

## OXIDATION OF MESOIONIC OXAZOLONES BY OXYGEN

H. Rodriguez\* (1), A. Marquez (1), C.A. Chuaqui\* (2) and B. Gomez (1)

(1) Departamento de Quimica Organica, Facultad de Ciencias Quimicas y Farmaceuticas, Universidad de Chile, Casilla 233, Santiago, Chile

(2) Radiation Applications Research Branch, Whiteshell Laboratories, AECL Research, Pinawa, Manitoba, ROE 1LO, Canada

(Received in USA 17 April 1991)

### ABSTRACT

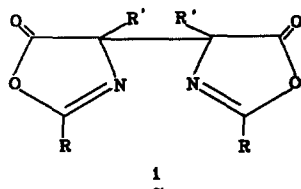
The reaction of molecular oxygen with several 2,4-disubstituted oxazolones (3a-3g) is studied in the present paper. It is shown that oxygen may induce oxidative dimerization to dehydrodimers (7a-7g) via the mesoionic form of the oxazolone. The equilibration between the ketonic and the mesoionic forms. It is demonstrated that this equilibrium and the dimerization process are dependent on the properties of the solvent and the type of substitution in the oxazolones.

### INTRODUCTION

Several groups have found that 2,4-disubstituted oxazolones are unstable in certain solvents in the presence of oxygen. For example, Huisgen et al (1) describe the decrease in the extinction coefficient of a solution of 2,4-diphenyl-2-oxazolin-5-one in oxygenated N-methylformamide. Similar changes are also observed in other solvents. The rate of change decreases when the solvents are purified and the solutions kept under nitrogen. Padwa et al (2) observed that a solution of 2,2-dimethyl-4-phenyl-2-oxazolin-5-one in carbon tetrachloride underwent reactions that produced at least two different dimers. The reaction occurred at room temperature and in 24 hours all the original oxazolone had reacted. One of the dimers produced corresponds to the structure 1a (R=Me, R'=Ph). The second dimer could not be totally identified because of its instability.

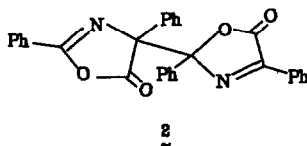
It has also been observed that during the preparation of the 2,4-diphenyl-2-oxazolin-5-one, by treating N-benzoylphenylalanine with acetic anhydride in the presence of air, small quantities of a dimeric product are formed. This dimer, which has very similar spectral features to those of the monomeric oxazolone (showing bands of C=O and C=N at 1818 and 1640 cm<sup>-1</sup> respectively and lack of a tertiary H, as shown by NMR), may be assigned the structure 1b (R=R'=Ph), corresponding to bis-4,4'-[2,4-diphenyl-2-oxazolin-5-

one]. The corresponding dehydrodimers 1c, 1d and 1e have been obtained by cyclization reactions of *N*-benzoylalanine derivatives (3).



	1a	1b	1c	1d	1e
R	Me	Ph	p-Cl-Ph	p-Me-Ph	p-NO <sub>2</sub> -Ph
R'	Ph	Ph	Me	Me	Me

Schmid *et al* (4) heated the 2,4-diphenyl-2-oxazolin-5-one at reduced pressure and obtained two products. One of them was obtained in 21% yield and was identified as 2,4-diphenyl-4-[5'-oxo-2',4'-diphenyl-3'-oxazolin-2'-ide]-2-oxazolin-5-one, 2. It is very likely that these reactions proceed via free radicals. Therefore, it is important to understand the chemical reactivity of these compounds and the factors that control their radicophylic character.



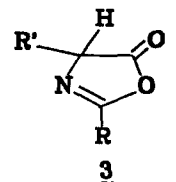
The present contribution analyses some of the factors that determine the radicophylic character of solutions of 2,4-diaryl-2-oxazolin-5-one in several organic solvents.

### RESULTS AND DISCUSSION

The behaviour of 2-oxazolin-5-ones toward solvents varies, depending on the solvent. For example, oxazolones 3a and 3g (Table 1) are stable for at least 48 hours when benzene, toluene, xylene or chloroform are the solvents, even when air is dissolved in them. However, the same oxazolones yield the corresponding 4,4'-dehydrodimer when the solvents

are dimethyl sulfoxide (DMSO) or dimethylformamide (DMF). These reactions seem to occur via free radicals initiated by molecular oxygen in some cases (1,3) or by  $\text{CCl}_4$  and molecular oxygen in others. They are relatively fast and the products are formed in high yields (2). Also, these products may be formed by photooxygenation (5) and by the action of nickel peroxide (5,6) on oxazolones.

