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Ketone formation from carboxylic acids by ketonic decarboxylation: the exceptional case of the tertiary carboxylic acids

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Abstract: For the reaction mechanism of the ketonic decarboxylation of two carboxylic acids, a β -keto acid is favored as key intermediate in many experimental and theoretical studies. Hydrogen atoms in α -position are an indispensable requirement for the substrates to react following this mechanism. However, isolated literature observations with tertiary carboxylic acids are not in accordance with it and these are revisited and discussed herein.

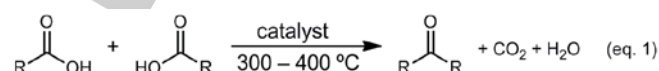
The experimental results obtained with pivalic acid indicated that the ketonic decarboxylation does not occur with this substrate. Instead, it is consumed in alternative reactions such as disintegration into *iso*-butene, carbon monoxide and water (retro-Koch reaction). In addition, the carboxylic acid is isomerized or loses carbon atoms which converts the tertiary carboxylic acid into carboxylic acids bearing α -proton atoms. Hence, the latter are suitable to react via the β -keto acid pathway.

A second substrate, 2,2,5,5-tetramethyladipic acid, reacted following the same retro-Koch pathway. The primary product was the mono-carboxylic acid 2,2,5-trimethyl-4-hexenoic acid (and its double bond isomer) which might be further transformed into a cyclic enone or a lactone. The ketonic decarboxylation product, 2,2,5,5-tetramethylcyclopentanone was observed in traces (< 0.2% yield).

Therefore, it can be concluded that the observed experimental results further support the proposed mechanism for the ketonic decarboxylation via the β -keto acid intermediate.

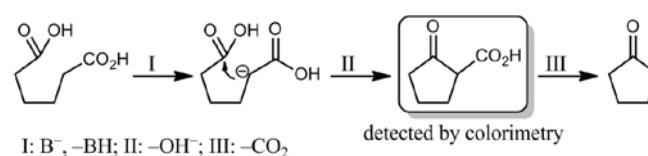
Introduction

The ketonic decarboxylation converts two molecules of carboxylic acid into a ketone together with carbon dioxide and water, one molecule each (eq. 1).^[1,2] When regarding the concept of Green Chemistry, the reaction can be considered as environmentally benign since a high percentage of the substrate atoms are recovered in the product and apart from the carboxylic acid no further reagents are required. Furthermore, this reaction is extremely suitable to remove selectively the oxygen content of the chemical compounds since only one carbon atom is eliminated together with three oxygen atoms out of four. This fact makes it predestined for the up-grade of biomass-derived product mixtures.^[3-8] The last oxygen atom in the ketone can be removed by hydrodeoxygenation via alcohol and olefin to produce linear alkanes which might serve as fuels or lubricants.^[9-12]



In the biomass transformations an additional desired characteristic is the formation of a carbon-carbon bond, joining small molecules into molecules with more advantageous properties for fuels and chemicals. Therefore, with the intended change from fossil-based chemistry towards a biomass-based one, the ketonic decarboxylation has become a highly trendy and beneficial reaction.

The mechanism of the ketonic decarboxylation has been matter of interest for a long period of time and has caused some trouble in literature. As early as 1939 Neunhoeffer and Paschke postulated a mechanism with a β -keto acid as intermediate (Scheme 1).^[13] For the formation of the latter, one molecule has to be deprotonated in α -position and this in turn excludes substrates without any α -hydrogen atoms from reacting. The mechanistic proposal was based on the colorimetric detection of the intermediate in an estimated concentration of 1% and it was in accordance with all experimental observations from literature at that time.

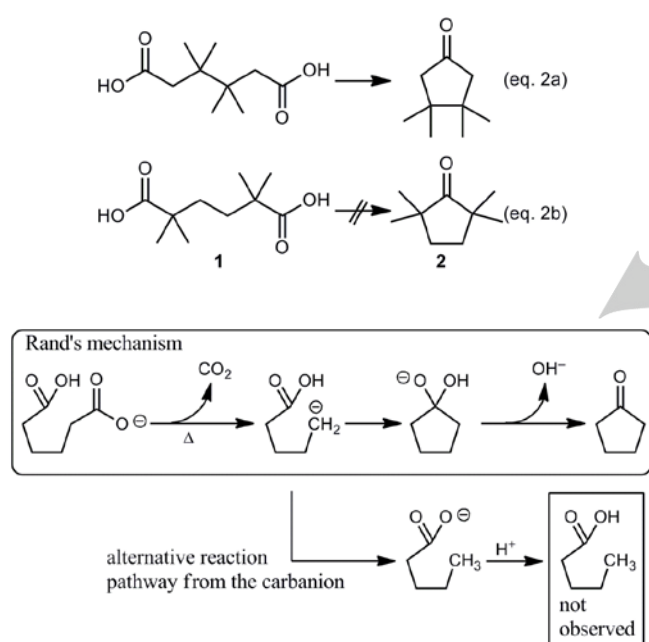


Scheme 1. Mechanism for the ketonic decarboxylation as proposed by Neunhoeffer and Paschke.^[13]

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A particular significance was attributed to the reaction of tetramethyladipic acid derivatives. Hence, 2,2,5,5-tetramethyladipic acid (**1**), without any α -hydrogen atoms, could not be converted into the cyclopentanone derivative **2** (eq. 2b)^[14,15] whereas the corresponding one was obtained from the 3,3,4,4-isomer (eq. 2a).^[14] However, in 1962 the transformation of 2,2,5,5-tetramethyladipic acid into the corresponding ketone has been reported in 52% to 72% yield in the presence of KF or BaO.^[16] These results were clearly incompatible with the widely accepted β -keto acid mechanism and the authors proposed a carbon centered anion as intermediate instead (Scheme 2). As this intermediate would deprotonate immediately other carboxylic acids and produce formally hydrodecarboxylation products (cf. Scheme 2, alternative pathway) which are not observed in general, this mechanism was modified and the decarboxylation and carbon-carbon bond formation were proposed to occur in a concerted fashion.^[1]



Scheme 2. Mechanism for the ketonic decarboxylation as proposed by Rand et al.^[16] and an alternative pathway from the carbanion to the hydrodecarboxylation product.

