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Organic reactions on the surface of silicon dioxide: synthetic applications

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Abstract. The literature data on the specific features of organic reactions in the presence of silicon dioxide (predominantly in the unmodified form) and its use for synthetic purposes are analysed. Oxidation (including dry ozonisation), reduction, alkylation and acylation, halogenation, elimination, hydrolytic and dehydration reactions, intermolecular cycloaddition and other cyclisation reactions, three-membered ring opening reactions, and peroxide decomposition reactions, as well as certain photochemical reactions are considered. In the processes investigated, the surface of silicon dioxide can function as a catalyst, as a solid medium for the occurrence of reactions, and/or as a matrix influencing the stereospecificity. The bibliography includes 214 references.

I. Introduction

Silicon dioxide is one of the most important inorganic compounds used in catalytic organic synthesis. In industrial catalysis, it is employed in the vast majority of cases as a carrier for substances with more pronounced catalytic properties.[1] However, in contrast to industrial organic synthesis, in organic synthesis as a whole the role of silicon dioxide is by no means restricted to its use as a simple more or less inert carrier. Like other generally known inorganic oxides (for example, Al_2O_3), it can be used not only in industrial processes such as hydrocarbon cracking but also in many heterogeneous reactions at the laboratory scale. Such reactions frequently take place under mild conditions (< 100 °C) and their characteristic features are more selective transformations (chemo-, regio-, and stereoselective) and simplified (compared with homogeneous analogues) methods for the isolation of the final products.[2] Many specialists in the field of laboratory fine organic synthesis are known to prefer commercially available silicon dioxide (usually silica gel) to catalytic systems with a platinum metal deposited on the oxide.

Many publications describe comparative studies on series of inorganic oxides in order to find optimum conditions for reactions and the optimum yield of their products. In some cases, the composition of the oxide may not affect the process or may affect it insignificantly, i.e. the oxides (for example, silicon and aluminium oxides, pure or mixed) are 'mutually replaceable'. Here it is appropriate to refer to certain studies involving the use of aluminium oxide (pure or with deposited reagents),[3-16] silicon–aluminium oxides,[17] zeolites,[18-23] and clays[24,25] in fine organic synthesis. A number of reviews[26-33] deal with processes with participation of various oxides. However, none of them presents complete information either about the employment of SiO_2 or about other oxides (for example, in the latest review[33] devoted to silicon and aluminium oxides, only about 50 publications were covered); furthermore, the data in the majority of these studies have become obsolete.

Bearing in mind the foregoing considerations, it appears entirely justified and timely to analyse in greater detail the role of silicon dioxide in fine organic synthesis. Attention is concentrated here on reactions involving the use of unmodified commercially available silicon dioxide (as a rule silica gel), in which its surface actually exhibits a catalytic effect (or other useful properties). Examples of the employment of SiO_2 as a carrier for any other catalyst (see, for example, Refs 34–39) are not considered in detail. However, sometimes it is extremely difficult to classify silica gel as a catalyst or as an inert carrier. Furthermore, in the literature considered certain terminological inaccuracies are encountered. In particular, it has been reported[40] that iron(III) chloride deposited on silica gel is an effective 'reagent' for the rapid and selective dehydration of alcohols and also for rearrangements of the pinacol and acyloin types. The use of the term 'reagent' is apparently illegitimate because a typical case of catalysis is considered. A still more striking example of a nonrigorous terminology is provided by the title of the book[41] *Catalysis of Organic Reactions by Supported Inorganic Reagents*. Nevertheless, these terms have become established and continue to be used, sometimes admittedly with the stipulation that the expression 'supported reagent' is understood both as a reagent, i.e. a stoichiometric agent, and as a catalyst.[42]

The classification of organic reactions used below (like virtually any classification) involves an arbitrary feature, reflecting synthetic aspects which are discussed in the literature analysed. For example, although dry ozonisation reactions formally belong to oxidation processes, they have been segregated in an independent section because they are of great synthetic value and are based on an unusual experimental approach.

Finally, a characteristic feature of the vast majority of publications on this topic is a purely practical approach, in which the main task (although not the only one) is to obtain the maximum yields of the target products, and is in no way concerned with the elucidation of the mechanism of the catalytic (or any other) action of silicon dioxide in the reactions employed.

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Because of this, the present review is inevitably one-sided in a certain sense: whilst there are numerous examples of synthetic applications of organic reactions on the surface of silicon dioxide, it is at present impossible to make serious generalisations about the characteristic features of their occurrence. Thus the data presented in this review will be more useful to specialists in synthetic organic chemistry rather than those engaged in catalysis and in the chemistry of the surfaces of inorganic oxides.

II. Organic reactions carried out in the presence of silicon dioxide

1. Dry ozonisation

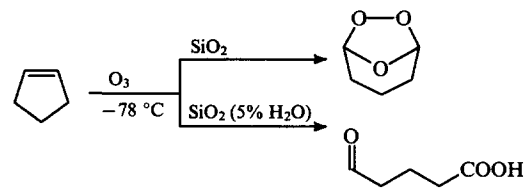
Dry ozonisation is one of the most important processes carried out in the presence of silicon dioxide and has great synthetic value because it makes it possible to introduce oxygen atoms into nonactivated C–H bonds.[43,44] Ozone is known to react slowly with saturated hydrocarbons at the C–H bonds, oxidising them to hydroxy- and keto-groups. Such insertion of oxygen takes place predominantly at tertiary carbon atoms with retention of the configuration of the substrate. However, the potential synthetic possibilities of these reactions are restricted by a number of factors, the most important of which is the low solubility of ozone in organic solvents and its high reactivity with respect to them.

These limitations can be removed by employing silica gel as the adsorbent and as the solid medium for the reaction.[45,46] The typical method proposed involves the preliminary deposition of the substrate (~1 mass%) on silica gel and the passage of a stream of ozone at −78 °C until saturation. A virtually quantitative conversion of the hydrocarbons (methyl- and dimethyl-cyclohexanes, decalins, adamantane, etc.) into the corresponding tertiary alcohols is achieved under these conditions with a virtually complete retention of the configuration of the *cis–trans* isomers and the absence of polyoxygenated products. Yet another important advantage of this method is the possibility of further stepwise oxidation of the product by repeating the ozonisation procedure. This has been demonstrated in relation to the introduction of a second hydroxy-group into monohydroxylated products (or their acyl derivatives) or in their oxidation to ketones.

According to the data of Proksch and de Meijere,[47–49] in the dry ozonisation of substituted cyclopropanes the attack by ozone is directed predominantly to the C–H groups in the α-position in the three-membered ring. This made it possible to develop a new approach to the α-functionalisation of the hydrocarbons indicated. The strained bicycloalkanes, containing a cyclopropane fragment, behaved differently under these conditions.[50] For example, the ozonisation of bicyclo[2.1.0]-pentane results in the formation of a 2 : 5 mixture of cyclopropylacetic acid and succinic dialdehyde. Comparison of the behaviour of aliphatic hydrocarbons and their cyclic analogues, led Tal et al.[51] to the conclusion that the degradation of the C–C bonds in the first case is more appreciable and the oxidative abstraction of alkyl groups results in the yields of the tertiary alcohols being lower and those of the ketones being higher.

The dry ozonisation of mono-, di-, and tri-alkyl-substituted alkenes leads to the formation of a mixture of ozonides (or polymeric peroxides) and carbonyl compounds.[52] Phenylethyl-alkenes afford almost exclusively aromatic aldehydes and ketones under these conditions, while alkynes give rise to a mixture of carbonyl and carboxy-compounds.

It has been shown in relative to the dry ozonisation of a series of alkenes adsorbed on silica gel[53] that the composition of the reaction products depends greatly on the presence of water in the system. In particular, the oxidation of cyclopentene on silica gel dehydrated beforehand affords the normal monomeric ozonide, which can be isolated in 80% yield whereas after the addition of 5% of water oxidative cleavage of the double bond takes place with formation of 5-oxopentoic acid in approximately the same yield.



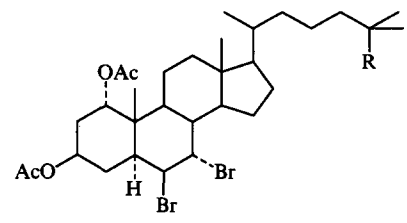
We may mention for comparison that, when the ozonisation is carried out in the usual way, the main product is a polymer.

Aromatic compounds without strong electron-accepting groups also undergo oxidative degradation under the conditions indicated.[54] For example, phenyl- and mesityl-cyclohexanes give rise to cyclohexanecarboxylic in 90% and 70% yields respectively (degrees of conversion of 95% and 90%), while tetralin affords adipic acid in 50% yield (degree of conversion 95%). The addition of 25% of water to the silica gel in the last case leads to an increase in the yield of adipic acid to 75%.

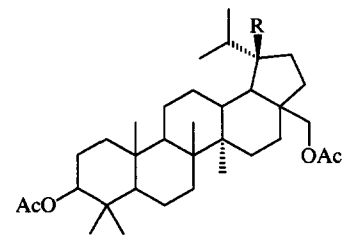
The possibility of the wide-scale employment of dry ozonisation on the silica gel surface for hydroxylation at tertiary aliphatic carbon atoms (which is particularly important in the chemistry of natural products) is limited by the reactivity to ozone of the double bond present in the molecule.

Since C–H bonds interact with ozone more slowly than C=C bonds, the latter must be protected by readily removable groups. It has been shown[55] that C–Br groups are less reactive to ozone than tertiary C–H groups, so that the bromination of the C=C bonds may be employed for protection.

Subsequently the dry ozonisation method was applied by the same investigators in the synthesis of the 1α,25-dihydroxy-derivative of vitamin D_3, for the oxidation of the dibromo-derivative **1** to the hydroxy-derivative **2** (yield 11%),[56] and also for the introduction of a functional group at the C(25) atom in other cholestane derivatives.[57] The dry ozonisation of 3β,28-diacetoxy-lupane **3** led to the 19-hydroxy-derivative **4**;[58] a mixture of 18β,19β-epoxyfriedelane **6** and the products of the oxidation of the CH_2 groups in the 19-position (compound **7**), the 15-position (compound **8**), and the 16-position (compound **9**) to the keto-groups (in 48%, 2%, 11%, and 11% yields respectively) was obtained from friedelane **5**.[59]

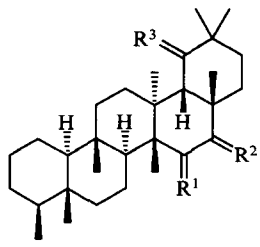


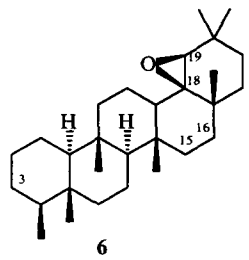
1, 2



3, 4

R = H (**1**, **3**), OH (**2**, **4**).