TABLE 1  
2,4-Disubstituted 2-oxazolin-5-ones used in this work.

	Oxazolone	3a	3b	3c	3d	3e	3f	3g
	Substituent							
R		p-MeOPh	Ph	p-NO <sub>2</sub> Ph	p-ClPh	p-MePh	Ph	Ph
R'		Ph	Ph	Ph	Ph	Ph	p-MeOPh	p-ClPh

In order to define the role of oxygen in these processes, we dissolved the oxazolone 3a in degassed DMSO. The resulting yellow solution did not produce dimeric products and was stable for more than a week, clearly indicating that oxygen was necessary to induce the dimerization reaction. When the same oxazolone was dissolved in xylene and dry air was bubbled through the solution, the corresponding dehydrodimer was produced in less than 24 hours. It is important to note that this oxazolone is stable in dry xylene that contains up to 59 ppm of oxygen dissolved in it (7). Similarly, oxazolones 3a and 3g are stable in xylene, toluene, benzene and chloroform containing between 35 and 40 ppm of oxygen dissolved (7); however, the same oxazolones are unstable in DMSO and DMF with a similar concentration of oxygen dissolved.

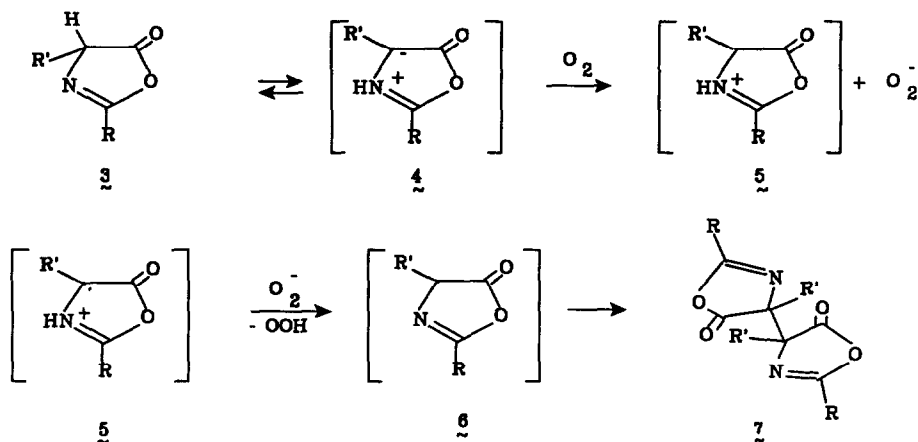
The nature of the products of these reactions and the fact that the oxazolone 3a is stable in degassed oxygen, indicates that the dimerization reaction is a free radical process in which oxygen plays a primary role. The behaviour towards oxygen in different solvents seems to be related to the equilibrium between the structures 3 and 4 (Scheme 1) corresponding to the ketonic and mesoionic forms of the oxazolones (1). Molecular oxygen is unable to react with the ketonic form (C-H bond 98.7 kcal/mole). The above equilibrium is solvent dependent. In apolar solvents the oxazolones exist predominantly in the ketonic form, i.e. 3, while in polar solvents, such as DMSO and DMF, there are significant amounts of the mesoionic forms, i.e. 4 (1).

