Journal of Organometallic Chemistry, 88 (1975) 121—128

CLEAVAGE OF ETHEREAL BOND

IX. THE REDUCING ACTION OF GRIGNARD REAGENTS ON 1,3-BENZOXATHIOLE AND 1,3-BENZODIOXOLE DERIVATIVES

S. CABIDDU and M. SECCI
Istituto Chimico, Università, 09100 Cagliari (Italy)
A. MACCIONI
Istituto di Chimica Farmaceutica e Tossicologica, Università, 09100 Cagliari (Italy)
(Received October 22nd, 1974)

Summary

Some reactions of 1,3-benzoxathioles and 1,3-benzodioxoles with Grignard reagents were examined in order to verify whether or not reduction products were present in addition to the substitution and elimination products previously observed. The reaction mixtures contain reduction products whenever the Grignard reagent has β-hydrogen atoms, in which case the reagent is likely to act as a hydride transfer agent. The product distribution also depends on steric hindrance by the halogen. 1,3-Benzodioxoles react with isopropylmagnesium bromide to give mixtures of alkanes and alkenes, the former arising from a double hydride ion migration, and the latter from a reduction and elimination process.

Introduction

Previously [1,2] we have shown that 1,3-benzodioxoles and 1,3-benzoxathioles react with Grignard reagents to give substitution and/or elimination products depending upon the organomagnesium employed and upon the presence of substituents in the α-position of the heterocyclic ring. These facts were interpreted in terms of the Grignard reagent functioning as a nucleophile or as a base.

On the other hand it is well known that Grignard reagents such as isopropylmagnesium halide react with sterically-hindered carbonyl compounds, generally to give products of reduction, the organometallic being converted to olefins [3-6].

In the light of these facts we have investigated further the cleavage of

the ethereal bond by suitable Grignard reagents in order to verify whether reduction products were present in addition to the substitution and elimination products observed previously.

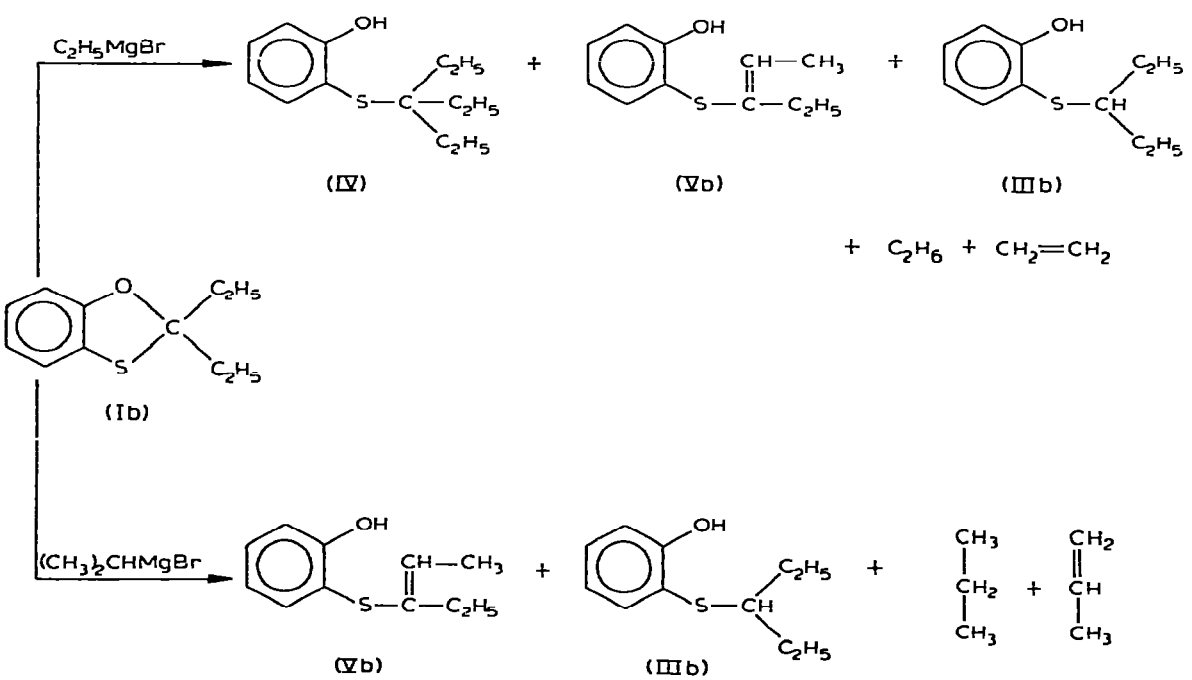
Results and discussion

We have examined the reactions between 1,3-benzoxathioles and 1,3-benzodioxoles and organomagnesium compounds with or without β-hydrogen atoms. The reaction mixtures were analyzed by gas—liquid chromatography (GLC); the products were, when possible, fractionally distilled and in the other cases separated by column chromatography. All compounds were characterized by elemental and spectral analyses and by comparison with authentic samples. Gaseous olefins were characterized as dibromo-derivatives, obtained by bubbling the reaction products through a solution of bromine in carbon tetrachloride.

