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α-Arylsulfanyl-α-fluoro Carbenoids: Their Novel Chemistry and Synthetic Applications

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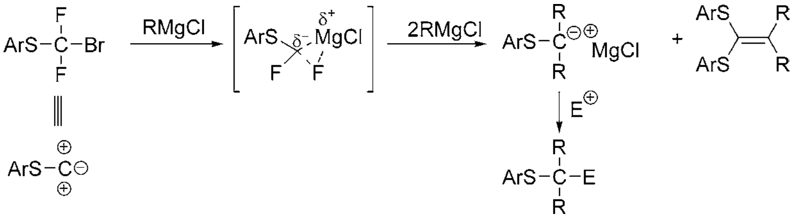
ABSTRACT



The bromine–magnesium exchange reactions of arylthiobromodifluoromethanes with Grignard reagents have been studied. Upon trapping with electrophiles, alkyl aryl sulfides and ketenedithioacetals are obtained. The reaction is proposed to occur via novel α-arylsulfanyl-α-fluoro carbenoids. The first examples of arylthiomethane multipole synthons are also reported.

Organofluorine compounds[1] have engendered considerable interest in recent years due to their wide ranging biological effects. The development of general synthetic routes to such compounds and investigations into the use of new fluorine compounds as building blocks are therefore of great importance.[2] Our recent efforts at developing new synthetic methods for the preparation of *gem*-difluoromethylene compounds have shown the utility of bromodifluorophenylthiomethane as a highly versatile *gem*-difluoromethylene building block. The reaction of the difluorophenylsulfanylmethyl radical with olefins affords adducts possessing a *gem*-difluoromethylene moiety.[3] As a result of these studies, it has been envisaged that arylthiobromodifluoromethanes **1** and **2** will be useful precursors of the difluoro carbanion **3**, which would be expected to form carbon−carbon bonds after trapping with suitable electrophiles. This protocol, if successful, would provide an important complementary method to those reported for the synthesis of *gem*-difluoromethylene compounds.[4]

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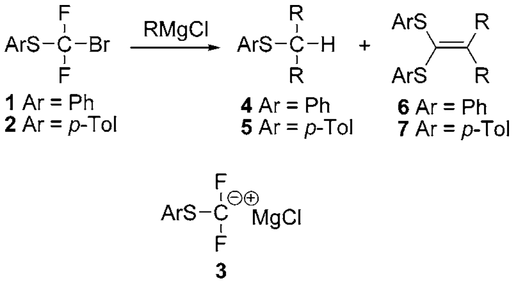
Table 1. Reactions of **1** and **2** with Grignard Reagents

				products (% yield)^a		
entry	sulfide **1** or **2**	RMgX (equiv)	conditions	**R**	**4**	**6**
1	**1**	*i*-PrMgCl (1.1)	−78 °C, 1 h	*i*-Pr	**4a** (19)	**6a** (7)
2	**1**	*i*-PrMgCl (1.5)	−78 °C, 1.5 h	*i*-Pr	**4a** (28)	**6a** (13)
3	**1**	*i*-PrMgCl (1.5)	−100 °C, 10 min	*i*-Pr	**4a** (29)	**6a** (13)
4	**1**	*i*-PrMgCl (4)	−78 °C, 5−10 min	*i*-Pr	**4a** (47−48)	**6a** (26−31)
5	**1**	*i*-PrMgCl (4)	−78 °C, 1.5 h	*i*-Pr	**4a** (48)	**6a** (30)
6	**1**	*i*-BuMgCl (4)	−78 °C, 30 min	*i*-Bu	**4b** (83)	**6b** (6)
7	**1**	EtMgCl (4)	−78 °C, 30 min	Et	**4c** (43)	**6c** (21)
8	**1**	*t*-BuMgCl (5)	−78 °C to rt, overnight	*t*-Bu	**4d** (63)	**6d** (0)
9	**2**	*i*-PrMgCl (4)	−78 °C, 1 h	*i*-Pr	**5a** (51)	**7a** (26)
10	**2**	*i*-BuMgCl (4)	−78 °C, 1 h	*i*-Bu	**5b** (84)	**7b** (2)
11	**2**	EtMgCl (4)	−78 °C, 1 h	Et	**5c** (42)	**7c** (13)
12	**2**	*t*-BuMgCl (5)	−78 °C to rt, overnight	*t*-Bu	**5d** (46)	**7d** (0)

[a] Isolated yield based on the starting sulfide **1** or **2**.

