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THE REACTIONS OF α- OXODITHIOESTER S-METHYLIDES

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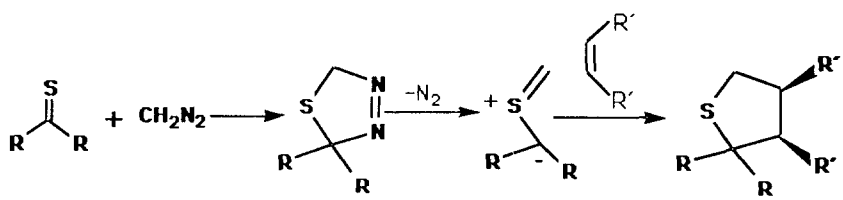
Abstract α-oxodithioesters react rapidly with diazomethane at -80° yielding thiadiazolines, which after N_2 extrusion form thiocarbonyl ylides These ylides undergo electrocyclic ring closure However, in the presence of strong dipolarophiles they can be trapped to yield the corresponding cycloadducts

Introduction The Huisgen method for obtaining thiocarbonyl ylides based on the reaction of thioketones and diazoalkanes is an attractive procedure owing to the mild nature of the conditions required [1]

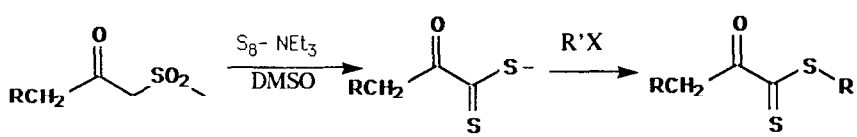


However, very few thioketones are readily available starting materials that are stable[2], this prompted us to study the reaction of diazomethane and other thiocarbonyl compounds

While the reaction of dithioesters and diazomethane is too slow to compete with the fast nitrogen extrusion from the thiadiazoline, activation of the dithioester with an adjacent carbonyl group allows the reaction to proceed and the thiocarbonyl ylides formed are easily interceptable with dipolarophiles[3] This is the case of dithioxalamide S-benzylide, however, dipolarophiles such as maleic anhydride or acroleine, which have strong electrofilic groups lead to complex mixtures, probably because of the presence of the nitrogen amide atom in the ylide

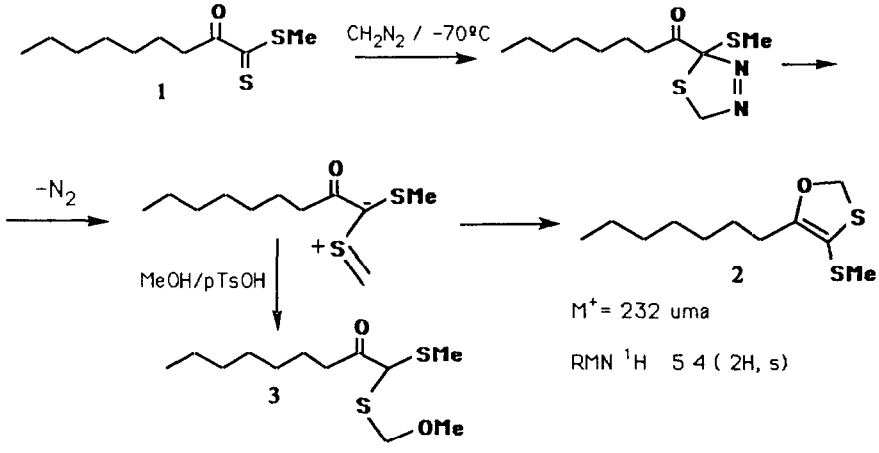
To increase the potential usefulness of this reaction in the present work we studied the reaction of diazomethane and α-oxodithioesters

Results α-oxodithioesters can be readily prepared from β-ketosulfones, triethylamine and sulfur[4]



Their deep purple colour and very fast reaction allow their titration with diazomethane at -80°, with the formation of a thiadiazoline When the temperature is raised to -50°, nitrogen extrusion produces the ylide We started our work with methyl 2-oxodithiononanoate **1**. In the absence of dipolarophiles, thiocarbonyl ylides usually dimerize[5], however, the reaction of **1** and diazomethane led only to a monomeric product **2** showing an M^+ at