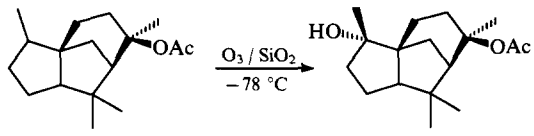


5, 7, 8, 9 6

5: $R^1 = R^2 = R^3 = H_2$; 7: $R^1 = R^2 = H_2$, $R^3 = O$;
8: $R^1 = O$, $R^2 = R^3 = H_2$; 9: $R^1 = R^3 = H_2$, $R^2 = O$.

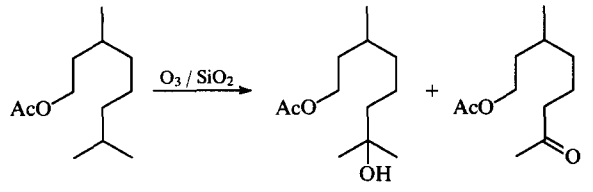
The dry ozonisation of friedelin (3-oxofriedelane) afforded analogous derivatives.[60]

This method has also been used to synthesise the hydroxy-derivative of cedrol acetate **10** and other sesquiterpenes.[61,62]



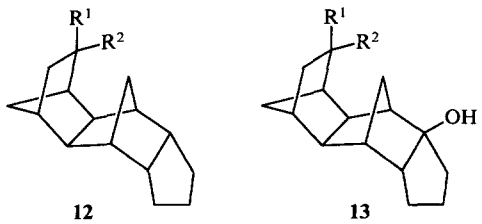
10 11

In contrast to ozonisation in solution, in the dry ozonisation of 3,7-dimethyloctyl acetate adsorbed in silica gel, the carboxy- or oxo-group is introduced predominantly in the 7-position, which is at a considerable distance from the functional group already present,[63,64] while oxidation in the 3-position is suppressed.

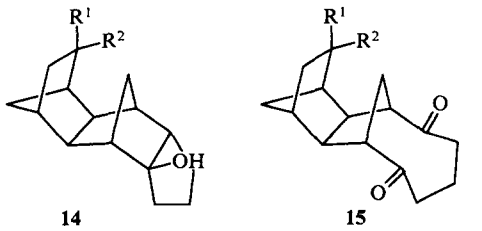


41%–69% 18%–31%

The maximum regioselectivity is attained when the initial compound is deposited on silica gel as a coating resembling a close-packed monomolecular layer. These results confirm the hypothesis that, by carrying out the reaction in adsorption layers, it is possible to increase the regioselectivity as a result of the mutual orienting effect of the substrate molecules. The ozonisation of cyclododecyl acetate under these conditions led to the formation of a mixture of its 5-, 6-, and 7-oxo-derivatives in 15%, 27%, 9% yields respectively.[65] The oxidation of the substituted cyclopentadiene trimers **12** led to the formation of the alcohols **13** and **14** and of the diketone **15**.



12 13



14 15

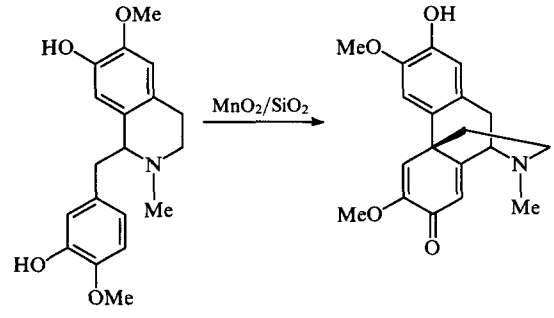
Substituents	(Yield %)		
	13	**14**	**15**
$R^1 = OAc$, $R^2 = H$	35	25	20
$R^1 + R^2 = O$	18	12	18

However, the authors[65] concluded that the proposed method of synthesis suffers from a series of disadvantages (difficulty of monitoring the course of the reactions, poor reproducibility, etc.) and subsequently modified it by introducing Freon 11 [trichlorofluoromethane (Ed. of Translation)] into the reaction medium and also by depositing the substrates on silica gel in the form of succinates to ensure their firmer fixation.[66] The advantages of the new approach were demonstrated by the authors in the ozonisation of the succinates of 6-methylheptan-2-ol, 3,7-dimethyloctanol, adamantan-2-ol, and two hydroxydecalins.

Among other reactions which take place effectively on treatment with ozone in the presence of silica gel, mention should be made of the oxidation of primary aliphatic amines to the corresponding nitro-compounds.[67] The synthesis lasts from several minutes to tens of minutes and the yields of the nitro-compounds reach 70%. The formation of more far-reaching oxidation products — ketones and carboxylic acids — is also possible, but their yields do not exceed 6%.

2. Other oxidation reactions

The use of solid inorganic oxidants in organic synthesis is limited by their insolubility in weakly polar media. This limitation can be overcome by the preliminary deposition of the oxidant on inert solid carriers, for which silica gel has been recommended among other substances. The first example of the use of SiO_2 in such reactions was the oxidation of a substituted benzyltetrahydroisoquinoline **16** by deposited manganese dioxide[68] with formation of isosalutaridine **17** (yield 4%).



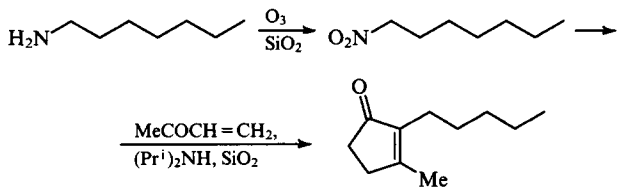
16 17

The oxidation of alcohols to aldehydes and ketones by potassium permanganate is a typical example.[69] The oxidation of benzyl alcohol to benzaldehyde,[70] of alkynes to diketones, of cyclic ketones to dicarboxylic acids, of acylated amines to acylimides, and of sulfides to sulfones,[71] as well as the conversion of ethers into lactones, of cyclic ketals into ketones, and of nitro-groups into carbonyl groups[72] on treatment with potassium and zinc permanganates have been investigated.

Chromic acid adsorbed on silica gel can also serve as a convenient reagent for the oxidation of alcohols to aldehydes and ketones in high yields (68%–90%).[73] Deposited potassium dichromate oxidises selectively benzyl alcohols and halo-derivatives to the corresponding ketones, the reactions being carried out in a neutral medium.[74] Chromic acid adsorbed on silica gel can be employed also for the synthesis of menthone from menthol (yield 96%). It has also been reported that deposited pyridinium chromate is suitable for the effective oxidation of a wide variety of secondary and primary alcohols containing labile acid groups.[75]

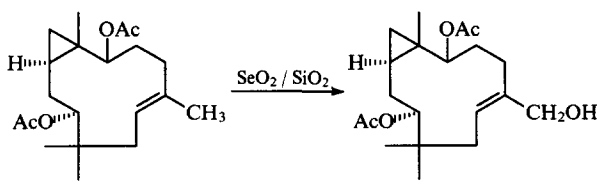
A mild method of synthesis of quinones from hydroquinones and catechols with the aid of deposited cerium(IV) and chromium(VI) salts has been described.[76] The homogeneous oxidation of 1-naphthol by cerium(IV) ammonium nitrate leads to 2,4- and 4,6-dinitro-derivatives.[77] However, the above reaction on silica gel leads to the formation of 2- and 4-nitro-1-naphthols in 42% and 38% yields respectively. Polynuclear arenes afford under these conditions the mononitro-derivatives and not quinones; for example, phenanthrene is converted into 2- and 3-nitrophenanthrenes (45% and 28%).

It is believed[78] that sodium methoxide deposited on silica gel is an ideal medium for the Nef reaction. Aldehydes and ketones may be obtained from primary and secondary nitro-compounds in yields exceeding 60%. The method has been used in the last stage of the synthesis of dihydrojasmone **18** from n-heptylamine and for the conversion of 1-(nitromethyl)cyclohexene into the corresponding aldehyde in 82% yield.[79]

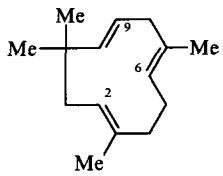


18

Among other inorganic oxidants deposited on silica gel and used in similar syntheses, mention should be made of sodium metaperiodate ($NaIO_4$, see, for example, the synthesis of quinones from hydroquinones[80]), potassium dimesoperiodate ($K_4I_2O_9$), and paraperiodic acid (H_5IO_6),[81] as well as selenium dioxide, which oxidises selectively allylmethyl groups to the corresponding primary alcohols and aldehydes.[82]

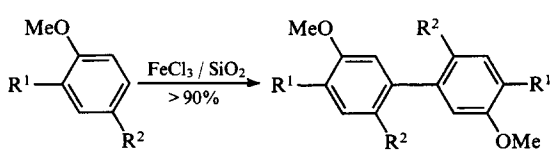


The oxidation of humulene (a sesquiterpene)



by perbenzoic acid and silver nitrate on silica gel[83] leads to the epoxidation of the double bonds in the 2,3-positions (the main product), the 6,7-positions, and the 9,10-positions; the $\Delta^{2,3},\Delta^{6,7}$-diepoxide is formed simultaneously. On the other hand, the dominant product in the homogeneous oxidation of this sesquiterpene is the $\Delta^{6,7}$-epoxide.

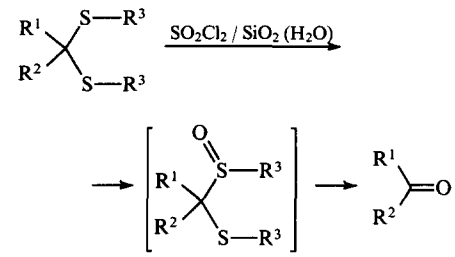
Iron(III) chloride deposited on silica gel can be used as the carrier for methoxy-substituted aromatic compounds.[84]



R^1, R^2 = Me, OMe.

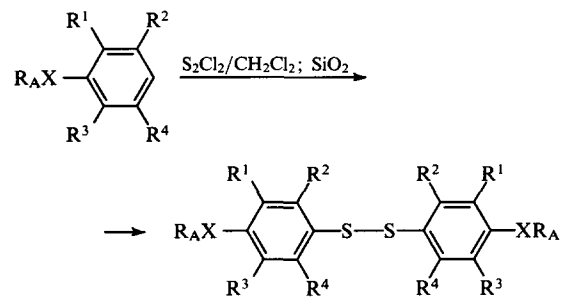
The rate of reaction increases after the complete removal of the solvent.