It is known that nickel peroxide oxidises organic compounds by free radical reactions initiated by hydrogen abstraction (6,9). Therefore, this peroxide may be used towards oxazolones to study the action of oxygen and the products formed via the free radical processes involved (6). For instance, the reaction of oxazolones 3a and 3g with nickel peroxide in benzene at room temperature produces the corresponding 4,4'-dehydrodimers in yields higher than 70%. The structural assignments of the reaction products were based in comparisons with described dehydrodimers (5,6), quantitative elemental analysis, chromatographic analysis in di-n-butyl ether (where R<sub>f</sub> values of these products are known), melting points and their characteristic decarboxylation during melting and their spectroscopic properties. These products do not possess tertiary C-H and therefore, that absorption is absent in the <sup>1</sup>H-NMR. Also, their IR are very similar to that of the corresponding parent oxazolone in the ketonic form. Examples are the IR of dehydrodimers 7a, 7b, 7e-7g. Particularly interesting are the dehydrodimers 4,4'-bis-[2-p-nitrophenyl-4-phenyl-2-oxazolin-5-one] and 4,4'-bis-[2-p-chlorophenyl-4-phenyl-2-oxazolin-5-one], since the corresponding reactant oxazolones are in their mesoionic form in the reaction mixture (10,11), while the products are unsaturated β,γ-lactones, as evidenced by the characteristic absorption at 1820 cm<sup>-1</sup> in the IR spectra of the 4,4'-dehydrodimers, which otherwise are very similar to that of the parent oxazolones. These results, as well as the similarities between the UV spectra of oxazolones and their corresponding reaction product, show that the two heterocyclic rings in the reactants have not been destroyed during the reaction and exist in the reaction product as unsaturated β,γ-lactones.

Our work and that of other authors (1,3) indicates that the oxazolone undergoes oxidation via its mesoionic form, which reacts with oxygen and yields the reaction products. This is supported by the fact that oxazolones 3a and 3g are stable in oxygenated solutions in xylene, benzene, toluene, chlorophorm and other solvents that do not induce the production of the mesoionic form.

Instead, nickel peroxide is able to oxidize both the ketonic and mesoionic forms of oxazolones. The oxidation of 2-oxazolin-5-ones with nickel peroxide proceeds according to the mechanism proposed by Marquez *et al* (6). The dimerization of oxazolones in aerated solutions may proceed according to the scheme below, where the ketonic oxazolone form is in equilibrium with the corresponding mesoionic form. The position of the equilibrium is solvent dependent. In solvents such as benzene, toluene, xylene, etc. (solvents of low polarity) the ketonic form predominates, yielding colourless solutions. However, DMSO solutions yield deeply coloured solutions of the mesoionic form. The mesoionic form undergoes reaction with oxygen, yielding the radical 5 and superoxide radical anion. These products may undergo further reaction to produce radicals HOO and 6. Since the

SCHEME 1



latter is a captodative radical (12), it reacts mainly via dimerization, while the HOO may abstract a hydrogen from the oxazolone substrate, establishing a chain reaction and yielding hydrogen peroxide. Hydrogen peroxide has been detected as a product of the reaction of oxazolone 3a in DMSO (13).

The proposed mechanism has precedents in the oxidation of anions; which is a synthetic pathway to produce C-C bonds in dimerizations (14). There are many examples of oxidative dimerization of anions that use a variety of oxidating agents, such as electrochemical oxidation (15), cupric chloride (16), ammonium or sodium persulfate (17), potassium ferricyanide (18), iodine (12) and oxygen (19). Our work points out the importance of solvent effects, the generality of oxygen oxidations and the importance of structural factors in the substrate that determine whether oxidative dimerization or degradative oxidation occurs.

#### EXPERIMENTAL

##### Synthesis of Oxazolones.

The following oxazolones were synthesized in very good yields following described methods: 2-p-Methoxyphenyl-4-phenyl-2-oxazolin-5-one (3a) (6,20); 2,4-diphenyl-2-oxazolin-5-one (3b) (1,6); 2-p-nitrophenyl-4-phenyl-3-oxazolone-5-one (3c) (1, 10); 2-p-

chlorophenyl-4-phenyl-2-oxazolin-5-one (3d) (11) and 2-p-methylphenyl-4-phenyl-2-oxazolin-5-one (3e) (21).

2-Phenyl-4-p-methoxyphenyl-2-oxazolin-5-one (3f) was synthesized according to the following procedure: 1g (3.5 mM) of N-benzoyl- $\alpha$ -p-methoxyphenylglycine is added to 2 mL of acetic anhydride heated at 80-90°C and under nitrogen. After 5 minutes all the solid dissolves yielding a golden yellow solution. Then, the acetic anhydride is distilled at reduced pressure and the residue is crystallized from a solvent mixture of petroleum ether 60-80°C and benzene. The product obtained has a melting point of 101°C, while the reaction yield was 0.43 g (46.3%). Other product characteristics are as follows. The elemental analysis (%) gave C 71.82; H 4.89 and N 4.96 (required for  $C_{16}H_{13}NO_3$  is C 71.90; H 4.90 and N 5.24). The  $^1\text{H}$ NMR spectra ( $\text{CDCl}_3$ ) shows the following bands (ppm): 8.29-8.03 (d, 2H,  $J_d=9.0$  Hz); 7.76-7.27 (m, 5H); 6.95 (d, 2H,  $J_d=9.0$  Hz); 5.5 (s, 1H); 3.84 (s, 3H). The IR (KBr)  $\text{cm}^{-1}$  shows bands at 1821 (s), 1658 (m), 1613 (s), 1258, 1163, 1026, 969, 841, 735 and 699. The UV spectrum in dioxane shows a band with maximum absorption at 232.6 nm ( $\epsilon=18800 \text{ dm}^3\text{cm}^{-1}\text{mol}^{-1}$ ).