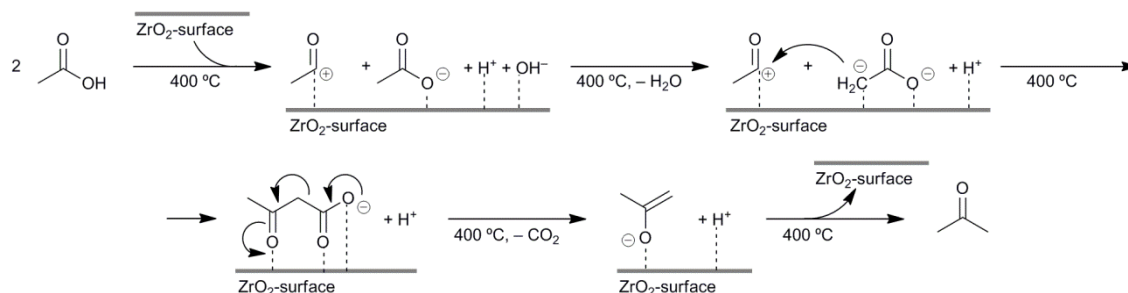
As already mentioned, with the increasing interest due the relevance to biomass transformation, the ketonic decarboxylation and its mechanism has become matter of interest again. This is manifested in the number of catalytic studies appeared recently^[17–21] and the experimental and theoretical evaluations of the mechanism.^[22–29] For the theoretical examination it was mandatory to “fix” the reaction centers on a crystalline surface to get reliable information and to avoid excessive freedom for reactants and catalysts/catalytic sites. Furthermore, it was of paramount interest that the catalyst was stable under the reaction conditions and the geometry unchanged after the transformation. This condition excludes oxides with low lattice energy, which form bulk carboxylates, such as lead, bismuth, zinc or magnesium

oxide.^[30] Instead, oxides having a high lattice energy, such as alumina, chromia, titania and zirconia, remain unaltered in presence of carboxylic acids.^[30] Hence, zirconium oxide has been identified experimentally as a suitable catalyst out of several metal oxides upon its catalytic activity^[25,31] and its stability.^[11,20] With this material full conversion was achieved at 400 °C and several hundreds of grams per gram of metal oxide were passed through the catalytic bed with intermediate reactivation steps.

In a theoretical DFT study with this material, again a mechanistic pathway via the β -keto-acid has been favored kinetically, fully in accordance with the initial work of Paschke and Neunhoeffer. Hence, two molecules of carboxylic acid are adsorbed in a different fashion, one by dehydroxylation and the other by double deprotonation (Scheme 3). Then, the resulting dianionic species attacks the acylium fragment nucleophilically forming a carbon-carbon bond and therewith the β -keto-acid. The latter is decarboxylated and the resulting enolate protonated. Desorption of all products closes the catalytic cycle. A very similar mechanism via the β -keto-acid has been described for rutile titania by DFT calculation differing only in the moment of the second deprotonation.^[27] Essential reaction steps such as carbon-carbon bond formation to the β -keto-acid followed by decarboxylation are identical. The carboxylic acid anhydride may also be an intermediate, since both precursors for the β -keto-acid can be formed from one molecule of acid anhydride. Therefore, in this case the principal kinetic effect should be: to carry out the reaction under “less humid conditions” avoiding water desorption within the catalytic cycle.^[22] The latter turned out to be highly endothermic on zirconium oxide.^[25]

The reaction via the β -keto-acid intermediate was favored over the concerted mechanism or radical reactions for substrates without steric impediments in α -position.^[25] It was further assured, experimentally and theoretically, that the same mechanism also applies for substrates with an additional methyl substituent in α -position.^[26] This additional group has a strong retarding effect on the reaction kinetics, for instance one additional methyl group lowers the reaction rate by a factor of 30 (in the temperature range from 350 to 400 °C).^[26] In addition, it was concluded that the substrates with a higher steric demand react preferentially at edges and corners of the catalyst crystals.^[26]

The only result in literature which is not in accordance with the mechanism via a β -keto-acid is the transformation of 2,2,5,5-tetramethyladipic acid (**1**) into 2,2,5,5-tetramethylcyclopentanone (**2**) mentioned before (eq. 2b).^[16] The solution to this inconsistency seems to be the last missing puzzle piece for an entire and comprehensive picture for the mechanism of the ketonic decarboxylation. Therefore, we revisited this reaction employing the catalyst used in the combined theoretical and experimental study, i.e., zirconium oxide, and carried out the reaction under the best conditions used in the 1962-publication, i.e., in presence of barium oxide. In addition, we selected pivalic acid (2,2-dimethylpropanoic acid, **3**) as a model substrate. This molecule can be reacted under the same reaction conditions in the gas phase as valeric and 2-methylbutyric acid whereas carboxylic acid **1** cannot be volatilized easily. Moreover, pivalic acid (**3**) has the same number of carbon atoms as both carboxylic acids used before for the theoretical/experimental study so that

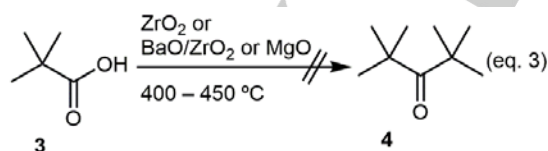


Scheme 3. Kinetically favored pathway by DFT calculations for the ketonic decarboxylation. Two molecules adsorb in a different fashion, namely by dehydroxylation and double deprotonation. A nucleophilic attack forms a carbon–carbon bond and subsequent decarboxylation and protonation the ketone product. Reproduced from Ref.^[32]

similar physical properties (e.g. boiling point, vapor pressure, etc.) can be expected with respect to the reaction temperature. It has been reported also for pivalic acid (**3**) that the corresponding ketone 2,2,4,4-tetramethyl-3-pentanone (**4**) was not observed under standard reaction conditions.^[13] With these proposed experiments, the present study will help to eliminate these last obstacles for a comprehensive understanding of the ketonic decarboxylation.

