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IN SITU SELECTIVE PROTECTION OF ALDEHYDES *VIA* ALDIMINES

SIMPLE CONVERSIONS OF KETOALDEHYDES TO METHYLENE ALDEHYDES AND TO METHYLHYDROXY ALDEHYDES

G. PAGANI ZECCHINI, M. PAGLIALUNGA PARADISI* and I. TORRINI
Centro di Studio per la Chimica del Farmaco del C.N.R., Istituto di Chimica Farmaceutica dell'Università, 00185 Rome, Italy

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Abstract—Selective methylenation with $Ph_3P{=}CH_2$ and methylation with MeMgI or MeLi of keto group of ketoaldehydes was accomplished by protection of aldehyde with t-butylamine. The intermediate aldimines were cleaved during chromatographic purifications on silica to afford the corresponding methylene aldehydes and methylhydroxy aldehydes as the only isolable reaction products.

The remarkable site selectivity achieved in the one pot reduction of the keto group of ketoaldehydes by the *in situ* protection of the aldehyde with t-butylamine[1] prompted us to extend the use of this imine protecting group to other carbonyl reactions.

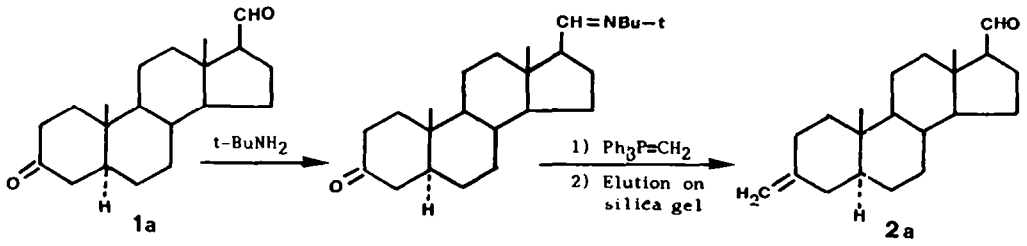
Since the discovery of the Wittig reaction, olefination of aldehydes and ketones has been extensively investigated and several modifications have been suggested in order to increase the scope of the original procedure. Nevertheless, little attention has been paid to the site selectivity of ylides toward polycarbonyl compounds. Thus, the reaction between steroidal diketones with methylenetriphenylphosphorane afforded mixtures of mono and dimethylene derivatives.[2] Reagents like $Me_3Si{-}CH_2{-}TiCl_3$ caused carbonyl-olefination of aldehydes but not of ketones,[3] and the possibility of selective olefinations was suggested by Cainelli *et al.* by the use of polymer-supported phosphonates.[4] It has also been reported that Schiff bases react with Wittig reagents only under drastic conditions.[5]

As a useful application of the title protection method we report here a convenient preparation of some methylene aldehydes (e.g. **2a**), starting from the appropriate ketoaldehydes (e.g. **1a**).

In a preliminary experiment carried out on a mixture of n-octanal and 2-dodecanone (2 mmol each), t-butylamine (0.6 ml) and n-tetradecane (internal standard for GLC analysis), the aldehyde was recovered almost quantitatively (98%) and 2-methyldodecene generated in high yield (97%). The results of methylenation of ketoaldehydes (**1a–g**) are collected in Table 1. The yields of methylene aldehydes (**2a–g**) are in most cases good and seem to depend on the reactivity of keto group toward the phosphorane. It is noteworthy that we have never been able to isolate methylene ketones arising from a preferential reaction of ylide with aldehyde group.

