Ketonic Decarboxylation Catalysed by Weak Bases and Its Application to an Optically Pure Substrate

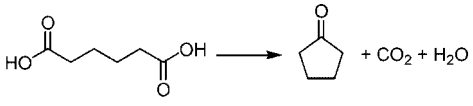
Michael Renz*[a] and Avelino Corma[a]

Keywords: Asymmetric synthesis / Base catalysis / Carboxylic acids / Cyclopentanone / Ketonic Decarboxylation

Ketonic decarboxylation is a very old reaction that transforms two carboxylic acids into a ketone or a dicarboxylic acid into a cyclic ketone, in particular adipic acid into cyclopentanone. Herein it is reported that catalytic amounts of weak bases such as sodium carbonate can carry out this reaction selectively. This is in accordance with a mechanism involving decarboxylation and nucleophilic attack at a second carboxyl group. The reaction can be employed in asymmetric syntheses since the stereogenic centres in the β-positions retain their stereochemistry.

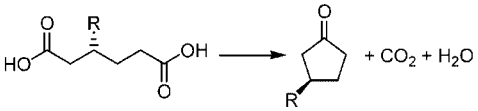
Introduction

Cyclopentanone is a valuable fine chemical with increased demand in recent years since it is the starting material for many fragrances or pharmaceuticals and is also used as a special solvent for the synthesis of polycarbonates.[1] It can be produced from adipic acid in a dry distillation at elevated temperatures (300−450 °C) by ketonic decarboxylation [Equation (1)]. This transformation of adipic acid into cyclopentanone is very interesting from an economic point of view since adipic acid is a cheap bulk chemical that is often obtained as a by-product in oxidation reactions of cyclohexane derivatives.



(1)

Although ketonic decarboxylation has been known for more than 140 years (dry distillation of calcium acetate to produce acetone),[2] the mechanism is still under discussion.[3] This might be the reason why so many different catalysts have been proposed as promoters for this reaction. In general, thorium oxide is recommended as catalyst for the ketonic decarboxylation.[4] In the special case of adipic acid, the decarboxylation has also been carried out in presence of catalytic amounts of barium hydroxide,[5,6] potassium fluoride (reacting as base),[7] or without any additive at all.[8,9] More recently, iron oxide has been identified as the origin of the catalytic activity of graphite for this reaction.[10] In the patent literature a multitude of metals as their oxides, hydroxides, phosphates, other salts, or combinations of these have been proposed as catalysts for carrying out the reaction at high temperatures (300−450 °C).[3,11−15] Metal salts of adipic acid such as calcium, lead, or thorium salts are less useful for the production of cyclopentanone since they only give 43%, 35%, and 15% yields, respectively.[16]



(2)

The cyclopentanones used in the fragrance industry are often highly substituted ones.[17] Whereas the introduction of substituents in the α-position to the carbonyl group is relatively easy, the possibilities for the β-position are quite limited. Furthermore, the organoleptic properties depend not only on the position of the substituent but also on the absolute stereochemical configuration. One alternative entry to substituted cyclopentanones may be the cyclization of the corresponding adipic acid derivatives. Therefore, it would be interesting to know if these β-substituents disturb the cyclization under the normal reaction conditions and if a stereogenic centre in the β-position maintains its stereochemistry during the ketonic decarboxylation [Equation (2)].

In the present article we show that the transformation of adipic acid into cyclopentanone can be carried out with catalytic amounts of an environmentally friendly weak base. Moreover, we will show that this reaction system allows the production of asymmetric precursors of interest in the fragrance industry.

[a] Instituto de Tecnología Química, UPV-CSIC, Universidad Politécnica de Valencia
Avda. de los Naranjos s/n, 46022 Valencia, Spain
Fax: (internat.): + 34-96-387-7809
E-mail: mrenz@itq.upv.es

