Tetrahedron Vol. 46, No. 20, pp. 7011-7018, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

Reaction of Ketene Silyl Acetals with Unsaturated Nitriles in the Presence of Titanium Tetrachloride

Syed Masarrat Ali, and Gérard Rousseau*

Laboratoire des Carbocycles, Unité Associée au C.N.R.S., Bât. 420
Université de Paris-Sud, 91405 ORSAY CEDEX (France)

(*Received in Belgium* 18 *July* 1990)

Abstract The reaction of ketene alkyl silyl acetals with acrylonitrile in the presence of titanium tetrachloride in dichloromethane at -80°C leads to coupled compounds. Formation of these products can be explained by the transformation of ketene acetals into enoxy radicals, trapping of these radicals by acrylonitrile and then dimerization. With bisketene acetals derived from glutarate and pimelate , a ring closure reaction was observed leading to the formation of cyclopentane and cyclononane derivatives. No cyclisation was observed with ketene acetals derived from higher diesters.

Addition of titanium tetrachloride to ketene alkyl silyl acetals was reported to give succinates [1]. A similar reaction was observed with vinylketene silyl acetals [2a], and formation of *trans*-cyclopropane 1,2-dicarboxylate was reported with bisketene acetals derived from glutarates [2b]. A dimerization of intermediate enoxyradical can be postulated for these reactions [1,2].

Recently [3] we observed that the reaction of ketene alkylsilyl acetals with acrylonitrile led to cyclobutanoic compounds ([2+2] cycloaddition) or to γ-cyanoesters, depending on the solvent and the Lewis acid used. Here we would like to report a very interesting behaviour of acrylonitrile with ketene alkylsilyl acetals when used in the presence of titanium (IV) chloride.

Monoketene alkylsilyl acetals **1a - 1c** were prepared from the corresponding esters following a standard procedure [4]. The yields of bisketene acetals **1d-1g** were improved when prepared by Corey's procedure[5] and distilled under very high vacuum to avoid decomposition. All attempts to prepare the bis ketene acetal derived from ethyl adipate were unsuccessful and only the enol ether resulting from the Dieckmann condensation was obtained.

The reactions were carried out by mixing monoketene acetals **1a - 1c** (10 mmol) with acrylonitrile (20 mmol) in dichloromethane (20 mL) and by adding at -80°C with stirring titanium tetrachloride (10 mmol). The color of the reaction mixture changed immediately from colorless to dark red. After forty-five minutes the reaction mixture was hydrolyzed with water. The mixture was allowed to stand at room temperature and the colorless solution was extracted with ether. The organic extract and washings were collected. Removal of solvent gave an oil (or a solid) which was purified by liquid chromatography (or crystallization from ether). Twice the amounts of acrylonitrile and titanium tetrachloride were used with bisketene acetals **1d - 1g** and the dienic compound **1h**. Results are summarized in Table 1. The products were fully characterized on the basis of spectral data (^{1}H NMR, IR and mass) and elemental analysis. The products **2a - 2c** obtained from mono ketene acetals **1a-1c** resulted from the addition of acrylonitrile to the ketene

Table 1. Reaction of Ketene Silyl Acetals with Unsaturated Nitriles in the Presence of $TiCl_4$