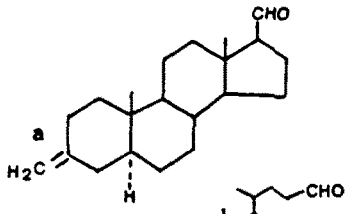
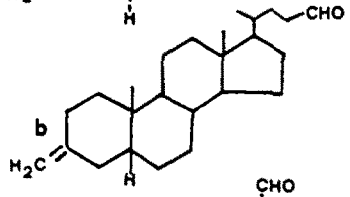
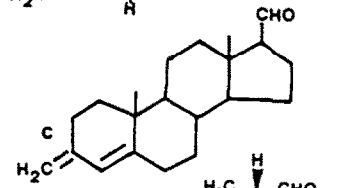
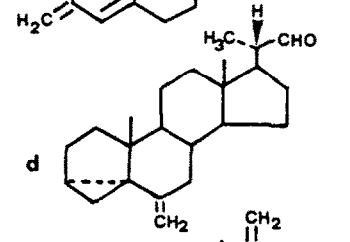
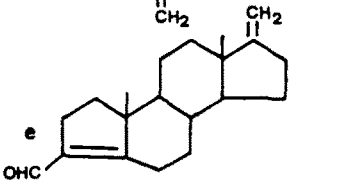
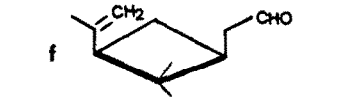
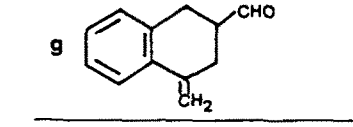
According with previous data reported on the lower reactivity of 17-keto group of steroids,[2] the selective olefination of 17 - oxo - A - norandrost - 3(5) - ene - 3 - carboxaldehyde[6] (**1e**), performed under our mild conditions, afforded **2e** in low yield. Since in this case we employed the less hindered isopropylamine to form the imine (Experimental), a partial protection of the keto group cannot be ruled out.

Final cleavage of the aldimines occurred during the chromatographic elution of the reaction products on silica. In order to minimize epimerization at C-20 chiral center, the residue arising from methylenation of (20*S*) - 6 - oxo - 3α,5 - cyclo - 5α - pregnane - 20 - carboxaldehyde was passed through a column packed with basic alumina (B IV).[1b] The selective introduction of a methylene group at C-6 position of



Scheme 1.

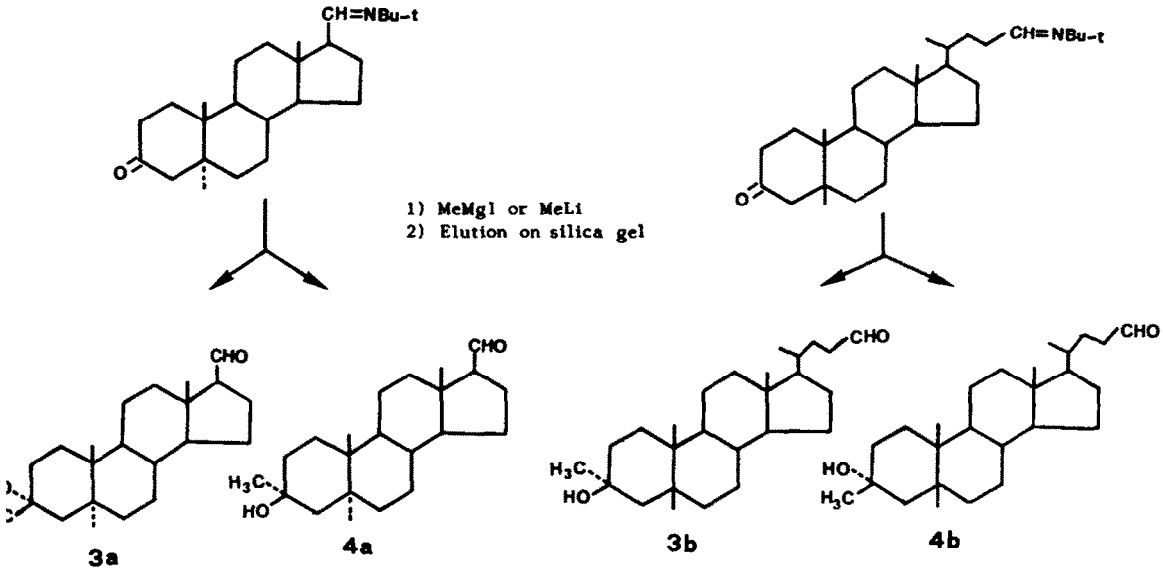
Table 1. Yields and analytical data[a] of methylene aldehydes (**2a–g**)

Product **2**	Yield[b] (%)	Protection time (h)[1]	M.p.°C[c]	$[\alpha]_D$
a 	85	3	105–107	+62°
b 	79	3	96–98	+49°
c 	66	6	102–104	+244°
d 	51	12	122–123	+89°
e 	16 (27)[d]	5	114–115	+112°
f 	84[e]	3	oil 2,4-DNP 150–151[f]	racemic
g 	44	3	oil 2,4-DNP 107–112	racemic

