Unusual reaction of Grignard reagents with bis(trifluoromethyl)disulfide

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Abstract

Simultaneous scission of the C–S and S–S bonds of bis(trifluoromethyl)disulfide occurs on treatment with Grignard reagents at −78 °C and gives rise to unsymmetrical disulfides and sulfides as well as alkyl sulfides. Under similar experimental conditions, alkyl disulfides are recovered unreacted. Probable mechanisms of the cleavage reactions are presented.

Introduction

Disulfides occur widely in nature and play a prominent part in physiological processes. This has created considerable interest in the chemistry of the sulfur–sulfur bond, which regulates important biochemical reactions. The scission of the S−S bond and its chemical consequences have been discussed in detail [1]. The reactions at the sulfur atom have been described as a cascade of reactions with sulfur enlarging its electronic octet rather than a one-step displacement process [2].

Disulfides react with Grignard reagents to give sulfides [3, 4]. Primary alkylmagnesium halides have been observed to react with di-t-butyl disulfide, while t-butylmagnesium chloride under similar experimental conditions did not react [5]. Addition of phenylmagnesium bromide to 2,2-thienyl- and di-*p*-tolyl disulfides yielded phenyl-3-thienyl- and phenyl-*p*-tolyl sulfides [6].

Photolysis of a mixture of two different symmetrical disulfides has been reported to give a single mixed disulfide [7]. Also, the formation of an unsymmetrical disulfide via thiyl radical displacement has been mentioned [8]. Irradiation of t-butylmagnesium chloride and di-t-butyl disulfide produced t-butyl radicals, the ESR spectrum of which has furnished the most direct evidence of an S_H2 reaction of a Grignard reagent [5]. Polar, free-radical and single-electron-transfer (SET) mechanisms have been advanced to explain and rationalize the products formed during the reaction with Grignard reagents

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[9]. The radical nature of the Grignard reagent itself has been established using CIDNP [10]. Ashby and coworkers have documented evidence for the participation of the SET mechanism in the Grignard reaction in a series of elegant papers [9f–g]. Thus, it appears that the reaction of Grignard reagents with disulfides is much more complex than possibly suspected.

We have examined the reaction of bis(trifluoromethyl)disulfide (**1**) with Grignard reagents and have observed a simultaneous scission of the C–S and S–S bonds leading to unsymmetrical disulfides and sulfides as well as alkyl disulfides and sulfides. The formation and distribution of the various products, the probable mechanism of the simultaneous cleavage of the C–S and S–S bonds and the mass spectral fragmentation patterns are discussed in this communication.

Experimental

Warning! Because of the high toxicity associated with bis(trifluoromethyl)disulfide by inhalation, efficient hoods and extreme care should be used in working with this compound. Mass spectra were obtained on a Finnigan model 5100 GC–MS instrument equipped with a silica 25 m × 0.3 mm (i.d.) SE-54 capillary column (J & W Scientific, Rancho Cordova, CA). Routine GC separations were carried out on a Hewlett-Packard 5890A gas chromatograph equipped with a 30 × 0.53 mm (i.d.) DB-5 column (J & W Scientific, Folsom, CA). Bis(trifluoromethyl)disulfide was procured from PCR, Inc., Gainesville, FL. The solvents used were dry and freshly distilled. The reactions were carried out in a flame dried, argon gas-purged 10 or 25 ml three-necked flask equipped with a magnetic stirrer, a gas inlet, a pressure equalizing dropping funnel and a reflux condenser carrying a Dry Ice/acetone-cooled trap. The temperature of the coolant passing through the condenser was maintained at −20 °C. All reactions were carried out by adding the cold Grignard reagent (0.01 mol) to the disulfide (0.01 mol) cooled to −78 °C. The reactions were terminated by the addition of moist ether and a saturated solution of ammonium chloride, followed by extraction with ether and drying the solution over sodium sulfate and processing in the usual manner.