On the basis of this assumption, methods for the generation of the *gem*-difluoro carbanion **3** from **1** and **2** have been studied. Eventually it was found that the treatment of **1** with 1.1 equiv of *i*-PrMgCl (2 M in THF) at −78 °C provided the unexpected products **4a** and **6a** in 19 and 7% yield, respectively (Scheme 1). The same products **4a** (24%) and **6a** (13%) were obtained when the reaction was carried out at −100 °C for 10 min, employing 1.5 equiv of *i*-PrMgCl. Attempts to trap the proposed initial intermediate **3** with benzoyl chloride or methyl iodide were unsuccessful. Better yields of **4a** (47−48%) and **6a** (26−31%) were obtained when 4 equiv of *i*-PrMgCl were used at −78 °C for 5−10 min (Table 1, entry 4), and comparable yields were obtained with prolonged reaction time (Table 1, entry 5).

Scheme 1. Bromo−Magnesium Exchange Reactions of Arylthiobromodifluoromethanes with Grignard Reagents



To gain more insight into the bromine−magnesium exchange reaction,[5] **1** was reacted with other Grignard reagents. As summarized in Table **1** (entries 6−8), the reactions of **1** with *i*-BuMgCl, EtMgCl, and *t*-BuMgCl afforded the sulfides **4b**, **4c**, and **4d** in moderate to good yields, together with ketenedithioacetals[6] **6b** and **6c** as the minor products. However, compound **6d** could not be detected when *t*-BuMgCl was employed (Table 1, entry 8). Similar results were obtained with compound **2**. Thus, treatment of **2** with *i*-PrMgCl, *i*-BuMgCl, and EtMgCl under the conditions indicated in Table 1 (entries 9−12) provided sulfides **5a−d** in moderate to good yields (42−84%), together with ketenedithioacetals **7a−c** in 2−26% yields. Again, compound **7d** was not detected (Table 1, entry 12).

The formation of the sulfide **4** or **5** is proposed to proceed via the bromine−magnesium exchange reaction of the starting compound **1** or **2** with a Grignard reagent, leading to a magnesium carbanion **3**, which undergoes a rapid α-elimination of a fluoride ion, due to stabilizing of the arylthio group to an intermediate **10**, to give the hitherto unknown magnesium carbenoid **9**.[7−10] Subsequent reaction of the intermediate **9** with another equivalent of RMgCl affords the magnesium carbanion **11**. The α-elimination of fluoride ion from **11** gave another unknown carbenoid derivative **12**, and upon addition of another equivalent of

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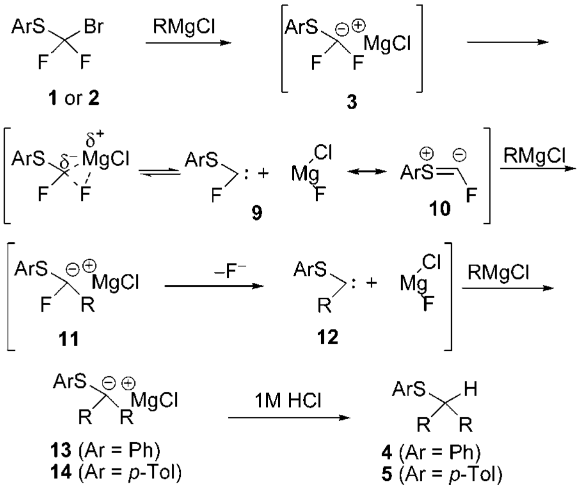
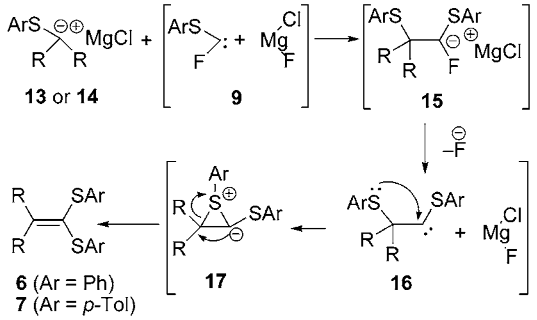
the Grignard reagent, the α-sulfur-stabilized anion **13** or **14** was obtained. Acidic workup furnished sulfide **4** or **5** (Scheme 2). Attempts to trap the carbenoid **9** or **12** by carrying out the reaction with cyclohexene as a solvent were unsuccessful.