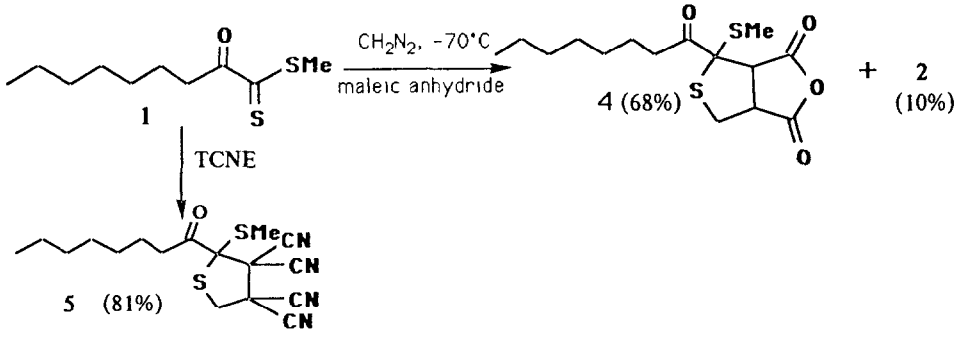
232 amu The presence of a singlet at 5 4ppm in its ^1H NMR spectrum is in agreement with an electrocyclic ring closure of the ylide This reaction is already known for thiocarbonyl ylides[6]



The presence of the intermediate ylide can easily be shown when the reaction is carried out in MeOH and a trace of pTsOH acid Under these conditions, the ylide is protonated and adds a MeOH molecule to yield compound 3

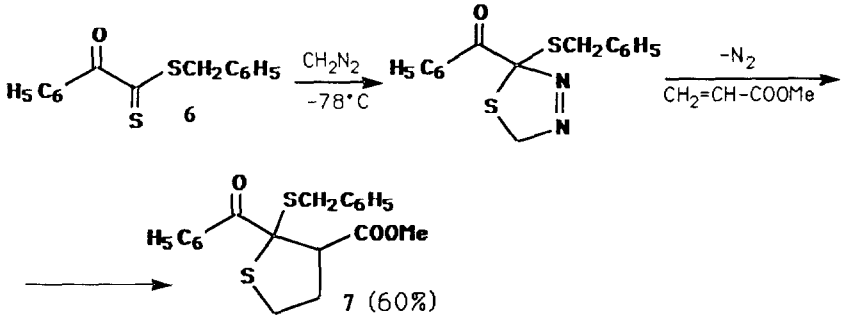
The ylide, however, must undergo a very fast ring closure because even if the ylide is generated in pure methyl acrylate, no cycloadduct is obtained

Stronger dipolarophiles such as maleic anhydride mainly produce the cycloaddition compound (4, 68%, 2, 10%), while no electrocyclic ring closure can be detected with TCNE (compound 5, 81%) .

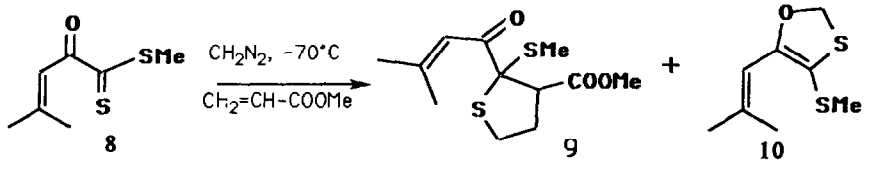


To increase the number of useful dipolarophiles it is desirable to retard the ring closure of the ylide This can be achieved by conjugating the carbonyl group of the ylide Non-bonding electrons, as in the case of dithioxalamide S-benzylide, are the most effective kind This ylide only dimerizes in the absence of dipolarophiles, and no electrocyclic ring closure can be detected An aromatic ring is also efficient in fact the

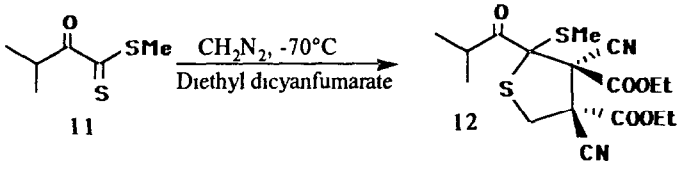
cycloaddition of the benzoyl dithioester 6 with methyl acrylate allowed us to isolate the corresponding cycloadduct 7 at a yield of 60%



