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MIXED METAL BASES AS PROMOTERS OF 1,4-ELIMINATIONS

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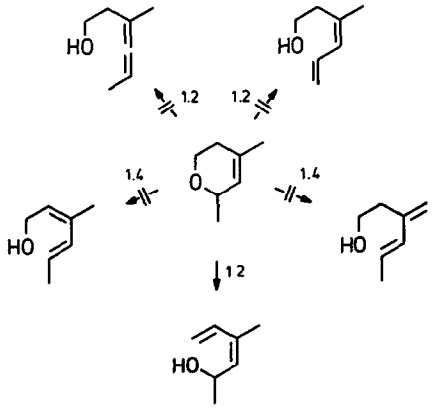
Summary : When treated with the LIDAKOR mixture, allyl type ethers very readily undergo 1,4-elimination to afford conjugated dienes (**1** - **3**). In typical cases, the reaction is brought about stereo- and regioselectively (**1** and **2**, respectively). Under suitable conditions, lithium dimethylamide or even lithium diisopropylamide adds to the dienes generated *in situ* thus leading to a variety of new allyl amines (**5** - **8**).

The LIDAKOR promoted ring opening of 2,4-dimethyl-5,6-dihydro-2*H*-pyran gives (*Z*)-4-methyl-3,5-hexadien-2-ol as the sole product [1]. The absence of other 1,2-elimination products can be well understood : their formation would imply proton abstraction from non-allylic, hence unactivated positions. It is, however, less obvious why no concomitant 1,4-elimination should occur. Especially the route leading to 3-methylene-4-hexen-1-ol looks quite promising since it involves the favorable [2] attack of the base at an allylic methyl rather than methylene group.

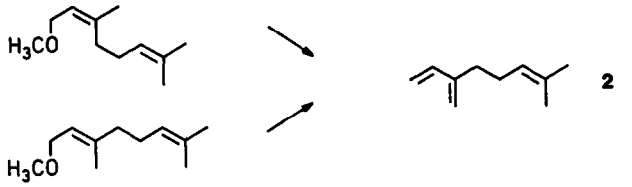


Apparently, 1,2-eliminations allow a better synchronization of electron flow, hence assure a higher degree of concertedness than do 1,4-eliminations. Do we have to conclude that LIDAKOR promoted 1,4-eliminations are not feasible at all ?

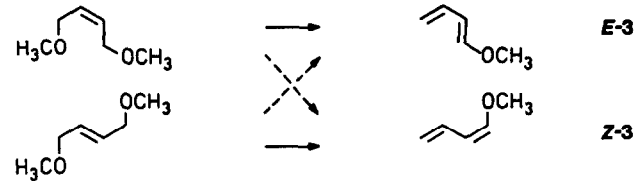
Certainly not. It can be quite readily be brought about whenever no 1,2-elimination is possible. Thus, treatment of (*Z*)-1-methoxy-2-nonene in tetrahydrofuran at -50 °C with lithium diisopropylamide in the presence of catalytic amounts of potassium *tert*-butoxide produces (*E*)-1,3-nonadiene (*E*-**1**) and 2,4-nonadiene stereoisomers

(evidently resulting from subsequent base catalyzed isomerization) with regioisomeric ratios varying from 1 : 0.4 and 1 : 20 as function of the base concentration with an 80% yield and a 5 : 95 *cis/trans* ratio.

Also in the case of 1.4-eliminations, protons are faster abstracted from allylic methyl than methylene groups. Both neryl and geranyl methyl ether give 7-methyl-3-methylene-1,6-octadiene (**2**, myrcene, 60 and 76%), although the neryl substrate reacts 9 times more slowly.

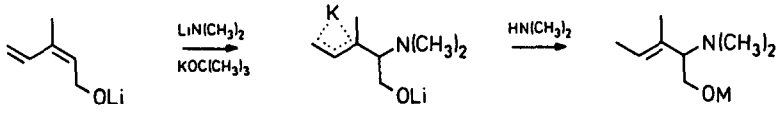


In contrast, *cis*- and *trans*-1,4-dimethoxy-2-butene show practically no difference in elimination rates. The *cis* bisether leads preferentially to the (*E*)-1-methoxy-1,3-butadiene (**3**, *cis : trans* = 25 : 75) while the *trans* bisether forms mainly (*Z*)-1-methoxy-1,3-butadiene (**3**, *cis : trans* = 80 : 20).



