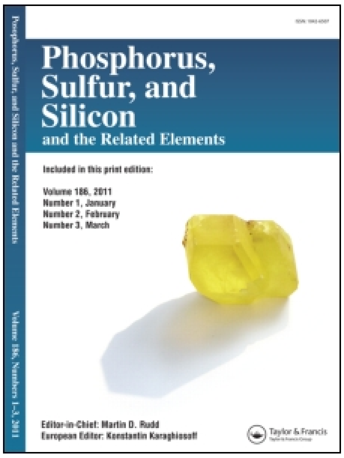


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Addition Of Organometallics To α,β-Unsaturated Thiocarbonyl Compounds. Iv. Five-Membered Sulfur Heterocycles By 1,4-Addition Of The Carbenoid Ich,Mgcl

Jean-Pierre Guemas[a]; Jean Villieras[a]
[a] Laboratoire de Chimie Organique, Nantes Cedex, U.A., France

To cite this Article Guemas, Jean-Pierre and Villieras, Jean(1986) 'Addition Of Organometallics To α,β-Unsaturated Thiocarbonyl Compounds. Iv. Five-Membered Sulfur Heterocycles By 1,4-Addition Of The Carbenoid Ich,Mgcl', Phosphorus, Sulfur, and Silicon and the Related Elements, 26: 3, 299 — 305

To link to this Article: DOI: 10.1080/03086648608084584

URL: http://dx.doi.org/10.1080/03086648608084584

Phosphorus and Sulfur, 1986, Vol. 26, pp. 299–305
0308-664X/86/2603-0299/$15.00/0

ADDITION OF ORGANOMETALLICS TO α,β-UNSATURATED THIOCARBONYL COMPOUNDS. IV. FIVE-MEMBERED SULFUR HETEROCYCLES BY 1,4-ADDITION OF THE CARBENOID ICH_2MgCl

JEAN-PIERRE GUEMAS and JEAN VILLIERAS

Laboratoire de Chimie Organique, U.A. C.N.R.S. 475, 2, rue de la Houssinière, 44072 Nantes Cedex (France)

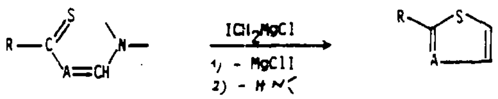
(*Received July 16, 1985*)

2,3-Dihydrothiophenes, 2-arylthiophenes, 2-methylthio-3-arylthiophenes and 2-substituted thiazoles are prepared by 1,4-addition of iodomethylmagnesium chloride with β-aminopropenethiones, methyl β-aminopropenedithioate and thioacylformamidines.

INTRODUCTION

The insertion of a sulfur atom between two carbons of the same chain is a general procedure used to form sulfur heterocycles; most of the thiophene derivatives can be prepared by this method.[1-4] Only some recent works describe the thiophenic ring formation by insertion of a carbon atom in a chain which already contains a sulfur atom: the reaction of bromonitromethane on adducts of enamine isothiocyanate leads to 2-nitrothiophenes,[5] the alkylation of (thioacyl)malonic acid derivatives with *O*-ethyl α-chlorothioacetate gives thiothenoic acid *O*-esters,[6] 2-thenoic compounds are obtained by the addition of α-halogenocarbonyl compounds on 3-amino substituted dithioacrylate,[7] monothio β-diketones[8] and vinylogous thioamides.[9,10]

In a previous paper,[11] we related the formation of five-membered heterocyclic compounds by addition reaction of lithium enolates of α-chlorinated esters on α-unsaturated thiocarbonyl compounds; thus 2,3-dihydrothiophene and Δ^2-thiazolines were prepared from β-aminopropenethione **1** and from *N*-thioacylformamidines **3**. In this work we describe an original synthesis of arylthiophenes and thiazoles by the addition reaction of iodomethylmagnesium chloride on the α-unsaturated thiocarbonyl substrates **1**, **2** and **3** (1).



