Unexpected isomerization of oxetane-carboxylic acids

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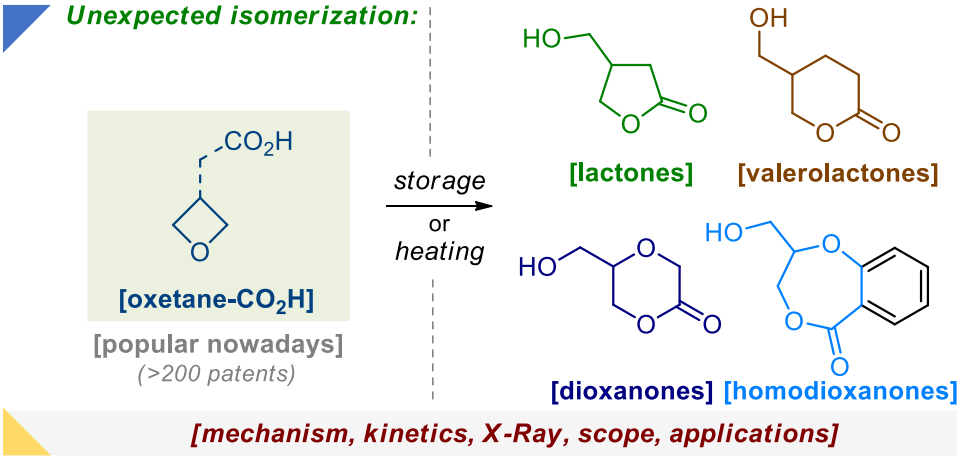
Dedicated to people of Ukraine