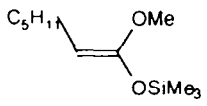
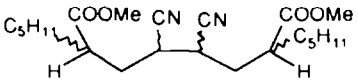
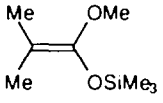
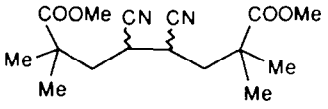
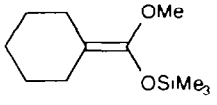
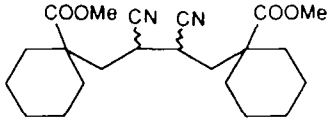
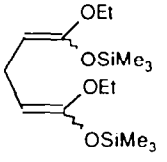
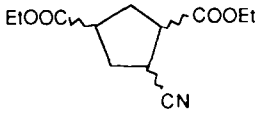
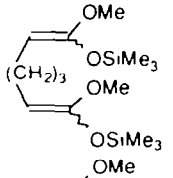
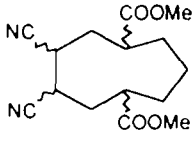
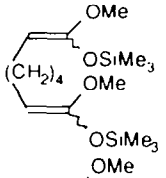
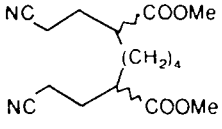
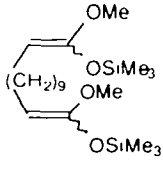
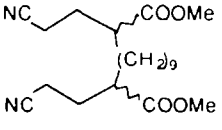
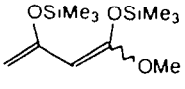
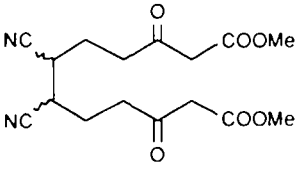
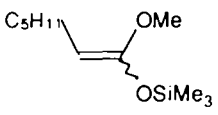
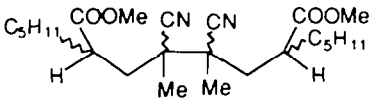
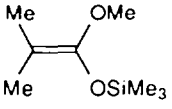
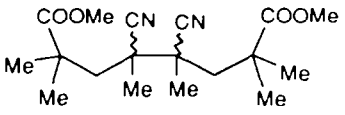
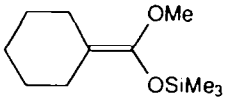
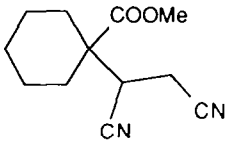
Entry	Ketene Silyl Acetal 1	Product 2	Diastereoisomeric ratio[a]	Yield (%)
Reaction with acrylonitrile				
a			5:9:10:76	62
b			46:54	63[b]
c			50:50	66[c]
d			14:15:33:38	52
e			<1:<1:40:60	53
f			46:54	60
g			25:75	40
h			50:50	61

Table 1 : continued

Reaction with methacrylonitrile

i			7:12:34:47	37
j			10:90	27

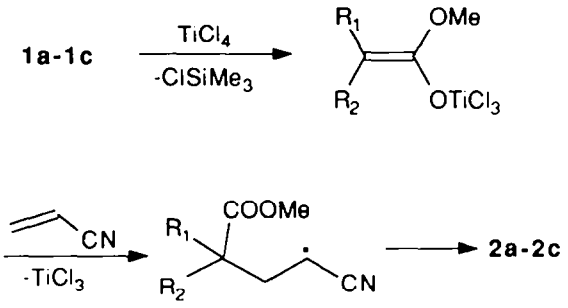
Reaction with fumaronitrile

k			-	69

[a]Determined by ^{1}HNMR after liquid chromatography or crystallization [b]4% of methyl 4-cyano-2,2-dimethyl butanoate[3] were also isolated.[c] 5% of (2-cyanoethyl)-1-cyclohexane carboxylate[3] were also isolated

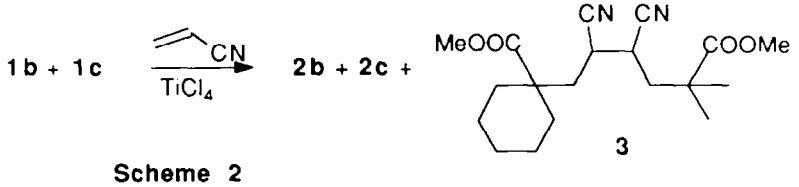
acetals and subsequent dimerization. Bisketene acetals **1d-1e** under similar reaction conditions undergo intramolecular cyclization (entries d, e) leading to cyclic systems. For the ketene acetal **1d** we observed the incorporation of only one molecule of acrylonitrile while with ketene acetal **1e** an equivalent reaction to those of monoketene acetals was obtained ; this allows an easy preparation of 9-membered carbocyclic compounds, the synthesis of which is usually difficult. We were not be able to isolate any cyclized product for 10-membered and larger rings (entries f, g) Only the more electron rich double bond of 1,3-bis-(trimethylsiloxy)-1-methoxybuta-1,3-diene **1h**[6] reacted, and the expected dimer **2h** was isolated.

