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2-Diethoxyphosphoryl alcanoic acid dianions (lithium α-lithiocarboxylates)

IV. A direct route to 2-fluoro-2-alkenoic acids by the Horner synthesis. Application in the field of pyrethroids

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Abstract

2-Diethoxyphosphoryl-2-fluoroacetic acid was converted into the lithium α lithiocarboxylate dianion by treatment with n-butyllithium in hexane/tetrahydrofuran at −70 °C. The Horner reaction between this new dianion and carbonyl compounds gave various 2-fluoro-2-alkenoic acids. Application of the method to the *cis,trans* caronaldehyde ethyl esters led to the 2-fluoroethenyl pyrethroid derivatives (*Z-cis, E-cis, Z-trans, E-trans*).

Introduction

Fluorinated ethylenic derivatives have attracted considerable interest, especially, in studies on the prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). Structural modifications of the terminal portion of the retinoid molecules have resulted in significant biological activity [1]. On the other hand, synthetic pyrethroids are well known compounds derived from modifications of the insecticidal esters formed in natural pyrethrum. Among the various substituted vinyl groups in the compounds very few fluoro derivatives are known [2]. For these reasons it was of interest to devise a new and simple method of preparing 2-fluoro-2-alkenoic acids in order to apply it in the field of pyrethroids.

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Of the possible methods for the synthesis of 2-fluoro-2-alkenoic acids, the Horner synthesis is one of the most convenient. Only a few reports deal with methyl 2-diethoxyphosphoryl fluoroacetate as Horner reagent and describe the preparation of methyl 2-fluoro-2-alkenoates [3,4]. To avoid the possibly troublesome ester hydrolysis step when the goal is the alkenoic acid, we suggest here the use of the new lithium α-lithiocarboxylate derived from 2-diethoxyphosphoryl fluoroacetic acid $(C_2H_5O)_2P(=O)-C(F)(Li)COOLi$ (**2**) as the Horner reagent.

In previous studies we demonstrated the advantages of several carboxylic acid dianions avoiding ester hydrolysis, for the direct synthesis of carboxylic acids, viz.: dichloracetic acid dianion [5], 2-diethoxyphosphoryl chloroacetic acid dianion [6], and 2-diethoxyphosphoryl alcanoic acid dianions [7,8].

The last two lithium α-lithiocarboxylates are very convenient reagents for the one step synthesis of 2-chloro-2-alkenoic acids and 2-alkyl-2-alkenoic acids, respectively, from carbonyl compounds with possible application to the stereoselective synthesis of the pheromone manicone [8].

One of us, previously described a synthesis of 2-fluoro-2-alkenoic acids by another method, the reaction between the lithiated carbanion derived from trifluorochloroethylene and carbonyl compounds [9].

In continuation of these investigations we report here the direct synthesis of 2-fluoro-2-alkenoic acids by the Horner reaction between diethoxyphosphoryl fluoroacetic acid dianion (lithium α-carboxylate) (**2**) and carbonyl compounds, and the application of this method to the caronaldehyde ethyl esters.

Results and discussion

The reaction between diethoxyphosphoryl fluoroacetic acid (**1**) (1 equiv.) in tetrahydrofuran and n-butyllithium (2 equiv.), in hexane at −78° C, readily gave the lithium α-lithiocarboxylate **2**. After addition of the carbonyl compound **3** at this temperature and subsequent hydrolysis, the 2-fluoro-2-alkenoic acids **4** and diethylhydrogenphosphate **5** were obtained (eq. 1).