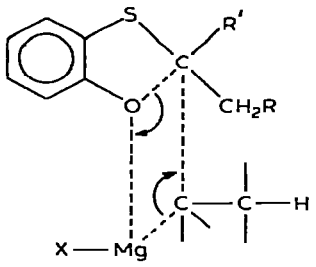
From the results, listed in Tables 1-4, it can be seen that cleavage of the ethereal bond gives, in addition to the substitution and elimination products previously described [1,2], reduction products whenever the Grignard reagent contains β-hydrogen atoms capable of functioning as a hydride transfer agent [5,6]; this latter reaction becomes prevalent as the number of β-hydrogen atoms increases.

Thus 2,2-diethyl-1,3-benzoxathiole (Ib) reacts with ethylmagnesium halide to give a mixture of substitution (IV), elimination (Vb) and reduction (IIIb) products, whereas with isopropylmagnesium bromide it gives only elimination (Vb) and reduction (IIIb) products, the latter predominating (Scheme 1).

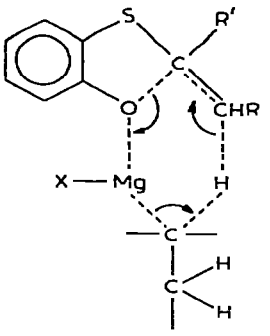
SCHEME 1



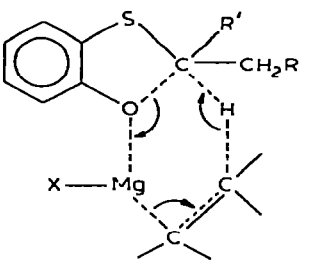
We believe that cleavage of the ethereal bond follows coordination of the heterocycle to the Grignard reagent, resulting in (*i*) a substitution product, if the Grignard reagent behaves as a nucleophile (A), or (*ii*) elimination if the Grignard functions as a base (B), or (*iii*) reduction if the Grignard can furnish a hydride ion (C). In the latter case the presence of an olefin is essential and in fact, an olefin was found in an equimolar amount with respect to the reduction product.*



(A)



(B)



(C)

On the basis of these results we studied the varying yields of substitution, elimination and reduction products depending on both the organic reactant and the halogen in the organomagnesium compound employed.

We found (Tables 1 and 2) that reductions do not occur when the organomagnesium compound has no β-hydrogen, and that increasing steric hindrance of a Grignard reagent inhibits substitution [1], promoting elimination and reduction; the latter process is prevalent even over elimination when the number of β-hydrogen atoms increases [$(CH_3)_3C > (CH_3)_2CH > (C_6H_5CH_2)_2CH > C_6H_5CHCH_3 \approx CH_3CH_2$]. This probably depends upon the fact that an increase in the number of β-hydrogens makes migration of hydride ions to the starting substrate carbonium ion statistically more probable (C). In addition, we found (Table 3) that the product distribution depends on steric hindrance of the halogen. Thus on passing from chlorides to bromides and iodides, the percentage of elimination and reduction increases at the expense of substitution. On the other hand, the first two processes were independent of the quantity of the organo halogen. This fact was justified assuming that, whatever the reaction mechanism, steric hindrance of the halogen atom has a greater effect upon the transition state leading to substitution than on the transition state leading to elimination and to reduction.

It is remarkable that the 1,3-benzoxathiole substitutions occur to a lesser extent than in the analogous 1,3-benzodioxoles [1]. This fact is also related to the greater steric hindrance of sulphur compared to oxygen, and for this reason the reaction will be directed towards the transition state which offers minimal crowding.

The reactions with 1,3-benzodioxoles involve, as previously described [1], both oxygen atoms in the heterocyclic ring. With isopropyl-Grignards no

---

* These diagrams account for the results and do not reflect the actual course of reaction.

