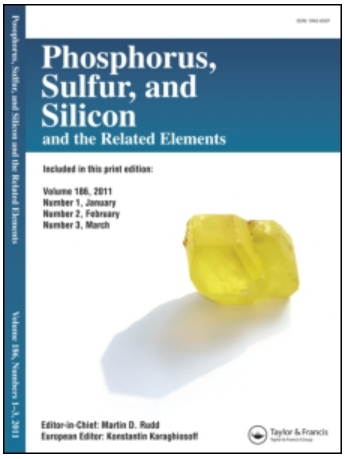

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THIONO AND DITHIOCARBOXYLIC ESTERS WITH ADDITIONAL FUNCTIONAL GROUPS

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Abstract Since powerful nucleophiles and reductants or electrophiles are required for the synthesis of thiono and dithio esters, severe difficulties arise if certain other functional groups are present in the precursor. Furthermore, strong interference may occur between a reactive substituent and the thio ester group once they are both present in a molecule. - It is, therefore, necessary - and possible - to choose thoroughly a selective method, if thiono or dithio esters with halogeno, nitro, or oxo substituents as well as bis-thiono and bis-dithio esters are to be prepared.

INTRODUCTION

Thiono and dithiocarboxylic esters with additional functional groups are of special interest to the organic chemist. They should exhibit both particular physical and spectroscopic properties resulting from electronic interactions between the functional groups and a chemical reactivity typical of bifunctional compounds, e. g. the capability of forming heterocycles by intra or intermolecular cyclization. They are also suitable substrates for studying the selectivity of reactions.

Since dithio and especially thiono carboxylic esters are compounds of marked chemical reactivity the preparation of derivatives with further reactive sub-

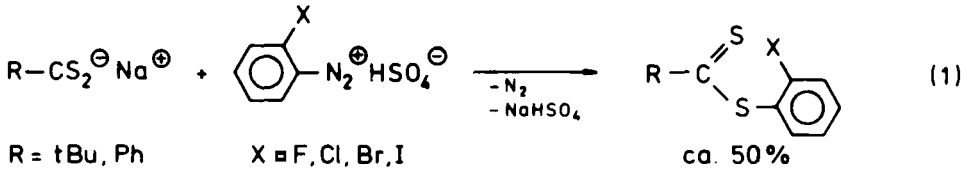
stituents is a challenge. Not only do they exhibit the electrophilic properties of esters - they are efficient thioacylating and alkylating reagents - but also the particular redox behaviour of thiocarbonyl compounds.[1,2] It is, therefore, to be expected that an intra or intermolecular reaction takes place once a thiono or dithio ester group and another reactive functional group including a carbon-carbon double bond are present in a molecule. - Furthermore, synthesizing a thiono or dithio ester requires reagents, which are strong reductants or oxidants or at least considerably strong nucleophiles, since the educts exhibit a higher (e. g. carbon disulfide) or lower (e. g. benzyl chloride) oxidation state than the products, or have to be converted by a substitution reaction (e. g. carboxylates or imidates). Thus, functional groups that are sensitive to redox or nucleophilic substitution reactions may be transformed or destroyed by the reagents used to prepare the thio ester. On the other hand, it is not easy to introduce a functional group into a thiono or dithio ester molecule by any reagent which can also attack the labile thiocarbonyl group.

In the following the preparation and some of the properties of selected halogeno-, nitro-, and α-oxo-substituted as well as bis- and tris- thiono- and dithiocarboxylates are dealt with.

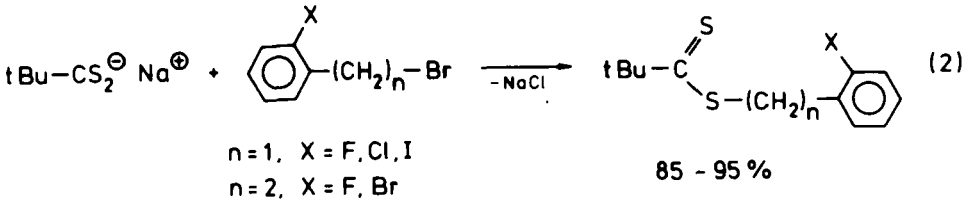
CHLORO AND BROMO SUBSTITUTED DITHIOCARBOXYLIC ESTERS

It is, of course, not too complicated to prepare dithioesters of bromo and chlorobenzoic acids, because normal methods such as the sulfurization of halogeno-

benzyl chlorides and subsequent alkylation of the intermediate halogenodithiobenzoate salts or the synthetic route via thioamides and thioimidates work very well.[2,3] - The same is true for S-halogenoaryl or S-halogenoaralkyl dithiocarboxylates, which can be obtained from dithiocarboxylate salts and arenediazonium hydrogensulfates or halogenoaralkyl bromides [Eq. (1) and (2)].[2,4]



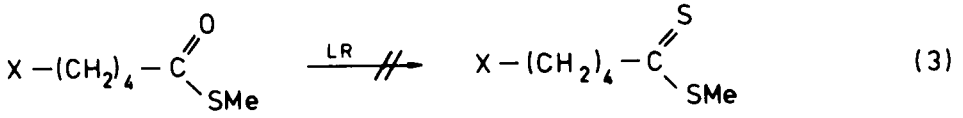
(1)



(2)

The problem arises if derivatives with halogeno-substituted alkyl groups are to be prepared. - It has been shown, that S-methyl 5-chloropentanethioate cannot be thionated with Lawesson's reagent (LR), since the

chloroester polymerizes during the thionation reaction.[5] Furthermore, it was impossible to obtain methyl 5-mesyloxy- or 5-tetrahydropyranyloxy-pentanedithioate - suitable precursors of the chloro- or bromoderivatives - from the corresponding thiolesters [Eq.(3)].[6]

