EXOCYCLIZATION OF NOVEL β,β-DIFLUORO-α-PHENYLVINYL SULFIDE WITH BIDENDATE HETEROATOM(N, O, S) NUCLEOPHILES

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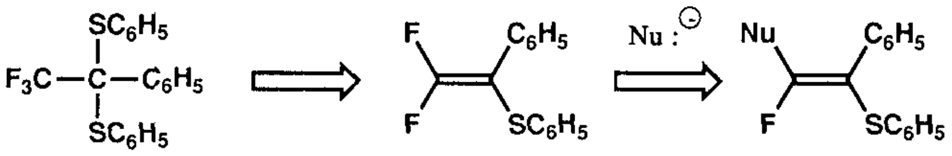
Abstract-The exocyclization of novel β,β-difluoro-α-phenylvinyl sulfide with bidentate heteroatom (N, O, S) nucleophiles afforded various types of heterocyclic ketene acetals (O,O-, O,S-, S,S-, N,N-, N,O-, N,S-). The ease of exocyclization depended on the ring size of heterocyclic ketene acetals.

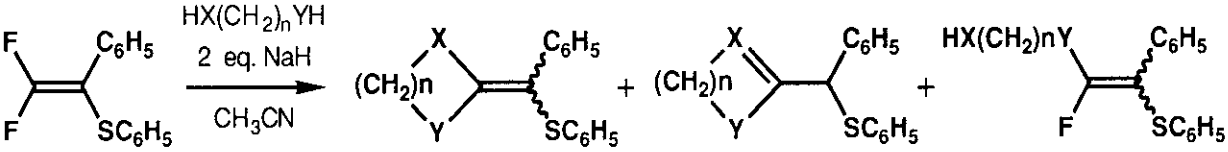
Recently, considerable effort has been paid to the synthesis of various types of heterocyclic N,N-,[1] S,S-,[2] and N,S-acetals,[3] because these compounds are useful synthetic intermediates for the preparation of a wide variety of fused heterocycles. The general approach to synthesize those heterocyclic acetals was established by the reactions of α-oxoketene dithioacetals[4] or electro-negatively substituted olefins such as 1,1-diiododinitroethylene[5] with bidentate heteroatom (N, O, S) nucleophiles. Although a reaction of symmetrical *gem*-dichlorinated and *gem*-difluorinated ketene dithioacetals with only a bidentate sulfur nucleophile has been reported in recent years,[2] a reactivity study on the reaction of unsymmetrical *gem*-difluorinated vinyl sulfides with various types of bidentate heteroatom nucleophiles has not been initiated. The paucity of studies related to unsymmetrical *gem*-difluorinated vinyl sulfides ascribes to the lack of suitable methods for the preparation of unsymmetrical *gem*-difluorinated vinyl sulfides. Of particular interests in this unsymmetrical *gem*-difluorinated vinyl sulfides is β,β-difluoro-α-phenylvinyl sulfide (**2**), because this sulfide (**2**) may have a unique reactivity toward ionic species to yield substitution product (**3**) *via* loss of fluoride and utilize to synthesis of a variety of heterocyclic acetals *via* exocyclization with bidentate heteroatom nucleophiles. Recently, we found that β,β-difluoro-α-phenylvinyl sulfide (**2**) can be easily prepared from the reaction of 2,2,2-trifluoro-1,1-bis(phenylthio)ethylbenzene (**1**) with a mixture of 2 equiv. $TiCl_4$ and 4 equiv. $LiAlH_4$.[6] In this communication, we wish to describe a reactivity on the exocyclization of **2** with various types of bidentate heteroatom (N,O,S) nucleophiles.