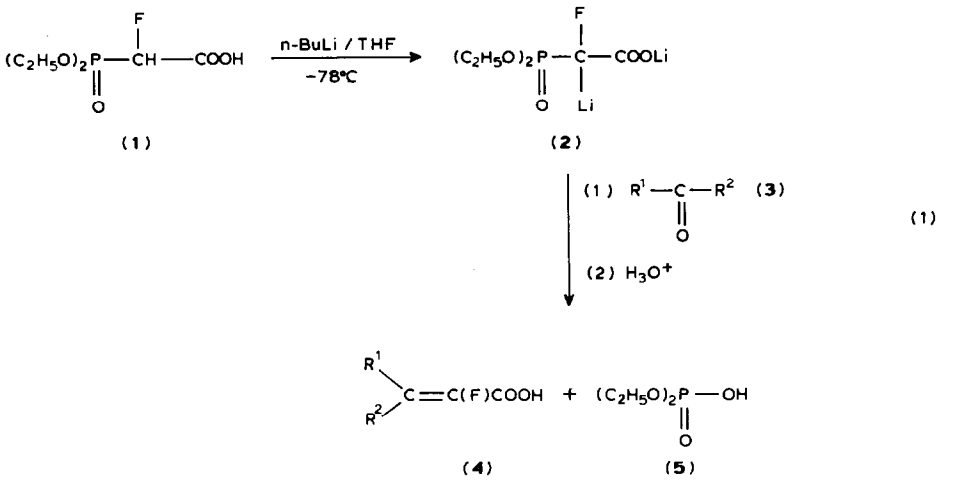
Aryl-substituted 2-fluoro-2-alkenoic acids **4** (R^1 or R^2 = Ar) were directly precipitated by acidification to pH 1 of the aqueous-alkaline phase of the hydrolysed reaction mixture, and separated from the diethylhydrogen phosphate **5** by filtration.

Table 1

2-Fluoro-2-alkenoic acids, **4**, yields and stereochemistry

4	R^1	R^2	4E/4Z [a]	Yield (%)
a	i-C_3H_7	H	60/40	76 [b]
b	s-C_4H_9	H	60/40	74 [b]
c	n-C_6H_{13}	H	55/45	86 [b]
d	CH_3	C_2H_5	44/56	91 [b]
e	C_6H_5	H	0/100	91 [c]
f	*p*-$CH_3OC_6H_4$	H	0/100	90 [c]
g	C_6H_5	CH_3	35/65	87 [c]

[a] *E/Z* ratios were determined from relative signal intensities in the ^{19}F NMR spectrum: The ^3J(H–F) coupling constants for the *Z* isomers are greater (33–36 Hz) than those for the *E* isomer (21–22 Hz). The fluorine nucleus in the *Z* isomer resonates at higher field than the corresponding nucleus in the *E* isomer. [b] Yield of crude **4** based on the starting carbonyl compound. [c] Yield of recrystallized product.



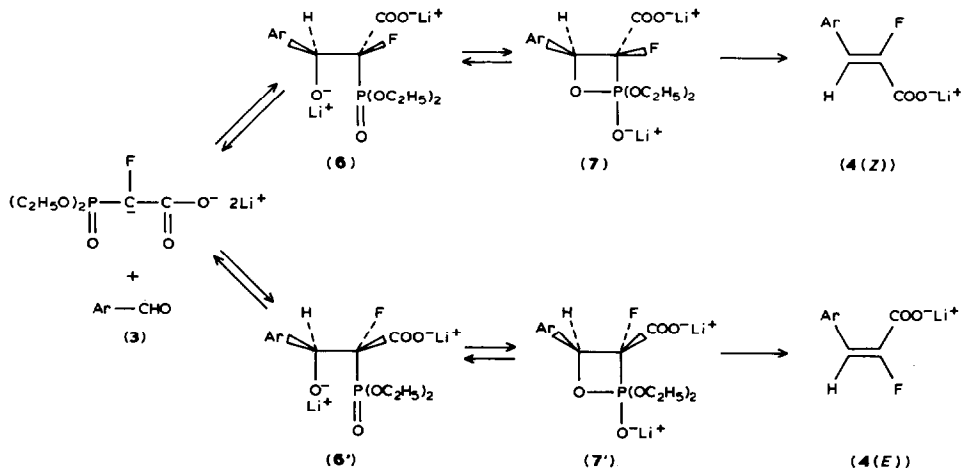
In the cases of soluble fluoro carboxylic acids **4**, the aqueous alkaline phase of the hydrolysed reaction mixture was adjusted to pH 4 before selective extraction of the acids **4** with ether (**4a**, **4b**, **4c**, **4d**). At pH < 4 diethylphosphate also was extracted.

