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New Three-Step Domino Reaction, "Thiophilic Addition–β-Elimination of Fluoride–[3,3] Sigmatropic Rearrangement": Synthesis of α-Allylic and α,α-Bis(allylic) α-Trifluoromethyl Dithioesters

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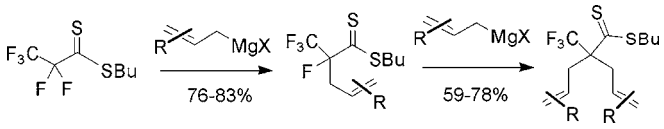
ABSTRACT



The three-step domino reaction, "thiophilic addition of an organomagnesium reagent onto dithioester–β-elimination of fluoride–[3,3] sigmatropic rearrangement", provides the product of formal regiospecific substitution of a fluorine atom by an allyl group. This mild and versatile methodology was applied to the synthesis of various α-allylic and α,α-bis(allylic) α-trifluoromethyl dithioesters.

The reaction of dithioester derivatives with various nucleophiles has been extensively studied.[1] Noteworthy, due to the peculiar properties of thiocarbonyl function, is that aliphatic Grignard reagents add selectively at sulfur ("thiophilic attack")[2] leading to an intermediate carbanion stabilized by two sulfur atoms, analogous to the Corey−Seebach dithiane anion. In contrast, allylic and vinylic grignard reagents react with dithioesters exclusively at carbon ("carbophilic attack").[3]

In fluorinated series, we have previously shown that the presence of an electron-withdrawing group adjacent to the thiocarbonyl function also favored the thiophilic addition of aliphatic organomagnesium and organolithium reagents.[4] The thiophilic addition was followed by a subsequent β-elimination of a fluoride ion leading directly to ketene dithioacetals (Scheme 1). A few years later, Lequeux and co-workers applied this methodology to difluorophosphonodithioacetate for the synthesis of the corresponding monofluoro ketene dithioacetals.[5] Interestingly, not only ethylmagnesium bromide reacted at sulfur but also the unsaturated phenyl- and vinylmagnesium bromides reacted at sulfur (Scheme 1).

The Claisen rearrangement of oxygenated substrates has been widely used in organic reactions because of its ability to form new carbon−carbon single bonds with regiospecific allylic transposition.[6] There have been a number of studies

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(1) For reviews on thiocarbonyl compounds and dithioesters in particular, see: (a) Metzner, P. *Synthesis* **1992**, 1185−1199. (b) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Academic Press: London, 1994; Chapter 4, pp 96−126.

(2) Léger, L.; Saquet, M. *Bull. Soc. Chim. Fr.* **1975**, 657−666.

(3) Masson, S.; Saquet, M.; Thuillier, A. *Tetrahedron* **1977**, *33* (22), 2949−2954.

(4) Portella, C.; Shermolovich, Y. *Tetrahedron Lett.* **1997**, *38* (23), 4063−4064.

(5) Pfund, E.; Masson, S.; Vazeux, M.; Lequeux, T. *J. Org. Chem.* **2004**, *69*, 4670−4676.

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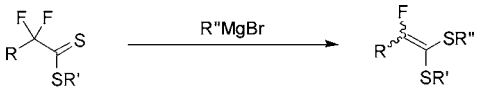
Scheme 1. Reaction of Grignard Reagents with Various Fluorodithioesters



R	R'	R"	yield
F	Bn	Et	86%[4]
CF_2CF_3	Et, Bn, nPr	Et	60-70%[4]
$P(O)(OEt)_2$	Me	Et, Ph, $CH=CH_2$	85-88%[5]

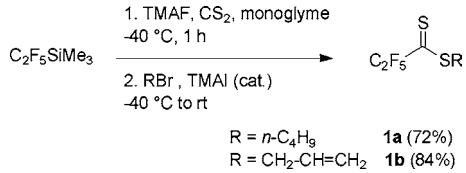
on the effect of fluorinated substituents at various sites of the pericyclic array,[7] and to date, this [3,3] sigmatropic rearrangement is one of the most attractive reactions for the interconversion of fluorinated substrates and the preparation of simple and readily available fluorinated building blocks. Whereas its sulfur variant, the thio-Claisen rearrangement, has received considerable attention as a useful synthetic method for the transposition of a carbon−sulfur single bond to a carbon−carbon bond and has been used in complex target-oriented synthesis,[1,8] no studies have been considered so far with fluorinated substrates.