Results and discussion

Table 1 lists the Grignard reagents used in this investigation and the various products that have been identified by their GC–MS data. The reaction of stoichiometric amounts (usually 0.01 mol) of CF_3SSCF_3 (**1**) with phenyl- and isopropyl-magnesium halides at −78 °C gave CSF_2, R_fSSR, R_fSR and RSR [$R_f = CF_3$ and $R = C_6H_5$, $CH(CH_3)_2$]. Biphenyl (**2**) and isopropylsulfenyl chloride (**3**) were also detected. While dimerization of the phenyl radical

TABLE 1

Compounds characterized from the reaction of bis(trifluoromethyl)disulfide with Grignard reagents

$CF_3SSCF_3 + RMgX \rightarrow$ Products

R	Products (% yield)				
	CSF_2	CF_3SSR	CF_3SR	RSR	Dimerized product
C_6H_5	4.8	4.0	88.5	–	2.7
n-C_4H_9[a]	–	–	71.4	3.3	7.8
$CH(CH_3)_2$[b]	2.2	10.7	40.4	12.9	–
C_2H_5[c]	1.0	–	15.9	–	34.6

[a]Three mixed disulfides, $CF_3SSC_5H_{11}$ (4.8%), $CF_3SSC_5H_9$ (7.9%) and n-$C_4H_9SSC_4H_9$-n (7.9%) were identified as products.
[b]Two additional compounds, $CF_3SC_3H_7$(-n) (2.3%) and $(CH_3)_2CHSCl$ (17.4%) were detected in this reaction.
[c]Two other compounds, t-$C_4H_9SC_4H_9$-t and C_4H_9Br, were also characterized (see Discussion).

TABLE 2

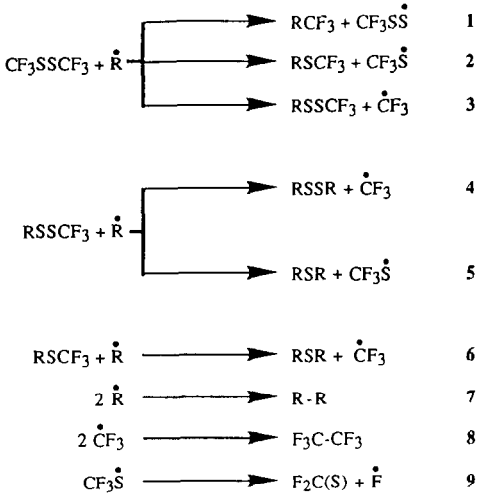
Temperature dependence of the Grignard reaction with disulfide

$C_2H_5SSC_2H_5$ +	RMgX ⟶	$C_2H_5SSC_2H_5$ +	C_2H_5SR +	R–R +	R–R(=H_2)
	R = Bu^t $\xrightarrow{-78\ °C}$	99.6[a]	0.4	0	0
	R = Bu^t $\xrightarrow{25\ °C}$	41.9	31.1	0.9	0.7[b]
	R = C_6H_5 $\xrightarrow{55–60\ °C}$	8.6	82.9	3.1	–

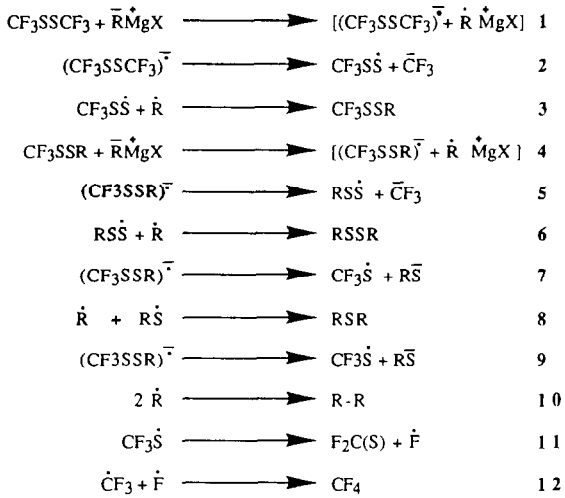
[a]Percentage yield throughout.
[b]Octene was identified as a byproduct of this reaction.

led to **2**, **3** must have arisen from a halogen-exchange reaction. There are precedents for halogen exchanges [11]. Using n-C_4H_9MgCl (0.01 mol), **1** gave R_fSR (71.4%), RSR (3.3%), C_8H_{18} (7.8%) and mixed pentyl and pentenyl disulfides ($R_f = CF_3$ and R = n = C_4H_9). The source of the pentyl moiety is attributable to the presence of pentylmagnesium halide as an impurity in the Grignard reagent. The pentenyl compound must have been formed from $R_fSSC_5H_{11}$ via the abstraction of hydrogen by the free radicals. In the reaction of C_2H_5MgBr with **1**, CSF_2, R_fSR, $R_fSC_4H_9$-t, t-C_4H_9Br and C_8H_{18} were characterized as products. The origin of the C_4H_9 moiety in these products must be the solvent, t-butyl methyl ether, used to prepare the Grignard reagent. The reaction of the t-C_4H_9· with Br· derived from C_2H_5MgBr results in t-C_4H_9Br. Again, there are precedents for the participation of the solvent in free-radical-catalyzed reactions [12]. Thiocarbonyl fluoride is definitely formed from either the trifluoromethylthiyl radical [13a] or from the trifluoromethylthiol derived from it [13b].

