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Solvent- and Metal-Free Ketonization of Fatty Acid Methyl Esters and Triacylglycerols with Nitrous Oxide

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Abstract: Herein we report a new, one-step procedure for the metal-free ketonization of unsaturated fatty acid methyl esters and triacylglycerol mixtures with nitrous oxide (N_2O). The conversion of various substrates can be tuned by parameters such as temperature, reaction time and N_2O partial pressure. This ketonization chemistry offers various advantages over the classic Wacker catalytic process and a state-of-the-art two-step procedure *via* intermediate epoxides.

Keywords: fatty acids; nitrous oxide; oxidation; sustainability; triglycerides

Exploring the potential of renewable oils and fats of vegetable and animal origin is an important issue in modern chemistry since a shift from petrochemical feedstocks to renewable resources can contribute to a sustainable development. To extend the large-scale potential of renewables, efficient and green functionalization strategies must be elaborated. In the past, oleochemistry mainly focussed on the carboxy functionality of fatty acids, but nowadays, procedures are being developed for the functionalization of the fatty alkyl chain in these compounds. An overview of many state-of-the-art techniques and strategies has been published.[1] Of particular interest is the synthesis of keto fatty compounds, applied as plasticizers, surfactants, detergent formulations and ingredients of multipurpose greases.[2–4] Poly-ketone products also have an interesting potential as environmentally friendly lubricants, adhesives and additives in, e.g., PVC processing.[1–7] Although several keto fatty acids can be found in nature, only licanic acid (4-keto-*Z*,*E*,*E*-9,11,13-octadecatrienoic acid) can be obtained in significant amounts from natural sources. Many microorganisms are known for their selective oxidation of fatty acids, albeit often at a relatively low rate.[9]

A well known procedure for the air oxidation of olefins to ketones is the $PdCl_2$/CuCl-catalyzed Wacker chemistry.[10] Unfortunately, this homogeneous catalytic reaction is carried out in a solvent, faces catalyst recycling problems and has various environmental drawbacks such as the formation of chlorinated byproducts. The Wacker oxidation of methyl oleate (methyl *cis*-9-octadecenoate), a mono-unsaturated model substrate, has been studied in DMF (10 mol% $PdCl_2$ + 50 mol% CuCl). At 80 °C, a ketone yield of 70%, encompassing both 9-oxo- and 10-oxostearate methyl esters, can be achieved, corresponding to a volume-time yield of 7 $g L^{-1} h^{-1}$.[11] Under ultrasound, the Wacker oxidation of the same substrate in aqueous THF (17 mol% $PdCl_2$ and 150 mol% *p*-benzoquinone) results in a 65% keto yield at room temperature.[12] The Wacker oxidation of 1,5-dienes (50 mol% $PdCl_2$ + 100 mol% CuCl), *viz.*, substituted 1,5-hexadienes, was found to yield mainly 5-hexenal derivatives in yields ranging from 19 to 99%, depending on the substituents.[13] Using a Pd(II)/molybdovanadophosphate system, Ishii et al. succeeded in the ketonization of various terminal (di)enes in an ethanol/water mixture.[14] To the best of our knowledge, no reports exist on the direct ketonization of internal, nonconjugated dienes *via* Wacker-type catalysis.

The oxyfunctionalization of fatty acids is also possible *via* a two-step process in which the unsaturated bond is first epoxidized and the epoxide subsequently isomerized.[7,8] Fatty epoxides are produced in more than 350,000 tons/year and are mainly used as stabilizing plasticizers in PVC processing.[15] While peracids are commonly used as the stoichiometric oxidant for the first step, recent reports focus on the development of a (bio)catalytic process with commercial H_2O_2 or

alkyl hydroperoxides.[16–21] Three important isomerization strategies are reported, *viz.*, reaction in alkaline[22] or acidic conditions,[23] and nucleophilic catalysis.[24] The inability of the aforementioned isomerization methods to selectively produce poly-ketones from poly-epoxides should be stressed. Ketalization of ketones with neighbouring epoxides may give rise to the formation of intra- and intermolecular cyclic ethers.[25]