[a] The microanalyses of compounds 2a–e and 2,4-dinitrophenylhydrazones of 2f,g were in satisfactory agreement with the calculated values: C, ±0.20; H, ±0.03; N, ±0.26. [b] Yields from weights of homogeneous chromatographic fractions. [c] The steroidal derivatives 2a–e were crystallized from light petroleum. [d] 6 Molar equivalents of the Wittig reagent employed. [e] Yield calculated by GLC. [f] Sample inserted into a Büchi oil bath at 100°.

steroids may be of particular synthetic value, in view of the biological activity of the corresponding 6-Me derivatives.[7]

As a further application of this imine protecting group, the selective introduction of a Me group into steroidal ketoaldehydes was achieved by the preferential attack of MeMgI or MeLi at the keto group. Both the above selective reactions were carried out on 3-oxo-5α-androstane-17β-carboxaldehyde (**1a**) and 3-oxo-5β-cholan-24-al (**2a**), and better results were obtained when the excess of t-butylamine was evaporated before adding the protected ketoaldehyde to the MeMgI or MeLi solution (Experimental). It has been reported[8] that hindered azomethines do not react with MeMgI even under forced conditions. Accordingly, the usual conversion of **1a** and **2a** to the corresponding aldimines followed by treatment with the Grignard reagent, afforded mixtures of the two



Scheme 2.

epimeric 3-methyl-3-hydroxyaldehydes **3a,b** and **4a,b**.

A similar product distribution was observed using MeLi (Table 2), and secondary amines arising from a possible attack at C=N bond[8,9] could not be isolated.

Configurational assignment to the OH group in **3a,b** and **4a,b** has been made on the basis of literature mechanistic[10] and spectroscopic[11] data. We have thus assigned the structures **3a,b** (axial OH group) to the less polar tertiary alcohols obtained in major yield, whose 3-Me protons resonate at slightly higher field than those of the corresponding epimers **4a,b**. This assignment may be also supported by the analogous chromatographic behaviour of the epimeric 3-hydroxyaldehydes obtained by selective reduction[1b] of **1a,b**.

From all our reported results it follows that this imine protection procedure is suitable to perform in mild conditions selective nucleophilic additions at keto group in presence of aldehydic one.

EXPERIMENTAL

General experimental details have been described previously.[1b] IR spectra for oily products **1f**, **2f** and **2g** were recorded using $CHCl_3$ as the solvent. Mass spectra for **1f** and **2f** were taken with an AEI MS 12 spectrometer at 70 eV with an all glass heated inlet system. All the reported reactions, but the solvolysis of the tosylate, were performed under N_2 at room temp. All the new ketoaldehydes were obtained by oxidation of the corresponding diols as previously described.[12] GLC analyses were obtained on a Carlo Erba Fractovap 2350 chromatograph, equipped with a 0.5 m × 2 mm i.d. column, packed with 3% Carbowax 20M on Chromosorb G, using n-tetradecane as internal standard. Pinonic derivatives, obtained from commercial (±)-*cis*-pinonic acid (98%), were mixtures of *cis* and *trans* isomers (98% and 2%, respectively), as shown by GLC analyses. Routes to steroidal ketoaldehydes **1a**, **b**, **c**, **e** were described elsewhere.[1b,6,12]

(±)-*Cis-pinonic aldehyde* **1f**. (±)-Methyl *cis*-pinonate (13.88 g) was reduced with $LiAlH_4$ (7.98 g) as described for (+)-ethyl pinonate[13] to give a residue (12.84 g), which was passed through a column of silica gel (300 g) (CH_2Cl_2–Et_2O 9:1 and 1:1 as eluents), to obtain a mixture of diols (9.99 g). A soln of the above compounds (1.55 g) in CH_2Cl_2 (20 ml) was added to the Collins reagent and stirred for 15 min. The oxidation residue (1.2 g) was chromatographed on silica (60 g), eluting with CH_2Cl_2–Et_2O (8:2) to afford homogeneous **1f** (0.68 g) as an oil; NMR, IR and Mass data in accord with those reported for the ketoaldehyde previously described.[14]

(±)-1-*Oxotetralin-3-carboxaldehyde* **1g**. A soln of (±)-*cis*-3-hydroxymethyltetralin-1-ol[15] (2.8 g) in THF

