Catalysis Letters Vol. 88, Nos. 1–2, May 2003 (© 2003)

Different acylating agents in the synthesis of aromatic ketones on sulfated zirconia

J. Deutsch[a,]*, A. Trunschke[a], D. Müller[a], V. Quaschning[b], E. Kemnitz[b], and H. Lieske[a]

[a] *Institut für Angewandte Chemie Berlin-Adlershof e.V., Richard-Willstätter-Strasse 12, 12489 Berlin, Germany*
[b] *Humboldt-Universität zu Berlin, Institut für Chemie, Brook-Taylor-Strasse 2, 12489 Berlin, Germany*

Received 5 November 2002; accepted 27 February 2003

Sulfated zirconia (SZ) has been used as a heterogeneous catalyst in the synthesis of aromatic ketones. A number of carboxylic anhydrides and acid chlorides proved to be appropriate acylating agents in the reaction with anisole and chlorobenzene. The rate of anisole acylation was found to be dependent on the type of acylating agent used. Thus, acetic anhydride and benzoic anhydride reacted faster on SZ with anisole than benzoyl chloride. Successful SZ-catalyzed acylations of chlorobenzene were limited to acceptor substituted benzoyl chlorides as acylating agents. Acetic anhydride and benzoic anhydride did not react with chlorobenzene in the presence of SZ.

KEY WORDS: sulfated zirconia; aromatics; acylation; aromatic ketones.

1. Introduction

Acylation of aromatics is a key reaction in organic chemistry. The resulting aromatic ketones are used as intermediates or final compounds in the production of pharmaceuticals, cosmetics, agrochemicals, dyes, and special chemicals. Owing to economic and ecological drawbacks, such as the necessity of stoichiometrically activating the acylating agent with Lewis acids (Friedel–Crafts acylation), their irreversible loss during product isolation, and extensive formation of acid wastes, there is much effort made to substitute this widely established method.

Numerous papers report attempts to turn the current stoichiometric methods into catalytic processes. For example, the synthesis of benzophenones was achieved in the presence of the homogeneous catalyst triflic acid [1,2]. Moreover, hafnium(IV) triflate is able to catalyze the formation of aromatic ketones, but the required use of the solvent system nitromethane/lithium perchlorate [3,4] is not convenient for industrial applications.

Solid acids are attractive catalysts for the acylation of aromatics because of their easy separation from the reaction mixture by filtration. The acylation of anisole using common acylation agents, such as acetic anhydride, was performed over zeolites [5–10], clays [11–13], nafion-H on silica [14], heteropoly acids [15], and microencapsulated scandium(111) triflate in combination with nitromethane/lithium perchlorate [16]. Modified metal oxides such as SZ [17], sulfated alumina [18], Al-promoted SZ [19], Al-promoted sulfated titania [20], and tungsten oxide on zirconia [21] were applied to the benzoylation of toluene.

Currently there is a lack of detailed information about the reactivity of various acylating agents and aromatics under the conditions of heterogeneous catalysis. This paper reports on a systematic investigation of the reactivity of several acylating agents toward anisole and chlorobenzene over SZ.

2. Experimental

2.1. Chemicals

Anisole (99.7%, anhydrous), chlorobenzene (99.8%, anhydrous), acetic anhydride (98%), propionic anhydride (97%), decanoic anhydride (98%), octadecanoic anhydride (98%), isobutyric anhydride (97%), pivalic anhydride (99%), (*S*)-2-methylbutyric anhydride (94%), phenylacetyl chloride (98%), 3-phenylpropionyl chloride (98%), succinic acid monomethyl ester chloride (97%), benzoyl chloride (99%), 4-methylbenzoyl chloride (98%), 4-methoxybenzoyl chloride (99%), 4-chlorobenzoyl chloride (99%), 4-nitrobenzoyl chloride (98%), and 1,3,5-benzenetricarboxylic acid trimethyl ester (98%) were purchased from Aldrich, and benzoic anhydride (97%) from Fluka. The chemicals were used without further purification. 2-Methylbutyric anhydride was synthesized from 2-methylbutyric acid (Aldrich, 98%) and *N*,*N*′-dicyclohexyl-carbodiimide (Aldrich 99%) according to a previous study [22].