In a number of studies,[85-89] silica gel was regarded not as the reaction medium but as a catalyst of oxidation processes. Sulfuryl chloride is known to interact with methyl phenyl sulfide to form chloromethyl phenyl sulfide. It was found that, when reactions of this type are carried out in the presence of small amounts of moist silica gel, the corresponding sulfoxides are formed exclusively, while the chlorination of the alkyl groups is fully suppressed under these conditions.[85] The oxidation reaction takes place at room temperature in methylene dichloride; the yields of the sulfoxides exceed 80% (up to the quantitative yields for the unpurified products). When thioacetals are treated with sulfuryl chloride, the oxidative elimination of the thioacetal group takes place, the corresponding carbonyl derivatives being formed in almost quantitative yields at room temperature.[86,87]



These results[86,87] have been used to develop a convenient method of synthesis of sulfoxides and carbonyl compounds labelled with the ^{18}O isotope.[88] The source of the isotope was the water $H_2{}^{18}O$ deposited on silica gel.

The interaction of adsorbed reagents of the type RSCl, $RSCH_2Cl$, and S_2Cl_2 with aromatic compounds has been investigated.[89] For example, when durene is acted upon by chloromethyl phenyl sulfide, a ring-substitution product — phenylthiomethyldurene — is formed (28%). The reaction of S_2Cl_2 with mesitylene leads to a mixture of dimesityl sulfide (29%) and dimesityl disulfide (52%). In the analogous method of synthesis of aryl disulfides, patented by Japanese investigators,[90] the formation of sulfides is suppressed.

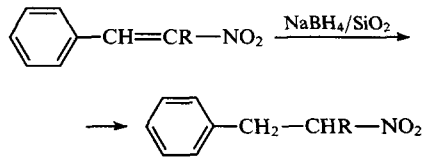


R^1, R^2, R^3, R^4 = H, Alk, AlkO; R_A = 4-BrC_6H_4; X = O, S.

For example, when X = O and $R^1 = R^2 = R^3 = R^4$ = H, the yield of the disulfide reaches 61% (25 °C, 20 h).

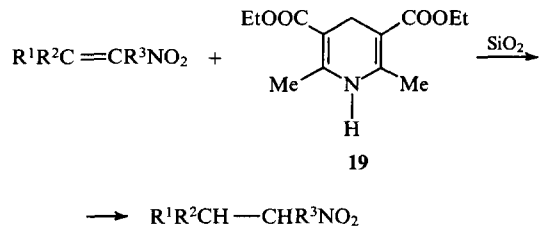
3. Reduction

The use of inorganic reagents for the reduction of organic compounds is not always possible, as in the case of solid oxidants, owing to their poor solubility in weakly polar solvents. One of the first reductants employed in the form deposited on silica gel was sodium tetrahydroborate.[91,92] Being commercially available, it proved to be extremely convenient for a wide variety of selective reactions involving the reduction of functional groups of one kind in the presence of others. However, a significant disadvantage of this reagent is its sensitivity to the presence of adsorbed water on silica gel — up to complete deactivation. An alternative stable and effective reductant proved to be tetrabutylammonium tetrahydroborate deposited on silica gel from solution in tetrahydrofuran.[93] The following reaction may serve as an example of selective reduction by tetrahydroborates on the surface of silica gel:[94]

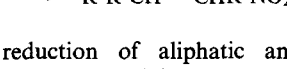


In contrast to the analogous homogeneous reaction, the formation of dimeric reduction products is almost fully suppressed under these conditions and high yields of nitroalkanes (92%–98%) are attained.

Another approach to the synthesis of nitroalkanes from nitroalkenes involves the interaction of the latter with the Hantzsch ester **19** in benzene in the presence of silica gel.[95]



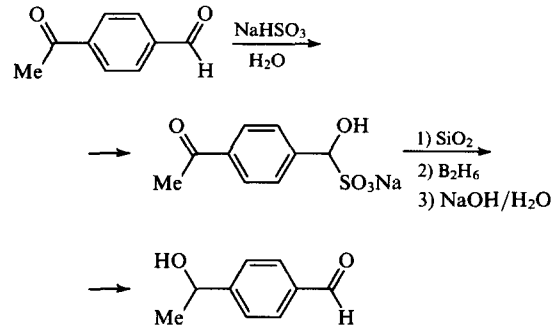
19



The reduction of aliphatic and aromatic nitroalkenes proceeds smoothly and is not accompanied by the reduction of the nitro-groups and the dimerisation of the olefinic groups. Other groups, such as the ester groups, are inert under the given conditions; only the C=C bonds conjugated with the nitro-group are reduced.

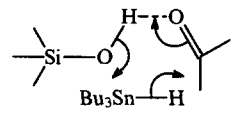
The deposition of the pyridine–borane complex on silica gel makes it possible to carry out the reduction of aldehydes and ketones under milder conditions.[96] For example, the heterogeneous reduction of benzaldehyde to benzyl alcohol in cyclohexane takes place at room temperature and is completed after 45 min with a yield in excess of 95%, whereas in the homogeneous system is takes place on refluxing in toluene or benzene and the yields are by no means always satisfactory.

The use of sodium bisulfite as the protecting agent for aldehyde groups and of silica gel as a solid matrix made it possible to carry out the selective reduction of 4-acetylbenzaldehyde.[97,98]



4-(1-Hydroxyethyl)benzaldehyde is formed with a selectivity of 70%–93% [4-acetylbenzyl alcohol and 1-(4-hydroxymethylphenyl)ethanol are minor products]. Positive results were also achieved when Al_2O_3 was used as the carrier. 4-Acetylbenzophenone was reduced in accordance with a similar scheme to 4-acetyl-α-phenylbenzyl alcohol with a selectivity of 80%.[99,100] (Carboxymethyl)trimethylammonium chloride hydrazide (the Girard reagent T) and lithium tri(*tert*-butoxy)hydroaluminate served as the protecting and reducing agents respectively.

The silica gel-catalysed reduction of aldehydes and ketones by tributyltin hydride is characterised by a high selectivity, but the yields of the corresponding alcohols vary from 69% to 94% under these conditions.[101] According to the authors,[101] the advantages of this method are simplicity, relatively mild conditions, and the absence of the need to neutralise the alkoxide salts, as well as the possibility of the selective reduction of aldehydes in the presence of ketones. One of the most probable mechanisms of the process involves the formation of a six-centre transition state:



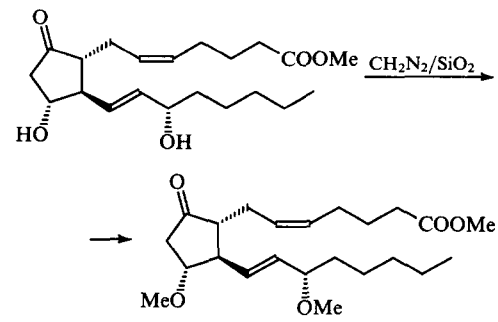
The cyano- and nitro-groups are not reduced by lithium tetrahydroaluminate on silica gel, in contrast to the reaction in the homogeneous system. This feature has been used[102] for the selective reduction of ketones and esters containing the above groups to the corresponding cyano- and nitro-alcohols, which were obtained in 54%–82% yields. Methyl *p*-nitrophenyl sulfoxide was reduced similarly to the nitrosulfide (yield 73%).

The use of lithium tetrahydroaluminate deposited on silica gel for the reduction of aldehydes, ketones, and carboxylic acid chlorides and esters in nonpolar solvents (hexane, benzene) has been considered.[103,104] For the compounds of the first three classes, the process is rapid at room temperature, whereas esters are more inert and their reduction requires the heating of the reaction mixture. Because of these differences in the reactivities, the selective reduction of ketoesters to hydroxyesters is possible (the yields in different syntheses vary from 62% to 100%).

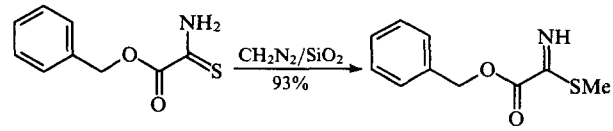
Silica gel treated beforehand with thionyl chloride has been used to reduce sulfoxides to sulfides.[105] The reaction occurred at room temperature for 10 min in CCl_4 or CH_2Cl_2.

4. Alkylation and acylation

In contrast to carboxylic acids, alcohols and phenols are difficult to methylate by diazomethane because of the low acidity of the OH groups. However, following adsorption on inorganic oxides, the acidity of these groups increases appreciably. Because of this, it has been possible to obtain ethers in quantitative yields from aliphatic alcohols and phenols adsorbed on silica gel by treatment of the latter with gaseous diazomethane.[106] The authors showed that, in the methylation of 1-decanol, Al_2O_3, a type NaY zeolite, and other similar carriers exhibit a comparatively weak catalytic effect. Polyhydric alcohols, including prostaglandins and carbohydrates, can also be used as the substrates.[107] For example, treatment of prostaglandins with a large excess of diazomethane makes it possible to obtain the corresponding diesters in quantitative yields.



The methylation of lactams and acyclic amides by diazomethane in the presence of silica gel also proceeds effectively.[108] The thioamide groups are methylated more readily than the amide groups, which may be used to carry out a selective reaction of the type



A simpler procedure has been used for the acetylation of phenols[109] and aliphatic (including secondary and tertiary) alcohols by ketene.[110] Apart from silica gel, aluminium, zinc, and magnesium oxides exhibited a high catalytic activity (the yields of the esters were 70%–91%).

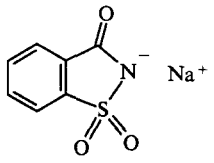
Adsorption on silica gel (and also on aluminium oxide) makes it possible to carry out selectively the monoalkylation of malonic ester anions by 1,5-dibromopentane in the presence of sodium methoxide.[111]

$$CH_2(COOMe)_2 + Br(CH_2)_5Br \xrightarrow{MeONa/SiO_2} Br(CH_2)_5CH(COOMe)_2$$

The reaction takes place at room temperature, but is fairly slow: the attainment of a satisfactory (28%–52%) yield of the product requires up to 13 days.

It has been shown[112] that silica gel is an effective catalyst for the alkylation of phenols by *tert*-butyl bromide. 2-*tert*-Butyl-, 2,6-di-*tert*-butyl-, and 2,4,6-tri-*tert*-butyl-phenols, which are difficult to obtain directly by the Friedel–Crafts reaction, can be synthesised readily by this procedure. $Et(Me_2)CBr$, *p*-$TolCH_2Cl$, $H_2C{=}CH-CHMeCl$, and $MeOCH_2Cl$ can also be used as the alkyl halides; thiophene, benzothiophene, furan, and 1-methylindole can serve as the aromatic substrates. The yields of the alkylation products vary in the range 6%–98% under these conditions.

The alkylation of saccharin



by benzyl, allyl, and hexadecyl bromides, benzyl chloride, and similar reagents has been carried out on silica gel (and also on aluminium oxide) in a microwave oven.[113] Depending on the nature of the alkylating agent, the reaction terminated after 1–10 min and the yields were 21%–91%.