A possible interpretation of these coupling reactions implies the formation of radicals. The ketene silyl acetals are first converted to enoxy radicals, via the titanium enolates [1,2] ; trapping of these radicals with acrylonitrile, an excellent radical acceptor[7] give new radicals which undergo coupling [8] to the obtained dimers (Scheme 1). For entropic reasons the intramolecular cyclisation did not occur with bisketene acetals **1f**,and **1g**. In these two cases quenching of the



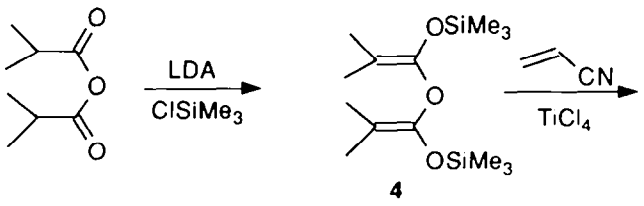
Scheme 1

reaction mixture with deuterium oxide did not give any deuterium incorporation. Formation of products **2f**, **2g** can be explained by abstraction of hydrogen from dichloromethane. The radical nature of the intermediate was supported by a cross coupling experiment : an equimolar mixture of ketene acetals **1b** and **1c** was treated under similar reaction conditions. After the usual work-up and column chromatography three compounds were isolated : the two homo-coupling products **2b**, **2c** and the hetero-coupling product **3** in the ratio 32:38:30 (Scheme 2). However attempts to trap the radical intermediates by adding compounds such as $FeCl_3$, CCl_4, CBr_4 and tributyltin hydride failed.

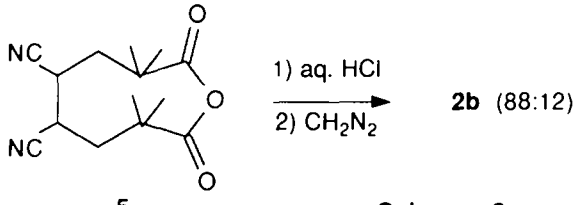


Scheme 2

We observed no peculiar stereoselectivity in these reactions, except in one case (table 1, entry e). A mixture of all possible diastereoisomers was obtained but no structural assignment was performed. This isomeric distribution is probably due to the fact that the stereochemical course of the reactions is controlled by the thermodynamic stability of the products.[2b] In order to obtain selectivity or to influence the stereochemical course of the reaction we designed an experiment to modify the structure of ketene acetal. Starting from ketene acetal **4**, prepared from the corresponding anhydride, after reaction with acrylonitrile in the presence of titanium (IV) chloride (vide supra) we obtained product **5** which was immediately hydrolyzed (20% aqueous HCl, 3 h) and esterified (CH_2N_2) to give the coupled compound in a diastereoisomeric ratio of 88:12 (60% yield) (Scheme 3).



4



5

Scheme 3

We also checked the reactivity of methacrylonitrile (table 1, entries i, j) where the same reaction was observed in low yields. This is probably due to the steric hindrance introduced by the methyl group during the coupling reaction. With fumaronitrile no dimer was obtained (table 1, entry k). Methyl acrylate in the same conditions led to a complex mixture of products in which we could not detect any coupled compound.

Experimental Section

Nuclear magnetic resonance spectra were recorded on Bruker AC200 spectrometer at 200 MHz. Infrared spectra were recorded on a Perkin Elmer 682 spectrometer and mass spectra were determined with a Nermag R10-10 spectrometer at an ionizing voltage of 70 eV. Chemical ionizations (CI) were made with ammonia. Elemental analyses were performed by the Service de Microanalyse de Gif-sur-Yvette. Melting points were determined on a Mettler FPS apparatus. Column chromatography was performed with SDS silica gel (70 - 230 Mesh). Thin layer chromatography was performed on 0.25 mm silicagel (Merck $60F_{254}$).

Dry dichloromethane was obtained by distillation over calcium hydride. Titanium (IV) chloride was purified by distillation under argon before used. Ketene silyl acetals **1a - 1c**, were prepared by a literature procedure [4]. Bisketene acetals **1d - 1g** and **4** were obtained by Corey's method [5]. 1,3-Bis(trimethylsiloxy)-1-methoxy-buta-1,3-diene **1h** is a known compound [6].

1,5-Bis(trimethylsiloxy)-1,5-diethoxy-1,4-pentadiene (1d).[9] oil (70%)

1,7-Bis(trimethylsiloxy)-1,7-dimethoxy-1,6-heptadiene (1e). oil (65%), bp 71°C/0.1 mmHg ; ^{1}H NMR (E,E isomer - $CDCl_3$) δ 4.80 (t, J = 4.2 Hz, 2H), 3.53 (s, 6H), 2.32 (m, 2H), 2.10 (m, 2H), 1.61 (m, 2H), 0.18 (s, 18H).

