur. Thorough literature searches provided very scarce information about MAACl dimers, which have been described sporadically in the literature as impurities in samples of commercial methacryloyl chloride.[5] To our knowledge, only one publication describes a study on structure elucidation of MAACl dimers.[5a] Therein, a mixture of three different dimers **3**–**5** (Fig. 2) was proposed by Fisher et al. as a common MAACl impurity. However, only the formation of dimers **4** and **5** was proved on the basis of ^{1}H NMR spectra, while the existence of **3** could not been directly verified and no investigations on the mechanism of their formation have been reported.[6] In contrast to the observations of

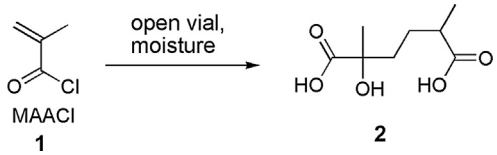

Fig. 1. Molecular structures of methacryloyl chloride **1** and product **2**, which was isolated after exposure of a sample of commercial methacryloyl chloride to air.

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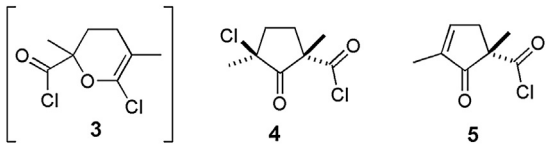


Fig. 2. Previously reported dimers of methacryloyl chloride.[5a] The structure of **3** is shown in brackets as the formation of this compound has not been directly verified.

Fisher et al., we observed the selective formation of one particular dimerization product **2** with a distinctly different chemical structure. Therefore, we decided to look into the chemical processes that lead to the formation of **2** from a commercial methacryloyl chloride sample upon its contact with air.

2. Results and discussion

We started with the analysis of several samples of commercially available methacryloyl chloride. Independent of supplier, label, stabilizer, and storage time (all samples were stored at −20 °C as advised), we found that all these samples always contain about 10–15 mol % of another substance (determined by integration of ^{1}H NMR spectra), although the labels stated the purity at 97%. Samples could also contain minor quantities of other impurities (Fig. 3), such as compound **6**. Besides, one commercial sample, packed in a bottle with a crown cap and a septum, contained relatively small amount of one additional impurity not found in all other samples we have tested.

Removal of MAACl under vacuum resulted in a slightly tanned liquid, which was in turn purified by distillation under high vacuum at ca. 1 mbar affording a colorless liquid with a pungent odor.[7] A detailed molecular structure analysis enabled identification of this compound as the cyclic dimer **3** (Fig. 2). Compound **3** has been suggested before as a common impurity of methacryloyl chloride due to the presence of its esters or amides in esterification or amidation reactions of MAACl,[5a–c] respectively, but it was never isolated and characterized in a pure form. Our investigations have now clearly shown that **3**, but not the dimers **4** and **5**, constitutes the main impurity in MAACl. Moreover, dimer **3** is readily available upon vacuum distillation and may serve as a useful synthetic intermediate.

The formation of **3** can be formally explained by an oxo-Diels–Alder reaction between two methacryloyl chloride molecules, which is similar to the dimerization reactions of acrolein,[8] methyl vinyl ketone,[9] and methacrolein[10] known for more than 60 years.[11] The reaction is thermally induced and is not accelerated by addition of a Lewis acid (LA).[12] Samples of freshly distilled pure methacryloyl chloride stored at 40 °C for two months reach an equilibrium state containing ca. 40 mol % of **3**, while samples kept at 4 °C for several months show only traces of the dimerization product. Heating of a sample of MAACl or of **3** at 110 °C in a sealed tube for 4 h results in formation of an equilibrated mixture with the 94:6 molar ratio of **1**/**3**, indicating that the fraction of dimer **3** in the equilibrium mixture drops with the temperature, as would be expected from considerations of entropy. Thus, dimer **3** can be generated in an equilibrium reaction and can be then separated from methacryloyl chloride by vacuum distillation. Dissociation of **3** into **1** was studied in dilute toluene-d_8 solution at 110 °C and afforded a first order kinetic dissociation constant[13] of 6×10^{-3} s^{-1} (see Supplementary data for the details). Thermal decomposition of **1** is not observed at this temperature.[14]

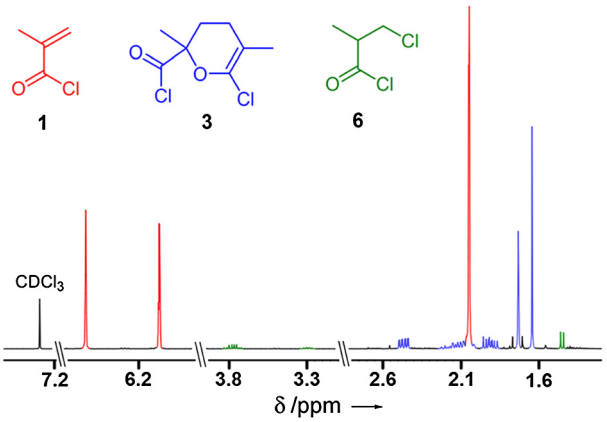
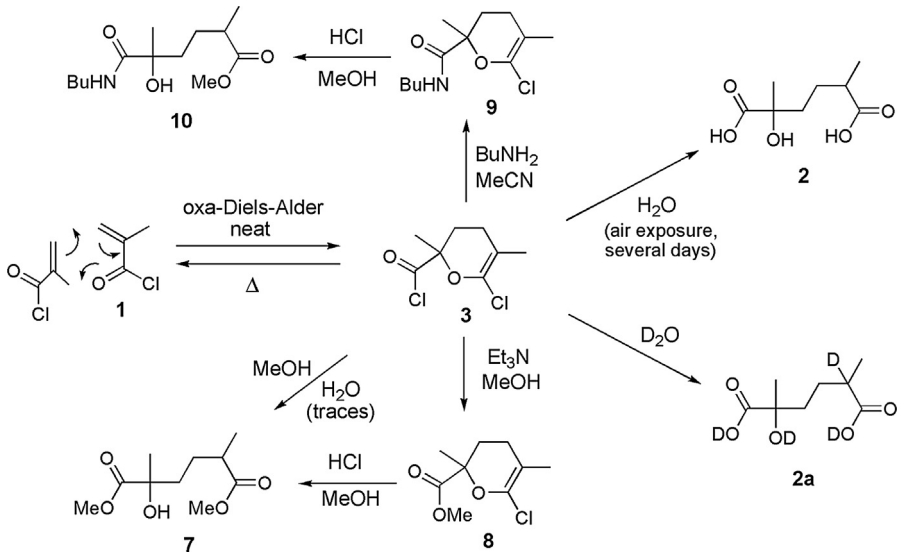


