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Silica gel in organic synthesis

A K Banerjee, M S Laya Mimó, W J Vera Vegas

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Abstract. The data on the use of silica gel in organic synthesis are presented. Some specific features of cyclisation (both intra- and intermolecular) reactions, rearrangements, reduction, oxidation, condensation, formylation, hydration and dehydration, protection of functional groups, *etc*., in the presence of silica gel, are discussed. The bibliography includes 96 references.

I. Introduction

Silica gel represents a uniform, non-deformable, three-dimensional network consisting of densely packed colloidal silicon oxide particles.[1] It contains substantial amounts of water which is retained tenaciously in the gel network even after drying, which points to the presence of hydrates or silicic acids.

Owing to its highly developed surface (5 – 800 $m^2\ g^{-1}$) and high porosity, silica gel is generally used as a sorbent for dehydration of gases and fluids, chromatographic separation of organic compounds, as a catalyst support, an enhancer of thixotropic properties of fluids, *etc*. Various chemical applications of silica gel have been described in the monograph of Vail.[2]

In addition, silica gel plays an important role in fine organic synthesis. Chemical reactions catalysed by silica gel usually proceed under mild conditions and with high chemo-, regio- and stereoselectivities and involve operationally more simple procedures for the isolation of final products in comparison with the corresponding homogeneous reactions.

A vast number of papers published over the past 20 years have been devoted to the use of silica gel in organic synthesis (see, *e.g*., Ref. 3), and their number is steadily increasing. This review is an attempt to generalise the published data. The overwhelming majority of studies in this area were aimed at obtaining maximum yields of target products rather than at elucidating mechanisms underlying catalytic (or any other) effects of silica gel in these reactions.

Although this review does not give an exhaustive account of reactions on silica gel, it sheds more light on its usefulness for organic synthesis.

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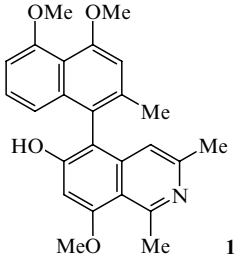
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II. Cyclisation reactions

Most of the studies published over the past 20 years and devoted to various applications of silica gel in organic synthesis provide a description of various cyclisation reactions. This can be explained by the fact that these reactions have found wide application in the synthesis of diverse physiologically active compounds, particularly, of alkaloids.

1. Intramolecular cyclisation reactions

A simple procedure for the synthesis of isoquinoline and naphthalene fragments of an unusual alkaloid, *viz*., ancistrocladein (**1**), has been proposed by Bringmann.[4]

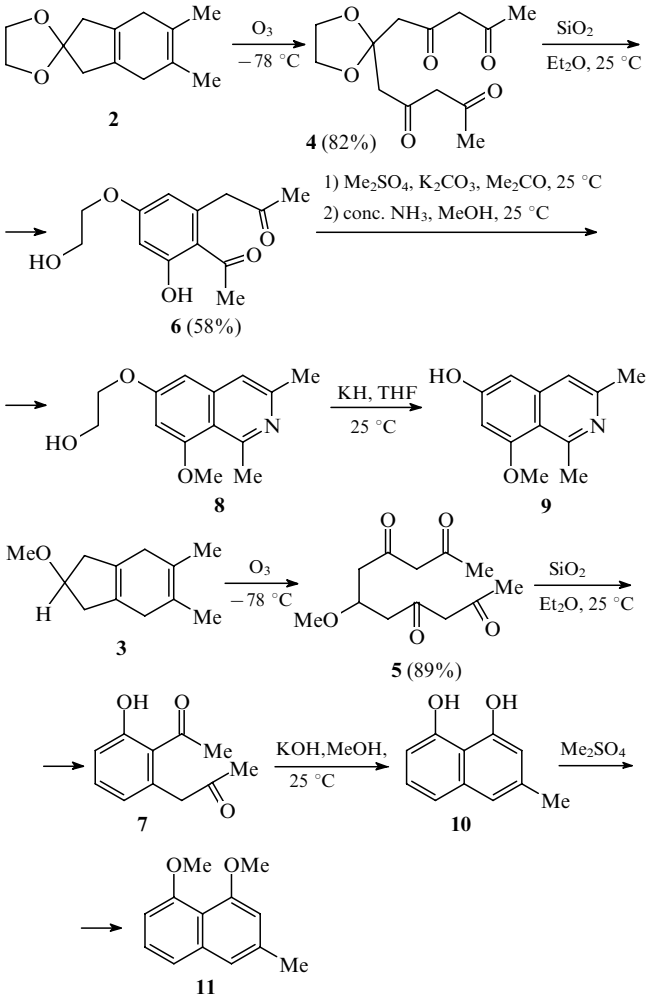


1

This synthesis employed the indan derivatives **2** and **3** as the starting compounds. They were converted into the corresponding polyketones **4** and **5** by mild ozonolysis (in the absence of oxygen) followed by cyclisation into the phenolic derivatives **6** and **7** in the presence of silica gel.†

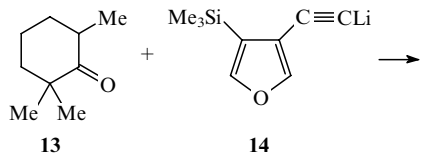
† The possibility of cyclisation of polyketone **4** under the action of bases was postulated long ago by Birch *et al*.,[5] however, the reaction products have not been studied.

The conversion of phenol **6** into the isoquinoline derivative **8** was carried out by consecutive methylation by dimethyl sulfate and cyclisation by concentrated ammonia in methanol. Selective removal of the 2-hydroxyethyl group afforded 6-hydroxy-8-methoxy-3-methylisoquinoline (**9**). In turn, treatment of the phenol **7** with a base resulted in 1,8-dihydroxy-3-methylnaphthalene (**10**);‡ its methylation by dimethyl sulfate gave the dimethoxy derivative **11**. Further reaction of isoquinoline **9** with naphthalene **11** resulted in ancistrocladein **1**.

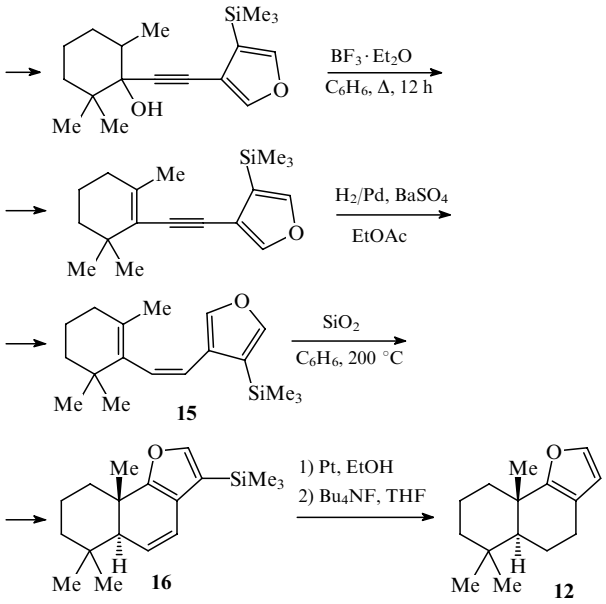


2 **4** (82%) **6** (58%) **8** **9** **3** **5** (89%) **7** **10** **11**

The use of silica gel in the synthesis of the sesquiterpene pallescensin A (**12**) has been described.[6] Trimethylcyclohexanone **13** and furylacetylenide **14** were used as the starting compounds. The addition of acetylenide **14** to cyclohexanone **13** and subsequent dehydration of the reaction product followed by hydrogenation over Lindlar's catalyst yield the derivative **15**; its cyclisation on silica gel affords the *trans*-fused tricyclic product **16**. Selective hydrogenation and desilylation of the product **16** yield pallescensin A (**12**). It is of note that hydrogenation is accompanied by partial reduction of the furan ring.



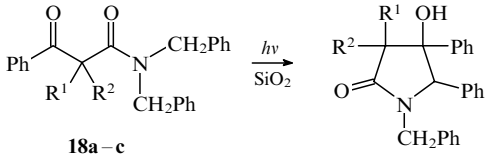
13 **14**



15 **16** **12**

In this reaction, silica gel not only facilitated the cyclisation of the furyl derivative **15** but also ensured control over the stereochemistry of ring fusion, which made this procedure attractive on the whole.

The synthesis of five-membered lactams **17a**–**c** by photocyclisation of *N*,*N*-dibenzyl-2-benzoylcarboxamides **18a**–**c** adsorbed on silica gel has been reported.[7]



18a–**c** **17a**–**c**

Compound	R^1	R^2	Yield of **17** (%)	
			C_6H_6	SiO_2
a	H	H	80	83
b	Me	H	90	91
c	Me	Me	65	63

It is suggested that this reaction, similar to that performed in solution,[8] occurs as an intramolecular 1,3-hydrogen shift towards the carbonyl oxygen atom.

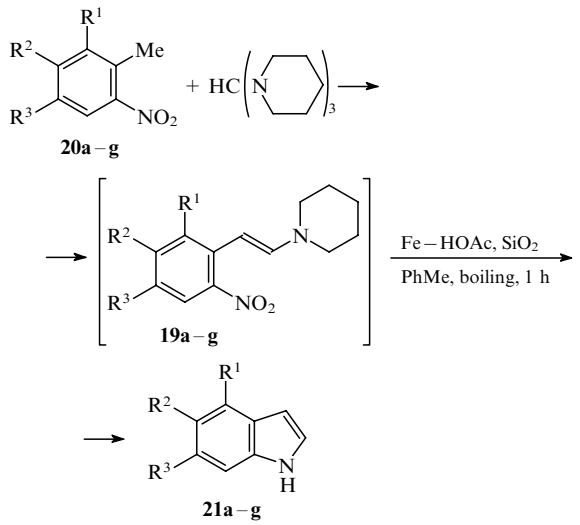
The rate of consumption of the starting β-oxo amides **18a**–**c** depends on their surface densities, *i.e.*, the amount of β-oxo amide adsorbed per g of silica gel. If solid β-oxo amides are irradiated in the absence of silica gel, the yields of lactams are low.

The use of silica gel as adsorbent in photoconversions of β-oxo amides is very effective, since it ensures uniform distribution of the latter over the whole surface of silica gel. The yields of lactams **17a**–**c** obtained by photocyclisation on silica gel are comparable to those obtained in solutions.[9]

Reductive cyclisation on silica gel of a series of 2-nitro-β-piperidinostyrenes **19a**–**g** prepared§ by condensation of substituted 2-nitrotoluenes **20a**–**g** with tripiperidinomethane has been described.[10] In this study, the Fe–AcOH system was used as the reducing agent and toluene as the solvent. The yields of the reaction products, *viz.*, indoles **21a**–**g**, were 62%–94%.

‡ The derivative **10,** which is extremely sensitive to oxidation, was found in the berries *Diospyros mollis* possessing anti-helminthic activity.

§ This procedure for indole synthesis is a modification of the Leimguber–Batcho method,[11] which includes aminovinylation of 2-nitrotoluenes followed by reductive cyclisation of *trans*-β-dialkylamino-2-nitrostyrenes formed.



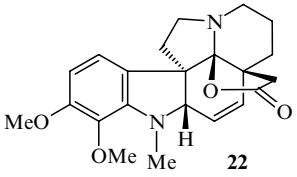
Compound	R^1	R^2	R^3	Yield of **21** (%)
a	H	H	H	82
b	F	H	H	87
c	H	H	Cl	90
d	OMe	H	H	94
e	OCH_2Ph	H	H	85
f	H	H	OMe	81
g	H	OCH_2Ph	OCH_2Ph	62

In the absence of silica gel, the yields of indoles are much lower, which can be ascribed to intramolecular reactions involving β-dialkylamino-2-nitrostyrenes.[12]

This approach was successfully employed in the synthesis of 5,6-bis(benzyloxy)-4-fluoro-, 5,6-bis(benzyloxy)-7-fluoro- and 4,7-difluoro-5,6-diphenylmethylenedioxyindoles (yields 61%, 53% and 53%, respectively); these products are intermediates in the synthesis of halogeno-substituted analogues of pharmaceutically useful neurotoxins, *viz*., 5,6- and 5,7-dihydroxytryptamines. If $TiCl_3$–$AcONH_4$ and Ni-Raney–N_2H_4 are used as reducing agents in the condensation, the yields of indoles are much lower. Thus the yields of 5,6-bis(benzyloxy)-7-fluoroindole were as low as 19% and 23%, respectively, apparently due to side reactions,[13] whereas these undesirable intramolecular reactions are suppressed in the processes carried out in non-polar solvents (*e.g*., toluene) in the presence of silica gel.

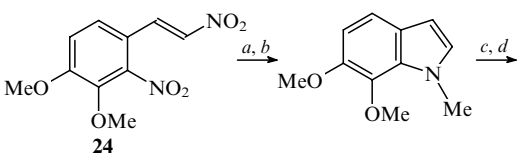
It is noteworthy that the use of silica gel together with toluene increases sharply the yields of indoles in reductive cyclisation with Fe–AcOH. Thus the yield of indole **21a** was 82%, while that obtained with the Fe–AcOH system in ethanol was as low as 17%.

The system mentioned (iron + acetic acid, toluene and SiO_2) was used by Corey *et al*.[14] in the synthesis of a substituted tryptamine, a starting compound in the synthesis of the indole alkaloid aspidophytin **22**.

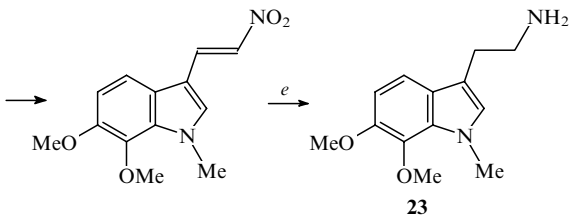


22

Dinitrostyrene **24** was used as the starting compound in the synthesis of tryptamine **23**.