The *N*-alkylation of pyrazoles by alcohols or ethers proceeds effectively on silicon, aluminium, titanium, and zirconium oxides at 200–500 °C.[114] For example, the interaction of 3,5-diphenylpyrazole and methanol results in the formation of 1-methyl-3,5-diphenylpyrazole in 96% yield.

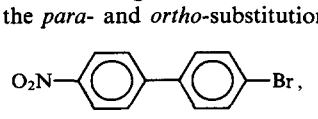
5. Halogenation

According to the results of Stoldt and Turk,[115] when cyclohexene is brominated on silica gel in the absence of solvents, the formation of only *trans*-1,2-dibromocyclohexane is observed. Diethyl fumarate, in which the olefinic function is deactivated, is also effectively brominated under these conditions, the reaction being fully stereospecific and leading exclusively to the *trans*-adduct — *meso*-diethyl 2,3-dibromosuccinate.

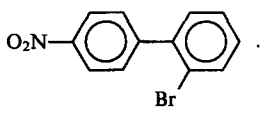
The chlorination of adamantane and other hydrocarbons adsorbed on silica gel by molecular chlorine and sulfuryl chloride has also been studied.[116] In all cases, products involving bridgehead chlorination were obtained in high yields.[116]

Under 'dry' conditions, the process takes place more effectively and selectively than, for example, in the presence of dichloromethane or under homogeneous conditions.

The bromination of biphenyl, 4-bromobiphenyl, and 4-nitrobiphenyl deposited on silica gel by gaseous bromine has been investigated.[117] The ratios of the yields of the products of the *para*- and *ortho*-substitution, for example



and



proved close to those obtained for the reaction carried out in a homogeneous system (~4:1). A control experiment involving biphenyl showed that the reaction does not occur in CCl_4 in the absence of silica gel.

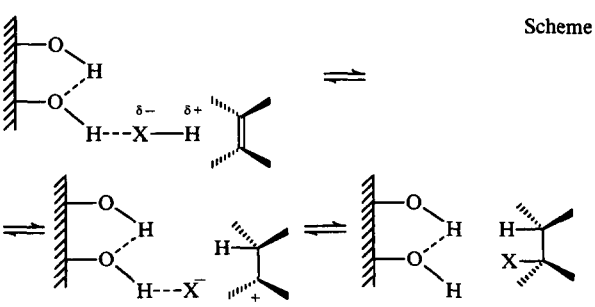
When alkylbenzenes are treated with sulfuryl chloride in the presence of silica gel, preferential substitution in the aromatic ring is observed (whereas in the absence of the catalyst, the chlorination takes place either in the alkyl substituents or does not occur at all).[118] Similar results have been obtained by Yaroslavksy.[119]

A series of studies[120–123] have been devoted to the catalytic introduction of halogen atoms into an aromatic ring. In particular, it has been established[120] that the chlorination of toluene by dichloramine T in the presence of silica gel takes place under very mild conditions (CCl_4, 25 °C) with formation of a mixture of the *o*- and *p*-isomers (65% and 35% respectively). Only fairly acid forms of silicon dioxide, for which the pH of a 10% aqueous suspension did not exceed 5, exhibited catalytic properties in these reactions. The activity increased after preliminary dehydration.[121]

The chlorination of naphthalene by *tert*-butyl hypochlorite (CCl_4, room temperature) leads preferentially to 1-chloronaphthalene (93%), while the chlorination of alkylbenzenes and anisole affords a mixture of the *o*- and *p*-isomers in proportions typical for the usual homogeneous methods of synthesis. Depending on the amount of the brominating agent, the bromination of scatole by *N*-bromosuccinimide (CH_2Cl_2, 30 min) leads to the formation of 2-bromo- or 2,6-dibromoscatole (the substitution in the ring of 2-methyl- and 3-cyanomethylindoles takes place in the same way); the analogous reaction with benzimidazole affords 2-bromo- or 2,5-dibromo-benzimidazole, while the reaction with 2-methylbenzimidazole gives rise to only the 5-bromo-substituted product.[122] The same method has been used to brominate carbazole, where it is possible to introduce up to four bromine atoms into the ring.[123] It is of interest that in the case of *N*-ethylcarbazole the process stops at the stage involving the formation of the tribromo-derivative.

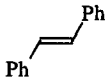
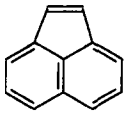
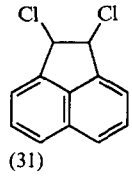
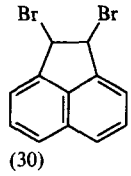
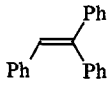
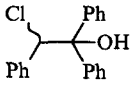
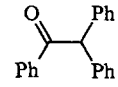
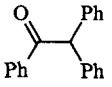
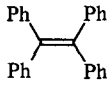
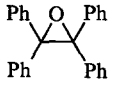
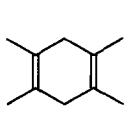
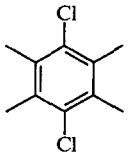
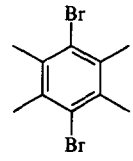
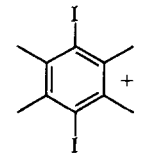
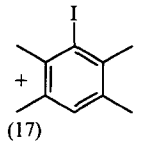
The addition of the hydrogen halides (HCl, HBr, and HI) to alkenes (cycloheptene, oct-1-ene, pinene, etc.), catalysed by silicon and aluminium oxides, has been investigated in detail.[124,125] The best medium for the reactions proved to be methylene dichloride and diethyl ether, the catalysts exhibiting the maximum activity after preliminary exposure to air at 120 °C until the attainment of equilibrium with atmospheric moisture, promoting more complete hydroxylation of the surface. Bearing in mind that the addition reaction results as a rule in the formation of products with the *cis*-configuration, the authors[124,125] proposed the most probable mechanism of the catalytic reaction, according to which the adsorption of the molecules of the hydrogen halide on the acid hydroxy-groups of the surface results in the polarisation of the X–H bond and in the protonation of the alkene with subsequent rapid transfer of the anion X^- (Scheme 1).

Scheme 1



An interesting example of solid-phase tribochemical reactions is the interaction of aryl-substituted alkenes and alkynes with iodosobenzene described by Sohmiya et al.[126] The silica gel with the adsorbed hydrogen halide (HCl, HBr, or HI), the alkene (or alkyne), and iodosobenzene were placed in a mortar and ground with a pestle at room temperature for 5 min. The substrates employed, the products and their yields, are presented in Table 1.

Table 1. The products of the tribochemical reactions of solid alkenes and diphenylethyne with adsorbed hydrogen halides and iodosobenzene (according to the data of Sohmiya et al.[126])

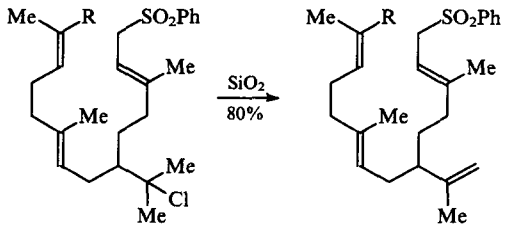
Substrate	Products [yield (%)]		
	HCl	HBr	HI
	 (65)	 (39)	 (>5)
	 (58)	 (58)	[a]
	 (31)	 (30)	[a]
	 (74)	 (51)	 (<6)
	 (66)	 (47)	 (58)
	 (82)	[a]	[a]
	 (60)	 (50)	 (12)
			 (17)

[a] The adducts were absent or their composition had not been established.

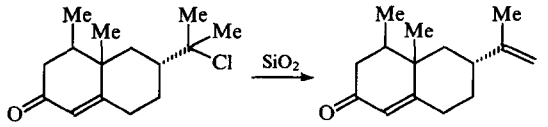
Attempts to carry out the reaction without the mechanochemical treatment were unsuccessful. Having established (for the reaction of *trans*-1,2-diphenyl- and 1,2,3,4-tetraphenylethene with adsorbed HCl) that the presence (absence) of water on the surface hardly affects the halogenation reaction, the authors[126] concluded that the reaction medium is provided directly by the silica gel surface.

6. Elimination

When the chloro-derivatives **20** and **22** are kept in the presence of silica gel, selective dehydrochlorination to give the isopropenyl derivatives **21** and **23** respectively takes place.[127,128]



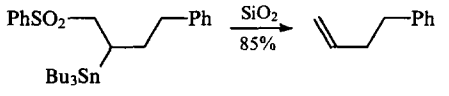
20 **21**



22 **23**

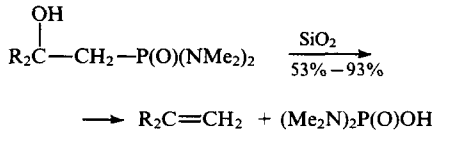
When the elimination reaction is carried out using other reagents, products containing admixtures of the isopropylidene isomers are formed.

The use of silica gel for the removal of trialkylstannyl groups in the last stage of the synthesis of alkenes by the desulfonylation of α,β-unsaturated sulfones has been reported.[129-132]



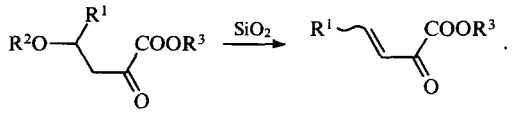
The β-elimination reaction,[129] the vinyl cyclisation of enynes,[130,131] and the methylenation of ketones[132] may serve as examples.

The phosphonamide approach to the synthesis of alkenes[133] includes as the final stage the elimination of phosphoric acid bisdimethylamide from the corresponding amides of β-hydroxyalkylphosphonic acids on refluxing their benzene or toluene solutions in the presence of silica gel.



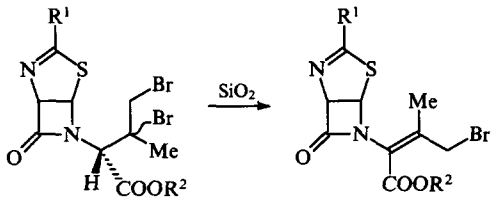
According to the authors,[133] this method is general.

A procedure for the synthesis of β,γ-unsaturated α-ketoesters in accordance with the following scheme has been patented:[134]



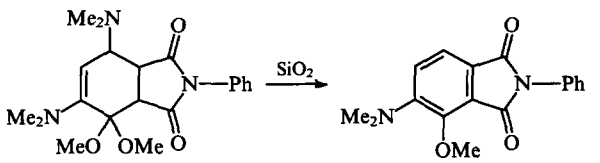
For example, when R^1 = Ph, R^2 = Me, and R^3 = Et, refluxing in benzene for 1 h leads to the corresponding α-ketoester in 92% yield.

The dehydrobromination of the intermediates in the synthesis of derivatives of antibiotics of the cephem group by chromatography on a silica gel column has been reported.[135]

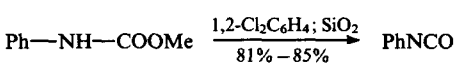


R^1 = $PhOCH_2$, Ph, Bu^t, p-$BrC_6H_4OCH_2$;
R^2 = Me, Ph_2CH.

