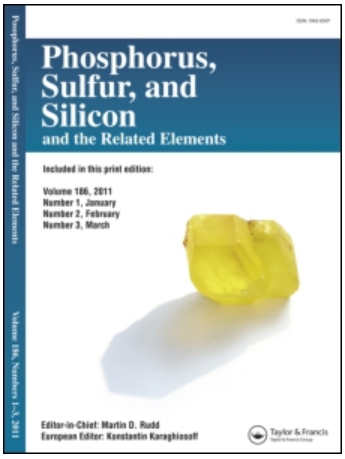

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REACTIONS OF TRIFLUOROMETHYLSULFENYL CHLORIDE AND TRIFLUOROMETHYLTHIOCOPPER WITH 2-(TRIMETHYLSILYL)THIAZOLE

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The treatment of 2-(trimethylsilyl)thiazole with trifluoromethylsulfenyl chloride furnishes the expected 2-(trifluoromethylthio)thiazole in satisfactory yields along with the ring contraction product of the azirine-type. However, the reaction of 2-bromothiazol with trifluoromethylthiocopper gives poor yields of the above compound. The mechanism of formation and the mass spectral characterization of the products are presented in this article.

Keywords: Ring contraction; silylthiazole; trifluoromethylthiolation; trifluoromethylthiocopper

INTRODUCTION

The thiazolyl moieties are present in bioactive natural products.[1] The synthetic usefulness and versatility of 2-(trimethylsilyl)thiazole, known as the Dondoni reagent, has been amply documented.[2] The synthesis and reactions of 2-(trimethylsilyl)thiazole with carbon electrophiles has attracted considerable attention.[2] It has been used as an effective formyl anion equivalent in the homologation of chiral aldehydes to higher sugars.[2] However, there are not many examples of synthetically useful carbon-sulfur bond formation at the thiazole carbon.[3] In continuation of our interest in the chemistry of the trifluoromethylthio group,[4] the reactions between 2-bromothiazole (**1**) with

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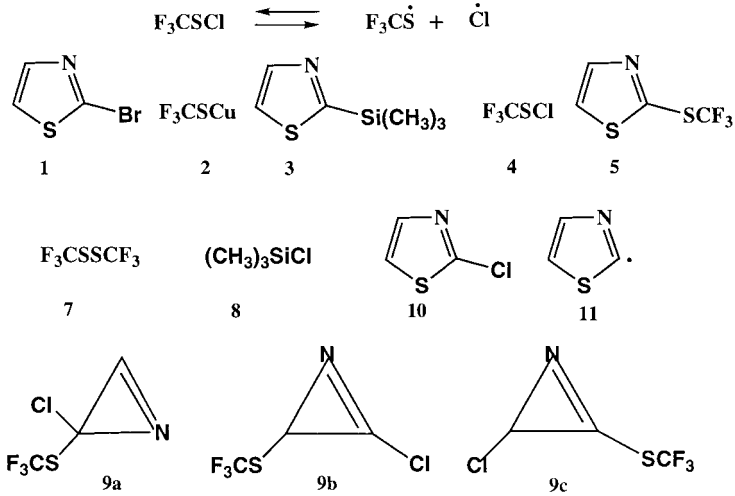

FIGURE 1 Structures of the compounds cited in the narrative.

trifluoromethylthiocopper (**2**) and 2-(trimethylsilyl)thiazole (**3**) with trifluoromethylsulfenyl chloride (**4**) respectively have been investigated and the results thus obtained (Figure 1) are presented in this article.

RESULTS AND DISCUSSION

Recently, we described the trifluoromethylthiolation of enolacetates[5a] and silylenol ethers.[5b] We also reported a procedure for introducing the trifluoromethylthio group on a reactive methylene moiety using (trifluoromethylthio)phthalimide.[5c] In this context, the regio- and chemoselective cleavage of the carbon-silicon bond of 2-(trimethylsilyl)thiazole (**3**, Figure 1) by sulfur "electrophiles" has been examined with the hope that 2-(trifluoromethylthio)thiazole (**5**) may be useful in effectively transferring the trifluoromethylthio group to bioactive organic compounds and hence might be able to enhance their potency. Thus, the reactions of 2-bromothiazole (**1**) with trifluoromethylthiocopper (**2**) and 2-(trimethylsilyl)thiazole (**3**) with trifluoromethylsulfenyl chloride (**4**) respectively were caried out. Three compounds were characterized from the reaction with trifluoromethylthiocopper (**2**) via th GC-MS analysis of the reaction mixture: (a) 2-bromothiazole (**1**, 95.5%, starting material), (b) 2-(trifluoromethylthio)thiazole (**5**, 2.4%) and an unknown compound (**6**, 2.0%). Since the molecular ion peak was absent in the mass spectrum of the latter component (**6**), it was not possible to identify this unknown compound.