Table 2. Yields[a] and analytical data[b] of 3-methyl-3-hydroxyaldehydes (**3a,b** and **4a,b**)

Ketoaldehyde 1	Tertiary ax. alcohol 3			Tertiary eq. alcohol 4		
	Yield (%)	M.p.°C[c]	$[\alpha]_D$	Yield (%)	M.p.°C[c]	$[\alpha]_D$
a	47(39)	160–165 dec[d]	+66°	36(23)	168–173 dec[e]	+67°
b	35(39)	135–139	+31°[f]	21(19)	170–175 dec[e]	+26°

[a]Yields from weights of homogeneous chromatographic fractions; the values in parentheses refer to MeLi addition. [b]Satisfactory microanalyses obtained: C, ±0.22; H, ±0.11. [c]The compounds 4a,b were crystallized from AcOEt; 3a,b from ether. [d]Sample inserted into a Büchi oil bath at 145°. [e]Sample inserted into a Büchi oil bath at 155°. [f]c, 1.0 in MeOH.

Table 3. Spectral data for methylene aldehydes (**2a–g**) and methylhydroxy aldehydes (**3a,b–4a,b**)

Compound	MS m/e(M^+)	IR (cm^{-1})	NMR (δ)
2a	300	3080,2725, 1730,1655	0.73 (3H,s,13-Me),0.83 (3H,s,10-Me), 4.57 (2H,s,=CH_2),9.83 (1H,d,J=1,5 Hz, CHO)
2b	356	3070,2735, 1730,1650	0.66 (3H,s,13-Me),0.91 (3H,s,10-Me), 4.58 (2H,s,=CH_2),9,80 (1H,apparent t, CHO)
2c	298	2730,1725, 1640	0,78 (3H,s,13-Me),1.06 (3H,s,10-Me), 4.67 (2H,apparent d, =CH_2),5.85 (1H, br s, 4-H),9.85 (1H,d,J=1.5 Hz,CHO)
2d	326	3070,2730, 1715,1635	0.40 (1H,apparent t,cyclopropyl),0.72 (3H,s,13-Me),0.84 (3H,s,10-Me),1.10 (3H,d,J=6.5 Hz,20-Me),4.59 and 4.67 (2H,two m,$W\frac{1}{2}$=5Hz, =CH_2),9.65 (1H, d, J=3Hz,CHO)
2e	284	3050,2730, 1655	0.83 (3H,s,13-Me),1.07 (3H,s,10-Me), 4.63 (2H,m,$W\frac{1}{2}$=5 Hz,=CH_2),10.05 (1H,s,CHO)
2f	166	3080,2720, 1730,1650	0.76 and 1.18 (6H,two s,>$C(Me)_2$), 1.64 (3H,s,=C-Me),4.59 and 4.83 (2H,s and m,$W\frac{1}{2}$=4Hz, =CH_2),9.80 (1H,t,J=1.5 Hz,CHO)
2g	172	2730,1730, 1635	3.13-2.47 (5H,m,-CH_2-CH-CH_2-),5.07 and 5.56 (2H,two s,=CH_2),7.20 and 7.67 (3 and 1 H, two m,aromatic), 9.80 (1H,s,CHO)
3a	318	3535,2700, 1715,1385	0.73 and 0.74 (6H,two s,13-Me and 10-Me),1.18 (3H,s,3β-Me),9.87 (1H, d,J=1.5 Hz,CHO)
4a	318	3495,2755 1710,1380	0.73 (3H,s,13-Me),0.80 (3H,s,10-Me), 1.23 (3H,s,3α -Me),9.86 (1H,d,J=1.5 Hz,CHO)
3b	374	3540,2730 1720,1375	0.65 (3H,s,13-Me),0.94 (3H,s,10-Me), 1.20 (3H,s,3α -Me),9.83 (1H,apparent t,CHO)
4b	374	3520,2720 1715,1370	0.63 (3H,s,13-Me),0.93 (3H,s,10-Me), 1.23 (3H,s,3β-Me),9.83 (1H,apparent t,CHO)

(23 ml) was added to the Collins reagent and stirred for 15 min. The residue (1.88 g) was chromatographed on silica (113 g), eluting with benzene–CH_2Cl_2 (8:2 and 1:1) to obtain nearly pure **1g** (1.06 g). Further chromatography on silica (106 g) (CH_2Cl_2 as eluent) afforded pure **1g** (0.71 g), m.p. 51–52° (from Et_2O); ν_{max} 2750 (w), 1725, 1685 and 1605 cm^{-1}; δ 2.5–3.4 (5H, m, $-CH_2-CH-CH_2$), 7.2–7.65 and 8.0 (3H and 1H, two m, aromatic), 9.77 (1H, s, CHO); mass spectrum *m/e* 174 (M^+). (Found: C, 75.77; H, 5.89. $C_{11}H_{10}O_2$ requires: C, 75.84; H, 5.79%).