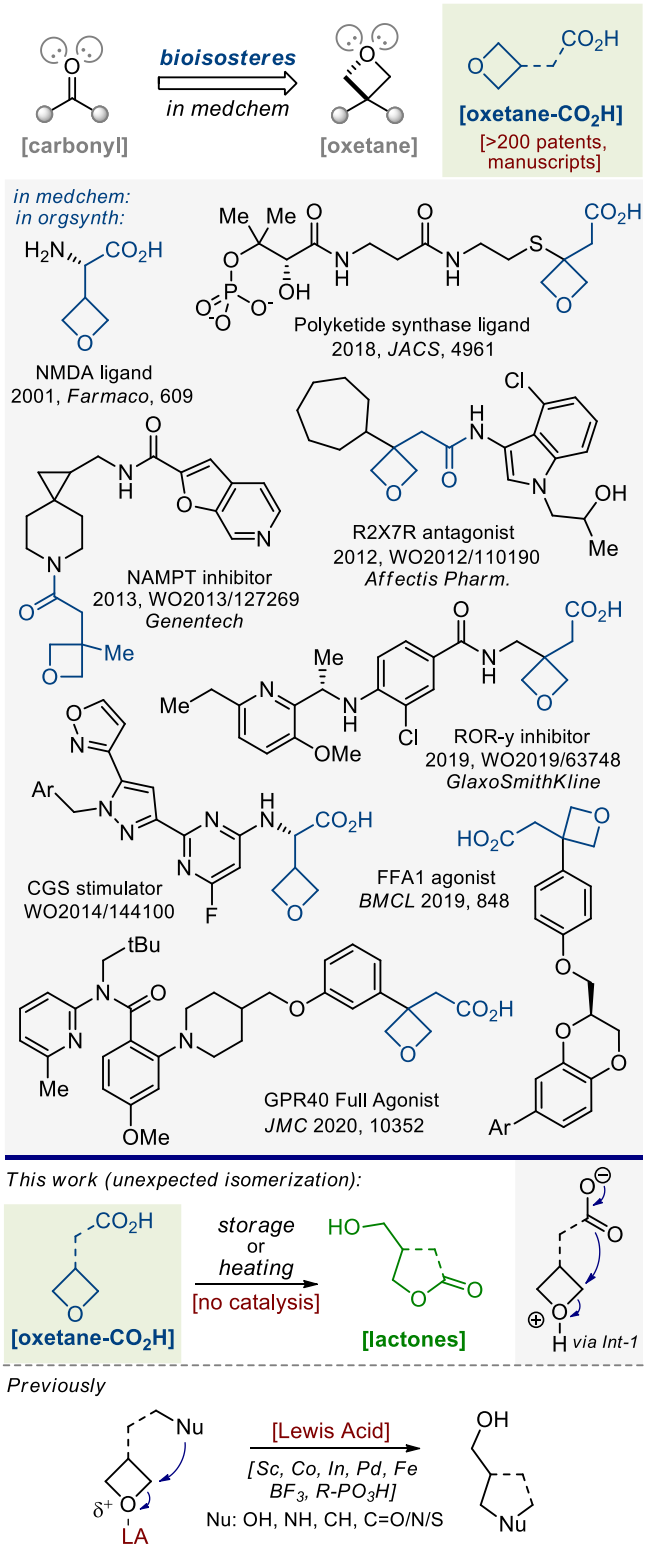


ABSTRACT: We unexpectedly discovered that popular oxetane-carboxylic acids are intrinsically unstable. They easily isomerize into lactones under storage at rt, or under slight heating. Chemists should keep in mind the high instability of these common molecules, as this could dramatically affect the reaction yields and lead to negative results (especially in those reactions that require heating).

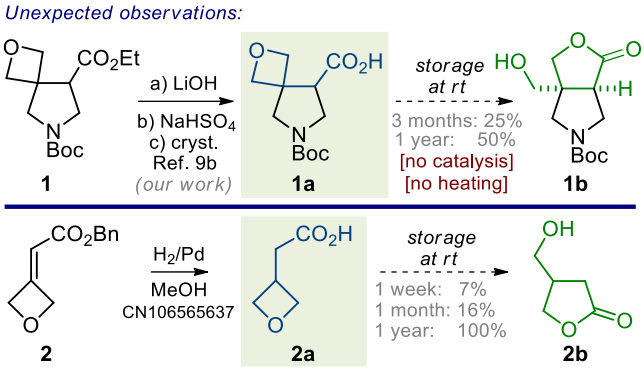
Introduction. More than a decade ago, oxetanes received a second breath, when they were shown to mimic a carbonyl group in bioactive compounds (Scheme 1). Moreover, the oxetane fragment was demonstrated to increase water solubility, improve metabolic stability, and lower the lipophilicity of organic molecules.[1] Since that time oxetanes have been gaining popularity in different areas of chemistry including organic synthesis, chemical biology, and medicinal chemistry.[2-4] In particular, oxetane-carboxylic acids have been mentioned in >200 peer-reviewed manuscripts and patents as both bioactive compounds[5] and starting materials in synthesis (Scheme 1).[6] Not surprising that during the past years, we received many requests for their preparation. Some oxetane-carboxylic acids were known in the literature, some of them we needed to synthesize for the first time. Over time, however, we realized that many oxetane-carboxylic acids were intrinsically unstable – they easily isomerized into lactones under storage at room temperature or under slight heating. Here, we want to disclose this unknown in the literature phenomenon, as chemists keep on using these molecules (Scheme 1), without realizing that many of them are unstable, as that could dramatically affect reaction yields and lead to negative results (especially in those reactions that require heating).