2-Phenyl-4-p-chlorophenyl-2-oxazolin-5-one (3g) was obtained according to the following method: 0.5 g (1.7 mM) of N-benzoyl- $\alpha$ -p-chlorophenylglycine is added to 1.1 mL of acetic anhydride heated at 80-90°C under helium. The mixture turns yellow and after 5 minutes fine yellow crystals of the reaction product precipitate. The reaction is continued for another 15 minutes and then is filtered under vacuum. The solid material is washed with benzene. The reaction product is a yellow powder (yield: 0.38 g or 83%) with a melting point of 163-170°C. Other product characteristics are shown below. Elemental analysis (%): C 66.04; H 3.72; N 4.97 (required for  $C_{15}H_{10}NO_2Cl$ : C 66.31; H 3.71; N 5.16). The  $^1\text{H}$ NMR spectra ( $\text{CDCl}_3$ ) shows the following bands (ppm): 8.2-7.3 (2m, 9H) and 5.5 (s, 1H). The IR (KBr)  $\text{cm}^{-1}$  shows bands at 3413, 1835 (w), 1661 (s), 1097, 948, 830, 720 and 697. The UV spectrum in dioxane shows a band with a maximum at 221 nm ( $\epsilon=18800 \text{ dm}^3\text{cm}^{-1}\text{mol}^{-1}$ ).

### Synthesis of dehydrodimers 7.

Two methods of synthesis were used.

Method 1: This method consists in the reaction of oxazolones with nickel peroxide (nickel peroxide was prepared according to the method of Nakagawa (22)), by dissolving 1.5 mM of oxazolone in 25 mL of benzene and adding nickel peroxide in an amount equal to twice the weight of oxazolone (10 meq of nickel peroxide per each meq of oxazolone). The reaction mixture is stirred at ambient temperature. The reaction progress may be monitored by means of thin layer chromatography. After the reaction is over, the mixture is filtered and the solid is crystallized.

Method 2: In this method, the oxazolones are dissolved in DMSO. The resulting solution reacts to yield the corresponding dehydrodimer.

The following dehydrodimers were obtained using method 1 (the characteristics of the corresponding dehydrodimer are given in parenthesis): 4,4'-bis-[2-p-nitrophenyl-4-phenyl-2-oxazolone] (7c) (mp=215°C; Rf=0.71 (n-dibutyl ether); elemental analysis (%): C 64; H 3.14 ( $C_{30}H_{18}N_4O_8$  requires C 64.06; H 3.23). IR (KBr)  $\text{cm}^{-1}$ : 1818 (s), 1845, 1786, 1661 (s).  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ) ppm: 8.4-8.0 (m, broad, 4H), 7.73-7.10 (m, broad, 14H). UV (dioxane):  $\lambda_{\text{max}}=278$  nm ( $\epsilon=49300 \text{ dm}^3\text{cm}^{-1}\text{mol}^{-1}$ ), 4,4'-bis-[2-p-chlorophenyl-2-oxazolin-5-one] (7d) (mp=206-207°C; Rf=0.91 (n-dibutyl ether); elemental analysis (%): C 66.77, H 3.63 ( $C_{30}H_{18}N_2O_4Cl_2$  requires C 66.55, H 3.35). IR (KBr)  $\text{cm}^{-1}$ : 3049 (w), 1825 (s), 1653 (s), 840 (s), 741 (s), 735 (s), 702 (s).  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ) ppm: 7.38 (two overlapping signals). UV (dioxane):  $\lambda_{\text{max}}=282$  nm ( $\epsilon=41000 \text{ dm}^3\text{cm}^{-1}\text{mol}^{-1}$ ), 4,4'-bis-[2-p-methylphenyl-4-phenyl-2-oxazolin-5-one] (7e) (mp=208-209°C; Rf=0.83 (n-dibutyl ether); elemental analysis (%): C 76.85, H 4.89, N 5.45 ( $C_{32}H_{24}N_2O_4$  requires C 76.78, H 4.83, N 5.60). IR (KBr)  $\text{cm}^{-1}$ : 1812 (s), 1639 (s), 909 (s), 826 (s), 752 (s), 729 (s), 700 (s).  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ) ppm: 8.07-6.97

