Unsymmetrical Unsaturated Ketones from Lactones and Carboxylic Acids in One Step

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Dedicated to *Günther Ohloff* on the occasion of his 80th birthday

A one-step transformation of γ- and δ-(spiro)lactones into γ,δ- and δ,ε-unsaturated ketones in the presence of carboxylic acids in the vapor phase at 400° over a supported manganese catalyst is reported for the first time. The scope of this new transformation is exemplified with a series of lactones, and a mechanistic rationale is proposed.

1. Introduction. – In the preceding publication [1], we reported a new method for making unsaturated aldehydes from five- and six-membered lactones by reacting them in the gas phase with formic acid over a supported manganese(II) catalyst. We asked ourselves what might happen if we replaced in this same reaction formic acid with acetic acid or a higher homologue?

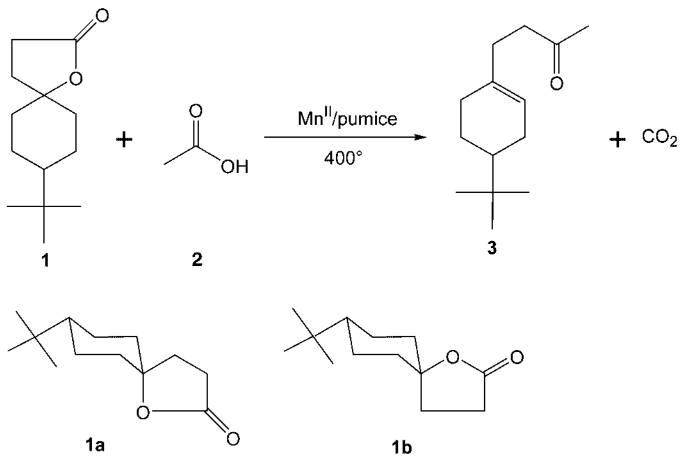
The thermolysis (300–400°) of carboxylic acid salts for the preparation of symmetrical and unsymmetrical ketones is well-documented and, to the best of our knowledge, was mentioned for the first time by *Williamson* in 1850 [2] who pyrolyzed potassium acetate to isolate acetone, and pyrolyzed a mixture of sodium acetate and potassium valerate (= potassium pentanoate) to obtain hexan-2-one. The use of dicarboxylic acids led to cyclic ketones [3], and *Ruzicka* and co-workers [4][5] used this method to synthesize macrocyclic ketones, an important class of musk odorants [6]. The reaction was first rendered catalytic by *Squibb* [7] by means of supported catalysts at 350° in the gas phase (for a review, see [8]).

2. Results. – When we passed lactone **1** (64 : 36 mixture **1a**/**1b**) [9] with an excess of acetic acid (**2**) over a Mn^{II} catalyst supported on pumice at 400°, we obtained unsaturated ketone **3** in 63% yield with the concomitant liberation of CO_2 (*Scheme 1*).

We next explored the scope and limitations of this transformation by reacting different lactones (see **1**, **4**, **9**, and **12**) with a series of carboxylic acids (see **2**, **5**, and **10**; *Table*). In general, the yields of the obtained ketones (see **3**, **6**–**8**, **11**, and **13**–**17** in the *Table*) were better than when aldehydes were made from lactones and formic acid [1], mainly due to the increased thermal stability of ketones.

3. Discussion. – As seen from the *Table*, the yields of the formed ketones seem to be greatly influenced by the ease of ring opening of the lactones tested, whilst being independent of the chain length of the carboxylic acid. Although the yields never

Scheme 1



exceed *ca.* 50%, this one-step transformation is unique and difficult to achieve by other synthetic methodology. Catalyst optimization is still needed, and a stepwise procedure from the lactone *via* the unsaturated acid, and the mixed anhydride (as outlined below for mechanistic studies) may be advantageous in certain cases, despite the two additional steps.