24

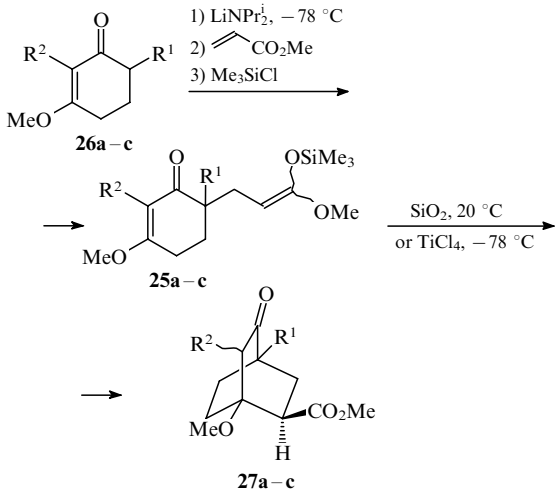


23

(*a*) Fe–HOAc, SiO_2, MePh, Δ; (*b*) MeI, KOH, Bu_4NI, THF, 23 °C; (*c*) $POCl_3$, DMF, 35 °C, 1 h, NaOH(aqueous), Δ; (*d*) $MeNO_2$, NH_2OAc, Δ, 1 h; (*e*) $LiAlH_4$, THF, Δ, 1 h.

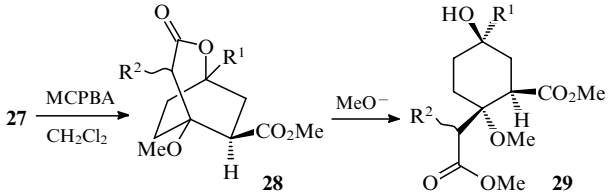
The use of silica gel for cyclisation of several ketene acetals resulting in polyfunctional bicyclo[2.2.2]octanones has been described.[15]

Ketene mixed acetals **25a**–**c** were prepared from 3-methoxycyclohex-2-enone (**26a**) and its 6-methyl- (**26b**) and 2,6-dimethyl derivatives (**26c**). To this end, cyclohexenones following treatment with lithium diisopropylamide (LDA) at low temperature reacted with methyl acrylate with subsequent silylation. In this case, the reaction of cyclohexenones with methyl acrylate was stopped in the step of formation of mixed ketene acetals **25a**–**c**; no twofold Michael addition products were detected. The cyclisation of acetals **25a**–**c** was carried out in two ways, *viz*., by passage through a short column packed with silica gel and by treatment with titanium tetrachloride at low temperature. In the former case, the reaction is stereoselective and the yields of the corresponding bicyclo[2.2.2]octanones **27a**–**c** exceed 98%. The yields of reaction products prepared by an alternative route are much lower.



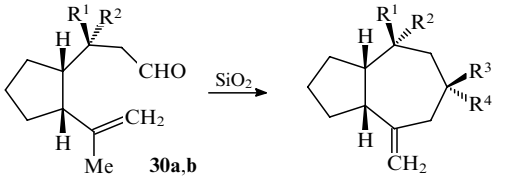
Compound	R^1	R^2	Yield of **27** (%)	
			SiO_2	$TiCl_4$
a	H	H	> 98	72
b	Me	H	> 98	83
c	Me	Me	> 98	54

Bicyclooctanones **27** present certain interest as precursors of cyclic products having several asymmetric centres. To this goal, compounds **27** are converted into lactones **28** by regioselective Baeyer–Villiger oxidation. Opening of the lactone ring affords the cyclic products **29**, which contain three asymmetric centres with defined configurations.



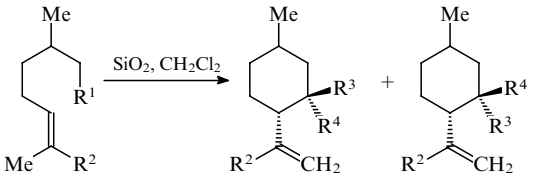
Later, Schinzer and Kalesse[16] used this method to obtain other bicyclo[2.2.2]octanone derivatives. 3-Vinyl- and 3-(*N*-methyl-*N*-tosylamino)-substituted cyclohex-2-enones were used as the starting compounds. It was found that the former derivative reacts with methyl acrylate similarly to the 3-methoxy derivative, *viz*., first, the corresponding ketene acetal is formed, which is then cyclised on silica gel into the final vinyl-substituted bicyclo[2.2.2]octanone. On the other hand, the amino derivative affords directly bicyclooctanone at −78 °C as a result of twofold Michael addition.

Acid-catalysed cyclisation of unsaturated carbonyl compounds in the presence of Lewis acids has been studied in sufficiently great detail (see, *e.g*., the review[17] and references cited therein). This approach is very attractive in the generation of a new C−C bond. However, the use of ordinary Lewis acids does not always ensure high selectivity, the reactions are accompanied by the formation of side products. The use of silica gel as a catalyst for this reaction has been recommended by Marshall *et al*.[18] Thus, silica gel catalyses efficiently the cyclisation of unsaturated aldehydes **30**.[19,20]



30a: R^1 = Me, R^2 = H, R^3 = H, R^4 = OH (from **30a**),
30b: R^1 = H, R^2 = Me, R^3 = OH, R^4 = H (from **30b**).

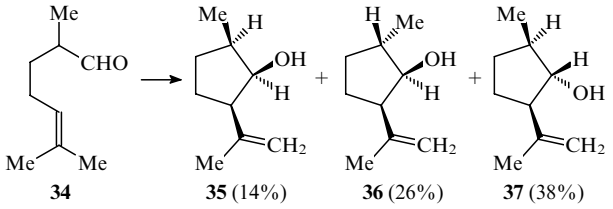
The results of studies[21] of different reagents absorbed on silica gel provide convincing evidence that silica gel always contains some amount of bound water molecules, particularly as silicic acid. It is known that high pressure increases the pK_a of acids. Although we still have no direct proof of the effect of high pressure on the acidity of silica gel, it can be assumed, with a high degree of certainty, that the acidity of silica gel will increase with pressure. According to Dauben and Hendricks,[22] oven-dried silica gel efficiently catalyses the cyclisation of various unsaturated carbonyl compounds. Acid-catalysed cyclisation on silica gel as a mild acid catalyst under a pressure of 15 kbar was used in the synthesis of six- and five-membered carbocycles.



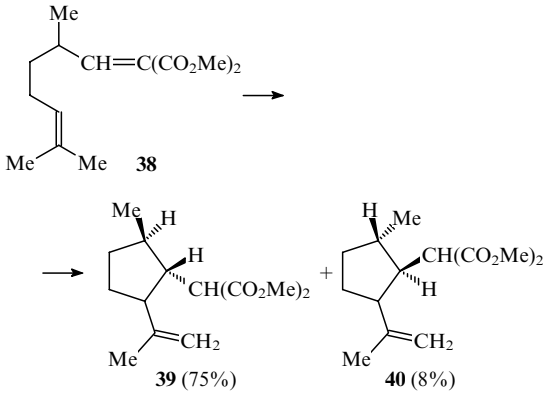
Compound	R^1	R^2	R^3	R^4	Yield (%)	
					32	**33**
a	CHO	Me	OH	H	58	15
b	CHO	H	OH	H	5	20
c	COMe	Me	OH	Me	46	20
d	$CH=C(CO_2Me)_2$	Me	$CH(CO_2Me)_2$	H	66	7

The cyclisation of unsaturated carbonyl compounds **31a**–**d** yields the six-membered stereoisomeric cyclic products **32a**–**d** and **33a**–**d**. The yields of the carbocyclic products from compounds **31a**, **31c** and **31d** on silica gel at 15 kbar are comparable to those obtained previously with Me_2AlCl[23] and $ZnBr_2$.[24,25] In the case of the aldehyde **31b**, the yields of the cyclisation products **32b** and **33b** are low (5% and 20%, respectively), whereas the yield of the product **32b** prepared with Me_2AlCl is 90%. Under normal pressure, compound **31c** is not cyclised on silica gel; compound **31a** is cyclised but the yields of the reaction products are < 10% after 7-day exposure on silica gel. No cyclisation of compounds **31a** and **31d** takes place at 15 kbar in the absence of silica gel.

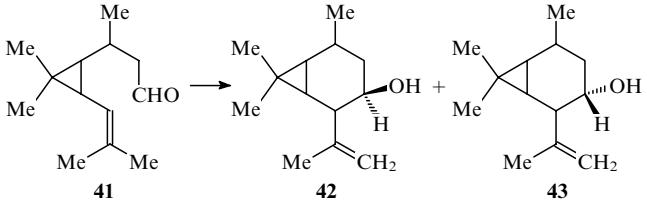
The unsaturated aldehyde **34** undergoes cyclisation on silica gel at 15 kbar to yield a mixture of five-membered cyclic products **35**–**37**. The methyl ketone homologue of the aldehyde **34** is not cyclised under these conditions.



The unsaturated ester **38** yields the cyclic derivatives **39** and **40** under identical conditions.

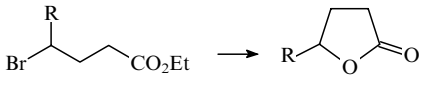


The use of silica gel in combination with a pressure of 15 kbar was also found to be helpful in the cyclisation of the labile vinylcyclopropane-containing aldehyde **41** into compounds **42** and **43**. An attempt to cyclise compound **41** under the action of zinc bromide failed, the products **42** and **43** were detected but in trace amounts.

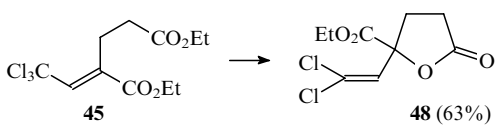


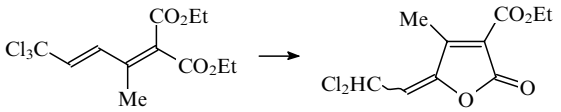
It was shown[22] that the yields and selectivities in ene-type cyclisations on silica gel at 15 kbar are comparable to those obtained by other methods (see, *e.g*., Refs 26 and 27). The conditions mentioned proved to be of choice in certain cases, as in the cyclisation of the aldehyde **41**.

Treatment of γ-halogeno-substituted esters **44a**,**b** and their vinylogues **45** and **46** with silica gel in xylene results in high yields of γ-butyrolactones **47a**,**b**, **48** and **49**, respectively.[28]



47a: R = H (66%),
47b: R = n-C_6H_{13} (79%).





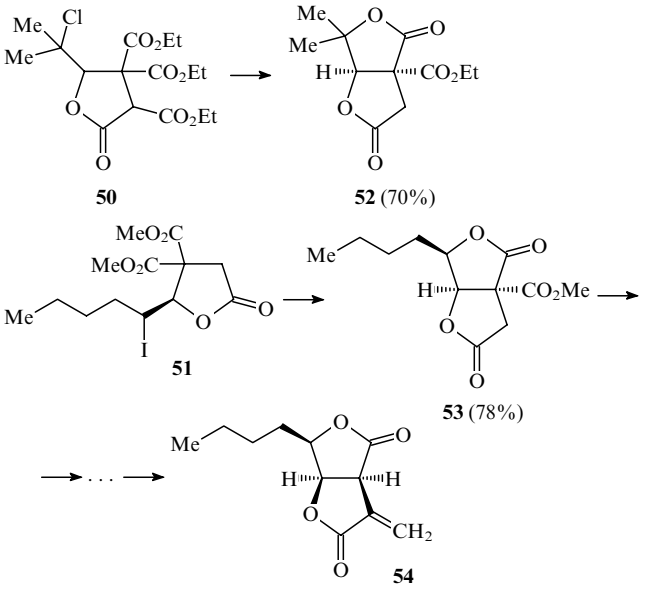
46 **49** (46%)

The silica gel used in this reaction was dried for 3 h at 200–250 °C and 20 Torr. The reactions were performed by heating the substrates with silica gel in xylene for 3–15 h.

The efficacy of silica gel was demonstrated in the conversion of ethyl 4-bromobutyrate (**44a**) as an example. Boiling of compound **44a** in xylene in the presence of SiO_2 results in γ-butyrolactone **47a** in 66% yield, whereas heating of the haloester in xylene in the absence of silica gel affords no lactonisation product.

Acid-catalysed lactonisation of γ-halogeno-substituted carboxylic acids is one of the most attractive methods for the synthesis of γ-butyrolactones. However, this is inapplicable to substrates containing easily hydrolysable functional groups. The use of silica gel not only lifts these restrictions, but also increases the yields of the target products. Previous reports describe moderate yields of γ-butyrolactones prepared upon heating of γ-halogeno esters in the absence of solvents. It is of note that the conditions for this reaction (170–180 °C) are more drastic than those used for the lactonisation on silica gel.

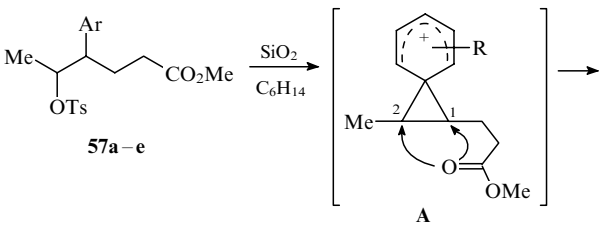
This method was also used in the synthesis of bis-γ-butyrolactones. Thus the triester **50** and the diester **51** are converted into dilactones **52** and **53** in high yields by treatment with silica gel.



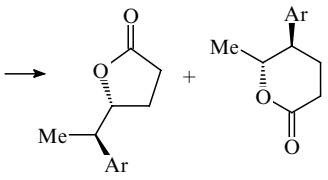
50 **52** (70%) **51** **53** (78%) **54**

Compound **53** is the key intermediate in the synthesis of (+)-canadensolide (**54**), a metabolite isolated from *Penicillium canadense*.

A novel method of the synthesis of γ- (compounds **55a–e**) and δ-lactones (compounds **56a–e**) by conversion of methyl 4-aryl-5-tosyloxyhexanoates **57a–e** in the presence of silica gel in hexane has been reported.[29]



57a–e **A**

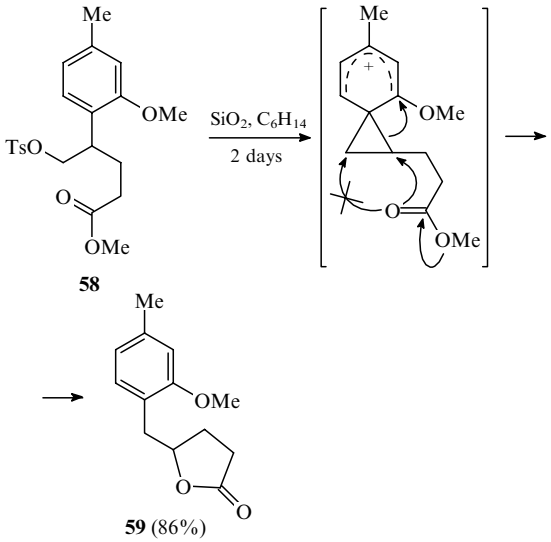


55a–e **56a–e**

Compound	Ar	Yield (%)	
		55	**56**
a	4-$MeOC_6H_4$	30	42
b	2-$MeOC_6H_4$	11	67
c	3,4-$(MeO)_2C_6H_3$	34	36
d	4-MeO-2-MeC_6H_3	7	73
e	2-MeO-4-MeC_6H_3	14	68

The structures of the resulting lactones were determined from spectroscopic data. In all cases studied, the yields of δ-lactones exceeded those of γ-lactones.