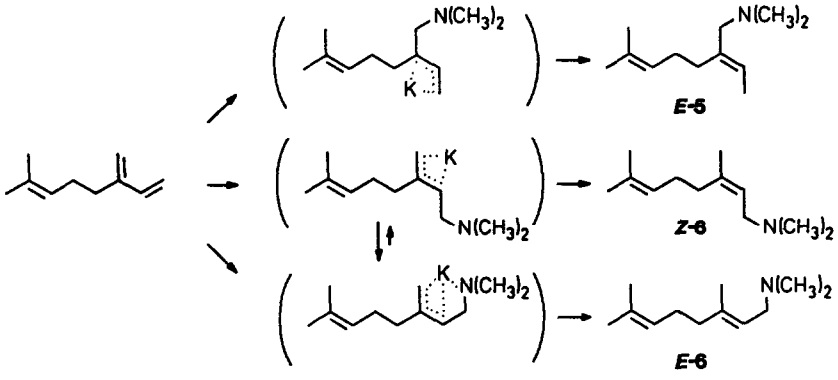
Literature reports on base promoted, typical 1,4-elimination reactions are relatively scarce. Usually they require powerful reagents or drastic conditions unless benzyl type ethers such as *o*-(methoxymethyl)toluene [3] are chosen as substrates. The conversion of *cis*-1,4-dialkoxy- or *cis*-1,4-dialkylthio-2-butenes to 1-alkoxy- or 1-alkylthio-1,3-butadienes can already be brought about with sodium amide in refluxing liquid ammonia [4]. Treatment of 3-methyl-2-buten-1-ol with butyllithium and potasssium *tert*-butoxide seems to set free isoprene which polymerizes [5]. Butyllithium alone suffices to produce 1-ethoxy-3-methyl-1,3-butadiene by ethanol abstraction from 3-methyl-2-butenal ("prenal") diethyl acetal [6]. Myrcene (**2**, 7-methyyl-3-methylene-2,6-octadiene) is obtained with high yields when geraniol is added dropwise to solid potassium hydroxide at 200 °C [7] and when 2-(geranyloxy)- or 2-(neryloxy)tetrahydropyran are exposed to a large excess of potassium *tert*-butoxide and 1,4,7,10,13,16-hexaoxacyclooctadecane during 2 h in refluxing tetrahydrofuran [8]. On the other hand, the palladium catalyzed reaction with propargylzinc chloride gives myrcene only if neryl acetate is employed as the substrate while geranyl acetate forms the regioisomeric ocimene (3,7-dimethyl-1,3,7-octatriene) as a 1 : 3 *cis/trans* mixture [9]. In the case of methyl (*E*)-2,6-dimethyl-2,7-octadienyl ether no such choice between two possible regioorientations does exist : under the combined action of sodium methoxide and a nickel complex it affords *trans*-2,7-dimethyl-1,3,7-octatriene [10].

Potassium *tert*-butoxide enhances not only the basicity but also the nucleophilicity of lithium dialkylamides. Although dienes do not react with the sterically crowded lithium or potassium diisopropylamide, they undergo smooth nucleophilic addition of dimethylamine if catalytic amounts of a lithium amide and potassium alcoholate are present. *In situ* generated lithium (*Z*)-3-methyl-2,4-pentadienolate [1], for example, is completely consumed after 4 h at -50 °C and (*E*)-2-dimethylamino-3-methyl-3-penten-1-ol (*E*-**4**, 68%) is isolated as the sole volatile product.

