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Letter

Unexpected Isomerization of Oxetane-Carboxylic Acids

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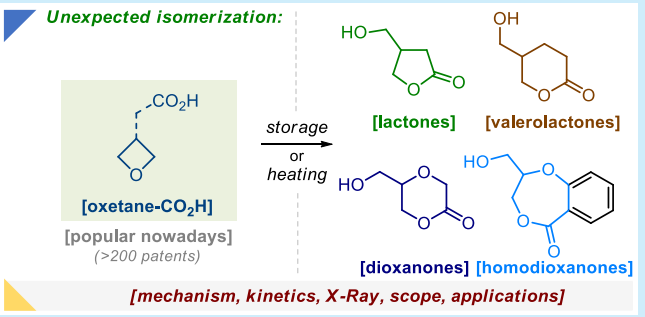
ABSTRACT: Many oxetane-carboxylic acids were found to be unstable. They easily isomerized into new (hetero)cyclic lactones while being stored at room temperature or slightly heated. Chemists should keep in mind the high instability of these molecules, as this could dramatically affect the reaction yields and lead to negative results (especially in those reactions that require heating).



More than a decade ago, oxetanes were given a second life 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 growing in 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] It is not surprising that during the past few years we have received many requests for their preparation. Some oxetane-carboxylic acids were known in the literature; others needed to be synthesized for the first time. Over time, however, we realized that many oxetane-carboxylic acids were unstable; they easily isomerized into lactones while being stored at room temperature or slightly heated. Here, we want to disclose this previously unknown phenomenon in the literature, as chemists continue to use these molecules (Scheme 1) without realizing that many of them are unstable.

Intended intramolecular isomerizations of oxetanes by nucleophiles have been 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 while being stored or slightly heated, which required no external catalysis.

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 the pure product **1a** by washing the crude material with MeO*t*Bu to remove soluble impurities. Inspection of this product three months later revealed the presence of ∼25% of the individual impurity according to ^{1}H NMR. After storage for one year at room temperature, ∼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 about the synthesis of oxetane-carboxylic acid **2a** (Scheme 2). This acid was known in the literature,[6b,10] and scientists often used it in amide coupling.[6b,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 1 week revealed the presence of ∼7% of an impurity. After storage for one month at room temperature, already 16% of this impurity was present. After storage for one year, the compound completely isomerized into the "impurity". We isolated and identified it as lactone **2b**. Moreover, even under slight heating at 50 °C in a dioxane/water mixture, acid **2a** cleanly isomerized into lactone **2b**. At this point, it became obvious that a tendency of oxetane-carboxylic acids to isomerize into lactones is general. We were very much