Fig. 3. ^{1}H NMR spectrum (360 MHz, 8.4 T, $CDCl_3$) of a commercial sample of methacryloyl chloride. Signals of methacryloyl chloride **1** are shown in red, signals of the dimer **3** are marked in blue. Compound **6**, the product of HCl addition to MAACl, was also detected in small amounts in some samples, signals are marked green.

The methacryloyl dimer **3** contains a relatively uncommon structural element, i.e., a C–C double bond with a geminal chlorine and oxygen substituents at one of the carbon atoms. We decided to investigate the reactivity of **3** (Scheme 1) in more details. As expected, hydrolysis of **3** using D_2O led to the formation of **2a**, containing three DO-groups, as well as one deuterium in the α-position to one of the carboxyl groups. Upon action of MeOH, the formation of dimethyl ester **7** was observed.[15] The acid chloride group can be selectively transformed into ester **8** or amide **9** through the reaction with the corresponding amine or alcohol under basic conditions. In successive reactions the second 'masked' carboxyl group can be esterified under acidic condition with the formation of **7** or **10**, respectively.[16] Thus, selective preparation of the derivatives of **2** with different substituents of two carboxyl groups are readily achievable, making it possible to use **3**, for example, as an intermediate in macromolecular chemistry for the production of polyester/polyamide polymers comprising two different diamide/diester linkers.

To clarify the reaction process leading to the ring opening of **3** with the formation of **2**, we followed up the hydrolysis of **3** by exposing a sample of pure **3** to air and measuring NMR spectra at different stages of the process.[17] Analysis of 1D and 2D NMR spectra (Figs. S45, S46)[18] gave evidence for the formation of one key intermediate, to which structure **11** (Scheme 2) can be tentatively ascribed.[19] During the hydrolysis process, the amount of **11** first rises up to 50% of the sample composition accompanied by disappearance of **3**. After the maximum amount of **11** is reached, it starts to vanish slowly, whereas the signals of the final product **2** arise in the NMR spectra. Subsequently the latter starts to crystallize at the bottom of the flask. All attempts to isolate **11** in pure form were unsuccessful, and no other intermediates could be detected in any significant (>5%) amounts before completion of the process. We conclude that after the first stage of hydrolysis of **3** either carboxylic acid **12**, or more likely, anhydride **13**, is formed (Scheme 2), which is then attacked by HCl and cyclizes into **11**. After most of highly reactive **3** is consumed, hydrolysis of **11** becomes dominant, affording final product **2** at the end of the process.

Thus, we have proved that the previously undescribed adipic acid derivative **2** was generated via the dominant contamination **3** present in all MAACl samples. However, it was still unclear why the samples investigated by Fischer et al. contained significant amounts of dimers **4** and **5** and how they could form from **1**. Therefore, we turned our attention to the sample packed in a bottle with a crown cap that contained small amounts of an additional impurity. ^{1}H NMR analysis of the sample after removal of **1** under vacuum showed the presence of **3** together with another minor component (Fig. S51). Comparison of the ^{1}H NMR spectrum of the unknown compound with the spectra of other dimers reported previously,[5a] as well as the analysis of 2D NMR spectra identified



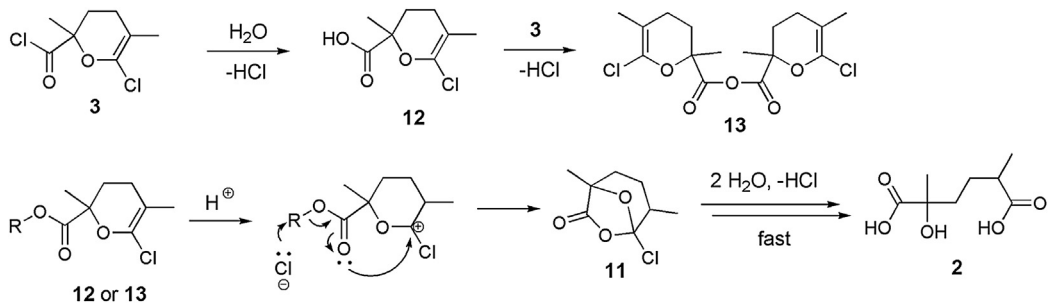
Scheme 1. Reactivity of the MAACl dimer **3**.