On the basis of the previously reported results which showed that organomagnesium reagents reacted with fluorinated dithioesters to give the corresponding fluorinated ketene dithioacetals via a domino "thiophilic addition−defluorination",[4,5] we anticipated that *S*-allyl fluorinated ketene dithioacetals would be easily reached either by treatment of *S*-alkyl fluorinated dithioesters with allylic Grignard reagents or by treatment of *S*-allyl fluorinated dithioesters with alkyl Grignard reagents. As the thio-Claisen rearrangement of nonfluorinated substrates occurs at ambient temperature or by heating at 101 °C at most[1,8] and as the presence of an electron-withdrawing group on the vinylic moiety of the six-atom backbone generally has a rate-accelerating effect on [3,3] sigmatropic rearrangements,[7,8] we expected that the thio-Claisen transposition of *S*-allyl fluorinated ketene dithioacetals should be thermally facile.

Herein, we describe our results and show that the domino reaction, thiophilic addition of an organomagnesium reagent−β-elimination of fluoride−[3,3] sigmatropic rearrangement, is a versatile approach for the synthesis of various unsaturated fluorinated dithioesters.

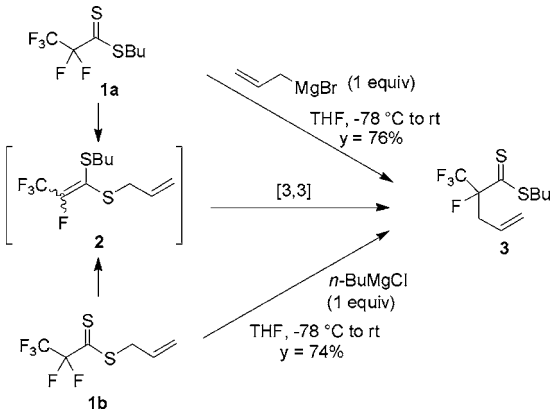
Several synthetic methods have been published for the preparation of perfluoroalkyl dithioesters,[9] but most of them have serious disadvantages such as the use of volatile or toxic reactants or reagents, the requirement of special techniques, or low yields. The synthesis reported recently by Yagupolskii and co-workers,[9f] which involved the direct reaction of perfluoroalkyltrimethylsilane with carbon disulfide in the presence of a fluoride ion followed by the subsequent alkylation of the isolated salt, seemed to be the most attractive one. However, as the intermediate tetramethylammonium pentafluorodithiopropanoate salt was highly hygroscopic, we developed a modified *one-pot* procedure to prepare the starting pentafluorodithioesters **1a**,**b** required for this study (Scheme 2).[10]

Scheme 2. One-Pot Synthesis of Pentafluorodithioesters **1a**,**b**



n-Butyl pentafluorodithiopropanoate **1a** was reacted with an allyl Grignard reagent to evaluate the relevance of the proposed approach. We were delighted to observe that the reaction led directly to α-fluoro α-trifluoromethyl α-allyl dithioester **3** isolated in 76% yield after purification on a pad of silica gel (eluent: pentane) (Scheme 3). Dithioester

Scheme 3. Reaction of Allyl or Butyl Magnesium Halide with Butyl or Allyl Pentafluorodithioesters **1a**,**b**



3, which is formally the product of substitution of an α-fluorine atom by the allyl group, results from a domino process involving three successive steps: thiophilic nucleophilic allylation−fluoride elimination−σ [3,3] rearrangement, with the two first ones leading to the intermediate ketene dithioacetal **2**.[11] This reaction pathway has been corroborated

(6) For a recent review on Claisen and related rearrangements, see: Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939−3002.

(7) For short reviews on [3,3] sigmatropic rearrangements of fluorinated compounds, see: (a) Purrington, S. T.; Weeks, S. C. *J. Fluorine Chem.* **1992**, *56*, 165−173. (b) Percy, J. M.; Prime, M. E. *J. Fluorine Chem.* **1999**, *100*, 147−156.

(8) For a review on thio-Claisen rearrangement, see: Majumdar, K. C.; Ghosh, S.; Ghosh, M. *Tetrahedron* **2003**, *59*, 7251−7271.