The retarding effect of a conjugated double bond is less striking The reaction of the ylide corresponding to the thiocarbonyl compound 8 with methyl acrylate led to a 3 / 1 mixture of the cycloaduct 9 and the ring closure compound 10



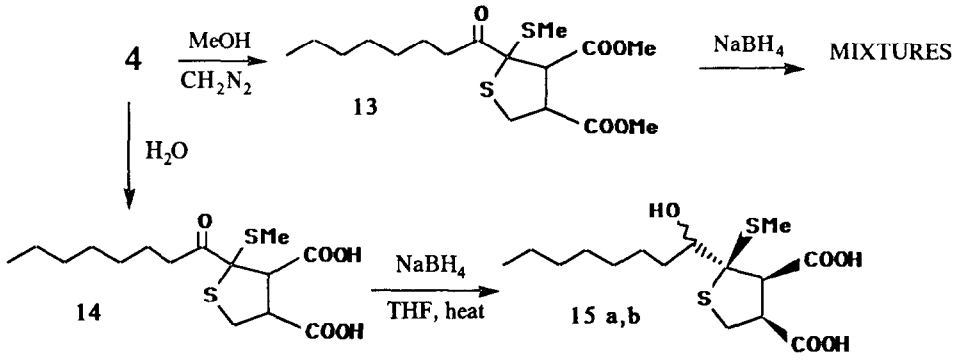
The stereoespecifity of these cycloadditions was investigated using diethy dicyanfumarate as the dipolarophile A single cycloadduct 12 was obtained at a 81% yield, showing complete stereoespecifity



To study the stereochemistry of these reactions, we attempted to reduce the carbonyl function of the cycloadduct 4 to the corresponding alcohol In the case of a *cis* relationship between the C-2 alkyl chain and the C-3 carboxylate, spontaneous lactonization could be expected However, if the compound is *trans* the tension of the two fused cyclopentane rings should preclude lactone formation

To reduce the carbonyl function, we first prepared the dimethyl ester 13, treating the anhydride 4 with MeOH and diazomethane Reduction of this compound with $NaBH_4$ led however only to mixtures which show a loss of the thiomethyl group in its ^1H NMR spectrum We believe that this point to an anti arrangement between the thiomethyl and the C-3 proton

A cleaner reaction was obtained when the diacid 14 was reduced with $NaBH_4$ in boiling THF In this case salt formation prevents elimination of the thiomethyl group After work up, two epimeric alcohols 15a and 15b were isolated Lactonization could not be achieved from either hydroxyacid and hence a *trans* structure was deduced



EXPERIMENTAL PART

Melting points are uncorrected All solvents and reagents were purified by standard methods before use ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200 SY (200 MHz) All the ^1H and ^{13}C NMR spectra were run on $CDCl_3$ solutions, unless implied otherwise Mass spectra were obtained on a VG TS 250 mass spectiometer under 70 eV IR spectra were recorded on a Beckmann Acculab 8 Chromatographies were run on SiO_2 columns, eluting with hexane-ether mixtures of increasing polarity

Synthesis of 4-methylthio-5-heptyl-1,3-oxathiolene 2 Thiocarbonyl compound **1** (500 mg) was dissolved in a CH_2Cl_2 (10 ml)/ hexane (15 ml) mixture, at -80°C, with stirring and under a nitrogen atmosphere An ethereal solution of diazomethane -previously cooled to -80°C - was then dropped until the purple colour of the solution disappeared The thiadiazoline precipitated as a white solid The reaction mixture was allowed to warm to -60°C and nitrogen began to be formed When the extrusion of N_2 had finished, the reaction mixture was warmed to room temperature, the solvent was removed by concentrating *in vacuo,* and the crude residue (550 mg) was purified by chromatography on silica gel The electrocyclic ring closure compound **2** was isolated (370 mg, 70%) IR (film) υ 3000-2950, 1620, 1470, 1040 cm^{-1} ^1H NMR($CDCl_3$) δ 5 4 (2H, s, OCH_2S), 2 3 (2H, t, J=7 6Hz), 2 2 (3H, s, SMe), 1 4 (2H, m), 1 3 (8H, m), 0 8 (3H, t) ^{13}C NMR ($CDCl_3$) δ 154 5 (s), 103 (s), 73 (t), 32 (t), 29 (t, 2C), 27 (t), 26 (t), 22 5 (t), 19 (q), 14 (q) MS (m/e, %) 232 (M^+, 40), 175 (73), 147 (90), 127 ($C_7H_{15}CO^+$, 100), 57 (95)

