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Synthesis and Diels-Alder Reactivity of simple 1-Phenoxy-1,3-Dienes

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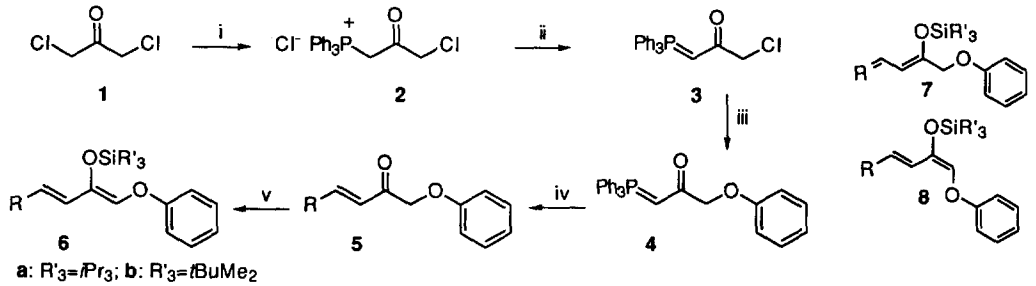
Abstract.- An easy and useful method for the preparation of simple 1-phenoxy-2-trialkylsiloxy-1,3-dienes in high yields, has been established and their reactivity in the Diels-Alder reaction at room temperature has been studied. By this procedure, phenoxy substituted cyclohexenes and cyclohexanones of known relative stereochemistry can be obtained.

As a part of a research project directed at the synthesis and study of the antineoplastic, antiviral and other pharmacological activities of several families of compounds, we are interested in the synthesis of derivatives bearing substituted phenyl and phenoxy moieties. This could be achieved by means of the Diels-Alder reaction with adequately substituted dienes, since it is a well known synthetic process that produce regio and stereocontrolled compounds. With this purpose, we have initiated the preparation of simple phenoxy-dienes. Alkoxy-dienes are known as useful building blocks, as it is the case of Danishefsky's diene,[1] whereas other aryl-heterosubstituted dienes as arylthio and arylamino[2,3] dienes have also been described and used in the Diels-Alder reaction. Surprisingly, phenoxy-dienes are less known and few examples of their preparation and Diels-Alder reactivity have been published.

Among the described phenoxy-dienes, several of them have been obtained with other purposes different than their use in the Diels-Alder reaction,[4] while others have been applied for the synthesis of phenoxy-substituted cyclohexenes by cycloaddition reaction with suitable dienophiles.[5] A potential synthetic application of this reaction is the mild preparation of polysubstituted diaryl ethers by oxidation of these phenoxy-cyclohexenes. These ethers are present in the structure of interesting natural and synthetic products, for example: vancomycines,[6] bouvardine[7] and other antitumorals,[8] piperazinomycine,[9] combretastatin D[10], acifluoren[11] and cyclic peptides.[12]

There are only four general procedures that have been applied for the preparation of this type of dienes: 1) conjugate elimination of unsaturated acetals promoted by bases,[13] 2) ring cleavage of benzodioxinic allylic alcohols in xylene at reflux,[14] 3) methylenation of α,β-unsaturated aryl esters by Tebbe reagent,[15] and 4) enol silylation of α-(aryloxy)-β-heterosubstituted enones.[15] Because most of these procedures yield dienes with different substitution pattern than the 1-phenoxy-2-trialkylsiloxy-1,3-dienes suitable for the synthesis of our targets, we have first established a general procedure for the preparation of these dienes. In this paper we communicate our results in the preparation of these uncommon dienes, which were obtained in high overall yields, and the initial studies on their behaviour in the Diels-Alder reaction.

Our strategy for the synthesis of these dienes is based on the enol silylation of an α-phenoxy substituted enone, that is obtained by Wittig olefination of a phenoxy-keto-phosphorane (Scheme 1). This is a powerful approach which allows a step by step controlled preparation of the dienes. The starting material for this synthesis is the commercially available 1,3-dichloroacetone (**1**).



a: R'3=*i*Pr3; **b**: R'3=*t*BuMe2

Scheme 1. Synthesis of 1-aryloxy-2-trialkylsiloxy-1,3-dienes: i) PPh_3/THF/reflux, 4h; ii) Na_2CO_3/MeOH-H_2O, r.t., 30 min; iii) PhOH, NaH/DMF, r.t., 6h; iv) R-CHO, C_6H_6, reflux, 4h; v) R'3SiOTf/CH_2Cl_2/NEt_3, 4h (**6a**), 1h (**6b**)

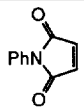
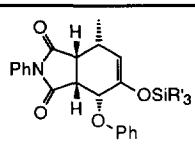
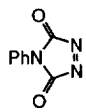
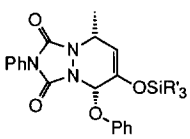
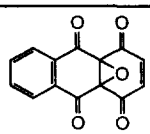
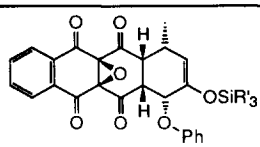
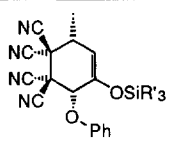
According to this methodology, the treatment of 1,3-dichloroacetone with triphenylphosphine produces the monophosphonium chloride (**2**), which precipitates from the reaction mixture. The conversion into the phosphorane **3** is followed by the easy substitution of the α-chloroketone by phenol, which produces the phenoxy-ketone (**4**). Wittig olefination to the α-phenoxy-enones (**5**) and subsequent enol silylation produce the expected 1-phenoxy-2-trialkylsiloxy-1,3-dienes (**6**). By this procedure it is possible to obtain 1-aryloxy-2-trialkylsiloxy-1,3-dienes carrying diverse aryloxy and R moieties, depending on the structure of the phenol used in the substitution reaction and the aldehyde employed in the Wittig olefination.