For the aryl-substituted 2-fluoro-2-alkenoic acids the extraction procedure had advantages over filtration procedure, the purity of the carboxylic acid being better.

2-Fluoro-2-alkenoic acids **4** were obtained in good yields (pure isolated products). However, the 2-fluoro-2,4-pentadien-phenyl-5-oic acid was unstable and decomposed during the treatment with acid and base.

With aliphatic aldehydes and ketones the olefinic product was a mixture of *Z* and *E* configurations.

With aromatic aldehydes the reaction was completely stereoselective and gave only the *Z* isomer (**4e**, **4f**). It is noteworthy that when the methyl diethoxyphosphoryl fluoroacetate was used instead of acid **1**, the reaction gave the corresponding methyl ester of **4** as a major *E* stereoisomer [3]. Thus the stereochem-



Scheme 1

ical course of the present reaction deserves further comment. The mechanism widely accepted for phosphonate-olefin formation is analogous to that of the Wittig reaction [10]. In the present case, under the conditions used (15 h, 20 °C), the aldol condensation step is probably reversible [3] (Scheme 1).

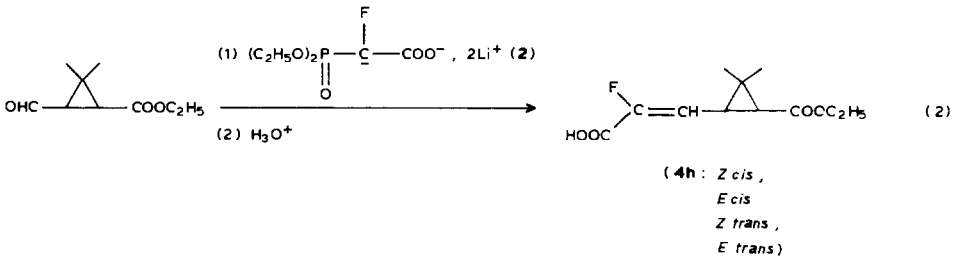
The oxianion **6** should be more stable than the oxianion **6′**, and should stereospecifically lead to the *Z* olefin, while **6′** should lead to the *E* olefin. The relative stabilities of oxianions **6** and **6′** must be the important factor governing the product stereochemistry when the reaction is carried out at room temperature.

From these results and those described in ref. 3, it appears that the stereoelectronic interactions between a carboxylate group and a phenyl group in **6′** are obviously more important than the corresponding interactions between a phenyl group and an ester group.

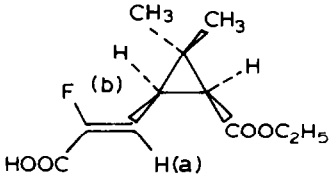
Application to the field of pyrethroids

Fluorine has appeared only rarely among the numerous substituents of the pyrethroid vinyl group, however, methyl *trans*-3-(2,2-difluorovinyl)-2,2-dimethyl cyclopropanecarboxylate [2] and various esters of 3-(3-ethoxy-2-fluoro-3-oxo-1-propenyl)-2,2-dimethyl cyclopropanecarboxylic acid [11] are known. To our knowledge, related species with a free carboxylic acid function and a fluorine atom in position 2 of the vinylic chain have not previously been described.

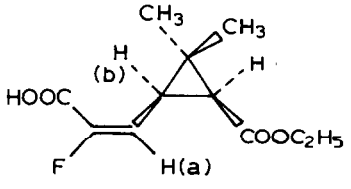
To demonstrate the synthetic utility of our method used it to make caronaldehyde ethyl esters (eq. 2).