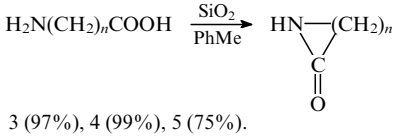
The stereochemistry of δ-lactones **56a–e** suggests that these compounds, like γ-lactones **55a–e**, are formed *via* an intermediate phenonium ion (**A**), rather than by direct substitution of the tosyloxy group by the ester group. It was concluded that the regioselectivity of the lactonisation reaction, which proceeds *via* the intermediate phenonium ion (**A**), is controlled by electronic factors. It was also found that the lactonisation of compounds **57a–e** under conditions of thermodynamic control is selective and yields γ-lactones **55a–e**, whereas that under conditions of kinetic control yields predominantly δ-lactones **56a–e**. It should be noted that methyl 4-(4-methyl-2-methoxyphenyl)-5-tosyloxypentanoate (**58**) is converted exclusively into γ-lactone **59** upon lactonisation on silica gel in hexane.



58 **59** (86%)

We believe that lactonisation on silica gel will find broad application in synthetic organic chemistry.

A simple procedure for lactam synthesis, which includes cyclodehydration of the corresponding amino acids by treatment with silica gel in boiling toluene, has been described.[30]



n = 3 (97%), 4 (99%), 5 (75%).

The corresponding lactams are formed in very high yields. This reaction proceeds smoothly on alumina as well.

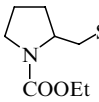
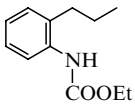
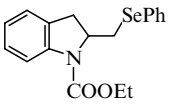
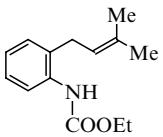
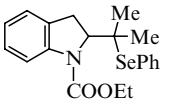
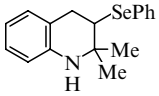
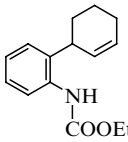
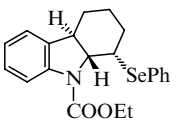
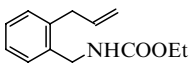
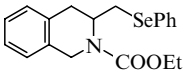
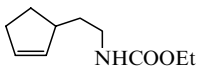
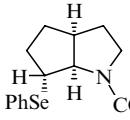
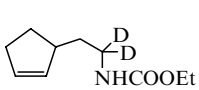
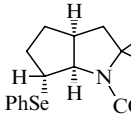
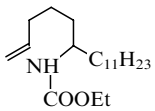
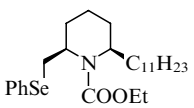
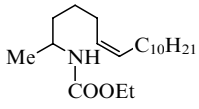
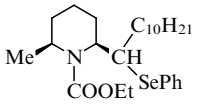
An efficient procedure for the synthesis of nitrogen heterocycles, which includes cyclisation of *N*-(Δ^4- or Δ^5-alkenyl)carbamates under the action of PhSeCl in the presence of silica gel, has been developed (Table 1).[31] Presumably, this reaction proceeds in two steps, *viz*., initial rapid addition of PhSeCl in CH_2Cl_2 to the double bond of the urethane and subsequent cyclisation of the adduct formed on the surface of silica gel.

The PhSe-groups were removed by treatment of the selenides with triphenyltin hydride in boiling toluene.

It was noted that the ring closure occurs more easily in the presence of predried silica gel (Merck 60 PF-254) and the yield of the target products (the corresponding pyrrole and piperidine derivatives) is increased (Table 1). In the case of *N*-ethoxycarbonyl-2-(3-methylbut-2-enyl)aniline both 5-*exo*- and 6-*endo*-cyclisation products were obtained.[32]

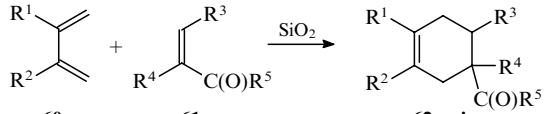
This method provides a reasonable alternative to Hg^{2+}-induced cyclisation commonly used in the synthesis of nitrogen heterocycles and a good supplement to palladium-assisted cyclisation, which affords products at a different level of hydrogenation.

Table 1. Cyclisation of urethanes.

Urethane	Product	Yield (%)	
		in solution	on SiO_2
		77	93
		73	85
	 + 	–	76
		59	82
		52	87
		–	94
		–	83
		–	84
		–	35

2. Intermolecular cycloaddition reactions

The efficiency of silica gel in intermolecular cycloaddition reactions has been described in numerous papers (see, *e.g*., reviews [3,21] and references cited therein). Here we shall consider only some of the most interesting studies devoted to [4 + 2]-cycloaddition reactions (the Diels – Alder reaction). A new methodology for [4 + 2]-cycloaddition of dienes **60** to dienophiles **61** on the surface of chromatographic adsorbents (*e.g*., SiO_2, $MgO \cdot SiO_2$, Al_2O_3) under solvent-free conditions has been described.[33,34]



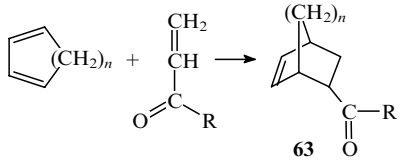
60 **61** **62a – i**

Compound	R^1	R^2	R^3	R^4	R^5	Yield of **62** (%)
a	H	H	H	H	Me	85
b	H	H	H	H	H	67
c	Me	H	H	H	Me	72
d	Me	H	H	H	H	56
e	Me	Me	H	H	Me	92
f	Me	Me	H	Me	H	89
g	Me	Me	Me	H	H	83
h	$(CH_2)_2CH=CMe_2$	H	H	H	Me	73
i	$(CH_2)_2CH=CMe_2$	H	H	H	H	66

With SiO_2, the yields of the [4 + 2]-adducts **62a – i** were 56% – 92%. Condensation of these compounds in the liquid phase in the absence of catalysts usually requires drastic conditions (120 – 160 °C, 3 – 6 h). If the reaction is carried out on SiO_2 without solvents, the temperature can be decreased considerably (*e.g*., by 50 – 100 °C). In some cases, the Diels – Alder diene products are obtained in higher yields. Presumably, the role of silica gel is to ensure polyfunctional catalysis (due to multicentre adsorption), and the absence of a solvent favours formation of pre-reaction complexes due to weak van-der-Waals interactions of adsorbed substrates devoid of shielding solvation shells. If the reaction is carried out on the surface of SiO_2 in the presence of solvents (*e.g*., C_6H_{14}, CH_2Cl_2), the efficiency of cycloaddition decreases considerably, presumably due to partial desorption of the reactants from the surface of SiO_2.

It is suggested that the activity of silica gel depends critically on the water content. The highest yields were obtained with silica gel dried at 200 °C for 6 h in order to remove physically adsorbed water. Florisil ($MgO \cdot SiO_2$, Florisil) tested in this reaction appeared to be less efficient. With $MgO \cdot SiO_2$, the reaction temperature had to be increased by 20 – 30 °C in order to make the yields of [4 + 2]-adducts comparable to those obtained with dried SiO_2.

The main advantage of this method is that cycloaddition reactions on silica gel in the absence of solvents are highly regio- and stereoselective, whereas reactions in liquid media yield mixtures of isomers. Thus the SiO_2-catalysed addition of methyl vinyl ketone and acrolein to cyclopenta- and cyclohexadienes results in the predominant formation of the *endo*-isomers **63**, whereas the liquid-phase reaction involving these substrates yields a mixture of isomers where the *exo*-isomer content is > 20%.

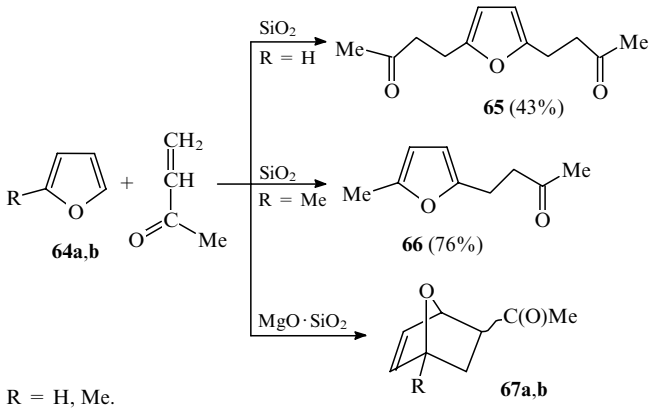


63

R = H, Me.

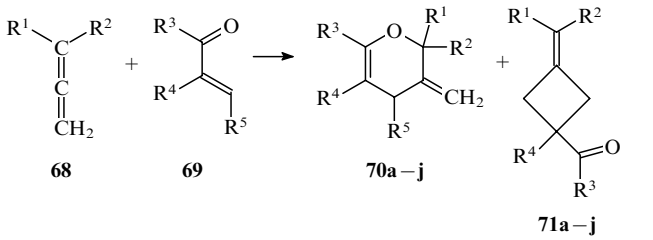
The reaction of furan (**64a**) and silvane (**64b**) with methyl vinyl ketone occurs differently under these conditions. This reaction is fast, but yields exclusively addition products, *viz*., compounds **65**

and **66**, respectively. This can be attributed to high lability of methyl vinyl ketone on such a sorbent as silica gel. At the same time, the use of florisil ($MgO \cdot SiO_2$) as a sorbent affords the expected [4 + 2]-cycloaddition products **67a**,**b**.



R = H, Me.

An illustrative example of the high efficiency of the dry-adsorption method is provided by the hetero-Diels–Alder synthesis.[35] It was found that the cycloaddition of alkoxyallenes **68** to α,β-enals and α,β-enones **69** results in the [4 + 2]-adducts **70**.



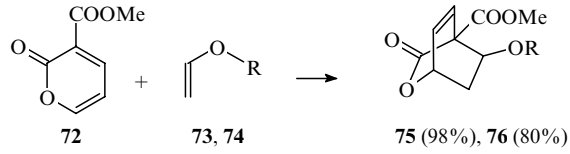
Compound	R^1	R^2	R^3	R^4	R^5	Yield of **70** + **71** (%)
a	EtO	H	H	H	H	71 (with predominance of **70**)
b	EtO	H	Me	H	H	68 (with predominance of **70**)
c	EtO	H	H	Me	H	58 (with predominance of **71**)
d	EtO	H	H	H	Me	< 5
e	MeO	Me_3Si	H	H	H	47 (**70**) + 26 (**71**)
f	MeO	Me_3Si	Me	H	H	47 (with predominance of **70**)
g	MeO	Me_3Si	H	Me	H	38 (**70**) + 43 (**71**)
h	MeO	H	H	H	H	47 (with predominance of **70**)
i	MeO	H	Me	H	H	65 (with predominance of **70**)
j	MeO	H	H	Me	H	82 (1 : 1)

In addition to the dihydropyran derivatives **70**, which represent [4 + 2]-cycloaddition products, this reaction affords a small amount of [2 + 2]-cycloaddition by-products, *viz*., the cyclobutane derivatives **71**.

The highest yields of the [4 + 2]-cycloaddition products were obtained when dried silica gel deactivated with triethylamine (0.2% – 0.5%) was used. It is of note that the acidity of ordinary silica gel is a factor which is responsible for the destruction and polymerisation of cycloaddition products. The use of more basic florisil as a medium for the hetero-Diels–Alder reaction helps avoid undesired side reactions,[34] but the reaction rate decreases. Alumina manifests no catalytic activity in this reaction.

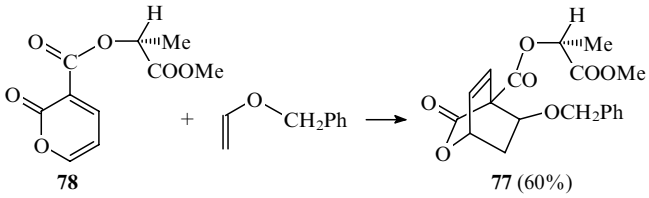
The 2-alkoxy-5-methylidene-3,4-dihydro-2*H*-pyrans **70** formed are the starting products in the synthesis of valuable derivatives of glutaraldehyde.

According to Posner *et al*.,[36] preparative [4 + 2]-cycloaddition of commercial 3-methoxycarbonyl-2-pyrone (**72**) to vinyl ethers **73** and **74** is strongly accelerated under the action of silica gel (EM Science 60) at room temperature, resulting in *endo*-bicyclic products (**75** and **76**) diastereoselectively and in extremely high yields.



R = Bu^n (**73**, **75**), $PhCH_2$ (**74**, **76**).

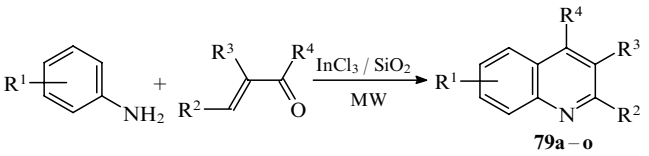
The *endo*-adducts **77** (the diastereomer ratio is ~4 : 1) are also formed upon cycloaddition of benzyl vinyl ether (**74**) to the enantiomerically pure (*R*)-methyl pyrone-3-carbonyl lactate **78**. This reaction was carried out on dried (200 °C, 16 h) silica gel (Syloid 221) in toluene.



No [4 + 2]-cycloaddition products are formed in the absence of silica gel.

The above-described silica gel-catalysed cycloaddition reactions are operationally simple, stereoselective methods for the synthesis of bicyclic lactones and represent 'atom-economical' procedures¶ in which all the atoms of both reactants are incorporated into the final products.

Despite the immense diversity of synthetic methods used to obtain nitrogenous heterocycles, the interest of investigators in simple and convenient procedures does not fade, since nitrogenous heterocycles are constituents of many physiologically active compounds. Recently, Ranu *et al*.[37] have developed a simple and efficient method for quinoline synthesis from anilines and alkyl vinyl ketones by treatment with indium(III) chloride on silica gel under microwave irradiation without any solvent.