The silica gel-catalysed elimination of Me_2N and MeO groups described by Gompper and Sobotta[136] required more severe conditions — heating to a temperature >110 °C (the yield was quantitative).

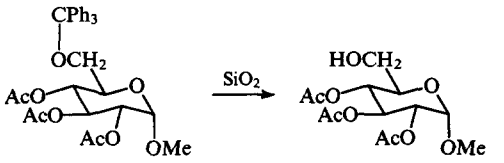


Finally, mention should be made of the synthesis of phenyl isocyanate by the thermal decomposition of methyl *N*-phenylcarbamate (elimination of MeOH).[137]



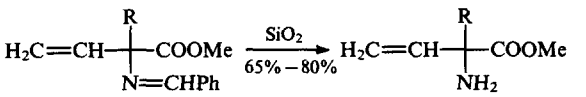
7. Hydrolysis and dehydration

The removal of the trityl protecting group in the synthesis of carbohydrates, reported by Lehrfeld,[138] is virtually the first example of the use of silica gel as a catalyst for hydrolytic processes.

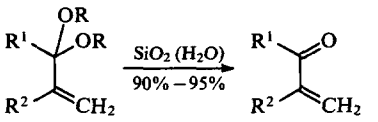


The hydrolysis was carried out by keeping a benzene solution of the initial compound on the chromatographic column for 16 h at room temperature. The yield of the purified detritylated product was 81%.

The hydrolysis of Schiff bases by chromatography on silica gel has been used in the synthesis of α-vinyl-substituted derivatives of valine, serine, histidine, tyrosine, and other aminoacids.[139]

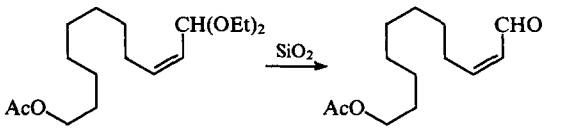


Moist silica gel has been used in the synthesis of alkenes for the removal of the ketal protecting group from the products of the reactions of α-ketoketals with Wittig reagents.[140]



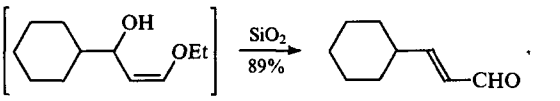
α-Cyclopropylideneketones can be obtained by the same procedure.[141]

The hydrolysis of the diethyl acetals of (*Z*)-α,β-unsaturated aldehydes in the presence of moist silica gel as the catalyst (two days at 23 °C) affords the corresponding (*Z*)-unsaturated aldehydes[142] in 47%–98% yields.

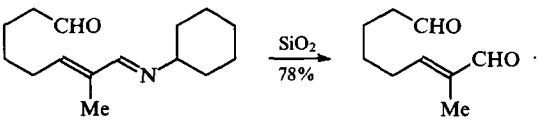


The product usually contains an admixture of the (*E*)-isomer (4%–14%) formed as a result of isomerisation. Other examples of the silica gel-catalysed hydrolysis of acetals have also been described.[143]

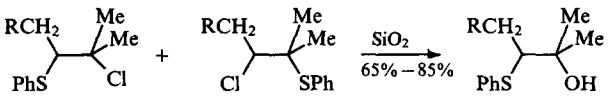
α,β-Unsaturated aldehydes are likewise formed when enol ethers — labile products of the reactions of aldehydes and ketones with (*Z*)-2-ethoxyvinyllithium — are chromatographed on silica gel,[144,145] i.e.



and also when the corresponding aldimines are passed through moist silica gel:[146]

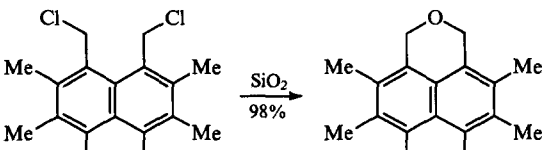


The addition of benzenesulfenyl chloride to isoprenoid compounds at the terminal isopropylidene groups can be used, for example, for the hydroxylation of these substrates. The mixtures of the regioisomers **24** and **25**, formed as intermediates, do not require separation when they are converted into the β-hydroxysulfide **26** in the presence of silica gel.[147]



24 **25** **26**

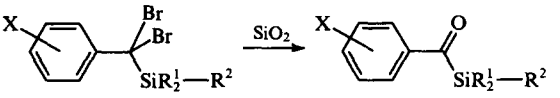
The chromatography of 1,8-di(chloromethyl)-2,3,4,5,6,7-hexamethylnaphthalene **27** on silica gel affords the ether **28** in an almost quantitative yield.[148]



27 **28**

The diether is formed similarly in 84% yield from 1,4,5,8-tetra(chloromethyl)-2,3,6,7-tetramethylnaphthalene.

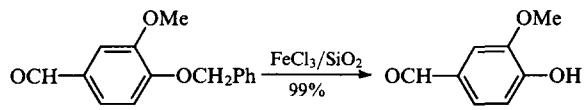
Acylsilanes may be synthesised in high yields by moderate heating (50 °C) of substituted α,α-dibromobenzylsilanes with silica gel in the absence of solvents.[149]



X = H, p-Cl, m-Cl; R^1, R^2 = Me, Ph, m-ClC_6H_4.

The authors[149] noted the importance of the degree of hydration of the silica gel; for example, the reaction was appreciably retarded when the silica gel had been dehydrated beforehand for 48 h at 200 °C. When aluminium oxide was employed, the rate of reaction was also comparatively low.

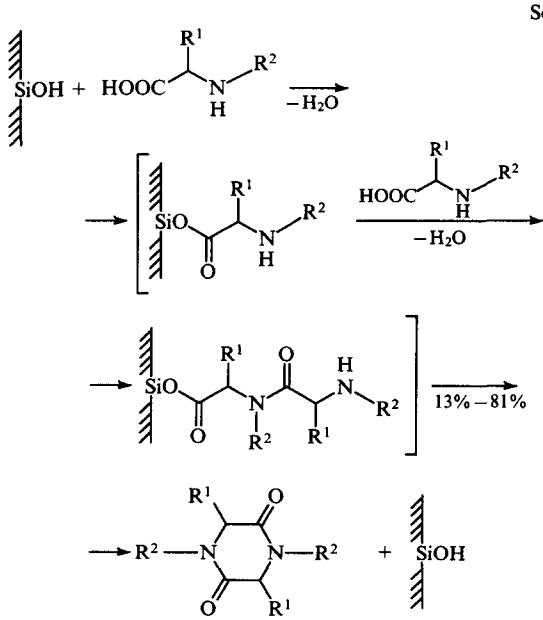
Iron(III) colloids deposited on silica gel can likewise catalyse certain hydrolytic reactions.[84]



The conversion of acetic acid into the amide by treatment with gaseous n-butylamine (200 °C in a stream of nitrogen) may be quoted as the simplest example of SiO_2-catalysed nucleophilic substitution,[150] but the yield of the amide in the presence of silica gel (87%) is lower than in the case where zirconium, titanium, and tin oxides are employed.

It has been established that carboxylic γ-, δ-, and ε-aminoacids are readily cyclodehydrated to the corresponding lactams on refluxing in toluene in the presence of silica gel or aluminium oxide.[151] In most cases their yields exceed 70%, quantitative yields being attained sometimes. For the optically active aminoacids (glutamic acid, lysine, and ornithine), appreciable racemisation is observed. The 'gas–solid phase' synthesis of 2,5-dioxopiperazines from aminoacids is similar in its essential chemical features.[153,152] It has been shown that aliphatic bifunctional aminoacids and proline undergo cyclodimerisation on sublimation in the presence of SiO_2 (170–220 °C) to cyclic dipeptides in 13%–81% yields (silochrome—a silica gel analogue obtained by the hydrothermal treatment of pyrogenic silicon dioxide—was used in the above studies). It has been suggested that the process mechanism involves the condensation of the carboxy-groups of the substrate and the surface silanol groups; the ester-type activated intermediate arising under these conditions is capable of condensing with the next aminoacid molecule attacking from the gas phase. The resulting dipeptide, chemically bound to the silicon dioxide, is readily split off from the surface, affording the corresponding symmetrical 2,5-diketopiperazine (Scheme 2).

Scheme 2

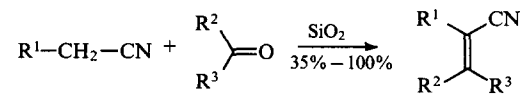


R^1 = H, Me, Bu^s, Pr^i; R^2 = H;
R^1, R^2 = $-(CH_2)_3-$

It is of interest that, despite the fairly severe thermal conditions, appreciable racemisation of the aminoacid residues is not observed. On the grounds that the intermediates are surface-bound dipeptides (see Scheme 2), the authors[154] suggested that simple linear dipeptides can also be used as the initial reactants. Such modification of the 'gas–solid phase' method makes it possible to synthesise both symmetrical and asymmetric diketopeperazines in 40%–82% yields.

The synthesis of lactones with different ring sizes by the intramolecular cyclisation of carboxylic hydroxyacids has been patented.[155]

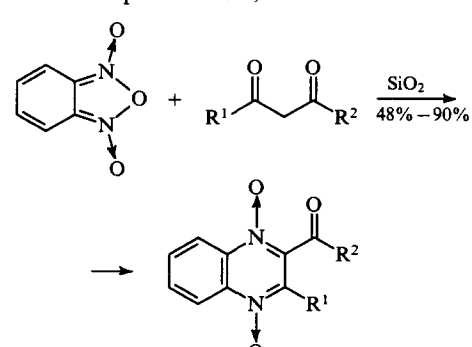
The reactions of carbonyl compounds with substrates containing an activated methylene unit (the Knoevenagel condensation) is accelerated in the presence of silica gel.[156]



R^1 = NC, O_2N, PhCO, *N*-Ac-L-Phe, *N*-Ac-L-Leu-L-Phe, *N*-Ac-L-Leu-D-Phe;
R^2 = H, Me; R^3 = Me, $HOCH_2$, HO(Me)CH, Ph, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 4-$O_2NC_6H_4$, 2-$HOOCC_6H_4$, 3-MeO(4-HO)C_6H_3;
R^2, R^3 = $-(CH_2)_4-$, $-(CH_2)_5-$.

The interaction takes place when the reactants and the catalyst are mixed in methylene dichloride and lasts from 13 to 72 h. A necessary condition for the success of the synthesis is the presence of two strongly electron-accepting substituents in the methylene component.