1 **2** **3**

Treatment of **2** with dianionic sodium salts of 1,2-ethanediol, 2-mercaptoethanol, 1,2-ethanedithiol, and 2-aminoethanethiol resulted in the formation of only heterocyclic ketene acetals (**4a**, **4b**, **4c**, and **4f**) in good yields. Although two methylene protons of **4b** and **4f** were showen as one set of peaks in ^{1}H-nmr spectrum, it seems likely that **4b** and **4f** exist as a (*E*) and (*Z*) isomeric mixture, since it is very diffcult to distinguish two methylene protons in (*E*) and (*Z*) isomers of **4b** and **4f**. In contrast, the similar reactions of **2** with dianionic sodium salts of ethylenediamine and 2-aminoethanol afforded only tautomers of heterocyclic ketene acetals (**5d**) and (**5e**) in good yields. In these cases, no corresponding heterocyclic ketene acetals was observed. The products (**5d**) and (**5e**) were confirmed by ^{1}H-nmr and ir spectra. The methine proton signals of **5d** and **5e** in ^{1}H-nmr spectrum were shown as a singlet peak at 5.20 and 5.05 ppm, respectively and an NH absorption peak was not detected in the ir spectrum. To support this spectroscopic analysis, the reaction of **4f** and **5e** with acetyl chloride in the presence of pyridine were performed. N-Acetylated product formed only from the reaction of **4f** with acetyl chloride was obtained in quantative yield. This result indicates that only **4f** contains NH functionality in the structure. Tautomerization of **4f**, **5d**, and **5e** under basic condition was examined. When **4f**, **5d**, and **5e** were reacted with sodium ethoxide in ethanol, however, tautomers of **4f**, **5d**, and **5e** were not dected and only starting materials were recovered. This result implies that **4f**, **5d**, and **5e** are very stable compounds even under basic condition. The use of longer chained alkanediols in the reaction of **2** with bidentate heteroatom nucleophiles caused to diminish the formation of heterocyclic ketene acetals (**4**), while monosubstituted vinyl sulfides (**6**) were obtained as major products. Therefore, the reaction of **2** with dianionic sodium salt of 1,4-butanediol afforded monosubstituted vinyl sulfide (**6h**) in 68% yield, while heterocyclic ketene acetals (**4h**) was obtained in only 5% yield.[7] An attempt to cyclize the compound (**6h**) in the presence of 1 equiv. of NaH was performed. However, only trace amount of **4h** was obtained, which indicates that it is very difficult to prepare heterocyclic ketene acetals with more than six-membered ring *via* exocyclization of **2**. The reactions of **2** with bidentate heteroatom nucleophiles are summarized in Table I.

Table I. The Reaction of 2 with Dianionic Sodium Salts of Hetereoatom 1,n-Disubstituted Alkane



2 4 5 6

X	Y	n	Products(Yield, %)[a]		
			4	5	6
O	O	2	**4a** (82)	-	-
O	S	2	**4b** (88)[b]	-	-
S	S	2	**4c** (89)	-	-
N	NH	2	-	**5d** (87)	-
N	O	2	-	**5e** (85)	-
N	S	2	**4f** (86)[b]	-	-
O	O	3	**4g** (77)	-	**6g** (12)[b]
O	O	4	**4h** (5)	-	**6h** (68)[b]
O	O	5	**4i** (3)	-	**6i** (72)[b]
O	O	6	**4j** (2)	-	**6j** (77)[b]
O	O	7	**4k** (trace)	-	**6k** (78)[b]

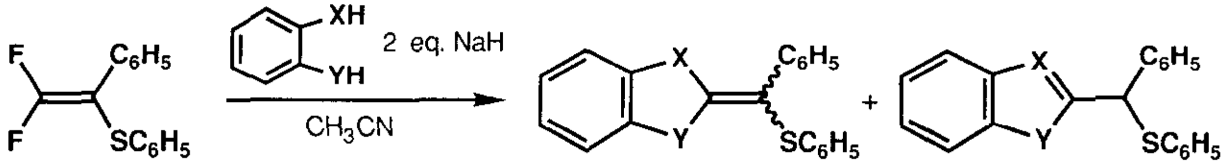
[a] All products were isolated by silica gel column chromatography.