1,2,3 **4,5,6** (1)

1 → **4**	R = Ar	A = CH
2 → **5**	R = CH_3S	A = CAr
3 → **6**	R = C_6H_5	A = N

RESULTS AND DISCUSSION

Unsaturated thiocarbonyl compounds, like α-ethylenic thioamides,[12-16] β-aminopropenethiones **1** (thioamide vinylogs) and β-aminopropenedithioates[11,17,18] **2** (dithiocarbamate vinylogs) react regioselectively with organometallic reagents to give a 1,4-addition reaction, the nucleophilic agent attacking at the β-carbon atom of the thiocarbonyl group. Alkylation of the 1,4-adduct by iodomethane occurs at the sulfur atom.

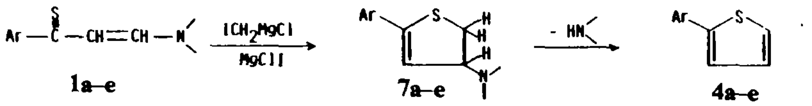
The study of the gem-halogenated Grignard reagents previously carried out by one of us[19] showed that the iodomethylmagnesium chloride ICH_2MgCl is a carbenoid which presents both nucleophilic and electrophilic reactivities: its nucleophilic properties are apparent in the condensation with aldehydes and halogen compounds, whereas the presence of the iodine atom gives rise to an electrophilic reactivity, which was established by reaction with organomagnesium reagents.

The condensation of iodomethylmagnesium chloride with 1-aryl 3-dialkylaminopropenethiones **1a–e** at −50°C in tetrahydrofuran and in the presence of hexamethylphosphotriamide gives the corresponding 3-dialkylamino-2,3-dihydrothiophenes **7a–e** (Table I) with good yields, which were obtained as crude oils after hydrolysis. Attempts at purification by distillation and chromatography of the compounds **7** failed because of decomposition on heating or on silica gel. However, ^1H NMR spectra of the crude oils showed that the 2,3-dihydrothiophenes **7** are prepared with satisfactory purity.

On heating, or better, on quaternization of the dialkylamino group with iodomethane followed by the action of triethylamine, the 3-dialkylamino-2,3-dihydrothiophenes **7** easily eliminate the amine to give the 2-arylthiophenes **4**. Melting

TABLE I

Addition of ICH_2MgCl with the thioamide vinylogs **1**



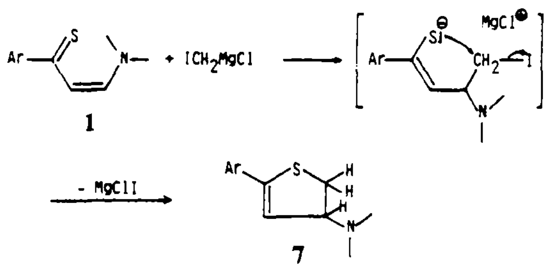
1a–e **7a–e** **4a–e**

	7			4			
Compounds	Ar	—N<	yield (%)	m.p. (°C)	M^+	yield ( )[a] (%)	Ref.
a	C_6H_5	pyrrolidino	82	40–41 aq.ethanol	160	61 (50)	20–23
b	p-$CH_3C_6H_4$	piperidino	94	63 aq.ethanol	174	54 (51)	20, 22
c	p-$CH_3OC_6H_4$	diethylamino	95	108–109 aq.ethanol	190	76 (72)	20, 24
d	p-ClC_6H_4	pyrrolidino	84	84–85 ethanol	194	85 (71)	20, 23
e	p-BrC_6H_4	pyrrolidino	100	98–100 aq.methanol	238	55 (55)	20, 23

[a] Calculated from the thioamide vinylog.

points and ^{1}H NMR spectra of compounds **4** are consistent with literature data,[20-24] the results are given in Table I.

