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# (Z)- and (E)-2-Phenyl-4-benzylidene-5(4H)-oxazolones as Dienophiles. Improved Selectivity by the Use of Heterogeneous Catalysts

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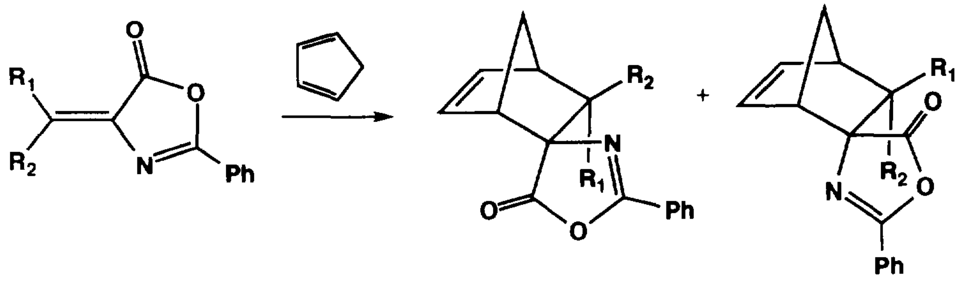
***Abstract:*** Silica gel treated with $AlEt_2Cl$ or $TiCl_4$ efficiently promotes the reaction of cyclopentadiene with (*Z*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1a**) with very little *Z/E* isomerization. Silica gel treated with $TiCl_4$ and $ZnCl_2$ supported on silica gel leads to very high yields for the reaction of cyclopentadiene with (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1b**). Furthermore, *E/Z* isomerization is almost suppressed, which is not achieved with homogeneous Lewis acids. Whereas for the reaction of **1a** with cyclopentadiene the *exo* cycloadduct (**3a**) is always the major product, for the reaction of cyclopentadiene wth **1b** the *endo*(**2b**)/*exo*(**3b**) selectivity is reversed as a function of the catalyst. Thus, in the reactions catalyzed by silica gel, alumina and exchanged clays, *endo* (**2b**) is the major product. However, the *exo* cycloadduct (**3b**) is preferably obtained for reactions catalyzed by silica gel and alumina treated with $TiCl_4$ and $ZnCl_2$ supported on silica gel.

2-Phenyl-4-arylmethylene-5(4H)-oxazolones are versatile intermediates in the synthesis of a variety of products, in particular they are among the most important precursors of α-amino acids.[1] During the last few years we have investigated the behaviour of (*Z*)- and (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolones,[2–5] since their Diels–Alder reactions are the key steps in the synthesis of cyclic α-amino acids that are conformationally rigid analogues of phenylalanine. Unfortunately, the usefulness of these compounds as dienophiles is rather limited due to the isomerization between both the *Z* and *E* isomers in the presence of a Lewis acid or by heating. In the case of the more stable *Z* isomer (**1a**) this drawback can be overcome by carrying out the reactions without a catalyst[5] or using a small amount of a Lewis acid and low reaction temperatures.[2–4] However, the less stable *E* isomer (**1b**) easily isomerizes to the *Z* compound,[3,5] and a mixture of both dienophiles and their corresponding cycloadducts is obtained.

The use of solid catalysts to promote organic reactions is a field of increasing interest, which is due in part to the practical advantages of using these catalysts, but also to the improved selectivities frequently obtained. It has been shown that several solids are efficient catalysts for Diels–Alder reactions, and very good results have been obtained with silica gel,[6] alumina,[7] clays,[8] $AlPO_4$,[9] and silica and alumina modified by treatment with Lewis acids.[10] Recently we have tried to extend the application of these catalysts to the Diels–Alder reactions of poor dienophiles, such as N-acetyl-α,β-dehydroalaninates, whose Diels–Alder reactions are the key step in the synthesis of cycloaliphatic amino acids.[11] The excellent results obtained in this work prompted us to study the reactions of cyclopentadiene with (*Z*)- and (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolones.