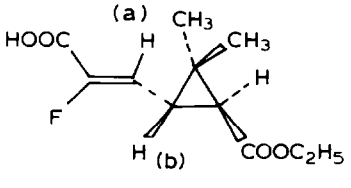
(2)



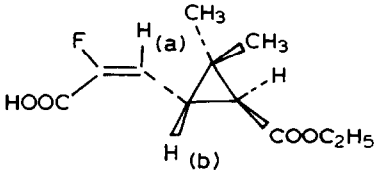
Z-cis 15%



E-cis 26%



Z-trans 23%



E-trans 36%

Reaction under the above conditions between the lithium α-lithiocarboxylate **2** and the ethyl esters of a mixture of *cis* and *trans* caronaldehyde (*cis/trans* 63/37) gave a mixture of the four expected stereoisomers **4h** (*Z-cis, E-cis, Z-trans, E-trans*) in good yield (75%).

The ^1H NMR spectrum of the crude mixture of the four isomers was complex, and assignment of all the signals was not possible. However combined use of 400 MHz ^1H NMR and ^{19}F NMR spectra permitted unambiguous identification of all the stereoisomers: the F signals in the ^{19}F NMR spectrum and H^a signals in 400 MHz ^1H NMR spectrum were characteristic for each stereoisomer.

The fluorine atom, the olefinic proton H^a and the cyclopropane ring proton H^b constituted an AMX-type system with $J_{A\text{-}X} \simeq 0$ Hz. The ^{19}F NMR spectrum of the mixture shows four doublets only, one doublet for each stereoisomer. The fluorine–proton coupling was greater for the *Z* olefins ($J(F\text{–}H^a)$ 30.5–32.0 Hz than for the *E* olefins ($J(F\text{–}H^a)$ 19.1–20.6 Hz), and these values were only little dependent on the *cis* or *trans* relationship of the ring substituents.

In the 400 MHz ^1H NMR spectrum the olefinic protons (H^a) of the four isomers were observed as doublets ($J(H^a\text{–}H^b)$ 10.5 Hz) of doublets ($J(H^a\text{–}F)$ 30.5–32.0 Hz for the *Z* olefin or $J(H^a\text{–}F)$ 19.1–20.6 Hz for the *E* olefin). The olefinic protons (H^a) in the *cis* isomers appeared at lower field. (δ 6.80 ppm, *Z-cis*, and δ 6.55, *E-cis*) than the corresponding protons in the *trans* isomers (δ 6.00 ppm, *Z-trans* and δ 5.77, *E-trans*). These differences, which are associated with the relative location of the protons with respect to the neighbouring ester function, were used to determine the percentages of the various isomers in the mixture [12].

Conclusion

The procedure described has been shown to be applicable with aliphatic and aromatic aldehydes and ketones and to give easy access to 2-fluoro-2-ethylenic acids in good yields. Although the stereoselectivity depends on the nature of the aliphatic aldehydes or ketones, with aromatic aldehydes only the *Z* stereoisomers were formed.

The procedure has been applied to an aldehyde group linked to a cyclopropane ring to provide a way to new pyrethroids.

Experimental

Solvents were dried and distilled before use and all reactions were carried out under argon. IR spectra were recorded on a Perkin–Elmer 580B spectrometer (KBr), ^1H NMR spectra on a Perkin–Elmer R12 (60 MHz) and on a Bruker AM 400 (400 MHz) spectrophotometers ($CDCl_3$, TMS, δ (ppm), *J* (Hz). ^{19}F NMR spectra were recorded on a Jeol FX 90Q ($CDCl_3$, $C_6H_5CF_3$, δ (ppm), *J* (Hz). Microanalyses were performed by the Microanalytical Laboratory CNRS and gave satisfactory results (C, H, F $\pm$0.3%).