Taking into account our previous results on the condensation of organomagnesium compounds on thioamide vinylogs,[17] the heterocycle formation can be explained by two successive reactions: in a first step, the iodomethylmagnesium chloride reacts with the thioamide vinylog according to a 1,4-addition, the ring closure is then obtained from the attack of the electrophilic carbon atom by the negative charge localised on the sulfur atom and the depart of the iodine atom (2).

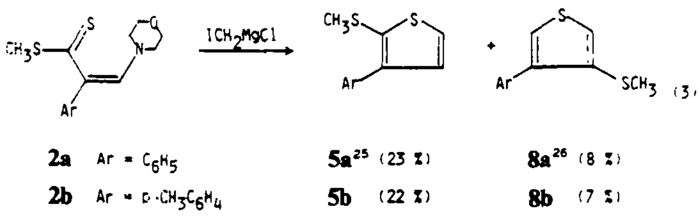


(2)

According to this scheme the carbenoid ICH_2MgCl only reacts as nucleophile with the α-unsaturated thiocarbonyl substrate, its electrophilic reactivity is not involved in the heterocycle formation which results from the electrophilic properties of the iodomethyl group just fixed on the carbon chain.

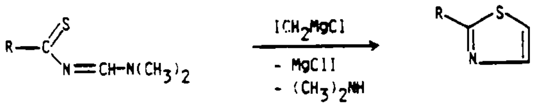
Thiophenic ring formation from α-unsaturated thiocarbonyl compounds was first observed by Smutny[7] in the condensation reaction of α-halogenocarbonyl derivatives with dithiocarbamate vinylogs. However in this latter case, the reactional scheme is quite different because the carbon insertion begins with the formation of a sulfur ylide.

Condensation of the iodomethylmagnesium chloride on the methyl 2-aryl-3-morpholinopropenedithioates **2a** and **2b** leads to the expected 3-aryl-2-methylthiothiophenes **5a**[25] and **5b** with yields of only 23% and 22%. Analysis by ^{1}H NMR of the crude oil obtained after hydrolysis did not show the corresponding intermediate 3-morpholino-2,3-dihydrothiophene but a mixture of several products among which we isolated the 3-aryl-2-methylthiothiophene **5** and its isomer, the 3-aryl-4-methylthiothiophene **8** (3).



(3)

From the thioacylformamidine **3**, which presents a carbon-nitrogen double-bond conjugated with the thiocarbonyl group, addition of the iodomethylmagnesium chloride gave similar results to those obtained with dithiocarbamate vinylogs **2**. The intermediate Δ^2-thiazolines were not isolated as they eliminate the amine spontaneously to give thiazolic compounds; **3a** and **3b** thus gave the 2-phenylthiazole[27] **6a** and the 2-benzylthiothiazole[28] **6b** with yields of 21% and 19% respectively (4).



3a R = C_6H_5 **6a** yield 21 %

3b R = $C_6H_5CH_2S$ **6b** yield 19 % (4)

The low yields found for compounds **5** and **6** can be explained by the lesser reactivity of the dithiocarbamate vinylogs **2** and the thioacylformamidines **3** compared to the thioamide vinylogs **1** towards the organometallic reagent. Attempts at higher temperature (−40°C) were unsuccessful because at this temperature the decomposition of ICH_2MgCl proceeds faster than the addition reaction.

Addition of carbenes to α-ethylenic carbonyl compounds does not affect the carbonyl group and leads to cyclopropane derivatives.[29,30] In this study, the addition of the carbenoid reagent ICH_2MgCl to some α-unsaturated thiocarbonyl compounds occurs regioselectively as a 1,4-addition, which finally gives five-membered sulfur heterocycles.

EXPERIMENTAL

Proton NMR spectra were recorded in chloroform-d solution at 60 MHz with a Perkin-Elmer R24 spectrometer, at 100 MHz with a Varian XL 100 spectrometer or at 250 MHz with a Cameca spectrometer. ^{13}C NMR spectra were obtained on a Bruker WH 90 spectrometer. Chemical shifts are reported as δ values in ppm to the internal standard (TMS).

Mass spectra were determined with a Varian MAT 112 spectrometer at 70 eV.