**1** **2** **3**

**a**: $R_1$=H, $R_2$=Ph
**b**: $R_1$=Ph, $R_2$=H

Scheme 1

## Results and Discussion

Table 1 shows the best results obtained for the reaction of (*Z*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1a**) with cyclopentadiene. Many other solids (silica gel, alumina, alumina treated with $TiCl_4$ or $AlEt_2Cl$, $ZnCl_2$ supported on silica gel, and K10 montmorillonite exchanged with Ti(IV) and Cu(II)) were tested, but the chemical yields obtained were less than 15%. Only silica gel treated with $TiCl_4$ or $AlEt_2Cl$ are efficient catalysts for this reaction, and the best results are obtained by carrying out the reaction at low temperature and without a solvent. Although these catalysts are, as expected, less efficient than $TiCl_4$ in solution, they have some advantages as far as selectivity is concerned, given that a reasonable percentage of conversion is obtained with a low degree of *Z/E* isomerization.

Table 2 gathers the results obtained for the reaction between cyclopentadiene and (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1b**). In this case the use of homogeneous Lewis acids is precluded due to the extensive conversion to the more stable Z-isomer (**1a**). Under these conditions the reaction leads to a mixture of both dienophiles (**1a**,**1b**) and their corresponding cycloadducts (**2a**, **2b**, **3a**, and **3b**). In the absence of a catalyst and using methylene chloride as a solvent, the reaction does not take place at room temperature, but the dienophile partially isomerizes.

Silica gel and alumina, activated by heating at 140 °C under vacuum, and K10 montmorillonite exchanged with Ti(IV) and calcined at 550 °C are not very efficient catalysts, and the *E/Z* isomerization takes place to a considerable extent. However, cycloadducts arising from the Z-isomer (**2a** and **3a**) are not obtained, which indicates the lower reactivity of the (*Z*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1a**) in comparison with its corresponding *E*-isomer (**1b**). In spite of the low catalytic activity of the abovementioned solids, a reasonable chemical yield (about 60%) can be obtained, mainly when the reactions are carried out in the absence of a solvent.

Silica gel and alumina treated with $AlEt_2Cl$ and alumina treated with $TiCl_4$ are not good catalysts for this reaction, which may be due to the higher percentage of isomerization. This drawback is reduced by working at low temperatures, but the reaction rate is then reduced and only 39% conversion is obtained after 24 h of reaction.

Table 1. Results obtained from the reaction of (*Z*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1a**) with cyclopentadiene.[a]

| Catalyst | Solvent | T (°C) | %**1a** | %**1b** | %**2a** | %**3a** | %**2b** | %**3b** |
|---|---|---|---|---|---|---|---|---|
| – | $CH_2Cl_2$ | 20 | 100 | – | – | | – | |
| – | – | 20 | 100 | – | – | | – | |
| $TiCl_4$[b] | $CH_2Cl_2$ | 0 | 0 | 2 | 14 | 39 | 15 | 30 |
| $TiCl_4$[c] | $CH_2Cl_2$ | -25 | 42 | – | 19 | 39 | – | |
| $SiO_2/TiCl_4$[d] | $CH_2Cl_2$ | 20 | 78 | 2 | – | | 7 | 13 |
| | – | 20 | 77 | 1 | 4 | 14 | 4 | |
| | – | -20 | 20 | 5 | 21 | 54 | – | |
| $SiO_2/AlEt_2Cl$[e] | $CH_2Cl_2$ | 20 | 91 | 3 | 6 | | – | |
| | – | 20 | 90 | 0 | 3 | | 7 | |
| | – | -20 | 16 | 1 | 26 | 55 | 2 | |
| K10-Ce(IV)[f] | $CH_2Cl_2$ | 20 | 74 | 2 | 6 | 15 | 3 | |
| | – | 20 | 100 | – | – | | – | |
| K10-Ag(I)[f] | $CH_2Cl_2$ | 20 | 77 | 1 | 5 | 13 | 5 | |
| | – | 20 | 100 | – | – | | – | |

[a] Results determined by HPLC. Results are reproducible within ±2%, as determined by replicated experiments [b] With a 1:1 dienophile:$TiCl_4$ ratio. [c] With a 2:1 dienophile:$TiCl_4$ ratio. [d] Silica gel treated with $TiCl_4$. [e] Silica gel treated with $AlEt_2Cl$. [f] K10 montmorillonite exchanged with the corresponding cation and calcined at 550 °C.