The reaction of benzofuroxan with 1,3-dicarbonyl compounds on the silica gel surface leads to the formation of 2,3-disubstituted quinoxaline 1,4-bisoxides.[157]

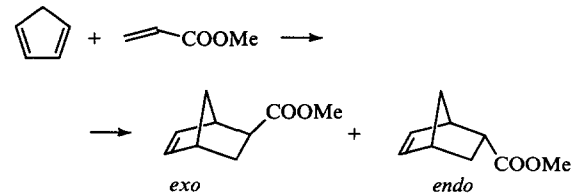


R^1, R^2 = Me, OMe, Ph, etc.

The reaction takes place in the absence of solvents for 1–2 weeks at room temperature. Its effectiveness depends on the acidity of the silica gel: more acid forms have better catalytic properties. The use of aluminium oxide gives rise to less satisfactory results, in particular, the formation of side products is observed.

8. Intermolecular cycloaddition reactions

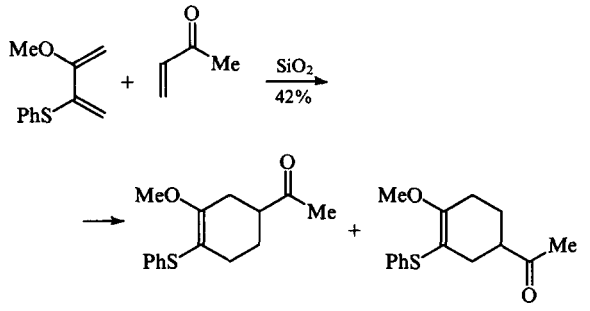
The Diels–Alder addition of the type



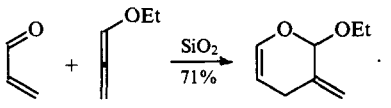
in the absence of a catalyst leads to a ~1 : 3 mixture of the *exo*- and *endo*-adducts. The adsorption of the dienophile on the SiO_2 surface makes it possible to alter their relative yields (10.5% and 87.5%); even better results are achieved when aluminium oxide is employed (2.9% and 93.7%).[158]

The Diels–Alder reaction between 1-acetoxybuta-1,3-diene and tetrafluoro-*p*-benzoquinone with formation of 5-acetoxy-2,3,4a,8a-tetrafluoro-4a,5,8,8a-tetrahydro-1,4-naphthoquinone on a silica gel column takes place at room temperature and is completed after 60 h,[159] whereas in the absence of a catalyst refluxing of the reactants in benzene is needed. The addition of *p*-benzoquinone as the dienophile takes place similarly, but the adduct eliminates acetic acid and the resulting dihydro-intermediate is dehydrogenated by the benzoquinone to 1,4-naphthoquinone (yield 87%).

The adsorption of a mixture of 2-methoxy-3-phenylthiobuta-1,3-diene and methyl vinyl ketone on the silica gel surface without a solvent and subsequent maintenance of the reactants for 24 h at room temperature lead to the formation of a mixture of adducts.[160]

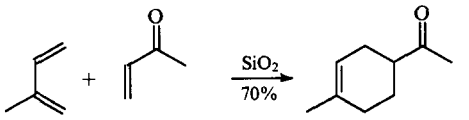


The Diels–Alder cycloaddition of 1-ethoxypropa-1,2-diene to α,β-unsaturated carbonyl compounds proceeds especially effectively on the silica gel surface in the absence of solvents.[161] High yields are attained under relatively mild conditions (50–70 °C, 1–15 h). The following reaction may be quoted as an example:



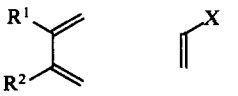
Since the dihydropyrans formed tend to polymerise on the acid centres of the surface of silicon dioxide, the latter was deactivated beforehand by treatment with triethylamine.

A similar approach in carrying out the [4+2]-cycloaddition reaction has been used by Vesselovskii and coworkers.[162,163] Depending on the nature of the diene component (butadienes, cyclopentadiene, furan, etc.) and the dienophile (methyl vinyl ketone, acrolein, methacrolein, crotonaldehyde, and ethyl vinyl ether), the synthesis was carried out at temperatures from −20 to 100 °C and lasted 0.5–14 h. For example, the cycloaddition



took place at room temperature. In an attempt to account for the mechanism of the promotion of the reaction, the authors postulated that adsorption may facilitate the formation (and possibly the stabilisation) of the prereaction complexes between the functional groups firmly fixed on the active surface centres; under these conditions, the absence of a solvent is a favourable factor.

Vesselovskii et al.[164] used chromatographic silica gel, dried beforehand at 200 °C, as the catalyst of the Diels–Alder reactions and other [4+2]-cycloaddition reactions involving substituted butadienes **29**, cyclopentadiene, and cyclohexadiene, as well as the dienophiles **30**.

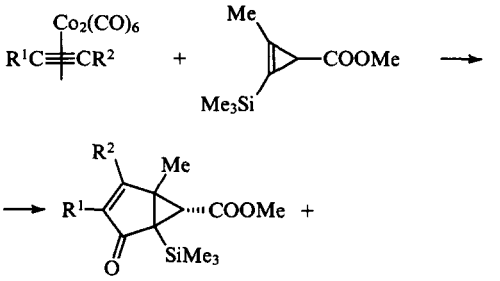


29 **30**

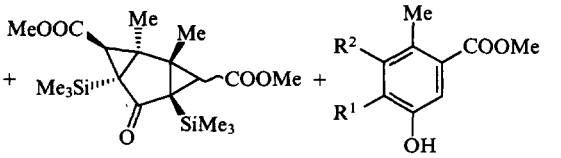
$R^1 = R^2 = H$, Me;
$R^1 = H$, R^2 = Me, $Me_2C{=}CH(CH_2)_2$;
X = CHO, COMe, COOMe.

The adducts were formed stereoselectively with yields up to 92%.

The [2+2+1]-cycloaddition reactions involving cyclopropenes and ethynecobalt hexacarbonyl complexes, described by Kireev et al.,[165] lead to a mixture of three products.



31

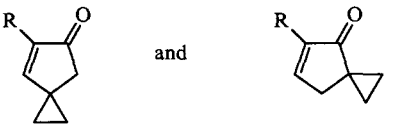


32

$R^1 = R^2 = H$, Me;
R^1 = Ph, R^2 = H.

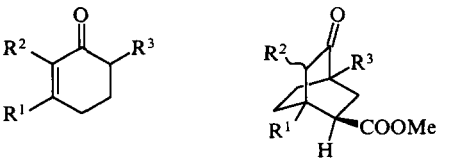
When silica gel was used as the catalyst of this reaction, the product **31** was found to predominate, whereas in the presence of the NaX zeolite mainly compound **32** was formed.

The silicon dioxide-catalysed Khand–Pauson addition[166] of methylenecyclopropane to ethyne and its methyl-, phenyl-, and cyclopropyl-substituted derivatives leads to a mixture of two products, viz.



in proportions of (4.4.–6):1. The addition of methylenecyclobutane proceeds similarly.[167]

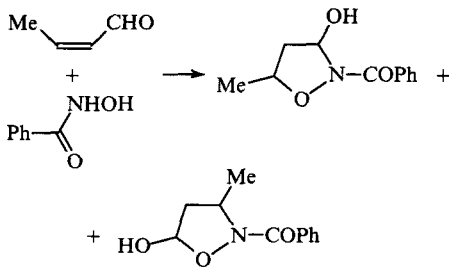
The regio- and stereo-selective Michael addition of methyl acrylate to the cyclohexenone derivatives **33** with subsequent silylation in situ and cyclocondensation in the presence of silica gel at room temperature results in the formation of the bicyclooctanone derivatives **34**.[168,169]



33 **34**

R^1 = H, Me, OMe, Bu, $CH{=}CH_2$;
R^2, R^3 = H, Me.

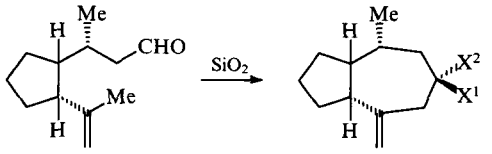
The reaction of phenylhydroxamic acid with crotonaldehyde in methanol leads to a mixture of *N*-substituted 3- and 5-hydroxyisoxazolidines.



The dominant product is the first isomer. The rate of this reaction increases significantly when it is carried out on an adsorbent without a solvent.[170] Best results were obtained when silica gel was employed: the reaction was completed in 30–40 min with the exclusive formation of the 3-hydroxy-derivative (yield 80%–90%).

9. Other cyclisation reactions

Silica gel may serve as an effective catalyst of the cyclisation of unsaturated carbonyl compounds. The cyclisation at atmospheric pressure was investigated in early studies.[171–173] For example, chromatography on a silica gel column proved to be the simplest procedure for the cyclisation of the aldehyde **35** and its stereoisomers to the epimeric bicyclic alcohols **36**,[173] whereas the analogous reaction in a homogeneous system required the treatment of the aldehydes with tin(IV) chloride in benzene.

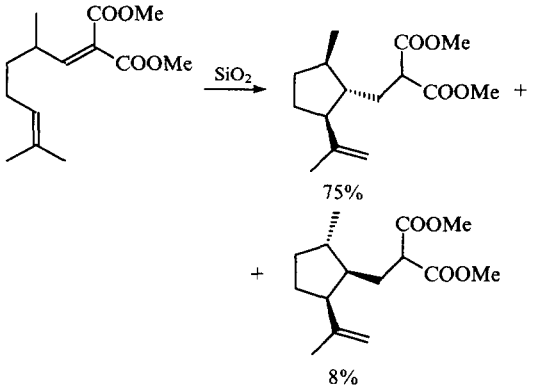


35 **36**

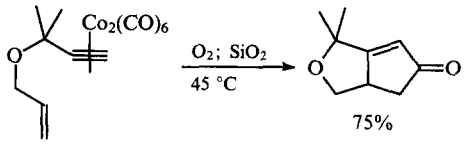
X^1 = H, X^2 = OH (86%);
X^1 = OH, X^2 = H (2%).

It has been shown in the syntheses of a series of five- and six-membered carbocycles that the effectiveness of the process increases significantly when it is carried out under a pressure of 15 kbar (solutions in methylene dichloride, 1.5–53 h, 25–60 °C). In individual instances, a fairly high stereoselectivity was noted.