The purity of compounds was tested by thin layer chromatography on silica gel plates (E. Merck, Art. 5714). Column chromatography was carried out by using silica gel 60 (E. Merck, Art. 9385 or 7734). Melting points are uncorrected.

Preparation and reactions of the iodomethylmagnesium chloride were carried out under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) was freshly distilled from lithium aluminium hydride and stored under nitrogen over molecular sieve, diethyl ether was dried over calcium chloride, then sodium, hexamethylphosphotriamide (HMPT) was purified by distillation.

Preparation of starting materials **1**, **2** *and* **3**. 1-Aryl-3-dialkylamino-2-propen-1-thiones **1a–e** were prepared by the action of the appropriate amine, diethylamine (**1c**), pyrrolidine (**1a**, **1d**, **1e**) or piperidine (**1b**) on 3-aryl-1,2-dithiolylium perchlorate.[31]

Methyl 3-morpholino-2-phenyl-2-propendithioate **2a** and methyl 3-morpholino-2-*p*-tolyl-2-propendithioate **2b** were prepared according to Smutny[32] by the reaction of morpholine on 3-methylthio-4-phenyl- and 3-methylthio-4-*p*-tolyl-1,2-dithiolylium iodide.

The procedure of Weidinger and Eilingsfeld[33] was used to prepare N^1,N^1-dimethyl-N^2-thiobenzoylformamidine **3a** and benzyl *N*-(dimethylaminomethylen)dithiocarbamate **3b** by condensation of dimethylformamide diethylacetal on thiobenzamide and benzyl dithiocarbamate.

Preparation of the iodomethylmagnesium chloride ICH_2MgCl. The iodomethylmagnesium chloride ICH_2MgCl is prepared by a halogen-magnesium exchange reaction between the diiodomethane and the isopropylmagnesium chloride accoding to Villieras[19]:

$$CH_2I_2 + (CH_3)_2CHMgCl \rightarrow ICH_2MgCl + (CH_3)_2CHI$$

In a flame-dried 500 mL round-bottomed flask, equipped with a magnetic stirrer, a low-temperature thermometer (−100°C, +50°C) and a pressure-equalizing addition funnel, were placed 5.36 g (20.0

mmol) of diiodomethane in 30 mL of diethylether and 50 mL of THF. After cooling to − 80°C, a solution of 20.2 mmol of isopropylmagnesium chloride in THF was added dropwise under vigourous stirring over a period of 30 min. After warming to − 70°C, the white suspension obtained is stirring during 30 min.

3-Dialkylamino-2,3-dihydrothiophenes **7a–e**. At − 70°C, HMPT (3.6 mL, 20.0 mmol) was introduced with stirring in the ICH_2MgCl suspension, which was allowed to warm to − 50°C. The solution of the thioamide vinylog (4.0 mmol) in 40 mL of THF was then added dropwise (1 h) and the reaction mixture maintained at − 50°C during 3 h, at the end of which the initial colour of the thiocarbonyl compound had disappeared.

After cooling to − 80°C, the hydrolysis was performed rapidly with vigourous stirring by the addition of 100 mL of a saturated aqueous solution of ammonium chloride. The reactional mixture was then allowed to warm to room temperature and extracted three times with 100 mL portions of toluene. The toluene extracts were combined, washed with water and dried over Na_2SO_4.

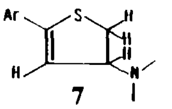
Evaporation of the solvent under reduced pressure gave the crude 3-dialkylamino-2,3-dihydrothiophene **7** as a yellow oil. Yields are given in Table I, ^1H NMR spectra data of the compounds **7** are collected in Table II.

Attempts at purification of the crude oils **7** by distillation or column chromatography on silica gel were unsuccessful, because of their decomposition into 2-arylthiophenes **4**.