Based on the results presented in Table 1, a number of observations may be made. The formation and characterization of the mixed disulfides



Scheme 1.



Scheme 2.

(R_fSSR) clearly suggests scission of the C—S bond of **1** by Grignard reagents at −78 °C. Under similar low-temperature conditions, we observed that alkyl and aryl disulfides failed to react with Grignard reagents. Diethyl disulfide was quantitatively recovered from its reaction with ethylmagnesium bromide at −78 °C. The reaction with alkyl disulfides appears to be temperature-dependent and at elevated temperatures only mixed disulfides and dimerized products were formed from alkyl disulfides. Table 2 gives additional details of the temperature dependence of this reaction. The formation of dimerized products is a definite proof of the participation of free radicals in the Grignard reaction. In view of the above and the reported failure of methyl radicals

TABLE 3

Mass-spectral fragmentation of the products formed from the simultaneous scission of the C–S and S–S bonds

CSF_2:	$M^+ = 82$ (100%); 63 (M – F); 50 (CF_2) and 44 (CS).
$CF_3SC_2H_5$:	$M^+ = 130$ (100%); 115 (M – CH_3); 111 (M – C_2H_5); 101 (SCF_3); 83 (CF_2SH); 69 (CF_3); 61 (SC_2H_5); 58 (SC_2H_2); and 50 (CF_2).
t-$C_4H_9SC_4H_9$-t[a]:	$M^+ = 146$; 117 (M – C_2H_9); 103 (M – C_3H_7); 90 (M – C_4H_8); 61 (CH_3SCH_2); 56 (100%; C_4H_8); 47 (CH_2SH); 45 (CSH); 41 (C_2H_5); and 39 (C_3H_3).
t-C_4H_9Br[a]:	$M^+ = 137$ (not seen); 123 (M – ^{81}Br); 121 (M – ^{79}Br); 57 (100%; C_4H_9); 55 (C_4H_7); 41 (C_3H_5); and 39 (C_3H_3).
n-$C_4H_9SCF_3$:	$M^+ = 158$; 139 (M – F); 89 (M – CF_3); 69 (CF_3); 57 (100%, C_4H_9); 55 (C_4H_7); 47 (CH_2SH); and 41 (C_3H_5).
n-$C_4H_9SC_5H_{11}$:	$M^+ = 160$; 103 (M-C_4H_9), 71 (C_5H_{11}); 69 (C_5H_9); 57 (C_4H_{11}); 55 (C_4H_7); 47 (CH_2SH); 43 (C_3H_7); 41 (100%, C_3H_5); and 39 (C_3H_3).
$CF_3SSC_5H_{11}$:	$M^+ = 204$; 171 (M – CF_3S); 133 (M – C_5H_{11}); and 101 (CF_3S).
$CF_3SC_3H_7$-i:	$M^+ = 144$ (100%); 129 (M – CH_3); 125 (M – F); 115 (F_3CSCH_2); 101 (SCF_3); 82 (SCF_2); 75 (C_3H_7S); 69 (CF_3); 63 (SCF); 59 ($CSCH_3$); 50 (CF_2); 47 ($HSCH_2$); and 45 (CSH).
$CF_3SC_3H_7$-n:	$M^+ = 144$ (100%); 115 (CF_3SCH_2) or (M – C_2H_5); 101 (SCF_3); 82 (CSF_2); 69 (CF_3); 63 (CSF); and 45 (CSH).
$CF_3SSC_3H_7$-i:	$M^+ = 176$ (100%); 157 (M – F); 133 (M – C_3H_7); 114 (157-C_3H_7); 101 (SCF_3); 82 (CSF_2); 69 (CF_3); 64 (S–S); 59 ($CSCH_3$); and 45 (CSH).
i-$C_3H_7SC_3H_7$-i:	$M^+ = 118$; 103 (M – CH_3); 76 [$HSC(CH_3)_2$]; 61 [100%, (CH_2SCH_3)]; 59 ($SCCH_3$); and 47 ($HSCH_2$).
$C_5H_9SC_3H_7$-i[b]:	$M^+ = 144$; 129 (M – CH_3); 101 (M-C_3H_7); 87 (C_4H_6S); 69 (100%, C_5H_9); 61 (SC_2H_5); 59 (SC_2H_3); 47 (SCH_3); and 45 (CSH).
$CF_3SC_6H_5$:	$M^+ = 178$; 159 (M – F); 109 (100%, M – CF_3); 82 (SCF_2); and 77 (C_6H_5).
$CF_3SSC_6H_5$:	$M^+ = 210$; 141 (100%, M – CF_3); 109 (M – SCF_3); 82 (SCF_2); 77 (C_6H_5); and 69 (CF_3).
$C_6H_5–C_6H_5$:	$M^+ = 154$ (100%); and 77 (C_6H_5).