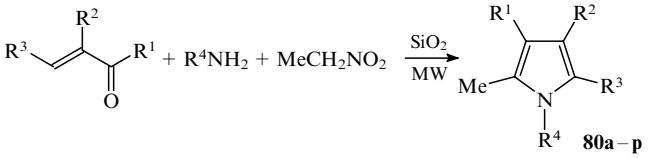


Compound	R^1	R^2	R^3	R^4	Yield of **79** (%)
a	H	H	H	Me	85
b	2-Me	H	H	Me	81
c	3-Me	H	H	Me	84
d	4-Me	H	H	Me	85
e	2-OMe	H	H	Me	80
f	4-OMe	H	H	Me	83
g	3-OH	H	H	Me	81
h	3-Cl	H	H	Me	87
i	4-Cl	H	H	Me	80
j	4-Br	H	H	Me	80
k	2-Me-4-I	H	H	Me	83
l	C_4H_4	H	H	Me	82
m	H	Me	H	*p*-$MeOC_6H_4$	81
n	3-Cl	Me	H	*p*-$MeOC_6H_4$	83
o	H	Pr^n	Et	Me	55

¶ This term was originally suggested by B Trost.

This method allows one to obtain quinolines **79a–o** in high yields irrespective of the nature of substituents in the anilines and alkyl vinyl ketones. This reaction includes the Michael addition of aniline to vinyl ketone followed by cyclisation and aromatisation catalysed by $InCl_3/SiO_2$. When $InCl_3$ is used without silica gel, the reaction is sluggish, while imines are formed on silica gel in the absence of $InCl_3$.

The same authors have developed a convenient one-step method for the synthesis of polysubstituted pyrroles.[38] It was found that the reaction of α,β-unsaturated carbonyl compounds with amines and nitroalkenes on the surface of silica gel (HF 254) under microwave irradiation without any solvent affords various polysubstituted pyrroles **80a–p**.



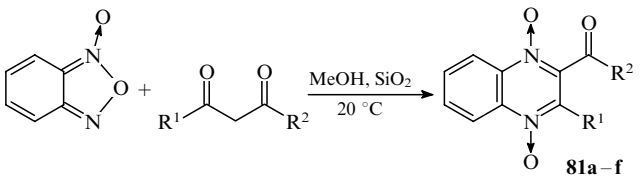
80a–p

Compound	R^1	R^2	R^3	R^4	Yield of **80** (%)	
					SiO_2	THF, Δ
a	Ph	H	H	$PhCH_2$	60	30
b	Ph	H	Ph	$PhCH_2$	65	32
c	Ph	H	Me	$PhCH_2$	64	35
d	H	H	Me	$PhCH_2$	60	31
e	H	H	Me	cyclo-C_6H_{11}	60	32
f	Ph	H	H	C(Ph)HMe	62	33
g	Ph	H	Me	C(Ph)HMe	66	33
h	Ph	H	H	Pr^i	64	35
i		H	Me	Pr^i	68	36
j		H	Me	$PhCH_2$	72	40
k	Pr^n	Et	H	$PhCH_2$	60	28
l	Pr^n	Et	H	cyclo-C_6H_{11}	65	35
m	Ph	H	H	Pr^n	62	31
n	Ph	H	Me	Bu^n	65	40
o	Ph	H	H	Bu^n	61	32
p	$-(CH_2)_4-$		Me	Bu^n	68	40

Heating of mixtures of starting compounds in the absence of silica gel results in resinification. When this reaction is carried out in solution (*e.g.*, boiling in THF), the yields of the reaction products decrease significantly, whereas the reaction time increases.

In our opinion, the one-step syntheses of quinolines and pyrroles from readily available compounds developed by Ranu *et al.*[37,38] are among the best methods presently available. To obvious advantages of these methods one can relate simple procedures, high product yields, high reaction rates and the possibility to obtain a broad array of quinolines and pyrroles.

A convenient procedure for the preparation of quinoxaline di-*N*-oxide derivatives **81a–f** from β-dicarbonyl compounds and benzofuroxan in methanol in the presence of silica gel has been proposed.[39]



81a–f

Compound	R^1	R^2	Enol content (%)	Yield of **81** (%)
a	OMe	OMe	0	0
b	Me	OMe	12.6	16
c	Ph	OEt	27	63
d	Me	Me	84	58
e	Ph	Ph	90–100	66
f	Me	Ph	94	88

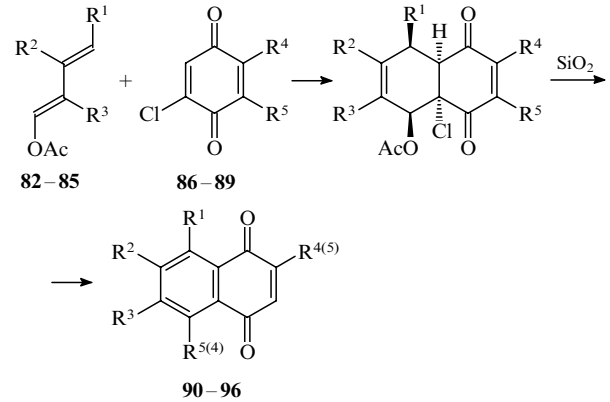
This reaction is carried out as follows. Benzofuroxan and the β-dicarbonyl compound are dissolved in methanol, the solution is mixed with silica gel and concentrated at 20 °C. The resulting mixture containing the adsorbed reagents is kept at room temperature for 1–2 weeks without drying after which the corresponding quinoxaline di-*N*-oxide is isolated. The efficacy of this reaction strongly depends on the type of silica gel used. Convenient gels are Wako gel C-200 (Wako Pure Chemical Industries) and Silica gel 60 (Merck).

It is assumed that the yields of the products **81a–f** correlate with the per cent content of the enol form of the carbonyl compound. When alumina (basic, neutral or acidic) was used instead of silica gel, the yields of quinoxaline di-*N*-oxides **81a–f** were much lower. In all cases studied, the main product appeared to be contaminated with side products.

III. Rearrangements

Many organic compounds undergo diverse molecular rearrangements under the action of acids and bases. The papers published before 1979 provide examples of interesting rearrangements of certain classes of organic compounds, such as aminopyrrolidines,[40] hydroxycyclopropanes,[41] oxazolidines[42] and aldehydes, on silica gel.[18] A great variety of interesting rearrangements induced by silica gel have been described in the review of McKillop and Young,[21] therefore we shall omit them from consideration and shall confine ourselves to a few cases only.[43–45]

Thus multiple passage of addition products of methyl-substituted 1-acetoxybuta-1,3-dienes **82–85** to chlorobenzoquinones **86–89** through a column with silica gel leads to rearrangement and concomitant aromatisation leading to naphthoquinones **90–96**.[43]



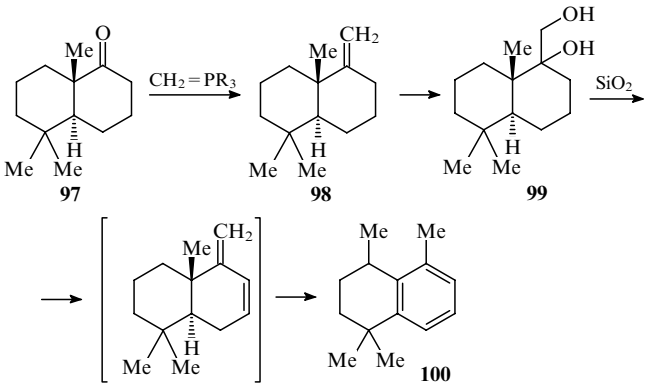
82–85 **86–89** **90–96**

Reaction	Product	R^1	R^2	R^3	$R^{4(5)}$	$R^{5(4)}$	Yield (%)
82+**87**	**90**	H	H	H	Cl	H	92
83+**86**	**91**	H	H	Me	Cl	H	79
83+**87**	**92**	H	H	Me	(H)	(Cl)	65
84+**86**	**92**	H	Me	H	Cl	H	88
84+**87**	**91**	H	Me	H	(H)	(Cl)	80

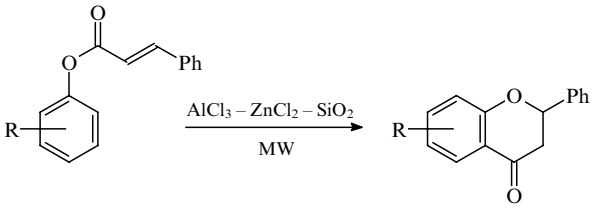
Reaction	Product	R^1	R^2	R^3	$R^{4(5)}$	$R^{5(4)}$	Yield (%)
85 + 86	**93**	Me	H	H	Cl	H	80
85 + 87	**94**	Me	H	H	(H)	Cl	90
84 + 88	**95**	H	Me	H	OMe	H	96
84 + 89	**96**	H	Me	H	(H)	(OMe)	79

This method is especially convenient for the synthesis of substituted naphthoquinones which represent fragments of many natural alkaloids.

Yet another interesting rearrangement coupled with aromatisation has recently been observed in studies of the conversion of ketone **97**.[44] This was first transformed into alkene **98** by the Wittig reaction and then into the target diol **99** by treatment with Woodward's reagent (MeCOOAg, I_2, MeCOOH, H_2O) followed by alkaline hydrolysis. An attempt to purify the diol **99** on a column with silica gel (Silica gel 60, Merck) gave unexpectedly tetralin **100** in 90% yield. Apparently, during its passage through the column diol **99** first undergoes dehydration and then rearrangement.



A simple procedure for flavanone synthesis from esters (the Fries rearrangement) has been proposed.[45] This rearrangement is effected by microwave irradiation in the presence of the catalytic system $AlCl_3 - ZnCl_2 - SiO_2$.



IV. Reduction

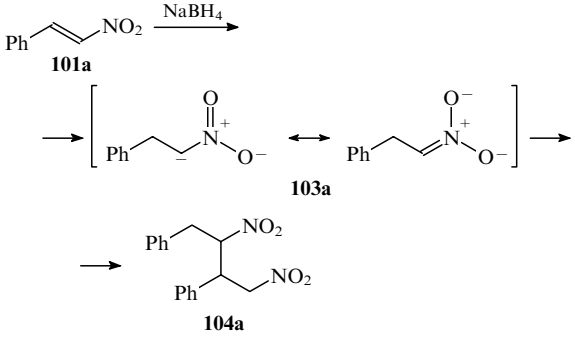
Reduction of nitrostyrenes **101a – e** to nitroethylbenzenes **102a – e** was carried out by treatment with sodium borohydride in chloroform – isopropyl alcohol in the presence of silica gel.[46]

$$R^1C_6H_4CH{=}CR^2NO_2 \xrightarrow[SiO_2]{NaBH_4} R^1C_6H_4CH_2CHR^2NO_2$$

101a – e **102a – e**

Compound	R^1	R^2	Yield of **102** (%)
a	H	H	93
b	H	Me	93
c	2-Me	H	99
d	4-Me	H	92
e	3-Me	H	92

The reduction results in highly polar negatively charged intermediates **103**. In the absence of silica gel, such intermediates bind a proton or a second molecule of the original styrene resulting in a mixture of products **102** and **104** in a nearly equal ratio. The formation of the dimer **104a** in solution shown in the scheme below is an example.

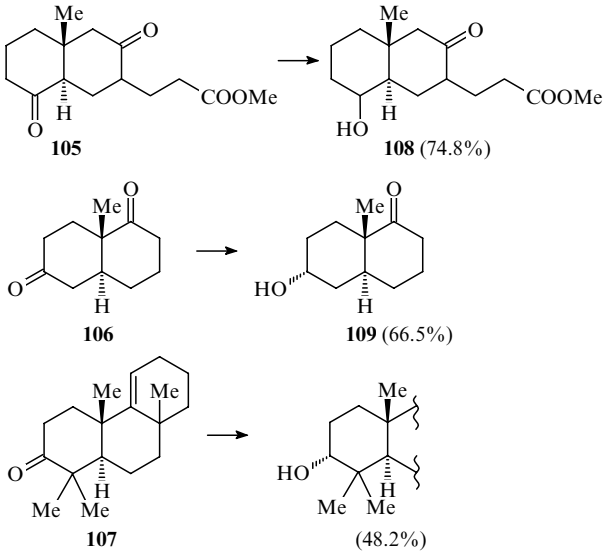


In the presence of silica gel, the intermediates **103** are formed most probably on the surface. In this case, the addition of the second styrene molecule is hindered, and the reaction yields nitroethylbenzenes **102** as the main products.

The use of chloroform as a solvent in this reaction is more preferable than the use of dichloromethane, ether or benzene. The reason is that the dissolution of the intermediate in this solvent is minimal due to the low dielectric permeability of chloroform, whereas its high density favours uniform distribution of silica gel in the reaction mixture.

For the same reasons, the use of isopropyl alcohol is more preferable than the use of methanol and ethanol, for it dissolves sodium borohydride to a lesser extent and, correspondingly, the formation of the dimeric side products **104** is less probable.

The reduction of bicyclic diketones **105** and **106**, tricyclic ketone **107** and several steroidal ketones (5α and 5β-androstane-3,17-diones, methyl esters of di- and trioxocholanoic acids, *etc.*) by treatment with the $BH_3 \cdot NMe_3$ complex has been described.[47] It was shown that the reaction carried out in the presence of silica gel impregnated with $FeCl_3 \cdot 6H_2O$ or $ZnCl_2$ resulted in selective reduction of only one keto group. Thus diketones **105** and **106** are reduced to the corresponding hydroxy ketones **108** and **109** in good yields; this reaction does not require protection of the second carbonyl group.



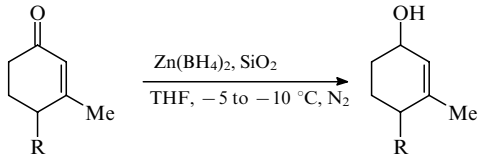
The presence of a small amount of water (5%) in silica gel accelerates the reaction, apparently due to enhanced adsorption of the amine.

Compounds containing several carbonyl groups can be regioselectively adsorbed on silica gel. Thus IR-spectroscopic studies of 5α- and 5β-androstane-3,17-diones revealed that during adsorption of these steroids on silica gel one of the carbonyl groups, *viz.*, C(17)O, forms stronger hydrogen bonds with the OH groups

present on the surface of silica gel in comparison with C(3)O. Thus, the former becomes protected from reduction with the $BH_3 \cdot NMe_3$ complex. In the cases of all steroidal ketones studied, it was the carbonyl group at position 3 that underwent reduction preferentially to the carbonyl groups at positions 7, 12, 17 and 20.

