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The Use of Heterogeneous Catalysis in Diels–Alder Reactions of N-Acetyl-α,β-dehydroalaninates

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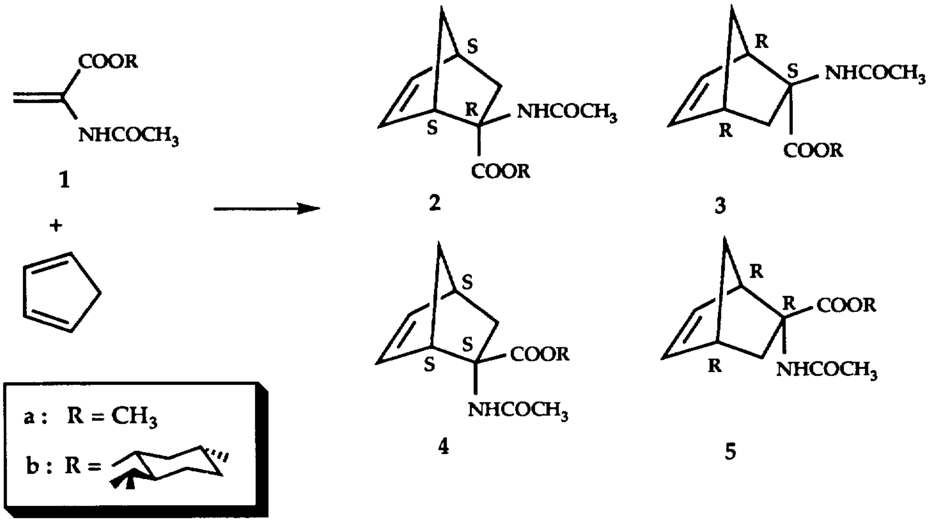
Abstract: Several solids have been tested as heterogeneous catalysts in the Diels–Alder reactions of the relatively unreactive dienophiles methyl (**1a**) and (–)-menthyl (**1b**) α,β-dehydroalaninates with cyclopentadiene, which is the key step in the asymmetric synthesis of cycloaliphatic α-amino acids. Reactions were carried out in toluene and in the absence of a solvent, the latter method leading to higher percentages of conversion. Silica gels modified with Lewis acids are the best catalysts for the reaction of the non-chiral dienophile **1a**, but they are completely inefficient in the reaction of the chiral dienophile **1b**, probably due to diffusional limitations. In the case of the chiral dienophile **1b**, silica gel is the best catalyst. Both *exo/endo* and diastereofacial selectivities are very similar to those obtained using homogeneous catalysts. The complete diastereofacial selectivity obtained in *exo* cycloadducts constitutes the best asymmetric induction described to date in asymmetric Diels–Alder reactions with heterogeneous catalysts.

INTRODUCTION

The Diels–Alder reaction, which is one of the most effective methods for obtaining six-membered rings with high stereochemical control, is usually catalyzed by Lewis acids. However, the use of these catalysts has drawbacks, such as the problem of disposing of environmentally hazardous residues. A great deal of effort has been devoted to the development of heterogeneous systems able to catalyze these reactions. It has been reported that several inorganic solids, such as silica gel,[1,2] magnesium silicate,[2] alumina,[2–4] zeolites,[5,6] clays,[6–8] silica and alumina modified by treatment with Lewis acids,[9,10] and $AlPO_4$.[11] act as catalysts in Diels–Alder reactions. Most of these solids have also been tested as catalysts in asymmetric Diels–Alder reactions between prochiral 1,3-dienes and chiral acrylates,[4,6,8,10,11] with the best asymmetric induction obtained being 74% diastereomeric excess (d.e.) in the reaction between cyclopentadiene and the acrylate of (–)-8-phenyl menthol catalyzed by amorphous $AlPO_4$.[11] In most of these examples, the catalytic activity of each solid was tested using reactive dienophiles, but Diels–Alder reactions of less reactive dienophiles are the key step in the synthesis of interesting products. A good example is the synthesis of cycloaliphatic α-amino acids through Diels–Alder reactions of N-acyl-α,β-dehydroalaninates,[12] whose asymmetric version has lead to excellent asymmetric inductions.[13,14] In view of this, we considered it interesting to carry out these reactions with heterogeneous catalysts. In this paper we compare the catalytic activity of several solid acids on the reactions of cyclopentadiene with a non-chiral, methyl, and a chiral (–)-menthyl N-acetyl-α,β-dehydroalaninate.[15]