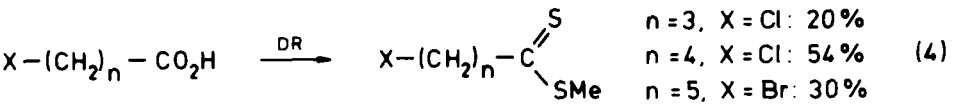


(3)

X = Cl, O-Mes, O-THP

However, Davy's reagent (DR)[7] is an effective tool for converting chloro- and bromoalkanoic acids as well as halogenoarylacetic acids into the corresponding methyl dithiocarboxylates [Eq.(4) and (5)]. [4,6,7] The yield of methyl 4-chlorobutanedithioate is only low because a considerable amount of the intermediate S-methyl 4-chlorobutanethioate is left, but 20% of γ-dithiobutyrolactone are formed on prolonged reaction times. We have also tried to prepare methyl 2-bromomethyldithiobenzoate using DR, but the only product was thionophthalide [Eq.(6)].

These latter two examples illustrate the above mentioned strong tendency of halogeno-substituted thioesters to form heterocycles, especially five-membered rings.



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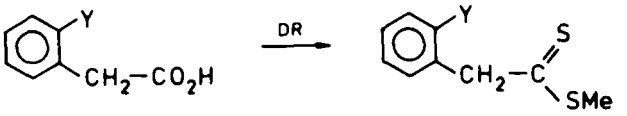
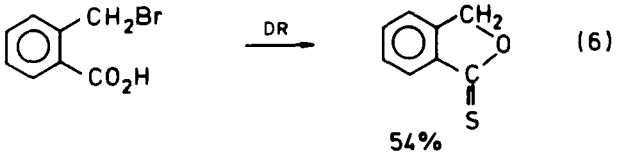


(5)

Y = F, Br

40%

DR ≡ MeS-P(=S)(S)-P(=S)(S)-SMe



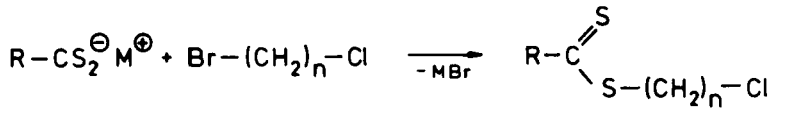
(6)

54%

Chloroalkyl dithiobenzoates have been claimed by American chemists in 1933 [8]; but the products have not been properly characterized and obviously did not exhibit the correct structure. In fact halogenoalkyl dithiocarboxylates can be prepared by alkylation of dithiocarboxylate salts [Eq.(7)] as has been shown in 1985 independently by the French group of Levesque [9] and ourselves.[10, 11] The dithioesters are relatively stable distillable orange (R=tBu) or red (R=Ph) liquids. Bromoalkyl dithiocarboxylates are also accessible but undergo decomposition much easier.

Interestingly ortho-bromobenzyl chloride can be lithiated selectively at the aromatic ring.[12] The resulting aryllithium compound reacts with carbon disulfide and iodomethane to form methyl 2-chloromethyl-

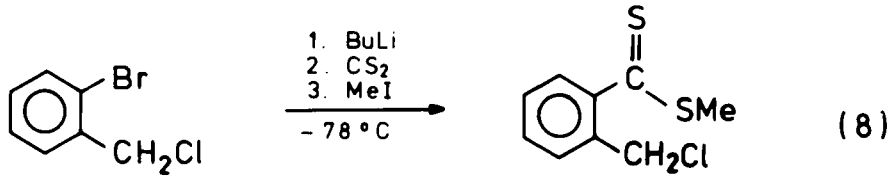
dithiobenzoate with a yield of 20 % (not yet optimized) [Eq.(8)].



(7)

M = Na, $PhCH_2NMe_3$

R =	tBu	tBu	tBu	tBu	Ph	Ph	Ph
n =	2	3	4	5	2	3	4
yield [%] =	70	80	66	60	70	80	75

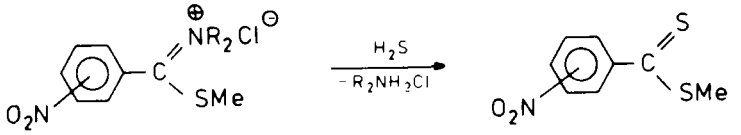


(8)

Obviously quite a number of halogenosubstituted dithio but only few thionocarboxylate esters are now available if the method of preparation is carefully chosen.

NITRO THIONO AND DITHIOCARBOXYLIC ESTERS

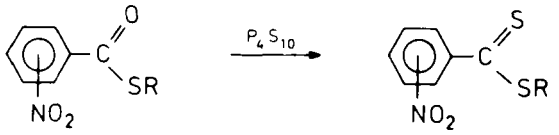
Alkyl nitroarenecarbodithioates are known compounds. They can be prepared by current methods [2] but the yields are only moderate in many cases. The nitro group is not reduced by hydrogen sulfide during the sulfhydrolysis of thioimidates according to Eq. (9).[13,14] On the other hand, elemental sulfur in the



(9)

3-NO_2 39 %
4-NO_2 46 %

presence of triethylamin is not a suitable reagent for the conversion of 3-nitrobenzyl chloride to 3-nitrobenzenecarbodithioate, the yield being only 5%.[14] Interestingly, even Lawesson's reagent fails to react with S-methyl 2-nitrobenzenecarbothioate or the three isomeric S-phenyl nitrobenzenecarbothioates, but phosphorus pentasulfide proves good in these cases [Eq.(10)].[14,15] The task of thionation is still more