2.2. Catalyst preparation and characterization

The catalyst, SZ, was prepared by adding aqueous ammonia to an aqueous solution of $ZrOCl_2$ until a pH

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* To whom correspondence should be addressed.

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of 8 was achieved. The precipitate was filtered, washed several times until free of chloride, dried at 110 °C for 15 h, impregnated with diluted sulfuric acid (10%), filtered again, and calcined at 500 °C in air for 1 h. The resulting white solid contained 1.64% sulfur. After filling into a bottle, the catalyst was stored in a desiccator over dry silica gel.

X-ray powder diffraction measurements of SZ were performed using Cu K_α radiation (RD 7, R. Seifert & Co., Freiberg, Germany). The catalyst exhibited the tetragonal modification of ZrO_2 (PDF-No. 42-1164).

Specific surface area and pore diameters were measured using nitrogen adsorption at 77 K (ASAP 2000 system, Micromeritics). The acidity of SZ was characterized by temperature-programmed desorption (TPD) of ammonia, which was pre-adsorbed at 100 °C before starting the TPD run. The ammonia desorbed was quantified by reaction with 0.1 N sulfuric acid and backtitration. BET surface area, average pore diameter, and number of acid sites were found to be 155 m^2/g, 59 Å, and 0.31 mmol/g, respectively.

2.3. Acylation experiments

The catalytic experiments were carried out in liquid phase in a 100 ml three-necked flask with thermometer and reflux condenser with $CaCl_2$ tube. An amount of 0.45 g of the freshly calcined (air, 3 h, 500 °C) SZ was placed into a heated, vigorously stirred (700 rpm) mixture of 0.15 mol of the aromatic (anisole or chlorobenzene) and 0.015 mol of the acylating agent (carboxylic anhydride or acid chloride). The reaction temperature was kept constant over the whole experiment. All yields given are calculated relative to the acylating agent.

2.3.1. Monitoring of ketone formation

The kinetic monitoring of anisole acetylation (formation of 4- and 2-methoxy acetophenone (4-/2-MAP)) and benzoylation (formation of 4- and 2-methoxy benzophenone (4-/2-MBP)) was performed by ^1H NMR spectroscopy (solvent: $CDCl_3$). Before starting the experiment with the addition of the SZ catalyst, 0.005 mol of 1,3,5-benzenetricarboxylic acid trimethyl ester as an inert reference substance were added to the mixture of the aromatic and the acylating agent. After reaction times of 5, 10, 20, 30, 60, 120, and 180 min, 0.3 ml of the slurry were taken via syringe, filtered (removal of the SZ), concentrated in vacuum (removal of non-reacted anisole, acetic anhydride, benzoyl chloride, and formed acetic acid, respectively), and analyzed. The distinct $C\underline{H}_3O$ singlets resulting from standard substance (1-, 3-, 5-$(C\underline{H}_3OOC)_3C_6H_3$; $\delta = 3.96$ ppm) and ketones formed (4-/2-$C\underline{H}_3O$–C_6H_4COR; 4-MAP: $\delta = 3.87$ ppm, 2-MAP: $\delta = 3.91$ ppm, 4-MBP: $\delta = 3.85$ ppm, 2-MBP: $\delta = 3.69$ ppm) were used for determining the product yield (peak area integration).

2.3.2. Preparative experiments

The acylation experiments were performed without using the above mentioned internal reference substance. The clear solution was concentrated in vacuum after cooling to room temperature and separating the catalyst from the reaction mixture. Non-reacted acylating agents with high boiling points were removed by diluting the solution with 75 ml of dichloromethane followed by extraction with 25 ml of 5% aqueous NaOH (twice) and 25 ml of water (twice). Small amounts of non-reacted decanoic and octadecanoic anhydride had to be saponified with 100 ml of 10% KOH. The remaining organic solution was dried with anhydrous Na_2SO_4, filtered, and again concentrated in vacuum. The resulting crude ketones (mixtures of isomers) were purified by Kugelrohr distillation and identified by ^1H NMR, ^{13}C NMR (Unity plus 300 MHz, Varian), and GC–MS (MD 800, Thermo).