Synthesis of 5-methylthio-2-oxa-4-thia-6-tridecanone 3 A solution of the thiocarbonyl compound **1**(186 mg) in MeOH (10 ml) at -80°C was titrated with diazomethane pTsOH (50 mg) in MeOH (2ml) was then added and the reaction mixture was allowed to warm The extrusion of nitrogen took place at -50°C When no bubbles of N_2 were visible, the solvent was evaporated off and the crude residue was washed with $NaHCO_3$ and extracted with ether Usual work up afforded compound **3** (196 mg, 88%) IR (film) υ 2950-2840, 1710, 1470, 1190, 1090, 900 cm^{-1} ^1H NMR ($CDCl_3$) δ 4 7 (2H, AB, J=11 5Hz), 4 5 (1H, s), 3 3 (3H, s), 2 8-2 4 (2H, m), 1 9 (3H, s), 1 5 (2H, m), 1 2 (8H, m), 0 8 (3H, t) ^{13}C NMR ($CDCl_3$) δ 73 (t), 56 6 (d), 56 (c), 38 (t), 31 (t), 29 (t, 2C), 24 (t), 22 (t), 13 7 (q), 12 (q)

Synthesis of the anhydride 4 The thiocarbonyl compound **1** (2 9 g) was dropped onto an ethereal solution of diazomethane cooled to -80°C, with vigorous stirring When titration was complete, maleic anhydride (1 46 g) in

acetone (1 ml) was added The reaction mixture was allowed to warm to -65°C and the nitrogen was extruded After stirring at this temperature for 12 hours, the solvent and the maleic anhydride in excess were removed by concentrating *in vacuo*, to afford a crude material in which compound 2 (10%) and **4** were identified **4** IR (film) υ 1840, 1780, 1700 cm^{-1} ^1H NMR ($CDCl_3$) δ 4 45 (1H, d, J=8 2Hz), 3 85 (1H, t), 3 15 (1H, m), 3 00 (1H, m), 2 65 (2H, m), 2 05 (3H, s), 1 50 (2H, m), 1 15 (8H, m), 0 75 (3H, t) ^{13}C NMR ($CDCl_3$) δ 201 6 (s), 171 5 (s), 168 2 (s), 73 (s), 52 (d, 2C), 344 8 (t), 34 0 (t), 31 4 (t), 29 (t, 2C), 25 4 (t), 22 3 (t), 14 7 (q), 13 8 (q) The cycloadduct was purified by treating the reaction mixture with Na_2CO_3 and heating in a steam bath until all the anhydride had been hydrolyzed The mixture was then extracted with ethyl acetate to remove impurities The aqueous phase was acidified with HCl c and extracted twice with ethyl acetate, isolating the diacid **14** (2 60 g, 57%) ^1H NMR ($CDCl_3$) δ 4 31 (1H, d, J=5 6Hz), 3 82 (1H, m), 3 40-2 70 (4H, m), 2 00 (3H, s), 1 67 (2H, m), 1 30 (8H, m), 0 88 (3H, t) ^{13}C NMR ($CDCl_3$) δ 201 2 (s), 168 7 (s), 169 6 (s), 68 3 (s), 50 3 (d), 49 0 (d), 34 2 (t), 31 1 (t), 29 8 (t), 27 1 (t, 2C), 23 7 (t), 20 6 (t), 13 3 (q), 11 8(q)

Synthesis of 3,3,4,4-tetracyan-2-methylthio-2-octanoyltetrahydrothiophene 5 A solution of the thiocarbonyl compound **1** (200 mg) in a 1/1 hexane- CH_2Cl_2 mixture was titrated at -80°C with diazomethane according to the procedure previously described TCNE (120 mg) in ethyl acetate (2 ml) was then dropped The reaction mixture was allowed to warm to -55°C and the evolution of nitrogen took place slowly The solution was then warmed to room temperature and the solvent removed by concentrating *in vacuo* to afford a crude residue which was chromatographed on silica gel (ether as eluent) isolating compound **5** (300 mg, 91%) IR (film) υ 2250 (CN), 1710 (C=O) cm^{-1} ^1H NMR ($CDCl_3$) δ 3 91 (2H, AB, J=12Hz), 2 85-2 76 (2H, m), 2 26 (3H, s, SMe), 1 80-1 52 (2H, m), 1 29-1 22 (8H, m), 0 93-0 80 (3H, m) ^{13}C NMR ($CDCl_3$) δ 197 6 (s, C=O), 109 4 (s, 2C), 108 4 (s, 2C), 74 5 (s), 53 7 (s), 46 8 (s), 38 4 (t), 37 6 (t), 31 4 (t), 28 7 (t, 2C), 23 9 (t), 22 4 (t), 17 7 (q), 13 6 (q) MS (m/e, %) 360 (M^+, 5), 267 (15), 127($C_7H_{15}CO^+$, 100)