Intended intramolecular isomerizations of oxetanes by nucleophiles were reported in the literature (Scheme 1).[7,8] In most cases these reactions required additional activation of the oxetane ring by Lewis-acid catalysts (In, Sc, Fe, BF_3, Co, Pd, phosphoric acids, *etc*). In our case, many oxetane-carboxylic acids easily isomerized under simple storage or slight heating and required no external catalysis.

Results and Discussion. *Unexpected discovery*. Previously, we developed an approach to spirocyclic pyrrolidines via [3+2]-cycloaddition.[9] As a part of this project, we synthesized several oxetane-carboxylic acids. In particular, alkali saponification of ester **1** followed by acidification with $NaHSO_4$ gave crude acid **1a**. At that time, we obtained pure product **1a** by simple washing the crude product with MeO*t*Bu to remove soluble impurities. Inspection of this product three months later revealed the presence of ca. 25% of the individual impurity according to ^{1}H NMR. After one year of storage at room temperature, ca. 50% of this impurity was present. Simple heating of this mixture in isopropanol led to the exclusive formation of the "impurity" that was isolated and identified as lactone **1b**. At that point, we did not pay much attention to that observation. Several months later, however, we received a request from a pharmaceutical company on the synthesis of oxetane-carboxylic acid **2a** (Scheme 2). This acid was known in the literature[6e,10] and scientists often used it in amide coupling.[6e,11] Synthesis of **2a** was described in a patent,[10a] and we followed the procedure: hydrogenation of alkene **2** (obtained in one step from 3-oxetanone) using palladium on charcoal in methanol smoothly gave the desired product **2a**. However, an inspection of this product by ^{1}H NMR after one week revealed the presence of ca. 7% of an impurity. After one month of storage at room



Scheme 1. Oxetane-carboxylic acids in organic synthesis and medicinal chemistry. Aim of this work.