Three catalytic systems, *viz*., $SiO_2 \cdot FeCl_3 - PhH$, $SiO_2 - ZnCl_2 - PhH$ and $ZnCl_2 - PhH$, were tested in the reduction of 5α- and 5β-androstane-3,17-diones with $BH_3 \cdot NH_3$. All these reactions afforded mixtures of 3α- and 3β-hydroxy derivatives. The catalytic system $SiO_2 - FeCl_3 - PhH$ proved to be the best as the reaction was complete within 2 h, whereas reduction in the presence of the other two systems required 18–20 h. It should be noted also that in the absence of silica gel (the third catalytic system) the yields of steroid alcohols were very low.

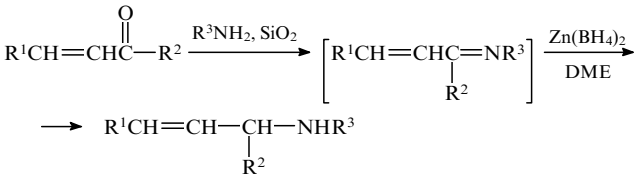
Ranu and Das[48] have proposed an excellent method for the synthesis of cyclic and acyclic allylic alcohols by reduction of the corresponding conjugated unsaturated ketones and aldehydes by zinc borohydride supported on silica gel. This reaction was carried out with unsaturated aldehydes (crotonic aldehyde, citral, *etc*.) and ketones (substituted 3-methylcyclohex-2-enones, α-ionone, pent-2-enone, *etc*.); in most cases, the yields of the corresponding allylic alcohols were quantitative. Thus the yields of alcohols in the reduction of substituted 3-methylcyclohex-2-enones exceeded 80%.



R = H (80%), COOEt (82%), COOMe (85%).

Zinc borohydride manifested high selectivity in hydrogenation, which affected exclusively carbonyl groups, but no double bonds.

Later, Ranu *et al*.[49] recommended this reagent for use in reductive amination of conjugated aldehydes and ketones in the presence of silica gel (substitution of the amino group for the carbonyl group is a very important process in organic synthesis).



R^1, R^3 = Alk, Ar; R^2 = H, Alk.

Attempts to use other catalysts, *e.g*., $BF_3 \cdot Et_2O$ or $ZnCl_2$, in this reaction were unsuccessful; good yields (75%–90%) of the corresponding imines were obtained only in the case when the reaction was carried out on silica gel.

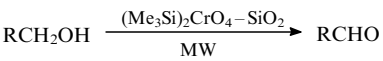
Among other recent studies devoted to hydrogenation of carbonyl compounds, special mention should be made of the one[50] where the reduction of ketones and aldehydes into the corresponding alcohols was effected with sodium borohydride in the presence of silica gel in an aprotic solvent (hexane). The main advantages of this reaction are easy availability, low cost of reagents and catalysts, mild reaction conditions, ease of isolation of final products and, which is even more important, high yields.

V. Oxidation

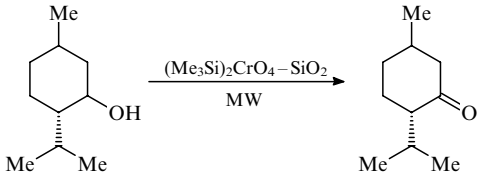
The use of inorganic oxidants in organic synthesis is often limited by their poor solubilities in low-polar media. One of the most popular oxidants is ozone. Dry ozonisation in the presence of silica gel for the insertion of oxygen atoms into non-activated C–H bonds has been described in sufficiently great detail by Basyuk;[3] therefore, we shall not discuss this process in this chapter and shall confine ourselves to the consideration of some other inorganic oxidants.

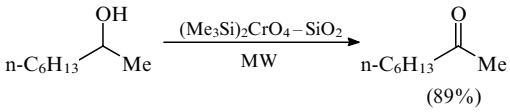
1. Oxidation of alcohols

The use of bis(trimethylsilyl) chromate supported on silica gel for the oxidation of some alcohols to carbonyl compounds has been described.[51] This reaction is initiated by microwave irradiation and takes place in the absence of solvents.



R = *p*-MeC_6H_4 (98%), n-C_7H_{15} (86%).



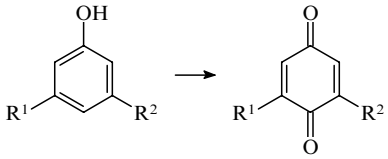


The reaction is complete within a short period of time. High yields of carbonyl compounds, simple methodology, easy isolation of reaction products and stability of the oxidant make this procedure especially attractive for synthetic chemists.

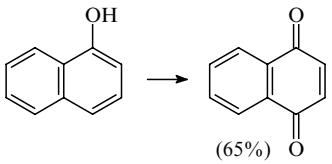
Oxidation of alcohols in CH_2Cl_2 with bis(trimethylsilyl) chromate supported on silica gel had been described earlier.[52]

2. Oxidation of phenols

Despite the great diversity of methods employed in quinone synthesis, studies in this field are currently under way, since many quinones possess biological activities and some of them are valuable semi-products in the synthesis of medicinal drugs. Recently, Hashemi and Bni[53] have proposed a very convenient, from our point of view, procedure for quinone synthesis which consists in oxidation of phenols with oxygen in the presence of a mixture of manganese and cobalt salts of 4-aminobenzoic acid supported on silica gel.



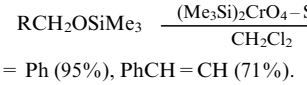
$R^1 = R^2 = H$ (64%); R^1 = Me, R^2 = H (53%); $R^1 = R^2$ = Me (57%)



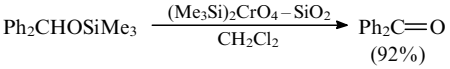
Benzene, toluene and ethylbenzene can be used as solvents in this reaction.

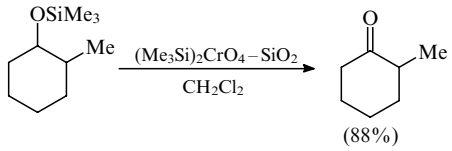
3. Oxidation of silyl ethers

Bis(trimethylsilyl) chromate supported on silica gel was also used for the oxidation of trimethylsilyl ethers of primary and secondary alcohols.[54] This reaction was run in dichloromethane.



R = Ph (95%), PhCH = CH (71%).



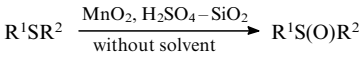


It is worth noting that in addition to the expected cinnamic aldehyde, the oxidation of 3-phenylallyl silyl ether yielded an appreciable amount (28%) of benzaldehyde, which points to the vulnerability of the double bond under these conditions.

Special mention should be made of the oxidation of trimethylsilyl ethers by atmospheric oxygen which is catalysed by manganese and cobalt salts of 4-aminobenzoic acid supported on silica gel.[55] This reagent is also effective in the transformation of acetals and ketals into the corresponding carbonyl compounds.

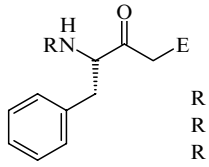
4. Oxidation of sulfides

An effective procedure for the synthesis of sulfoxides by oxidation of sulfides in the absence of solvents has been developed.[56] The oxidation is carried out with manganese dioxide in the presence of a catalytic system, $H_2SO_4-SiO_2$.



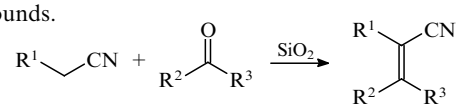
VI. Condensations

Silica gel is an efficient catalyst for the Knoevenagel condensation. The condensation of peptidylacetonitriles derived from *N*-acetyl-L-phenylalanine, *N*-acetyl-L-leucyl-L-phenylalanine and *N*-acetyl-L-leucyl-D-phenylalanyl-L-phenylalanine with aromatic aldehydes and ketones has been described.[57]



R = Ac: E = CN, CO_2Me, NO_2;
R = *N*-Ac-L-Leu, E = CN;
R = *N*-Ac-L-Leu-D-Phe, E = CN.

When this reaction is performed under homogeneous conditions, it requires weak bases, but even in this case the yields of reaction products are moderate. High yields can be achieved in heterogeneous conditions, *viz*., on silica gel. It is assumed that silica gel, which is acidic, catalyses enolisation of cyanomethyl ketones R^1CH_2CN and activates electrophilic carbonyl compounds.

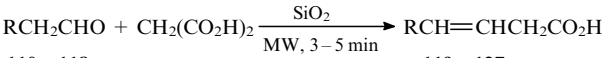


R^1	R^2	R^3	Yield (%)
L-PhCH$_2$CH(AcNH)C(=O)	H	4-$MeOC_6H_4$	100
	H	Ph	85
	H	4-$Me_2NC_6H_4$	58
	H	4-$O_2NC_6H_4$	37
	H	2-$HO_2CC_6H_4$	97
	H	3-MeO-4-HOC_6H_3	93
	$-(CH_2)_5-$		46
	$-(CH_2)_4-$		35
	Me	Me	44
	$HOCH_2$	Me	80
	MeC(OH)H	Me	61
L-PhCH$_2$CH(*N*-Ac-L-Leu)NHC(=O)	H	4-$MeOC_6H_4$	98
L-PhCH$_2$CH(*N*-Ac-L-Leu-D-Phe)NHC(=O)	H	4-$MeOC_6H_4$	94

This reaction holds great promise in the synthesis of peptide inhibitors of α-chymotrypsin by virtue of its operational simplicity, high yields of the reaction products and the fact that it is not accompanied by epimerisation. The condensation of (*N*-acetylphenylalanyl)acetonitrile with 2-formylbenzoic acid and vanillin has demonstrated that no preliminary protection of functional groups is necessary when this reaction is performed on silica gel. These data altogether suggest that silica gel is a mild selective acidic catalyst of the Knoevenagel reaction.

In addition to peptidylacetonitriles, other compounds, such as R^1CH_2E (E = CN, CO_2Me, NO_2; R = CN, NO_2, C(O)Ph, CO_2Me, CO_2Et and SO_2Ph) containing activated methylene groups, were tested in this reaction. It was found that the reaction takes place only if compounds with E = CN and R^1 = CN, NO_2 and C(O)Ph are used; compounds with E = CO_2Me and R^1 = CO_2Me, CO_2Et and SO_2Ph do not enter into this reaction, presumably, due to steric hindrances.

The reaction of malonic acid with carbonyl compounds is an important synthetic route to the preparation of valuable unsaturated acids. α,β-Unsaturated acids are formed upon heating of the starting compounds in the presence of bases (pyridine and piperidine). The Knoevenagel condensation catalysed by SiO_2 was recommended for the synthesis of β,γ-unsaturated acids.[58] This reaction was performed under microwave irradiation without any solvent.



110 – 118 **119 – 127**

R = Et (**110**, **119**, 84%), Pr^n (**111**, **120**, 83%), Bu^n (**112**, **121**, 84%), n-C_5H_{11} (**113**, **122**, 84%), n-C_6H_{13} (**114**, **123**, 88%), n-C_7H_{15} (**115**, **124**, 86%), n-C_8H_{17} (**116**, **125**, 90%), Ph (**117**, **126**, 92%), Bn (**118**, **127**, 89%).

Thus the reactions of aldehydes **110**–**118** with malonic acid afforded unsaturated acids **119**–**127**. The target products are formed in high yields and are stereochemically pure. The method is distinguished by the ease of preparation and rapidity.

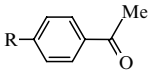
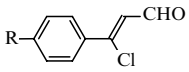
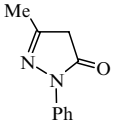
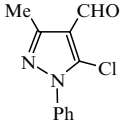
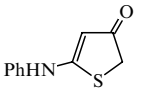
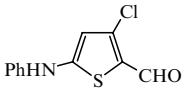
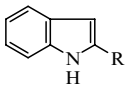
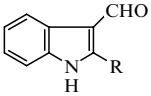
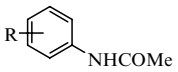
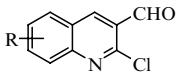
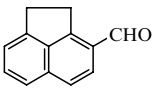
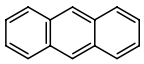
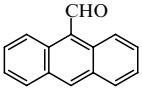
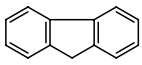
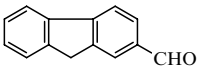
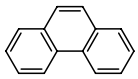
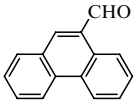
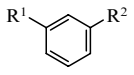
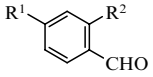
VII. Formylation

The Vilsmeier–Haack reaction is widely employed for the introduction of aldehyde groups into aromatic rings. Taking into account the great importance of this reaction in organic synthesis, Paul *et al*.[59] made an attempt to find optimum conditions for its performance. It was found that irradiation in a conventional microwave oven of substituted aromatic compounds and the Vilsmeier–Haack reagent ($POCl_3$–DMF) supported on silica gel affords maximum yields of the corresponding aldehydes and decreases reaction time to 1.5–2.5 min (Table 2).

The amount of the reagent is crucial for achieving maximum yields. For liquid substrates supported on silica gel, the amount of the Vilsmeier-Haack reagent may not exceed 2 equiv., whereas formylation of solid substrates requires no less than 3 equiv. The amount of silica gel pre-irradiated for 5 min at 700 W needed for the formylation also depends on the amount of the reagent. Evidence for the important role of microwave irradiation in this reaction follows from the fact that the yields of aromatic aldehydes formed upon microwave irradiation exceed significantly those obtained upon conventional heating of the reactants at the same temperature.

The use of microwave irradiation in combination with silica gel is an excellent procedure for the rapid (within 1.5–2.5 min) and quantitative Vilsmeier–Haack reaction.

Table 2. The Vilsmeier – Haack reaction.

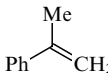
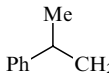
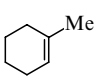
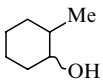
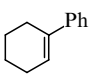
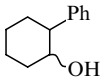
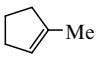
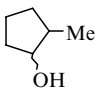
Starting compound	Product	Yield (%)
		
	R = Cl	79
	R = Br	75
	R = OMe	88
		66
		64
		
	R = Ph	71
	R = 4-MeC$_6$H$_4$	68
	R = 4-ClC$_6$H$_4$	75
		
	R = H	79
	R = 6-OMe	58
	R = 6-Me	65
	R = 8-Me	75
	R = 7-Me	68
		89
		92
		72
		78
		
	R^1 = R^2 = OH	81
	R^1 = R^2 = OMe	85
	R^1 = NMe$_2$, R^2 = H	78

VIII. Hydration and dehydration reactions

Dehydration of alcohols resulting in the formation of alkenes and the inverse reaction, *viz*., hydration of alkenes, are valuable synthetic conversions widely applicable in organic synthesis.