2-Arylthiophenes **4a–e**. The crude oil of the compounds **7a–e**, prepared from 4.0 mmol of the thioamid vinylog **1a–e** was dissolved in pure methyl iodide (10 mL) and stirred overnight. After removing the iodomethane in vacuo, the resulting viscous residue was stirred in 25 mL of a toluene-triethylamine mixture (4 : 1) for 1 h and heated under reflux for 12 h. After cooling, the toluene and the excess amine were removed by rotary evaporation under reduced pressure, the residue was then recovered by toluene (15 mL). After filtration to eliminate the salt of the amine, the solution was chromatographed on a silica gel column; elution with a petroleum ether-toluene mixture (1 : 1) afforded 2-arylthiophenes, which were

TABLE II

^1H NMR spectra data of compounds **7** (δ in ppm/TMS, solvent $CDCl_3$)



7

Composé	Ar	—N<	CH—N	CH_2	CH=
7a	C_6H_5 6.83–7.60, m, 5 H	pyrrolidino 1.60–1.97, m, 4 H 2.47–2.97, m, 4 H	4.32, dt, 1 H J = 6.8 Hz, J = 2.8 Hz	3.33, d, 2 H J = 6.7 Hz	5.90, d, 1 H J = 2.8 Hz
7b	p-$CH_3C_6H_4$ 2.28, s, 3 H 6.97, d, 2 H 7.23, d, 2 H J = 8.2 Hz	piperidino 1.40–1.77, m, 4 H 2.47–2.77, m, 4 H	4.30, dt, 1 H J = 6.7 Hz, J = 2.7 Hz	3.33, d, 2 H J = 6.7 Hz	5.87, d, 1 H J = 2.7 Hz
7c	p-$CH_3OC_6H_4$ 3.75, s, 3 H 6.80, d, 2 H 7.40, d, 2 H J = 8.7 Hz	diethylamino 1.07, t, 6 H 2.57, q, 2 H 2.52, q, 2 H J = 7.0 Hz	4.62, dt, 1 H J = 6.8 Hz, J = 2.9 Hz	3.27, d, 2 H J = 6.8 Hz	5.80, d, 1 H J = 2.9 Hz
7d	p-ClC_6H_4 7.13, qs, 4 H	pyrrolidino 1.55–1.92, m, 4 H 2.43–2.80, m, 4 H	4.25, dt, 1 H J = 6.7 Hz, J = 2.7 Hz	3.25, d, 2 H J = 6.7 Hz	5.80, d, 1 H J = 2.7 Hz
7e	p-BrC_6H_4 7.33, qs, 4 H	pyrrolidino 1.63–1.97, m, 4 H 2.50–2.87, m, 4 H	4.27, dt, 1 H J = 7.0 Hz, J = 2.8 Hz	3.30, d, 2 H J = 7.0 Hz	5.93, d, 1 H J = 2.8 Hz

recrystallised as white crystals from aqueous ethanol (or methanol). Physical constants and yields are indicated in Table I, melting points and ^1H NMR spectra data are consistent with the literature.[20-24]

2-Methylthio-3-phenylthiophene **5a**. Iodomethylmagnesium chloride (20.0 mmol) was condensed with the methyl 3-morpholino-2-phenylpropendithioate (1.12 g, 4.0 mmol) according to the general procedure described above for the preparation of the compounds **7**. After hydrolysis and extraction with toluene, the toluene extracts were combined, washed with water, dried (Na_2SO_4) and concentrated on a rotary evaporator under reduced pressure.