Regarding the mechanism of this new transformation, the first step is almost certainly lactone opening to give either an unsaturated acid or directly an unsaturated mixed anhydride, as exemplified by **1** + **2** → **18** or **19** (*Scheme 2*). Both acids [2–5][7][8] and symmetric anhydrides [10–13] are known to give ketones. *Koch* and

Scheme 2

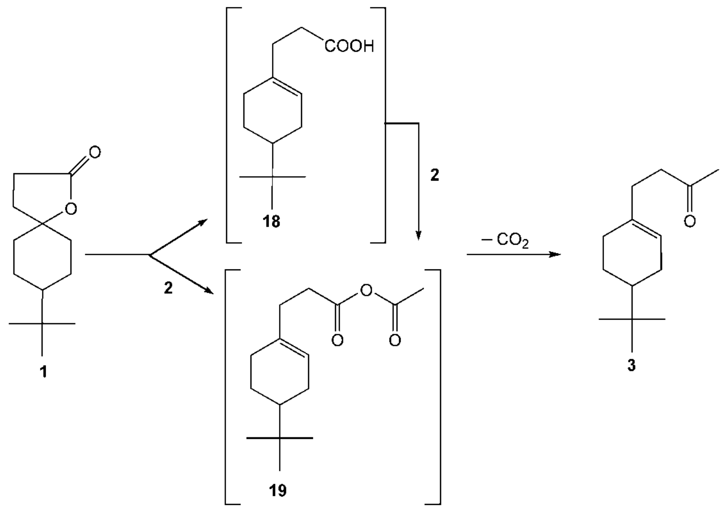


Table. *Thermal Reaction of Carboxylic Acids with Lactones at 400°*

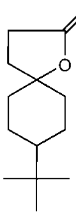
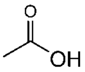
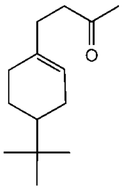
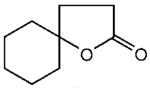
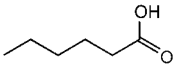
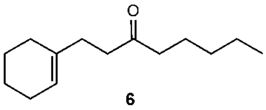
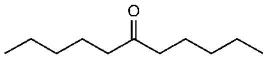
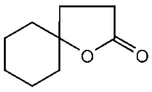
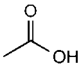
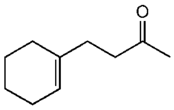
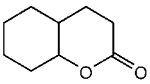
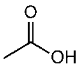
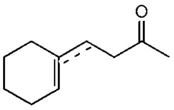
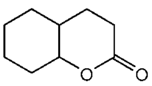
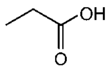
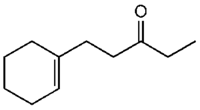
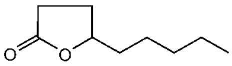
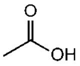
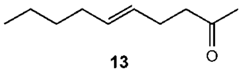
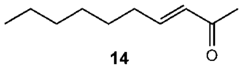
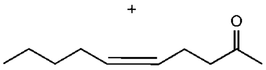
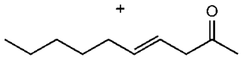
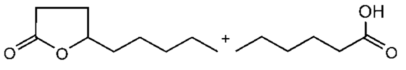
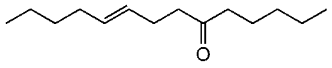
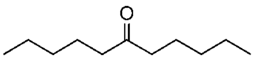
Entry	Starting materials	Catalyst	Product(s)	Yield
1	 **1** +  **2**	Mn^{II}/pumice	 **3**	63%
2	 **4** +  **5**	Mn^{II}/Zn^{II}/pumice	 **6** +  **7**	12% 50%
3	 **4** +  **2**	Mn^{II}/Zn^{II}/pumice	 **8**	41%
4	 **9** +  **2**	Mn^{II}/pumice	 **8**	48%
5	 **9** +  **10**	Mn^{II}/pumice	 **11**	*ca.* 30%
6	 **12** +  **2**	Mn^{II}/pumice	 **13** +  **14** +  **15** +  **16**	52% [a]); 68.7% [b]) 10.3% [b]) 9.6% [b]) 4.6% [b])

Table (cont.)