RESULTS AND DISCUSSION

Table 1 shows the results obtained in the reaction between methyl N-acetyl-α,β-dehydroalaninate (**1a**) and cyclopentadiene. As can be seen, when the reaction was carried out in solution none of the solids tested displayed good catalytic activity, and the conversions obtained after 24 h. did not exceed 7% at 25 °C and 58% at 60 °C. It has been shown that good results can be obtained in heterogeneously-catalyzed reactions carried out in the absence of a solvent.[4,11] Indeed, the use of this method allowed us to obtain greatly improved results compared with those observed in solution. The best results are obtained by using catalysts that have been previously described as good Lewis acids, namely silica and alumina modified by treatment with Lewis acids[10] and, as happens with homogeneous catalysts,[13] titanium derivatives are slightly better than the aluminium analogues. Amongst the clays, the Ti(IV)-exchanged K10 montmorillonite, calcined at 550 °C to eliminate most of Brønsted acid sites, leads to the best results. Strong Brønsted acids are not suitable catalysts for this reaction, as shown by the poor results obtained with the proton-exchanged clay. As in the homogeneous reactions,[12] cycloadducts with the ester group in the *exo* configuration are obtained preferentially, with *exo*/*endo* ratios of about 70:30.

Table 2 gathers the results obtained from the reaction between the chiral dienophile (–)-menthyl N-acetyl-α,β-dehydroalaninate (**1b**) and cyclopentadiene. Reactions carried out in toluene again lead to very low percentage conversions, which were noticeably improved using the "non solvent" methodology. Cation-exchanged clays are not efficient catalysts and only 20% conversion was obtained with the Ti(IV)-exchanged K10 montmorillonite calcined at 550 °C. Surprisingly, silica gel modified by treatment with $AlEt_2Cl$ or $TiCl_4$ does not lead to the highest percentages of conversion. Moreover, these solids behave as very good catalysts in the reaction between methyl N-acetyl-α,β-dehydroalaninate (**1a**) and cyclopentadiene, which makes it difficult to account for the differences in catalytic activity in comparison with the closely related chiral dienophile **1b**. It may be speculated that in the case of dienophile **1b** polymerization of the cyclopentadiene competes favourably with the most active catalysts, an argument supported by the results of the reaction catalyzed by SiO_2–$TiCl_4$.

The solid displays a reasonably good catalytic activity and the reaction is quite fast, as shown by the conversion reached after 4 h, but after this time further progress was not observed

Table 1. Results obtained from the reaction of methyl N-acetyl-α,β-dehydroalaninate (**1a**) with cyclopentadiene

Catalyst	Solvent	T (°C)	%conversion 24h[a]	*exo*/*endo*[a]
SiO_2[b]	toluene	60	22	73:27
SiO_2+$AlEt_2Cl$	toluene	25	0	–
		60	50	72:28
SiO_2+$TiCl_4$	toluene	25	4	–
		60	58	65:35
Zn(II)–K10[c]	toluene	25	1	–
Ti(IV)–K10[c]	toluene	25	7	–
Ce(IV)–K10[c]	toluene	25	7	–
SiO_2[b]	–	25	34	72:28
Al_2O_3	–	25	65	63:37
SiO_2+$AlEt_2Cl$	–	25	95	65:35
SiO_2+$TiCl_4$	–	25	100	68:32
Al_2O_3+$TiCl_4$	–	25	77	68:32
Zn(II)–K10[c]	–	25	25	68:32
Ti(IV)–K10[c]	–	25	49	66:34
Ce(IV)–K10[c]	–	25	22	69:31
H^+–K10[d]	–	25	1	–

[a] Determined by gas chromatography. [b] Activated at 140 °C under vacuum. [c] Calcined at 500 °C. [d] Dried at 120 °C.