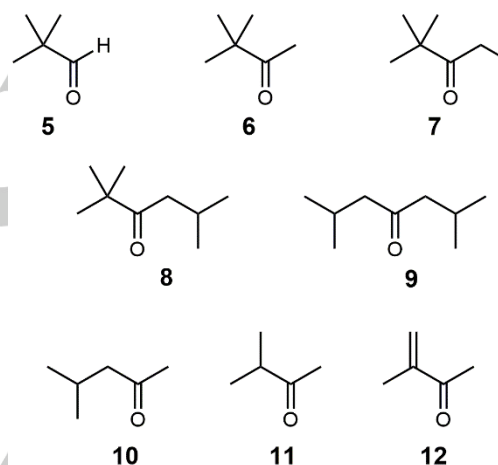
Results and Discussion

Pivalic acid (**3**) was chosen as test molecule and reacted under standard conditions for the ketonic decarboxylation in the 400 – 450 °C temperature range. In general, most ketonizations are carried out even below 400 °C.^[1,2] As catalyst zirconium oxide^[33,34] was employed first, which has turned out to be an active and stable catalyst for the reaction with valeric acid, i.e., the carboxylic acid with linear chain and also five carbon atoms.^[35] No conversion was observed under these conditions (eq. 3). The result should be generalized and, therefore, other classical oxides were tested for this reaction such as barium oxide (supported on zirconium oxide) and magnesium oxide.^[36] But, again, no conversion was observed under the standard conditions (eq. 3). These results were in accordance with literature reports since also calcium pivalate has been resistant to the conversion into a ketone,^[13] and neither was the symmetrical ketone observed in cross coupling reactions.^[25]



The reaction set-up for the gas phase reaction over zirconium oxide allowed to raise the temperature further. This was done to force the reaction conditions and to facilitate the ketonic decarboxylation via kinetically less favored pathways (if these existed) or to identify and allow alternative reaction pathways which cannot be accessed at standard temperature. Hence, when increasing reaction temperature to 500 °C a low conversion of 11% was observed, which reached already 63% at 550 °C.

However, the symmetrical ketonic decarboxylation product, i.e., 2,2,4,4-tetramethyl-3-pentanone (**4**, eq. 3), was not observed. This was assured unambiguously by comparison with an authentic sample. Instead, more than 15 different products were detected and identified (see Table 1).



At 550 °C, the most abundant gas products detected were CO₂ with 20% yield, CO with 14% yield, isobutene (12%) and H₂ (10%). Isobutane and methane (~3%) were also observed in the gas phase, but in lower yield. In the liquid phase, a large variety of carbonyl compounds (**5-12**) was obtained which were identified by GC-MS and some confirmed by comparison with the authentic sample (compounds **5**, **6**, **10** and **11**). Most of them have a lower molecular weight than the hypothetical symmetrical ketonic decarboxylation product.

At a glance, approximately a yield of 20% of ketones was detected and a superior amount of carbon dioxide, which is in accordance with the hypothesis that the ketones were obtained by ketonic decarboxylation. In addition, 12 to 14% of carbon monoxide and isobutene were obtained (Table 1). The similar yields of the latter two products suggest that they are formed from a retro-Koch type reaction (eq. 4). The ability of pivalic acid to undergo a retro-Koch type reaction was further supported when it was reacted over SiO₂, FeSO₄/SiO₂, and Fe₂O₃/SiO₂ at 500 °C: both products were observed with approximately 90% selectivity in each case (Supp. Inf., Figure S1).

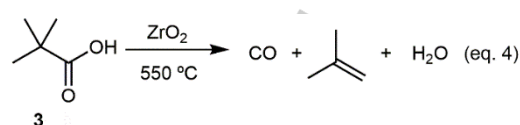


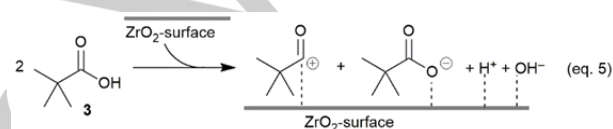
Table 1. Yields (in mol%) of products observed in the reaction of pivalic acid (**3**) at 500 °C and at 550 °C over zirconium oxide. Yields of products in the gas phase are estimated by determination of their concentration in the gaseous effluent and the concentration of N₂ and the total volume of N₂, employed during the experiment as carrier gas. Products in the organic phase (condensed with an ice bath at the exit of the reactor) were quantified by GC using dodecane as external standard and are related to one equivalent of acid **3** for the gaseous products and to two equivalents for the ketone products (For formulas see Supp. Inf.).

Catalyst	ZrO ₂	ZrO ₂	ThO ₂ ^[a]
Reaction temperature/°C	500	550	490
conversion/%	11	63	79
	yield/%	yield/%	yield/%
<i>products in the gas phase</i>			
carbon dioxide	1.6	20.1	20.0
carbon monoxide	1.5	13.7	2.7
hydrogen	0.0	9.8	0.3
<i>iso</i> -butene	1.3	11.8	(2.6) ^[b]
<i>iso</i> -butane	0.3	2.0	(5.0) ^[c]
methane	0.2	2.9	0.6
propylene	0.1	1.0	0.03
others	0.3	0.3	0.3
<i>products in the condensed phase</i>			
2,2,4,4-tetramethyl-3-pentanone (4)	0.00	0.00	0
2,2-dimethylpropanal (5)	0.33	4.14	3
3,3-dimethylbutanone (6)	0.00	6.86	9
2,2-dimethyl-3-pentanone (7)	0.00	2.09	0.7
2,2,5-trimethyl-3-hexanone (8)	0.83	2.56	15
2,6-dimethyl-4-heptanone (9)	0.09	0.68	^[d]
4-methyl-2-pentanone (10)	0.00	0.52	^[d]
3-methylbutanone (11)	0.00	0.70	^[d]
3-methyl-3-butanone (12)	1.78	5.25	^[d]
(total ketones and aldehydes)	(3.03)	(22.8)	(27)
3-methylbutyric acid (13)	0.09	0.53	^[d]
others	1.83	1.95	20

[a] From literature ^[37]. [b] Indicated as butanes. [c] Indicated as butenes. [d] Not specified.

For the ketone products, formation via ketonic decarboxylation can be discussed, even through the β-keto acid mechanism since all ketone compounds **6–12** possess an α-hydrogen atom with respect to the carbonyl group. In any case, pivalic acid (**3**) has to undergo rearrangement or fragmentation reaction prior to the carbon-carbon bond formation, i.e., before reacting with a second, unchanged pivalic acid molecule.

For establishing the reaction network for the product formation the same surface species, with the exception of the doubly deprotonated carboxylic acid as before in the theoretical and experimental study, should be taken into account, i.e., a deprotonated one and a dehydroxylated one (eq. 5).