Scheme 2. Unexpected isomerization of oxetane-carboxylic acids **1a**, **2a** under storage at room temperature.

temperature, already 16% of this impurity was present. After one year of storage, the compound completely isomerized into the "impurity." We isolated and identified it as lactone **2b**. Moreover, even under slight heating at 50 °C in dioxane/water mixture, acid **2a** cleanly isomerized into lactone **2b**. At this point, it became clear that a tendency of oxetane-carboxylic acids to isomerize into lactones has a general character. We were very much surprised because while chemists have been actively using oxetane-carboxylic acids (including **2a**) in the research (Scheme 1), we could not find any systematic studies of that phenomenon. Only one example of such transformation was found in a patent with no detailed experimental data.[12]

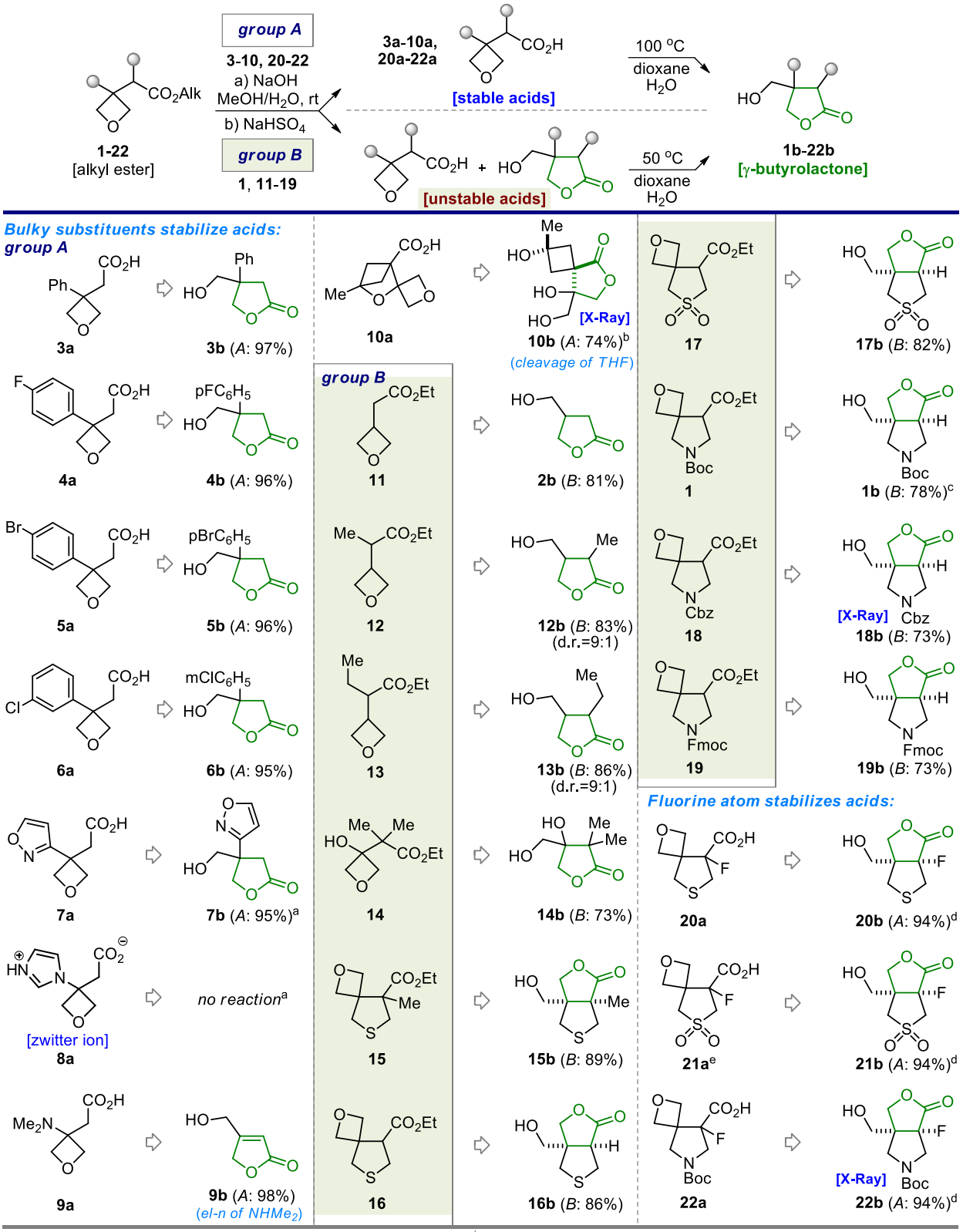
Scope and stability. We decided next to inspect all oxetane-carboxylic acids that we had on stock. Most of these compounds were synthesized by simple saponification of ethyl/methyl esters with NaOH and acidification with $NaHSO_4$. These results are summarized in Scheme 3. Acids **3a**-**10a** were obtained from esters **3**-**10**. They were stable upon storage at room temperature, and after one year we did not observe any decomposition according to ^{1}H NMR. Presumably, bulky (hetero)aromatic substituents (**3a**-**7a**), zwitterionic structures (**8a**, **9a**), or polycyclic conformationally rigid core (**10a**) stabilized these molecules. Nevertheless, compounds **3a**-**7a**, **9a**, **10a** isomerized into lactones **3b**-**7b**, **9b**, **10b** under heating in dioxane/water at 100 °C. Zwitterionic acid **8a** remained stable. It seems that the high basicity of the imidazole group prevented an intramolecular protonation of the oxetane-ring by the carboxylic group (intermediate *A* in Scheme 1), stabilizing thereby the compound. The strained structure of core **10a** led to additional hydrolytic cleavage of the tetrahydrofuran ring. The structure of product **10b** was proven by crystallographic analysis (Figure 1).[13] Importantly, all isomerizations took place under simple heating with no external activation of the oxetane ring by HCl, HBr, or other Lewis acids.