We have applied this methodology to synthesize 1-phenoxy-2-triisopropylsiloxy and 1-phenoxy-2-*tert*-butyldimethylsiloxy-1,3-pentadienes (**6a**: R'3= *i*Pr3, R=Me; **6b**: R'3= *t*BuMe2, R=Me), which were obtained in five steps, with 68-75% overall yield from the starting 1,3-dichloroacetone (**1**). The final products are mixtures of the desired dienes **6** and their regioisomers **7** in a ratio higher than 5/1[16], that are used in the Diels-Alder reaction without further purification[17]. Compounds **6**, obtained by this methodology have the 1*Z*,3*E* configuration of both double bonds, which are produced by: the *E* preference of products obtained by Wittig reaction with stabilized phosphoranes[18] and the higher stability of the *Z* isomers of Δ^1 (in comparison with Δ^1*E* stereoisomers **8**), that are produced under the thermodynamic conditions of the employed enol silylation reaction.[19] Theoretical calculations showed a higher heat of formation for 1*E* stereoisomers **8** than the obtained 1*Z* stereoisomers **6**, high enough to explain the formation of the latter as single stereoisomers.[20]

This approach to the synthesis of 1-aryloxy-1,3-dienes was followed by the study of their behaviour in the Diels-Alder reaction with representative dienophiles, in order to know their synthetic utility. With this purpose we selected as dienophiles: *p*-benzoquinone, dimethyl acetylenedicarboxylate, *N*-phenyl-maleimide, 4-phenyl-1,2,4-triazoline-3,5-dione, 4*a*,9*a*-epoxy-4*a*,9*a*-dihydroanthracene-1,4,9,10-tetraone[21] and tetracyanoethylene. *p*-Benzoquinone and dimethyl acetylenedicarboxylate were no reactive enough to undergo the Diels-Alder reaction with these phenoxydienes at room temperature or even at reflux. The other dienophiles reacted with dienes **6a** and **6b** after 24 hours at room temperature without catalyst, yielding the expected Diels-Alder adducts (Table 1).

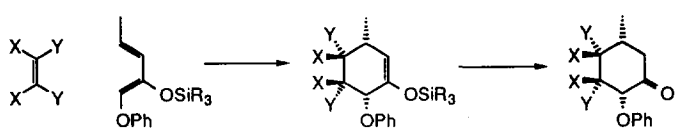
Products **9a-12b** are obtained as single diastereomers by insolubilization with ether from the reaction mixture. Their stereochemistry was established by comparison with products obtained in the Diels-Alder reaction between other siloxy-1,3-dienes and the same dienophiles,[22] which also produce single stereoisomers. The *cis* relationship between the substituents in the cyclohexene ring is the result of an *endo* reaction. Theoretical calculations[23] for **11b** also agree with the formation of the *endo* product through an approach of the diene from the face opposite to the epoxide. In fact, the energy of the transition state for this approach is 24 Kj/mol lower than that of the other *endo* transition state, and the energy of both *exo* transition states is also higher. Furthermore, the calculated coupling constants[24] for the most stable conformation of the *exo* adducts are in disagreement with those obtained for products **9-12**.

Table 1. Cycloaddition reactions of 1-phenoxy-2-trialkylsiloxy-1,3-pentadienes **6a** (R'=*i*Pr) and **6b** (R'=*t*BuMe$_2$) with selected dienophiles

Entry	Diene	Dienophile	Product[c]		Yield[d](%)
1[a]	**6a**			**9a** (R'=*i*Pr)	60
2[a]	**6a**			**10a** (R'=*i*Pr)	65
3[a]	**6b**	"	"	**10b** (R'=*t*BuMe$_2$)	25
4[b]	**6a**			**11a** (R'=*i*Pr)	70
5[b]	**6b**	"	"	**11b** (R'=*t*BuMe$_2$)	50
6[a]	**6b**			**12b** (R'=*t*BuMe$_2$)	50

a) All these reactions were carried out in benzene under Argon, at r. t. for 24 h, except b) that were carried out in a mixture of benzene and CH_2Cl_2, to solubilize the material. c) Determined by IR, ^1H and ^{13}C-NMR and EA of these products. d) Isolated by insolubilization with ether from the crude reaction mixtures

Products of the Diels-Alder reaction were hydrolyzed, to produce cyclohexanones (**13**) of known stereochemistry, completing the synthetic scheme depicted below, that is very convenient for the synthesis of many phenoxy substituted compounds.



6 **13**

We are currently exploring the utility of this methodology for the synthesis of phenoxy analogues of compounds with biological activity, as well as its assets to the preparation of polysubstituted diaryl ethers.

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