The thermolysis of the adsorbed substrate in a stream of

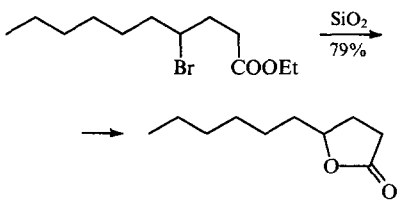


oxygen has been proposed as a general method for the promotion of the Khand–Pauson cyclisation of dicobalt hexacarbonyl complexes of allyl propargyl ethers to derivatives of 3-oxabicyclo[3.3.0]oct-5-en-7-one.[175–177]



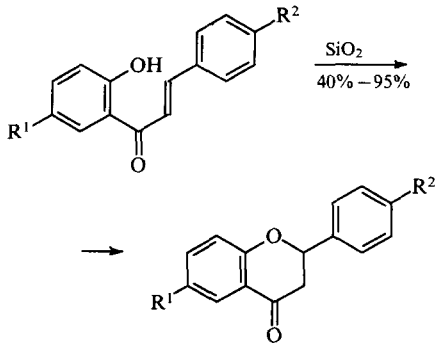
The reactions were completed in 30 min and the yields of the products were 46%–92%. Apart from silica gel, aluminium oxide may be used with different degrees of success and it has therefore been concluded[175–177] that the promoting effect should not be attributed to the specific surface properties of the oxides. The adsorption process itself probably influences the conformation of the initial compound: the attraction of the ether groups to the polar surface centres and the simultaneous repulsion from them of the hydrophobic fragments promote the mutual approach of the latter and a lowering of the entropy barrier.

The lactonisation of γ-haloethers on refluxing them in xylene for 3–15 h has been described (yields greater than 60%).[178]



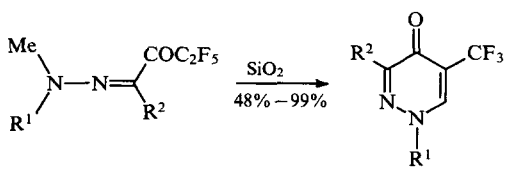
Bis-γ-butyrolactones can also be obtained by this procedure.

The intramolecular cyclisation of 2′-hydroxychalcones in the presence of silica gel (and also of ethylenediamine or the hydrochloride of hydroxylamine) affords flavones.[179]



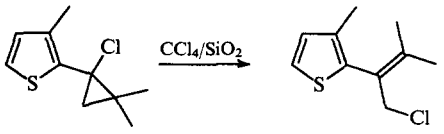
R^1 = H, Me, Cl; R^2 = H, MeO.

The cyclisation of 1,1,1,2,2-pentafluoroalkane-3,4-dione 4-dialkylhydrazones on silica gel (70–90 °C, 6–48 h) is a convenient method of synthesis for 5-(trifluoromethyl)-4-pyridazinones.[180]

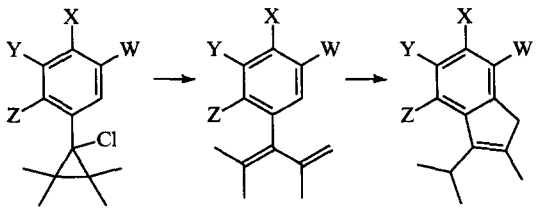


10. The opening of three-membered rings

The opening of the ring in chlorocyclopropanes in the presence of silicon dioxide, leading to the formation of dienes or allyl halides, has been investigated.[181–183]



On the other hand, in the case of 1-aryl-1-chloro-2-methylcyclopropanes **37**, silica gel in carbon tetrachloride catalyses the tandem opening of the three-membered ring accompanied by cyclisation to the indenes **39**.[184]

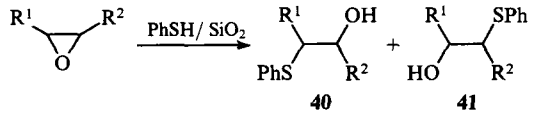


37 **38** **39**

W, X, Y, Z = H, OMe, etc.

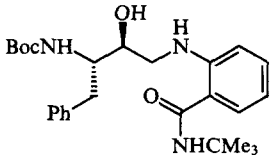
The reaction proceeds at room temperature for 18 h (yields 63%–100%) and in some cases stops at the stage involving the formation of the intermediate dienes **38**, which may be isolated in 33%–90% yields.

The opening of epoxide rings on treatment with thiophenol in the presence of silica gel leads to the α- and β-adducts **40** and **41**.[185–187] In the case of α,β-epoxysilanes, the reaction takes place regioselectively and the isomers **40** are formed in 72%–98% yields.



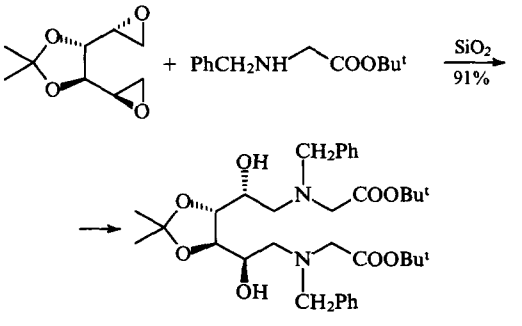
40 **41**

The formation of intermediates of the type



via the silica gel catalysed aminolysis of epoxides by anthranilic acid derivatives was the key stage in the synthesis of new inhibitors of HIV proteases.[188]

The aminolysis of certain epoxides by *tert*-butyl *N*-benzylglycinate in the presence of silica gel as the acid catalyst has been used as a convenient method of synthesis of the corresponding *N*-(β-hydroxyalkyl)glycine esters (in the absence of silica gel, a mixture of regioisomers was isolated).[189]



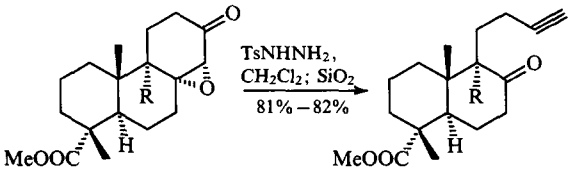
The synthesis was carried out in two ways:

(1) the reactants and the catalyst were kept in methylene dichloride for 1–1½ days under a pressure of 10 kbar and a temperature ranging from room to 65 °C

(2) the reactants were deposited on silica gel and allowed to stand at room temperature for 1–6 days.

Best results were obtained in the second case. According to preliminary data, aliphatic amines may be used as the nucleophiles.

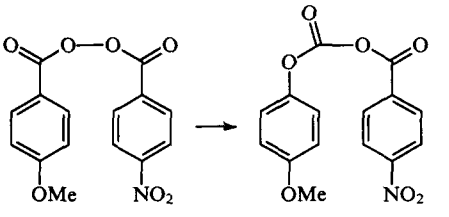
It has been shown that silica gel is an effective catalyst for the opening of the ring in α,β-epoxycycloalkanones by tosylhydrazine (the Eschenmoser reaction).[190] The reaction takes place under fairly mild conditions (at a temperature not exceeding room temperature), high yields (up to 96%) of the products [hept-6-yn-2-ones and 2-(3-butynyl)cycloalkanones] being attained even for relatively unreactive substrates of the type of podocarpanones (R = H, OH).



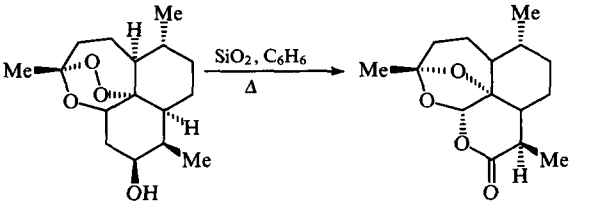
It has been noted that the catalytic effect of silicon dioxide is manifested not only in the formation of the intermediate tosylhydrazone but also in the course of its fragmentation to give the final acetylenic ketone.

11. The decomposition of peroxides

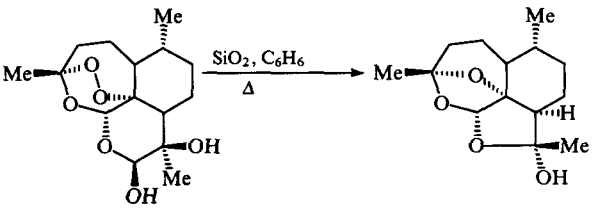
Silica gel is known to catalyse the decomposition of organic peroxides.[191–193] The reaction accelerating factor in the decomposition of di(β-phenylpropionyl), di(β-phenylisovaleroyl), and *p*-nitrobenzoyl β-phenylisovaleroyl peroxides on the silica gel surface reaches 160 relative to the analogous reactions in homogeneous systems. The rate of decomposition of *p*-methoxybenzoyl *p*-nitrobenzoyl peroxide increases by five orders of magnitude in the presence of silica gel.



Interesting reactions of dihydroartemisin **42** and 11β-hydroxy-11-epidihydroartemisinin **44**, leading to the formation of compounds **43** and **45** respectively, have been described.[194] The reactions take place on refluxing in benzene (6 h and 10 min respectively) in the presence of silica gel.



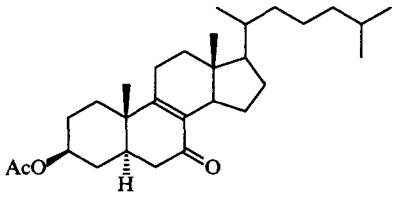
42 **43**



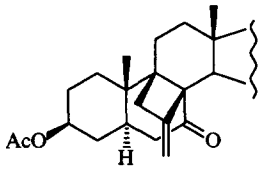
44 **45**

12. Photochemical reactions

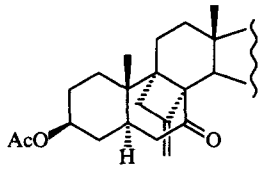
The specific features of the photochemical cycloaddition of enones to allene have been investigated.[195] It was established that, in the case of the steroid enone **46** adsorbed on silica gel, the process is partly displaced towards the more sterically hindered β-addition, leading to the derivative **47**, together with the formation of the α-adducts **48** and **49** and the rearrangement product **50**.



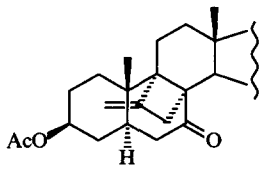
46



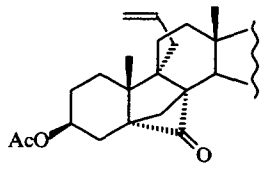
47



48



49

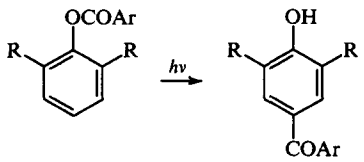


50

For the series of other, simpler examples of the enone–allene photocycloaddition, it was shown that the formation of the β,γ-adducts, which is preferred to homogeneous systems, becomes a minor process on the silica gel surface and the main products are the γ,δ-regioisomers.

The reactions involving the photocycloaddition of alkenes and allene to α,β-unsaturated steroid ketones have been investigated similarly.[196,197] In this case, the adsorption of the ketone on silica gel or aluminium oxide promotes the occurrence of the more sterically hindered β-addition, while α-addition is characteristic of the reaction in homogeneous systems.