Scheme 2. Proposed Mechanism for the Formation of Alkyl Aryl Sulfides



Rationalization of the formation of ketenedithioacetal **6** or **7** involves addition of the magnesium carbanion **13** or **14** to the carbene intermediate **9** to give an intermediate **15**, which then leads to carbenoid **16**. Neighboring group participation by the lone pair electrons on the sulfur atom to the carbenic center gives an intermediate **17**, which further rearranges[7c,7d,10] to ketenedithioacetal **6** or **7** (Scheme 3). The absence of the products **6d** and **7d** could be attributed to the steric hindrance of the *tert*-butyl group making the formation of the intermediate **15** unfavorable. The structure of ketenedithioacetal **6b** was confirmed by a single-crystal X-ray crystallography as shown in Figure 1.[11,12]

Scheme 3. Proposed Mechanism for the Formation of Ketenedithioacetals



The existence and the synthetic utility of the magnesium carbanions **13** and **14** were demonstrated by trapping with electrophiles methyl iodide, allyl bromide, crotyl bromide, or benzoyl cyanide, in the presence of CuCN•2LiCl (1 equiv).[5] This provided *t*-alkyl aryl sulfides or α-keto-sulfides in moderate yields. Moreover, hydroxybenzylated products were obtained with benzaldehyde or *p*-tolualdehyde in the absence of CuCN•2LiCl at −78 °C following warming to room-temperature overnight. The results are summarized in Table 2.

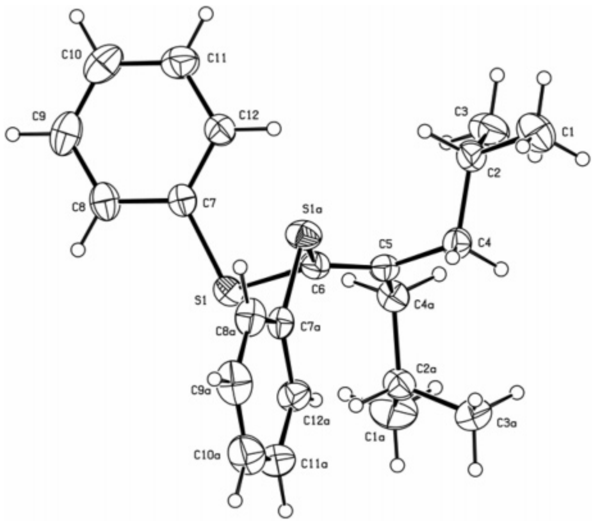


Figure 1. X-ray crystal structure of ketenedithioacetal **6b**.

In conclusion, our results, for the first time, provide evidence for the novel chemistry of the proposed carbenoids **9** and **12**. The resulting α-sulfur-stablized magnesium

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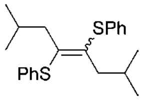
(11) Alternative structure of **6b** is as shown below, which presumably could be formed by the dimerization of the carbenoid **12** (R = *i*-Bu). The formation of the ketenedithioacetal **6b** provides support for the mechanism proposed in Scheme 3.