However, the reaction of 2-(trimethylsilyl)thiazole (**3**) with trifluoromethylsulfenyl chloride (**4**) at −78°C furnished five compounds: (a) bis(trifluoromethyl)didulfide (**7**, 20.6%, $M^+ = 202$); (b) trimethylsilyl chloride (**8**, 4.8%, $M^+ = 108$); (c) an unknown, (**9**, 2.3%, $M^+ = 175$); (d) 2-chlorothiazole (**10**, 4.5%, $M^+ = 119$) and (e) 2-(trifluoromethylthio)thiazole (**5**, 70.0%, $M^+ = 185$). The mass spectra of the thiazole derivatives have been discussed and the primary fragmentation patterns have been delienated.[6] Three structures (**9a**, **9b**, and **9c**) were considered for the unknown compound **9**. Based on the mass spectral breakdown behavior, this unknown compound has been characterized as 2-chloro-2-(trifluoromethylthio)azirine (**9a**, Figure 2). The mass spectra of **7** and **8** have been described.[5,10]

The azirine must have been formed via the ring contraction involving the extrusion of the CSH moiety. Figure 2 attempts to rationalize the formation of 2-chloro-2-(trifluoromethylthio)azirine (**9a**). The homolytic cleavage of the carbon-sulfur bond of the thiazole ring of **5** would give the intermediate (**13**), which then would recyclize to furnish thioformylazirine (**14**). The elimination of the thioformyl moiety from the latter would result in the allylic radical intermediate (**15**), the resonance hybrid of which is represented by **16**. The addition of the chlorine radical

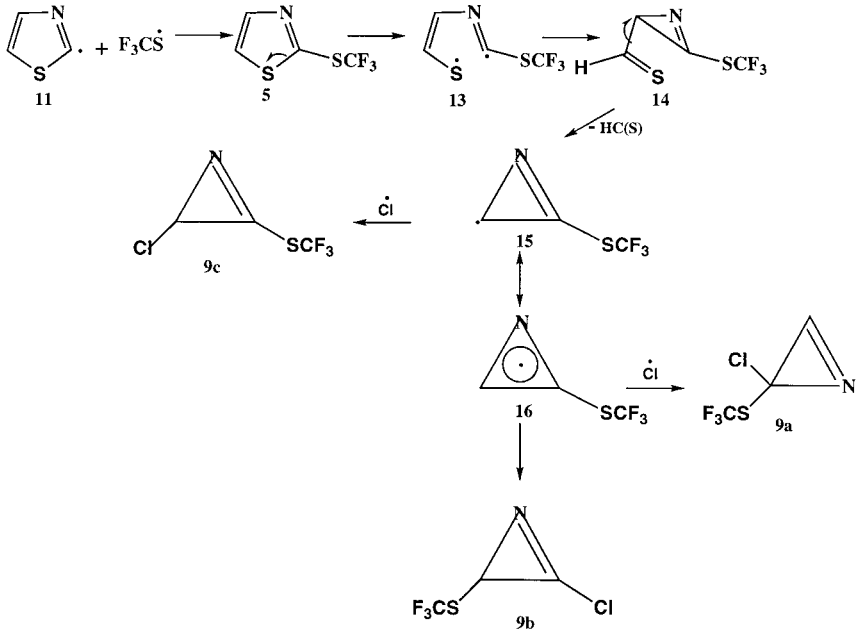

FIGURE 2 Probabale mechanism of the formation of the azirine derivative.

would then lead to either **9a** or **9b** or **9c**. The proposed cleavage of the five-membered thiazole molecule and recyclization to azirine intermediate derive their support from a similar postulation.[6c,7] However, based on the facile fragmentation of the SCF_3 entity and the ease of elimination of chlorine atom from the azirine moiety, structure **9a** was selected for this compound. The formation of 2-chlorothiazole (**10**) is attributed to the presence of the 2-thiazyl radical (**11**, Figure 1), which combines with the chlorine radical to form of 2-chlorothiazole (**10**). The suggested 2-thiazyl radical (**11**) has been indirectly observed.[8]