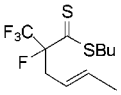
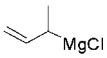
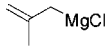
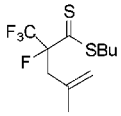
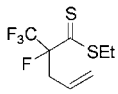
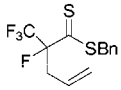
(9) (a) Brown, H. C.; Pater, R. *J. Org. Chem.* **1962**, *27*, 2858−2863. (b) Middleton, W. J.; Howard, E. G.; Sharkey, W. H. *J. Org. Chem.* **1965**, *30*, 1375−1384. (c) Shermolovich, Yu. G.; Slusarenko, Y. I.; Timoshenko, V. M.; Rozhenko, A. B.; Markovski, L. N. *J. Fluorine Chem.* **1991**, *55*, 329−333. (d) Portella, C.; Shermolovich, Yu. G.; Tschenn, O. *Bull. Soc. Chim. Fr.* **1997**, *134*, 697−702. (e) Laduron, F.; Nyns, C.; Janousek, Z.; Viehe, H. G. *J. Prakt. Chem.* **1997**, *339*, 697−707. (f) Badadzhanova, L. A.; Kirij, N. V.; Yagupolskii, Yu. L. *J. Fluorine Chem.* **2004**, *125*, 1095−1098. (g) Timoshenko, V. M.; Tchachenko, A. V.; Shermolovich, Yu. G. *J. Fluorine Chem.* **2005**, *126*, 361−364.

(10) For details, see Supporting Information.

by the inverse approach, where the intermediate **2** is produced by the reaction of allyl pentafluorodithiopropanoate **1b** with butylmagnesium chloride under similar conditions (Scheme 3). Noteworthy is the absence of any trace of the intermediate ketene dithioacetal in the crude mixture at the end of the reaction which is significant of a nonreversible rearrangement, in contrast to what was observed in nonfluorinated series.[12]

Both approaches were extended to various Grignard reagents giving the results summarized in Table 1. As typical

Table 1. Reaction of Pentafluoropropanoate **1a**,**b** with Various Grignard Reagents[a]

entry	starting material	Grignard reagent	product		yield[b]
1	**1a**			**4**	76%
2	**1a**				83%
3	**1a**			**5**	83%
4	**1b**	EtMgBr		**6**	90%
5	**1b**	BnMgBr		**7**	85%

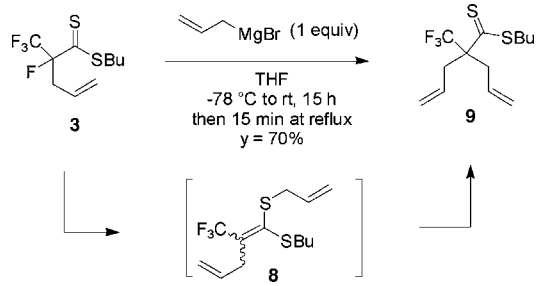
[a] Reaction conditions: dithioester **1** (1 equiv), Grignard reagent (1 equiv), THF, −78 °C to room temperature, 15 h. [b] Yields refer to isolated material after purification on a pad of silica gel (eluent: pentane).[14]

procedure, completion of the sigmatropic rearrangement was checked by ^{19}F NMR after 15 h of reaction.[13] The rearrangement also occurred on warming the reaction to room temperature with a substituted allylic group (entries 1−3). All dithioesters **4**−**7** were obtained cleanly and in good to very good yields (76−90%).

The last step of the domino reaction released a dithioester moiety which is available for a further sequence. To broaden the synthetic utility of this methodology, we were keen to study the feasibility of a second three-step sequence from unsaturated dithioesters **3**−**7**, and this approach allows access to various symmetrical or nonsymmetrical α-trifluoromethyl α-bis(unsaturated) dithioesters.

In this aim, dithioester **3** was treated with 1 equiv of allylmagnesium bromide according to the previous conditions. Despite the fast formation of the intermediate *S*-allyl ketene dithioacetal **8**,[15] the second rearrangement was slower due to the bulky trifluoromethyl and allyl groups borne on the vinylic carbon (Scheme 4).[16] Complete conversion of **8**

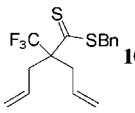
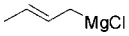
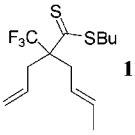
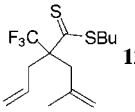
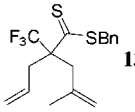
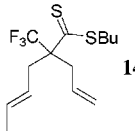
Scheme 4. Reaction of an Allyl Grignard Reagent with Unsaturated Dithioesters **3**



into **9** was achieved after 3 days at room temperature or within 15 min under reflux.