Preparation of diethoxyphosphorylfluoroacetic acid (1)

The starting material, product **1** was obtained from ethyldiethoxyphosphoryl fluoroacetate [3] by saponification and then acid treatment.

A mixture of ethyldiethoxyphosphoryl fluoroacetate (10 mmol), and potassium carbonate (15 mmol) in water (15 ml) was refluxed for 10 min, then the mixture was cooled to room temperature and extracted with ether. The aqueous phase was acidified with hydrochloric acid (2*N*), saturated with sodium chloride, and extracted with dichloromethane (6 × 20 ml). After drying over magnesium sulfate, the solvent was evaporated under reduced pressure to leave the crude diethoxyphosphoryl fluoroacetic acid **1** as a white crystalline solid; yield 73%. IR: 1760 cm^{-1}; 2200–3700 cm^{-1}. ^1H NMR: 1.50 (t, 6H), 4.32 (m, 4H), 5.20 (dd, 1H), J(H–F) 48, J(H–P) 13.

Preparation of 2-fluoro-2-alkenoic acids (4). General procedure

A solution of n-butyllithium in hexane (21 mmol, 2.5 *M*) was added dropwise at −78 °C to a solution of diethoxyphosphoryl fluoroacetic acid (**1**) (10 mmol) in tetrahydrofuran (50 ml). After 30 min stirring at −78 °C the carbonyl compound **3** (10 mmol) in tetrahydrofuran (10 ml) was added dropwise at −78 °C. Stirring was continued for 3 h at −78 °C in the case of ketones and aliphatic aldehydes and for 1 h at −78 °C in the case of aromatic aldehydes, and the mixture was then allowed to warm to room temperature. After an additional 15 h stirring to complete the reaction, the mixture was treated with water (20 ml), the organic layer was washed with 10% aqueous hydrogen sodium carbonate (2 × 10 ml) and the combined aqueous layers extracted with ether (2 × 40 ml). The aqueous phase was acidified to pH 4 (pH variations were monitored with a pH meter) with hydrochloric acid (12*N*), and extracted with ether (5 × 20 ml). After drying over magnesium sulfate the solvent was removed under vacuum to leave the crude product as an oil, in the case of aliphatic acids, or a solid in the case of aromatic acids. The solids were purified by recrystallisation.

*2-Fluoro-4-methyl-2-pentenoic acid (**4a**) (E / Z 60 / 40).* IR: ν(C=C) 1660, ν(C=O) 1710, ν(OH) 2200–3700 cm^{-1}. *E* isomer: ^1H NMR (400 MHz): 1.09 (d, 6H) ^3J(H–H) 11, 3.36 (m, 1H), 5.93 (dd, 1H), ^3J(H–F) 22, ^3J(H–H) 11, 10.95 (s, 1H); ^{19}F NMR: −61.8 (d) ^3J(F–H) 22. *Z* isomer: ^1H NMR (400 MHz): 1.07 (d, 6H) ^3J(H–H) 10, 2.88 (m, 1H), 6.14 (dd, 1H), ^3J(H–F) 33, ^3J(H–H) 10, 10.95 (s, 1H), ^{19}F NMR: −69.2 (d), ^3J(F–H) 33.

*2-Fluoro-4-methyl-2-hexenoic acid (**4b**) (E / Z 60 / 40).* IR: ν(C=C) 1660; ν(C=O) 1710, ν(OH) 2200–3700 cm^{-1}. *E* isomer: ^1H NMR (60 MHz): 1.05 (t, 6H), 0.8–1.7 (m, 5H), 3.2 (m, 1H), 5.7 (dd, 1H), ^3J(H–F) 22, ^3J(H–H) 11, 11 (s, 1H). *Z* isomer ^1H NMR (60 MHz): 1.0 (t, 6H), 0.8–1.7 (m, 5H), 2.6 (m, 1H), 6.0 (dd, 1H) ^3J(H–F) 33, ^3J(H–H) 11,11 (s, 1H).