this substance as dimer **4** (Fig. 2). Because of the thermal lability of **3**, which undergoes retro-Diels–Alder reaction forming volatile **1**, the dimer **4** could be isolated by boiling off **1** at 120 °C for several minutes. This way, thermally stable **4** could be isolated before by Fischer et al., while the dominant dimer **3** decomposed during the distillation of the mixture.[5a]

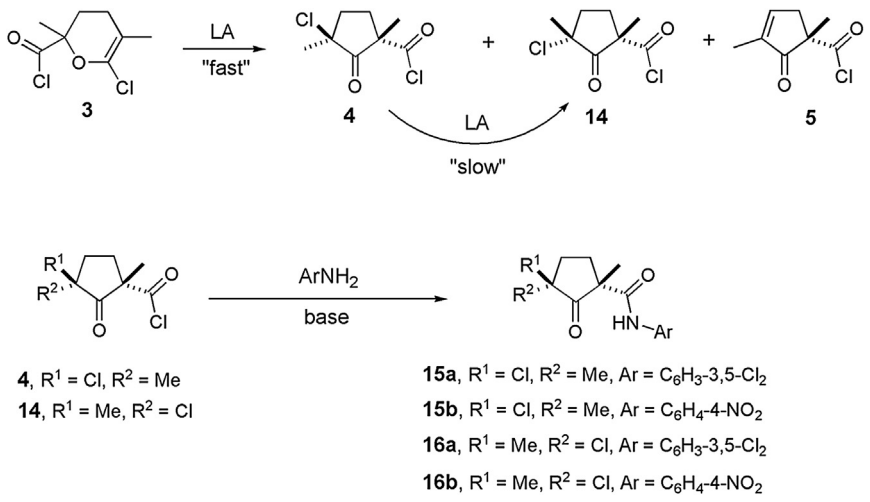
Inspection of the crown cap after its removal has shown that it was significantly corroded from inside and traces of oxidized metal in form of chlorides could get in contact with the contents of the bottle. Since transition metal chlorides in high oxidation states are known to be strong Lewis acids (LA), we studied the influence of various LAs on the dimer **3** adding catalytic amounts of $AlCl_3$, $TiCl_4$, $SnCl_4$, $FeCl_3$, and $Et_2O{\cdot}BF_3$ to ca. 300 μL samples of **3**. For all samples, fast darkening of the reaction mixture was observed, and in the case of $TiCl_4$ the reaction showed significant exothermicity. NMR analysis[20] has evidenced that all reaction mixtures contained predominantly **4**, as well as its previously undescribed diastereomer **14** (ca. 30–50 % initially). The isomerization of **3** was completed within several days (Scheme 3).

Notably, the reaction rate depended on the activity of the Lewis acid,[21] and the fastest reaction was observed with $TiCl_4$. In the case of $AlCl_3$, traces of the third dimer **5** described by Fischer et al. have also been detected. Unquestionable identification of compounds **4**, **5**, and **14** in the reaction mixture was possible by correlation of the methyl group hydrogens in HMBC NMR spectra (Fig. S48). All samples showed formation of minor (<3–5%) byproducts, with the $SnCl_4$-containing sample being the most impure one. The best selectivity for generation of **4** and **14** was achieved with $TiCl_4$ and $Et_2O{\cdot}BF_3$ as catalysts, although in the case of the latter the isomerization process was slower. Moreover, it was observed that upon standing, compound **4** slowly isomerizes into its diastereomer **14**, which presumably is thermodynamically more stable than **4**. The fastest reaction was detected for the sample containing $TiCl_4$, for which isomerization into **14** was complete within 1–2 weeks (Fig. 4).

Relative configuration of the two stereocenters in **4** had been determined before by X-ray crystallography of its aromatic amide **15a**[22] (Scheme 3). To confirm the expected relative configuration of the two stereocenters in **14**, analogous amides **16a** and **16b** have been prepared by us from **14**. Amide **16a** readily afforded crystals suitable for X-ray structural analysis[18] that established the *cis*-disposition of two methyl substituents of the cyclopentanone ring (Fig. 5), in contrast to the *trans*-disposition in the previously reported amide **15a**, thus proving the diastereomeric identity of compound **14**. The conformation of **16a** is stabilized by two intramolecular hydrogen bonds with a $S_1^1(6)$ graph set motif:[23] one classical N1–H1···O2 H-bond ***a***, and one non-classical C14–H14···O1 H-bond ***b***. Quite surprisingly, no classical intermolecular hydrogen bonds are present in crystals of **16a**. The crystal packing is dominated by the stacking of aromatic rings with an interplanar distance of 3.4382(5) Å (distance between ring centroids of 3.6983(9) Å), as well as a number of borderline (distance is slightly below or equal to the sum of VdW radii) contacts involving Cl-atoms and O-atom of the amido-group with different aliphatic and aromatic H-atoms, which can be classified as weak non-classical H-bonds.[24]



Scheme 2. Proposed pathway for the hydrolysis of **3**.



Scheme 3. Lewis acid (LA) catalyzed transformation of **3** and preparation of aromatic amides **15a**, **b** and **16a**, **b**. Amides **15a**, **b** have been prepared before.[5a]

A tentative mechanism for the Lewis acid catalyzed transformation of **3** into **4**, **5**, and **14** is suggested in Scheme 4. At first, the chloroformyl group is activated by a Lewis acid affording a highly reactive electrophile **17**, which intramolecularly attacks the double bond forming a cyclic carboxonium cation **18**.[25,26] Breakage of the C–O bond leads to tertiary carbocation **19**, which can either split off a proton giving **5**, or attach Cl^- with the formation of **4** or **14**. As was noted above, product **4** is likely to be the kinetically preferred one, whereas upon standing compound **14** is formed predominantly (most likely via the same carbocation **19**), indicating its higher thermodynamic stability.