Methyl (20S) - 6β - *hydroxy* - 3α,5 - *cyclo* - 5α - *pregnane* - 20 - *carboxylate*. Methyl (20*S*) - 3β - hydroxypregn - 5 - ene - 20 - carboxylate[16] (3.8 g) in dry pyridine (40 ml) was treated with tosyl chloride (4 g) at room temp in the dark. After 24 hr the soln was poured into ice-cold $KHCO_3$ aq (4% w/v; 400 ml). The mixture was partitioned between CH_2Cl_2 and water, washed to neutrality, dried and evaporated under *vacuum* to give a solid residue (4.42 g). The crude tosylate was refluxed for 8 hr in a soln of KOAc (3.25 g) in acetone (65 ml) and water (17 ml). The solvent was partially removed by evaporation and the mixture was partitioned between Et_2O in excess and water. The organic layers were dried and evaporated under *vacuum* to give a foam (3.73 g), which was chromatographed on silica (74.5 g). Elution with benzene–Et_2O (9:1) gave the title compound (2.83 g), m.p. 127–128° (from Et_2O–light petroleum); $[\alpha]_D$ + 34°; ν_{max} 3480, 3430, 1750 and 1720 cm^{-1}; δ 0.38 (1H, apparent t, cyclopropyl), 0.73 (3H, s, 13-Me), 1.05 (3H, s, 10-Me), 1.17 (3H, d, J = 6.5 Hz, 20-Me), 3.30 (1H, apparent t, 6α-H), 3.64 (3H, s, $-CO_2Me$); mass spectrum *m/e* 360 (M^+). (Found: C, 76.67; H, 9.98. $C_{23}H_{36}O_3$ requires: C, 76.62; H, 10.07%). Further elution with benzene–Et_2O (8:2) gave nearly pure starting material (0.53 g).

(20S) - 6 - *Oxo* - 3α,5 - *cyclo* - 5α - *pregnane* - 20 - *carboxaldehyde* **1d**. Methyl (20*S*) - 6β - hydroxy - 3α,5 - cyclo - 5α - pregnane - 20 - carboxylate (0.726 g, 2 mmol) was dissolved in dry THF (25 ml) and $LiAlH_4$ (0.23 g) was carefully added. After stirring for 1 hr the mixture was treated as in the case of (20*S*) - 22,23 - dinor - 5α - cholane - 3β,24 - diol,[12] to obtain a foam, which was oxidized in the usual manner.[12] The resulting mixture (0.65 g) was chromatographed on alumina (33 g), eluting with benzene to obtain nearly pure **1d** (0.47 g), m.p. 105–106° (from Et_2O–light petroleum); $[\alpha]_D$ + 34°; ν_{max} 2740 (w), 1715 and 1685 cm^{-1}; δ 0.68 (1H, apparent t, cyclopropyl), 0.77 (3H, s, 13-Me), 1.00 (3H, s, 10-Me), 1.12 (3H, d, J = 6.5 Hz, 20-Me), 9.63 (1H, d, J = 2.5 Hz, CHO); mass spectrum *m/e* 328 (M^+). (Found: C, 80.28; H, 9.81. $C_{22}H_{32}O_2$ requires: C, 80.44; H, 9.83%).

General procedure for selective methylenation of ketoaldehydes. Methylenetriphenylphosphorane was prepared by adding BuLi in n-hexane (1.1 mmol) to a suspension of methyltriphenylphosphonium bromide (1.1 mmol) in 5 ml of dry Et_2O. The mixture was stirred for 2 hr.