1,8-Bis(trimethylsiloxy)-1,8-dimethoxy-1,7-octadiene (1f). oil (60%), bp 92°C/3.10^{-4} mmHg ; ^{1}H NMR (E,E-isomer , $CDCl_3$) δ 4.18 (t, J = 6.9 Hz, 2H), 3.49 (s, 6H), 1.94 (m, 4H), 1.26 (m, 4H), 0.2 (s, 18H).

1,13-Bis(trimethylsiloxy)-1,13-dimethoxy-1,12-tridecadiene (1g). oil (68%), bp 150°C/3.10^{-3} mmHg ; ^{1}H NMR (E,E-isomer , $CDCl_3$) δ 3.67 (t, J = 5.8 Hz, 2H), 3.51 (s, 6H), 1.95 (m, 4H), 1.28 (m, 14H), 0.23 (s, 18H).

Di(1-trimethylsiloxy-2-methyl-1-propenyl) ether (4). oil (92%), bp 50°C/0.2 mmHg ; ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 6H), 1.53 (s, 6H), 0.2 (s, 18H).

General procedure for the reaction of ketene acetals 1 with acrylonitrile in the presence of $TiCl_4$. In a small flask, under argon, were placed ketene acetal (10 mmol for **1a - 1c** or 5 mmol for **1d - 1h** and **4**), acrylonitrile (20 mmol) and dichloromethane (20 mL). After cooling at -80°C, titanium (IV) chloride (10 mmol) was added rapidly using a syringe. After 45 min, water was added (10 mL) and the cooling bath was removed. When the mixture was warmed to room temperature the organic phase was separated and the aqueous phase extracted with ether (3 x 30 mL). The organic phases were dried (Na_2SO_4) and concentrated to give an oil or a solid which was purified by liquid chromatography (SiO_2 ; ether-hexane) or by crystallization (ether). See table 1 for results.

Dimethyl 4,5-dicyano-2,7-dipentyloctanedioate (2a). The four isomers were separated by liquid chromatography. Main isomer : ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 6H), 3.00 to 2.72 (m, 2H), 2.07 to 1.82 (m, 2H), 1.82 to 1.47 (m, 4H), 1.27 (m, 16H), 0.89 (m, 6H), IR (neat, cm^{-1}) : 2240 (CN), 1740 (CO); MS *m/e* 392 (M^+, 0.7), 361 (15), 350 (17), 207 (22), 166 (67), 144 (24), 87 (100), 55 (98).

Dimethyl 4,5-dicyano-2,2,7,7-tetramethyloctanedioate (2b). The mixture of the two diastereoisomers crystallized together ; mp : 112°C ; ^{1}H NMR ($CDCl_3$, mixture) δ 3.75 (s, 6H), 2.90 (m, 2H), 2.23 to 1.84 (m, 4H), 1.37 (s, 6H), 1.26 (s, 6H); IR (nujol, cm^{-1}) : 2235 (CN), 1715 (CO). MS (CI) *m/e* 326 (M^+, +18, 100) ; Anal calcd for $C_{16}H_{24}N_2O_4$: C, 62.30 ; H, 7.83. Found : C, 62.40 ; H, 8.09.

Dimethyl 4,5-dicyano-2,2,7,7-dipentamethyleneoctanedioate (2c). The mixture of the two diastereoisomers crystallized together ; mp : 149°C ; ^{1}H NMR ($CDCl_3$, mixture) δ 3.75 (s, 6H), 2.82 (m, 2H), 2.30 to 2.05 (m, 4H), 2.05 to 1.70 (m, 4H), 1.70 to 1.50 (m, 8H), 1.50 to 1.15 (m, 8H) ; IR (nujol, cm^{-1}) : 2240 (CN), 1730 (CO) ; MS *m/e* 388 (M^+, 4), 329 (33), 247 (33), 195 (32), 187 (12), 142 (46), 136 (39), 95 (54), 81 (72), 67 (100), 55 (68), 41 (71) ; Anal calc for $C_{22}H_{32}N_2O_4$: C, 68.01 ; H, 8.30 ; N, 7.21. Found : C, 67.67 ; H, 8.42 ; N, 6.97.