In the course of our study, we found that **3** is highly sensitive to residual moisture in closed vessels. Addition of traces of water leads to fast decomposition of **3** with the formation of **4**, as well as several other decomposition products of unknown nature. Presumably, the catalytic activity of HCl, a strong Brønsted acid, generated upon reaction of water with the acid chloride, is similar to the one of other LAs tested in the study, although it is affected by the possibility of an attack of HCl on the double bond of **3** (Scheme 2). On the other hand, samples of **3** containing methacryloyl chloride are much more stable due to deactivation of HCl by binding to the double bond of MAACl in Michael fashion with the formation of compound **6**. Still, in open vials, pure **3** does not isomerize to **4** due to the fast escape of HCl, but hydrolyzes selectively forming **2**.

Finally, the following suggestions on handling of methacryloyl chloride can be proposed. To obtain pure MAACl, commercial samples should be distilled and then kept at temperatures preferentially not higher than −20 °C without any contact with metal surfaces. Under these conditions, MAACl can be stored without any detectable formation of dimer **3** for at least several months. To recycle MAACl from the remaining dimer **3**, which can constitute up to 15% of a batch, the distillation residue should be heated slightly above the boiling temperature of MAACl until dimer **3** starts to decompose into **1**, which can be collected upon cooling using a common distillation setup.

3. Conclusion

To summarize, we have found that commercial methacryloyl chloride, even if marked as a pure reagent, usually contains significant amounts of the Diels–Alder dimer **3**, as well as, occasionally, other high-boiling impurities, and, thus, should be always distilled before use to avoid the formation of non-desired reaction byproducts. We were able to isolate and characterize dimer **3** and have studied its reactivity. Upon action of different reagents it can be easily transformed into various derivatives of 2,5-dimethyl-2-hydroxyadipic acid. Isomerization pathways of **3** leading to the build-up of acid chlorides **4**, **5**, and **14** have been studied and the mechanism of their formation upon action of Lewis acids has been proposed. Future work will focus on the development of conditions for selective transformation of **3** and **14** into other potentially useful compounds.

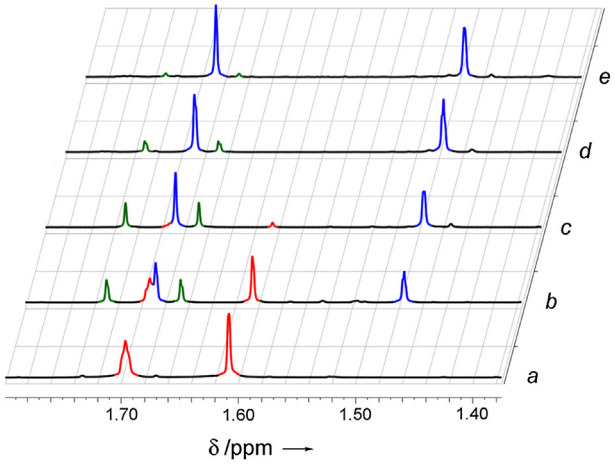


Fig. 4. Isomerization of **3** followed using ^{1}H NMR spectra ($CDCl_3$, 360 MHz) recorded: (a) before the addition of $TiCl_4$ and (b) 1 day after, (c) 3 days after, (d) 10 days after, and (e) 17 days after addition of $TiCl_4$. Signals are shown in red for **3**, green for **4**, and blue for **14**.

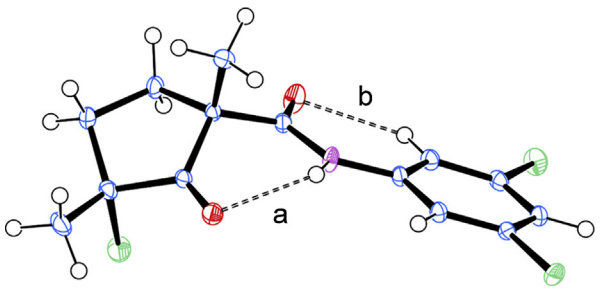
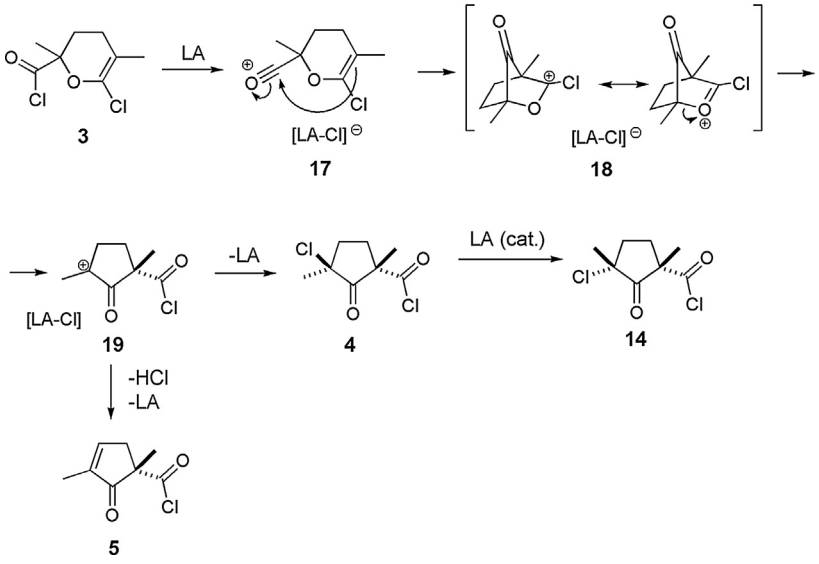


Fig. 5. ORTEP plot of **16a** confirming the *cis*-disposition of two Me-groups and showing two weak intramolecular H-bonds. Thermal ellipsoids are drawn at the 50% probability level.