To a stirred mixture of ketoaldehyde (0.5 mmol) in dry THF (1 ml) (1.5 ml in the case of **1a**, **d**, **e**), 4 Å molecular sieves (0.5 g) and 0.15 ml of dry t-$BuNH_2$ (0.2 ml in the case of **1d**,**f**,**g**) were added. Less hindered i-$PrNH_2$ (0.15 ml) was employed to protect **1e**, since even after 24 hr the protection with bulkier t-$BuNH_2$ was incomplete. After the appropriate period of stirring the soln was poured into the above Wittig reagent, washing the sieves with 1 ml of dry THF. After stirring for 15 hr water was added and then the mixture extracted with Et_2O in excess, washed with water, dried and evaporated under *vacuum*. The residue was chromatographed on silica† (10 g) eluting with n-hexane-benzene (3:1, 2:1 and 1:1). For GLC analyses of the reaction products arising from methylenation of **1f** and the mixture of n-octanal and 2-dodecanone, the ethereal solution was passed through a column of silica (10 g), washing with Et_2O.

Procedures for selective alkylation of steroidal ketoaldehydes **1a**,**b**

(a) *With* MeMgI. After the previously described protection procedure of ketoaldehyde (1 mmol), the imine THF soln was evaporated under reduced pressure. A soln of MeMgI was prepared in a flask from 0.091 g Mg turnings, 0.426 g MeI and 2.6 ml dry ether. After stirring for 30 min the preparation of MeMgI was complete. An imine ether soln (protected **1a** in 7 ml and the other derivative in 2 ml) was added to the Grignard reagent from a pressure-equalized dropping funnel. The mixture was then stirred for 1 hr, after which it was carefully hydrolyzed with satd NH_4Cl cooling at 0°, and AcOEt was added. After stirring for 30 min at room temp the organic layers were washed with water, dried and evaporated under reduced pressure.

† Basic alumina (B IV, 20g) and then silica (10g) were used in the case of **1d**.

(b) *With* MeLi. 2 ml 2M MeLi in ether (1 ml in the case of **1b**) were syringed into a flask at − 15°. An imine ether soln (protected **1a** in 6 ml and the other derivative in 4 ml) was then syringed in dropwise under stirring at − 15°. The reaction was allowed to warm to room temp and stirred for 1 hr, after which it was hydrolyzed and worked up as above.

All the reaction residues were chromatographed on a column of silica (1:50), eluting the androstanic derivatives with light petroleum–ether (2:1) and the cholanic ones with benzene–ether (9:1).

REFERENCES

[1a]M. Paglialunga Paradisi, G. Pagani Zecchini and G. Ortar, *Tetrahedron Letters* 5085 (1980); [b]M. Paglialunga Paradisi and G. Pagani Zecchini, *Tetrahedron* **38**, 1827 (1982).

[2]F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.* **80**, 3087 (1958).

[3]T. Kauffmann, R. König, C. Pahde and A. Tannert, *Tetrahedron Letters* 5031 (1981).

[4]G. Cainelli, M. Contento, F. Manescalchi and R. Regnoli, *J. Chem. Soc.* Perkin 1 2516 (1980).

[5]H. J. Bestmann and F. Seng, *Tetrahedron* **21**, 1373 (1965).

[6]J. R. Hanson and H. J. Wadworth, *J. Chem. Soc.* Perkin 1 933 (1980).

[7]K. Annen, H. Hofmeister, H. Laurent and R. Wiechert, *Synthesis* 34 (1982) and refs cited.

[8]B. L. Emling, R. J. Horvath, A. J. Saraceno, E. F. Ellermeyer, L. Haile and L. D. Hudac, *J. Org. Chem.* **24**, 657 (1959).

[9]J. Huet, *Bull. Soc. Chim. Fr.* 952, 960, 967, 973 (1964).

[10]D. N. Kirk and M. P. Hartshorn, *Steroid Reaction Mechanisms*, pp. 147–148. Elsevier, Amsterdam (1968).

[11]C. R. Narayanan and A. K. Kulkarni, *Indian J. Chem.* **12**, 677 (1974).

[12]M. Paglialunga Paradisi and G. Pagani Zecchini, *Tetrahedron* **37**, 971 (1981).

[13]M. Harispe and A. Bargeboer, *C.R. Acad. Sci., Paris* **245**, 1550 (1957).

[14]H. H. Quon and Y. L. Chow, *Tetrahedron* **31**, 2349 (1975).

[15]S. Julia and Y. Bonnet, *Bull. Soc. Chim. Fr.* 1340 (1957).

[16]E. Fernholz, *Ann. Chim.* **507**, 128 (1933).