Diethyl 2-cyanocyclopentane-1,4-dicarboxylate (2d). The four isomers were separated by liquid chromatography. Main isomer : ^{1}H NMR ($CDCl_3$) δ 4.41 to 4.22 (m, 4H), 3.68 to 2.98 (m, 3H), 2.73 to 2.49 (m, 2H), 2.49 to 2.19 (m, 2H), 1.50 to 1.30 (m, 6H) ; IR (neat, cm^{-1}) : 2245 (CN), 1735 (CO) ; MS *m/e* 240 (M^+ +1, 5), 239 (M^+, 2), 194 (100), 167 (20), 166 (46), 138 (29), 126 (24), 92 (34), 67 (59), 55 (67) ; Anal calcd for $C_{12}H_{17}NO_4$: C, 60.24, H, 7.16, N, 5.85. Found : C, 60.32, H, 6.91, N, 5.63.

Dimethyl 3,4-dicyanocyclononane-1,6-dicarboxylate (2e). The mixture of the two diastereoisomers crystallized together ; mp : 276.6°C ; ^{1}H NMR ($CDCl_3$, mixture) δ 3.73 (s, 6H), 3.47 (d,d, J = 4.4 and 10.2 Hz, 1.2H), 3.40 (d,d, J = 4.4 and 10.4 Hz, 0.8H), 2.98 to 2.92 (m, 1.2H), 2.70 to 2.65 (m, 0.8H), 2.30 to 1.50 (m, 10H) ; IR (nujol, cm^{-1}) : 2240 (CN), 1740 (CO). MS *m/e* 292 (M+, 10), 260 (21), 222 (16), 218 (23), 190 (18), 136 (24), 124 (26), 79 (30), 67 (45), 55 (100) ; Anal calcd for $C_{15}H_{20}N_2O_4$: C, 61.61 ; H, 6.90. Found : C, 61.37 ; H, 6.94.

Dimethyl 2,7-di(2'-cyanoethyl)octanedioate (2f). oil. The two isomers were separated by liquid chromatography. *Less polar isomer* ; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 3.66 (s, 3H), 2.59 to 2.44 (m, 1H), 2.44 to 2.22 (m, 3H), 2.07 to 1.89 (m, 1H), 1.89 to 1.72 (m, 1H), 1.72 to1.40 (m, 6H), 1.40 to 1.19 (m, 6H) ; IR (neat, cm^{-1}) : 2244 (CN), 1740 (CO) ; MS *m/e* 279 (M+ - CN, 4), 249 (8), 182 (20), 155 (38), 122 (16), 108 (11), 87 (63), 59 (61), 55 (100) ; MS (CI) *m/e* 326 (M+18,100). *More polar isomer* : ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 6H), 2.60 to 2.22 (m, 4H), 2.08 to 1.76 (m, 2H), 1.76 to1.40 (m, 6H), 1.40 to 1.17 (m, 6H) ; IR (neat, cm^{-1}) : 2250 (CN), 1735 (CO) ; MS *m/e* 309 (M+ +1, 2), 279 (2), 249 (8), 217 (20), 182 (29), 155 (44), 122 (18), 108 (11), 96 (24), 87 (76), 59 (56), 55 (100).

Dimethyl 2,12-di(2'-cyanoethyl)tridecanedioate (2g). oil. The two isomers were not separated by liquid chromatography. ^{1}H NMR ($CDCl_3$, mixture) δ 3.71 (s,4.8H), 3.67 (s,1.2), 2.60 to 2.25 (m, 4H), 2.25 to 1.70 (m, 2H), 1.70 to 1.38 (m, 4H), 1.38 to 1.17 (m, 18H) ; IR (neat, cm^{-1}) : 2240 (CN), 1740 (CO) ; MS (CI) *m/e* 468 (54), 451 (14), 343 (100).

Dimethyl 6,7-dicyano-3,10-dioxododecanedioate (2h). The mixture of the two diastereoisomers crystallized together ; mp : 176.5°C ; ^{1}H NMR ($CDCl_3$, mixture) δ 3.78 (s, 6H), 3.51 (s, 4H), 3.05 (m, 2H), 2.90 (m, 4H), 2.31 to 1.87 (m, 4H) ; IR (nujol, cm^{-1}) : 2250 (CN), 1745 (CO), 1715 (CO). MS (CI) *m/e* 354 (M+, +18, 100) ; Anal calcd for $C_{16}H_{20}N_2O_6$: C, 57.12 ; H, 5.99 ; N, 8.33. Found : C, 57.00 ; H, 6.04, N, 8.04.