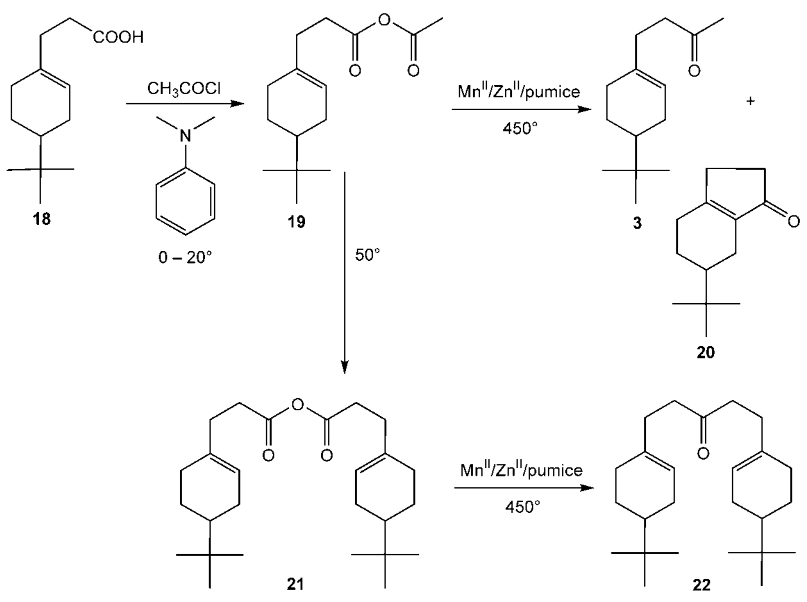
Entry	Starting materials	Catalyst	Products	Yield
7	 **12** + **5**	Mn^{II}/Zn^{II}/pumice	 **17** +	5%
			 **7**	50%

[a]) Total yield of **13**–**16**. [b]) Product composition by GC.

Leibnitz [11] showed that, in the case of carboxylic acids, the corresponding anhydrides are intermediates, which then decompose to the ketones.

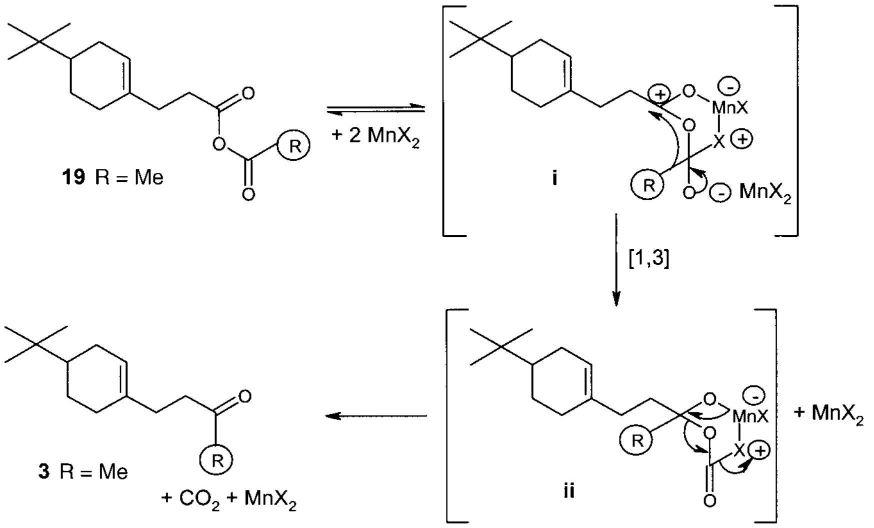
To establish that, in our case, anhydrides are also intermediates, we specifically prepared the mixed anhydride **19** from carboxylic acid **18** and acetyl chloride (*Scheme 3*) and subjected it to catalytic pyrolysis at 450°. Exclusively the asymmetric ketone **3** was obtained as major product, besides cyclic ketone **20**. Since it is known that thermolysis of mixed anhydrides leads to disproportionation and the formation of symmetric anhydrides [14], a first attempted preparation of the mixed anhydride **19** at 50° gave mainly the symmetric anhydride **21** (besides a small amount of **19**), which upon catalytic pyrolysis at 450° led predominantly to the symmetric ketone **22**.