Various dithioesters **3**−**5**,**7** were then treated with allylic Grignard reagents (data collected in Table 2). As typical

Table 2. Reaction of *S*-Butyl Pentafluorodithioesters **3**−**5**,**7** with Allylic Grignard Reagents[a]

starting material	allylic Grignard reagent	time of reflux	product		yield[b]
7		15 min		**10**	75%
3		15 min		**11**	59%
4		15 min			68%
3		45 min		**12**	78%
5		1 h 30			65%
7		1 h		**13**	88%
4		45 min		**14**	51%

[a] Reaction conditions: starting dithioester (1 equiv), Grignard reagent (1 equiv), THF, −78 °C to room temperature for 15 h then reflux for 15 min−1 h 30 min. [b] Isolated yield.

procedure, the progress of each reaction was monitored by ^{19}F NMR after 15 h of stirring and the reaction mixture was then heated at reflux until the complete conversion of intermediate *S*-allyl ketene dithioacetals of type **8**[15] into the corresponding dithioesters **10**−**14**.

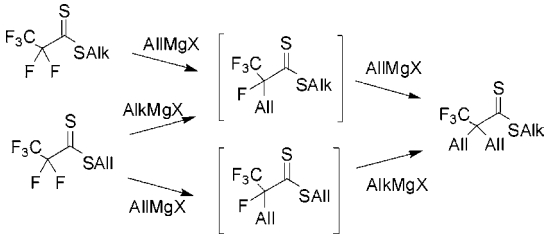
(11) All attempts to isolate intermediate *S*-allyl fluorinated ketene dithioacetals of type **3** were unsuccessful due to their propensity to rearrange.

(12) For an example of reversible thio-Claisen rearrangement of dithioester derivatives, see: Metzner, P.; Pham, T. N.; Vialle, J. *Tetrahedron* **1986**, *42* (7), 2025−2036.

(13) For practical reasons, the progress of the reaction was checked after 15 h for all reactions, but the rearrangement was faster.

Finally, we attempted a one-pot procedure to convert directly the pentafluoro dithioesters **1a**,**b** into bis(unsaturated) compounds. As depicted in Scheme 5, three approaches are

Scheme 5. Flexibility of the Synthesis of Symmetrical α-Trifluoromethyl α-Bis(unsaturated) Dithioesters

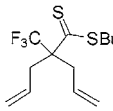
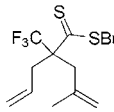


possible for the synthesis of symmetrical bis(unsaturated) dithioesters depending on the *S*-substituent of the starting dithioester and on the order of the addition of each organomagnesium reagent.

Symmetrical as well as nonsymmetrical bis(unsaturated) dithioesters **9**,**12** have been prepared following this pathway (Table 3).

In summary, this study shows that the three-step domino reaction, thiophilic addition of an organomagnesium reagent−*β*-elimination of fluoride−*σ* [3,3] rearrangement, represents an easy, straightforward, and versatile synthesis of monounsaturated and symmetrical or unsymmetrical bis(unsaturated) fluorinated dithioesters. Good to very good yields were indeed obtained for a significant variety of representative compounds.

Table 3. One-Pot Preparation of α-Trifluoromethyl α-Bis(unsaturated) Dithioesters **9**,**12** Starting from **1a**,**b**[a]

starting material	1st Grignard reagent	2nd Grignard reagent	product		yield[b]
1a	MgBr	MgBr		**9**	61%
	n-BuMgCl	MgBr			74%
1b	MgBr	*n*-BuMgCl			68%
1a	MgBr	MgCl		**12**	74%

[a] Reaction conditions: dithioester 1 (1 equiv), first Grignard reagent (1 equiv), THF, −78 °C to room temperature, 15 h, then second Grignard reagent (1 equiv), −78 °C to room temperature for 15 h and reflux for 15 min−1 h. [b] Isolated yield.

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Supporting Information Available: Experimental procedures 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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(14) Purification of unsaturated fluorinated dithioesters by distillation under reduced pressure gave lower yields due to their thermal instability. For example, **6** was isolated in 48% yield after distillation at $T = 99-101$ °C and $P = 0.3$ mBar.

(15) Intermediate *S*-allyl ketene dithioacetals of type **8** were detected by ^{19}F NMR ($\delta CF_3 \sim 57$ ppm). For the ^{19}F NMR chemical shift of various trifluoromethyl ketene dithioacetals, see, for example: (a) Muzard, M.; Portella, C. *Synthesis* **1992**, *10*, 965−968. (b) Sotoca, E.; Bouillon, J.-P.; Gil, S.; Parra, M.; Portella, C. *Tetrahedron* **2005**, *61* (18), 4395−4402.

(16) Désert, S.; Metzner, P.; Ramdani, M. *Tetrahedron* **1992**, *48* (47), 10315−10326.