  DOI: 10.1002/ejoc.200300778

Results and Discussion

For comparison purposes, we first carried out the dry distillation of adipic acid without introduction of any additive. Thus, 10 g of acid were placed in a round-bottomed flask fitted with a short Vigreux column and connected to a distillation apparatus. The flask was heated to 350 °C (heating mantle temperature) and, after a period of 30 to 35 min, a biphasic mixture of two colourless liquids — cyclopentanone and water — started to distil. The progress of the reaction was followed by the quantification of the liberated CO_2. Indeed, from Figure 1 it can be seen that the acid is converted into cyclopentanone and after 3.5 h a 90% yield of carbon dioxide was obtained with a sticky black residue remaining in the distillation flask. The yield of cyclopentanone obtained as distillate at the end of the reaction is always 5−10% lower than the yield of carbon dioxide. When only 1.8 mol % of sodium hydroxide was added to the acid before heating, the reaction time was reduced by half and the yield was slightly improved (Figure 1). The purity of cyclopentanone was determined by GC analysis and ^{1}H NMR spectroscopy and was found to be 99% or higher in all cases. The reaction rate can be enhanced successively by adding increasing amounts of base. However, with more than 3.3 mol % the yield started to decrease and was significantly lower when carrying out the reaction in the presence of 21 mol % of sodium hydroxide. This is probably due to the formation of disodium adipate, which is not transformed into cyclopentanone. This result is in agreement with published results indicating that sodium salts, in general, give poor results for the ketonic decarboxylation[3] and that salts of adipic acid give low yields, as already mentioned above. The residue, in this case a white-brownish solid, can be re-used and employed instead of the base, i.e. a new batch of adipic acid can be added and the cyclopentanone obtained in a shorter reaction time. For example, 10 g of adipic acid were added to 0.5 g of NaOH (0.18 equiv.) and the mixture distilled as above. Six more 10 g portions of adipic acid were added successively and distilled each time. In 320 min an accumulated yield of 90% in cyclopentanone was achieved.

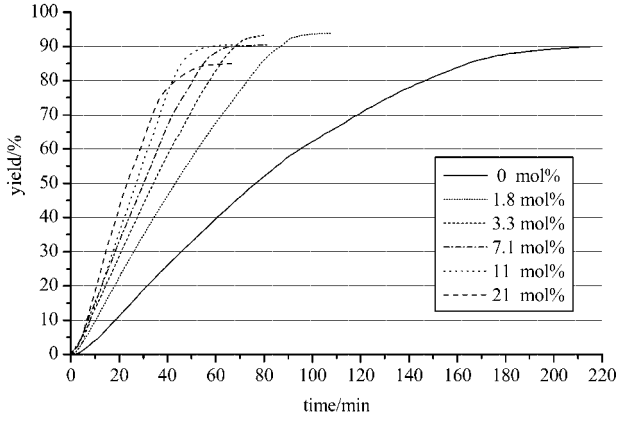


Figure 1. Conversion of adipic acid to cyclopentanone in the presence of different amounts of NaOH obtained by quantification of the evolved CO_2; time measurement was started when the reaction temperature was reached

When the weak base Na_2CO_3 is used instead of NaOH, exactly the same trends are observed, and even small amounts of salt increase the initial rate of the reaction. Upon increasing the quantity of Na_2CO_3, the initial rate increases further, although the yield starts to decrease (Figure 2). The sodium carbonate reacts with adipic acid to form carbonic acid and sodium adipate, and the thermodynamic equilibrium is shifted towards sodium adipate upon decomposition of carbonic acid into water and carbon dioxide. This demonstrates clearly that no strong base is necessary to initiate the reaction. In order to show that the increase of the initial rate is not influenced by the nature of the base but depends instead on its quantity, several carbonates and hydroxides of alkali and alkaline-earth metals were tested as additives. In Table 1 it can be seen that they perform similarly from a kinetic point of view. No special contribution was detected, for example, for barium cations, which have been proposed as reaction promoters. Consequently, the choice of additive should only be influenced by the cost of the metal salt, its potential environmental impact, and disposal facilities. Furthermore, it should be noted that with catalytic amounts of calcium hydroxide (0.05 equiv.) an 84% yield of cyclopentanone is obtained whereas distillation of calcium adipate itself only provides 43%, as mentioned above.