Scheme 3



Exactly what role the catalyst is playing in this anhydride decomposition is not clear. However, in analogy to the closely related *Piria–Limpricht* reduction of carboxylic acids and lactones [1], we propose complexation of the amphoteric Mn^{II} salt (acid and base character) with the anhydride **19** as depicted in the polar intermediate structure **i** (R=Me) in *Scheme 4*. A 1,3 shift of the alkyl group R, driven by CO_2 formation and facilitated by the Mn^{II} salt, would then lead *via* intermediate **ii** to ketone **3**.

Scheme 4



4. Conclusions. – This surprising one-step transformation provides a simple approach to a variety of ketones that, by other routes, are not easily accessible. Further examples and improved catalysts will be needed to evaluate the preparative usefulness of this reaction.

The authors are indebted to Mrs. *V. Revillet* and *C. Bise* for careful experimental work, to Prof. *P. Vogel*, EPF-Lausanne, for helpful mechanistic discussions, to Mr. *W. Thommen* for having recorded the spectral data, to Dr. *O. Haefliger* for LC/MS measurements, and to Dr. *E. Walther* for reference samples.

Experimental Part

1. *General*. See [1].

2. *Thermolysis: General Procedure*. See [1]. 2.1. *(±)-4-[4-(*tert*-Butyl)cyclohex-1-en-1-yl]butan-2-one* (**3**). A soln. of 8-(*tert*-butyl)-1-oxaspiro[4.5]decan-2-one (**1**) (20 g, 95 mmol) in **2** (30 g, 0.5 mol) was introduced at the top of the column filled with the catalyst $Mn(OAc)_2$ on pumice[1]) at 400°. The crude pyrolysate was washed twice with brine and then distilled at 160°/0.6 mbar (bath temp.): 14.0 g (*ca.* 63%) of **3** (90% purity). ^1H-NMR: 0.85 (*s*, 9 H); 2.2 (*s*, 3 H); 5.4 (br. *s*, 1 H). ^{13}C-NMR: 24.2 (*t*); 26.8 (*t*); 27.2 (*t*); 29.8 (*q*); 29.9 (*t*); 31.4 (*t*); 32.2 (*s*); 42.2 (*t*); 44.1 (*d*); 121.6 (*d*); 136.1 (*s*); 208.9 (*s*). MS: 208 (17, M^+), 190 (6), 175 (5), 150 (25), 134 (22), 109 (22), 94 (100), 79 (33), 57 (59), 43 (51).

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[1]) For catalyst preparation, see [1].

2.2. *1-(Cyclohex-1-en-1-yl)octan-3-one* (**6**). A soln. of 1-oxaspiro[4.5]decan-2-one (**4**) [15] (5 g, 32 mmol) and hexanoic acid (**5**; 3.8 g, 32 mmol) was thermolyzed over Mn(OAc)$_2$/Zn(OAc)$_2$ on pumice[1]) at 450° and the product distilled at 125°/0.25 mbar: 3.8 g of **6** (21%) and undecan-6-one[2]) (**7**; 50%) mainly.

Data of **6**: MS: 208 (10, M^+), 190 (2), 165 (24), 152 (13), 137 (10), 119 (9), 99 (100), 79 (47), 71 (47), 43 (38).

Data of **7**: MS: 170 (6, M^+), 127 (8), 114 (8), 99 (81), 71 (81), 58 (58), 43 (100).