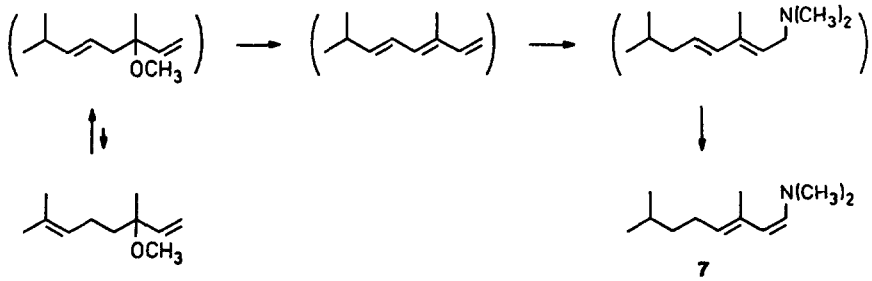


E-**4**: OM = OH

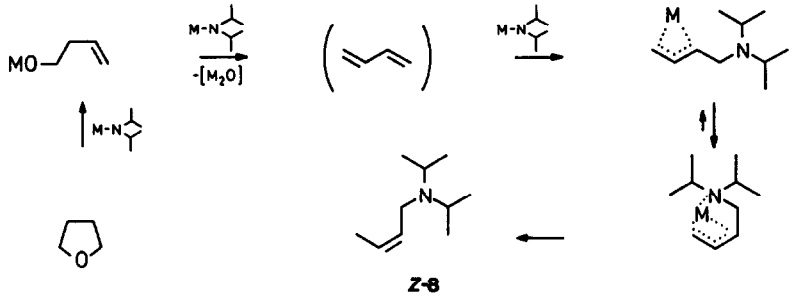
Myrcene reacts during 2 h at 0 °C almost quantitatively (> 86%) to produce a 2 : 2 : 3 mixture of the adducts *E*-**5**, *Z*-**6** and *E*-**6**. The related addition of diethylamine to isoprene [11, 12] and myrcene [12, 13] has already been previously described.



Linalyl methyl ether proved to be completely inert towards lithium dimethylamide and potassium *tert*-butoxide under the usual reaction conditions. After 72 h at 0 °C, however, 68% of 3,7-dimethyl-1-dimethylamino-1,3-octadiene (**7**, two stereoisomers) were isolated. Evidently, a base catalyzed double bond shift must have preceded the allyl assisted 1,2-elimination of methanol.



Unstrained and saturated ethers such as diethyl ether or tetrahydropyran do not react at all with the LIDAKOR mixture. Tetrahydrofuran, however, does slowly get attacked at 25 °C. After 24 h, 45% of (*Z*)-2-butenyldiisopropylamine (*Z*-**8**) were isolated. Treatment of lithium 3-butenolate or 1,3-butadiene [11, 12, 14] with lithium diisopropylamide in the presence of potassium *tert*-butoxide gave the same product *Z*-**8**.



EXPERIMENTAL PART

Generalities : see first article [2] of this series of three.

1. Conversion of Allyl Ethers to 1,3-Dienes

a) **(*E*)-1,3-Nonadiene (1)** [15] : The solvent was stripped off from a solution of butyllithium (25 mmol) in hexane and tetrahydrofuran (25 mL), precooled to -75 °C, diisopropylamine (3,5 mL, 2,5 g, 25 mmol), potassium *tert*-butoxide (0.28 g, 2.5 mmol) and methyl (*Z*)-2-nonenyl ether (3.9 g, 25 mmol) were consecutively added. After 10 min at -50 °C, 13% of *E*-**1** and 42% 2,4-nonadienes (mixture of stereoisomers) besides 36% starting material were identified by gas chromatographic comparison with authentic samples [1, 15, 16]. With 2.5 equivalents of the LIDAKOR base, only 3% *E*-**1** and 62% nonadienes were obtained. If LIDAKOR was generated *in situ* from diisopropylamine (0.2 eq.), butyllithium (1.0 eq.) and potassium *tert*-butoxide (1.0 eq.), 38% *E*-**1**, 16% nonadienes and 14% starting material were found.