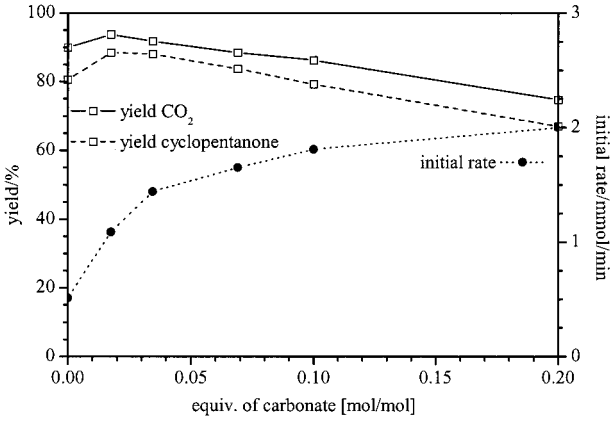
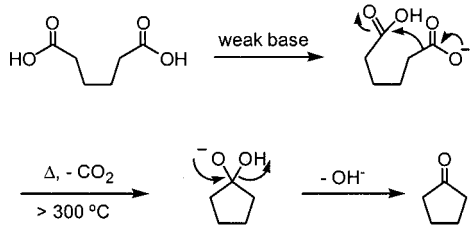


Figure 2. Yield of carbon dioxide and cyclopentanone and the initial rate for the dry distillation of adipic acid in the presence of different amounts of Na_2CO_3

Table 1. Yield of carbon dioxide and cyclopentanone and the initial rate for the dry distillation of adipic acid in presence of different bases

Entry	Base (equiv.)	Initial rate (mmol/min)	Yield CO_2 (%)	Yield ketone (%)
1	Li_2CO_3 (0.05)	1.39	90.4	83.8
2	NaOH (0.10)	1.50	91.2	84.3
3	K_2CO_3 (0.05)	1.55	91.4	86.1
4	$Mg(OH)_2$ (0.05)	1.46	94.1	84.5
5	$Ca(OH)_2$ (0.05)	1.51	91.0	84.2
6	$Ba(OH)_2$ (0.05)	1.45	91.5	90.0

These findings are in accordance with the mechanism proposed by Rand et al. and depicted in Scheme 1.[7] In a first step one of the two acid functionalities is deprotonated and decarboxylated at elevated temperatures. The corresponding carbanion then attacks the second carboxyl group and cyclopentanone is formed by elimination of a hydroxide anion. The base is thereby regenerated and immediately deprotonates a new substrate molecule. Decarboxylation and nucleophilic attack may be concerted (as depicted) to avoid the formation of an unstable carbanion. The simultaneous coordination of the two carboxylic groups to one metal centre, which has also been proposed as a possible reaction step,[3] is not supported by our results, since we observe that all metal cations, despite their higher or lower tendency to coordinate two acid groups, give the same results. We can therefore conclude that this reaction does not require any specific base. For the deprotonation of the carboxylic acid, a carbonate or any other material that may be protonated temporarily (e.g. glassware) can act as catalyst for this reaction. The radical mechanism that has been proposed for other cases[18] cannot be expected to occur when simple alkali or alkaline-earth cations are involved.



Scheme 1. Proposed mechanism for the ketonic decarboxylation of adipic acid to give cyclopentanone involving deprotonation, decarboxylation and nucleophilic attack

In order to check if ketonic decarboxylation can be used in asymmetric synthesis, we first submitted racemic 3-methyl- and 3-*tert*-butyladipic acid to the dry distillation in the presence of 5 mol % of sodium carbonate. From Table 2 it can be seen that both cyclopentanone derivatives are obtained in the same way as the unsubstituted one (entries 1 and 3). When optically pure (+)-3-methyladipic acid was employed, the yield of carbon dioxide was in the same range as before but the yield of the ketone dropped to only 72% (Table 2, entry 2). This is probably due to the lower quantity (only one third) of starting material used. Under these conditions, the amount of substance lost in the volume of the apparatus becomes more important with respect to the whole amount. However, the obtained product, 3-methylcyclopentanone, was optically pure as demonstrated by GC analysis with a chiral column (Figure 3). This indicates that we can follow an easier synthesis strategy for obtaining chiral cyclopentanone derivatives, in which substituents in the β-position to the carbonyl group can be introduced before cyclization.