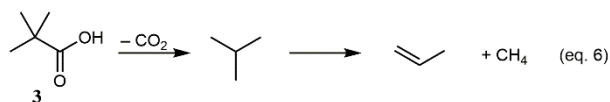
When dehydroxylating pivalic acid (**3**) the resulting carbocationic species can decompose easily into isobutene (releasing one proton to the surface) and carbon monoxide in a retro-Koch-type reaction (eq. 4), providing both molecules in a equimolar ratio as observed in the reaction over zirconium oxide at 550 °C or over other materials at 500 °C (Supp. Inf., Figure S1). This fragmentation of pivalic acid (**3**) has been observed before in the presence of a strong Brønsted acid (HBr).^[38] In addition, pivalic acid (**3**) has been used for transcarboxylation reactions together with tertiary alkanes catalyzed by sulfuric acid.^[39] Again, cationic intermediates are proposed and the transfer of a CO fragment.

On the zirconium oxide surface strong Brønsted acid sites are not present, only Lewis acidic zirconium sites. This might be one of the reasons why such a high reaction temperature is required. However, the bond rupture may also be “assisted” by the surface: for instance by basic sites, which are responsible for the proton abstraction in carboxylic acids in α-position, and which might stabilize the *tert.*-butyl cation or remove a proton from a methyl group to form the olefin. In light of the experimental data, combined with the theoretical knowledge on the surface activity and the literature references on the reactivity of pivalic acid (**3**), it seems reasonable to propose that one of the reaction pathways for the pivalic acid (**3**) on zirconium oxide at 550 °C is the disintegration via the retro-Koch reaction as described in eq. 4. This means that isobutene, carbon monoxide and water are produced in equimolar amounts from one molecule of pivalic acid (**3**).

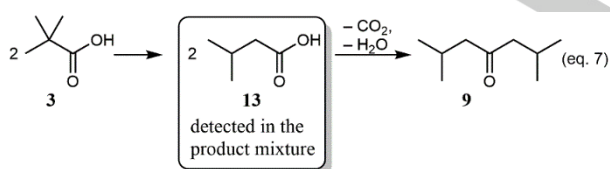
Isobutane was detected in the gas phase with 2% yield (Table 1). Formally, this is the decarboxylation product of pivalic acid (**3**), i.e., it is co-produced with carbon dioxide (eq. 6). Hence, this is a plausible formation under the present reaction conditions and may be induced by deprotonation of the acid and further promoted by surface protons which might stabilize the leaving group. Once formed, isobutane may be fragmented into propene and methane

FULL PAPER

(eq. 6) which both were detected in the gas phase in 1.0% and 2.9% yield, respectively (Table 1). Such fragmentation has been observed at high temperature over solid materials.^[40–42] However, having in mind the product ratios, it becomes evident that further sources (precursors) for the methane formation must exist.



For the liquid carbonyl compounds, formation by ketonic decarboxylation was assumed as a working hypothesis. The second product of this reaction, carbon dioxide, is present in the gaseous effluent in sufficient yield, which is in accordance with the hypothesis. However, for enabling the reaction via the β -keto acid pathway, at least part of the pivalic acid (**3**) has to undergo modifications in its carbon skeleton: either undergo rearrangement reactions or lose carbon atoms. This is clearly in line with the experimental results since the symmetrical ketone **4** obtained from two molecules of carboxylic acid **3** was not observed. Very clear evidence for a rearrangement of the carbon skeleton is the formation of ketone **9**, i.e., 2,6-dimethylbutanone, which is observed in 0.7% yield. This product can be formed from two molecules of 3-methylbutyric acid (**13**), which was detected in the liquid product mixture in traces (Table 1), via the established β -keto-acid mechanism since this substrate contains two α -hydrogen atoms. Consequently, for the formation of ketone **9** the reaction sequence depicted in eq. 7 was assumed involving skeleton rearrangement of the carboxylic acid **3** into carboxylic acid **13** followed by ketonic decarboxylation via the β -keto-acid mechanism. Probably, the rearrangement occurs in one of the surface stabilized species, further supported by other surface functionalities, but for a more detailed description of the mechanism at molecular level theoretical calculations should be carried out.



Having in mind this carbon skeleton rearrangement, also the explanation of the formation of ketone **8** is straightforward: it is the cross-coupling product of the rearranged acid and the original one. In the other ketone products carbon atoms are missing indicating fragmentation reactions either at the substrate stage or in the product (formed with the rearranged acid). If it is assumed that these reactions occur already in the substrate, again the ketonic decarboxylation may occur since all the ketones involve α -hydrogen atoms.

Apart from the ketone product one aldehyde was observed: pivaldehyde (**5**). The latter can be produced by hydrogenation in an analogous way as reported for benzoic acid which is hydrogenated to benzaldehyde over zirconium oxide.^[43] The aldehyde was also observed experimentally with a 32% yield at 400 °C when pivalic acid (**3**) was fed together with hydrogen as carrier gas. The required hydrogen was also observed in the

gaseous effluent of the reaction at elevated temperature (550 °C) and with nitrogen as carrier gas (Table 1).

The reaction of pivalic acid (**3**) over a metal oxide has been carried out before at high temperatures (490 °C) over thorium oxide with similar results.^[37] The main products at a conversion of 79% were *t*-butyl isobutyl ketone (**8**) and *t*-butyl methyl ketone (**6**) with selectivities of 19% and 11%, respectively (Table 1). Also in this case, the symmetrical ketonic decarboxylation product, i.e., 2,2,4,4-tetramethyl-3-pentanone (**4**) was not identified in the product mixture. This means that similar reaction pathways may apply here as for the ZrO₂ case, although a different interpretation has been originally provided by the Authors, possibly due to the fact that the most indicative products, i.e., *iso*-butene and carbon monoxide, have been observed in lower concentration.

These experimental results with pivalic acid (**3**) over zirconium oxide, and also with thorium oxide, indicate that the ketonic decarboxylation with two molecules of the substrate does not occur, not even under forced reaction conditions. Instead, the substrate is consumed in alternative surface-catalyzed reactions such as base-induced disintegration into *iso*-butene, carbon monoxide and water (retro-Koch reaction). This reactivity follows the prediction of the DFT calculations that show high barriers for alternative ketonic decarboxylation reactions without abstraction of α -hydrogen atoms. Activation energies are so high that carbon-carbon bond scission can compete.

