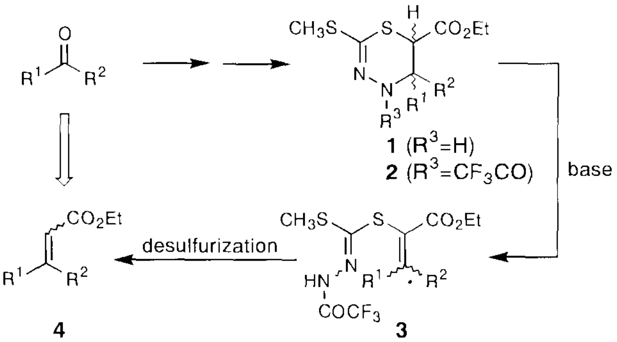
Conversion of 2-Methylthio-4-trifluoroacetyl-5,6-dihydro-*4H*-1,3,4-thiadiazines into *α,β*-Unsaturated Esters *via* Carbanion-Induced Ring Opening and Desulfurization

Kazuaki Shimada, Akihiro Otaki, Masaki Yanakawa, Shosuke Mabuchi, Naoya Yamakado, Takeshi Shimoguchi, and Yuji Takikawa*
Department of Applied Chemistry and Molecular Science, Faculty of Engineering, Iwate University, Morioka, Iwate 020-8551

(Received December 19, 1997; CL-970958)

A convenient conversion of 2-methylthio-5,6-dihydro-*4H*-1,3,4-thiadiazines **1** into α,β-unsaturated esters was achieved through the procedure including trifluoroacetylation of **1**, carbanion-induced ring opening of trifluoroacetamides **2**, and reductive removal of heteroatom functionality of the resulting *S*-alkenyl hydrazinecarbodithioates **3**. Treatment of **3** with a base under an aqueous condition also gave the corresponding 6-alkylidene-*4H*-1,3,4-thiadiazin-5-ones **6**.

Ongoing studies in our laboratory focus on exploring the synthetic uses of sulfur-containing heterocyclic compounds. Previously, we have reported a Pummerer-type ring fission of 2-methylthio-5,6-dihydro-*4H*-1,3,4-thiadiazines **1** to give α,β-unsaturated esters **4**.[1] However, the sequence was not applicable to the acid-labile substrates, and the alternative methods for the ring opening of **1** have been required to expand the synthetic use of **1**. It was naturally expected that the introduction of an easily removable electron-deficient functional group to the N-4 position of **1** and the subsequent treatment with a base would cause ring-opening to give *S*-alkenyl hydrazinecarbodithioates **3** possessing an ester group,[2] and, furthermore, compounds **3** would be easily converted into α,β-unsaturated esters **4** by reductive desulfurization. In this paper, we would like to describe a convenient conversion of **1** into **4** through the sequence including trifluoroacetylation of **1**, ring opening of trifluoroacetamides **2**, and desulfurization of *S*-alkenyl hydrazinecarbodithioates **3** using Al-Hg.



Scheme 1.

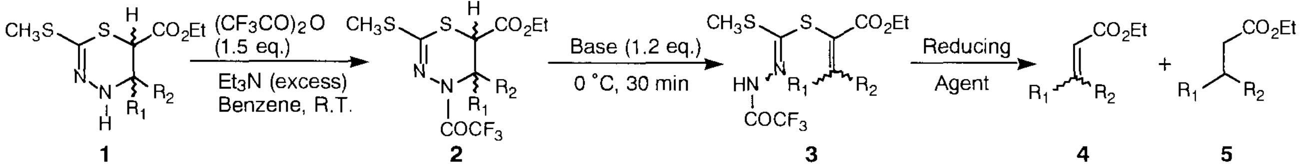
2-Methylthio-5,6-dihydro-*4H*-1,3,4-thiadiazines **1** were prepared by starting from aldehydes or cyclohexanone, *S*-methyl hydrazinecarbodithioate,[3] and ethyl bromoacetate according to our previously-reported method.[1] Subsequently, a benzene solution of *cis*-**1**, *trans*-**1**, or the mixture of *cis*- and *trans*-**1**, was treated with $(CF_3CO)_2O$ (1.5 mol amt.) and an excess amount of Et_3N to give the corresponding epimeric mixture of trifluoroacetamides **2** in almost quantitative yields.[4] Interestingly, the ratios of two epimers of **2** were substantially equal by starting the reaction either from *cis*-**1** or *trans*-**1**. For example, the trifluoroacetylation of either *trans*-**1a**(R^1=H, R^2=C_6H_5) or *cis*-**1a**(R^1=C_6H_5, R^2=H) gave a chromatographically separable mixture of the epimers of trifluoroacetamides **2a** in high yields (major-**2a**:minor-**2a**=89:11, in both cases). The treatment of a benzene solution of either *trans*-**2a** or *cis*-**2a** with Et_3N at room temperature also gave the same mixture of **2a** in quantitative yield. Apparently, the ethoxycarbonyl groups at the C-6 position of **2** caused epimerization during the usual trifluoroacetylation of **1** under basic condition. However, the relative stereochemistry of the major or minor isomers of **2** was not determined in all cases.