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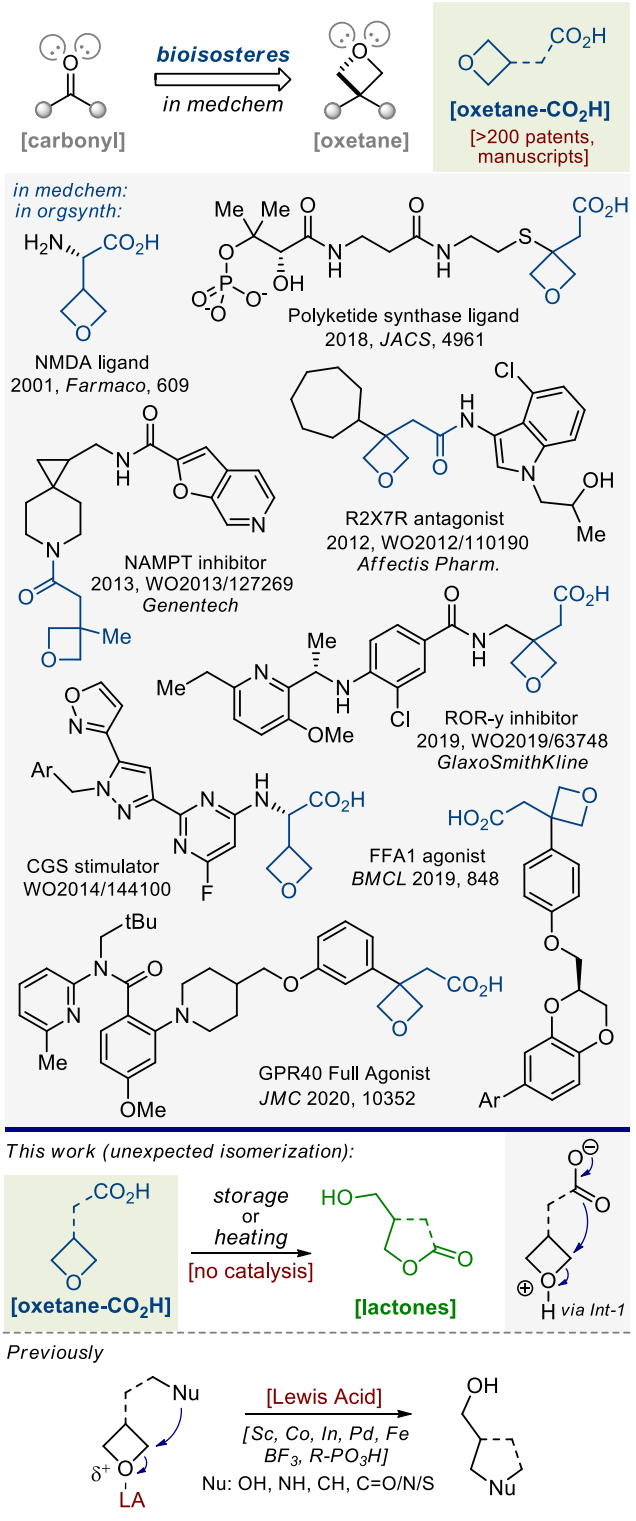
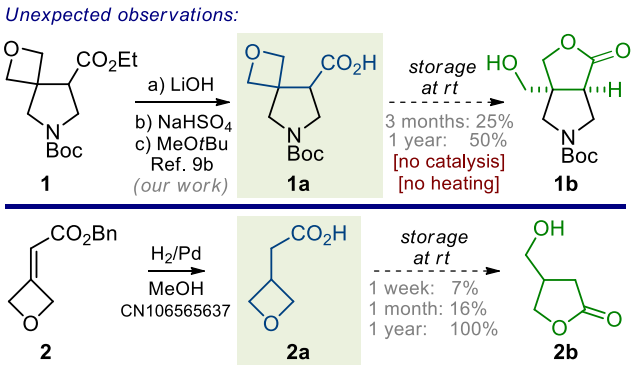
Scheme 1. Oxetane-Carboxylic Acids in Organic Synthesis and Medicinal Chemistry (aim of this work)



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 a transformation was found in a patent with no detailed experimental data.[12]

We decided next to inspect all oxetane-carboxylic acids that we had in stock. Most of these compounds were synthesized by

Scheme 2. Unexpected Isomerization of Oxetane-Carboxylic Acids 1a and 2a during Storage at Room Temperature



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**, respectively. They were stable while being stored 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** and **9a**), or a polycyclic conformationally rigid core (**10a**) stabilized these molecules. Nevertheless, compounds **3a**−**7a**, **9a**, and **10a** isomerized into lactones **3b**−**7b**, **9b**, and **10b**, respectively, under heating in a dioxane/water mixture 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 Int-1 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 confirmed by crystallographic analysis.[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** and **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 the external water bath at ∼40 °C, it was enough for the cyclization to occur. Indeed, heating of all reaction mixtures after saponification in a dioxane/water mixture at 50 °C smoothly completed the isomerization, and the corresponding pure lactones **1b**, **2b**, and **11b**−**19b** were obtained (Scheme 3). The structure of product **18b** was confirmed by crystallographic analysis.[13] Interestingly, in contrast to unstable nonfluorinated analogues, fluorine-containing acids **20a**−**22a** were stable during storage. After one year at room temperature on the shelf, we did not observe their decomposition according to ^{1}H NMR. Presumably, a fluorine atom stabilized compounds by reducing the nucleophilicity of the carboxylate anion in intermediate Int-1 via a negative inductive effect. However, all three acids isomerized into the corresponding lactones **20b**−**22b** under heating at 50 °C in a dioxane/water mixture.