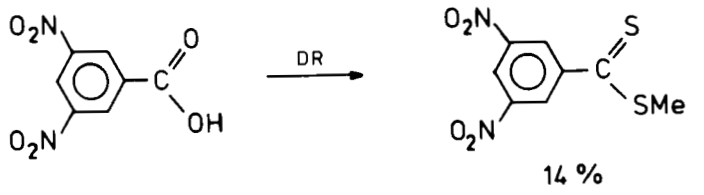


2-NO_2, R = Me 36 %
2-NO_2, R = Ph 50 %
3-NO_2, R = Ph 97 %
4-NO_2, R = Ph 89 %

(10)

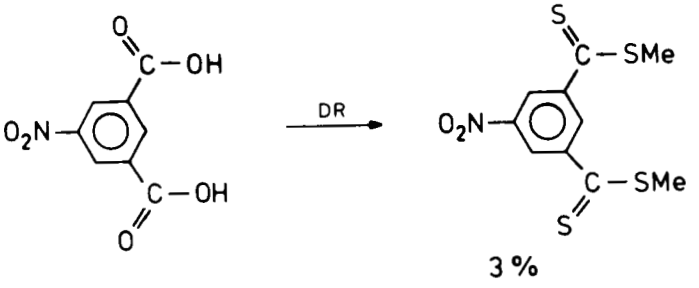
difficult if dinitrocompounds or nitroisophthalic acid are used as starting material or if O-alkyl nitrobenzenecarbothioates are to be prepared from esters. The yields are only about 10% even if the most powerful

tool, Davy's reagent, is used [Eq.(11) and (12)]. The latter thionocarboxylate esters are, however, obtained with satisfactory yields from imidates according to Eq.(13).



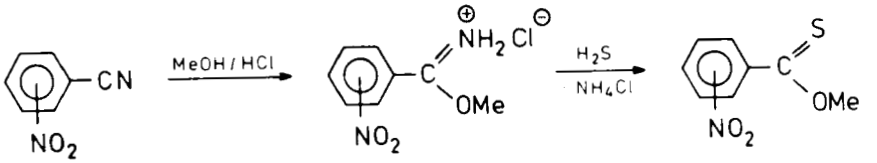
(11)

14 %



(12)

3 %

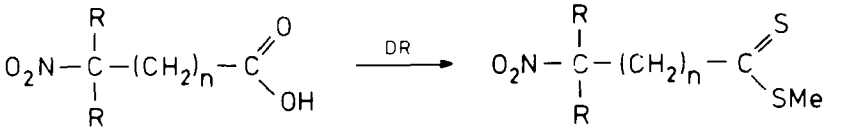


(13)

2-NO_2: 86 %
3-NO_2: 68 %
4-NO_2: 50 %

Methyl nitroalkanedithioates represent a new class of compounds which we have recently prepared and begun to study. Without exception, Davy's reagent was used to thionate the corresponding nitroalkanoic acids, which

were prepared from suitable precursors [Eq.(14)]. The yields - not yet optimized - are moderate but they are acceptable with regard to the simple procedure. We have



(14)

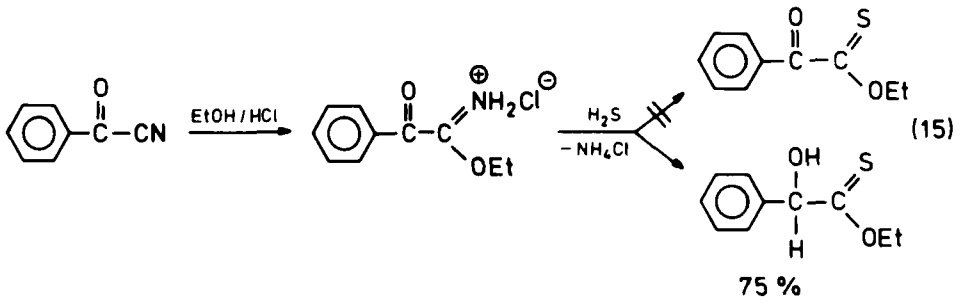
n = 3, R = H: 8 %
n = 4, R = H: 30 %
n = 5, R = H: 50 %
n = 2, R = Me: 17 %

not tried to prepare the nitroalkanedithioates by nucleophilic substitution of the corresponding halogenoalkanedithioates because thiocarbonyl compounds are known to react with nitrous acid.[16]

2-OXO-DITHIO- AND 2-OXO-THIONOCARBOXYLIC ESTERS

Whereas 3-oxo-thiono- and 3-oxodithiocarboxylic esters are well known compounds which have been shown to exist mainly as hydrogen-bridged enol tautomers, [17] the 2-oxo derivatives have only recently been studied to some extent. Obviously standard methods of preparation cannot be applied because the presence of a vicinal carbonyl group prevents a Grignard reaction and even the use of hydrogen sulfide during the course of the reaction. For instance, an early attempt to obtain O-methyl 2-oxo-2-(phenyl)thioacetate via the corresponding imidate resulted in the exclusive formation of its reduc-

tion product, O-methyl 2-hydroxy-2-(phenyl)thioacetate [Eq.(15)].[18]



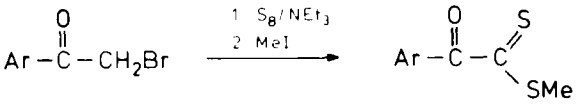
(15)