The second critical reaction for the ketonic decarboxylation reported in literature with respect to the β -keto-acid mechanism was the transformation of carboxylic acid **1**. Therefore, also this reaction was revisited. As this acid cannot be volatilized without decomposition, the reaction had to be carried out under different conditions, i.e., with a different reaction setup. Hence, the acid was treated in a batch reactor, from which lower-boiling-point products were distilled off, as it has been employed in the transformation of the unsubstituted adipic acid into cyclopentanone.^[44,45]

When 2,2,5,5-tetramethyladipic acid (**1**) was contacted with zirconium oxide (10 wt%) or with barium oxide (10 mol%) at 350 to 370 °C, or heated in absence of any catalyst, gas evolution was observed (Figure 1). Thereby, it can be seen that the thermal reaction proceeded smoothly, but barium oxide, and even more zirconium dioxide, accelerated the reaction rate. The analysis of the gas composition indicated immediately that the reaction occurred was not the standard ketonic decarboxylation since carbon dioxide was obtained only as a minor product together with more than 80% yield of carbon monoxide in each case (Table 2).

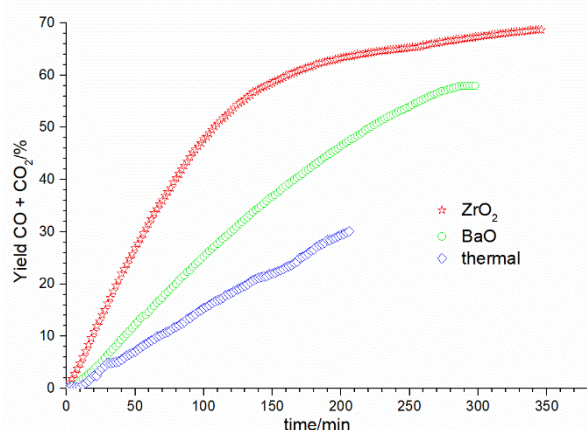
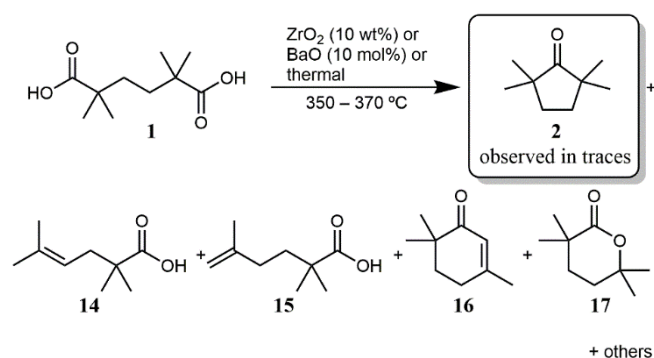


Figure 1. Yield of the gas evolution during the thermal treatment of 2,2,5,5-tetramethyladipic acid (**1**) and in the presence of ZrO_2 (10 wt%) or BaO (10 mol%) at 350 – 370 °C. The composition of the gas is specified in Table 2.

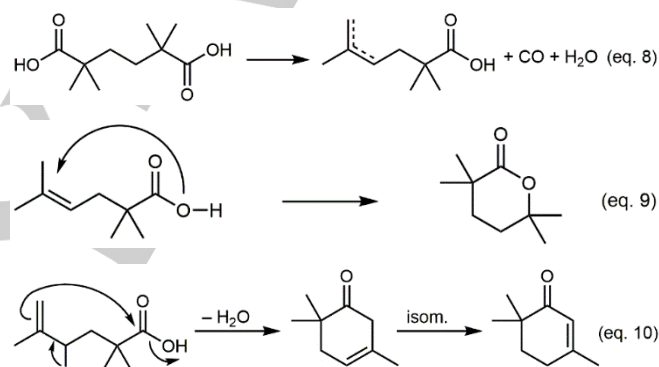
An organic distillate of approximately 45 to 50 wt% was obtained and 5 to 10 wt% of water whereas the gaseous phase accounted for more or less 10 wt% in each case. In the distillate, the ketonic decarboxylation product, i.e., ketone 2,2,5,5-tetramethylcyclopentanone (**2**), was not found by comparison with an authentic sample in the GC analysis when carrying out the reaction with BaO as catalyst and in less than 0.2% yield with ZrO_2 as catalyst or without any catalyst. A six-membered ring ketone, namely 3,6,6-trimethylcyclohex-2-en-1-one (**16**) was obtained instead, together with a lactone, namely $\alpha,\alpha,\delta,\delta$ -tetramethylvalerolactone (**17**), and two unsaturated monocarboxylic acid isomers as main products for the catalyzed reactions, 2,2,5-trimethyl-4-hexenoic acid (**14**, main isomer) and 2,2,5-trimethyl-5-hexenoic acid (**15**, Scheme 4; for product ratios see Table 2).



Scheme 4. Product mixture observed for the treatment of dicarboxylic acid **1** in the presence of ZrO_2 , BaO or without any catalyst. Formation of 2,2,5-trimethyl-4-hexenoic acid (**14**), 2,2,5-trimethyl-5-hexenoic acid (**15**), 3,6,6-trimethylcyclohex-2-en-1-one (**16**), $\alpha,\alpha,\delta,\delta$ -tetramethylvalerolactone (**17**) were detected. For product ratios see Table 2.

When establishing the reaction network, 2,2,5-trimethyl-4-hexenoic acid (**14**), and its double bond isomer **15**, can be assumed to be primary products. These molecules can be formed by a retro-Koch-type reaction (eq. 8), in an analogous manner to the reaction proposed above for the pivalic acid (**3**) transformation into carbon monoxide and *iso*-butene. This assumption is further supported by the detection of carbon monoxide in large amounts in the gas phase effluent.

In the present case the selectivity towards this reaction pathway was considerably higher with 75%, when considering ketone and lactone as secondary, 2,2,5-trimethyl-4-hexenoic acid (**14**)-derived products. Hence, the lactone **17** can be obtained by a simple intramolecular addition of the carboxylic acid to the double bond (eq. 9).^[46] This cyclization has been described in literature and was utilized for the synthesis of an authentic sample. The ketone **16** can be formed by an intramolecular attack of the double bond onto the carbonyl group (eq. 10), although at present the mechanism has not been explored in detail. This ketone has also been identified by comparison with an authentic sample.