*2-Fluoro-2-nonenoic acid (**4c**) (E / Z 55 / 45).* IR: ν(C=C) 1670, ν(C=O) 1710, ν(OH) 2200–3700 cm^{-1}. *E* isomer ^1H NMR (60 MHz): 0.5–1.9 (m, 11H), 1.9–2.8 (m, 2H), 5.85 (dt, 1H), ^3J(H–F) 21, ^3J(H–H) 8, 10.5 (s, 1H). ^{19}F NMR: −59.9 (d) ^3J(F–H) 21. *Z* isomer ^1H NMR (60 MHz): 0.5–1.9 (m, 11H), 1.9–2.8 (m, 2H), 6.3 (dt, 1H), ^3J(H–F) 33, ^3J(H–H) 8, 10.5 (s, 1H). ^{19}F NMR: −69.0 (d) ^3J(F–H) 33.

*2-Fluoro-3-methyl-2-pentenoic acid (**4d**) (E / Z 44 / 56).* IR: ν(C=C) 1660, ν(C=O) 1700, ν(OH) 2200–3700 cm^{-1}. *E* isomer: ^1H NMR (400 MHz): 1.06 (t, 3H), ^3J(H–H) 7.5, 1.91 (d, 3H) ^4J(H–F) 4, 2.57 (dq, 2H) ^4J(H–F) 1, ^3J(H–H) 7.5, 11.5 (s, 1H). ^{19}F NMR: −64.4 (s). *Z* isomer: ^1H NMR (400 MHz): 1.06 (t, 3H) ^3J(H–H) 7.5, 2.13 (d, 3H), ^4J(H–F) 3, 2.30 (dq, 2H), ^4J(H–F) 3.5, ^3J(H–H) 7.5, 11.5 (s, 1H). ^{19}F NMR: −66.3 (s).

2-Fluoro-3-phenyl-propenoic acid (4e) (Z). White solid, m.p. 154°C (recrystallized from $CHCl_3$). IR ν(C=C phenyl) 1615, ν(C=C) 1670, ν(C=O) 1720, ν(OH) 2200–3700 cm^{-1}. ^1H NMR (400 MHz) ($CDCl_3$/DMSO-d_6 1/1): 6.96 (d, 1H) ^3J(H–F) 36, 7.34–7.72 (m, 5 H), ^{19} F NMR ($CDCl_3$/DMSO 1/1): −61.6 (d) ^3J(F–H) 36. Lit. [13]: ^1H NMR: 7.10 (d, 1H) ^3J(H–F) 36.

2-Fluoro-3-(4-methoxy-phenyl)-propenoic acid (4f) (Z). White solid, m.p. 180°C (recrystallized from $CHCl_3$). IR: ν(C=C phenyl) 1615, ν(C=C) 1670, ν(C=O) 1720, ν(OH) 2300–3700 cm^{-1}. ^1H NMR (400 MHz) ($CDCl_3$/DMSO-d_6 1/1): 3.8 (m, 3H), 5.0 (s, 1H), 6.7–7.0 (m, 3H), 7.5–7.7 (m, 2 H). ^{19}F NMR ($CDCl_3$/DMSO-d_6 1/1): −65.1 (d), ^3J(F–H) 36. Lit. [13]: ^1H NMR: 7.08 (d, 1H) ^3J(H–F) 36.5.