On the other hand, silica gel treated with $TiCl_4$ is an excellent catalyst and, although it also promotes *E/Z* isomerization, the use of low reaction temperatures allowed us to obtain very good results. Particularly noteworthy is the almost complete conversion to **2b** and **3b** obtained at -20 °C in the absence of a solvent.

$ZnCl_2$ supported on silica gel[12] is a catalyst similar to $ZnCl_2$ suported on K10 montmorillonite.[13] Both solids catalyze Diels–Alder reactions and they behave as mild Lewis acid catalysts. In our case, $ZnCl_2$ supported on silica gel does not promote the reaction of (*Z*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1a**), but it is a very efficient in the reaction of the corresponding *E*-isomer (**1b**), leading to very high percentages of conversion with very little isomerization.

Given that silica gel treated with $TiCl_4$ and $ZnCl_2$ supported on silica gel promotes the reaction between (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1b**) and cyclopentadiene with almost complete supression of *E/Z* isomerization, they are, for this reaction, a better choice than classical homogeneous Lewis acid catalysts.

In a previous work[11] we showed that carrying out the reactions in the absence of a solvent can be a suitable method to follow, especially when not very reactive dienophiles are involved. The results described in the present work also supports this conclusion.

For the reactions of (*Z*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1a**) the *exo* cycloadduct (**3a**) is preferably obtained for all the experimental conditions tested. However, for the reactions of (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1b**) the *endo/exo* selectivity is reversed as a function of the solid used to promote the reaction. Thus, with poor catalysts, such as silica gel or alumina, the *endo* cycloadduct (**2b**) is preferably obtained, whereas with efficient catalysts, such as silica gel treated with $TiCl_4$ or $ZnCl_2$ supported on silica gel, the *exo* product (**3b**) is the major one.

Table 2. Results obtained from the reaction of (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (**1b**) with cyclopentadiene.[a]

| Catalyst | Solvent | T (°C) | **%1a** | **%1b** | **%2a** | **%3a** | **%2b** | **%3b** |
|---|---|---|---|---|---|---|---|---|
| – | $CH_2Cl_2$ | 20 | 37 | 63 | – | | – | |
| – | $CH_2Cl_2$ | -20 | – | 100 | – | | – | |
| $SiO_2$[b] | $CH_2Cl_2$ | 20 | 55 | 13 | 6 | | 15 | 11 |
| | – | 20 | 11 | 28 | – | | 37 | 24 |
| $Al_2O_3$[b] | $CH_2Cl_2$ | 20 | 61 | 20 | – | | 11 | 7 |
| | – | 20 | 17 | 21 | – | | 37 | 25 |
| K10-Ti(IV)[b] | $CH_2Cl_2$ | 20 | 12 | 30 | – | | 31 | 27 |
| | – | 20 | 18 | 30 | – | | 31 | 21 |
| $SiO_2/AlEt_2Cl$ | $CH_2Cl_2$ | 20 | 67 | 10 | – | | 12 | 10 |
| | $CH_2Cl_2$ | -20 | 1 | 83 | – | | 6 | 10 |
| | – | 20 | 44 | 42 | – | | 7 | 7 |
| | – | -20 | 4 | 57 | – | | 15 | 24 |
| $Al_2O_3/AlEt_2Cl$ | $CH_2Cl_2$ | 20 | 46 | 32 | – | | 13 | 9 |
| | – | 20 | 17 | 45 | – | | 15 | 23 |
| $SiO_2/TiCl_4$ | $CH_2Cl_2$ | 20 | 37 | 8 | – | | 21 | 34 |
| | $CH_2Cl_2$ | -20 | 17 | – | – | | 32 | 51 |
| | – | 20 | 13 | 1 | 11 | 19 | 21 | 35 |
| | – | -20 | 0.5 | 0 | – | | 38 | 61.5 |
| $Al_2O_3/TiCl_4$ | $CH_2Cl_2$ | 20 | 86 | 10 | – | | 4 | |
| | – | 20 | 21 | 71 | – | | 8 | |
| | – | -20 | 45 | 5 | – | | 20 | 30 |
| $SiO_2/ZnCl_2$[c] | $CH_2Cl_2$ | 20 | 5 | – | – | | 41 | 54 |
| | $CH_2Cl_2$ | -20 | 3 | 32 | – | | 21 | 44 |
| | – | 20 | 1 | – | – | | 40 | 59 |
| | – | -20 | 5 | – | – | | 36 | 59 |