In 1978 R. Mayer and coworkers [19] described the preparation of 2-oxo-dithiocarboxylic esters from bromoketones and elemental sulfur in the presence of base [Eq.(16)]. This method works quite well and can be widely applied. [20,21] The bromoketones are, however, lachrymatory and not easily available in certain cases. We have therefore developed an alternative route which starts from acid chlorides [Eq.(17)]. [21,22] Formally the chlorine atom of the starting compounds is substituted by an alkylthio-thiocarbonyl group, the thiocarbonyl carbon atom of which stems from the diazomethane used for the preparation of the diazoketone.By chance we discovered that addition of calcium chloride to the usual sulfurization mixture, elemental sulfur plus triethylamine in dimethylformamide, substantially increases the yields (cf. Table 1). In fact, the alipatic 1-diazo-3,3-dimethyl-2-butanone or ethyl diazoacetate did only react in the presence of calcium chloride.

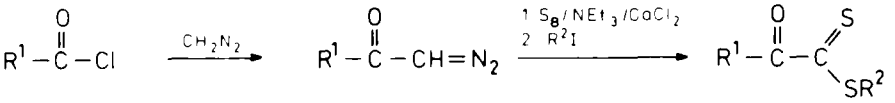
TABLE I 2-Oxo-dithiocarboxylic esters R-CO-CS-SMe from diazomethyl ketones R-CO-CH=N_2 [Eq.(17)]

R	Yields (%) without $CaCl_2$	with $CaCl_2$	a)
t-Bu	0	64	84
EtO-CO	0	41	
C_6H_5	63		66
p-MeO-C_6H_4	14	77	43
p-O_2N-C_6H_4	42		
o-Me-C_6H_4		50	
o-Br-C_6H_4		35	
o-O_2N-C_6H_4	24		

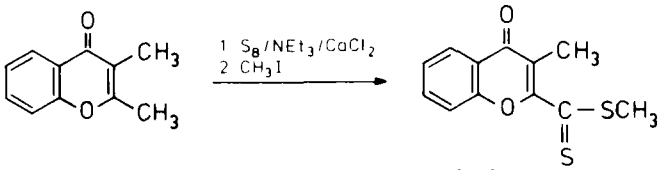
a) Yields of dithiocarboxylic esters as prepared by the bromoketone route [Eq.(16)].



(16)



(17)

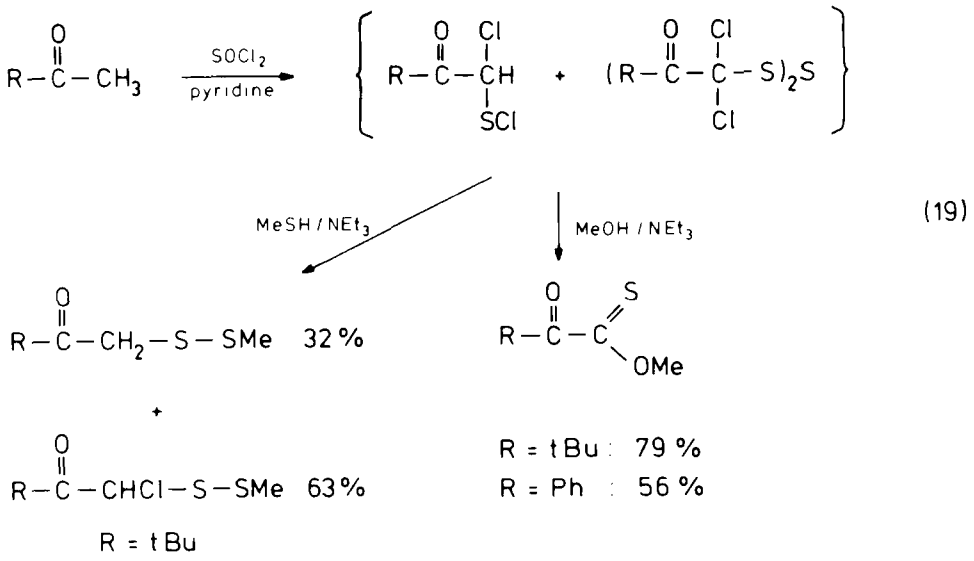


92 %

(18)

We suppose that cyclooctasulfur or some intermediate formed from S_8 and triethylamine are activated by the calcium chloride in a way we do not yet understand. The activating effect is, however, very significant since even unsubstituted methyl groups are attacked by the reagent [Eq.(18]. Remarkably only the vinylogous methyl group of 2,3-dimethylchromone is reactive enough. The structure of the product, methyl 3-methylchromone-2-carbodithioate, was confirmed by an X-ray analysis.

As mentioned above, 2-oxo-thionocarboxylic esters are particularly difficult to obtain. We have found two methods of preparation. Firstly, transesterification of the corresponding dithioates is possible, but the yields are low and we have applied this method only in the bis- and tris-2-oxo-thionocarboxylate series [cf. Eq.(27)].[21,23] More satisfactory results are obtained if methyl ketones are reacted with thionyl chloride and the resulting complex mixtures of sulfenyl chlorides and trisulfides - which do not, however, contain the corresponding 2-oxo-thiocarbonyl chlorides [20] - treated with alcohols [Eq.(19)].[20] Methanethiol does not react in the same way as methanol. Instead of 2-oxo-dithiocarboxylic esters disulfides are formed by reduction of the chlorinated intermediates [Eq.(19)].