2.3. *4-(Cyclohex-1-en-1-yl)butan-2-one/4-Cyclohexylidenebutan-2-one* (**8**). A soln. of **4** (5 g, 32 mmol) in **2** (9.7 g, 160 mmol) was thermolyzed as described in *2.2*. Distillation at 90°/0.1 mbar gave 2.55 g (41.2%) of **8** (80% purity). MS: 152 (37, M^+), 137 (4), 134 (4), 109 (50), 94 (100), 79 (93), 67 (53), 43 (48).

The same reaction of octahydro-2*H*-1-benzopyran-2-one (**9**; *Aldrich*, mixture of *cis/trans* isomers) with **2** gave **8** in 48% yield.

2.4. *5-(Cyclohex-1-en-1-yl)pentan-3-one* (**11**). A soln. of **9** (20 g, 132 mmol) in propanoic acid (**10**; 30 g, 0.4 mol) was thermolyzed over Mn(OAc)$_2$ on pumice[1]) at 450°. Distillation at 175°/30 mbar gave **11** (28%) and unreacted **9** (56%). Pure **11** was obtained with *Girard* reagent [16]. ^{1}H-NMR: 1.05 (t, $J = 7$, 3 H); 5.4 (br. s, 1 H). MS: 166 (47, M^+), 137 (14), 119 (10), 109 (58), 94 (100), 79 (96), 67 (83), 57 (85), 41 (34).

2.5. *(5*E*)-Dec-5-en-2-one* (**13**). A soln. of (±)-nonano-4-lactone (**12**; 5 g, 32 mmol) in **2** (45 g, 0.75 mol) was thermolyzed as described in *2.4*. Distillation at 200°/40 mbar gave 3.6 g (52%) of **3** (68.7%), **14** (10.3%), **15** (9.6%), and **16** (4.6%).

Data of **13**: ^{1}H-NMR: 0.96 (t, $J = 7$, 3 H); 1.33 (m, 4 H); 1.96 (m, 2 H); 2.09 (s, 3 H); 2.24 (m, 2 H); 2.49 (m, 2 H); 5.48 (m, 2 H). ^{13}C-NMR: 13.9 (q); 22.2 (t); 26.9 (t); 30.0 (q); 31.7 (t); 32.2 (t); 43.6 (t); 128.2 (d); 131.6 (d); 208.5 (s). MS: 154 (3, M^+), 125 (3), 111 (4), 90 (18), 81 (21), 67 (12), 54 (21), 43 (100).

*Data of (3*E*)-Dec-3-en-2-one* (**14**): MS: 154 (2, M^+), 139 (37), 125 (7), 111 (11), 97 (32), 69 (53), 55 (97), 43 (100).

*Data of (5*Z*)-Dec-5-en-2-one* (**15**): MS: 154 (3, M^+), 125 (3), 111 (5), 96 (19), 81 (22), 67 (13), 54 (23), 43 (100).

*Data of (4*E*)-Dec-4-en-2-one* (**16**): MS: 154 (4, M^+), 139 (62), 125 (11), 111 (19), 97 (51), 69 (69), 55 (85), 43 (100).

2.6. *(9*E*)-Tetradec-9-en-6-one* (**17**). A soln. of **12** (5 g, 32 mmol) and hexanoic acid (**5**; 20 g, 172 mmol) was thermolyzed at 450° over Mn(OAc)$_2$/Zn(OAc)$_2$ on pumice[1]). Distillation at 70°/0.6 mbar gave 14.6 g **12** (4.5%), **17** (5.0%), and the *Piria* ketone from hexanoic acid, undecan-6-one (**7**; 90%). **17**: MS: 210 (3, M^+), 167 (9), 154 (10), 139 (16), 99 (100), 71 (47), 55 (43), 43 (51).