The actual ketonic decarboxylation product, the ketone **2**, was not detected as one of the main products, but in traces in two cases. An authentic sample was synthesized by an alternative pathway, namely by complete methylation of cyclopentanone in the α -positions. With the substance in hand, the compound was identified unambiguously in the product mixtures of the thermal and the ZrO_2 catalyzed reactions, with a very low yield in both cases, below 0.2%. When the reaction was carried out in the presence of BaO , ketone **2** was not observed at all. These results are clearly opposed to the ones of Rand et al.^[16]

Already in 1966, Ebersson proposed that the catalytic transformation of 2,2,5,5-tetramethyladipic acid (**1**) produced 3,6,6-trimethylcyclohex-2-en-1-one (**16**), instead of 2,2,5,5-cyclopentanone (**2**).^[15] An identical melting point of the 2,4-dinitrophenylhydrazone was obtained as for the compound isolated by Rand et al., and a similar refractive index. Both analytical data were used by Rand for the identification of the product.^[16] Our results further support those of Ebersson and the mono-acids **14** and **15**, isolated and characterized herein, further explain the formation of this ketone.

Table 2. Results for the thermal treatment of 2,2,5,5-tetramethyladipic acid (**1**) and in the presence of ZrO₂ (10 wt%) or BaO (10 mol%) at 350 – 370 °C. For the structure of the organic compounds see Scheme 4.

	thermal	ZrO ₂	BaO
<i>yield of products</i>			
gaseous products/wt% ^[a]	6.6	11.8	8.0
organic distillate/wt%	26.0	60.5	51.2
water/wt%	4.4	5.3	8.3
residue/wt%	51.6	21.7	29.7
weight balance/%	88.4	99.3	97.2
<i>gas phase yield</i>			
carbon monoxide/mol%	36.0	60.1	60.6
carbon dioxide/mol%	7.0	8.7	1.5
<i>composition of the organic mixture</i>			
substrate 1 /%	9.70 ^[b]	0.59	5
ketone 2 /%	0.44	0.34	n. d. ^[c]
acid 14 and 15 /%	6.10	57.1	35
ketone 16 /%	47.8	12.2	20
lactone 17 /%	0	17.5	15
others/%	36.0	12.3	25

[a] estimated from volume and composition. [b] 9.11% was recovered as anhydride. [c] Compound was not detected in GC and GC-MS by comparison with the authentic sample.

In view of these experimental results and literature reports, it can be concluded that it is highly unlikely that carboxylic acid **1** is converted directly into the corresponding ketone in a selective manner under classical ketonic decarboxylation conditions. Traces may be produced by alternative mechanisms. Possible precursors are 2,2,5-trimethylcyclopentanone or 2,2,5,5-tetramethylcyclopent-3-en-1-one which have been observed both in the product mixture. The former can be produced by demethylation of the starting material **1**, classical ketonic decarboxylation involving the β -keto acid, and re-methylation. The second alternative pathways comprises the same reaction steps as the formation of ketone **16**. When reacting carboxylic acid **14**

instead of the isomer **15**, the five-membered cycle is formed (connecting carbon atoms 1 and 5, instead of 1 and 6). Hydrogenation of the double bond of the primary product 2,2,5,5-tetramethylcyclopent-3-en-1-one, or reduction of the intermediate carbo cation, provides ketone **2**. It is clear that both pathways are not suitable to form selectively ketone **2** from diacid **1**, but they may explain well the formation of the compound in traces.

Conclusions

The attempted ketonic decarboxylation of α,α -disubstituted carboxylic acids has been revisited employing 2,2,5,5-tetramethyladipic acid (**1**) and pivalic acid (**3**) as starting materials. For both substrates it was found that the preferred reaction pathway was a retro-Koch reaction in which the carboxylic acid group is converted into carbon monoxide and water, producing the olefin as main product. The primary retro-Koch product obtained from diacid **1** helps to understand controversial literature reports on the reaction since its identification allows the proposal of reasonable reaction mechanism to alternative products. The typical symmetrical ketone products were not obtained, except for two cases when the cyclic ketone **2** was detected in traces which, probably, was formed by an alternative pathway involving demethylation and methylation reactions or cyclization of the primary product followed by hydrogenation. Therefore, it can be concluded that all experimental observations were in accordance with the proposed mechanism for the ketonic decarboxylation, i.e., the formation of the β -keto acid and subsequent decarboxylation, which excludes α,α -disubstituted carboxylic acids as potential substrates. As a consequence, the β -keto acid mechanism can be regarded as universal mechanism of the ketonic decarboxylation of carboxylic acids.

Experimental Section

General. - Reagents and solvents were purchased from standard chemical suppliers as stated: dimethyl sulfoxide (Aldrich, 99%), dichloroethane (Aldrich, 98%), diethyl ether (Scharlau, reagent grade), pentane (Aldrich, 98%), acetic acid (Aldrich, glacial), cyclopentanone (Acros, 99%), 4,4-dimethyl-2-cyclohexen-1-one (Acros, 97%), MeMgBr in diethyl ether (3 M, Aldrich), methyl iodide (Aldrich, 99%), pyridinium chlorochromate (Fluka 98%), pivalic acid (**3**, Aldrich, 99%), adipic acid (Acros, 99%), silver triflate (Alfa Aesar, 98%), KOH (Scharlau, reagent grade), H₂SO₄ (Aldrich, 98%), HCl (Aldrich, 37%), hydrogen peroxide (35%, Aldrich), FeSO₄ · 7 H₂O (Aldrich, 99%), Fe(NO₃)₃ · 9 H₂O (Aldrich, 98%), NaHCO₃ (Acros, 99%), Ba(NO₃)₂ (Probus, pure grade), BaO (Aldrich, 99.99%), NaOH (Scharlau, synthesis grade). Monoclinic zirconium oxide (*m*-ZrO₂) was obtained as pellets from ChemPur, Germany, with a surface area of 100 m² g⁻¹, MgO was received as a powder from Riedel-de-Haën, Germany, with a surface area of 53 m² g⁻¹ and SiO₂ was obtained as pellets from ChemPur, Germany, with a surface area of 240 m² g⁻¹.