Chromatography of the residue on a silica gel column gave by elution with a petroleum ether-dichloromethane mixture (3 : 1) two fractions; the first fraction contained 0.19 g (yield 23%) of the 2-methylthio-3-phenylthiophene[25] **5a** mp = 51°C (aq.ethanol), (lit[25] 52°C), r.f. (TLC, petroleum ether) = 0.24; mass spectrum m/e 206 (m^+); ^1H NMR ($CDCl_3$) δ ppm. 2.36 (s, 3 H, CH_3) 7.09 (d, 1 H, H^5, $J = 5.5$ Hz) 7.29 (d, 1 H, H^4, $J = 5.5$ Hz) 7.26–7.44 and 7.52–7.58 (2m 5 H, aromatics); evaporation of the second fraction gave 65 mg (yield 8%) of the 3-methylthio-4-phenylthiophene[26] **8a**, mp = 76–77°C (petroleum ether), (lit[26] 76–78°C), r.f. (TLC, petroleum ether) = 0.16; mass spectrum m/e 206 (m^+); ^1H NMR ($CDCl_3$) δ ppm 2.36 (s, 3 H, CH_3) 6.96 (d, 1 H, H^2, $J = 3.25$ Hz) 7.26 (d, 1 H, H^5, $J = 3.25$ Hz) 7.31–7.43 and 7.50–7.56 (2m, 5 H, aromatics).

2-Methylthio-3-p-tolylthiophene **5b**. Prepared from the methyl 3-morpholino-2-*p*-tolylpropendithioate **2b** as described for **5a**, yield 22%, yellow liquid, r.f. (TLC, petroleum ether) = 0.34; ^1H NMR ($CDCl_3$) δ ppm 2.36 (s, 3 H, CH_3) 2.38 (s, 3 H, CH_3) 7.07 (d, 1 H, H^5, $J = 5.25$ Hz) 7.21 (d, 2 H, aromatics, $J = 8.2$ Hz) 7.25 (d, 1 H, H^4, $J = 5.25$ Hz) 7.44 (d, 2 H, aromatics, $J = 8.2$ Hz); mass spectrum m/e 220 (m^+). Anal. Calcd for $C_{12}H_{12}S_2$: C, 65.41; H, 5.49; S, 29.10. Found: C, 65.21; H, 5.53; S, 28.90.

From a second fraction, 60 mg of 3-methylthio-4-*p*-tolylthiophene **8b** (yield 7%) were recovered, colourless liquid, r.f. (TLC, petroleum ether) = 0.22; ^1H NMR ($CDCl_3$) δ ppm 2.36 (s, 3 H, CH_3) 2.38 (s, 3 H, CH_3) 6.94 (d, 1 H, H^2, $J = 3.25$ Hz) 7.21 (d, 2 H, aromatics, $J = 8.2$ Hz) 7.23 (d, 1 H, H^5, $J = 3.25$ Hz) 7.42 (d, 2 H, aromatics, $J = 8.2$ Hz); mass spectrum m/e 220 (m^+).

2-Phenylthiazole[27] **6a** and 2-benzylthiothiazole[28] **6b** were prepared in 21% and 19% yield respectively by hydrolysis of the addition compound of ICH_2MgCl with the corresponding formamidines **3a** and **3b** according to the procedure described for **5a**. Compounds **6a** and **6b** were isolated by column chromatography on silica gel, elution with a toluene-dichloromethane mixture (1 : 1), r.f. (TLC, dichloromethane) = 0.38 (**6a**), 0.57 (**6b**) and were identified by comparison of their ^1H NMR spectra data with the literature.[34,35]