[a]The source of these compounds was t-butyl methyl ether which was used as a solvent in preparing the Grignard reagent. The solvent underwent scission to furnish t-butyl and methyl radicals, which reacted with the substrate to yield these products.

[b]This compound is believed to arise from H-abstraction from its saturated parent compound and subsequent formation of the alkene.

to react with dimethyl disulfide in the gas phase [14], our results are indeed interesting. What is even more interesting is the formation of the alkyl sulfides (RSR) from bis(trifluoromethyl)disulfide. The Grignard reagents serve as the source of the alkyl moieties of the alkyl sulfides. They must have resulted from the attack on the S–S bond of R_fSR or more likely of R_fSSR by alkyl radicals (R·) derived from the Grignard reagents. The dimerization of phenyl and butyl radicals leads to biphenyl and octane. The origin of n-propyl-trifluoromethyl sulfide must again be due to the presence of small amounts

of n-propylmagnesium halide in the Grignard reagent, while isopropylsulfenyl chloride must have formed from a halogen-exchange reaction [11].

As for the mechanism of the reaction, two processes — free radical (Scheme 1) and single electron transfer (SET) (Scheme 2) — can be envisaged. The results described in Table 1 definitely suggest a simultaneous scission of the C—S and S—S bonds of **1** by Grignard reagents at −78 °C, although such a cleavage was not observed in the case of organolithium reagents [15]. Step 1 (Scheme 1) is similar to the one proposed by Whitesides and coworkers [16]. Steps 2 and 3 rationalize the formation of mixed mono- and di-sulfides, while steps 4 and 5 explain the origin of alkyl di- and monosulfides. The contribution of step 6 to alkyl sulfide formation must be minimal. Steps 7 and 8 obviously represent dimerization, although hexafluoroethane was not detected. Step 9 indicates the source of thiocarbonyl fluoride.

In Scheme 2, step 1 describes the transfer of the electron from the Grignard reagent to the substrate and the formation of the radical anion–radical cation pair, which collapses to give the trifluoromethyl perthiyl radical. The latter reacts with the alkyl radical derived from the Grignard reagent to give the mixed disulfide (step 3). The mixed disulfide undergoes a transformation (step 4) similar to step 1 and gives rise to an alkyl perthiyl radical (step 5), which then forms the dialkyl disulfide (step 6). The monosulfide (steps 7 and 8) can result from the same radical cation (step 5). Steps 9–11 are similar to those taking place in the free-radical-initiated process.

In view of the close similarities between the free radical and the single electron transfer processes and the possibility that some of the intermediate steps may be common to both, it is rather difficult to distinguish between the two. The two processes, namely the free radical and SET, appear to be competing with each other. It is concluded that the simultaneous scission of the C—S and S—S bonds of **1** by Grignard reagents at −78 °C is a direct consequence of the presence of the highly electron withdrawing CF_3 function.

The molecular ion is seen for all compounds except for t-C_4H_9Br. The splitting off of SCF_3 ($m/e = 101$), CSF_2 ($m/e = 82$) and CF_3 ($m/e = 69$) is a general feature of the compounds containing the trifluoromethylthiyl moiety. In the case of mixed sulfides containing both alkyl and trifluoromethyl groups, the ion corresponding to CSH ($m/e = 45$) is also seen. The fragmentation patterns of dialkyl disulfides and sulfides are similar to those reported by others [17].

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