(two complex signals, 18H), 2.37 (s, 3H). UV (dioxane):  $\lambda_{max}=258$  nm ( $\epsilon=41600$   $\text{dm}^3\text{cm}^{-1}\text{mol}^{-1}$ ), 4,4'-bis-[2-phenyl-4-p-methoxyphenyl-2-oxazolin-5-one] (7f) (mp=183°C; Rf=0.63 (n-dibutyl ether); elemental analysis (%): C 72.18, H 4.65, N 5.18 ( $\text{C}_{32}\text{H}_{24}\text{N}_2\text{O}_6$  requires C 72.18, H 4.54, N 5.26). IR (KBr)  $\text{cm}^{-1}$ : 1818 (s), 1653 (w), 1610 (s), 1258, 1160, 1026, 968, 840, 735, 699.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ) ppm: 8.60-6.70 (three overlapping signals, 18H). UV (dioxane):  $\lambda_{max}=230$  nm ( $\epsilon=31900$   $\text{dm}^3\text{cm}^{-1}\text{mol}^{-1}$ ) and 4,4'-bis-[2-phenyl-4-p-chlorophenyl-2-oxazolin-5-one] (7g) (mp=184°C; Rf=0.83 (n-dibutyl ether); elemental analysis (%): C 66.80, H 3.49, N 4.97 ( $\text{C}_{30}\text{H}_{18}\text{N}_2\text{OCl}_2$  requires C 66.55, H 3.35, N 5.17). IR (KBr)  $\text{cm}^{-1}$ : 1821 (s), 1653 (s), 820 (s), 751 (s), 704 (s), 690 (s).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ) ppm: 8.40-7.77 (m, 4H). UV (dioxane):  $\lambda_{max}=253$  nm ( $\epsilon=35000$   $\text{dm}^3\text{cm}^{-1}\text{mol}^{-1}$ ),  $\lambda_{max}=215$  nm ( $\epsilon=31200$   $\text{dm}^3\text{cm}^{-1}\text{mol}^{-1}$ )).

The following dehydrodimers were prepared according to method 2: 4,4'-bis-[2-p-methoxyphenyl-4-phenyl-2-oxazolin-5-one] (7a) (mp=195°C, Rf=0.56 (n-dibutyl ether), product identical to that described in (6)), 4,4'-bis-[2,4-diphenyl-2-oxazolin-5-one] (7b) (mp=199°C, Rf=0.76 (n-dibutyl ether), product identical to that described in (6)), 4,4'-bis-[2-p-chlorophenyl-4-phenyl-2-oxazolin-5-one] (7d) (mp=207°C), 4,4'-bis-[2-p-methylphenyl-4-phenyl-2-oxazolin-5-one] (7e) (mp=208°C, Rf=0.82 (n-dibutyl ether)), 4,4'-bis-[2-phenyl-4-p-methoxyphenyl-2-oxazolin-5-one] (7f) (mp=183°C, Rf=0.64 (n-dibutyl ether)), 4,4'-bis-[2-phenyl-4-p-chlorophenyl-2-oxazolin-5-one] (7g) (mp=184°C, Rf=0.83 (n-dibutyl ether)). Each of the products prepared by this method is identical to the corresponding product obtained by method 1.

#### Stability of oxazolones 3a and 3h in several solvents.

Oxazolones 3a and 3h yield the corresponding dehydrodimers when dissolved in dimethylformamide (DMF), acetonitrile or acetone, as they do in DMSO solutions. The reaction characteristics (reaction time, product yield) of the dimerizations in DMF are similar to those in DMSO; however, reactions in the other solvents occur at a slower rate and produce dehydrodimers in lower yields.