On the other hand, there is an increasing interest in the use of N_2O as a ketonization agent for several simple olefins.[26–28] This reaction is proposed to proceed *via* a 4,5-dihydro[1,2,3]oxadiazole intermediate, formed in a rate-determining 1,3-dipolar cycloaddition of N_2O to the unsaturated C=C bond. Thermal decomposition of the oxadiazole intermediate yields the desired carbonyl product.[29]

The aim of this work is to explore the opportunities of N_2O chemistry in the one-step ketonization of unsaturated renewables, in particular fatty esters and triacylglycerols (triglycerides). The ability to work in the absence of solvent and metals clearly offers economic and environmental advantages.

The ketonization of methyl oleate (methyl *cis*-9-octadecenoate) was investigated at 220 °C, using an STP N_2O partial pressure of 4.0 MPa. GC and GC-MS analyses of the reaction mixture reveal the formation of only 9- and 10-keto fatty products ($m/z = 312$) in very high selectivity (99 %), even at complete conversion (Figure 1). The volume-time yield of 85 $g L^{-1} h^{-1}$ is one order of magnitude higher than that obtained with conventional Wacker chemistry.[7,11] ^{13}C NMR on the non-purified sample reveals a 212 ppm signal which must be assigned to a keto carbon, R−C(=O)−R′, rather than an aldehyde, since it is not observed in the 135° DEPT ^{13}C NMR spectrum (see Supporting Information). The protons in α-positions to the ketone group, $-CH_2-C(=O)-CH_2-$, occur as a multiplet in the ^1H NMR spectrum with a resonance at 2.43 ppm. NMR analyses show no evidence for any other products. The ketonization of methyl oleate was also monitored by FT-IR. At 1707 cm^{-1}, a signal ascribed to the ketone C=O appears next to the ester carbonyl stretch (1740 cm^{-1}) (Figure 1). In parallel, a decrease of the sp^2 C−H stretch (3005 cm^{-1}) was observed. The ketone product shows a well-defined melting point at 47 °C in a differential scanning calorimetry (DSC) experiment (see Supporting Information), in accordance with the melting-point range published in the literature.[7] In addition to the absence of solvent and catalyst, this new chemistry allows tuning of the alkene conversion with parameters such as N_2O partial pressure and reaction time.

The excellent yields obtained with methyl oleate prompted us to investigate the ketonization of unsaturated triacylglycerols. The ketonization of high oleic sunflower oil (>90 % glycerol trioleate), with N_2O (STP partial pressure of 4.0 MPa) was performed at 240 °C (Figure 2). Identification and quantification of the reaction products in the unpurified reaction mixture was carried out by ^{13}C and ^1H NMR (see Supporting Information). Complete conversion, with a ketone selectivity of over 95 %, can be achieved within 24 h.

Olive oil, another high oleic fatty substrate (74 % glycerol trioleate), was also investigated. Using 5.0 MPa N_2O partial pressure, ^1H NMR shows a conversion at 240 °C of 30 and 80 % after 3 and 9 h reac-

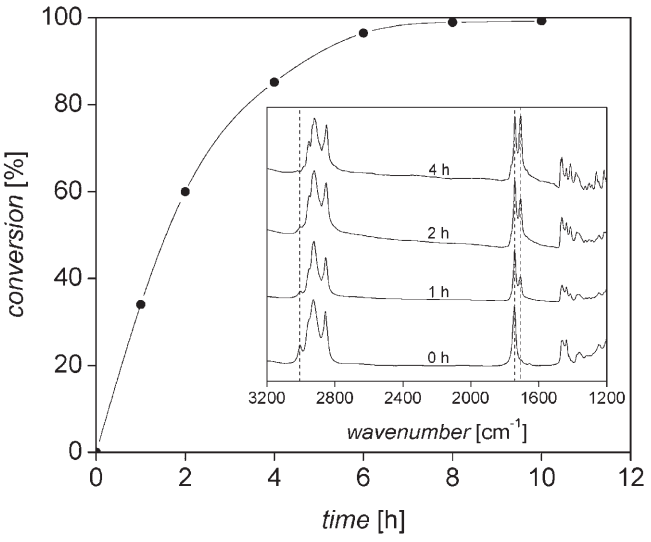


Figure 1. Conversion of methyl oleate at 220 °C and an STP N_2O partial pressure of 4.0 MPa; the inset shows the FT-IR spectra recorded at increasing reaction time.