Scheme 4. Mechanism for the Lewis acid (LA) catalyzed transformation from **3** to **5** or **14**. Although there are two possibilities for activation of the chloroformyl group by an LA, either by formation of an oxocarbenium cation or by formation of a donor–acceptor complexes by binding to the oxygen atom;[27] only the first option is shown.

4. Experimental section

4.1. General information

Methacryloyl chloride was purchased from *Aldrich*, *Fluka*, and *Alfa Aesar*. Reagent grade chemicals and solvents were used without further purification unless stated otherwise. NMR spectra were recorded using *Bruker Avance WB-360* or *Bruker Avance DRX600* spectrometers. NMR chemical shifts (δ) are reported in parts per million (ppm) relative to TMS, the residual solvent signals were used as reference $CDCl_3$ (7.26 ppm for ^1H, 77.0 ppm for ^{13}C). ^1H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicity is indicated as follows: b (broad signal), s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Low resolution mass spectra were measured on *Finnigan MAT 95* spectrometers for electron ionization (EI, 70 eV) and on a *Bruker Esquire-LC* spectrometer for electrospray ionization (ESI). High resolution MS-spectra (HRMS) were measured on a *Finnigan MAT 95* spectrometer (EI, 70 eV), and on a *Thermo Fisher Scientific LTQ Orbitrap* spectrometer (ESI). Melting points were determined using a capillary melting point apparatus and are uncorrected. Flash chromatography (FC) was carried out using 230–440 mesh (particle size 36–70 μm) silica gel. The X-ray structure of **16a** was solved by direct methods and refined by full-matrix least-squares analysis using *SHELXTL*[28] and *ShelXle*.[29]

4.2. Synthetic procedures

*4.2.1. 2-Hydroxy-2,5-dimethylhexanedioic acid (**2**).* Compound **2** was first obtained by leaving 1 mL (1.07 g, 10 mmol) of commercial methacryloyl chloride in an open flask for 3–4 weeks resulting in formation of 0.29 g (1.5 mmol) of **2**. Alternatively, **2** can be prepared by leaving **3** in an open vial for 2–3 weeks. On a larger scale, compound **2** can be prepared as follows: 0.50 g (2.4 mmol) of **3** were dissolved in MeCN (4 mL), and H_2O (1 mL) was added to the solution. Reaction mixture was stirred over the week-end and then evaporated to dryness. After drying over P_2O_5 0.456 g (2.4 mmol, 100%) of the product were obtained as a colorless crystalline powder. NMR analysis showed the presence of **2** as a diastereomeric mixture[3] with >95% purity together with several trace impurities of unknown origin. Recrystallization form MeCN afforded 0.298 g (1.57 mmol, 65%) of **2** in the diastereomerically pure form. Mp: 128–129 °C. ^1H NMR (360 MHz, CD_3CN): δ 2.40–2.31 (m, 1H), 1.76–1.69 (m, 2H), 1.63–1.51 (m, 1H), 1.31–1.21 (m, 1H), 1.33 (s, 3H), 1.11 (d, ^3J=7.0 Hz, 3H). ^{13}C NMR (90 MHz, CD_3CN): δ 177.9, 177.7, 74.8, 39.4, 38.0, 28.2, 26.1, 17.1. ^1H NMR (360 MHz, D_2O): δ 2.37–2.28 (m, 1H), 1.69–1.56 (m, 1H), 1.62–1.52 (m, 1H), 1.56–1.42 (m, 1H), 1.27–1.17 (m, 1H), 1.26 (s, 3H), 0.98 (d, ^3J=7.0 Hz, 3H). MS(ESI$^-$): m/z (%) 189 (100) $[M-H]^-$, 171 (10) $[M-H_2O-H]^-$. HRMS (ESI$^-$): m/z $[M-H]^-$ calcd for $C_8H_{13}O_5$ 189.07684, Found 189.07637.

*4.2.2. 6-Chloro-3,4-dihydro-2,5-dimethyl-2H-pyran-2-carbonyl chloride (**3**).* Compound **3** can be easily isolated from commercial methacryloyl chloride samples. First, methacryloyl chloride **1** is removed at 5 mbar at normal temperature, then dimer **3** is distilled at 0.5 mbar and 30–40 °C. Typically it is possible to obtain ca. 3–4.5 g of **3** from 25 g of commercial **1**. After keeping a sample of **1** at 40 °C for two months, about 5 g (47 mmol, 50%) of **3** can be obtained from 10 mL (10.7 g, 102 mmol) of **1** after vacuum distillation. d=1.25 g/mL. ^1H NMR (360 MHz, $CDCl_3$): δ 2.46–2.39 (m, 1H), 2.16–1.97 (m, 2H), 1.93–1.83 (m, 1H), 1.69 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 176.8, 136.1, 105.0, 86.5, 30.3, 24.9, 24.3, 18.1. MS (EI): m/z (%) 208 (35) $[M]^{+\bullet}$, 145 (75) $[M-COCl]^+$, 69 (100) $[C_4H_5O]^+$. HRMS (EI): m/z $[M]^{+\bullet}$ calcd for $C_8H_{10}Cl_2O_2$ 208.00579, Found 208.00537.