Oxazolones 3a and 3h do not yield dehydrodimers when dissolved in benzene, toluene, xylene, dimethoxyethane and chloroform. In all cases, dehydrodimers were undetected after 48 hours in solution in the corresponding solvent.

#### Stability of oxazolone 3a in degassed DMSO.

This test was performed in a Y-shaped tube. Oxazolone 3a (0.1 g) is placed in one arm of the tube and DMSO (2 mL) in the other arm and the tube is placed in liquid nitrogen. When the material is frozen, the pressure is reduced to  $10^{-4}$  Torr, the tube is sealed and let to stand at room temperature. After repeating this process four times, the oxazolone is mixed with the DMSO. This mixture does not yield detectable dehydrodimer even after eight days.

#### Detection of hydrogen peroxide as reaction product.

A solution of 3a (0.3 g) in DMSO (5 mL) is divided in two equal portions; 1 mL of DMSO is added to one portion and used as control in the test. Then, 1 mL of potassium titanium<sup>IV</sup> oxalate and sulfuric acid reagent ( $\text{K}_2\text{TiO}(\text{C}_2\text{O}_4)_2 \cdot 2\text{H}_2\text{O}$ ) (16) is added to the second portion and the reaction is followed at 410 nm.

### REFERENCES

1. Gotthardt, H.; Huisgen, R.; Bayer, H.O.; J. Am. Chem. Soc. 1970, 92, 4340-44.

2. Padva, A.; Akiba, M.; Cohen, L.A.; McDonnald, J.G.; *J. Org. Chem.* **1983**, 48, 695-703.
3. Maquestiau, A.; van Haverbecke, Y.; van der Einde, J.J.; Grunelle, G.; *Bull. Soc. Chim. Belg.* **1977**, 86, 81-85.
4. Gakis, N.; Marky, N.; Hansen, H.J.; Heimgartner, H.; Schmidt, H.; Oberhausly, H.; *Helv. Chim. Acta* **1976**, 56, 2149-2167.
5. Dixit, V.M.; Bhat, V.; Trozzolo, A.M.; George, M.V.; *J. Org. Chem.* **1979**, 44, 4169.
6. Marquez, A.; Chuaqui, C.A.; Rodriguez, H.; Zagal, L.; *Tetrahedron* **1985**, 41, 2341-2346.
7. Fieldlab catalog, Oxygen Analyzer, Beckman Instruments Inc., Fullerton; **1973**, 8.
8. Roberts, J.D.; Caserio, M.C.; "Basic Principles of Organic Chemistry" W.A. Benjamin Inc., New York, **1964**, p. 77.
9. George, M.V.; Balachandran, K.S.; *Chem. Revs.* **1975**, 75, 491.
10. Kille, G.; Fleury, J.P.; *Bull. Soc. Chim. Fr.* **1968**, 4636.
11. Petersen, H.J.; *Tetrahedron Letters* **1969**, 20, 1557-1560.
12. Viehe, H.G.; Merenyi, R.; Stella, L.; Janousek, Z.; *Angew. Chem. Intl. Ed. Eng.* **1979**, 18, 917.
13. Sellers, R.M.; *Analyst* **1980**, 105, 950-954.
14. Giese, B.; "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds"; Pergamon Press, Oxford, UK, **1986**, 113-119.
15. Schaefer, H.J.; *Angew. Chem. Intl. Ed. Eng.* **1981**, 20, 911.
16. Gronowitz, S.; Pedaja, P.; *Tetrahedron* **1978**, 34, 587-590.
17. Pagano, A.H.; Schleiter, H.; *J. Org. Chem.* **1970**, 35, 295-303.
18. Hartzler, H.D.; *J. Org. Chem.* **1966**, 58, 2654-2658.
19. Russell, G.A.; Kaupp, G.; *J. Am. Chem. Soc.* **1969**, 91, 3851-3859.
20. Gotthardt, H.; Huisgen, R.; *Chem. Ber.* **1970**, 103, 2356.
21. Rodriguez, H.; Pavez, H.; Marquez, A.; Navarrete, P.; *Tetrahedron* **1983**, 39, 23-27.
22. Nakagawa, K.; Konaka, R.; Nakata, T; *J. Org. Chem* **1962**, 27, 1597.

#### Acknowledgements.

The authors acknowledge with thanks grants from DTI (University of Chile, project Q 2312-8934) and FONDECYT (project 0999/90).