The (*Z*)-1-methoxy-2-nonene [methyl (*Z*)-2-nonenyl ether] was prepared by alkylation of (*Z*)-2-nonen-1-ol [17] as described for 1-nonen-4-ol [1]. A colorless liquid was isolated with 90% yield, b.p. 76 - 77 °C/10 mmHg; n_D^{20} 1.4389, ^{1}H-NMR : 5.55 (2 H, symm. m), 3.98 (2 H, d, *J* 6.1), 3.33 (3 H, s), 2.07 (2 H, q, *J* 7.0), 1.3 (8 H, m), 0.88 (3 H, t, *J* 6.9); Analysis : calc. for $C_{10}H_{20}O$ (156.27) C 76.86, H 12.90, found C 77.08, H 12.90%.

b) **7-Methyl-3-methylene-1,6-octadiene** (myrcene, **2**) [7] : As described in the preceding paragraph, geranyl methyl ether [18] (4.2 g, 25 mmol) was added to a solution of the LIDAKOR reagent (25 mmol) in tetrahydrofuran (25 mL). After 1 h at -50 °C the reaction was essentially complete and 2.6 g (76%) of myrcene (**2**) was isolated; bp 74 - 78 °C/45 mmHg, n_D^{20} 1.4712; ^{1}H-NMR : 6.38 (1 H, dd, *J* 18.0, 11.0), 5.24 (1 H, d, *J* 18.0), 5.15 (1 H, t, with fine structure, *J* ~ 7), 5.06 (1 H, d, *J* 11.0), 5.00 (2 H, d, *J* 5.5), 2.2 (4 H, m), 1.71 (3 H, s), 1.63 (3 H, s).

With methyl neryl ether [19] only 66% of myrcene were obtained even after 15 h at -30 °C. A competition experiment showed the geranyl derivative to react 9.3 times faster than did its neryl stereoisomer.

c) **(*Z*)- and (*E*)-1-Methoxy-1,3-butadiene** (*Z*- and *E*-**3**) [20] : As described for the methyl (*Z*)-2-nonyl ether (Section 1a), (*Z*)-1,4-dimethoxy-2-butene [20] (2.9 g, 25 mmol) was added to a 1 M LIDAKOR solution in tetrahydrofuran (25 mL). After 2 h at -50 °C, 1.6 g (76%) of *Z*- and *E*-**3** having a ratio of 1 : 3 (according to gas chromatography and nmr spectroscopy) was obtained; bp 87 - 88 °C; ^{1}H-NMR of the (*Z*)-isomer [21] : 6.65 (1 H, ddt, *J* 17.0, 10.7), 5.89 (1 H, d, *J* 6.0), 5.1 (2 H, m), 4.90 (1 H, d, *J* 10.6), 3.65 (3 H, s); ^{1}H-NMR of the (*E*)-isomer [21] : 6.63 (1 H, d, *J* 12.5), 6.22 (1 H, dt, broad, *J* 16.8, 10.5), 5.56 (1 H, dd, *J* 12.5, 10.8), 5.01 (1 H, d with fine structure, *J* 16.9), 4.83 (1 H, dd, *J* 10.5, 1.8), 3.60 (3 H, s).

Under the same condition, (*E*)-1,4-dimethoxy-2-butene [20] gave a 69% yield with a (*Z*/*E*)-ratio of 4 : 1. According to a competition experiment, both stereoisomers undergo the LIDAKOR promoted elimination reaction with precisely the same rate.