TABLE 1. ACTION OF ISOPROPYLMAGNESIUM BROMIDE ON 1,3-BENZOXATHIOLES[a]

Starting material	Products	Fraction (%)		Material balance (%)
2,2-Dimethyl-1,3-benzoxathiole (Ia)	2-isopropylidenethiophenol (Va)	(e)	40	48
	2-isopropylthiophenol (IIIa)	(r)	60	
2,2-Diethyl-1,3-benzoxathiole (Ib)	2-[(α-ethylpropylidene)thio]phenol (Vb)	(e)	35	40
	2-[(α-ethylpropyl)thio]phenol (IIIb)	(r)	65	
2-Methyl-2-phenyl-1,3-benzoxathiole (Ic)	2-[(α-phenylethylidene)thio]phenol (Vc)	(e)	36	45
	2-[(α-phenylethyl)thio]phenol (IIIc)	(r)	64	
2-Ethyl-2-phenyl-1,3-benzoxathiole (Id)	2-[(α-phenylpropylidene)thio]phenol (Vd)	(e)	41	43
	2-[(α-phenylpropyl)thio]phenol (IIId)	(r)	59	
Spiro[1,3-benzoxathiole-2,1′-cyclohexane] (Ie)	2-cyclohexylidenethiophenol (Ve)	(e)	35	46
	2-cyclohexylthiophenol (IIIe)	(r)	65	
Spiro[1,3-benzoxathiole-2,1′-cycloheptane] (If)	2-cycloheptylidenethiophenol (Vf)	(e)	38	42
	2-cycloheptylthiophenol (IIIf)	(r)	62	

[a] All percentages were obtained by GLC analysis., e and r = elimination and reduction products respectively, material balance = percentage of reacted starting material.

TABLE 2. ACTION OF ALKYL- AND ARYL-MAGNESIUM BROMIDES ON 2,2-DIETHYL-1,3-BENZOXATHIOLE[a]

Grignard reagent	Subst. (%)	Elim. (%)	Redn. (%)	Grignard reagent products	Material balance (%)
C_6H_5MgBr	0	100	0	benzene	60
$C_6H_5CH_2MgBr$	0	100	0	toluene	55
C_2H_5MgBr	68	26	6	ethane ethylene	75
CH_3 C_6H_5 >$CHMgBr$	0	73	27	ethylbenzene styrene	44
$(C_6H_5CH_2)_2CHMgBr$	0	61	39	1,3-diphenylpropane 1,3-diphenylpropene	46
$(CH_3)_2CHMgBr$	0	35	65	propane propene	40
$(CH_3)_3CMgBr$	0	29	71	2-methylpropane 2-methylpropene	33

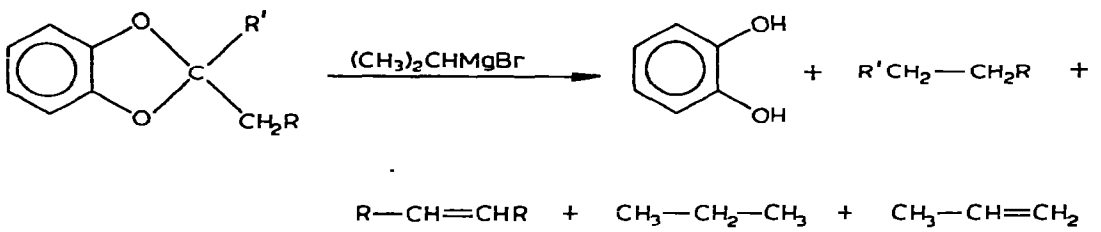
[a] The substitution product is, 2-[(α,α-diethylpropyl)thio]phenol (IV); elimination, 2-[(α-ethylpropylidene)-thio]phenol (Vb); reduction, 2-[(α-ethylpropyl)thio]phenol (IIIb). The alkenes arising from the Grignard reagent are in equimolar amount with respect to the reduction product; the gaseous alkenes were characterized as dibromo-derivatives; the gaseous alkanes were not characterized.

TABLE 3

ACTION OF ETHYLMAGNESIUM HALIDES ON 2,2-DIETHYL-1,3-BENZOXATHIOLE

Grignard reagent	Subst. (%)	Elim. (%)	Redn. (%)	Material balance (%)
C_2H_5MgCl	75	21	4	78
C_2H_5MgBr	68	26	6	75
C_2H_5MgI	55	37	7	71

substitution occurs (Table 4), but, under the experimental conditions employed, mixtures of alkanes and alkenes result, the former arising from a double hydride migration and the latter from reduction and elimination (eqn. 1).