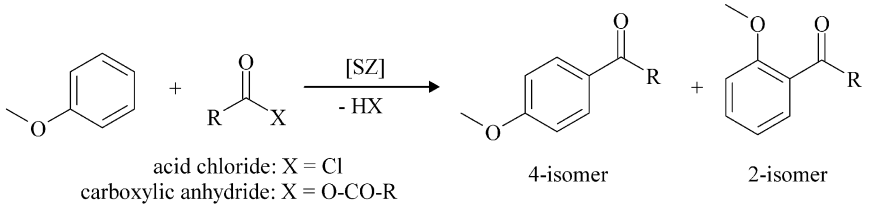
2.3.3. IR spectroscopic investigations

Infrared spectra were measured using a FTS-60 A spectrometer (Digilab). The samples were transferred into a heatable reaction and pretreatment chamber of a diffuse reflectance attachment (Harrick). A total of 64 scans were accumulated at a resolution of 2 cm^{-1}.

3. Results and discussion

3.1. Acylation of anisole

SZ was used as a heterogeneous catalyst in the acetylation and benzoylation of anisole (scheme 1). Compared with our former experiments [23–25] and in view of an economic use of SZ, the amount of catalyst in most of the acylation experiments was reduced significantly.



Scheme 1. SZ-catalyzed acylation of anisole with acid chlorides and anhydrides of aliphatic and aromatic carboxylic acids.

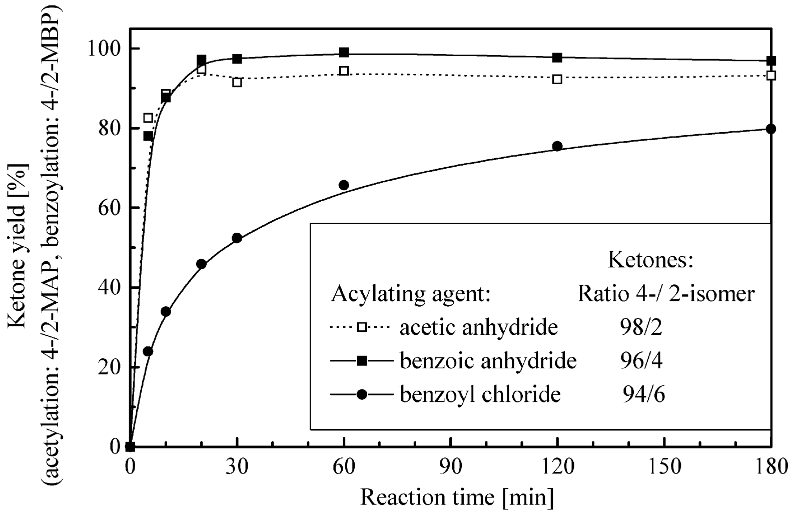


Figure 1. Kinetics of the SZ-catalyzed acetylation and benzoylation of anisole at 100 °C.

Roughly, about 0.01 mol of acid sites, determined by ammonia TPD, were applied to 1 mol of acylating agent.

3.1.1. *Acetylation and benzoylation of anisole*

Monitoring of ketone formation. Anisole was reacted with benzoic anhydride, benzoyl chloride, and acetic anhydride over SZ to give 4-/2-MBP and 4-/2-MAP, respectively. Figure 1 demonstrates that the two carboxylic anhydrides reacted faster than benzoyl chloride with the aromatic substrate. The conversion of the anhydrides was completed within 30 min at 100 °C. Full conversion of benzoyl chloride required a significantly longer reaction time.

Ketone formation was affected by hydrolysis of the acylating agent to a small degree (a possible cause being the presence of strongly adsorbed water on the catalyst surface).

The rate of the reaction of anisole with carboxylic anhydrides at 100 °C made lower reaction temperatures possible. The acylations with acetic and benzoic anhydride were sufficiently fast already at 85, 70, and 55 °C (figure 2). Unlike benzoyl chloride that yielded only a low amount of the desired product, the carboxylic anhydrides gave remarkable ketone yields (36 and 19%) even after only 5 min at 55 °C.