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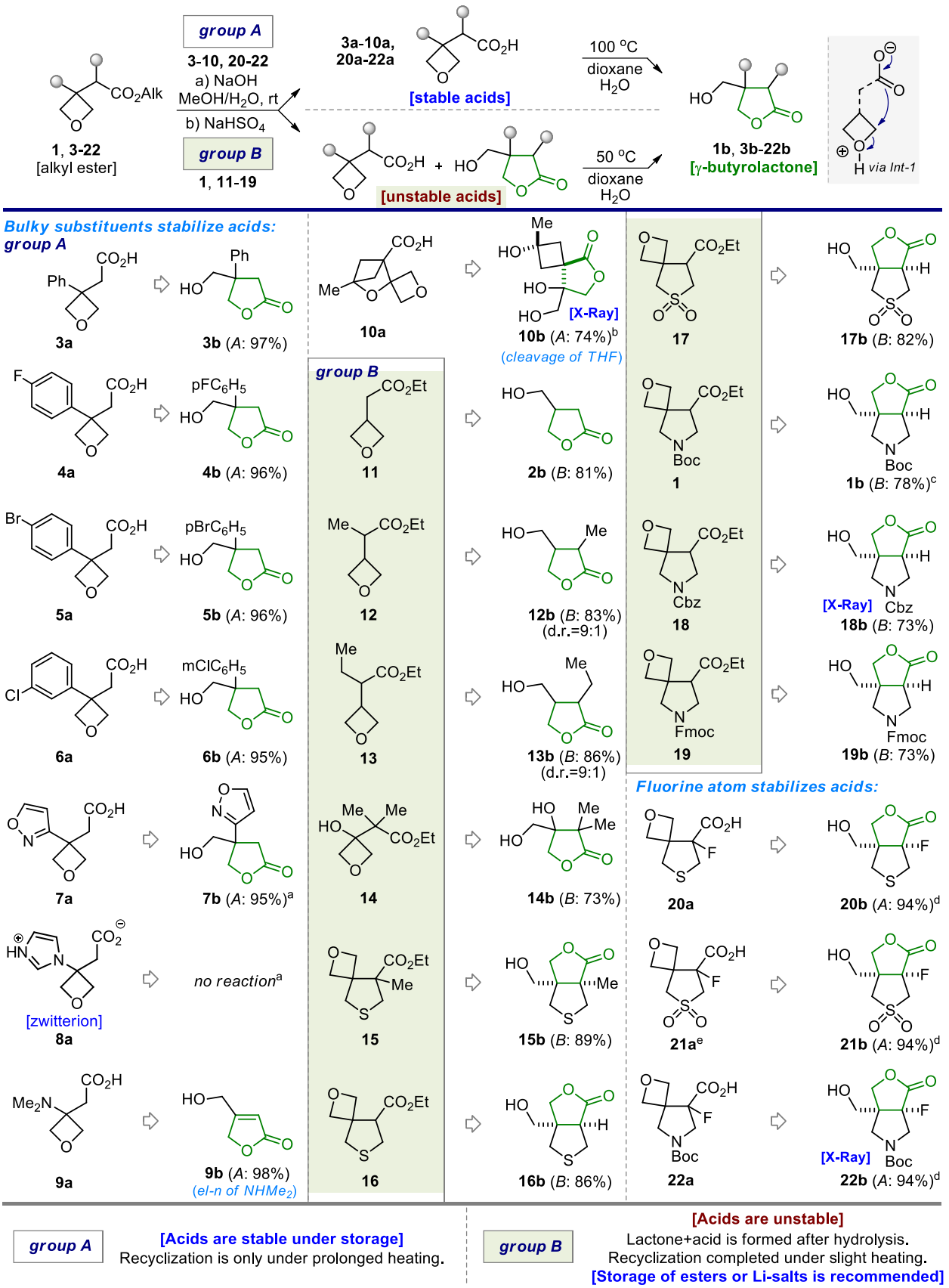
Scheme 3. Reaction Conditions [group A, dioxane/water (10/1), 100 °C, 12 h; group B, dioxane/water (10/1), 50 °C, 12 h]



[a]Reaction time of 48 h. [b]Water, 100 °C, 12 h. [c]*i*PrOH, 82 °C, 10 h. [d]Dioxane/water (10/1), 50 °C, 12 h. [e]**21a** was obtained from **20a** with *m*CPBA.