(1)

No alkynes, formed by a double elimination process, were found.

Experimental

General

IR spectra were recorded on liquid films using a Perkin—Elmer 325 spectrophotometer; ^1H NMR spectra were recorded on a JEOL C-60 HL spectrometer using TMS as internal reference. GLC analyses were performed on a Carlo Erba Fractovap, model C, 1000 × 2 cm column, packed with 10% SE 30 on C 22 Celite (30-60 mesh). Boiling points are uncorrected as are melting points, the latter determined on a Tottoli apparatus. All compounds were pure by GLC.

TABLE 4

ACTION OF ISOPROPYLMAGNESIUM BROMIDE ON 1,3-BENZODIOXOLE DERIVATIVES

Starting material	Products	Fraction (%)	Material balance (%)
2,2-Dipropyl-1,3-benzodioxole (IIa)	3-heptene (VIIa)	34	25
	n-heptane (VIa)	66	
2-Methyl-2-phenyl-1,3-benzodioxole (IIb)	styrene (VIIb)	30	23
	ethylbenzene (VIb)	70	
2-Ethyl-2-phenyl-1,3-benzodioxole (IIc)	1-phenylpropene (VIIc)	40	30
	1-phenylpropane (VIc)	60	

1,3-Benzoxathioles (Ia-f) and 1,3-benzodioxoles (IIa-c)

These compounds were obtained as previously described [1,2,7-10] from 2-hydroxythiophenol or from 1,2-dihydroxybenzene and ketones in the presence of hydrogen chloride or phosphorus pentoxide respectively.

Analytical and spectral data for new benzoxathiole (Id) and benzodioxole (IIc) derivatives are reported:

2-Ethyl-2-phenyl-1,3-benzoxathiole (Id). Yield 74%, b.p. 159-160° 1 mm, n_D^{19} 1.6171. (Found: C, 74.13; H, 5.66; S, 13.12. $C_{15}H_{14}OS$ calcd.: C, 74.34; H, 5.82; S, 13.23%.) ^{1}H NMR (CCl_4): δ 6.90 (m, 9 H_{arom}), 2.25 (m, 2H, $C\underline{H}_2$—CH_3) and 0.90 ppm (t, 3 H, CH_2—$C\underline{H}_3$). IR: ν(CO) 1240 cm^{-1}.

2-Ethyl-2-phenyl-1,3-benzodioxole (IIc). Yield 55%, b.p. 128-130° 2 mm, m.p. 38-40°. (Found: C, 79.54; H, 6.20. $C_{15}H_{14}O_2$ calcd.: C, 79.62; H, 6.24%.) ^{1}H NMR (CCl_4): δ 7.00 (m, 9 H_{arom}), 2.10 (m, 2 H, $C\underline{H}_2$—CH_3) and 0.90 ppm (t, 3 H, CH_2—$C\underline{H}_3$). IR: ν(CO) 1235 cm^{-1}.

General method for the preparation of 2-alkylthiophenols (IIIa-f)

2-Hydroxythiophenol (0.0685 mol), alkyl halide (0.0685 mol), anhydrous potassium carbonate (0.73 mol) and dry acetone (20 ml) were refluxed together for 15 h. The mixture was then poured into water and the organic products extracted with diethyl ether. The 2-alkylthiophenol was extracted with 10% aqueous sodium hydroxide, liberated with 10% sulphuric acid and extracted with diethyl ether. The ethereal solution was dried with anhydrous sodium sulphate, the solvent evaporated and the residue distilled.

In this manner, starting from 2-bromopropane and 3-chloropentane, 1-chloro-1-phenylethane and 1-chloro-1-phenylpropane respectively, the following compounds were obtained:

2-Isopropylthiophenol (IIIa). Yield 90%, b.p. 87-89° 5 mm, n_D^{20} 1.5598; ([11]: b.p. 96-98° 9 mm, n_D^{25} 1.5559).

2-[(α-Ethylpropyl)thio]phenol (IIIb). Yield 88%, b.p. 138-140° 7 mm, n_D^{24} 1.5480. (Found: C, 67.21; H, 8.15; S, 16.17. $C_{11}H_{16}OS$ calcd.: C, 67.30; H, 8.21; S, 16.33%.) ^{1}H NMR (CCl_4): δ 6.95 (m, 4 H_{arom}), 6.70 (s, 1 H, OH D_2O exchanged), 2.60 (m, 1 H, $C\underline{H}$—CH_2—CH_3), 1.50 (m, 4 H, CH—$C\underline{H}_2$—CH_3) and 0.95 ppm (m, 6 H, CH—CH_2—$C\underline{H}_3$). IR: ν(OH) 3430, ν(CO) 1230 cm^{-1}.