Next, we examined reaction mixtures after hydrolysis of ethyl esters **1**, **11**-**19** with NaOH at room temperature and acidification. We were surprised to find out that in all cases, >20% of lactone was already present. Moreover, with each compound that percentage significantly varied from 20% to 70% depending on a synthesis run. Finally, we understood that isomerization must have been taking place during evaporation of the solvent (EtOAc) on a rotary evaporator (extraction of the product after acidification). Even though we typically heated external water batch at ca. 40 °C, it was enough for the cyclization to happen. Indeed, heating of all reaction mixtures after saponification in dioxane-water at 50 °C, smoothly completed the isomerization, and the corresponding pure lactones **1b**, **2b**, **11b**-**19b** were obtained (Scheme 3). The structure of product **18b** was proven by crystallographic analysis (Figure 1).[13] Interestingly, in contrast to unstable non-fluorinated analogs, fluorine-containing acids **20a**-**22a** were stable under storage. After one year at room temperature on the shelf, we did not observe their decomposition according to ^{1}H NMR. However, all three acids easily isomerized into the corresponding lactones **20b**-**22b** under heating at 50 °C in dioxane-water.

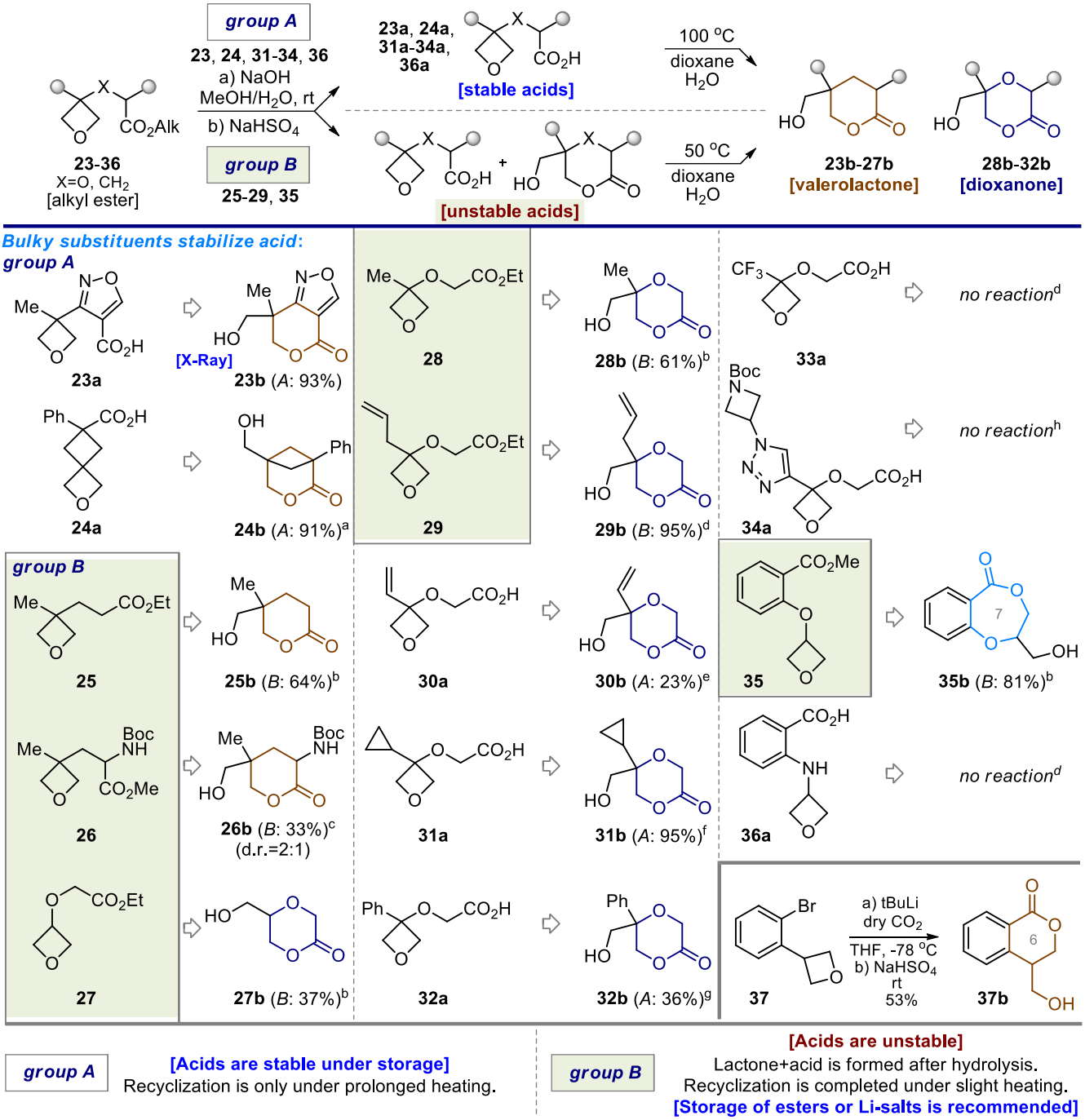
Next, we studied the stability of higher homologs of oxetane-carboxylic acids (Scheme 4). Acids **23a**, **24a** (obtained by standard saponification of the corresponding ethyl esters **23**, **24**) with bulky (hetero)aromatic substituents were stable under storage at room temperature at least for one year. Isomerization of **23**, **24** into valerolactones **23b**, **24b** took place only under prolonged heating in dioxane-water at 100 °C. The structure of product **23b** was proven by crystallographic analysis (Figure 1).[13] However, hydrolysis of alkyl ester **25** already gave a mixture of lactone and acid. The same trend was observed with alkyl esters **26**-**29**. Content of lactones varied dramatically in each case depending on the synthesis run, indicating again that the cyclization must have been taking place under heating during the evaporation of the solvent. Additional heating of those mixtures in dioxane-water gave valerolactones **25b**, **26b,** and dioxanones **27b**-**29b**.

Acids **30a**-**34a** with bulky substituents were stable under storage (Scheme 4). Moreover, heating of acids **33a** and **34a** in dioxane-water did not lead to isomerization – both compounds remained intact. Acids **31a**, **32a** under slight heating, however, gave the corresponding dioxanones **31b**, **32b**.

It was interesting to discover a dramatically different stability of structurally similar acids **35a** and **36a**. Pure compound **36a** was obtained by saponification of ethyl ester **36** under standard conditions. It was stable under storage, and under heating at 100 °C overnight did not isomerize at all. Presumably, an intramolecular hydrogen bonding between the N-H and the carbonyl group (**36a** is a derivative of 2-aminobenzoic acid) "freezes" the conformation and stabilizes hereby the molecule. Ester **35**, however, after hydrolysis with NaOH provided ca. 1/1 mixture of acid **35a** and lactone **35b**. Additional heating of this mixture at 50 °C led to complete isomerization into product **35b**.