Synthesis of 2-benzylthio-2-benzoyl-3-methoxycarbonyltetrahydrothiophene 7 Benzylbenzoyl-carbodithioate (450 mg) was dissolved in methyl acrylate (12 ml) and cooled down to -80°C The mixture was titrated with diazomethane until a colourless solution was obtained The temperature was raised to -60°C and the extrusion of nitrogen began After extrusion was complete, the solvent was evaporated under reduced pressure, isolating after chromatography the cycloadduct 7 (350 mg, 57%) IR (film) υ 1720, 1650, 1580, 1210, 740, 710 cm^{-1} ^1H NMR ($CDCl_3$) δ 8 36-8 31 (2H, d), 7 54-6 95 (8H, m), 4 36 (1H, t, J=5 7Hz), 3 76 (3H, s), 3 65 (2H, AB, J=11Hz), 3 58 (1H, m), 3 05 (1H, m), 3 67 (1H, m), 3 37 (1H, m) ^{13}C NMR ($CDCl_3$) δ 193 3 (s), 171 4 (s), 135 8 (s), 134 4 (s), 132 8 (d), 130 3 (d, 2C), 128 9 (d, 2C), 128 3 (d, 2C), 127 8 (d, 2C), 127 1 (d), 70 5 (s), 54 5 (d), 51 6 (q), 37 9 (t), 33 3 (t), 33 1 (t) MS (m/e, %) 372 (M^+, 3), 267 (M^+ -$C_6H_5CO^+$, 90), 105 ($C_6H_5CO^+$, 100)

Synthesis of the cycloadduct 9 A solution of the thiocarbonyl compound **8** (140 mg) in methyl acrylate (8 ml) at -80°C was titrated with diazomethane The temperature was raised to -60°C and nitrogen began to evolve When no further N_2 was extruded, the reaction mixture was warmed to room temperature and the solvent evaporated under reduced pressure The crude residue was chromatographed to afford **9** (70 mg, 32 %) IR (film) υ 1730 (C=O), 1660 (C=O), 1615, 1435, 1350, 1200, 1130 cm^{-1} ^1H NMR ($CDCl_3$) δ 6 69 (1H, broad s), 4 16-4 11 (1H, dd), 3 77 (3H, s, COOMe), 3 55-3 42 (1H, m), 2 95-2 85 (1H, m), 2 57-2 40 (2H, m), 2 16 (3H, s, SMe), 2 01 (6H, s) MS (m/e, %) 274 (M^+, 10), 191 (M^+-$C_4H_7CO^+$, 100), 132 (25), 83 ($C_4H_7CO^+$, 70)

Synthesis of the cycloadduct 12 A solution of the thiocarbonyl compound **11** (300 mg) in a CH_2Cl_2 (10 ml)/ hexane (10 ml) mixture was cooled to -80°C and titrated with diazomethane Diethyl dicyanfumarate (411 mg) was then added The temperature was raised to -50°C and nitrogen was extruded When all the N_2 had been evolved, the solution was warmed to room temperature and the solvent removed by concentrating *in vacuo* to afford a crude residue (690 mg) which was purified by crystallization (600 mg, 81%) ^{1}H NMR ($CDCl_3$) δ 4 40-4 26 (4H, m), 3 72-3 66 (1H, d), 3 45-3 40 (1H, d), 3 20 (1H, m), 2 13 (3H, s), 1 32-1 29 (6H, m), 1 21-1 18 (3H, d), 1 10-1 08 (3H, d) ^{13}C NMR ($CDCl_3$) δ 202 4 (s), 162 5 (s), 161 8 (s), 114 0 (s), 112 7 (s), 73 2 (s), 64 6 (t), 64 4 (t), 57 0 (s, 2C), 36 6 (d), 36 3 (t), 21 0 (q), 20 1 (q), 17 6 (q), 16 6 (q), 13 3 (q)