*4.2.3. trans-3-Chloro-1,3-dimethyl-2-oxocyclopentanecarbonyl chloride (**4**).* Compound **4** was isolated from ca. 20 mL of commercial methacryloyl chloride kept in a glass bottle with a metal crown cap. First, **1** was removed by vacuum distillation, then the residue in amount of 3 mL was heated to 120 °C for 20 min under the flow of nitrogen to remove **1** formed by decomposition of **3**. Compound **4** remained in the residue in amount of ca. 0.3 mL as a tarry brown liquid. ^1H NMR (600 MHz, $CDCl_3$): δ 2.60–2.54 (m, 1H), 2.44–2.39 (m, 1H), 2.35–2.30 (m, 1H), 2.25–2.18 (m, 1H), 1.70 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 205.7, 172.9, 68.6, 64.2, 38.0, 32.1, 24.5, 23.9. MS (EI): m/z (%) 208 (10) $[M]^{+\bullet}$, 173 (10) $[M-Cl]^+$, 145 (10) $[M-COCl]^+$.

*4.2.4. 1,3-Dimethyl-2-oxocyclopent-3-ene-1-carbonyl chloride (**5**).* Compound **5** could not be separated in a pure form, but could be characterized by NMR in the reaction mixture formed after addition of $AlCl_3$ to dimer **3**. ^1H NMR (360 MHz, $CDCl_3$): δ 7.42–7.39 (m, 1H), 3.34–3.25 (m, 1H), 2.65–2.55 (m, 1H), 1.86–1.84 (m, 3H), 1.44 (s,

3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 203.5, 172.2, 156.2, 132.7, 62.2, 40.0, 20.8, 10.2.

*4.2.5. 2-Hydroxy-2,5-dimethylhexanedioic acid dimethyl ester (**7**).* Compound **7** was prepared by dissolving of 0.50 mL of **3** (0.625 g, 3.0 mmol) in MeOH (10 mL). After that several drops (3–5) of water were added to the reaction mixture, which was then stirred for two days. The solvent was removed under vacuum, the product was purified by filtration through a short SiO_2 plug (CH_2Cl_2). Evaporation of the solvent afforded 0.593 g (2.7 mmol, 90%) of the product as a colorless liquid. Alternative method: compound **8** (0.410 g, 2.0 mmol) was dissolved in MeOH (5 mL), then 3–5 drops of concd HCl were added to the reaction mixture, which was then stirred for two days. Work up as above yielded 0.406 g (1.86 mmol, 93%) of the product as a colorless liquid. ^{1}H NMR (360 MHz, $CDCl_3$): δ 3.21 (br s, 1H), 2.43–2.33 (m, 1H), 1.84–1.69 (m, 1H), 1.77–1.65 (m, 1H), 1.66–1.52 (m, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 1.36 (s, 3H), 1.30–1.18 (m, 1H), 1.11 (d, ^3J=7.1 Hz, 3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 177.4, 176.7, 74.3, 52.7, 51.5, 39.1, 37.3, 27.5, 25.9, 16.8. MS (ESI$^+$): *m*/*z* (%) 241 (100) $[M+Na]^+$. HRMS (ESI$^+$): *m*/*z* $[M+Na]^+$ calcd for $C_{10}H_{18}O_5Na$ 241.10464, Found 241.10489.

*4.2.6. 6-Chloro-3,4-dihydro-2,5-dimethyl-2H-pyran-2-carboxylic acid methyl ester (**8**).* To a solution of 0.40 mL (0.50 g, 2.4 mmol) of **3** in MeCN (4 mL) were added 0.51 mL (0.367 g, 3.63 mmol) of Et_3N, reaction mixture was cooled to 0 °C, and then MeOH (0.15 mL, 0.120 g, 3.7 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred overnight, then triethylamine hydrochloride was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in hexane and filtered once again to remove the remains of triethylamine hydrochloride. After removal of the solvent, the residue was purified by column chromatography on SiO_2 (cyclohaxene/CH_2Cl_2, 1:1) affording 0.391 g (1.91 mmol, 80%) of **8** as a colorless liquid after solvent evaporation. ^{1}H NMR (360 MHz, $CDCl_3$): δ 3.75 (s, 3H), 2.33–2.26 (m, 1H), δ 2.10–1.93 (m, 2H), 1.85–1.74 (m, 1H), 1.67 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 173.0, 136.1, 103.3, 81.0, 52.6, 30.5, 25.4, 24.7, 18.2. MS (EI): *m*/*z* (%) 204 (25) $[M]^{+\bullet}$, 145 (20) $[M-COOMe]^+$, 69 (100) $[C_4H_5O]^+$. HRMS (EI): *m*/*z* $[M]^{+\bullet}$ calcd for $C_9H_{13}ClO_3$ 204.05532, Found 204.05516.