Scheme 3. *Reaction conditions*. Group A: dioxane/water (10/1), 100 °C, 12h; Group B: dioxane/water (10/1), 50 °C, 12h. [a]reaction time 48h; [b]Water, 100 °C, 12h; [c]*i*PrOH, 82 °C, 10h; [d]Dioxane/water (10/1), 50 °C, 12h. [e]**21a** was obtained from **20a** with *m*CPBA.



Scheme 4. *Reaction conditions.* Group A: dioxane/water (10/1), 100 °C, 12h; Group B: dioxane/water (10/1), 50 °C, 12h. [a]MeOH, reflux, 4h; [b]dioxane/water (10/1), 100 °C, 12h; [c]MeOH, 50 °C, 12 days; [d]dioxane/water (10/1), 100 °C, 48h. [e]reaction time 10 days; [f]reaction time 16 days; [g]reaction time 7 days. [h]dioxane/water (10/1), 50 °C, 48h.

In addition, we also observed similar isomerization from another project. When we treated bromide **37** with *t*BuLi in THF at -78 °C followed by the addition of dry ice, the crude lithium salt of the corresponding carboxylic acid was obtained (Scheme 4). However, careful acidification of the salt with $NaHSO_4$ led to the immediate formation of the bicyclic product **37b**, which was isolated in 53% yield. Formation of the eliminated alkene was also observed, but the expected acid **37a** was not seen.

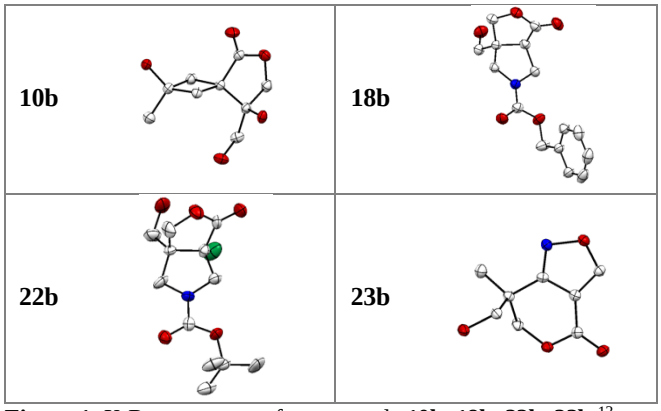
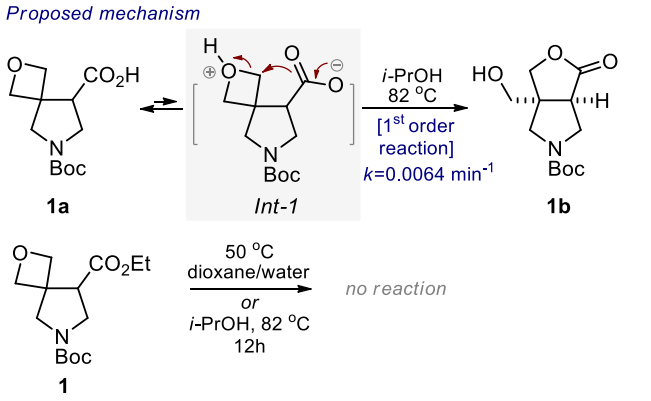