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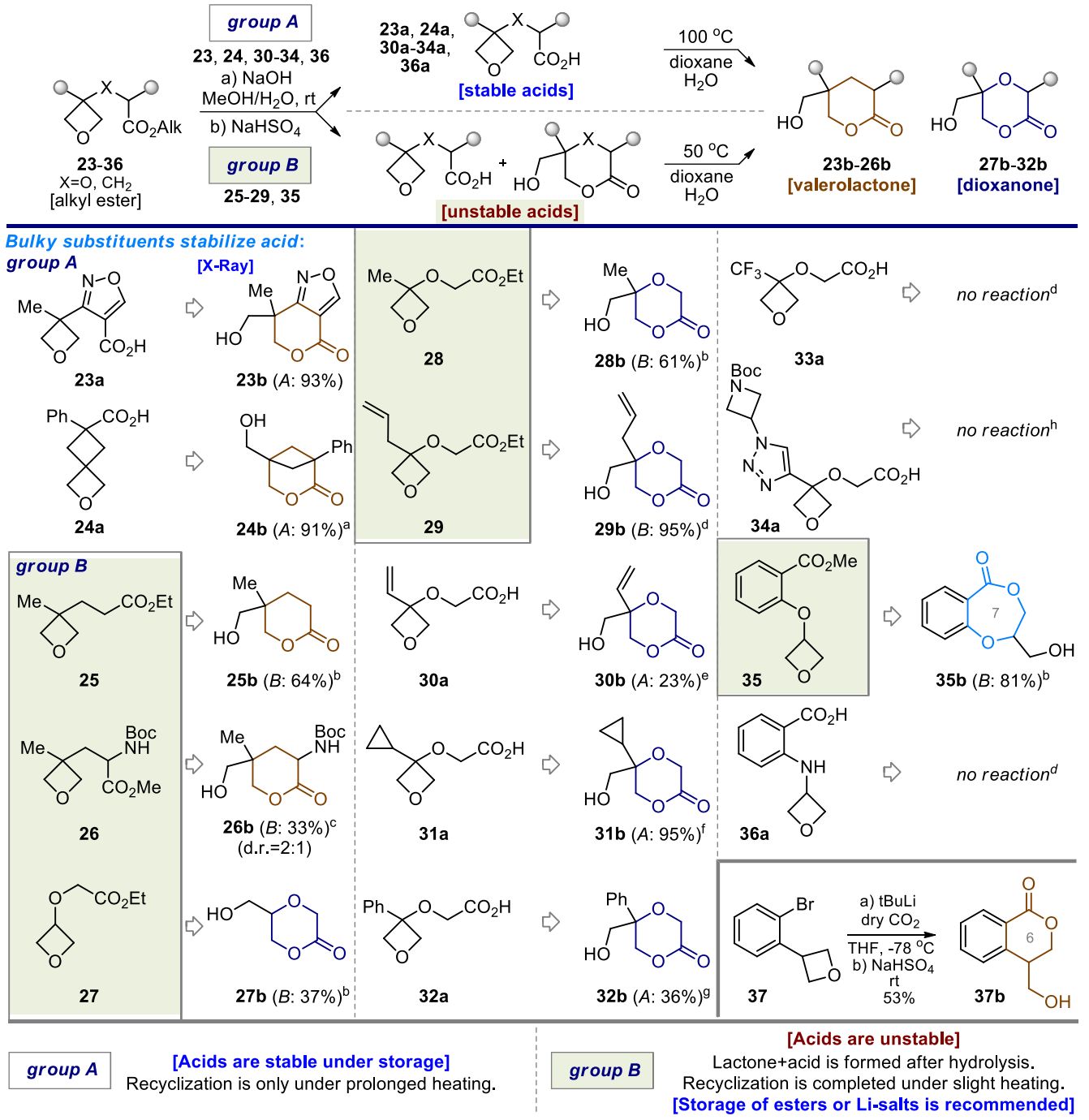
Scheme 4. Reaction Conditions [group A, dioxane/water (10/1), 100 °C, 12 h; group B, dioxane/water (10/1), 50 °C, 12 h]



[a]MeOH, reflux, 4 h. [b]Dioxane/water (10/1), 100 °C, 12 h. [c]MeOH, 50 °C, 12 days. [d]Dioxane/water (10/1), 100 °C, 48 h. [e]Reaction time of 10 days. [f]Reaction time of 16 days. [g]Reaction time of 7 days. [h]Dioxane/water (10/1), 50 °C, 48 h.

Next, we studied the stability of higher homologues of oxetane-carboxylic acids (Scheme 4). Acids **23a** and **24a** (obtained by standard saponification of the corresponding ethyl esters **23** and **24**, respectively) with bulky (hetero)-aromatic substituents were stable while being stored at room temperature at least for one year. Isomerization of **23** and **24** into valerolactones **23b** and **24b**, respectively, took place only under prolonged heating in a dioxane/water mixture at 100 °C. The structure of product **23b** was confirmed by crystallographic analysis.[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**. The lactone content 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 a dioxane/water mixture gave valerolactones **25b** and **26b** and dioxanones **27b**–**29b**.

Acids **30a**–**34a** with bulky substituents were stable while being stored (Scheme 4). Moreover, the heating of acids **33a** and **34a** in a dioxane/water mixture did not lead to isomerization; both compounds remained intact. Acids **31a**

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and **32a** under slight heating, however, gave the corresponding dioxanones **31b** and **32b**, respectively.