[a] Results determined by HPLC. Results are reproducible within ±2%, as determined by replicated experiments [b] Reactions carried out at -20 °C lead to chemical yields less than 15%. [c] $ZnCl_2$ supported on silica gel.

Steric interactions between diene and dienophile can account for this behaviour. When the phenyl group bonded to the double bond is coplanar with the rest of the molecule, or when there is little deviation from coplanarity, the interaction between this phenyl group and the methylene of the cyclopentadiene makes the approach of the diene *exo* to this phenyl group difficult, so that **3a** and **2b** are preferably obtained. The coordination of a Lewis acid to the carbonyl group does not modify the conformation of the *Z*-isomer (**1a**), but deviation of the phenyl group from planarity must increase for the *E*-isomer (**1b**). In this case, the steric influence of the phenyl group is modified and becomes particularly important for the dienic part of the diene when it approaches *endo* to the phenyl group, so that (**3b**) is preferably obtained (Figure 1).

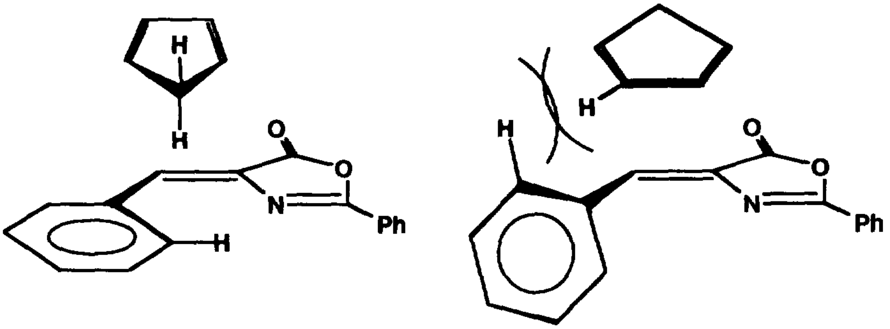


**Figure 1**

In view of this, it seems that with good catalysts the coordination to the carbonyl group plays an essential role. However, this coordination may not be so important with bad catalysts, and the catalytic effect may be due to concentration of the reagents in the pores of the solid or to coordination at the nitrogen atom.

## Experimental

### *Preparation of the Heterogenous Catalysts*

Cation-exchanged K10 montmorillonites were obtained, activated and characterized as previously described.[8] Before their use as catalysts, silica gel (Merck, silica gel 60, 63–200 nm) and alumina (Merck, aluminium oxide 60, 63–200 nm) were activated by heating under vacuum at 140 °C for 12 h. These solids were also used to support aluminium and titanium derivatives by treatment with 1M solutions of $AlEt_2Cl$ or $TiCl_4$, following a previously described method.[10] $ZnCl_2$ was supported on silica gel (EP11 from Crossfield, 415 $m^2g^{-1}$) as previously described.[12]

### *Reaction Procedures*

Reactions between (*Z*)- and (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolones (1a, 1b) and cyclopentadiene in methylene chloride. Under argon, 348.6 mg (1.4 mmol) of the dienophile (**1a**, **1b**) and freshly distilled cyclopentadiene (8.4 mmol for the reactions carried out at 20 °C and 14 mmol for the reactions carried out at –20 °C) were added to a suspension of the corresponding catalyst (1 g) in dry methylene chloride (8 ml). The mixture was stirred at the corresponding temperature and monitored by TLC. After 24 h, the catalyst was removed by filtration and repeatedly washed with methylene chloride, and the solution was analyzed by HPLC using the following methods.