Table 2. Yield of carbon dioxide and cyclopentanone derivative for the dry distillation of β-substituted adipic acid in the presence of 5 mol % of sodium carbonate

Entry	Substrate	Yield CO_2 (%)	Yield ketone (%)	*ee*[a] (%)
1	(±)-3-methyladipic acid	86	87	–
2	(+)-3-methyladipic acid	95	72	100
3	(±)-3-*tert*-butyladipic acid	89	83	–

[a] Enantiomeric excess.

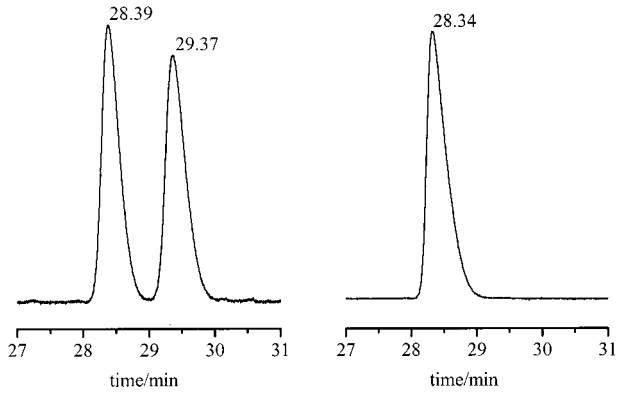


Figure 3. GC analysis on a chiral column of the products (3-methylcyclopentanone) obtained from (±)-3-methyladipic acid (left chromatogram) and from (+)-3-methyladipic acid (right chromatogram)

Conclusion

Ketonic decarboxylation can be carried out in the presence of catalytic amounts of environmentally friendly weakly basic catalysts such as Na_2CO_3. The stereogenic centres in the β-position maintain their stereochemistry and the reaction can be employed in asymmetric synthesis.

Experimental Section

General Remarks: All products were identified by GC-MS on an Agilent Technologies 6890N Network GC System coupled with an Agilent 5973 Network Mass Selective Detector and by NMR spectroscopy on a Bruker spectrometer at a frequency of 300 MHz for ^1H spectra and at a frequency of 75 MHz for ^{13}C spectra. The two enantiomers of 3-methylcyclopentanone were separated on a Fisons Instruments GC 8035 equipped with an ALPHA DEX 120 column from Supelco (30 m, 0.25 mm, 0.25 μm film) at 70 °C isotherm. Adipic acid (99% purity), (±)-3-methyladipic acid (99%), (*R*)-(+)-3-methyladipic acid (96%), and (±)-3-*tert*-butyladipic acid (99%) were purchased from Acros Organics. The products cyclopentanone, (±)-3-methylcyclopentanone, and (*R*)-3-methylcyclopentanone are commercially available.

General Procedure: The dry distillation was carried out in a 50 mL round-bottomed flask fitted with a 10-cm Vigreux column connected to a microdistillation apparatus and the gas outlet was connected to a gas burette. The flask was heated with a hemispherical

heating mantle and the reaction time was started when 350 °C reaction temperature had been reached (after ca. 25 min). Adipic acid (10.0 g, 68.4 mmol) was placed in the flask together with a magnetic stirring bar and the corresponding amount of base. The heating was started and the progress of the reaction was followed by measuring the gas evolution. When no gas was produced anymore, the reaction was stopped, the two phases separated and the organic layer analysed by GC analysis, GC-MS and NMR spectroscopy. The purity of the cyclopentanone was in all cases higher than 99%. Traces of unchanged adipic acid could be detected by ^{1}H NMR spectroscopy.

In the case of the re-use of the residue, adipic acid (10.0 g, 68.4 mmol) was placed in the flask together with NaOH (496 mg, 12.4 mmol) and distilled until gas production ceased. A new 10.0-g portion of adipic acid was placed in the flask and the distillation continued. Over seven cycles 36.4 g (90%) of cyclopentanone was obtained as a colourless liquid from 70.0 g of adipic acid.

(±)-3-Methylcyclopentanone: In the above described apparatus, (±)-3-methyladipic acid (10.0 g, 62.4 mmol) was placed in the flask together with a magnetic stirring bar and Na_2CO_3 (325 mg, 3.07 mmol). The heating was started and the progress of the reaction was followed by measuring the gas evolution. After 45 min no gas was produced anymore and the reaction was stopped. The two phases were separated and the organic one (5.33 g, 54.3 mmol, 87%) analysed by GC analysis, GC-MS, and NMR spectroscopy. The purity of the (±)-3-methylcyclopentanone was higher than 99%.