IR spectroscopic investigation of SZ used in acetylation and benzoylation of anisole. Using IR spectroscopy, carbonaceous deposits could be observed on the surface of SZ. The variation of the acylating agent generates differences in the nature of the species deposited. In figure 3 the IR spectrum of fresh SZ is compared with those of SZ used in the acylation of anisole with benzoyl chloride,

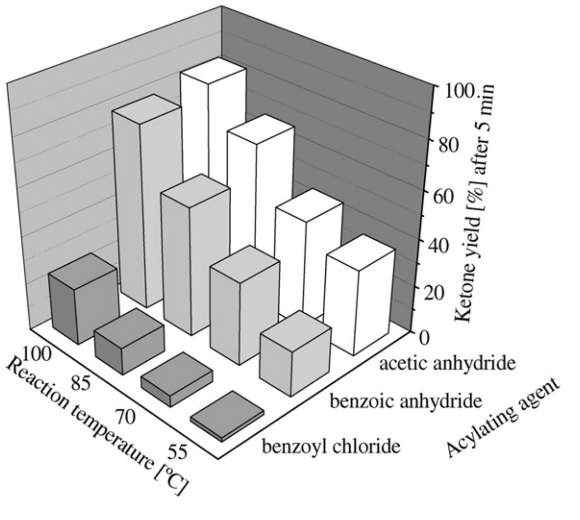


Figure 2. SZ-catalyzed acylation of anisole, dependence of the initial rate of the ketone formation (acetylation: 4-/2-MAP, benzoylation: 4-/2-MBP) on reaction temperature and acylating agent.

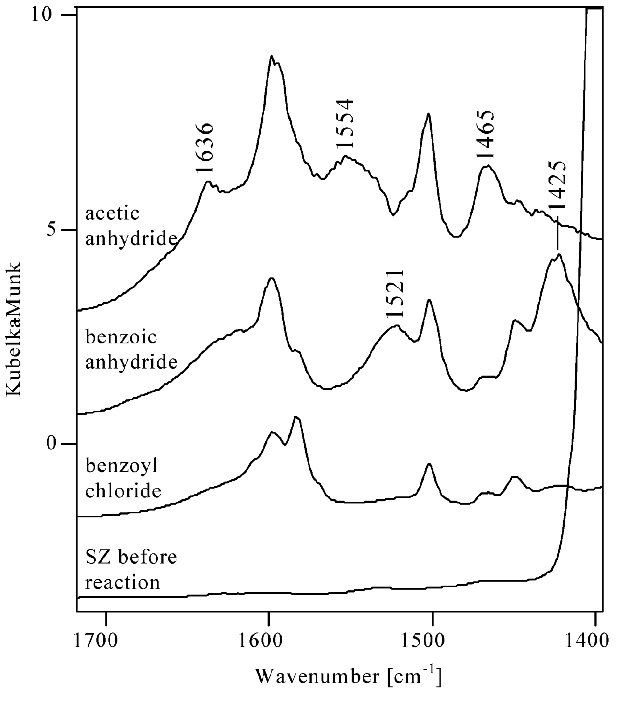


Figure 3. DRIFT spectra of SZ before reaction and after acylation of anisole with acetic anhydride, benzoic anhydride, and benzoyl chloride.

Table 1

SZ-catalyzed acylation of anisole with different types of aliphatic carboxylic anhydrides and acid chlorides at 100 °C according to scheme 1

Acylating agent, R =	Amount of SZ (g)	Reaction time (h)	Yield of the resulting purified ketones (%)	Ratio 4-/2-isomer
Carboxylic anhydrides				
CH_3–	0.45	1.5	91	98/2
CH_3–CH_2–	0.45	1.5	92	98/2
CH_3–$(CH_2)_8$–	0.45	1.5	90	98/2
CH_3–$(CH_2)_{16}$–	0.45	2.5	88	98/2
$(CH_3)_2$–CH–	0.45	1.5	96	99/1
$(CH_3)_3C$– [a]	1.125	72	27	94/6
CH_3–CH_2–$CH(CH_3)$– [b]	0.45	1.5	95	99/1
Acid chlorides				
C_6H_5–CH_2–	0.45	15	90	96/4
C_6H_5–$(CH_2)_2$–	0.45	15	92	97/3
CH_3O–CO–$(CH_2)_2$– [c]	1.125	1.5 [d]	31	96/4

[a] Pivalic anhydride.