The organic liquids and solids were analyzed on a Agilent 7890A apparatus equipped with a HP-5 column (30 m x 0.320 mm x 0.25 μ m) and the substances identified on a GC-MS apparatus Agilent 6890N, equipped with the same column and a mass selective detector Agilent Technologies 5973 Network. The gases were analyzed on a Varian 3800 gas

chromatograph equipped with three columns and three detectors. The first column was a Ultimetel Molsieve 5 Å 80-100 Mesh (1.5 m x 1/16" x 1 mm) connected to a thermal conductivity detector (TCD) for hydrogen analysis. The second column was a Molsieve 13X 80-100 Mesh (1.2 m x 1/16" x 1 mm) for other permanent gases also connected to a TCD and the third column an Al₂O₃ MAPD (25 m x 0.32 mm x 5 µm) for hydrocarbon separation with subsequent quantification with a flame ionization detector (FID). For the exact calculation of conversion and yields see Supp. Inf.

Synthesis of 2,2,5,5-tetramethyladipic acid^[47] (1).- In a beaker with mechanical stirring and cooled to 0 °C, water (600 mL), sulfuric acid (7.5 mL) and pivalic acid (3, 51.0 g, 500 mmol) were placed. During 15 min hydrogen peroxide (35%, 43 mL, 500 mmol), and a solution of FeSO₄ · 7 H₂O (139 g, 500 mmol) and sulfuric acid (27.5 mL) in 288 mL of distilled water were added. The mixture was concentrated to 250 mL, the solids collected by filtration, washed with cold distilled water, and dried in vacuum. The obtained solid was recrystallized twice from acetic acid (1 mL for each g of solid) and 2,2,5,5-tetramethyladipic acid obtained as colorless crystals (12.2 g, 60.3 mmol, 24% yield). The product was dissolved and analyzed by inductively coupled plasma optical emission spectrometry (ICP OES) and an iron content from 2421 to 5450 ppm (2.42 to 5.45 mg/g product) determined.

Reaction of 2,2,5,5-tetramethyladipic acid (1) in the presence of ZrO₂, BaO or without any catalyst (thermal).- With the aim to assure that the reaction conditions would work well for the ketonic decarboxylation, the reaction was carried out with unsubstituted adipic acid. A literature procedure was selected and tested with adipic acid as substrate.^[45] At a reaction temperature of 350 °C 85% of cyclopentanone and the corresponding amount of carbon dioxide were obtained after 46 min of reaction time. Apparatus and conditions were employed for the transformation of 2,2,5,5-tetramethyladipic acid (1). In a round-bottomed flask, placed on a heating mantle and connected to a gas burette, 2,2,5,5-tetramethyladipic acid (10.0 g, 49.4 mmol) and optionally BaO (0.769 g, 5.02 mmol, 5.02 equiv.) or ZrO₂ (1.00 g, 10 wt%) were filled and the mixture heated to 350 – 370 °C (internal temperature) under magnetic stirring. The gas evolution was monitored (Figure 1), the gas was analyzed offline as indicated above and the compositions are summarized in Table 2. A mainly liquid product mixture and water were obtained as distillate and a solid dark-colored residue. The composition of the product mixture is also summarized in Table 2. 2,2,5,5-cyclopentanone was observed only in traces (< 0.2% yield) as it was proven unambiguously by comparison with an authentic sample (synthesis see below). 2,2,5-trimethylhex-4-enoic acid was isolated in satisfactory purity from the crude product mixture to confirm its structure by NMR and comparison with literature data (see below). 3,6,6-trimethyl-2-cyclohexen-1-one (16) and the lactone 3,3,6,6-tetramethyl-2H-pyran-2-one (17) were synthesized by a literature procedure and the data of the authentic sample matched perfectly with the substance in the crude reaction mixture (see below).

Synthesis of 2,2,5,5-tetramethylcyclopentanone^[48] (2).- In a round-bottom flask, equipped with reflux condenser, dimethyl sulfoxide (19 mL) was placed and heated to 50 °C. Cyclopentanone (0.846 g, 10.1 mmol), methyl iodide (5.0 mL, 80.3 mmol) and potassium hydroxide (11.2 g, 200 mmol) were added and the mixture stirred magnetically for one hour. The mixture was cooled to 0 °C and extracted with pentane (3 x 7 mL). The combined three organic phases were washed with distilled water (3 x), dried with MgSO₄ and the solvent removed by distillation. The colorless oil obtained as crude reaction product consisted in pure 2,2,5,5-tetramethylcyclopentanone (2, 0.879 g, 6.28 mmol, 62% yield).

¹H NMR (300 MHz, CDCl₃):^[49] δ = 1.68 (s, 4H), 0.95 (s, 12H).- ¹³C NMR (75 MHz, CDCl₃):^[50] δ = 226.7, 45.1, 34.7, 24.8.- MS: m/z (%): 140 (33) [M⁺], 27 (7), 41 (39), 56 (100), 69 (20), 97 (5).

Isolation and identification of 2,2,5-trimethylhex-4-enoic acid (14) from the product mixture^[51].- The liquid organic product (2.50 g) was dissolved in dichloromethane and the solution was extracted with a saturated aqueous NaHCO₃ solution (2 x 25 mL). The combined aqueous solutions were acidified with hydrochloric acid to a pH of 2 and extracted with dichloromethane (25 mL). The solvent was evaporated and 2,2,5-trimethylhex-4-enoic acid (14, 0.175 g, 1.12 mmol, corresponding to 7 wt% of the crude product mixture) obtained as colorless crystals.

¹H NMR (300 MHz, CDCl₃):^[51] δ = 11.8 (s, 1H), 5.12 (tdq, J=7.3, 2.8, 1.4 Hz, 1H), 2.25 (dt, J=7.6, 1.2 Hz, 2H), 1.71 (d, J=1.3 Hz, 3H), 1.61 (d, J=1.4 Hz, 3H), 1.18 (s, 6H).- ¹³C NMR (75 MHz, CDCl₃):^[51] δ = 184.6, 134.6, 119.6, 42.7, 38.4, 26.0, 24.5, 17.9.- MS: m/z (%): 156 (23) [M⁺], 27 (6), 41(50), 55 (9), 69 (100), 88 (43).