2-[(α-Methylbenzyl)thio]phenol(IIIc). Yield 70%, b.p. 160-161° 5 mm Hg, n_D^{25} 1.6035; ([11]: b.p. 172-174° 10 mm, n_D^{25} 1.6048).

2-[(α-Ethylbenzyl)thio]phenol (IIId). Yield 68%, b.p. 138-140° 1 mm, n_D^{19} 1.6023. (Found: C, 73.50; H, 6.55; S, 13.05. $C_{15}H_{16}OS$ calcd.: C, 73.73; H, 6.60; S, 13.12%.) ^{1}H NMR (CCl_4): δ 6.80 (m, 9 H_{arom}), 6.35 (s, 1 H, OH D_2O exchanged), 3.60 (t, 1 H, $C\underline{H}$—CH_2—CH_3), 1.90 (m, 2 H, CH—$C\underline{H}_2$—CH_3) and 0.85 ppm (t, 3 H, CH—CH_2—$C\underline{H}_3$). IR: ν(OH) 3350, ν(CO) 1235 cm^{-1}.

2-Cyclohexylthiophenol (IIIe). Yield 75%, b.p. 148-150° 20 mm, n_D^{19} 1.5972. (Found: C, 68.10; H, 7.72; S, 15.28. $C_{12}H_{16}OS$ calcd.: C, 69.18; H, 7.74; S, 15.39%.) ^{1}H NMR (CCl_4): δ 6.95 (m, 4 H_{arom}), 6.25 (s, 1 H, OH D_2O exchanged), 2.65 (m, 1 H, $C\underline{H}$—CH_2—) and 1.40 ppm (m, 10 H, —CH_2—). IR: ν(OH) 3300, ν(CO) 1235 cm^{-1}.

2-Cycloheptylthiophenol (IIIf). Yield 70%, b.p. 164-165° 20 mm, n_D^{22} 1.5800. (Found: C, 70.11; H, 8.08; S, 14.34. $C_{13}H_{18}OS$ clacd.: C, 70.22; H, 8.16; S, 14.42%.) ^{1}H NMR (CCl_4): δ 6.95 (m, 4 H_{arom}), 6.30 (s, 1 H, OH D_2O

exchanged), 2.90 (m, 1 H, C<u>H</u>—CH_2—) and 1.60 ppm (m, 12 H, —CH_2—). IR: ν(OH) 3300, ν(CO) 1235 cm^{-1}.

Preparation of 2-[(α,α-diethylpropyl)thio]phenol (IV)

The method previously described was employed [8]. Finally the compound was chromatographed on acid-washed alumina using petroleum ether/benzene (10/1) as eluent. Yield 50%, b.p. 130-132° 2 mm, n_D^{22} 1.5772. (Found: C, 69.45; H, 8.90; S, 14.18. $C_{13}H_{20}OS$ calcd.: C, 69.59; H, 8.98; S, 14.29%.) ^{1}H NMR (CCl_4): δ 7.00 (m, 4 H_{arom}), 6.60 (s, 1 H, OH D_2O exchanged), 2.70 (m, 6 H, C<u>H</u>$_2$—CH_3) and 1.10 ppm (m, 9 H, CH_2—C<u>H</u>$_3$). IR: ν(OH) 3350, ν(CO) 1245 cm^{-1}.

2-(Alkylidenethio)phenols (Va-f)

These compounds were obtained, as previously described [2], from 2,2-disubstituted 1,3-benzoxathioles and phenylmagnesium bromide in toluene suspension. New analytical and spectral data of 2-(alkylidenethio)-phenol derivatives (Vd) and (Vf) are reported:

2-[(α-Phenylpropylidene)thio]phenol (Vd). Yield 58%, b.p. 160-162° 1 mm, n_D^{19} 1.6242. (Found: C, 74.16; H, 5.70; S, 13.11. $C_{15}H_{14}OS$ calcd.: C, 74.34; H, 5.82; S, 13.23%.) ^{1}H NMR (CCl_4): δ 7.10 (m, 9 H_{arom}), 6.40 (s, 1 H, OH D_2O exchanged), 5.50 (m, 1 H, C<u>H</u>—CH_3), and 1.50 ppm (d, 3 H, CH—C<u>H</u>$_3$). IR: ν(OH) 3435, ν(CO) 1230 cm^{-1}.