(19)

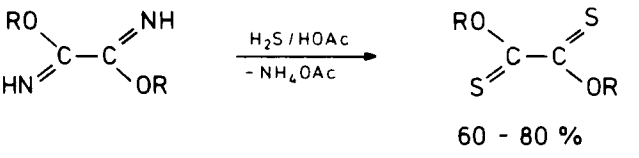
BIS AND TRIS THIONO AND DITHIOCARCOXYLIC ESTERS

In principle the thiono and dithio esters of di- and tricarboxylic acids can be prepared by standard methods. Fully characterized authentic compounds have however not been obtained until the seventies. A brief survey of the literature about this topic seems worthwhile and will be given in the following.

Synthetic problems expecially arise if the two thiocarboxylate groups are close enough to each other as to form heterocycles during their formation; e.g. in the case of phthalic or alkanedioic acids with two to five carbon atoms.

Dialkyl bis-thionooxalates can be obtained from imidates if the sulfhydrolysis is performed in the presence of acetic acid [Eq.(20)].[24] Dimethyl tetra-

thiooxalate is formed on photolysis of 4,5-bis(methylthio)-1,3-dithiole-2-one [25] or by methylation of tetraethylammonium tetrathiooxalate [26] [Eq.(21)].



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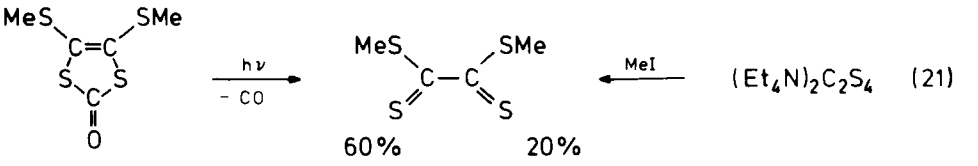
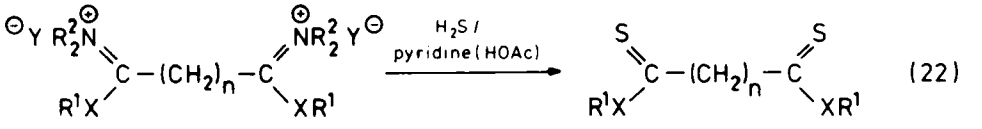


(21)

K Hartke and coworkers, 1976, 1980
P. Jeroschewski, P Hansen, 1982

The sulfhydrolysis route is also successful in case of the homologous dicarboxylic acids [Eq.(22)] [27-29] including the unsaturated fumaric acid. [30] The preparation and further reaction of the appropriate imidates and especially imidothioates is, however, not always straightforeward. As Hartke and coworkers [28-30] have shown, special substituents R^2 at the nitrogen atoms and carefully chosen reaction conditions are required to obtain good yields and pure products in each case. Dialkyl tetrathiomalonates,

which are the least stable compounds of the series (storable only at -77°C for a few days), can be also prepared by transesterification of the bis-thiono-malonates or alkylation of potassium ethyl tetrathio-malonate.[29]



(22)

R^1 = Me, Et

R_2^2 = H_2, Me_2, $(CH_2)_5$

X = O, S; n = 1-5 : 65-95 %

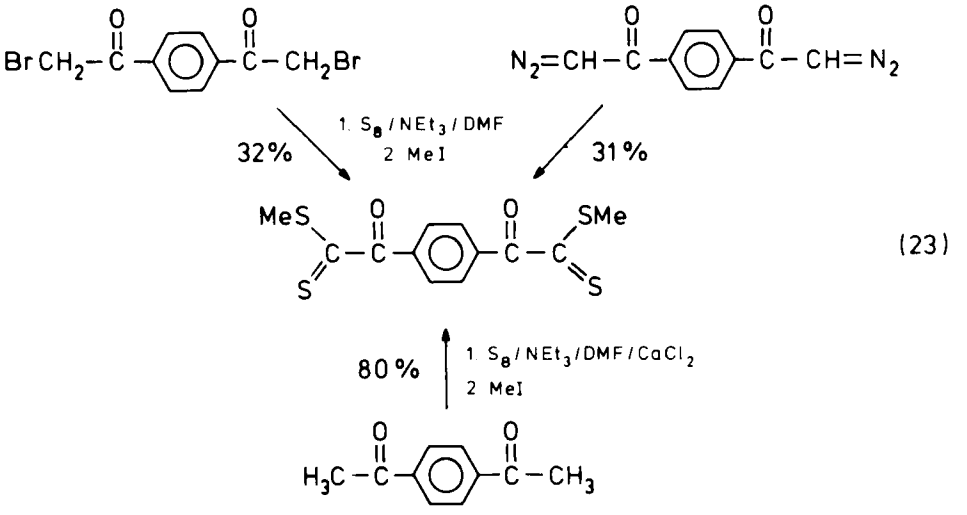
R. Mayer, G. Barnikow and coworkers, 1967

K. Hartke and coworkers, 1977, 1980.

Thionocarboxylic esters of isophthalic and terephthalic acid are available via the imidates or by thionation of the esters with phosphorus pentasulfide - though the yields are only moderate and purification of the products may be difficult.[31] Recently we have even obtained 13% of O,O'-diethyl dithiophthalate using Lawesson's reagent. The corresponding dithioates are prepared analogously[31] or by alkylation of tetrathio-terephthalate salts,[32] whereas the dithiocarboxylic esters of phthalic acid are unknown.

Two or three 2-oxo-ethanedithioate groups can be introduced as substituents at a benzene ring by above

mentioned methods [Eq.(23)-(25)].[21-23] Again calcium chloride proves to be a valuable additive in the sulfurization mixture. This is especially evident for the reaction of p-diacetylbenzene, cf. Eq. (23).