2-Fluoro-3-phenyl-2-butenoic acid (4g) (E/Z 35/65). Yellow solid, IR: ν(C=C) 1650, ν(C=O) 1710, ν(OH) 2300–3700 cm^{-1}. *E* isomer: ^1H NMR (400 MHz) ($CDCl_3$/DMSO-d_6): 2.09 (d, 3H) ^4J(H–F) 5, 5.5 (s, 1H), 7.11–7.47 (m, 5H). ^{19}F NMR ($CDCl_3$/DMSO-d_6) −58.3 (s). *Z* isomer: ^1H NMR (400 MHz) ($CDCl_3$/DMSO-d_6) 2.4 (d, 3H), ^4J(H–F) 3.5, 5.5 (s, 1H), 7.11–7.47 (m, 5H). ^{19}F NMR ($CDCl_3$/DMSO-d_6): −60.7 (s).

Ethyl-3-(2-fluoro-3-hydroxy-3-oxo-1-propenyl)-2,2-dimethylcyclopropane carboxylate (4h).

Isomer *Z-cis*: ^1H NMR (400 MHz): H^a signal 6.80 (dd, 1H), ^3J(H–H) 10.5, ^3J(H–F) 32. ^{19}F NMR −70.5 (d), ^3J(F–H) 32.

Isomer *Z-trans*: ^1H NMR (400 MHz): H^a signal 6.00 (dd, 1H), ^3J(H–H) 10.5, ^3J(H–F) 30.5, ^{19}F NMR −68.6 (d), ^3J(F–H) 30.5.

Isomer *E-cis*: ^1H NMR (400 MHz): H^a signal 6.55 (dd, 1H), ^3J(H–H) 10.5, ^3J(H–F) 20.6. ^{19}F NMR −57.2 (d), ^3J(F–H) 20.6.

Isomer *E-trans*: ^1H NMR (400 MHz): H^a signal 5.77 (dd, 1H), ^3J(H–H) 10.5, ^3J(H–F) 19.1. ^{19}F NMR −57.7 (d), ^3J(F–H) 19.1.

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References

1 R. Filler and S.M. Naqui in R. Filler and Y. Kobayashi (Eds.), Biomedicinal Aspects of Fluorine Chemistry, Elsevier Biomedical press, Amsterdam, New York, Oxford 1982, p. 17.
2 D. Arlt, M. Jautelat and R. Lantzsch, Angew. Chem. Int. Ed. Engl., 20 (1981) 703.
3 G. Etemad-Moghadam and J.J. Seyden-Penne, Bull. Soc. Chim. Fr., (1985) 448.
4 W. Grell and H. Machleidt, Justus Liebigs Ann. Chem., 693 (1966) 134.
5 Ph. Coutrot and A. Elgadi, Synthesis, (1984) 115.
6 Ph. Savignac, M. Snoussi and Ph. Coutrot, Synth. Commun., 8 (1978) 19.
7 Ph. Coutrot and Ph. Savignac, Synthesis, (1978) 133.
8 Ph. Coutrot and A. Ghribi, Synthesis, (1986) 790.
9 J.F. Normant, J.P. Foulon, D. Masure, R. Sauvetre and J. Villieras, Synthesis, (1975) 122.
10 W.S. Wadsworth, Jr., in "Organic Reactions" 25 (1977) 73.
11 (a) J. Tessier, A. Teche and J.P. Demoute, DE 3534336 (1986), Chem. Abstr. 105, 172781h (1986); (b) J. Tessier in "L'Actualité Chimique" Ed. Société Française de Chimie, 12 (1986) 5; (c) J. Tessier, J.P. Demoute and L. Taliani, French Patent 2569189 (1986); (d) J. Martel, J. Tessier and A. Teche, French

Patent 2560189 (1985); (e) J. Martel, J. Tessier and A. Teche, French Patent 2491060 (1986); (f) J. Martel, J. Tessier and A. Teche, US Patent 4489003 (1984); (g) J. Tessier and J.P. Demoute, Eur. Patent 114012 (1984).

12 A.F. Bramwell, L. Crombie, P. Hemesley, G. Pattenden, M. Elliott and N.F. Janes, Tetrahedron, 25 (1969) 1727.

13 E. Elkik, C. Francesch, Bull. Soc. Chim. France, 3 (1986) 423.