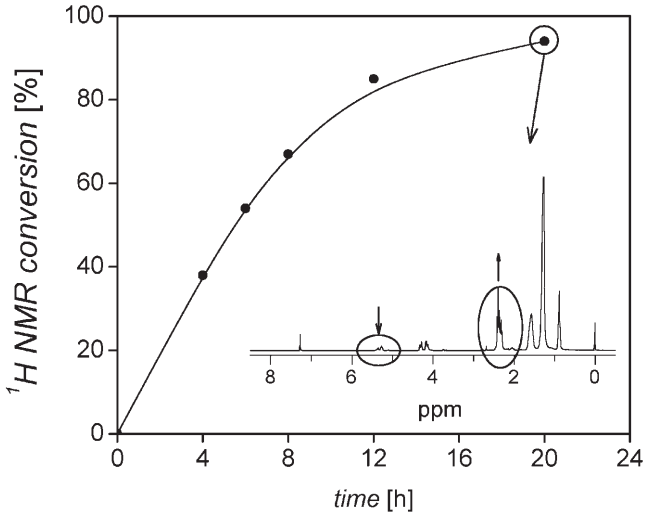


Figure 2. Conversion in time of the double bonds in sunflower oil at 240 °C with N_2O (STP partial pressure of 4.0 MPa), as monitored by ^1H NMR. The inset shows the ^1H NMR spectrum of the reaction mixture after 20 h: nearly all $-CH=CH-$ protons disappear (5.3 ppm), whereas new $-C(=O)-CH_2-$ protons appear (2.4 ppm).

tion time, respectively. As a proof of concept, the reaction mixture after 9 h was subjected to a stoichiometric $NaBH_4$ reduction in THF in the presence of Amberlyst-15. Whereas the 2.4 ppm peak of the protons in α-positions to the ketone disappeared, a 3.6 ppm peak arose, corresponding to protons in α-positions of an alcohol group [i.e., $-C\mathbf{H}_2(OH)-$; see Supporting Information]. This simple stoichiometric reduction illustrates the potential of ketonization by N_2O for new avenues to the synthesis of (poly-)alcohols. Currently, such alcohol functionalities are introduced *via* epoxidation (Scheme 1).

Next, the ketonization of methyl linoleate (methyl *cis,cis*-9,12-octadecadienoate) with N_2O (STP partial pressure of 5.0 MPa) was studied at 240 °C. This compound is a model for fatty methyl esters with two unsaturated bonds. The reaction was followed by GC-MS, revealing both partially ($m/z = 310$) and fully ketonized ($m/z = 326$) products. Figure 3 clearly shows the consecutive formation of mono- and diketones. For instance, after 3 h, when 36 % of the linoleate has reacted, the monoketones/diketones ratio equals 5.7, while after 12 h, when 98 % of the linoleate has reacted, this ratio is 0.4 (Figure 3). Within the monoketone fraction, 60 % of 1,4-enones are formed. It is worthwhile to mention that also traces of conjugated 1,2-enones could be detected with GC-MS, probably originating from thermal isomerization reactions. After 15 h, predominantly diketones could be observed with ^{1}H NMR. The reaction mixture was separated over a silica column, and the separated fractions were analyzed and quantified (see Experimental Section). Whereas in theory several diketone regioisomers can be formed upon ketonization of the intermediate enones, only two diketone fractions could be separated. The colorless solids were fully analyzed with NMR. The first diketone fraction eluting from the chromatographic column contained 9,12- and 10,13-diketostearic methyl esters as 1,4-diketones. The