EXPERIMENTAL PART

Utmost caution and care must be exercized while working with CF_3SCl (**4**) and CF_3SSCF_3S (**7**). Trifluoromethylthiocopper (**2**) was prepard as described by us elsewhere.[9] All solvents were dry and freshly distilled prior to their use. The reactions were carried out in a flame-dried, argon gas purged 10 or 25 ml three-necked flasks equipped with a magnetic stirring bar, gas in-let adaptors and reflux condenser carrying a dry-ice acetone cooled trap. The temperaure of the coolant circulating through the condenser was maintained at -20°C. Unless stated otherwise, all reactions were carried out by the addition of stoichiometric amounts as described below to the substrate cooled to -80°C. The reaction mixture was initially analyzed by GC, then the solvent was evaporated under reduced pressure, the residue ditilled under vacuum and then analyzed by GC-MS. Mass spectra were obtained using a Finnigan TSQ-7000 GC/MS/MS equipped with a 30 m $\times$ 0.25 mm. i.d. DB-5 capillary column (J and W Scientific, Folsom, CA) or a Finnigan 5100 GC/MS equipped with a 15 m $\times$ 0.25 mm. i.d. Rtx-5 capillary column (Restek, Bellefonte, PA). The conditions on 5100 were: oven temperature 60–270°C at 10°C/min, injection temperature was 210°, interface temperature 230°C, electron energy 70 eV, emission current 500 μA and scan time 1 s. The conditions on the TSQ-7000 were: oven temperature 60–270°C at 15°C/min, injection temperature 220°, interface temperature 250°C, source temperature 150°, electron energy 70 eV (EI) or 200 eV (CI) and emission current 400 μA (EI) or 300 μA (CI) and scan time 0.7 s. Data was obtained in both the electron ionization mode (range 45–450 da) and chemical ionization mode (mass range 60–450 da). Ultrahigh purity methane was used as the CI agent gas with a source pressure of 0.5 Torr (5100) or 4 Torr (TSQ-7100). Routine GC analyses were done with a Hewlett-Packard 5890A gas chromatograph equipped with a J and W Scientific 30 m $\times$ 0.53 mm i.d. DB-5 column (J and W Scientific, Folsom, CA).

Synthesis of 2-(Trifluoromethylthio)thiazole (5, Figure 1)

A. Reaction of 2-Bromothiazole (**1**) with Trifluoromethylthiocopper (**2**): A mixture of stoichiometric amounts of 2-bromothiazole (**1**) and trifluoromethylthiocopper (**2**) in freshly distilled dry acetonitrile (10 ml) was heated for 12 h at ~90–100°C (oil bath temperature). The reaction was cooled to ambient temperature, filtered over celite, the filtrate treated with a saturated solution of ammonium chloride and processed as usual. The GC-MS analysis of the reaction product showed it to consist of three compounds, namely 2-bromothiazole (**1**, 95.0%), 2-(trifluoromethylthio)thiazole (**5**, 2.4%) and an unknown compound (**6**, 2.5%). Since the mass spectrum of compound **6** did not show any molecular ion peak and the molecule undergoes extensive degradation, its structure could not be established.

B. Reaction of 2-(Trimethylsilyl)thiazole (**3**) with Trifluoromethylsulfenyl Chloride (**4**): To a solution of 2-(trimethylsilyl)thiazole (**3**, 1.0 g, 6.5 mmol) in freshly distilled dry pentane (5 ml), stoichiomteric amounts of trifluoromethylsulfenyl chloride (**4**, 0.87 g, 6.5 mmol) were added at −80°C via the vacuum line. The reaction mixture was stirred under dry argon for 2 h, allowed to come to room temperature and then stirred over night at ambient temperature. The solvent was removed under reduced pressure and the residue on GC-analysis showed it to primarily consist of one component (‘70%) and the remainder was composed of several components. The GC-MS analysis of the reaction mixture permitted the characterization of all the compounds present in the reaction product, namely (a) 2-(trifluoromethylthio)thiazole (**5**), (b) 2-chloro-2-(trifluoromethylthio)azirine (**9a**), (c) bis-(trifluoromethyl)disulfide (**7**), (d) trimethylsilyl chloride (**8**) and 2-chlorothiazole (**10**). Table I describes their mass spectral breakdown behavior.