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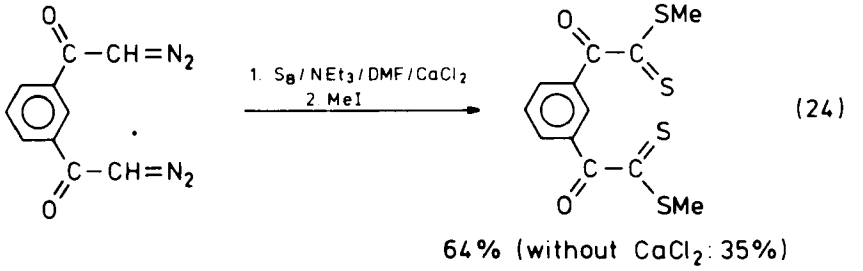

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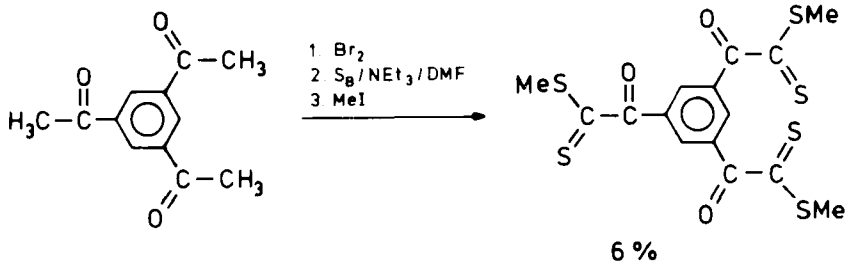
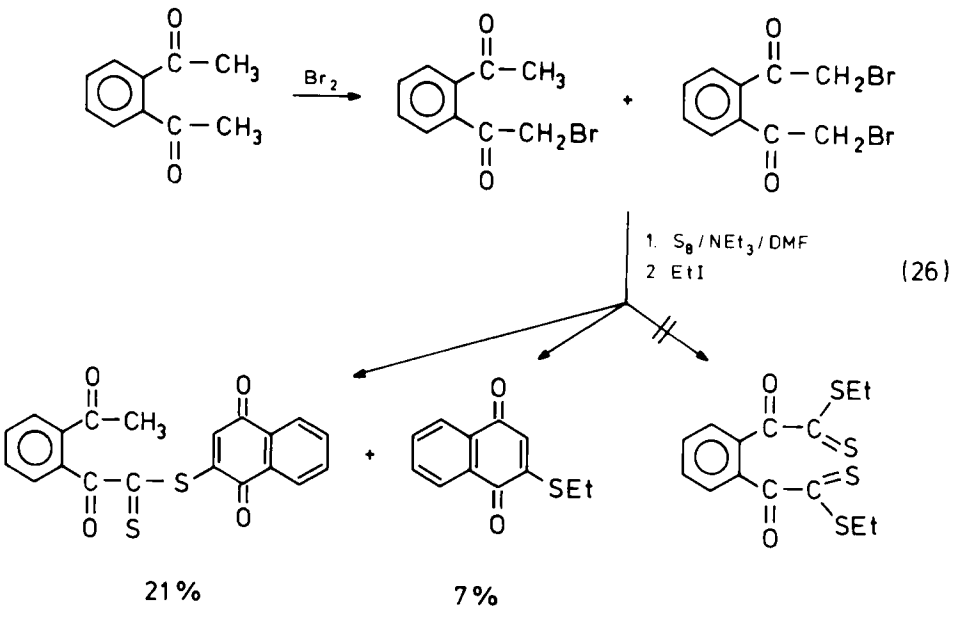


(25)

Starting with o-diacetylbenzene we were not able to prepare dialkyl 1,2-benzene-bis(dithioglyoxalates). The mixture of mono- and dibromoketone was instead transformed into 1,4-naphthoquinone derivatives [Eq.(26)].[21]

No arene-bis-2-oxo-thionocarboxylate esters can be prepared by an analogous route. It is, however, possible to isolate O,O'-diethyl 1,4-benzene-di-(2-oxo-ethanethioate) with the extremely low yield of 1% on reaction of the dithiocarboxylate ester with sodium ethoxide at -77 °C [Eq.(27)]. It seems that the tetrahedral intermediate is formed nearly quantitatively since the red colour of the educt disappears completely. But elimination of methanethiolate is restricted and 80% of the starting material is recovered on treatment with silicagel.[21]



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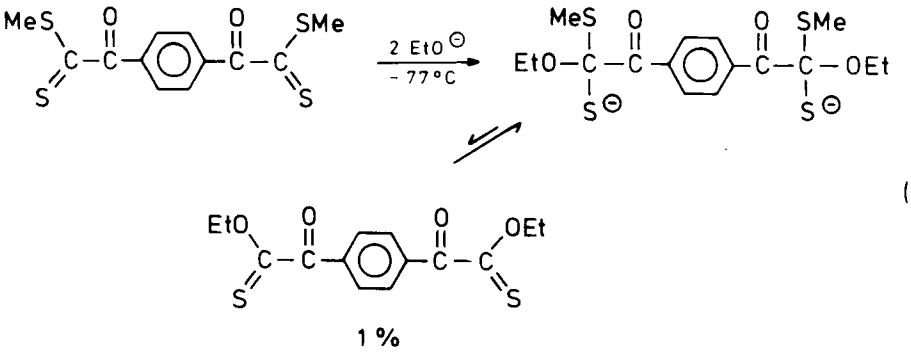


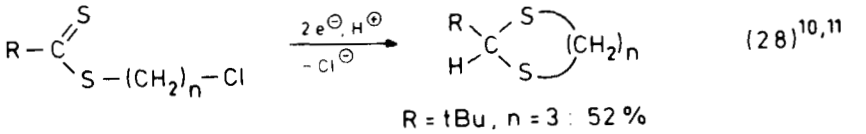
(27)

SELECTED PROPERTIES

As pointed out in the introduction thiono and dithiocarboxylate esters may exhibit particular properties if additional functional groups are present. Three selected examples will be briefly delineated in this concluding section.