[b] 2-Methylbutyric anhydride.

[c] Succinic acid monomethyl ester chloride.

[d] Longer reaction time results in a lower product yield.

benzoic anhydride, and acetic anhydride. A band at 1636 cm^{-1} exclusively appears after acetylation of anisole with acetic anhydride. This peak is tentatively assigned to the C=O stretching vibration of the carbonyl group in 4,4′-dimethoxy-β-methylchalcon, a condensation product of the reaction product 4-MAP [8,26]. Benzoyl chloride, benzoic anhydride, and benzoic acid form surface benzoates in the absence of anisole [27]. These species are not detected when benzoyl chloride is reacted with anisole (figure 3). In comparison, surface benzoates with bands at 1521 and 1425 cm^{-1} due to asymmetric and symmetric OCO stretching vibrations, respectively, are generated in the reaction of benzoic anhydride with anisole on SZ, because benzoic acid is released as a reaction product. In the case of acetic anhydride, bands at 1554 and 1465 cm^{-1} are attributed to the corresponding surface acetate species [28].

3.1.2. *Acylation of anisole with aliphatic carboxylic anhydrides and aliphatic acid chlorides*

The acylation experiments of anisole (scheme 1) were extended to other aliphatic acylating agents especially of higher chain length and higher molecular weight.

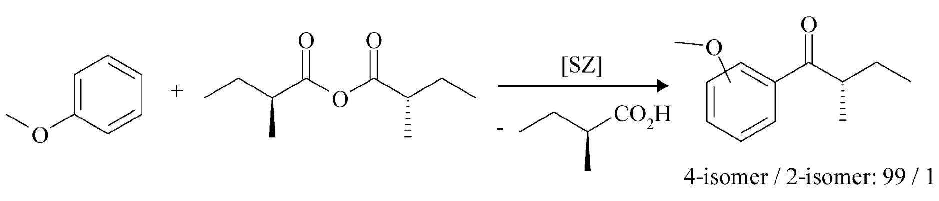
Generally, high yields of the desired aromatic ketones were obtained over the SZ catalyst (table 1), but there are exceptions.

In agreement with acylations of anisole over Hβ [7], pivalic anhydride was barely converted to the corresponding aromatic ketone. The carbonyl group is probably blocked by the bulky *t*-butyl group and is unable to interact with the acid sites on the catalyst surface. Furthermore, the reaction between anisole and succinic acid monomethyl ester chloride stagnated at a low conversion level. A rapid deep brown coloring of the SZ within the reaction mixture was observed.

The result with 2-methylbutyric anhydride is especially interesting, because it is a chiral acylating agent that may be used in the synthesis of chiral aromatic ketones. Thus, the SZ-catalyzed acylation of anisole with (*S*)-2-methylbutyric anhydride yielded enantiomerically pure (*S*)-1-(4-methoxy-phenyl)-2-methyl-butan-l-one (scheme 2; product analysis: ^{1}H NMR spectrum in $CDCl_3$; chiral shift reagent: $Eu(TFC)_3$; comparison with the corresponding spectrum of the racemate). The same ketone can also be obtained from anisole and (*S*)-2-methylbutyryl chloride under Friedel–Crafts conditions [29].

3.1.3. *Acylation of anisole with substituted benzoyl chlorides*

Substituted benzoyl chlorides are appropriate acylating agents for synthesizing a wide variety of benzophenones. Their behavior toward aromatic substrates is



Scheme 2. SZ-catalyzed acylation of anisole with (*S*)-2-methylbutyric anhydride.