A general method for the selective anti-Markownikoff addition of water to alkenes in the presence of silica gel has been described in detail by Ranu.[60] An alkene supported on preactivated silica gel (200 °C, reduced pressure) was treated with a solution of $Zn(BH_4)_2$ in 1,2-dimethoxyethane (DME) at room temperature and then hydrolysed. This reaction gives good yields of primary and secondary alcohols (Table 3).

Table 3. Anti-Markownikoff addition of water to alkenes.

Starting compound	Product	Yield (%)
Me(CH$_2$)$_6$CH=CH$_2$	Me(CH$_2$)$_6$CH$_2$—CH$_2$OH	95
Ph—CH=CH$_2$	Ph—CH$_2$—CH$_2$OH + Ph—CH(OH)—Me (4 : 1)	85
		90
		80
	cis : *trans* = 3 : 7	
		70
	cis : *trans* = 1 : 3	
		70
	cis : *trans* = 3 : 7	

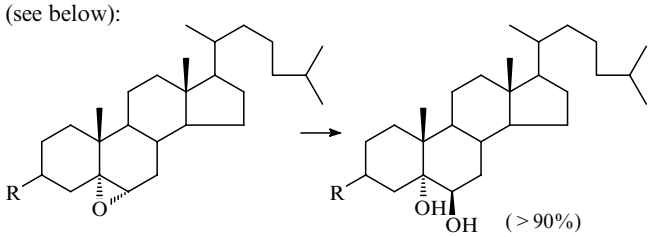
The obvious advantages of this method include ease of performance, mild conditions, lack of side reactions and high yields of reaction products. The reaction mechanism is not quite clear, but the authors exclude the possibility of conventional hydroboration – oxidation.

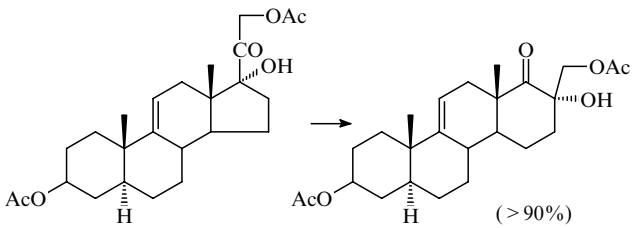
The efficiency of silica gel in the dehydration of alcohols is determined by the acidic properties of its surface (SiO_2 is a weak Lewis acid).

Thus application of iron(III) chloride hexahydrate dissolved in a volatile solvent (methanol, ether, *etc*.) onto the surface of commercial silica gel (Kieselgel 60, Merck) and subsequent evaporation of the solvent under high vacuum (0.1 Torr) yield a catalyst for selective dehydration of tertiary, allylic and sterically hindered secondary alcohols.[61] The corresponding alkenes are obtained in quantitative yields (Table 4).

This reaction is carried out under mild conditions using ether and acetone as solvents. The content of water affects the catalytic activity: the addition of H_2O (2 mass %) to the dry catalyst changes only slightly the catalytic activity, whereas at higher water content (> 10%) the activity is completely lost.

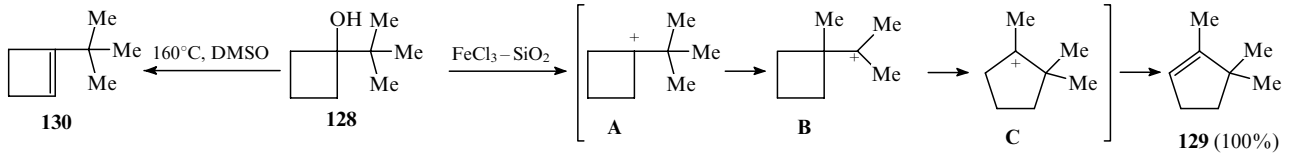
The $FeCl_3 \cdot 6H_2O - SiO_2$ system containing 2% of water also catalyses the epoxide ring opening and certain rearrangements (see below):



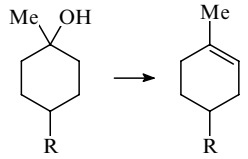


Later, the $FeCl_3 - SiO_2$ system prepared from anhydrous iron chloride by simple grinding of components was recommended for dehydration of alcohols.[62] This system proved to be efficient in

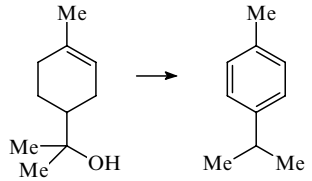
Scheme 1



dehydration of tertiary alcohols where the yields of reaction products were quantitative.



R = Me (95%), Bu^t (91%).

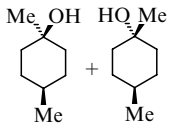
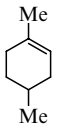
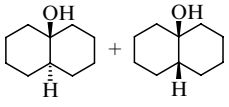
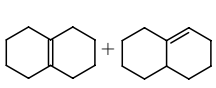
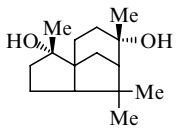
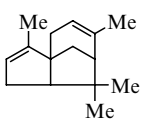
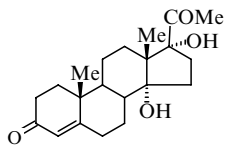
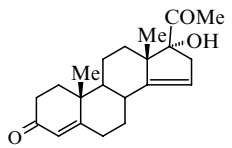
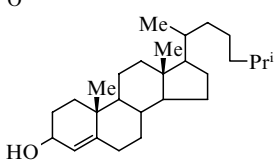
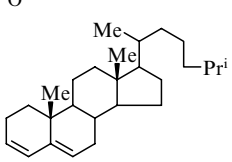


(90%)

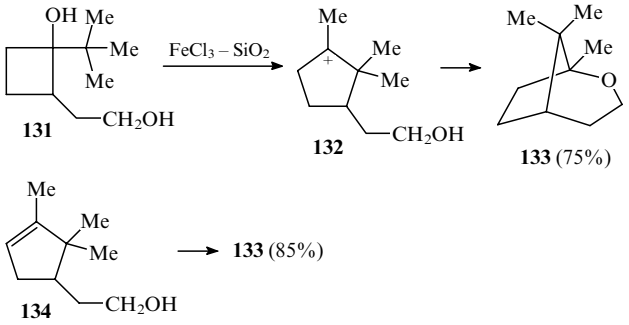
The reaction is carried out in the absence of the solvent. 1-*tert*-Butylcyclobutan-1-ol **128** undergoes an interesting rearrangement with ring enlargement and formation of 1,5,5-trimethylcyclopentene (**129**) (Scheme 1). In this case, the dehydration occurs *via* carbocations **A**, **B** and **C**.

If the dehydration of the alcohol **128** is carried out under different conditions, *viz*., by heating in DMSO at 160 °C, compound **129** is formed in low yield (5%), while the yield of the alkene **130** reaches 95%.

Table 4. Selective dehydration of alcohols by iron(III) chloride on silica gel.

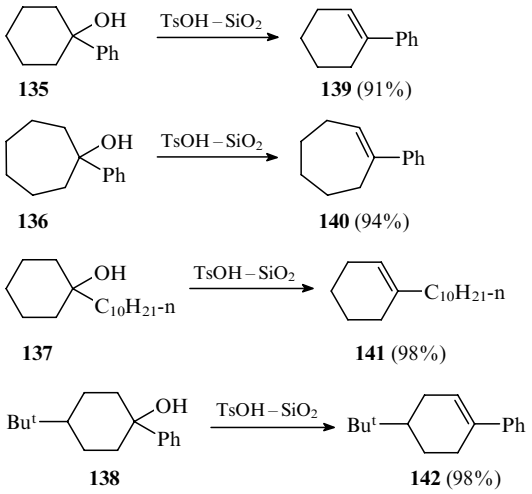
Starting compound	Product	Yield (%)
		>90
		>90
		>90
		>90
		>90

The dehydration of the alcohol **131** in the presence of the $FeCl_3 - SiO_2$ system also proceeds *via* the intermediate cyclopentyl cation **132** and results in the cyclic ether **133**. The same product (**133**) is obtained in good yield upon dehydration of the alcohol **134** under identical conditions.

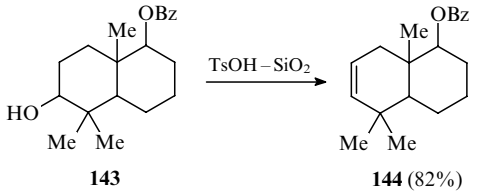


Thus, the $FeCl_3 - SiO_2$ system catalyses efficiently both dehydration reactions and rearrangements including ring enlargement. Some rearrangement products are key precursors in the synthesis of sesquiterpenoids.

Toluene-*p*-sulfonic acid supported on silica gel is an excellent catalyst in dehydration of secondary and tertiary alcohols (primary alcohols do not react under these conditions).[63] Thus alcohols **135** – **138** are converted into alkenes **139** – **142** in high yields.

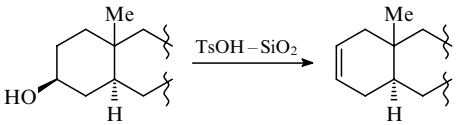


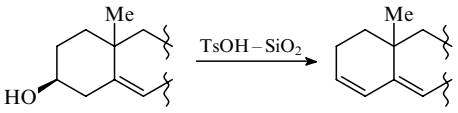
Dehydration of the alcohol **143** gave alkene **144** in somewhat lower yields under identical conditions.†



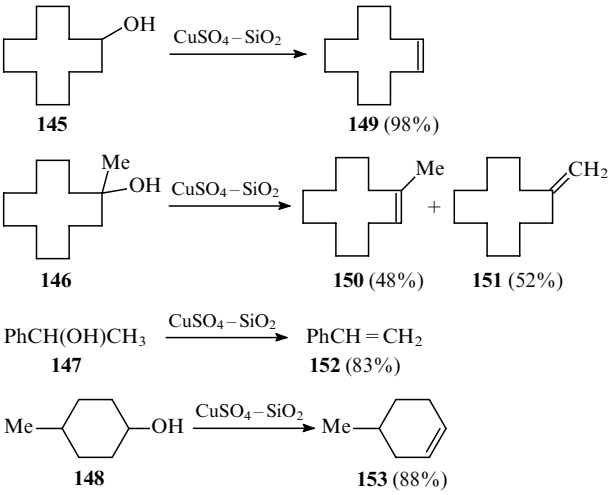
This system was also used for dehydration of 3-hydroxysteroids. The reaction occurred *via* carbocations and resulted in Δ^2-alkenes and $\Delta^{3,5}$-dienes.

† The authors' unpublished data.





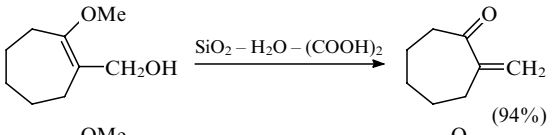
It was found [64] that silica gel-supported copper(II) sulfate is an efficient catalyst in smooth dehydration of secondary and tertiary alcohols into alkenes. The catalyst was prepared by mixing chromatographic silica gel with an aqueous solution of copper(II) sulfate with subsequent evaporation by heating at 2 Torr. The catalytic activity depended on the evaporation time and temperature and was maximum when the catalyst was dried at 200 °C for 3 h or at 240 °C for 1 h. With a further increase in the evaporation temperature (300 °C, 1 h), the catalyst lost its activity completely. The dehydration rate depended on the $SiO_2 : CuSO_4$ ratio (the optimum ratio is 4 : 1). Under these conditions, alcohols **145** – **148** are converted into alkenes **149** – **153** in high yields.

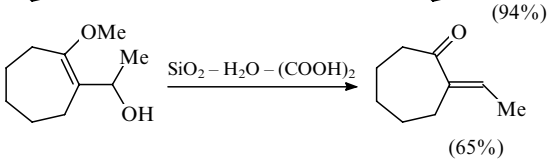


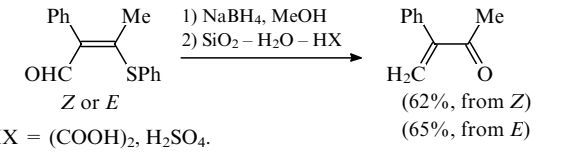
Tertiary alcohols are dehydrated more easily than secondary ones. The mechanism of this reaction is still unclear, but it is reasonable to assume the formation of carbenium cations, since dehydration rates of tertiary alcohols are higher than those of secondary and primary ones. This system can also be used for dehydration of 3-hydroxysteroids.

Special mention should be made of a detailed study [65] of dehydration of various primary, secondary and tertiary alcohols catalysed by transition metal sulfates supported on silica gel. The activities of various brands of silica gel in this reaction have been compared. The highest activity was manifested by Silica gel BW-300 (Fuji-Davidson). The catalytic activities of metal sulfates supported on silica gel decreased in the following order: Fe(III) = Ce(IV) = Ti(IV) > Sn(IV) > Al(III) > Cu(II) > Zn(II) > Co(III) > Ni(II) > Fe(II) > Mn(II) > Cd(II). The optimum conditions (time, temperature) for treatment of catalysts providing maximum yields of dehydration products have been found.[65] The effects of solvents, reagent ratios and reaction conditions on the product yields have been investigated. Some suggestions on the possible mechanism of this reaction have been put forward.

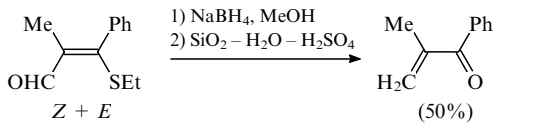
Interesting examples of the preparation of α-methylidenecarbonyl compounds from derivatives of cyclic β-(hydroxyalkyl)-vinyl ethers, β-alkylthio- and β-arylthioacroleins have been described,[66] which involved dehydration of intermediate alcohols in the presence of silica gel as one of the steps. The following catalytic systems, *viz.*, $SiO_2 - H_2O - HOOCCOOH - HgCl_2$, $SiO_2 - H_2O - HOOCCOOH$ and $SiO_2 - H_2O - H_2SO_4$ and dichloromethane as a solvent, were employed.