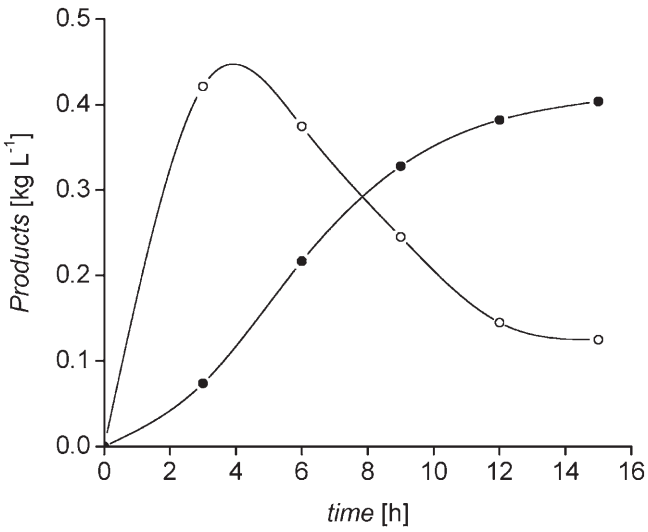
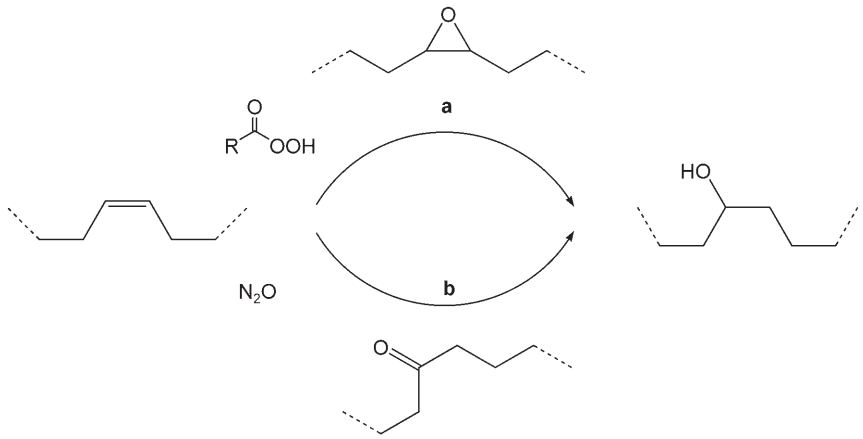


Figure 3. The ketonization in time of methyl linoleate at 240 °C with N_2O (STP partial pressure of 5.0 MPa); monoketone (○) and diketone (●) formation.

second diketone fraction contained only 1,5-diketone. No 1,3-diketones could be observed, either after column separation, or in the crude reaction mixture. At complete conversion, the ratio of the 1,4- to 1,5-diketones is equal to 1.3, which can be rationalized from their origins: the 1,5-diketone originates exclusively from the ketonization of 4-en-1-ones, while 1,4-diketones can originate from both 4-en-1-ones and 3-en-1-ones. The 1,4- and 1,5-dione fractions were characterized with DSC melting points of 36 and 60 °C, respectively (see Supporting Information).

The ketonization of a commercial "biodiesel" sample, consisting of 60 % methyl oleate, 30 % of methyl linoleate and 10 % of saturated methyl stearate (10 %), was monitored at 220 °C and 4.0 MPa of N_2O (STP). The disappearance of the ^{1}H NMR double bond H-signal at 5.35 ppm is a measure of the



Scheme 1. Strategies for the synthesis of fatty alcohols from unsaturated fatty compounds *via* (**a**) the reduction of epoxides, or (**b**) the reduction of ketones.

double bond conversion (Figure 4). DSC shows a smooth increase in melting point as the conversion increases, in accord with the increasing intramolecular forces resulting from ketonization. After 6 h, 60% of the double bond of the liquid starting material is converted into ketone groups, resulting in an oxidized fatty product with a melting point of 24 °C. The melting point increases to 29 °C after 12 h, showing 90% double bond conversion. C–C bond breaking was found to be a very minor reaction path.