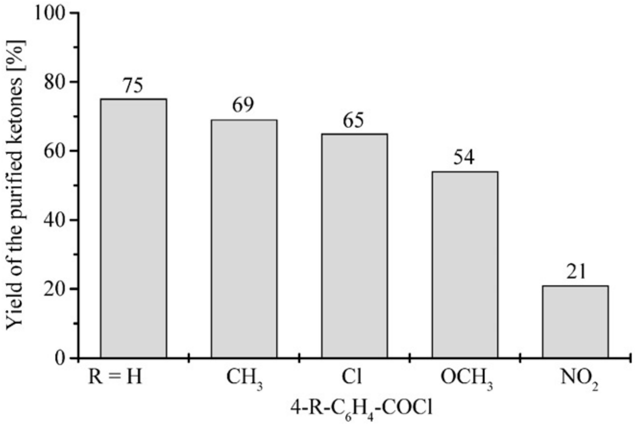


Figure 4. SZ-catalyzed acylation of anisole with 4-substituted benzoyl chlorides (4-R–C_6H_4–COCl) at 100 °C according to scheme 1 (reaction time 2 h).

Table 2

SZ-catalyzed acylation of anisole with 4-substituted benzoyl chlorides (4-R–C_6H_4–COCl) according to scheme 1 under optimized reaction conditions (reaction time 15 h)

Acylating agent 4-R–C_6H_4–COCl, R =	Reaction temperature (°C)	Yield of the resulting purified ketones (%)	Ratio 4-/2-isomer
H	100	92	96/4
CH_3	110	92	96/4
Cl	110	91	92/8
CH_3O	120	87	93/7
NO_2	140	~60 [a]	82/18

[a] Byproduct: ~4% 4-NO_2–C_6H_4–CO–OC_6H_5.

influenced strongly by functional groups in the 4- and/or 2-position. Thus, donor substituents, for example methoxy or methyl groups, favor the tendency to form more or less free benzoylium ions (deduced from IR, NMR, and X-ray investigations [30]), which are only weak electrophilic species. On the other hand, electron withdrawing substituents, for example the nitro group, suppress the dissociation of benzoyl chlorides and enhance their electrophilic power.

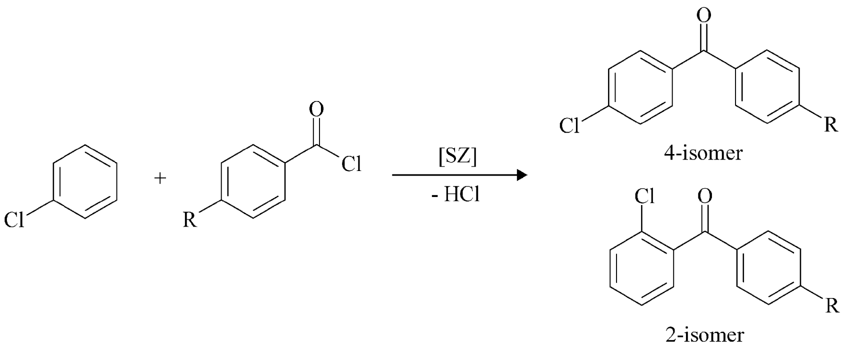
The acylation experiments over SZ using various substituted benzoyl chlorides (according to scheme 1) gave different ketone yields. The details are depicted in figure 4. In the benzoylation of anisole with benzoyl triflates (under homogeneous conditions) the reactivity decreased in the order 4-methyl- > 4-chloro- > 4-nitrobenzoyl triflate for the acylating agent [31]. Thus, the donor-substituted acid chlorides 4-methyl- and 4-methoxybenzoyl chloride were expected to be the most reactive acylating agents in the SZ-catalyzed reactions investigated. However, benzoyl chloride gave the highest ketone yield (figure 4).

The lower reactivity of 4-methoxy- and 4-methylbenzoyl chloride observed toward anisole may be due to the special conditions of heterogeneous catalysis that include adsorption and desorption processes. Thus, the reaction of substituted benzoyl chlorides could be influenced possibly by interactions of the different substituents in the acylating agent with the catalyst surface. Consequently, the adsorbed substituted benzoyl chlorides may exhibit a different reactivity order than their corresponding non-adsorbed species. To our knowledge, this question has not yet been discussed in the literature. To obtain complete conversion of the benzoyl chlorides, the reaction conditions were optimized. At higher reaction temperatures and prolonged reaction times, ketone yields of about 90% were achieved in most cases (table 2).