(*R*)-3-Methylcyclopentanone: In the above described apparatus, (*R*)-(+)-3-methyladipic acid (3.0 g, 18.7 mmol) was placed in the flask together with a magnetic stirring bar and Na_2CO_3 (100 mg, 0.943 mmol). The heating was started and the progress of the reaction was followed by measuring the gas evolution. After 25 min no gas was produced anymore and the reaction was stopped. The two phases were separated and the organic one (1.33 g, 13.5 mmol, 72%) analysed by GC analysis, GC-MS, and NMR spectroscopy. The purity of the (*R*)-3-methylcyclopentanone was higher than 99%. Only one enantiomer could be detected by GC analysis on a chiral ALPHA DEX column.

(±)-3-*tert*-Butylcyclopentanone:[19] In the above described apparatus, (±)-3-*tert*-butyladipic acid (12.5 g, 61.8 mmol) was placed in the flask together with a magnetic stirring bar and Na_2CO_3 (325 mg, 3.07 mmol). The heating was started and the progress of the reaction was followed by measuring the gas evolution. After 45 min no gas was produced anymore and the reaction was stopped. The two phases were separated and the organic one (7. 23 g, 51.6 mmol, 83%) analysed by GC analysis, GC-MS, and NMR spectroscopy. The purity of the (±)-3-*tert*-butylcyclopentanone was higher than 99%.

Acknowledgments

The authors thank ACEDESA and CICYT (MAT2003−07945-C02−01) for financing this work. M. R. is grateful to the Spanish Ministry of Science and Technology for a "Ramón y Cajal" Fellowship.

[1] H. Siegel, M. Eggersdorfer, in: *Ullmann's Encyclopedia of Industrial Chemistry, Vol. A15* (Ed.: Wolfgang Gerhartz), VCH Publishers, Weinheim **1990**, pp. 77−96.
[2] C. Friedel, *Justus Liebigs Ann. Chem.* **1858**, *108*, 125.
[3] H. Kwart, K. King, in: *The Chemistry of Carboxylic Acids and Esters* (Ed.: S. Patai), John Wiley & Sons, London, **1969**, pp. 362−373.
[4] M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 5th Ed., John Wiley & Sons, New York, **2001**, p. 573.
[5] J. F. Thorpe, G. A. R. Kon, *Organic Syntheses Coll. Vol. I* **1941**, 192−194.
[6] G. Vavon, A. Apchie, *Bull. Soc. Chim.* **1928**, *43*, 667−677.
[7] L. Rand, W. Wagner, P. O. Warner, L. R. Kovac, *J. Org. Chem.* **1962**, *27*, 1034−1035.
[8] O. Aschan, *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 1603−1609.
[9] O. Neunhoeffer, P. Paschke, *Ber. Dt. Chem. Ges.* **1939**, *72B*, 919−929.
[10] J. Marquie, A. Laporterie, J. Dubac, N. Roques, *Synlett* **2001**, 493−496.
[11] Farbenfabriken, German Patent 256622, **1911**.
[12] M. Decker, H. Wache, W. Franzischka, European Patent EP 0306873, **1988**.
[13] J. Graille, D. Pioch, European Patent EP 0457665, **1991**.
[14] M. Alas, M. Crochemore, European Patent EP 0626364, **1994**.
[15] S. Liang, R. Fischer, F. Stein, J. Wulff-Döring, PTC Int. Appl. WO 99/61402, **1999**.
[16] L. Ruzicka, W. Brugger, M. Pfeiffer, H. Schinz, M. Stoll, *Helvetica Chim. Acta* **1926**, *9*, 499−520.
[17] K. Bauer, D. Garbe, H. Suburg, *Common Fragrance and Flavor Materials*, Wiley-VCH, Weinheim, **1997**.
[18] R. A. Hites, K. Biemann, *J. Am. Chem. Soc.* **1972**, *94*, 5772−5777.
[19] S. H. Bertz, G. Dabbagh, *Tetrahedron* **1989**, *45*, 425−434.
Received December 12, 2003