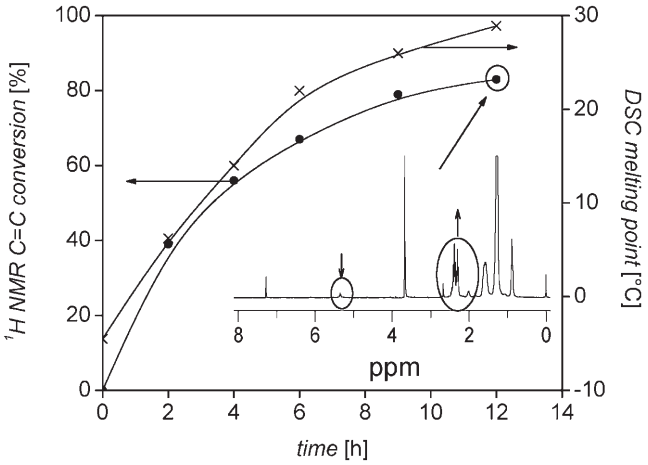


Figure 4. Double bond conversion (●) of biodiesel (60% methyl oleate, 30% methyl linoleate and 10% methyl stearate) at 220 °C and 4.0 MPa N_2O (STP), as monitored by ^{1}H NMR and DSC melting point (×) of the reaction mixture. (see Supporting Information for DSC method)

Safflower oil with 70% glycerol trilinoleate was also ketonized with N_2O (STP partial pressure of 4.0 MPa). The temperature dependency of this reaction is illustrated by Figure 5. From an Arrhenius plot of the data, an apparent activation energy of 113 kJ mol^{-1} is obtained, in line with the activation barrier observed for other but similar substrates.[29] At 260 °C, a volume-time yield of 90 g L^{-1} h^{-1} can be achieved. At 240 °C, a conversion of 84% can be achieved in 15 h time, corresponding with a diketone yield of 62%. The ratio between the 1,4- and the 1,5-diketones as derived from ^{1}H NMR is equal to 1.33, in line with the results obtained with methyl linoleate.

In this contribution, the one-pot production of fatty ketones from unsaturated fatty acid methyl esters and triacylglycerides by nitrous oxide is investigated. Various substrates are found to be smoothly ketonized in high volume-time yields, in the absence of a solvent or a metal catalyst. Clear advantages over the conventional Wacker catalytic process and the two-step procedure *via* intermediate epoxides exist. Whereas the latter procedures fail to convert dienes to diketones, the new N_2O-based chemistry affords high yields of these compounds. Hydrogenation of these (di)ketone products could present a simple new route to fatty-based (poly)alcohols.

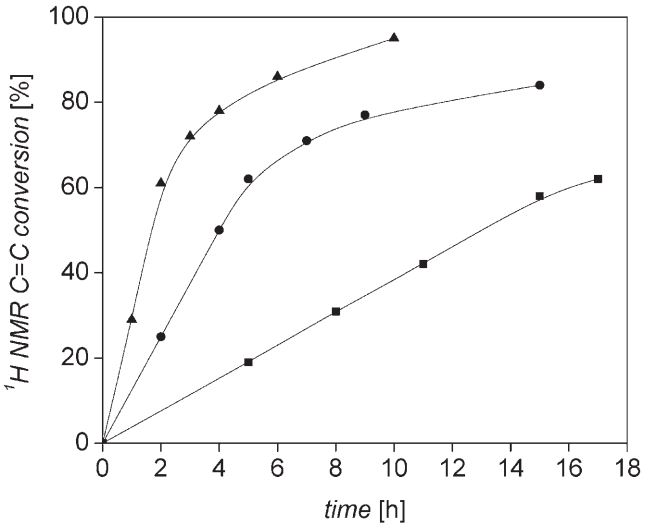


Figure 5. Conversion in time of safflower oil at 220 (■), 240 (●), and 260 °C (▲) with N_2O (STP partial pressure of 4.0 MPa).