3.2. *Acylation of chlorobenzene*

Deactivated aromatics are commonly acylated under Friedel–Crafts conditions (equimolar amount of $AlCl_3$). Successful heterogeneously catalyzed acylation of halogen-containing aromatics is a challenge, but is still unresolved. Only a few papers have been published on chlorobenzene acylation with acylating agents of outstanding electrophilic power, like 4-nitrobenzoyl chloride over Fe-doped K-10 [32] and nafion-H [33].

In contrast to the acetylation and benzoylation of anisole, neither acetic anhydride nor benzoic anhydride, but only benzoyl chlorides reacted with chlorobenzene in the presence of SZ (scheme 3, table 3).



Scheme 3. SZ-catalyzed acylation of chlorobenzene with 4-substituted benzoyl chlorides.

Table 3
SZ-catalyzed acylation of chlorobenzene with 4-substituted benzoyl chlorides (4-R–C_6H_4–COCl) according to scheme 3 at 132 °C (catalyst amount 3.375 g, reaction time 20 h)

Acylating agent 4-R–C_6H_4–COCl, R =	Yield of the resulting purified ketones (%)	Ratio 4-/2-isomer
H	17	70/27/3 (3-isomer)
Cl	40	72/25/3 (3-isomer)
NO_2	69	93/7

The trend observed was the opposite to that reported for the SZ-catalyzed anisole benzoylations. 4-Nitrobenzoyl chloride was found to be the most active acylating agent in the chlorobenzene benzoylations. 4-Chlorobenzoyl chloride was less reactive, but is well suited for acylating the more reactive aromatic benzene [34]. Benzoyl chloride revealed the lowest reactivity. In agreement with previous papers [32,33], the benzoylation of chlorobenzene over SZ is favored by electron withdrawing substituents in the benzoyl chloride. Due to the lower reactivity of chlorobenzene, the experiments required an increased amount of catalyst.

4. Conclusions

A variety of carboxylic anhydrides and acid chlorides could be reacted with anisole over SZ as an environmentally friendly catalyst to give high yields of the corresponding aromatic ketones. The regioselectivity of the heterogeneously catalyzed anisole acylations investigated was comparable to the corresponding Friedel–Crafts reactions.

Acetic anhydride and benzoic anhydride were found to acylate the aromatic substrate significantly faster than benzoyl chloride. Thus, the reaction between anisole and carboxylic anhydrides may be performed at 55 °C, whereas the use of benzoyl chloride demands a higher temperature.

Depending on the acylating agent, various carbonaceous deposits have been observed on the surface of used SZ catalysts. Carboxylic anhydrides cause carboxylate formation due to reaction of the released carboxylic acid with zirconia. In the case of acetylation, the reaction product undergoes secondary reactions and deposits are accumulated on the catalyst surface.

SZ was proved to be an active catalyst both for reacting small as well as sterically demanding acylating agents with anisole and gave high yields of aromatic ketones. As demonstrated for (*S*)-2-methylbutyric anhydride, chiral acyl groups may be transferred to anisole under conditions of heterogeneous catalysis without racemization.

Several benzophenones can be synthesized from 4-substituted benzoyl chlorides and anisole over SZ. Depending on their substituents, 4-substituted benzoyl chlorides reveal an inverse reactivity toward anisole and chlorobenzene.

In summary, SZ is an attractive heterogeneous catalyst and can substitute stoichiometric amounts of environmentally problematic Lewis acids in numerous acylation reactions to give aromatic ketones.

Acknowledgments

The authors acknowledge financial support by the Ministry of Education and Science of the Federal Republic of Germany within the framework of the project 03C0275A. Thanks are given to M. Bartoszek, S. Bäsler, and H. Gehrmann for valuable contributions.