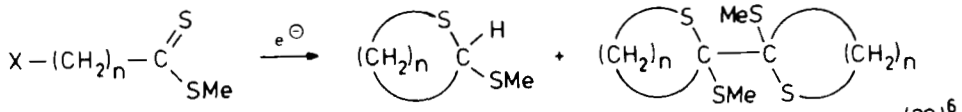
Electroreduction of halogeno derivatives [33]

We have studied the preparative electroreduction of halogeno-substituted dithiocarboxylate esters. As expected, in many cases cyclization by intramolecular nucleophilic substitution occurs after electron transfer at the cathode. Usually cyclic thioacetals are formed [Eq.(28)-(30)]. The yields are acceptable in



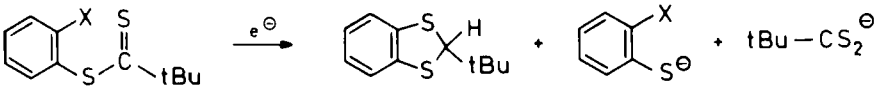
R = tBu, n = 3 : 52 %

(28)[10,11]



25 - 45 % 30 - 60 %

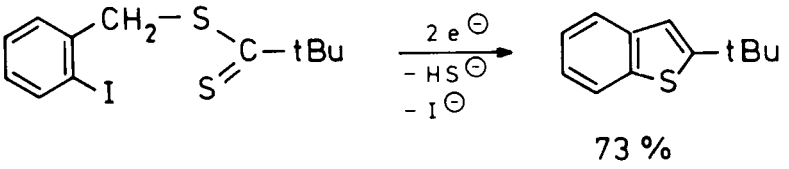
(29)[6]



X = Br	26 %	27 %	38 %
X = I	30 %	15 %	15 %

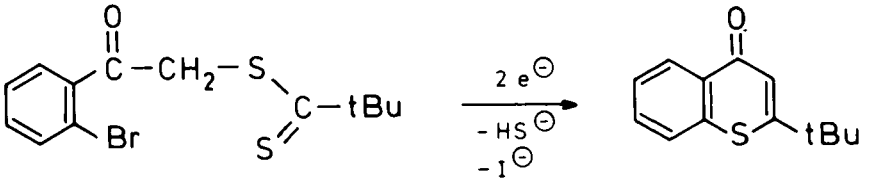
(30)[4]

favourable cases. Rearrangement and C,C-coupling results in the formation of thionaphthene or thiochromone derivatives according to Eq. (31) and (32).



73 %

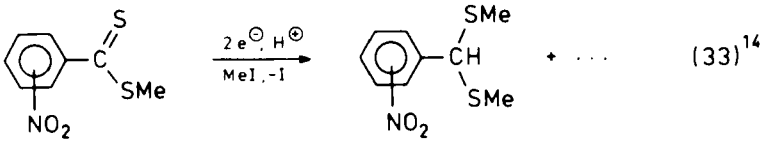
(31)[4]



(32)

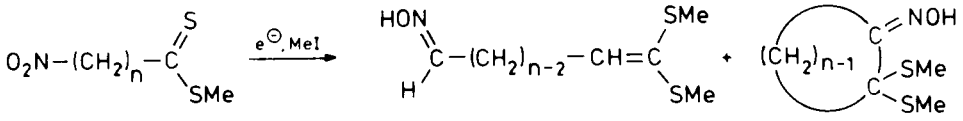
Electroreduction of nitro derivatives [34]

Nitrobenzenecarbodithioates are preferentially electroreduced at the dithiocarboxylate group [Eq.(33)]. The selectivity is not very pronounced since amino and



(33)[14]

azoxycompounds are also formed. But it is evident, though, that the electron attracting effect of an alkylthio-thiocarbonyl group can well compete with that of a nitro group. On the other hand, methyl ω-nitroalkanedithioates are reduced at the nitro group, and open-chained as well as cyclic oximes are formed [Eq.(34)]. The formation of ketene-S,S-acetals is due to the marked C,H-acidity of dithiocarboxylate esters. During cathodic reduction bases are generated, which abstract a proton from the α-position, and the enethiolate anion is methylated at the sulfur atom.



(34)

Radical oligoanions of bis- and tris-2-oxothiono- and -dithiocarboxylic esters [21,23,35]

Thioesters of phenylglyoxylic acid form exceptionally stable radical anions on one-electron reduction. Spin delocalization causes the expected coupling of the unpaired spin with aryl and side-chain protons. This is also true for the di- and trifunctional compounds. However, their radical monoanions are only observed if the reduction potential is very low. Several electrons are transferred if the potential is chosen more negative. Interestingly, the resulting oligoanions are also persistent species and can be readily studied by e.s.r. spectroscopy if the molecules exhibit an odd-numbered negative charge. The apparent symmetry of the molecule is no longer reflected in the spin density distribution. Instead, in case of the radical trianion of O,O'-diethyl 1,4-benzenedi-(2-oxoethanethioate) one functional group carries one unpaired electron and a negative charge and the other one two electrons (negative charges) with spin compensation (cf. Figure 1). The latter one is twisted out of the π-orbital plane of the benzene ring and, therefore, represents an "inert" substituent which disturbs the symmetry of the molecule. This is illustrated in Figure 2.