It was interesting to discover the 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 while being stored, and heating at 100 °C overnight did not lead to any isomerization. Presumably, intramolecular hydrogen bonding between the N−H and the carbonyl group (**36a** is a derivative of 2-aminobenzoic acid) "freezes" the conformation and stabilizes thereby the molecule. Ester **35**, however, after hydrolysis with NaOH provided an ∼1/1 acid **35a**/lactone **35b** mixture. Additional heating of this mixture at 50 °C led to the complete isomerization into product **35b**.

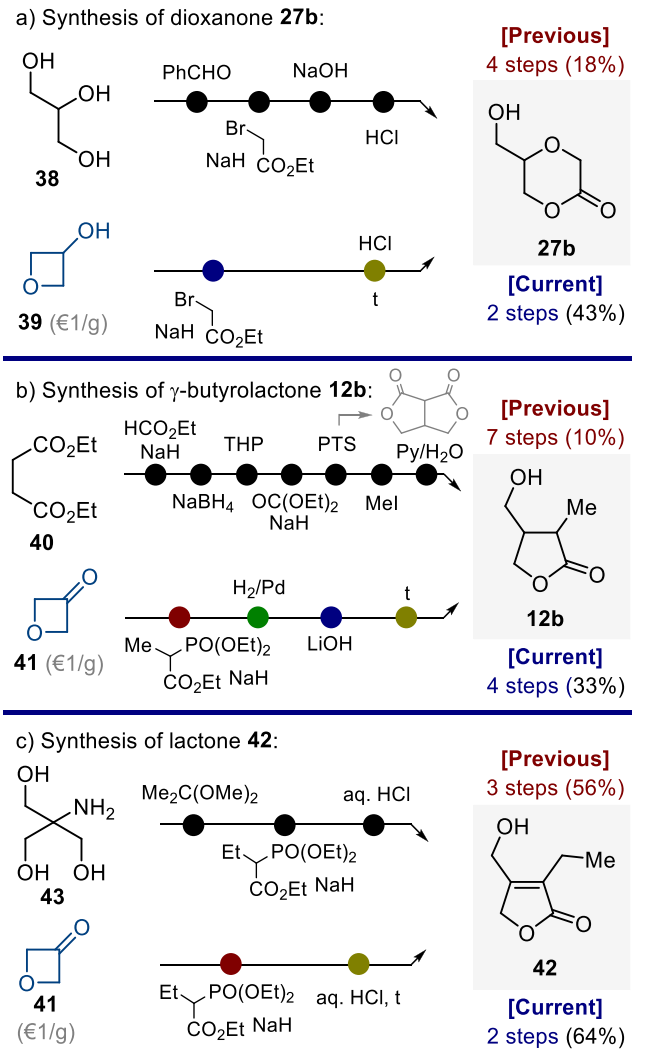
In addition, we also observed similar isomerization from another project. When we treated bromide **37** with *t*BuLi in THF at −78 °C followed by the addition of dry ice, the crude lithium salt of the corresponding carboxylic acid was obtained (Scheme 4). However, careful acidification of the salt with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

The innate tendency of oxetane-carboxylic acids to isomerization can be also beneficially used in organic synthesis to prepare novel molecules (Schemes 3 and 4) or to significantly simplify the synthesis of known ones. For example, dioxanone **27b** was previously synthesized in four steps (18% total yield) from glycerine (**39**).[14] Our approach allowed the two-step synthesis (43% total yield) of this product from the commercially available 3-oxetanol (**39**) (Scheme 5). Lactone **12b** was previously synthesized in seven steps (10% total yield) from diester **40**.[15] In this work, we could obtain this molecule in just four steps from commercially available 3-oxetanone (**41**). Unsaturated lactone **42** was prepared previously in three steps from triol **43**.[16] 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 and isomerization were performed in one step in aqueous hydrochloric acid.

During the past decade, oxetanes have played 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 were unstable. Some of them isomerized into lactones while being stored at room temperature, and others were being slightly heated. For these acids, we recommend storage of the corresponding esters or Li/Na salts [for most of the unstable acids, we could obtain their salts that could be stored for years at room temperature on the shelf (see the Supporting Information)].

Of course, the tendency of oxetane-carboxylic acids to isomerization can also be beneficially used in the synthesis to make new molecules (Schemes 3 and 4) and to simplify the preparation of the known ones (Scheme 5). However, the key message of this work is to inform chemists on the innate instability of many oxetane-carboxylic acids, as this could dramatically lower reaction yields and even lead to negative results (especially in those reactions that require heating).

Scheme 5. Synthesis of Compounds 27b, 12b, and 42 (literature approaches vs our approach)



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01402.

Experimental procedures, characterization data, and X-ray and NMR spectra for products (PDF)

Accession Codes

CCDC 1470391−1470392, 2090821, and 2096431 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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