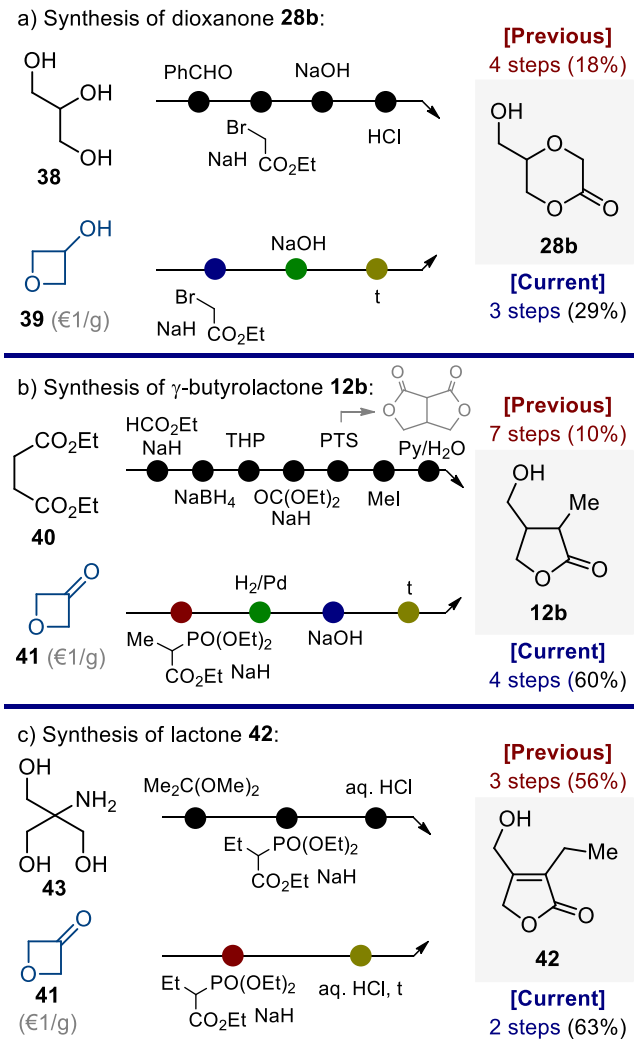
Figure 1. X-Ray structure of compounds **10b**, **18b**, **22b**, **23b**.[13]

Mechanism and kinetics. Ring-opening of oxetanes usually requires activation of the four-membered ring by Brønsted acids.[7,8] In our case, isomerization required no catalysis. Presumably, the internal carboxylic group activated the oxetane ring via the formation of intermediate *Int-1* (Scheme 5). This intermediate is dually activated towards isomerization: it has a protonated oxetane ring and an already deprotonated (more nucleophilic) carboxylate group. Indeed, in isopropanol under heating, isomerization of compound **1a** showed the 1st order kinetics with k=0.0064 min^{-1} (please, see SI). The proposed mechanism and obtained kinetics were in full accordance with the known data on the intermolecular aqueous hydrolysis of the oxetane ring.[14] In addition, ethyl ester **1**that cannot form analogous intermediate *Int-1* remained stable under these conditions (Scheme 5).



Scheme 5. Proposed mechanism for the isomerization of oxetane-carboxylic acid **1a** into lactone **1b**.

Application in synthesis. The innate tendency of oxetane-carboxylic acids to isomerization can be also beneficially used in organic synthesis to prepare novel molecules (Schemes 3, 4), or to significantly simplify the synthesis of known ones. For example, dioxanone **28b** was previously synthesized in four steps (18% total yield) from glycerine (**39**).[15] Our approach allowed the three-step synthesis (29% total yield) of this product from the commercially available 3-oxetanol (**39**) (Scheme 6). Lactone **12b** was previously synthesized in seven steps (10% total yield) from diester **40**.[16] In this work, we could obtain this molecule in just four steps from commercially available 3-oxetanone (**41**). Unsaturated lactone **42** was prepared before in three steps from triol **43**.[17] Here, we could also employ the isomerization strategy to obtain this compound in just two steps from 3-oxetanone (**41**). In that case, the final hydrolysis-isomerization was performed in one step in aqueous hydrochloric acid.



Scheme 6. Synthesis of compounds **28b**, **12b**, **42**: literature approaches *vs* our approach.

Summary. During the past decade, oxetanes have been playing an important role in chemistry as bioactive compounds and valuable starting materials in synthesis. Oxetane-carboxylic acids have been used in more than 200 manuscripts and patents (Scheme 1). Here, we unexpectedly discovered that many of these molecules are intrinsically unstable. Some of them isomerized into lactones under simple storage at room temperature, others - under slight heating. For these acids, we recommend storage of the corresponding stable esters or Li- or Na-salts (for most of the unstable acids we could obtain their stable salts – please see SI).

Of course, the innate tendency of oxetane-carboxylic acids to isomerization can be beneficially used in the synthesis to make new molecules (Schemes 3, 4), and to simplify the preparation of the known ones (Scheme 6). However, the key message of this work is to inform *chemists on the innate instability of oxetane-carboxylic acids, as this could dramatically lower reaction yields and even lead to negative results (especially in those reactions that require heating).*

Conflicts of interest

There are no conflicts to declare.

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Keywords: isomerization • medicinal chemistry • carboxylic acids • oxetanes • lactones

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