2. Conversion of 1,3-Dienes to Allyl Amines

a) **(*E*)-2-Dimethylamino-3-methyl-3-penten-1-ol** (*E*-**4**, OM = OH) : The solvent was stripped off from a solution of butyllithium (0.20 mol) in hexane and tetrahydrofuran (0.10 L), precooled to -75 °C, dimethylamine (7.3 mL, 5.0 g, 0.11 mol), potassium *tert*-butoxide (2.2 g, 20 mmol) and (*Z*)-3-methyl-2,4-pentadien-1-ol [1] (9.8 g, 0.10 mol) were consecutively added. After 4 h at -50 t (9.8 g, 0.10 mol) were consecutively added. After 4 h at -50 °C, the mixture was poured into water (150 mL) and extracted with *tert*-butyl methyl ether (5 × 30 mL). The combined organic layers were dried and concentrated. Distillation afforded 11.0 g (77%) of *E*-**4**; bp 98 - 100 °C/25 mmHg, n_D^{20} 1.4711; IR : 3300 (s, broad, ν[O-H]), 3070 (w, ν[=C-H]), 1675 (m, ν[C=C]), 1050 + 1040 (s, ν[C-O]), 820 (s, δ[=C-H]); ^{1}H-NMR : 5.44 (1 H, q, broad, *J* 6.7), 3.68 (1 H, dd, *J* 6.7, 10.5), 3.53 (1 H, dd, *J* 10.5, 6.8), 2.68 (1 H, t, *J* 6.7), 2.52 (1 H, s), 2.24 (6 H, s), 1.67 (3 H, dq, *J* 6.8, 1.1), 1.64 (3 H, q, *J* 1.1); ^{13}C-NMR : 133.6 (s), 124.2 (d, *J* 145), 74.6 (d, *J* 131), 61.1 (t, *J* 142), 43.0 (q, *J* 134), 13.6 (1, *J* 124), 13.1 (q, *J* 124); MS : 143 (3%, M^+), 125 (5%), 112 (95%), 97 (100%); Analysis : calc. for $C_8H_{17}NO$ (143.23) C 67.09, H 11.96, found C 67.37, H 11.72%.

When in an analogous reaction the 3-methylpentadienol was replaced by 4-methyl-5,6-dihydro-2*H*-pyran (9.8 g, 0.10 mol) a 68% yield of *E*-**4** was obtained.

b) **(*E*)-*N,N*-Dimethyl-(2-ethylidene-6-methyl-5-heptenyl)amine** (*E*-**5**) and (*Z*)- and (*E*)-***N,N*-dimethyl-(3,7-dimethyl-2,6-octadienyl)amine** (*Z*- and *E*-**6**) : A solution of lithium dimethylamide (prepared from butyllithium and dimethylamine, 0.17 mol), potassium *tert*-butoxide (20 mmol) and myrcene (20 g, 0.15 mol) in tetrahydrofuran (0.15 L) was kept 3 h at 0 °C. After extraction (see preceding paragraph) and distillation, 24 g (89%) of a colorless, viscous liquid was collected; bp 59 - 63 °C/0.1 mmHg. According to gas chromatography (3 m, 5%, SE-30 60 → 190 °C it contained the three isomers *E*-**5**, *Z*-**6** and *E*-**6** in the ratio of 5 : 6 : 9. Analysis : calc. for $C_{12}H_{23}N$ (181.32) C 79.49, H 12.79, found C 79.30, H 12.73%. - With geranyl methyl ether instead of myrcene the same products were obtained (86%).

The three components were separated by preparative gas chromatography (3 m, 10% C-20M, 80 → 180 °C by 5 °C/min). - *E*-**5** : n_D^{20} 1.4594; IR : 3070 + 3040 (w, ν[=C-H]), 1670 (w, ν[C=C]), 860 + 820 (m, δ[=C-H]); ^{1}H-NMR : 5.38 (1 H, q, broad, *J* 6.7), 5.14 (1 H, t, with fine structure, *J* 6.2), 2.76 (2 H, s, broad), 2.15 (6 H, s), 2.1 (4 H, m), 1.69 (3 H, s,), 1.64 (3 H, d, *J* 6.5), 1.63 (3 H, s); ^{13}C-NMR : 137.9 (s), 131.3 (s), 124.6 (d, *J* 147), 122.2 (d, *J* 146), 66.6 (t, *J* 132), 45.4 (qq, *J* 132, 5), 28.5 (t, *J* 128), 26.6 (t, *J* 127), 25.7 (t, *J* 125), 17.6 (q, *J* 124), 13.1 (q, *J* 125); MS : 181 (26%, M^+), 166 (100%), 121 (24%), 110 (87%). - *Z*-**6** : n_D^{20} 1.4628; IR : 1675 + 1650 (m, ν[C=C]), 840 + 825 + 815 (m, δ[=C-H]); ^{1}H-NMR [22] : 5.24 (1 H, tq, *J* 7.0, 1.8), 5.12, 1 H, t with fine structure, *J* 7.0), 2.88 (2 H, dd, *J* 7.1, ~ 1), 2.22 (6 H, s), 2.1 (4 H, m, narrow), 1.75 (3 H, dt, *J* 1.5, 1.0), 1.70 (3 H, s), 1.63 (3 H, s); MS : 181 (13%, M^+), 166 (7%), 124 (38%), 93 (100%). - *E*-**6** : n_D^{20} 1.4635; IR : practically identical with that of the (*Z*)-isomer; ^{1}H-NMR [22] : 5.26 (1 H, tq, *J* 7.0, 1.2), 5.10 (1 H, t with fine structure, *J* 7.0), 2.90 (2 H, d, *J* 7.0), 2.22 (6 H, s), 2.11 (2 H, te, *J* ~ 7), 2.04 (H, q, broad, *J* ~ 7), 1.70 (3 H, d, *J* 0.9), 1.66 (3 H, s), 1.62 (3 H, s); MS : 181 (7%, M^+), 166 (4%), 112 (100%), 93 (44%).