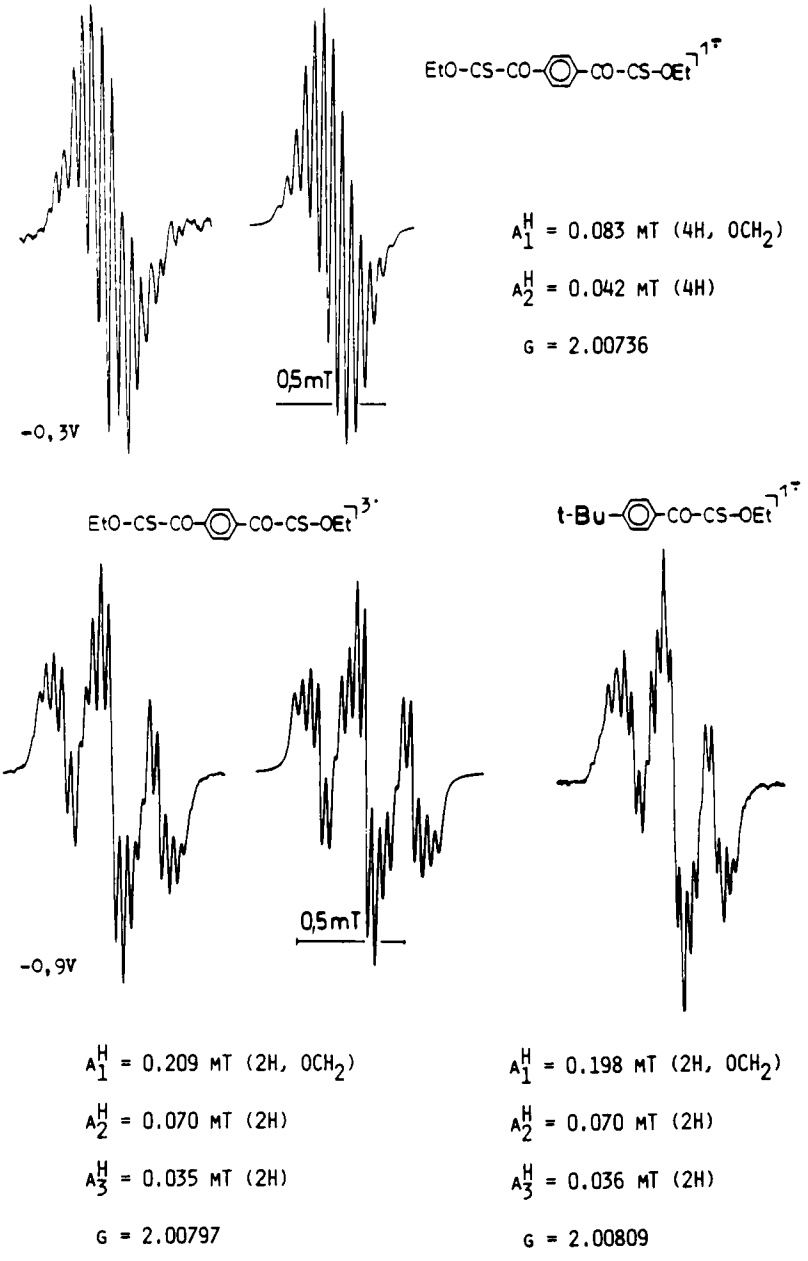


FIGURE 1 Experimental and simulated e.s.r. spectra of the radical anion and trianion of O,O'-diethyl 1,4-benzenedi-(2-oxoethanethioate).

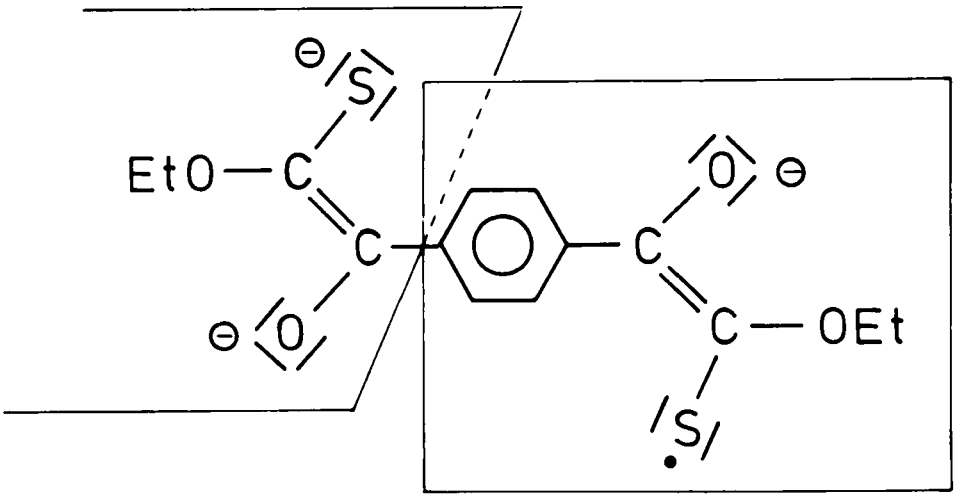


FIGURE 2 Twisted conformation of the O,O'-diethyl 1,4-benzenedi-(2-oxoethanethioate) radical trianion.

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