*4.2.7. 6-Chloro-3,4-dihydro-2,5-dimethyl-N-butyl-2H-pyran-2-carboxamide (**9**).* Solution of 0.40 mL (0.50 g, 2.4 mmol) of **3** in MeCN (4 mL) was cooled to 0 °C, and then $BuNH_2$ (0.59 mL, 0.437 g, 6.0 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred overnight, then butylamine hydrochloride was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in hexane and filtered once again to remove the remains of butylamine hydrochloride. After removal of the solvent the residue was purified by column chromatography on SiO_2 (CH_2Cl_2) affording 0.418 g (1.70 mmol, 71%) of **8** as a colorless liquid after solvent evaporation. ^{1}H NMR (360 MHz, $CDCl_3$): δ 6.41 (br s, 1H), 3.38–3.28 (m, 1H), 3.20–3.09 (m, 1H), 2.32–2.22 (m, 1H), 2.11–1.90 (m, 2H), 1.78–1.68 (m, 1H), 1.66 (s, 3H), 1.50–1.38 (m, 2H), 1.43 (s, 3H), 1.35–1.21 (m, 2H), 0.88 (t, ^3J=7.3 Hz, 3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 172.6, 134.7, 105.0, 82.8, 38.8, 31.5, 29.4, 25.2, 24.3, 19.7, 18.2, 13.6. MS (EI): *m*/*z* (%) 245 (20) $[M]^{+\bullet}$, 209 (20) $[M-HCl]^{+\bullet}$, 145 (10) $[M-CONHBu]^+$, 110 (100) $[M-CONHBuCl]^{+\bullet}$, 69 (35) $[C_4H_5O]^+$. HRMS (EI): *m*/*z* $[M]^{+\bullet}$ calcd for $C_{12}H_{20}ClNO_2$ 245.11826, Found 245.11787.

*4.2.8. 5-Hydrohy-2,5-dimethyl-6-butylamino-6-oxohexanoic acid methyl ester (**10**).* Compound **10** was prepared by dissolving 0.395 g of **9** (1.61 mmol) in MeOH (5 mL). After that several drops (3–5) of concd HCl were added to the solution, which was then stirred for two days. The solvent was removed under vacuum and the product was purified by column chromatography on SiO_2 (concentration gradient: $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH, 5%). After solvent evaporation 0.280 g (1.08 mmol, 67%) of **10** were obtained as a colorless liquid. ^{1}H NMR (360 MHz, $CDCl_3$): δ 6.88 (br s, 1H), 3.64 (s, 3H), 3.37 (br s, 1H), 3.26–3.16 (m, 2H), 2.46–2.33 (m, 1H), 1.94–1.83 (m, 1H), 1.79–1.64 (m, 1H), 1.52–1.45 (m, 1H), 1.49–1.40 (m, 2H), 1.37–1.29 (m, 2H), 1.36 (s, 3H), 1.34–1.25 (m, 1H), 1.12 (d, ^3J=7.3 Hz, 3H), 0.90 (t, ^3J=7.3 Hz, 3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 177.4, 175.3, 75.5, 51.7, 39.3, 38.9, 37.9, 31.6, 27.4, 27.0, 20.0, 17.5, 13.7. MS (ESI$^+$): *m*/*z* (%) 298 (12) $[M+K]^+$, 282 (100) $[M+Na]^+$, 260 (5) $[M+H]^+$. HRMS (ESI$^+$): *m*/*z* $[M+Na]^+$ calcd for $C_{13}H_{25}NO_4Na$ 282.16758, Found 282.16760.

*4.2.9. cis-3-Chloro-1,3-dimethyl-2-oxocyclopentanecarbonyl chloride (**14**).* Compound **14** was prepared by adding a drop of $TiCl_4$ to 0.30 mL (0.37 g, 1.78 mmol) of **3**. The reaction mixture immediately turned brown. After stirring for three weeks at rt, the sample turned deep blue and contained >97% of **14** according to NMR analysis. The reaction mixture can be used for acylation without additional purification, or it can be distilled under vacuum (1 mbar) affording 0.23 g (1.10 mmol, 62%) of **14** as a colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.97–2.90 (m, 1H), 2.52–2.44 (m, 1H), 2.09–2.04 (m, 1H), 2.02–1.97 (m, 1H), 1.69 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 203.7, 173.1, 68.2, 63.2, 36.5, 31.3, 24.7, 21.9. MS (EI): *m*/*z* (%) 208 (25) $[M]^{+\bullet}$, 173 (15) $[M-Cl]^+$, 145 (20) $[M-COCl]^+$, 69 (100) $[C_4H_5O]^+$. HRMS (EI): *m*/*z* $[M]^{+\bullet}$ calcd for $C_8H_{10}Cl_2O_2$ 208.00579, Found 208.00670.

*4.2.10. cis-3-Chloro-N-(3,5-dichlorophenyl)-1,3-dimethyl-2-oxocyclopentanecarboxamide (**16a**).* To a solution containing 0.145 g (0.90 mmol) of 3,5-dichloroaniline and 0.15 mL (0.109 g, 1.08 mmol) of Et_3N in THF (3 mL), 0.18 g (0.86 mmol) of crude **14** (containing catalytic amounts of $TiCl_4$) were added and stirred overnight at 50 °C. Then the reaction mixture was filtered through a plug of Celite, and the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 and purified by column chromatography on SiO_2 (CH_2Cl_2) affording 0.182 g (0.544 mmol, 63%) of **16a** as off-white crystals. X-ray quality crystals were grown by slow evaporation of CH_2Cl_2/hexane solution. Mp: 126–128 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 8.56 (br s, 1H), 7.53 (s, 2H), 7.09 (s, 1H), 2.88–2.78 (m, 1H), 2.46–2.38 (m, 1H), 2.08–2.02 (m, 1H), 2.02–1.96 (m, 1H), 1.69 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 212.5, 168.7, 139.3, 135.2, 124.4, 118.1, 69.7, 54.8, 35.7, 29.4, 24.8, 24.1. MS (EI): *m*/*z* (%) 333 (35) $[M]^{+\bullet}$, 173 (40) $[M-NHAr]^+$. HRMS (EI): *m*/*z* $[M]^{+\bullet}$ calcd for $C_{14}H_{14}Cl_3NO_2$ 333.00901, Found 333.00842.