[b] All products are (*E*) and (*Z*) isomeric mixtures.

The reactions of **2** with dianionic sodium salts of catechol and 1,2-benzenedithiol yielded only the corresponding heterocyclic ketene acetals (**7a**) and (**7b**) in 82% and 80% yields, respectively. In contrast, when the compound (**2**) was treated with dianionic sodium salts of 2-aminophenol and 1,2-phenylenediamine, only tautomers of heterocyclic ketene acetals (**8c**) and (**8d**) were obtained in 68% and 72% yields, respectively.[8]

However, the treatment of **2** with dianionic sodium salt of 2-aminothiophenol resulted in the formation of a mixture of corresponding benzothiazoline (**7e**) and benzothiazole (**8e**) in 35% and 38% yields, respectively.[9] This result is sharply contrast to that obtained from the reaction of **2** with dianionic sodium salt of 2-aminoethanethiol, in which only heterocyclic ketene acetal (**4f**) was obtained in 86% yield. The results are summarized in Table II. The partial formation of **8e** can be rationalized by a better stability due to the conjugation effect than **7e**.

Table II. The Reaction of **2** with Dianionic Sodium Salts of Heteroatom 1,2-Disubstituted Benzene



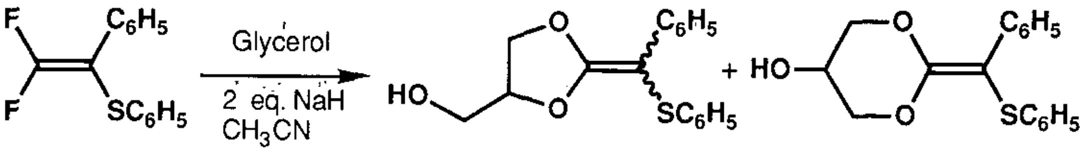
2 **7** **8**

X	Y	Products (Yield, %)[a]	
		7	8
O	O	**7a** (82)	-
S	S	**7b** (80)	-
N	NH	-	**8c** (68)
N	O	-	**8d** (72)
N	S	**7e** (35)[b]	**8e** (38)

[a] All products were isolated by silica gel column chromatography.

[b] Products is (*E*) and (*Z*) isomeric mixture.

Exocyclization reaction of **2** with triol, such as glycerol, provided a mixture of 5-membered and 6-membered heterocyclic ketene acetals (**9**) and (**10**) (ratio = 1:1).[10] No selectivity was found.



2 9 10

In a typical experiment, sodium hydride (2.2 mmol) and 2-aminoethanethiol (1.1 mmol) in dry CH_3CN (10 ml) were stirred at room temperature for 1 h under nitrogen atmosphere. β,β-Difluoro-α-phenylvinyl sulfide (**2**) (1.0 mmol) was added dropwise at room temperature and then stirred for further 2 h. The reaction mixture was poured into water (10 ml) and extracted with ethyl acetate (10 ml x 2). The ethyl acetate solution was dried and chromatographed on a SiO_2 column. Elution with a mixture of hexane and ethyl acetate (20:1) provided **4f** in 86% yield.

4f : colorless oil ; ^1H nmr ($CDCl_3$) δ 7.75-7.20 (m, 10H), 4.20 (t, J = 7.3 Hz, 2H), 3.60 (br s, 1H), 3.21(t, J = 7.3 Hz, 2H) ; ms, m/z (relative intensity) 285 (M^+, 77), 176 (100), 167 (21), 148 (33), 84 (27) ; ir (neat) 3250, 3000, 1640 cm^{-1}. The product (**5d**) and (**5e**) was obtained in a same manner. **5d** : white solid ; mp 129-130 °C ; ^1H nmr ($CDCl_3$) δ 7.60-7.20 (m, 10H), 5.20 (s, 1H), 4.35 (br s, 1H), 3.67 (m, 4H) ; ms, m/z (relative intensity) 268 (M^+, 100), 159 (7) ; ir (KBr) 3200, 3000, 1580 cm^{-1}. **5e** : white solid ; mp 31-33 °C ; ^1H nmr ($CDCl_3$) δ 7.70-7.20 (m, 10H), 5.05 (s, 1H), 4.25 (m, 2H), 3.95 (m, 2H) ; ms, m/z (relative intensity) 269 (M^+, 44), 160 (48), 132(100), 117(27), 91(37) ; ir (KBr) 2900, 1650, 1160, 980 cm^{-1}.