HX = $(COOH)_2$, H_2SO_4.



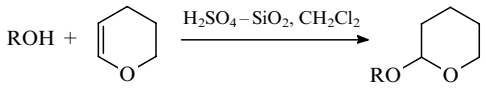
IX. Protection of functional groups

The use of silica gel as a catalyst for introduction of protective groups is a popular procedure in organic synthesis.

1. Tetrahydropyranylation of alcohols

The tetrahydropyran-2-yl group (THP) is one of the most popular groups used for the protection of alcohols and phenols. Many methods have been devised for its introduction.

It has been found [67, 68] that sulfuric acid adsorbed on silica gel can be used as a catalyst in tetrahydropyranylation of alcohols and phenols. Dichloromethane is generally used as a solvent in this reaction.



R = Ph (95%), $PhCH_2$ (96%), α-$C_{10}H_7$ (98%), $PhCH{=}CHCH_2$ (96%), $PhOCH_2\underset{|}{C}HC{\equiv}CH$ (94%).

This simple and inexpensive method gives the reaction products, as a rule, in high yields.

Recently, this reaction has been carried out [69] using microwave irradiation in the presence of the same catalyst but without solvent. This permitted one to obtain reaction products in a pure state and in high yields. The absence of solvents makes it possible to run this reaction under mild conditions. Other advantages include short reaction time (10 – 15 min), omission of the aqueous workup and environmental safety.

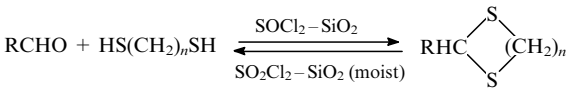
2. Thioacetalisation and acetalisation

Protection of carbonyl groups as acetals or thioacetals is a common procedure in the synthesis of organic compounds, in particular, of complex polyfunctional compounds. However, protic and Lewis acids and some silicon reagents [70] commonly used in (thio)acetalisation do not afford selective protection of aldehyde groups in the presence of keto groups.

Silica gel treated with thionyl chloride effects their protection. It was found that this silica gel effectively catalyses thioacetalisation ‡ of many aldehydes and ketones by 1,2-ethanedithiol or 1,3-

‡ The inverse reaction occurs upon treatment with sulfuryl chloride in the presence of wet silica gel.

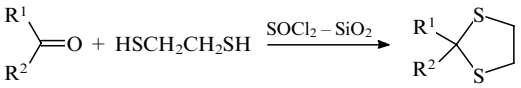
propanedithiol and affords selective protection of aldehyde groups when both these groups are present simultaneously.[71]



R	*n*	Yield of thioacetal (%)
C_6H_{13}	2	99
	3	99
PhCHMe	2	100
$H_2C=CH(CH_2)_8$	2	100
MeCH=CH	2	100
PhCH=CH	2	97
	3	100
Ph	2	100
	3	97
4-MeC_6H_4	2	98
4-ClC_6H_4	2	99
4-$MeOC_6H_4$	2	98
4-HOC_6H_4	2	88
4-$HO_2CC_6H_4$	2	98
4-$Me_2NC_6H_4$	2	98
2-$O_2NC_6H_4$	2	93

By itself, silica gel (without $SOCl_2$) does not manifest any noticeable catalytic activity in thioacetalisation of aldehydes. Treatment of heptanal with 1,2-ethanediol afforded the corresponding 1,3-dithiolane in as low a yield as 11%.

The reaction with ketones in benzene proceeds very slowly; however, this can be completed within 24 h in boiling toluene.

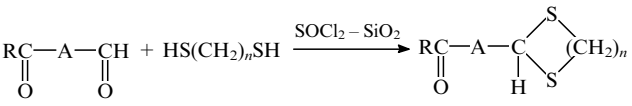


R^1	R^2	Yield (%)
Ph	Me	91
$-(CH_2)_5-$		100
$PhCH_2$	$PhCH_2$	93
Ph	Ph	31

The difference in the rates of thioacetalisation of aldehydes and ketones permits selective protection of aldehydes in the presence of ketones (Table 5) as well as selective thioacetalisation of oxo aldehydes.

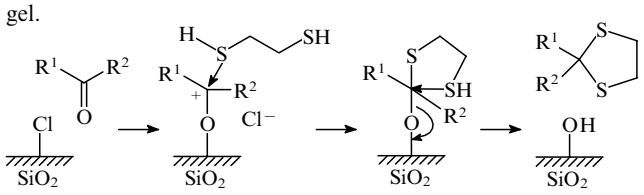
Table 5. Thioacetalisation of mixtures of aldehydes and ketones in the presence of $SOCl_2-SiO_2$.

Aldehyde	Ketone	Conversion	
		aldehyde	ketone
PhCHO	PhC(O)Me	100	0
4-ClC_6H_4CHO	PhC(O)Me	96	0
Bu^n(Et)CHCHO	$(PhCH_2)_2C=O$	100	0
4-$MeOC_6H_4CHO$	$Bu^i_2C=O$	100	0
Ph(Me)CHCHO	PhCH=CHC(O)Me	83	0
$C_6H_{13}CHO$	PhC(O)C(O)Ph	100	0



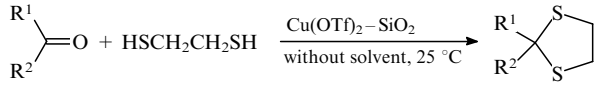
A	R	*n*	Yield (%)
$-C_6H_4-$	Me	2	90
	Me	3	99
	Ph	2	78
$-(CH_2)_3-$	Me	2	89
	Me	3	98
$-CH_2CH(Ph)CH_2-$	Me	2	98
	Me	3	99
$-CHMe-$	Ph	2	92
	Ph	3	92

All these reactions proceed with high selectivity and do not require complex equipment. The unusual chemoselectivity of this method can be attributed to the differences in spatial interactions of the aldehyde and ketone groups with the porous surface of silica gel.



This method holds especially great promise for multistep syntheses of complex molecules.

The synthesis of thioacetals from aldehydes (or ketones) and 1,2-ethanedithiol in the presence of catalytic amounts of copper(II) trifluoromethanesulfonate supported on silica gel in the absence of solvents has been described.[72] All thioacetals were obtained in high yields.

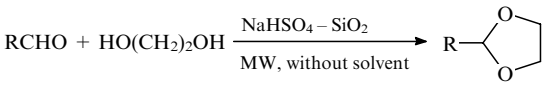


R^1	R^2	Yield (%)
n-C_6H_{13}	H	91
cyclo-C_6H_{11}	H	92
2-Furyl	H	91
2,5-$(MeO)_2C_6H_3$	H	98
PhCH=CH	H	89
2-HOC_6H_4	H	96
2-$O_2NC_6H_4$	H	93
4-ClC_6H_4	H	98
4-MeC_6H_4	H	99
4-$MeOC_6H_4$	H	99
4-HOC_6H_4	H	94
Ph	Me	92
$-CH_2CH_2CHBu^tCH_2CH_2-$		94
$-CH_2CH(CO_2Me)CH(CO_2Me)CH_2-$		93

In most cases, the reactions proceed selectively and at room temperature. This reaction can also be performed in the presence of the $CuCl_2-SiO_2$ system (in the absence of solvent), however, in this case the reaction rate and the product yields are lower.

In addition to thioacetals, cyclic acetals, which are stable in alkaline or weakly acidic media, are used to protect aldehydes and ketones in multistep syntheses.[73] The reaction of aldehydes with ethylene glycol in the presence of strong protic or Lewis acids is a common procedure for their synthesis; however, this method is characterised by low yields and long reaction time. Other methods for acetal synthesis require drastic conditions, the use of expensive or hazardous reagents, sophisticated synthetic and isolation procedures, *etc*.

An efficient method for protection of the aldehyde and ketone groups by treatment with ethylene glycol with microwave irradiation without any solvent has been developed.[74] Here, metal sulfates [$Ce(SO_4)_2$, $MgSO_4$ and $NaHSO_4$] supported on silica gel are used as catalysts.



R = Ph (85%), 2-$O_2NC_6H_4$ (98%), 2-$MeOC_6H_4$ (82%), 2-ClC_6H_4 (90%), 3-NCC_6H_4 (97%), 3-$PhOC_6H_4$ (85%), 3-$BnOC_6H_4$ (81%), PhCH(CN) (90%), β-$C_{10}H_7$ (87%), 4-[PhC(O)CH_2O]C_6H_4 (75%),

PhCH=CH (81%),  [X = O (94%), S (81%)],

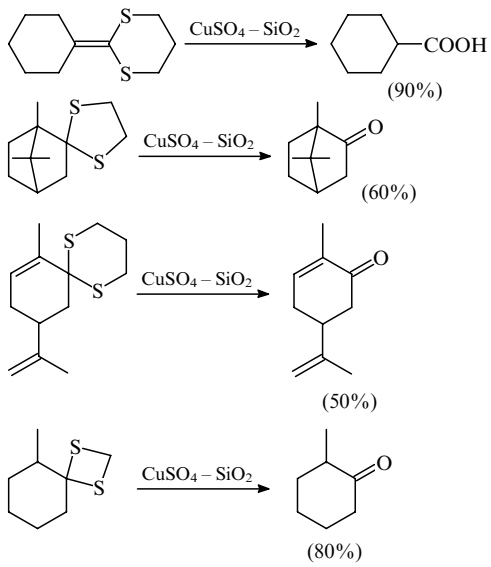
MeCH=CH (82%), $MeC(O)CH_2CH_2$ (82%), n-C_6H_{13} (90%), n-$C_{10}H_{21}$ (87%), $ClCH_2CH$=CH (78%), $MeO_2C(CH_2)_4$ (85%).

This technique provides selective protection of aldehyde groups in the presence of keto groups (the latter proved to be fairly resistant to microwave irradiation).

X. Deprotection of functional groups

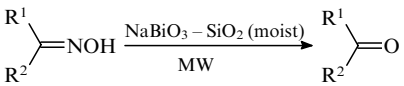
There is a vast body of evidence concerning the use of silica gel as a catalyst in hydrolytic reactions aimed at removal of protective (trityl, ketal, ester, *etc.*) groups.[3,21] Some examples of these reactions will be given below.

Very good yields of carbonyl compounds were obtained upon removal of the thioacetal group by boiling the dithioacetals in organic solvents with silica gel-supported copper(II) sulfate.[75]



The reaction is generally completed in 2–20 h. Its mechanism is still unclear.

Many oximes are converted into the starting carbonyl compounds under the action of chromium trioxide supported on silica gel.[76] These reactions occur on heating in such solvents as toluene, benzene or ether. Mitra *et al.*[77] have proposed to use sodium bismuthate supported on moist silica gel for removal of the oxime protective group. This reaction is initiated by microwave irradiation.



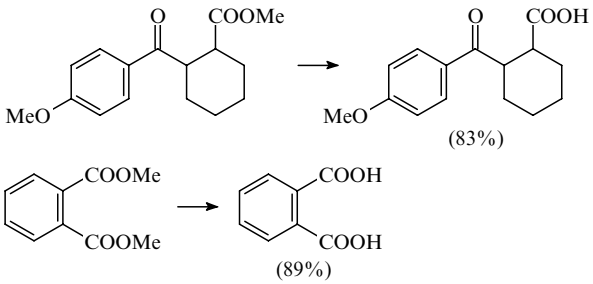
R^1	R^2	Yield (%)
Bu^i	Me	81
$-(CH_2)_5-$		73
Ph	Ph	90
$C_{10}H_7$	Me	90
Ph	Me	89
4-MeC_6H_4	Me	85
4-$MeOC_6H_4$	Me	94
4-$O_2NC_6H_4$	Me	82

This reaction is quantitative and is completed within several minutes at normal pressure.

Later, the same authors used this reagent to convert semicarbazones into the original carbonyl compounds.[78]

Hydrolysis of esters, which is usually carried out by heating in aqueous solutions of acids or bases, is one of the most common reactions in organic synthesis. These conditions can result in hydrolysis of compounds containing acid- or base-sensitive groups. Therefore, studies in this field are aimed at the search for conditions of ester hydrolysis in neutral media. An original procedure for ester hydrolysis by microwave irradiation on moist silica gel impregnated with indium triiodide has been proposed recently.[79] This approach made it possible to hydrolyse various acyclic and carbocyclic esters to the corresponding acids in high yields.

R = $PhCH_2$ (92%), n-$C_{17}H_{35}$ (70%), Ph_2CH (70%).



The duration of this reaction was 25–80 min. This reaction proceeded smoothly even in the case of sterically hindered esters and diesters. Mild reaction conditions make this reaction suitable for hydrolysis of compounds containing additional functional groups, *e.g.*, keto and hydroxy groups, as well as C=C bonds.

XI. Miscellaneous reactions

Among other reactions, we shall consider the Nef, Ritter, Wittig and Prins reactions as well as acylation, substitution, halogenation and ring-opening reactions. These types of conversions will be outlined below.

1. The Nef reaction

The use of silica gel in the Nef reaction has been described.[80] Nitroalkanes were converted into the corresponding carbonyl compounds in high yields by treatment with sodium percarbonate in the presence of silica gel in aqueous DMF (40 °C, 1 h).

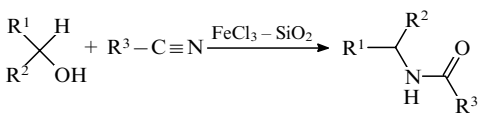


R^1	R^2	Yield (%)
$-(CH_2)_4-$		73
$-(CH_2)_5-$		68
n-C_5H_{11}	H	65
$PhCH_2$	Me	81

In the absence of silica gel, the reaction proceeds at a slow rate (12–15 h). If sodium carbonate is used instead of percarbonate, the reaction does not take place.

2. The Ritter reaction

The Ritter reaction of benzyl alcohols with nitriles initiated by iron(III) chloride supported on silica gel results in the corresponding amides in high yields.[81]



R^1	R^2	R^3	Yield (%)
Ph	Ph	Me	94
Ph	Me	Me	95
Ph	Ph	$PhCH_2$	92
4-$MeOC_6H_4$	H	Me	80
4-ClC_6H_4	H	$ClCH_2$	91
4-$O_2NC_6H_4$	H	Ph	–

This reagent has a number of advantages over concentrated sulfuric acid commonly used in this reaction; it is non-hygroscopic and does not require any special precautions. All reactions were conducted under solvolytic conditions using nitrile as a solvent. The iron salt and the substrate were used in equimolar amounts. *p*-Nitrobenzyl alcohol does not enter into the reaction under these conditions.