*4.2.11. cis-3-Chloro-N-(4-nitrophenyl)-1,3-dimethyl-2-oxocyclopentanecarboxamide (**16b**).* To a solution containing 0.130 g (0.94 mmol) of 4-nitroaniline and 0.15 mL (0.109 g, 1.08 mmol) of Et_3N in THF (3 mL), 0.18 g (0.86 mmol) of crude **14** (containing catalytic amounts of $TiCl_4$) were added and stirred overnight at rt. Then the reaction mixture was filtered through a plug of Celite, and the solvent was removed under vacuum. The residue was dissolved in $CHCl_3$ and purified by column chromatography on SiO_2 ($CHCl_3$) affording 0.146 g (0.47 mmol, 55%) of **16b** as pale yellow crystals. Mp: 129–130 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 8.89 (br s, 1H), 8.26–8.16 (m, 2H), 7.78–7.70 (m, 2H), 2.91–2.78 (m, 1H), 2.49–2.40 (m, 1H), 2.12–2.05 (m, 1H), 2.05–1.98 (m, 1H), 1.75 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 212.4, 168.9, 143.7, 143.3, 125.0, 119.3, 69.7, 55.0, 35.6, 29.4, 25.0, 24.1. MS (EI): *m*/*z* (%) 310 (85) $[M]^{+\bullet}$, 173 (85) $[M-NHAr]^+$. HRMS (EI): *m*/*z* $[M]^{+\bullet}$ calcd for $C_{14}H_{15}ClN_2O_4$ 310.07203, Found 310.07170.

Acknowledgements

We are grateful to Dr. T. Dülcks and Ms. D. Kemken (MS) and Dr. Uli Papke (HR-ESI-MS, TU Braunschweig) for their help with the

characterization of new compounds. The X-ray diffractometer was funded by NSF Grant 0087210, Ohio Board of Regents Grant CAP-491, and by Youngstown State University. We are also indebted to Prof. J. Beckmann, Dr. T. Dülcks, and Prof. Dietmar Kuck (Universität Bielefeld) for helpful discussions.

Supplementary data

Crystallographic data for the structure **16a** has been deposited to the Cambridge Crystallographic Data Centre under deposition number CCDC 987551. Supplementary data associated with this article and containing NMR spectra with signal assignments, MS spectra, X-ray data of **16a**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.07.019.

References and notes

1. Methacryloyl chloride is a simple derivative of methacrylic acid, an industrial chemical produced in amount of ca. 2×10^6 t/year and known since 1865, see: Bauer, W., Jr. *Methacrylic Acid and Derivatives. Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH GmbH, 2011.
2. SciFinder search for methacryloyl chloride using its CAS number (920-46-7) gives more than 7000 hits with nearly 1:1 ratio between patents and research papers (as of Jan. 2014).
3. Although compound **2** was isolated as a mixture of two diastereomeric pairs, ^{1}H NMR spectrum of **2** could not be used for the determination of the diastereomeric ratio due to the complete signal overlap. The diastereomeric ratio of ca. 5.5:1 was roughly estimated from ^{13}C NMR spectrum, in which separate resonances are observed for several corresponding carbon atoms of two diastereomers. Only the resonances of the major diastereomer are reported in the Experimental section.
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6. Although compound **3** was found to be present in PubChem (CID 13396407 and CID 641639), no details about its preparation and purification have ever been reported, no spectral characterization is available, and it has been never described as a major impurity of commercial methacryloyl chloride.
7. On average, 3–5 g of **3** can be isolated from 25 mL samples of commercial MAACl.
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12. Addition of $AlCl_3$, $TiCl_4$, $SnCl_4$, or $Et_2O{\cdot}BF_3$ does not lead to accelerated conversion of **1** into **3**.
13. Taking into account the composition of the **1**/**3** equilibrium mixture at the same temperature and making an assumption that the kinetics of the dissociation of **3** is not significantly influenced by the media, we can estimate the second order dimerization constant of MAACl to be 4×10^{-4} mol s^{-2}.
14. Pathways of thermal decomposition of **1** at 1500 K employing infrared laser-powered homogeneous pyrolysis (IR LPHP) technique have been investigated before, see: Allen, G. R.; Russell, D. K. *New J. Chem.* **2004**, *28*, 1107–1115.
15. Traces of water are necessary to complete the hydrolysis; reaction with dry MeOH led to formation of a non-pure product.
16. Although compounds **7** and **10** should be isolated as diastereomeric mixtures, no presence of additional signals is observed in NMR spectra of compound **7**. In ^{13}C NMR of **10**, separate signals are observed for several resonances, giving evidence for the predominant formation of one diastereomer with the diastereomeric ratio comparable to the one of compound **2**.
17. ca. 0.3 mL of **3** were left to hydrolyze in 5 mL round bottom flask under a hood. For the analysis, small aliquots of a sample were taken and NMR spectra in dry $CDCl_3$ were measured.
18. See Supplementary data for 1D and 2D NMR spectra, NMR signal assignment, MS spectra, complete X-ray data, and description of kinetics measurement.
19. Formation of a similar tricyclic lactone lacking Cl-atom has been reported before for the oxidation product of methacrolein dimer, see Refs. 10b,c.
20. Reaction mixtures were analyzed using NMR in $CDCl_3$. For $FeCl_3$ sample direct measurements could not be performed due to the paramagnetic character of Fe (III). In this case, the mixture of acid chlorides was first esterified with MeOH, purified, and then NMR analysis was performed.
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