Synthesis of 3,6,6-trimethylcyclohex-2-en-1-one^[52] (16).- 3,6,6-trimethylcyclohex-2-en-1-one (16) was synthesized in two steps. Under nitrogen atmosphere and at – 78 °C a solution of 4,4-dimethyl-2-cyclohexen-1-one (2.00 g, 16.1 mmol) in 20 mL anhydrous diethyl ether was placed in a round-bottom flask and stirred magnetically. The Grignard reagent MeMgBr in diethyl ether (3 M, 5.7 mL, 17.2 mmol) was added dropwise with a syringe and the mixture was allowed to warm to room-temperature. After two hours distilled water (10 mL) was added dropwise. The organic phase was washed with water (20 mL), dried with MgSO₄ and the solvent evaporated. The liquid obtained was a mixture of 84 to 16 of product (1,4,4-trimethylcyclohex-2-en-1-ol) to substrate that was used as such for the next step. In a round-bottom flask a solution of pyridinium chlorochromate (4.30 g, 20.0 mmol) in dichloromethane (30 mL) were placed and a solution of the product mixture obtained in the previous step (1.4 g, 8.21 mmol of 1,4,4-trimethylcyclohex-2-en-1-ol) in dichloromethane (10 mL) added. After stirring magnetically during two hours diethyl ether was added (40 mL). By this, two phases were obtained, one ethereal and another black viscous one. The latter is extracted with diethyl ether (20 mL). The combined organic phases were extracted with a 5% aqueous sodium hydroxide solution (2 x 100 mL), with a 5% aqueous hydrogen chloride solution (100 mL), and a saturated aqueous NaHCO₃ (2 x 50 mL). After drying with MgSO₄ the solvent was evaporated and 3,6,6-trimethylcyclohex-2-en-1-one (5, 1.11 g, 6.51 mmol, 79% yield) obtained as a colorless liquid.

¹H NMR (300 MHz, CDCl₃):^[53] δ = 5.74 (h, J=1.5 Hz, 1H), 2.27 (td, J=6.2, 1.7, 0.9 Hz, 2H), 1.90 (q, J=1.0 Hz, 3H), 1.78 (t, J=6.1 Hz, 2H), 1.06 (s, 6H).- ¹³C NMR (75 MHz, CDCl₃):^[53] δ = 204.4, 160.2, 125.0, 40.1, 36.0, 28.4, 24.1, 24.0.- MS: m/z (%): 138 (17) [M⁺], 39 (18), 54 (21), 67 (6), 82 (100), 110 (14).

Identification of 3,3,6,6-tetramethyl-2H-pyran-2-one (17).- The lactone 3,3,6,6-tetramethyl-2H-pyran-2-one (17) was identified in the crude reaction mixture (organic liquid) by ¹³C NMR by comparison with an authentic sample.^[46] In a round-bottom flask, equipped with a magnetic stirring bar and heated to 83 °C, a solution of 2,2,5-trimethylhex-4-enoic acid (0.102 g; 92% purity, GC, 0.654 mmol) in dichloroethane (4 mL) was placed. Silver triflate (8.0 mg, 0.03 mmol) was added and the mixture stirred for 15 h. The crude reaction mixture was extracted three times with a saturated aqueous sodium bicarbonate solution, dried with MgSO₄, and the solvent rota-evaporated. A slightly yellow solid (17, 90 mg, 0.562 mmol; 94% yield) was obtained with 97% (GC) purity.

¹³C NMR (75 MHz, CDCl₃):^[46] δ = 177.7, 82.5, 37.2, 32.0, 31.5, 28.9, 27.6.- MS: m/z (%): 41 (34), 56 (100), 70 (18), 95 (11), 113 (17), 141 (9).

Catalyst preparation for fixed-bed continuous flow reactions.- m-ZrO₂ and SiO₂ were crushed and sieved, employing the 0.4 – 0.8 mm fraction as

catalyst. MgO was pelletized, crushed and sieved and the 0.4 – 0.8 mm fraction was used. BaO(3 wt%)/ZrO₂ was obtained by the incipient wetness impregnation method: an aqueous solution of Ba(NO₃)₂ was prepared with the corresponding concentration to achieve the desired BaO content in the solid. The *m*-ZrO₂ (0.4 – 0.8 mm) was impregnated, dried at room temperature in vacuum during 2 h and afterwards overnight in an oven at 100 °C. The material was calcined in-situ in the reactor under air flow (atmospheric pressure) at 550 °C during 2 h (heating rate of 3 K/min).

Reaction of pivalic acid (3) in the presence of ZrO₂, BaO/ZrO₂, MgO, SiO₂, Fe(SO₄)/SiO₂ or Fe₂O₃/SiO₂. For the preparation of Fe(SO₄)/SiO₂ or Fe₂O₃/SiO₂ see Supp. Inf. The reactions were carried out in a tubular fixed-bed continuous flow reactor described in a previous work.^[25] The reactor was loaded with 2.50 g of catalyst (0.4 – 0.8 mm) diluted with silicon carbide. Pivalic acid was heated to 45 °C inside a syringe and fed at a rate of 0.15 mL min⁻¹ (8.5 g h⁻¹, WHSV = 3.4 h⁻¹). 50 mL min⁻¹ of nitrogen gas was used as carrier gas, or alternatively 50 mL min⁻¹ of hydrogen in the case of ZrO₂. The reactions were carried out at atmospheric pressure and a temperature between 400 and 550 °C. The products streams were condensed and analyzed off-line.

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Keywords: carbon-carbon bond scission • carbon monoxide • cyclization • lactonization • retro-Koch reaction

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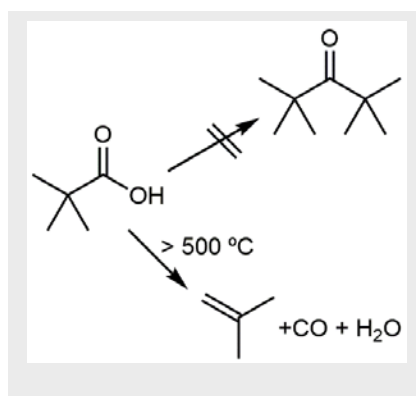
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Layout 1:

FULL PAPER

Carbon-carbon bond scission instead of carbon-carbon bond formation: when tertiary carboxylic acids are reacted, a retro-Koch reaction occurs instead of ketonic decarboxylation. For the latter, experimental results further support a mechanism via the β -keto acid intermediate. The primary retro-Koch product helps to resolve controversial reports on the reaction since it allows the proposal of reasonable pathways to secondary, obtained products.



Borja Oliver-Tomas, Michael Renz, and Avelino Corma**

Page No. – Page No.

Ketone formation from carboxylic acids by ketonic decarboxylation: the exceptional case of the tertiary carboxylic acids

Layout 2:

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Page No. – Page No.

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Text for Table of Contents