2-Cycloheptylidenethiophenol (Vf). Yield 43%, b.p. 140-141° 1 mm, n_D^{19} 1.5872. (Found: C, 70.79; H, 7.27; S, 14.43. $C_{13}H_{16}OS$ calcd.: C, 70.87; H, 7.32; S, 14.55%.) ^{1}H NMR ($CDCl_3$): δ 7.00 (m, 4 H_{arom}), 6.70 (s, 1 H, OH D_2O exchanged), 2.25 (m, 1 H, C<u>H</u>—CH_2—) and 1.40 ppm (m, 10 H, —CH_2—). IR: ν(OH) 3430, ν(CO) 1240 cm^{-1}.

Hydrocarbon derivatives (VIa-c), VIIa-c)

n-Heptane (VIa), ethylbenzene (VIb), 1-phenylpropane (VIc), 3-heptene (VIIa), styrene (VIIb) and 1-phenylpropene (VIIc) were obtained as commercial products (Schuchardt). 1,3-Diphenylpropane and 1,3-diphenylpropene were prepared by procedures described in the literature [12].

Halogen and dihalogen derivatives

Chloro-, bromo- and iodo-ethane, 2-bromopropane, 2-bromo-2-methylpropane, bromobenzene, benzyl bromide, 1,2-dibromoethane and 1,2-dibromopropane were obtained as commercial products (Schuchardt). 1-Bromo-1-phenylethane [13], 2-bromo-1,3-diphenylpropane [14] and 1,2-dibromo-2-methylpropane [15] were prepared by known literature methods.

Procedure in cleavage reactions

Grignard reagents (0.0645 mole) were prepared as previously described [1]. The solvent was then distilled in a nitrogen stream and replaced by the same amount of anhydrous toluene or benzene (70 ml); the derivatives examined (0.0258 mole) were added to the suspension, which was refluxed for 12 h under continuous stirring. The gases that developed in the reaction were bubbled into a cooled solution of bromine in carbon tetrachloride to yield

dibromo-derivatives. The reaction mixtures were then poured into iced water, acidified with 10% aqueous sulphuric acid and extracted with diethyl ether. After drying of the ethereal solution with anhydrous sodium sulphate, the mixtures were analyzed by GLC and compared with authentic samples. The mixed components, after GLC quantitative analysis, were chromatographed on acid-washed alumina using petroleum ether/benzene (10/1) as eluent. The dibromo-derivatives, after removal of carbon tetrachloride, were characterized by comparison with authentic samples.

The results are listed in Tables 1-4.

Acknowledgement

Financial support from the CNR (Rome) is gratefully acknowledged.

References

1 S. Cabiddu, A. Maccioni and M. Secci, Ann. Chim. (Rome), 61 (1971) 432, and references therein.
2 L. Bonsignore, S. Cabiddu and G. Cerioni, Synthesis, (1974) 732.
3 M. Chastrette and R. Amouroux, C.R. Acad. Sci., Ser. C, 270 (1970) 92.
4 M. Chastrette and R. Amouroux, Chem. Commun., (1970) 470.
5 G.E. Dunn and J. Warkentin, Can. J. Chem., 34 (1956) 75.
6 J.D. Morrison and G. Lambert, J. Org. Chem., 37 (1972) 1034.
7 S. Cabiddu, A. Maccioni and M. Secci, Gazz. Chim. Ital., 99 (1969) 771.
8 S. Cabiddu, G. Gelli and V. Solinas, Rend. Sem. Fac. Sci. Univ. Cagliari, 39 (1969) 473.
9 S. Cabiddu, G. Gelli and E. Marongiu, Ann. Chim. (Rome), 60 (1970) 580.
10 G. Sloff, Rec. Trav. Chim. Pays-Bas, 54 (1935) 995.
11 A.O. Pedersen, G. Schroll, J.O. Lawesson, W.A. Laurie and R.I. Reed, Tetrahedron, 26 (1970) 4449.
12 M. Tuot and M. Guyard, Bull. Soc. Chim. Fr., (1947) 1087.
13 E.D. Hughes, F. Juliusburger, A.D. Scott, B. Topley and J. Weiss, J. Chem. Soc., (1936) 1173.
14 W.H. Edgerton, R.L. Hull and J.R. Fisher, J. Amer. Pharm. Ass., Sci. Ed., 48 (1959) 320; Chem. Abstr., 53 (1959) 21732f.
15 K. Hess and W. Wustrow, Justus Liebigs Ann. Chem., 437 (1924) 265.