Method A. Column: Radial Pack from Waters, Silice 4 µm. Eluent: first hexane/ethyl acetate 99/1 at a flow rate of 2 ml·min$^{-1}$ for 2 min, and then hexane/ethyl acetate 96:4 at a flow rate of 2.5 ml·min$^{-1}$. Detection: $\lambda$=282 nm. Retention times: 4.3 min (**1a**), 5.9 min (**3a**), 6.9 min (**2a**), 7.6 min (**1b+2b**), 7.9 min (**3b**).

Method B. Column: Radial Pack from Waters, Silice 4 µm. Eluent: first hexane/ethyl acetate 95/5 at a flow rate of 2.5 ml·min$^{-1}$. Detection: $\lambda$=282 nm. Retention times: 2.5 min (**1a+3a**), 2.7 min (**2a**), 3.9 min (**2b**), 4.1 min (**1b**), 4.5 min (**3b**).

To obtain further confirmation of the results, methylene chloride was removed under reduced pressure and the mixture was analyzed by $^1$H-NMR.[2,3] The mixture of oxazolones was transformed into the corresponding mixture of benzamido methyl esters by treatment with $NaOH/CH_3OH$, which was also analyzed by $^1$H-NMR ($CDCl_3$, $\delta$ ppm): [2,3]

- Methyl *exo*-2-benzamido-*exo*-3-phenylbicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylate (ester from **2a**): 1.80 (dd, 1H, J=9.3, 1.5 Hz); 2.04 (d, 1H, J=9.3 Hz); 3.12 (br.s, 1H); 3.29 (br.s, 1H); 3.65 (d, 1H, J=1.5 Hz); 3.74 (s, 3H); 5.98 (br.s, 1H); 6.40 (dd, 1H, J=5.4, 3.0 Hz); 6.53 (dd, 1H, J=5.4, 2.9 Hz); 7.15–7.60 (m, 10H).

- Methyl *endo*-2-benzamido-*endo*-3-phenylbicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylate (ester from **3a**): 1.79 (d, 1H, J=9.2 Hz); 2.15 (d, 1H, J=9.2 Hz); 3.26 (br.s, 1H); 3.79 (d, 1H, J=1.5 Hz); 3.81 (s, 3H); 4.05 (br.s, 1H); 5.90 (br.s, 1H); 6.15 (dd, 1H, J=5.6, 3.3Hz); 6.62 (dd, 1H, J=5.6, 2.8 Hz); 7.25–7.55 (m, 10H).
- Methyl *exo*-2-benzamido-*endo*-3-phenylbicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylate (ester from **2b**): 1.82–1.87 (m, 1H); 2.60 (br.s, 1H); 3.00 (m, 1H); 3.17 (s, 3H); 3.25 (d, 1H, J=1.5 Hz); 3.66 (s, 1H); 6.25 (dd, 1H, J=5.7, 3.0 Hz); 6.80–6.82 (m, 2H); 7.18–7.29 (m, 5H); 7.38–7.52 (m, 3H); 7.73–7.77 (m, 2H).
- Methyl *endo*-2-benzamido-*exo*-3-phenylbicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylate (ester from **3b**): 1.89–1.94 (m, 1H); 2.76–2.80 (m, 2H); 3.03 (s, 3H); 3.06 (m, 1H); 4.00 (s, 1H); 6.20 (dd, 1H, J=5.6, 3.2 Hz); 6.57 (dd, 1H, J=5.6, 3.0 Hz); 6.68 (br.s, 1H); 7.18–7.29 (m, 5H); 7.38–7.52 (m, 3H); 7.73–7.77 (m, 2H).

Reactions between (*Z*)- and (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolones (**1a, 1b**) and cyclopentadiene in the absence of a solvent. A solution of the dienophile (**1a** or **1b**) (298.8 mg, 1.2 mmol) was mixed with the corresponding catalyst (2.5 g) and the solvent was removed under reduced pressure. Then, freshly distilled cyclopentadiene (7.2 mmol for the reactions carried out at 20 °C and 12 mmol for the reactions carried out at –20 °C) were added with a 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. Results were determined by HPLC and $^1$H-NMR as described above.

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