(12) Crystal data for compound (**6b**) at 298(2) K: $C_{22}H_{28}S_2$, $M_r = 356.59$, monoclinic, space group $C2/c$ (No. 15), $a = 18.2720$ (13) Å, $b = 7.8680$ (3) Å, $c = 15.9862$ (11) Å, $\beta = 116.643$ (2)°, $V = 2054.2(2)$ Å^3, $Z = 4$, $D_x = 1.153$ Mg m^{-3}. $F_{000} = 768$, λ (Mo Kα) = 0.71073 Å, $\mu = 0.260$ mm^{-1}. Data collection and reduction: crystal size 0.15 × 0.20 × 0.20 mm, θ range 1.00−25.03°, 7938 reflections collected, 1765 independent reflections ($R_{\text{int}} = 0.0254$), final R indices ($I > 2\sigma(I)$): $R_1 = 0.0385$, w$R_2 = 0.0991$ for 111 parameters, GOF = 1.052. CCDC 248269. These data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

Table 2. Reactions of Organomagnesiums **13** and **14** with Electrophiles

13 (Ar = Ph)
14 (Ar = *p*-Tol)

18 (Ar = Ph)
19 (Ar = *p*-Tol)

entry	**13 or 14**	Ar	R	electrophiles[a]	products, % yield[b]
1	**13a**	Ph	*i*-Pr	methyl iodide	**18a** (E = Me), 36%
2	**13b**	Ph	*i*-Bu	methyl iodide	**18b** (E = Me), 61%
3	**13b**	Ph	*i*-Bu	allyl bromide	**18c** (E = $CH_2{=}CHCH_2$), 76%
4	**13b**	Ph	*i*-Bu	crotyl bromide	**18d** (E = $CH_3CH{=}CHCH_2$), 78%
5	**13b**	Ph	*i*-Bu	benzoyl cyanide	**18e** (E = PhCO), 56%
6	**13b**	Ph	*i*-Bu	benzaldehyde	**18f** (E = PhCH(OH)), 45%
7	**13b**	Ph	*i*-Bu	*p*-tolualdehyde	**18g** (E = *p*-TolCH(OH)), 45%
8	**13c**	Ph	Et	methyl iodide	**18h** (E = Me), 35%
9	**13c**	Ph	Et	allyl bromide	**18i** (E = $CH_2{=}CHCH_2$), 39%
10	**13c**	Ph	Et	crotyl bromide	**18j** (E = $CH_3CH{=}CHCH_2$), 40%
11	**13c**	Ph	Et	benzoyl cyanide	**18k** (E = PhCO), 36%
12	**14a**	*p*-Tol	*i*-Pr	methyl iodide	**19a** (E = Me), 30%
13	**14b**	*p*-Tol	*i*-Bu	methyl iodide	**19b** (E = Me), 62%
14	**14b**	*p*-Tol	*i*-Bu	allyl bromide	**19c** (E = $CH_2{=}CHCH_2$), 64%
15	**14b**	*p*-Tol	*i*-Bu	crotyl bromide	**19d** (E = $CH_3CH{=}CHCH_2$), 79%
16	**14b**	*p*-Tol	*i*-Bu	benzoyl cyanide	**19e** (E = PhCO), 50%
17	**14b**	*p*-Tol	*i*-Bu	benzaldehyde	**19f** (E = PhCH(OH)), 49%
18	**14b**	*p*-Tol	*i*-Bu	*p*-tolualdehyde	**19g** (E = *p*-TolCH(OH)), 43%
19	**14c**	*p*-Tol	*i*-Bu	methyl iodide	**19h** (E = Me), 38%
20	**14c**	*p*-Tol	*i*-Bu	allyl bromide	**19i** (E = $CH_2{=}CHCH_2$), 42%
21	**14c**	*p*-Tol	*i*-Bu	crotyl bromide	**19j** (E = $CH_3CH{=}CHCH_2$), 46%
22	**14c**	*p*-Tol	*i*-Bu	benzoyl cyanide	**19k** (E = PhCO), 48%

[a] All reactions were carried out in the presence of CuCN·2LiCl except for entries 6, 7, 17, and 18. [b] Isolated yield based on the starting sulfide **1** or **2**.

carbanions **13** and **14** can be trapped with various electrophiles to give compounds **18** and **19** in synthetically useful yields. Arylsulfanylbromodifluoromethanes **1** and **2** can be regarded as synthetic equivalents of the multipole synthon **20**.

1 and **2**

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Supporting Information Available: General experimental details and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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