3. The Wittig reaction

The Wittig reaction with the use of silica gel[82] allows one to selectively synthesise α,β-unsaturated carbonyl compounds in high yields from stable phosphorylides and aldehydes. Thus irradiation of mixtures of ethoxycarbonylmethylidenetriphenylphosphorane with aldehydes in a microwave oven in the presence of silica gel yielded esters of the corresponding α,β-unsaturated carboxylic acids.

$$RCHO + Ph_3\overset{+}{P}-\overset{-}{C}HCOOMe \xrightarrow[n\text{-}C_6H_{14},\ MW]{SiO_2} RCH{=}CHCOOMe$$

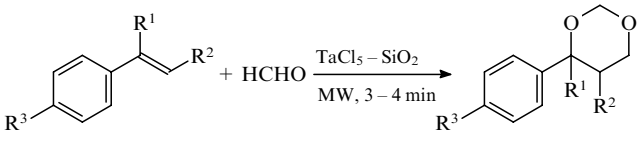
R = Pr^n (87%), Bu^t (78%), cyclo-C_6H_{11} (90%), $MeOCH_2$ (85%).

The use of silica gel not only accelerates the reaction, but also promotes the separation of the triphenylphosphine oxide formed. As a result, target products are formed in high yields and do not contain admixtures. In addition to aldehydes, ketones can also be involved in the reaction.

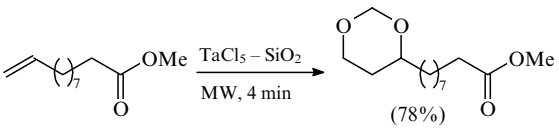
4. The Prins reaction

The Prins reaction, which includes condensation of alkenes with aldehydes (usually, formaldehyde), affords 1,3-diol derivatives. This reaction is catalysed by mineral acids, soft Lewis acids and solid catalysts, such as ion-exchange resins, zeolites and clays (montmorillonite K-10).

Recently, the Prins reaction has been carried out with microwave irradiation under solvent-free conditions using $TaCl_5$ supported on silica gel as a catalyst.[83] Under these conditions, alkenes were converted into 1,3-diol derivatives in high yields.



R^1	R^2	R^3	Yield (%)
H	H	H	90
Me	H	H	88
H	Me	H	86
H	H	Me	88
H	H	Cl	85
H	H	NO_2	80
H	Me	Me	90
H	Ph	H	85



These reactions are usually completed within 3 – 4 min, whereas under conventional conditions (in dioxane) it takes 10 – 13 h and the yields do not exceed 80%.

5. Substitution reactions

Thioamides were converted into the corresponding amides under mild conditions by treatment with Caro's acid (peroxymonosulfuric acid) supported on silica gel. The reaction was carried out in acetonitrile at room temperature in air.[84]

$$R^1C(S)NHR^2 \xrightarrow{H_2SO_5-SiO_2} R^1C(O)NHR^2$$

R^1	R^2	Yield (%)
Ph	CH_2Ph	84
4-$O_2NC_6H_4$	CH_2Ph	76
Ph	Bu^n	82
Me	C_6H_4Me	87

This reaction is operationally simple. However, it is not suitable for conversion of primary thioamides which yield a mixture of products difficult to identify. Despite this limitation, Caro's acid supported on silica gel allows mild conversion of secondary and tertiary thioamides into amides in the yields comparable and sometimes exceeding those described previously. This reaction is successfully employed in the chemistry of thio analogues of nucleic acids and nucleosides.[85]

6. Synthesis of nitriles from aldehydes

Nitriles are used as starting components in the synthesis of many biologically active compounds; therefore, elaboration of effective methods of their synthesis is a topical problem. The conversion of aldehydes into the corresponding nitriles represents an important transformation of functional groups. A simple and efficient procedure for the synthesis of nitriles from aldehydes and hydroxylamine using microwave irradiation in the presence of $NaHSO_4$ supported on silica gel has been described.[86]

$$RCHO \xrightarrow[NaHSO_4-SiO_2,\ MW]{NH_2OH-HCl} RCN$$

R = Ph (84%), 4-HOC_6H_4 (90%), 4-$MeOC_6H_4$ (91%), 3-Me-4-HOC_6H_3 (96%), 3-HOC_6H_4 (91%), 3,4-$(MeO)_2C_6H_3$ (97%), 3,4-$(CH_2O_2)C_6H_3$ (95%), PhCH = CH (85%), n-C_7H_{15} (81%), n-C_8H_{17} (80%).

This reaction proceeds very fast (1 – 3 min) and final products are formed in high yields. Presumably, the aldehyde is converted into the corresponding aldoxime which is immediately dehydrated to yield the nitrile.

7. Acylation, alkylation and esterification

The use of solid adsorbents in organic synthesis provides high selectivity in many chemical reactions including alkylation, acylation, esterification, *etc*. The most essential feature of these reactions is that they can be applied for selective protection of one functional group in bi- and polyfunctional compounds. Thus acetylation of a series of symmetrical 1,*n*-diols adsorbed on silica gel (Wako gel C-200, Wako Pure Chemical Industries) by heating with acetyl chloride in cyclohexane resulted in monoacetyl derivatives in quantitative yields.[87]

$$HO(CH_2)_nOH \xrightarrow[2\text{ h, boiling}]{AcCl,\ cyclo\text{-}C_6H_{12}} AcO(CH_2)_nOH$$

n	Yield on SiO_2 (%)		Yield in the homogeneous reaction (%)
	mono	bis	
4	99.5	0	52.3
6	99.5	0	58.6
8	99.8	0	54.3
10	99.8	0	56.5
12	99.0	1.0	66.5
16	99.9	0	30.2

n	Yield on SiO_2 (%)		Yield in the homogeneous reaction (%)
	mono	bis	
HO—⬡—OH	29.9	40.8	32.6
$HOCH_2$—⬡—CH_2OH	36.0	47.5	52.5

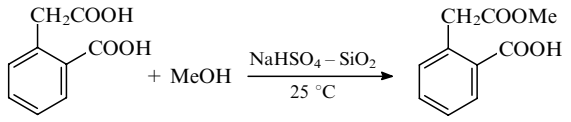
Under identical conditions, cyclic diols [cyclohexane-1,4-diol and 1,4-bis(hydroxymethyl)benzene] yield predominantly diol diacetates. The dependence of reaction selectivity on temperature was studied in the example of cyclohexane-1,4-diol; the yields of monoacetylated and bisacetylated products at 80 °C were 29.9% and 40.8% and at 0 °C, 52.4% and 19.3%.

The silica gel used in this reaction seems to play a protective role for one of hydroxy groups of the diol which is adsorbed on the silica gel surface. It is thought that the diol is adsorbed on the surface of silica gel resulting in the formation of a monomolecular layer, which has been demonstrated in the methylation of alcohols (1-decanol, geraniol and cyclohexanol), phenol, α- and β-naphthols, 2,6-di-*tert*-butylphenol, *etc*., by diazomethane.[88] Presumably,[88] it is alcohols (in the form of alkoxides) adsorbed on the surface of SiO_2 that enter into the reaction. This reaction does not take place in the absence of silica gel. Ogawa *et al*.[88] determined the maximum amount of the alcohol adsorbed on silica gel beyond which the reaction rate does not change further. For 1-decanol, it was equal to 4 mmol g^{-1} SiO_2, which corresponds to the formation of a monomolecular layer of the alcohol molecules on the surface of silica gel. It was found that 2,6-di-*tert*-butylphenol, which cannot be adsorbed on the surface of SiO_2 due to steric hindrances, is not methylated under these conditions.

An alternative procedure[89] for selective monoacylation of diols by reaction with esters (ethyl acetate, ethyl formate, methyl propionate, methyl isobutyrate) has been developed;[89] this reaction is catalysed by metal sulfates [$NaHSO_4$, $Ce(SO_4)_2$] supported on chromatographic silica gel. This method was used to prepare monoesters of ethylene glycol, butane-1,4-diol, pentane-1,5-diol and hexane-1,6- and -2,5-diols.

The reaction occurs in the presence of hexane at the controllable hexane : ester ratio of ~1 : 4. The yields of monoesters decrease with the increase in this ratio. This phenomenon is attributed to the effect of solvent polarity on the adsorption of alcohols and esters. With the above ratio, only alcohols are adsorbed, which are more polar than the monoesters.

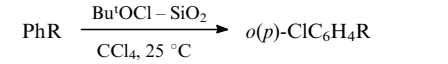
A selective procedure for esterification of aliphatic carboxylic acids in the presence of aromatic acids has been developed;[90] an interesting example of selective esterification of dicarboxylic acid **154** into the monoester **155** has been described.



154 **155** (96%)

8. Halogenation of aromatic compounds

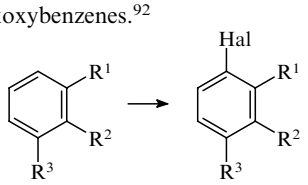
Preparation of novel effective reagents for electrophilic chlorination of aromatic compounds has been described.[91] It was found that many chlorine-containing organic compounds acquire strong electrophilic properties in the presence of silica gel, although they differ substantially in reactivities. The systems based on *N*,*N*-dichlorourethane, dichloramine-T and *tert*-butyl hypochlorite appeared to be the most active. They quantitatively chlorinate aromatic compounds under controlled conditions. The *tert*-butyl hypochlorite – chromatographic silica gel (BDH) system proved to be very convenient for monochlorination of some aromatic compounds.[91] In some cases, the yields of *ortho*- and *para*-chlorinated derivatives reached 100%.



R	Yield (%)	*ortho* : *para* Ratio
Me	100	65 : 35
Et	86	57 : 43
Pr^i	100	44 : 56
Bu^t	70	15 : 85
OMe	100	30 : 70
Ph	70	56 : 44

This reaction has significant advantages over classical electrophilic chlorination reactions involving chlorine and sulfuryl chloride and is characterised by high yields, ease of isolation of reaction products and the absence of HCl. The nature of silica gel is very important for the successful implementation of this reaction. Satisfactory results were obtained exclusively with strongly acidic (pH < 5) chromatographic silica gel dried at 120 °C. The dichlorourethane – silica gel system in acetonitrile was used for chlorination of benzene and the dichloramine – silica gel system in carbon tetrachloride was used for chlorination of toluene.

The addition of silica gel to *N*-bromosuccinimide in carbon tetrachloride resulted in a catalytic system, which allows selective monobromination (presumably, in the *para*-position) of some alkoxybenzenes.[92]



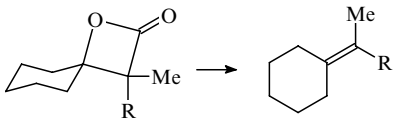
R^1	R^2	R^3	Yield (%)
OMe	H	OMe	99
OMe	OMe	H	98
Me	H	OMe	87
Pr^i	H	OMe	78
Et	H	OMe	90
H	H	OMe	90
H	H	OEt	96

Thus bromination of *m*-alkylmethoxybenzenes (Alk = Me, Et, Pr^i) occurs exclusively in the *para*-position relative to the methoxy group. 4-Bromo-3-*tert*-butyl-1-methoxybenzene is the major product even in the case of *m*-(*tert*-butyl)methoxybenzene. Quite unexpectedly, the ratio of 4-Br- to 6-Br-derivatives was found to be equal to 74 : 26, considering the large size of the *tert*-butyl substituent (bromination of this compound in the presence of Fe-catalysts yields exclusively the 6-Br derivative). The rate of this reaction strongly depends on the amount of silica gel and the mixing rate; this points to the heterogenous character of the reaction. No bromination occurs in the absence of silica gel. Many types of silica gels manifest catalytic activities in this reaction; noteworthy, acidic silica gels are more reactive, whereas neutral and basic ones are more selective. The acidic chromatographic silica gel Microbead 3A (Fuji – Davidson) exhibited the highest efficiency. Availability of the commercial reagent, ease of performance, excellent yields of reaction products and the absence of hydrogen bromide make this method especially attractive.[92]

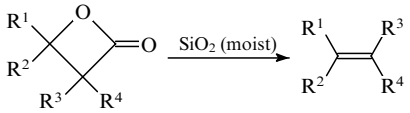
This reagent has been used in previous studies for the bromination of indoles and benzoimidazoles.[93]

9. Ring opening

A convenient method for the synthesis of high-boiling alkenes (b.p. = 250 °C) from β-lactones by heating the latter in benzene or cyclohexane in the presence of chromatographic silica gel has been proposed.[94]



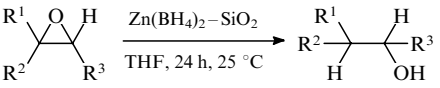
R = H (90%), Me (88%), CO_2Et (97%), CH_2OH (77%).



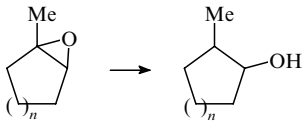
R^1	R^2	R^3	R^4	Yield (%)
Me	$Ph(CH_2)_2$	Me	Me	95
Me	$SiMe_2Bu^t$	H	H	93
Me	cyclo-C_6H_{11}	Me	H	95
Pr^i	H	n-C_7H_{15}	H	75

Distillation of lactones over moist silica gel is the best procedure for the preparation of alkenes with b.ps < 200 °C.[95] Silica gel was used to accelerate the decarboxylation of β-lactones; this is an excellent procedure for stereoselective synthesis of alkenes. Anhydrous silica gel fire-dried *in vacuo* is not always suitable for decarboxylation, since this may cause isomerisation of alkenes formed. In the above-described experiments, silica gel was used in the amount of 10 mass %, since the amount of water released in the course of distillation decreases with the silica gel dose.

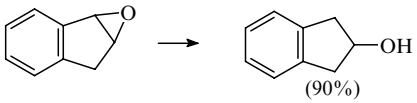
Zinc borohydride supported on silica gel proved to be a convenient reagent for the regio- and stereoselective opening of epoxides.[96] The least substituted alcohols are prepared by *anti*-opening of the rings.



R^1	R^2	R^3	Yield (%)
n-C_7H_{15}	H	H	88
$ClCH_2$	H	H	85
Ph	H	H	90
Ph	Me	H	91
Ph	H	Ph	88



n = 1 (84%), 2 (85%).



The main advantages of this method include high regioselectivity of epoxide opening, low toxicity and availability of the reagents.

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