3. Elimination/Addition Reactions of Linalyl Methyl Ether and of Tetrahydrofuran

a) **3,7-Dimethyl-1-dimethylamino-1,3-octadiene** (**7**) : A solution of lithium dimethylamide (22 mmol), dimethyl amine (20 mL, 14 g, 0.30 mol), potassium *tert*-butoxide (22 mol) and linalyl methyl ether [23] (3-methoxy-3,7-dimethyl-1,6-octadien, 3,4 g, 20 mmol) was kept 72 h at 0 °C. Extraction and distillation afforded 2.5 g (68%)of a liquid; bp 63 - 65 °C/0.1 mmHg, n_D^{20} 1.5031. According to nmr spectroscopy [24] the product is composed of two stereoisomers. - IR : 3060 + 3030 (w, ν[=C-H]), 1645 (s, ν[C=C(N)]), 928 (s, δ[=C-H]); ^{1}H-NMR : 6.19 (0.4 H, d, *J* 13.9), 6.10 (0.6 H, d, *J* 14.1), 5.48 (0.4 H, d, *J* 13.9), 5.36 (0.6 H, t, broad, *J* 7.2), 5.29 (0.6 H, d, *J* 14.1), 5.11 (0.4 H, t, broad, *J* 7.2), 2.35 (6 H, s), 2.3 (2 × 0.4 H, m), 2.22 (2 × 0.6 H, q, broad, *J* 7.8), 1.95 (3 × 0.4 H, s, with fine structure), 1.90 (3 × 0.6 H, s), 1.6 (1 H, m), 1.41 (2 × 0.4 H, q, *J* 7.5), 1.34 (2 × 0.6 H, q, *J* 7.5), 0.93 (6 × 0.4 H, dd, *J* 6.6, 1.0), 0.91 (6 × 0.6 H, dd, *J* 6.5, 1.0); MS : 181 (1%, M^+), 152 (26%), 126 (22%), 95 (100%).

b) (*Z*)-*N,N*-**Diisopropyl-2-butenylamine** (*Z*-**8**) : A solution of lithium diisopropylamide (0.10 mol) and potassium *tert*-butoxide (0.10 mol) in tetrahydrofuran (0.10 L) was kept 24 h at 25 °C. Aqueous neutralization, extraction and distillation allowed to isolate 3.5 g (45%) of *Z*-**8**, 95% isomerically pure according to gas chromatography; bp 142 - 147 °C; IR : 1640 (w, ν[C=C]), 970 (s, δ[=C-H]); ^{1}H-NMR : 5.5 (2 H, m), 3.1 (2 H, m), 3.07 (2 H, dd, *J* 6.5, 1.1), 1.68 (3 H, ddt, *J* 6.3, 1.1, 0.8), 1.00 (12 H, d, *J* 6.3); MS : 155 (39%, M^+), 140 (100%), 114 (10%), 86 (83%); Analysis : calc. for $C_{10}H_{21}N$ (155.28) C 77.35, H 13.63, N 9.02, found C 77.32, H 13.27, N 9.13%.

REFERENCES

[1] C. Margot, M. Rizzolio, M. Schlosser, *Tetrahedron* **45** (1989), preceding article.