REFERENCES

1. D. E. Wolf and K. Folkers, *Organic Reactions*, **6**, 412 (1957).
2. S. Gronowitz, *Advances in Heterocyclic Chemistry*, A. R. Katritzky Ed., Vol. 1, Academic Press, New York and London (1963) 24.
3. S. Gronowitz, *Organic Compounds of Sulphur, Selenium, and Tellurium, Specialist Periodical Reports*. The Chemical Society Ed., Vol. 2, London (1973), 353 and Vol. 3, London (1975), 400.
4. S. Gronowitz, *Heterocyclic Chemistry, Specialist Periodical Reports*. The Royal Society of Chemistry Ed., Vol. 1, London (1980), 68.
5. S. Rajappa and S. Sreenivasan, *Indian J. Chem.*, Sect. B, **16**, 752 (1978).
6. K. Hartke and G. Gölz, *Liebigs Ann. Chem.*, 1644 (1973).
7. E. J. Smutny, *J. Am. Chem. Soc.*, **91**, 208 (1969).
8. M. Takaku, Y. Hayasi and H. Nozaki, *Bull. Chem. Soc. Japan*, **43**, 1917 (1970).
9. J. C. Meslin and H. Quiniou, *C.R. Acad. Sci.*, **273C**, 148 (1971).
10. J. C. Meslin, *C.R. Acad. Sci.*, **277C**, 1391 (1973).
11. J-P. Guémas, M. Lees, A. Reliquet and J. Villiéras, *Phosphorus and Sulfur*, **12**, 325 (1982).
12. Y. Tamaru, T. Harada, H. Iwamoto and Z. Yoshida, *J. Am. Chem. Soc.*, **100**, 5221 (1978).
13. Y. Tamaru, T. Harada and Z. Yoshida, *J. Am. Chem. Soc.*, **101**, 1316 (1979).
14. Y. Tamaru, M. Kagotani and Z. Yoshida, *Tetrahedron Lett.*, **22**, 3409 (1981).
15. Y. Tamaru, M. Kagotani, Y. Furukawa, Y. Amino and Z. Yoshida, *Tetrahedron Lett.*, **22**, 3413 (1981).
16. Y. Tamaru, T. Harada, S. Nishi and Z. Yoshida, *Tetrahedron Lett.*, **23**, 2383 (1982).
17. J-P. Guémas, M. Lees, A. Reliquet, F. Reliquet and H. Quiniou, *Phosphorus and Sulfur*, **8**, 351 (1980).
18. J-P. Guémas, M. Lees and A. Reliquet, *Phosphorus and Sulfur*, **17**, 307 (1983).
19. J. Villiéras, *Bull. Soc. Chim. Fr.*, 1520 (1967).
20. A. Tundo, *Boll. Sci. Fac. Chim. Ind. Bologna*, **18**, 102 (1960).

21. P. Kues and C. Paal, *Ber. Dtsch. Chem. Ger.*, **19**, 3142 (1886).
22. A. Chrzasczewska, *Rocznicki Chem.*, **5**, 33 (1925); *Chem. Abs.*, **20**, 1078 (1926).
23. M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, **46**, 2339 (1924).
24. M. A. Al'Perovich and L. T. Bogolyusbkaya, *Zh. Obshch. Khim.*, **34**, 645 (1964).
25. J. P. Marino and J. L. Kostusyk, *Tetrahedron Lett.*, **27**, 2493 (1979).
26. C. M. Camaggi, G. De Luca and A. Tundo, *J. Chem. Soc., Perkin II*, 1594 (1972).
27. B. S. Friedmann, M. Spark and R. Adams, *J. Am. Chem. Soc.*, **59**, 2262 (1937).
28. P. Bastianelli, M. Chanon and J. Metzger, *Bull. Soc. Chim. Fr.*, 1948 (1967).
29. H. E. Simmons, T. L. Cairns, S. A. Vladuchick and C. M. Hoiness, *Organic Reactions*, **20**, 1 (1973).
30. J. M. Denis, C. Girard and J. M. Conia, *Synthesis*, 549 (1972).
31. J. Bignebat, H. Quiniou and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1699 (1966); 127 (1969).
32. E. J. Smutny, W. Turner, E. D. Morgan and R. Robinson, *Tetrahedron*, **23**, 3785 (1967).
33. H. Weidinger and H. Eilingsfeld, Belg. Pat. 629972 (1963): Ger. Pat. Applic. (DOS) 23.3.1962 (Badische Anilin und Soda Fabrik A. G.): *Chem. Abs.*, **61**, 1803 (1964).
34. J. P. Aune, R. P. T. Luu, E. J. Vincent and J. Metzger, *Bull. Soc. Chim. Fr.*, 2679 (1972).
35. H. J. M. Dou, P. Hassanaly, J. Kister, G. Vernin and J. Metzger, *Helv. Chim. Acta*, **61**, 3143 (1978).