The yield of the products of the Fries photorearrangement



R = Me, Pr^i; Ar = Ph, 2,4,6-$Me_3C_6H_2$.

increases from 5%–9% to 23%–70% after the introduction of silica gel into the reaction mixture, best results being attained in the absence of solvents.[198]

Like ozone, the forms of oxygen generated by microwave discharge in oxygen and carbon dioxide atmospheres are effective oxidants for organic compounds.[199,200] At 0 °C, the oxidation of alkenes adsorbed on silica gel affords mainly epoxides and carbonyl compounds, as in homogeneous systems; at temperatures below −60 °C, ozonolysis products are formed. Consequently the microwave discharge in an oxygen atmosphere at low temperatures can be regarded as an oxidation method which is an alternative to dry ozonisation; the comparatively slow formation of ozone, ensuring more selective oxidation, may be included among the advantages of the first method.

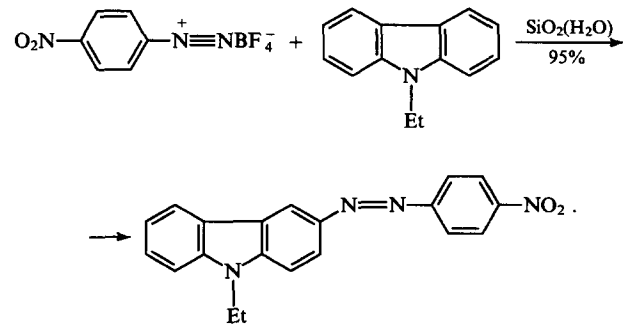
UV irradiation (λ = 350 nm) in the presence of molecular oxygen is also an effective oxidation method. Substituted phenylethenes adsorbed on silica gel are selectively cleaved to ketones or aldehydes under these conditions.[201]

Overall, despite the fact that extensive information has accumulated on the photochemistry of adsorbed molecules (see, for example, the review of de Mayo and Johnston[202]), the experimental data obtained are rarely employed for synthetic purposes.

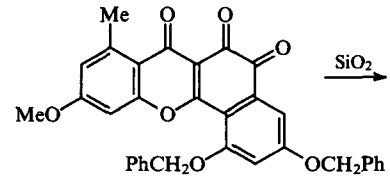
13. Various reactions

The oximes of toluene *p*-sulfonates may be converted into the corresponding amides (the Beckmann rearrangement) by stirring with silica gel at room temperature (yields 45%–90%).[203] The isomerisation of nontosylated aldoximes[204] on silica gel takes place on refluxing in xylene for 52–73 h, the yields amounting to 61%–93% for acetaldehyde derivatives and substituted benzaldehydes.

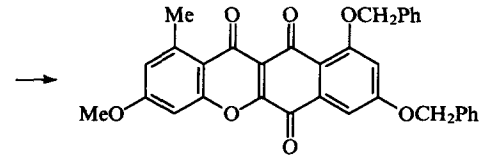
Silica gel facilitates azocoupling,[205] especially in the presence of small amounts of water (4%). The following reaction may serve as an example:



The unusual rearrangement of compound **51** to compound **52**, which takes place almost quantitatively, has been reported.[206]

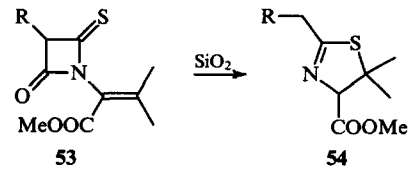


51



52

Treatment of the thiomalonimide **53** with a suspension of silica gel in chloroform gives rise to the thiazoline **54** also in an almost quantitative yield.[207]

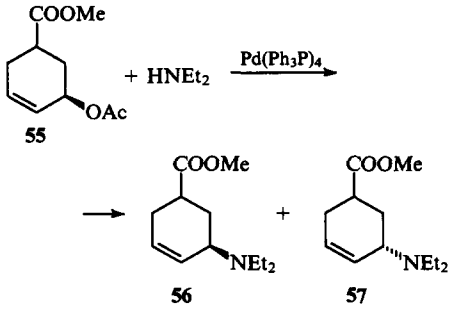


53 **54**

It has been suggested that the first stage of the rearrangement is the hydrolysis of the lactam **53** by the water adsorbed on silica gel.

The instance where silica gel functioning as the carrier for another catalyst nevertheless influences the stereospecificity of the process must be mentioned.[208] The homogeneous reaction of

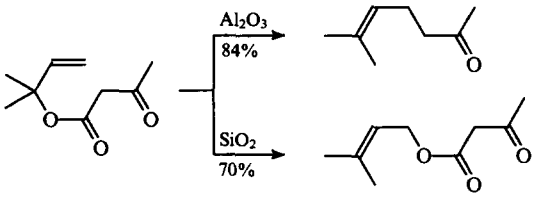
diethylamine with 5-methoxycarbonylcyclohex-3-enyl acetate **55** in the presence of tetrakis(triphenylphosphine)palladium gives a 67 : 33 mixture of the stereoisomers **56** and **57** in 85% yield. On the other hand, when the palladium catalyst is immobilised on silica gel, the only product is compound **56** (yield 72%).



An interesting approach to the creation of stereospecific catalysts has been proposed.[209,210] Chiral cavities, capable of catalysing enantioselective solvolysis (for example, 2,4-dinitrophenolysis) of the mixed anhydride of *N*-benzyloxycarbonyl-L-alanine and benzoic acid, were produced on the silica gel surface with the aid of the optically active *N*-benzoyl-(*N*-α-benzoyloxycarbonyl)-L-alanine amide. This series of studies will not be discussed in detail here because the chiral cavities possess catalytic properties only after the silica gel has been doped with aluminium ions in order to create active Lewis acid centres. Nevertheless, one may expect that this approach may prove applicable to other types of organic reactions catalysed by unmodified silicon dioxide.

Silica gel pretreated with thionyl chloride has been used as an effective catalyst of the thioacetalisation of aldehydes to give 1,3-dithiiranes and 1,3-dithianes (unmodified silica gel did not exhibit an appreciable activity).[211] On treatment with thionyl chloride, the adsorbed water is apparently removed and some of the surface silanol groups are converted into chlorosilyl groups.

In contrast to those cases where the behaviour of silicon and aluminium oxides is in general similar, chromatographic aluminium oxide catalyses the Carroll rearrangement, while the use of silica gel as the catalyst leads to the isomerisation of the alcoholic component of the initial acetoacetic ester.[212]



The last reaction proceeds on heating (60 °C) for 2–5 h.

Silica gel catalyses nucleophilic substitutions with thiocyanates.[213] For example, 1,2-epoxydecane cannot be converted into the corresponding epithio-derivative by treatment with finely ground potassium thiocyanate in toluene at 90 °C, whereas the introduction of silica gel into the reaction mixture ensures a quantitative yield of the thiirane. Best results are achieved in the presence of a small amount of water. Alkyl thiocyanates can be obtained similarly from haloalkanes, but this time preferably in the absence of organic solvents.[214] Silica gel proved to be the most active catalyst among the inorganic oxides investigated by the author.

III. Conclusion

The data examined in the present review show that the presence of chemically unmodified silicon dioxide (usually silica gel) can influence significantly the occurrence of a wide variety of organic reactions. Because of this, it has been frequently used for synthetic purposes in the oxidation (including dry ozonisation), reduction, alkylation and acylation, halogenation, elimination, hydrolytic and dehydration reactions of organic compounds, intermolecular cycloaddition reactions, and other reactions involving the formation of cyclic products as well as the opening of three-membered rings, the decomposition of peroxides, certain photochemical reactions, rearrangements, etc. The studies which have been carried out are largely phenomenological in character; in most cases, the principal or in general the only task was the attainment of the maximum yields of the target products. On the other hand, detailed information on the mechanism of the majority of the heterogeneous processes is not as yet available. Because of this, serious generalisations concerning the characteristic features of the influence of silicon dioxide on the reactions are at present impossible. On the basis of the available data, one can only reach the general conclusion that the silicon dioxide surface can function as a catalyst, as a solid medium for reactions (solid solvent), and/or as a matrix influencing the stereospecificity. In many cases, it is impossible to define clearly the role which the surface plays.

On the other hand, an unambiguous interpretation of the role of silicon dioxide as the catalyst can be found in by no means all publications describing clearly catalytic processes. It has been stated that silicon dioxide exhibits a catalytic activity in the reactions involving the oxidation of organic sulfides by sulfuryl chloride, the formation of sulfides and disulfides on treatment of aromatic compounds with RSCl, $RSCH_2Cl$, and S_2Cl_2, the reduction of aldehydes and ketones by tributyltin hydride, the alkylation and acylation of aromatic alcohols and phenols, the introduction of halogen atoms into an aromatic ring and the addition of hydrogen halides to alkenes, the dehydration of aminoacids, the Knoevenagel condensation, the Diels–Alder addition, cycloaddition and cyclisation, the opening of three-membered rings, the decomposition of peroxides, and certain other reactions.

Attempts to explain the mechanisms of the catalytic processes have been undertaken only for reactions involving the reduction of aldehydes and ketones by tributyltin hydride, the addition of hydrogen halides to double bonds, the cyclodimerisation of aminoacids to cyclic dipeptides, the Diels–Alder addition, and the Khand–Pauson cyclisation. In a number of instances, it has been stated that the degree of hydration of the silicon dioxide influences significantly the effectiveness of the process {for example, the introduction of halogen atoms into an aromatic ring, the addition of hydrogen halides to alkenes, the deketalisation of the products of the reactions of α-ketoketals with Wittig reagents, the hydrolysis of the diethyl acetals of (*Z*)-α,β-unsaturated aldehydes, the synthesis of acylsilanes by heating α,α-dibromobenzylsilanes, and the Diels–Alder reactions [(4 + 2)-cycloaddition], as well as nucleophilic substitution with participation of thiocyanates}. However, no general rules can be traced, since, overall, the state of the surface has different effects on different reactions. Only for the hydrolytic and hydration processes can one reach the unambiguous conclusion that the addition of water to the system should have a positive influence on the hydrolysis and conversely.

In the second case (silicon dioxide as a solid solvent), one may restate briefly that the chemistry of the silicon dioxide surface does not itself exert a significant influence on the course of organic reactions; the decisive factor is that the reactants become concentrated on the adsorbent surface and not the nature of the latter. This has been confirmed by instances of the successful employment of other inorganic oxides (for example Al_2O_3) together with silica gel. Adsorption can apparently facilitate the formation and/or stabilisation of the prereaction complexes between the functional groups of the reactants strongly fixed on the active surface centre; a favourable factor under these conditions is the absence of a liquid solvent.

Similar general considerations may prove legitimate also in the explanation of the role of silicon dioxide as a matrix

influencing stereospecificity. The results of various studies (in particular, on dry ozonisation) make it possible to claim that, by carrying out the reactions in adsorbed monolayers, it is possible in certain cases to increase the regioselectivity by means of the mutual orienting influence of the substrate molecules. Other carriers can apparently be used with equal success; however, unfortunately the limited number of literature data available at present makes it impossible to either confirm or reject the latter hypothesis.

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