Dimethyl 4,5-dicyano-4,5-dimethyl-2,7-dipentyloctanedioate (2i). The four isomers were separated by liquid chromatography. Main isomer . ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 6H), 2.69 to 2.37 (m, 4H), 1.77 to 1.40 (m, 6H), 1.55 (s, 6H), 1.40 to 1.15 (m, 12H), 0.88 (m, 6H) . IR (neat, cm^{-1}) : 2235 (CN), 1740 (CO). MS *m/e* 421 (M+ +1, 1), 389 (13), 359 (0.6), 329 (11), 210 (23), 194 (100), 179 (22), 157 (12), 144 (34), 101 (10), 87 (37), 69 (22), 55 (64).

Dimethyl 4,5-dicyano-2,2,4,5,7,7-hexamethyloctanedioate (2j). The mixture of the two diastereoisomers crystallized together mp 170°C ; ^{1}H NMR ($CDCl_3$, main isomer) δ 3.72 (s, 6H), 2.11 (q, AB system, J = 14 Hz, 4H), 1.50 (s, 6H), 1.39 (s, 6H), 1.35 (s, 6H) ; IR (nujol, cm^{-1}) : 2240 (CN), 1730 (CO). MS *m/e* 237 (M+ +1, 2.5), 277 (65), 245 (50), 217 (81), 190 (11), 168 (100), 102 (100), 83 (22), 59 (76).

Methyl 1-(1',2'-dicyanoethyl)cyclohexanecarboxylate (2k). Solid mp 159.5°C ; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.98 (dd, J = 6.0 and 7.5 Hz, 1H), 2.68 (d,d, J = 6 and 7.5 Hz 2H), 2.30 to 2.10 (m, 2H), 1.84 to 1.20 (m, 8H) ; IR (nujol, cm^{-1}) : 2250 (CN), 1740 (CO) . MS *m/e* 221 (M+ +1, 0.8), 220 (M+,0.8), 180 (24), 161 (42), 148 (34), 133 (16), 120 (20), 81 (100), 65 (29), 56 (16), 41 (48).

Dimethyl 1,2-dimethyl-7,7-pentamethylene-4,5-dicyanooctanedioate (3). Solid mp 93°C ; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.65 (s, 3H), 2.85 to 2.72 (m, 2H), 2.20 to 1.90 (m, 4H), 1.90 to 1.70 (m, 2H), 1.64 (s, 4H), 1.60 to 1.15 (m, 4H), 1.27 (s, 3H), 1.20 (s, 3H) ; IR (nujol, cm^{-1}) 2250 (CN), 1740 (CO) ; MS *m/e* 289 (M+-COOMe, 26), 247 (21), 229 (12), 142 (19), 136 (33), 108 (17), 97 (17), 85 (50), 81 (55), 67 (60), 57 (83), 55 (90), 41 (100) ; Anal calc for $C_{19}H_{28}N_2O_4$: C, 65.48 ; H, 8.10 ; N, 8.04 :Found : C, 65.46 ; H, 8.13 ; N, 7.89.

References

1) Inaba, S-I.; Ojima, I. *Tetrahedron Lett.* **1977**, 2009.

2) a) Hirai, K.; Ojima, I. *Tetrahedron Lett.* **1983**, *24*, 785. b) Wallace, I.H.M.; Chan,T.H. *Tetrahedron* **1983**, *39*, 847. c) Jacobson, E. N.; Totten, G. E. ; Wenke, G. ; Karydas, A. C. ; Rhodes, Y.E. *Synth. Commun* . **1985**, *15*, 301.

3) Quendo, A.; Rousseau, G. *Synth. Commun.* **1989**, *19*, 1551.

4) Ainsworth, C.; Chen, F.; Kuo, Y.N. *J. Organometal. Chem.* **1972**, *46*, 59.

5) Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* **1984**, *25*, 495.

6) Brownbridge, P.; Chan, T.H.; Brook, M.A.; Kang, G.J. *Can. J. Chem.* **1983**, *61*, 688.

7) Giese, B. Radicals in Organic Synthesis : Formation of Carbon-Carbon Bonds. Pergamon Press 1986.

8) Viehe, H.G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 917.

9) Miyazawa. S.; Ikeda, K.; Achiwa, K.; Sekiya, M. *Chem. Lett.* **1984**, 785.