References

[1] F. Effenberger and G. Epple, Angew. Chem. 84 (1972) 295.
[2] F. Effenberger, E. Sohn and G. Epple, Chem. Ber. 116 (1983) 1195.
[3] I. Hachija, M. Moriwaki and S. Kobayashi, Bull. Chem. Soc. Jpn. 68 (1995) 2053.
[4] I. Hachija, M. Moriwaki and S. Kobayashi, Tetrahedron Lett. 36 (1995) 409.
[5] A. Corma, M.J. Climent, H. Garcia and J. Primo, Appl. Catal. 49 (1989).
[6] K. Gaare and D. Akporiaye, J. Mol. Catal. A 109 (1996) 177.
[7] K. Smith, Z. Zhenhua and P.K.G. Hodgson, J. Mol. Catal. A 134 (1998) 121.
[8] D. Rohan, C. Canaff, E. Fromentin and M. Guisnet, J. Catal. 177 (1998) 296.
[9] E.G. Derouane, C.J. Dillon, D. Bethell and S.B. Derouane-Abd Hamid, J. Catal. 187 (1999) 209.
[10] U. Freese, F. Heinrich and F. Roessner, Catal. Today 49 (1999) 237.
[11] T.W. Bastock, J.H. Clark, P. Landon and K. Martin, J. Chem. Res. (1994) 104.
[12] B.M. Choudary, M. Sateesh, M.L. Kantam and K.V.R. Prasad, Appl. Catal. A 171 (1998) 155.
[13] R. Selvin, B. Sivasankar and K. Rengaraj, React. Kinet. Catal. Lett. 67 (1999) 319.
[14] A. Heidekum, M.A. Harmer and W.F. Hoelderich, J. Catal. 188 (1999) 230.
[15] Y. Izumi, M. Ogawa, W. Nohara and K. Urabe, Chem. Lett. (1992) 1987.
[16] S. Kobayashi and S. Nagayama, J. Am. Chem. Soc. 120 (1998) 2985.
[17] S. Goto, M. Goto and Y. Kimura, React. Kinet. Catal. Lett. 41 (1990) 27.
[18] K. Arata and M. Hino, Appl. Catal. 59 (1990) 197.
[19] Y. Xia, W. Hua and Z. Gao, Catal. Lett. 55 (1998) 101.
[20] W. Hua, Y. Xia, Y. Yue and Z. Gao, J. Catal. 196 (2000) 104.
[21] K. Arata, H. Nakamura and M. Shouji, Appl. Catal. A 197 (2000) 213.
[22] D.H. Rammler and H.G. Khorana, J. Am. Chem. Soc. 85 (1963) 1997.
[23] V. Quaschning, J. Deutsch, P. Druska, H.-J. Niclas and E. Kemnitz, J. Catal. 177 (1998) 164.
[24] J. Deutsch, V. Quaschning, E. Kemnitz, A. Auroux, H. Ehwald and H. Lieske, Topics Catal. 13 (2000) 281.
[25] V. Quaschning, A. Auroux, J. Deutsch, H. Lieske and E. Kemnitz, J. Catal. 203 (2001) 426.
[26] L.J. Mazza and A. Guarna, Synthesis (1980) 41.

[27] A. Trunschke, J. Deutsch, D. Müller, H. Lieske, V. Quaschning and E. Kemnitz, Catal. Lett. 83 (2002) 271.

[28] B.P. Straughan, W. Moore and R. McLaughlin, Spectrochim. Acta 42A (1986) 451.

[29] A.P. Desai, I.G. Vasi and K.A. Thaker, J. Indian Chem. Soc. 47 (1970) 117.

[30] G.A. Olah, A. Germain and A.M. White, in: *Carbonium Ions*, Vol. 5, eds. G.A. Olah and P.R. Schleyer (Wiley-Interscience, New York, 1976) p. 2049.

[31] F. Effenberger, J.K. Eberhard and A.H. Maier, J. Am. Chem. Soc. 118 (1996) 12572.

[32] A. Cornelis, A. Gerstmans, P. Laszlo, A. Mathy and I. Zieba, Catal. Lett. 6 (1990) 103.

[33] G.A. Olah, R. Malhotra, S.C. Narang and J.A. Olah, Synthesis (1978) 672.

[34] G.D. Yadav and A.A. Pujari, Green Chem. 1 (1999) 69.