Fortunately, chromatographic grade alumina (Merck, aluminium oxide 60, 63–200 nm) and above all silica gel (Merck, silica gel 60, 63–200 nm) are quite good catalysts, leading to reasonable percentages of conversion after 24 h. Both *exo*/*endo* and diastereofacial selectivities are very similar to those described for the same reaction catalyzed by homogeneous Lewis acids, the d.e. being higher in *exo* than in *endo* cycloadducts.[13] It has been reported[11] that in some heterogeneously-catalyzed asymmetric Diels–Alder reactions, the use of the "non solvent" method leads to a decrease in the asymmetric induction, which has been explained in terms of efficient competition of the less selective non-catalyzed reaction. This hypothesis seems to be confirmed with the relatively unreactive chiral dienophile **1b**. In this case, the non-catalyzed reaction is very slow and the asymmetric induction does not decrease when the reaction is carried out without a solvent. It is important to note that the complete diastereofacial selectivity obtained in *exo* cycloadducts constitutes the best asymmetric induction described to date in heterogeneously-catalyzed asymmetric Diels–Alder reactions. Conversion percentages are easily increased by increasing the amount of the economical silica gel catalyst present.

In summary, it has been shown that the use of the "non solvent" methodology is useful to carry out Diels–Alder reactions on fairly unreactive dienophiles, promoted by heterogeneous catalysts. As the non-catalyzed reaction does not compete efficiently, neither *exo*/*endo* nor diastereofacial selectivity decrease when reactions are carried out in the absence of a solvent. A close relationship between the nature of the dienophile and the catalyst exists, so that the best catalyst for one reaction is not necessarily the best for another. The complete asymmetric induction obtained in *exo* cycloadducts for the reaction between (–)-menthyl N-acetyl-α,β-dehydroalaninate (**1b**) and cyclopentadiene (catalyzed by several solids) is the best described to date for asymmetric Diels–Alder reactions with heterogeneous catalysts. Finally, it is important to emphasize the excellent results obtained using the economical chromatographic grade silica gel as a catalyst.

Table 2. Results obtained from the reaction of (–)-menthyl N-acetyl-α,β-dehydroalaninate (**1b**) with cyclopentadiene at 25 °C

Catalyst	Solvent	%conv. 24h[a]	*exo*/*endo*[a]	**3/2**[a]	**4/5**[a]
SiO_2[b]	toluene	18	70:30	70:30	96:4
SiO_2+$AlEt_2Cl$	toluene	0	–	–	–
SiO_2+$TiCl_4$	toluene	0	–	–	–
SiO_2[b]	–	70	71:29	70:30	>97:3 [c]
SiO_2[b,d]	–	88	71:29	70:30	>97:3 [c]
Al_2O_3[b]	–	55	64:36	69:31	>97:3 [c]
Al_2O_3[e]	–	48	67:33	71:29	>97:3 [c]
SiO_2+$AlEt_2Cl$	–	<10 [f]	–	–	–
SiO_2+$AlEt_2Cl$	–	49	67:33	80:20	>97:3 [c]
SiO_2+$TiCl_4$	–	50 [f]	62:38	78:22	>97:3 [c]
SiO_2+$TiCl_4$	–	45	61:39	75:25	>97:3 [c]
Ti(IV)-K10[f]	–	20	–	–	–

[a] Determined by ^{1}H-NMR. [b] Activated at 140 °C under vacuum. [c] Signals corresponding to 5 could not be found. [d] With double the amount of catalyst. [e] Activated at 400 °C under vacuum. [f] After 4h of reaction. [g] Calcined at 550 °C.