Synthesis of 13 Compound **4** (310 mg) was dissolved in MeOH (10 ml) and refluxed for half an hour The solvent was evaporated and the residue was treated with an ethereal solution of diazomethane to afford the dimethyl ester **13** (340 mg, 96%) IR (film) υ 1740, 1700 cm^{-1} ^{1}H NMR ($CDCl_3$) δ 4 26 (1H, d, J=5 1Hz), 3 70 (1H, t), 3 70 (3H, s, COOMe), 3 60 (3H, s, COOMe), 3 05 (3H, m), 2 6 (1H, m), 1 9 (3H, s), 2 54 (2H, m), 1 2 (8H, m), 0 8 (3H, t) ^{13}C ($CDCl_3$) δ 203 4 (s), 170 6 (s), 170 2 (s), 69 7 (s), 52 1 (q), 51 9 (d), 51 5 (q), 50 4 (d), 36 (t), 33 (t), 31 5 (t), 29 (t), 28 8 (t), 25 4 (t), 22 4 (t), 15 3 (q), 13 8 (q) MS (m/e, %) 376 (M^+, 2), 249(M^+-$C_7H_{15}CO^+$, 100), 189 (15), 131 (80)

Synthesis of the epimeric alcohols 15a and 15b The cycloadduct **14** (200 mg) was dissolved in THF and $NaBH_4$ pellets (50 mg) were added The reaction mixture was then refluxed for three hours The solution was poured into HCl and stirred for 15 minutes After extracting with ethyl acetate, esterification with diazomethane afforded a residue which was chromatographed, isolating the epimeric alcohols **15a** (70 mg, 35%) and **15b** (30 mg, 15%) **15a** IR (film) υ 3500, 1760-1740, 1450, 1150 cm^{-1} ^{1}H NMR ($CDCl_3$) δ 3 87-3 82 (1H, d), 3 72 (3H, s), 3 66 (3H, s), 3 60 (1H, t), 3 22-3 12 (1H, m), 2 23 (3H, s), 1 37-1 20 (12H, m), 0 88 (3H, t) ^{13}C NMR ($CDCl_3$) δ 170 9 (s), 170 7 (s), 78 4 (d), 74 6 (q), 55 0 (d), 52 6 (d), 52 0 (q), 51 5 (q), 33 3 (t), 32 0 (t), 31 8 (t), 29 5 (t), 29 2 (t), 27 2 (t), 15 8 (q), 14 0 (q) MS (m/e, %) 378(M^+, 2), 299 (40), 249 (M^+- $C_8H_{17}O$, 100), 203 (40) **15b** IR (film) υ 3460, 1740, 1430, 1120 cm^{-1} ^{1}H NMR ($CDCl_3$) δ 3 73 (3H, s), 3 71 (3H, s), 2 15 (3H, s), 1 34-1 28 (12H, m), 0 89 (3H, t) ^{13}C NMR ($CDCl_3$) δ 170 9 (s), 170 7 (s), 77 0 (d), 58 3 (d), 52 6 (d), 52 0 (q), 51 5 (q), 33 6 (t), 33 0 (t), 31 8 (t), 29 5 (t), 29 2 (t), 26 5 (t), 22 6 (t), 15 1 (q), 13 9 (q)

References

1 Huisgen, R , Fulka, C , Kalwinsch, I , Xingya, Li; Mloston, G , Morán, J R , Probstl, A , Bull Soc Chim Belg , **1984**, *93*, 511

2 (a) Schoberl, A , Wagner, A in " Methoden der Organischen Chemie", ed E Muller, Houben-Weyl, Berlin, 1955, vol IX, 699 (b) Campaigne, E in " The Chemistry of the Carbonyl Group" ed S Patai, Interscience, New York, 1966, chapter 17

3 Alcázar,V , Tapia, I ,Pascual Teresa, J de, Morán, J R , Olabarrieta, R , accepted in J Org Chem

4 To be published elsewhere

5 Kalwinsch, I , Xingya, Li, Gottstein, J , Huisgen, R , J Am Chem Soc , **1981**, *103*, 7032-7033

6 Ueno, Y and Okawara, M , Bull Chem Soc Japan, **1972**, *45*, 1797