Experimental Section

Materials

Methyl oleate (MP Biomedicals), methyl linoleate (Fluka) and olive oil (Extra Vierge from supermarket) were purchased from commercial sources, whereas high oleic sunflower oil, commercial biodiesel and safflower oil were a kind gift of Oleon N.V. The fatty acid distributions of the starting oils were obtained from GC analysis after methanolysis and are documented in the Supporting Information.

General Procedure

All ketonization reactions were carried out in 50 mL high pressure reactors (Autoclave France), connected to an expansion vessel and magnetically stirred at 500 rpm. Reactors were loaded with 20 mL of fatty substrate. After carefully flushing the reactor with N_2O (N25 grade) to avoid O_2 initiated autoxidation chemistry to occur, the reaction is pressurized at given N_2O pressure, and gently heated (15 °C min^{-1}) to reaction temperature.

As neither solvents nor metals are used in the N_2O reaction, the work-up procedure simply comprises reactor cooling and depressurizing. For analytic purposes, the fatty product mixture is dissolved in acetone, and analyzed with GC-FID and GC-MS (50 m CP-Sil5-CB, Chrompack column or a BPX 70 (SGE) column) in case of methyl fatty acids. ^{1}H NMR, ^{13}C NMR and DEPT 135° spectra of unpurified methyl fatty acids and triacylglyceride product mixtures were recorded in $CDCl_3$ and the chemical shifts reported in ppm downfield of internal tetramethylsilane reference.

Product Purification

Purification of the diketone isomers in the ketonization of methyl linoleate was typically carried out as follows: an aliquot of the reaction mixture was dissolved in ethyl acetate, and subjected to a chromatographic separation using a 30 cm silica column (silica gel 60, Fluka), initially eluted with 80:20 hexane-ethyl acetate mixture, gradually increasing the polarity using more concentrated ethyl acetate solutions, and finally using methanol to elute all the polar products. In this way, 26% of the two 1,4-diketone isomers and 18% of the 1,5-diketone were, for instance, isolated for reaction of methyl linoleate with N_2O (5.0 MPa) at 240 °C for 15 h. In comparison, total diketone yields based on ^{1}H NMR and GC were 46% and 42%, respectively.

^{1}H NMR of the 1,4-diketone fraction in the ketonization of methyl linoleate: $\delta = 3.65$ (s, 3H), 2.66 (s, 4H), 2.43 (t, 4H), 2.28 (t, 2H), 1.56 (m, 6), 1.27 (br m, 12H), 0.87 (t, 3H); ^{1}H NMR of the 1,5-diketone fraction: $\delta = 3.66$ (s, 3H), 2.42 (br m, 10H), 1.83 (q, 2H), 1.56 (br m, 6H), 1.3 (br s 10H), 0.89 (t, 3H).