TABLE I Mass Spectral Fragmentation of Compounds Cited in the Text

1. 2-(Trifluoromethylthio)thiazole (**5**): $M^+ = 185$ (100%); 166 (M—F); 155 ($C_4H_4F_3NS$); 139 (166-HCN); 116 (M—CF_3); 90 (CNS_2); 72 (C_2H_2NS); 69 (CF_3); 58 (C_2H_2S) and 45 (CSH).
2. 2-Chloro-2-(trifluoromethylthio)azirine (**9a**): $M^+ = 175$; 140 (M—Cl, 100%); 106 (M—CF_3); 101 (SCF_3); 82 (CSF_2); 74 (M—SCF_3); 69 (CF_3); 50 (CF_2) and 45 (CSH).
3. Bis-(trifluoromethyl)disulfide (**7**): $M^+ = 202$ (100%); 183 (M—F); 133 (M—CF_3); 114 (133-F) and 69 (CF_3).
4. Trimethylsilyl chloride (**8**): $M^+ = 108$; 93 (M—CH_3, 100%); 77 (M—Cl) and 63 (SiCl).
5. 2-Chlorothiazole (**11**): $M^+ = 119$ (100%); 92 (M—HCN); 79 [C(S)Cl]; 60 (CH_2NS); 58 (C_2H_2S) and 45 (CSH).

REFERENCES

[1] (a) P. C. Srivastava, G. R. Revankar, and R. K. Robins, *J. Med. Chem*., **27,** 266 (1984); (b) G. D. Kini, W. J. Hennen, and R. K. Robins, *J. Org. Chem*., **51,** 4436 (1986); (c) Y. Hamada, M. Shibata, and T. Shioiri, *Tetrahedron Lett*., **26,** 6501 (1985); (d) Y. Hamada, S. Kato, and T. Shioiri, *Tetrahedron Lett*., **26,** 3223 (1985); (e) N. Murugesan and S. M. Hecht, *J. Am. Chem. Soc*., **107,** 493 (1985); (f) J. D. White, T.-S. Kim, and M. Nambu, *J. Am. Chem. Soc*., **117,** 6512 (1995).

[2] (a) A. Dondoni, G. Fantini, M. Fogagnolo, A. Medici, and P. Pedrini, *J. Org. Chem*., **53,** 1748 (1988); (b) A. Dondoni, A. Mara, and M.-C. Scherman, *Tetrahedron Lett*., **34,** 7323 (1993); (c) A. Dondoni, A. Marr, and P. Merino, *J. Am. Chem. Soc*., **116,** 3324 (1994).

[3] J. Beraud and J. V. Metzger, *Bull. Soc. Chim*. (France), 2072 (1962).

[4] (a) S. Munavalli, A. J. Muller, D. I. Rossman, D. K. Rohrbaugh, and C. P. Ferguson, *J. Fluorine Chem*., **67,** 37 (1994); (b) C. P. Ferguson and L. J. Szafraniec, *J. Fluorine Chem*., **59,** 91 (1992); (c) C. P. Ferguson and L. Buettner, *J. Fluorine Chem*., **65,** 15 (1993); (d) A. Hessner, S. Singh, C. P. Ferguson, and L. Buettner, *J. Fluorine Chem*., **73,** 7 (1995); (e) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, C. P. Ferguson, and H. D. Durst, *J. Fluorine Chem*., **79,** 7 (1996); (f) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, and H. D. Durst, *J. Fluorine Chem*., **89,** 184 (1998); (g) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, L. R. McMahon, and H. D. Durst, *J. Organometal. Chem*., **587,** 160 (1999).

[5] (a) S. Munavalli, D. K. Rohrbaugh, F. R. Longo, and H. D. Durst (in press); (b) S. Munavalli, D. K. Rohrbaugh, F. R. Longo, and H. D. Durst, *Phosphorus, Sulfur, and Silicon*, **177,** 1021 (2002); (c) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner, and H. D. Durst, *Synth. Comm*., **30,** 2847 (2000).

[6] (a) G. M. Clarke, R. Grigg, and D. H. Williams, *J. Chem. Soc., (B)*, 339 (1966); (b) J. V. Metzger, *Comprehensive Heterocyclic Chemistry*, A. R. Katrtizky and C. W. Redd (eds), Pergamon Press, New York (1984), p. 244; (c) H. Buddzikiewicz, C. Djerassi and D. H. Williams, ed. Holden-Day Publishers, Inc., San Francisco (1967), vol. 6.

[7] L. Minier, R. Behrens, and S. Bulus, *J. Mass Spectrom*., **31,** 25 (1996).

[8] K. Torssell, *Tetrahedron*, **26,** 2759 (1970).

[9] S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, C. P. Ferguson, and F.-L. Hsu, *Heteroatom Chem*., **3,** 189 (992).

[10] (a) S. Munavalli, D. I. Rossman, D. K. Rohrbaugh, C. P. Ferguson, and H. D. Banks, *J. Fluorine Chem*., **60,** 85 (1993); (b) S. Munavalli, E. O. Lewis, A. J. Muller, D. I. Rossman, D. K. Rohrbaugh, and C. P. Ferguson, *J. Fluorine Chem*., **63,** 63 (1993).