2.7. *(±)-Acetic 3-[4-(*tert*-Butyl)cyclohex-1-en-1-yl]propanoic Anhydride* (**19**). To a soln. of (±)-3-[4-(*tert*-butyl)cyclohex-1-en-1-yl]propanoic acid (**18**; 1 g, 4.8 mmol) in *N,N*-dimethylaniline (5 ml) was added dropwise at 0° with stirring acetyl chloride (0.33 ml, 4.8 mmol). After 3 h, now at r.t., ice was added to the mixture which was then extracted with pentane. The org. layer was washed with ice-cold 10% HCl soln., ice-cold $NaHCO_3$ soln. and ice-cold brine, dried (Na_2SO_4), and evaporated at 20°: 1.08 g (90%) of crude **19**. ^{1}H-NMR: 0.87 (s, 9 H); 1.2 (m, 2 H); 1.7 (m, 2 H); 2.0 (m, 3 H); 1.68 (s, 3 H); 2.22 (s, 3 H); 2.3 (m, 2 H); 2.55 (m, 2 H); 5.43 (br. s, 1 H). ^{13}C-NMR: 22.2 (q); 24.1 (t); 26.8 (t); 27.6 (q); 29.7 (t); 31.7 (t); 32.2 (s); 33.8 (t); 44.0 (d); 122.5 (d); 135.0 (s); 166.5 (s); 169.1 (s).

2.8. *3-[4-(*tert*-Butyl)cyclohex-1-en-1-yl]propanoic Anhydride* (**21**). As described in *2.7*, but after 3 h at 0° → r.t., the mixture was stirred at 50° for 5 h: 0.8 g (67%) of **21**, containing some **19** (15%). **21**: IR: 1750, 1815. ^{1}H-NMR: 0.87 (s, 18 H); 5.45 (br. s, 2 H). ^{13}C-NMR: 24.1 (t); 26.8 (t); 27.2 (q); 29.7 (t); 31.7 (t); 32.2 (s); 33.9 (t); 44.0 (d); 122.5 (d); 135.1 (s); 169.3 (s). LC/MS: 402 (M^+).

2.9. *(±)-4-[4-(*tert*-Butyl)cyclohex-1-en-1-yl]butan-2-one* (**3**). A soln. of **19** (850 mg) in THF (3.5 ml) was passed over Mn(OAc)$_2$/Zn(OAc)$_2$ on pumice[1]) at 450°. The product was distilled at 200°/0.8 mbar: 210 mg of **3** (65%) and **20** (30%).

Data of **3**: ^{1}H-NMR: 0.85 (s, 9 H); 5.4 (br. s, 1 H). ^{13}C-NMR: 24.2 (t); 26.8 (t); 27.2 (q); 29.9 (t); 31.4 (t); 32.2 (s); 42.2 (t); 44.1 (d); 121.6 (d); 136.1 (s); 208.9 (s). MS: 208 (17, M^+), 190 (6), 175 (5), 150 (26), 134 (22), 109 (22), 94 (100), 79 (33), 57 (59), 43 (52).

*Data of 6-(*tert*-Butyl)-2,3,4,5,6,7-hexahydro-1*H*-inden-1-one* (**20**): see [1].

2.10. *1,5-Bis[4-(*tert*-butyl)cyclohex-1-en-1-yl]pentan-3-one* (**22**). The soln. of **21** (0.8 g) containing some **19** (15%) was thermolyzed as described in *2.9*. After a pre-run, distillation at 250°/0.8 mbar) furnished 250 mg of **22**. ^{1}H-NMR: 0.87 (s, 18 H). ^{13}C-NMR: 24.2 (t); 26.8 (t); 27.2 (q); 29.9 (t); 31.4 (t); 32.2 (s); 41.2 (t); 44.1 (d);

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[2]) *Piria* reaction product of hexanoic acid.

121.5 (*d*); 136.2 (*s*); 210.9 (*s*). MS: 358 (97, M^+), 340 (22), 325 (6), 301 (11), 283 (10), 259 (8), 221 (17), 206 (27), 193 (53), 175 (22), 149 (27), 137 (39), 119 (33), 109 (40), 93 (57), 57 (100), 41 (24).

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