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7. Spectroscopic data of **4h** and **6h** are as follows. **4h** : white solid ; mp 64-65 °C ; ^{1}H nmr ($CDCl_3$) δ 7.50-7.05 (m, 10H), 4.10 (m, 4H), 1.85 (m, 4H) ; ms, m/z (relative intensity) 298 (M^+, 34), 199 (27), 166 (75), 161(66), 121(100), 105(78) ; ir (KBr) 2900, 1580, 1470, 1260, 1100 cm^{-1}. **6h** : colorless oil ; ^{1}H nmr ($CDCl_3$) δ 7.60-7.10 (m, 10H), 4.15 (t, J = 6.3 Hz, 2H), 3.55 (t, J = 6.2 Hz, 2H), 1.75 (s, 1H), 1.70-1.40 (m, 4H) ; ms, m/z (relative intensity) 318 (M^+, 35), 226 (97), 199 (96), 165 (100), 121 (98) ; ir (neat) 3300, 1465, 1425, 1060, 740 cm^{-1}.
8. Spectroscopic data of **8c** and **8d** are as follows. **8c** : yellowish oil ; ^{1}H nmr ($CDCl_3$) δ 7.80-7.20 (m, 15H), 6.00 (s, 1H) ; ms, m/z (relative intensity) 316 (M^+, 100), 236 (25), 210 (63), 165 (32) ; ir (neat) 3250, 2900, 1580, 1440, 1260 cm^{-1}. **8d** : yellowish oil ; ^{1}H nmr ($CDCl_3$) δ 7.75-7.15 (m, 14H), 5.62 (s, 1H) ; ms, m/z (relative intensity) 317 (M^+, 5), 209 (29), 208 (100), 180 (7) ; ir (neat) 3000, 1650, 1160, 980 cm^{-1}.
9. Spectroscopic data of **7e** and **8e** are as follows. **7e** : yellowish oil ; ^{1}H nmr ($CDCl_3$) δ 11.50 (br s, 1H), 7.78-7.10 (m, 14H) ; ms, m/z (relative intensity) 333 (M^+, 100), 240 (25), 165 (42) ; ir (neat) 3450, 1450, 1330, 1160, 720 cm^{-1}. **8e** : yellowish solid ; mp 83-84 °C ; ^{1}H nmr ($CDCl_3$) δ 8.10-7.10 (m, 14H), 5.95 (s, 1H) ; ms, m/z (relative intensity) 333 (M^+, 100), 240 (83), 165 (32) ; ir (KBr) 3000, 1580, 1495, 1150, 770 cm^{-1}.
10. Spectroscopic data of **9** and **10** are as follows. **9** : colorless oil ; ^{1}H nmr ($CDCl_3$) δ 7.80-7.05 (m, 10H), 5.10-4.70 (m, 1H), 4.60-4.20 (m, 2H), 3.90-3.60(m, 2H) ; ms, m/z (relative intensity) 300 (M^+, 55), 199 (45), 165 (47), 121 (100) ; ir (neat) 3450, 1490, 1160, 760 cm^{-1}. **10** : colorless oil ; ^{1}H nmr ($CDCl_3$) δ 7.80-7.10 (m, 10H), 4.90-4.70 (m, 1H), 4.50-4.10 (m, 4H) ; ms, m/z (relative intensity) 300 (M^+, 35), 199 (100), 165 (15), 121 (21) ; ir (neat) 3450, 1580, 1450, 750, 700 cm^{-1}.

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