EXPERIMENTAL

Preparation of the heterogeneous catalysts

Zn(II), Ce(IV) and H^+-exchanged K10 montmorillonites were obtained, activated and characterized as previously described.[8d]

Before use as a catalyst, silica gel (Merck, silica gel 60, 63–200 nm) was activated by heating under vacuum at 140 °C for 12 h and alumina (Merck, aluminium oxide 60, 63–200 nm) was activated by heating under vacuum at 140 °C for 12 h or by heating under vacuum at 400 °C for 4 h.

Catalysts modified with Lewis acids were obtained by treating silica gel or alumina, activated at 140 °C, with 1M solutions of $AlEt_2Cl$ or $TiCl_4$ following the previously described method.[9]

Reaction procedures:

Reaction between methyl N-acetyl-α,β-dehydroalaninate (1a) and cyclopentadiene in toluene. Under argon, 214.5 mg (1.5 mmol) of **1a** and 594 mg (9 mmol) of freshly distilled cyclopentadiene were added *via* syringe to a suspension of the corresponding catalyst (1 g) in toluene (4 ml). The mixture was stirred at the corresponding temperature (25 or 60 °C, Table 1) and the reaction was monitored by gas chromatography (FID from Hewlett-Packard 5890 II, cross-linked methyl silicone column 25 mm x 0.2 mm x 0.33 µm, helium as carrier gas, 18 p.s.i., injector temperature 230 °C, detector temperature 250 °C, oven temperature program 50 °C (4 min) – 5 °C/min – 190°C – 25 °C/min – 250 °C (5 min), retention times: N-acetyl-α,β-dehydroalaninate (**1a**) 3.3 min, *exo* cycloadduct 10.2 min, *endo* cycloadduct 10.4 min). After 24 h the catalyst was removed by filtration and repeatedly washed with methylene chloride and diethyl ether. The solution was analyzed by gas chromatography, the solvents were removed under reduced pressure and the results confirmed by ^{1}H–NMR.[12b]

Reaction between methyl N-acetyl-α,β-dehydroalaninate (1a) and cyclopentadiene without a solvent. A solution of 71.5 mg (0.5 mmol) of **1a**, in methylene chloride was mixed with the corresponding catalyst (1 g) and the solvent was removed under reduced pressure. 198 mg (3 mmol) of freshly distilled cyclopentadiene was added *via* syringe. The mixture was shaken for 24 h and after this time methylene chloride was added. The catalyst was removed by filtration and repeatedly washed with methylene chloride and diethyl ether. Results were determined by gas chromatography and ^{1}H-NMR as described above.

Reaction between (–)-menthyl N-acetyl-α,β-dehydroalaninate (1b) and cyclopentadiene in toluene. Under argon, 400.5 mg (1.5 mmol) of **1b** and 594 mg (9 mmol) of freshly distilled cyclopentadiene was added *via* syringe to a suspension of the corresponding catalyst (1 g) in toluene (4 ml). The mixture was stirred at 25 °C and the reaction monitored by TLC. After 24 h the catalyst was removed by filtration and repeatedly washed with methylene chloride and diethyl ether. The solvents were eliminated under reduced pressure and the mixture was analyzed by ^{1}H-NMR, integrating the methyl singlet of the acetamido group[13] ($CDCl_3$, **1b**: 2.08 ppm, **5b**: 2.03 ppm, **3b**: 1.98 ppm, **2b**: 1.96 ppm, **4b**: 1.89 ppm).

Reaction between (–)-menthyl N-acetyl-α,β-dehydroalaninate (1b) and cyclopentadiene without a solvent. A solution of 133.5 mg (0.5 mmol) of **1b**, in methylene chloride was mixed with the corresponding catalyst (1 or 2g, Table 2) and the solvent was removed under reduced pressure. 198 mg (3 mmol) of freshly distilled cyclopentadiene was added *via* syringe. The mixture was shaken for 24 h and after this time methylene chloride was added. The catalyst was removed by filtration and repeatedly washed with methylene chloride and diethyl ether. Results were determined by ^{1}H-NMR as described above.

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