[2] A. Mordini, C. Margot, E. Ben Rayana, M. Schlosser, *Tetrahedron* **45** (1989; first article of this series of three.

[3] R.J. Moss, B. Rickborn, *J. Org. Chem.* **49** (1984), 3694; see also : K. Naito, B. Rickborn, *J. Org. Chem.* **45** (1980), 4061.

[4] R.H. Everhardus, A. Peterse, P. Vermeer, L. Brandsma, J.F. Arens, *Recl. Trav. Chim. Pays-Bas* **93** (1974), 90.

[5] J. Hartmann, R. Muthukrishnan, M. Schlosser, *Helv. Chim. Acta* **57** (1974), 2261.

[6] C. Mioskowski, S. Manna, J.R. Falck, *Tetrahedron Lett.* **25** (1984), 519.

[7] G. Ohloff, *Chem. Ber.* **90** (1957), 1554; see also K. Alder, W. Roth, *Chem. Ber.* **88** (1955), 407; G. Ohloff, G. Schade, *Angew. Chem.* **67** (1955), 427; G. Ohloff, *Liebigs Ann. Chem.* **627** (1959), 79.

[8] J. Otera, Y. Niibo, K. Okuda, *Chem. Lett.* **1986**, 1829.

[9] H. Matsushita, E. Nigishi, *J. Org. Chem.* **47** (1982), 4161.

[10] M. Hidai, H. Mizuta, H. Yagi, Y. Nagai, K. Hata, Y. Uchida, *J. Organomet. Chem.* **232** (1982), 89.

[11] K. Takabe, T. T. Katagiri. J. Tanaka, *Tetrahedron Lett.* **13** (1972), 4009; *Bull. Chem. Soc. Japan* **46** (1973), 218.

[12] K. Takabe, T. Katagiri, J. Tanaka, *Bull. Chem. Soc. Japan* **46** (1973), 222.

[13] T. Fujita, K. Suga, S. Watanabe, *Aust. J. Chem.* **27** (1974), 531.

[14] For analogies see : N. Imai, T. Narita, T. Tsuruta, *Tetrahedron Lett.* **12** (1971), 3517; R.J. Schlott, J.C. Fal, K.W. Narducy, *J. Org. Chem.* **37** (1972), 4243; T. Fujita, K. Suga, S. Watanabe, *Aust. J. Chem.* **27** (1974), 531; G.K. Noren, *J. Org. Chem.* **40** (1975), 967; T. Narita, Y. Nitadori, T. Tsuruta, *Polymer J. (Tokyo)* **9** (1977), 191.

[15] D. Seyferth, J. Pornet, R.M. Weinstein, *Organometallics* **1** (1982), 1651.

[16] B. Psaume, M. Montury, J. Goré, *Synth. Commun.* **12** (1982), 409.

[17] R. Delaby, S. Guillot-Allegre, *Bull. Soc. Chim. Fr.* **53** (1933), 301.

[18] L. Bateman, J.I. Cunneen, H.P. Koch, *J. Chem. Soc.* **1950**, 3045.

[19] R. Grandi, A. Marchesini, U.M. Pagnoni, R. Trave, *J. Org. Chem.* **41** (1976), 1755.

[20] R.H. Everhardus, A. Peterse, P. Vermeer, L. Brandsma, J.F. Arens, *Recl. Trav. Chim. Pays-Bas* **93** (1974), 90.

[21] See also : J.P. Dorie, M.L. Martin, S. Odiot, F. Tonnard, *Org. Magn. Res.* **5** (1973), 265.

[22] For comparison, see the corresponding *N,N*-diethylamino derivatives [12 - 14].

[23] US-Patent 2'841'620 (disclosed 1 July 1958) to Hoffmann-LaRoche Inc. (inventors : L.J. Colaianni, M.L. Tanzer); *Chem. Abstr.* **53** (1959), 2'090i.

[24] For comparison, see the corresponding *N,N*-diethylamino derivatives : M. Tanaka, G. Hata, *Chem. Ind. (London)* **1977**, 202; K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, S. Otsuka, *J. Am. Chem. Soc.* **106** (1984), 5208.