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References

[1] U. Bierman, W. Friedt, S. Lang, W. Lühs, G. Machmüller, J. O. Metzger, M. R. gen. Klaas, H. J. Schäfer, M. P. Schneider, *Ang. Chem. Int. Ed.* **2000**, *39*, 2206.
[2] J. W. Hagemann, J. A. Rothfus, *J. Am. Oil Chem. Soc.* **1991**, *68*, 139.
[3] H. E. Kenney, E. T. Donnahue, (Maeker), *US Patent* 3,832,368, **1974**.
[4] H. E. Kenney, E. T. Donnahue, (Maeker), *US Patent* 3,836,468, **1974**.
[5] O. Grummit, K. G. Siedschlag, *J. Am. Oil Chem. Soc.* **1949**, *26*, 690.
[6] K. Worschech, G. Stoll, E.-U. Brand, P. Wedl, *German Patent* DE4018293 DE, **1991**.
[7] G. Von Stoll, K. Worschech, *Fat. Sci. Technol.* **1992**, *94*, 332.
[8] A. Steger, J. Van Loon, P. J. van Vlimmeren, *Fette u. Seifen* **1944**, *51*, 49.
[9] For example, T. M. Kuo, L. K. Nakamura, A. C. Lanser, *Curr. Microb.* **2002**, *45*, 265.
[10] J. M. Takacs, X.-T. Jiang, *Curr. Org. Chem.* **2003**, *7*, 369.
[11] S. Warwel, W. Pompetzki, E. A. Deckwirth, *Fat Sci. Technol.* **1991**, *93*, 210.
[12] S. F. Marcel, L. K. Jie, C. K. Lam, *Chem. Phys. Lip.* **1996**, *81*, 55.
[13] T.-L. Ho, M. H. Chang, C. Chen, *Tetrahedon Lett.* **2003**, *44*, 6955.
[14] T. Yokota, A. Sakakura, M. Tani, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett.* **2002**, *43*, 8887.
[15] J. T. Lutz, *Encyclopedia of Chemical Technology*, Vol. 9, (Ed.: M. Grayson), Wiley, New York, **1980**, p 251.
[16] M. g. K. Rüsch, S. Warwel, *Ind. Crops. Prod.* **1999**, *9*, 125.
[17] M. g. K. Rüsch, S. Warwell, *J. Am. Oil Chem. Soc.* **1996**, *73*, 11.
[18] I. V. Kozhevnikov, G. P. Mulder, M. C. Steverink-de Zoete, M. G. Oostwal, *J. Mol. Catal. A: Chem.* **1998**, *134*, 223.
[19] M. Guidotti, N. Ravasio, R. Psaro, E. Gianiotti, L. Marchese, S. Colucchia, *Green Chem.* **2003**, *5*, 421.
[20] M. A. Camblor, A. Corma, P. Esteve, A. Martinez, S. Valencia, *Chem. Commun.* **1997**, *8*, 795.
[21] E. Ucciani, *Fat. Sci. Technol.* **1993**, *95*, 236.
[22] J. K. Crandall, M. Apparu, *Org. React.* **1983**, *29*, 345.
[23] a) W. F. Hölderich, *German Patent* DE 10,212,593 A1, **2003**; b) W. F. Hölderich, *German Patent* DE 10,200,971 A1, **2003**.
[24] G. Stoll, K. Worschech, *Fat. Sci. Technol.* **1992**, *94*, 332.
[25] R. J. Capon, R. A. Barrow, *J. Org. Chem.* **1998**, *63*, 75.
[26] a) F. S. Bridson Jones, G. D. Buckley, L. H. Cross, A. P. Driver, *J. Chem. Soc.,* **1951**, 2999; b) G. D. Buckley, F. S. Bridson Jones, W. J. D. C. Levy, *UK Patent* 668,309, **1949**; c) G. D. Buckley, A. P. Driver, F. S. Bridson Jones, *UK Patent* 649,680, **1949**.
[27] a) G. I. Panov, K. A. Dubkov, E. V. Starokon, V. N. Parmon, *React. Kinet. Catal. Lett.* **2002**, *76*, 401; b) G. I. Panov, K. A. Dubkov, E. V. Starokon, V. N. Parmon, *React. Kinet. Catal. Lett.* **2002**, *77*, 197.
[28] E. V. Starokon, K. A. Dubkov, D. E. Babushkin, V. N. Parmon, G. I. Panov, *Adv. Synth. Catal.* **2004**, *346*, 268.
[29] a) V. I. Avdeev, S. Ph. Ruzankin, G. M. Zhidomirov, *Chem. Commun.* **2003**, 42; b) V. I. Avdeev, S. Ph. Ruzankin, G. M. Zhidomirov *Kinetics and Catalysis* **2005**, *46*, 177; c) I. Hermans, B. Moens, J. Peeters, P. A. Jacobs, B. F. Sels, *Phys. Chem. Chem. Phys.* **2007**, DOI:10.1039/B704351 A.