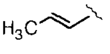
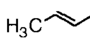
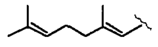
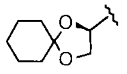
Subsequently, according to the method of Babudri,[2] a dry THF or a dry benzene solution of a diastereomeric mixture of **2** was treated with NaH or *t*-BuOK (1.2 mol amt.) at room temperature to give ring-opening products **3** as single geometrical isomers.[4] In all cases, compounds **3** were inert toward the exposure to air and sunlight, and the treatment with an aqueous HCl solution also caused neither isomerization of the double bonds of **3** nor the acidic hydrolysis of the heteroatom functionality of **3**. It was supposed that either major or minor isomers of **2**, formed by base-induced equilibration, would exclusively cause carbanion-induced ring cleavage to give **3** possessing a sole geometry of the newly-formed double bonds. However, the determination of the geometry of the double bonds of **3** was not achieved in all cases.[5] An ether-ethanol solution (3:1) of **3** was then treated with Aluminium-amalgam (Al-Hg)[6] under a N_2 atmosphere at room temperature for overnight to give the corresponding α,β-unsaturated esters **4**. The geometry of the resulting double bonds of the products was *E* exclusively in all cases.[7] On the other hand, reductive desulfurization of **3a** by using Raney Nickel (W-2) only gave perhydogenated ester **5a**(48%), and Birch reduction of **3** predominantly caused hydrolytic cleavage of the ester groups to give several undesired products. The sequence mentioned above was also applied to protected glyceraldehyde derivative **1f** to give the corresponding α,β-unsaturated ester **4f**, in which sequence no separation and purification of the stereoisomers of **1f**, **2f**, and **3f** was needed. All the results of the conversion of **1** into **4** including trifluoroacetylation of **1**, the subsequent carbanion-induced ring opening of **2**, and the reductive desulfurization of **3** are summarized in Table 1.

On the other hand, when an excess amount of base was treated with **2** at room temperature followed by quenching the reaction by adding a small amount of water, 2-methylthio-6-alkylidene-*4H*-1,3,4-thiadiazin-5-ones **6**[4] were obtained in good yields. Treatment of an ethanolic solution of **2** with an aqueous KOH solution at room temperature also gave the same products efficiently. In all cases, the signals of the vinyl protons of the major-**6** revealed the significant downfield shifts in the ^1H NMR spectra comparing with those of the minor-**6**.[8] These results suggested that major-**6** possessed *Z* geometry. However, the geometry of the double bonds of **6** was not finally determined in all cases. It was assumed that compounds **6** were formed through hydrolytic cleavage of trifluoroacetylhydrazide and ethoxycarbonyl groups followed by facile lactamization.

In conclusion, we have found a conversion of 2-methylthio-5,6-dihydro-*4H*-1,3,4-thiadiazines **1** into α,β-unsaturated esters **4** *via* carbanion-induced eliminative ring opening of trifluoroacetamide **2** as well as the route for the synthesis of 6-alkylidene-*4H*-1,3,4-thiadiazin-5-ones **6**. Further attempts for non-reductive removal of the heteroatom functionalities of **1** are underway in our laboratory.

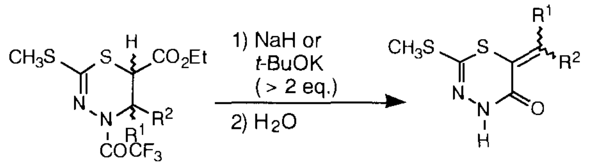
Table 1. Trifluoroacetylation of **1**, Carbanion-induced Ring Opening of Trifluoroacetamides **2**, and Reductive Desulfurization of the Resulting **3**



Substrate			Yield of **2** / % [a, b]	Base	Solvent	Yield of	Reducing	Solvent	Yield / % [a]	
R[1]	R[2]	**1**	(major:minor) [c]			**3** / % [a, d]	Agent		**4**	**5**
C_6H_5	H	*cis*-**1a**	98 (**2a**, 89:11)	*t*-BuOK	Benzene	91 (**3a**) [e]	Al-Hg [f]	Et_2O-EtOH	66 (**4a**)	0
							Raney Ni	EtOH	0	48 (**5a**)
							Li-liq. NH_3	Et_2O-EtOH	complex mixture	
H	C_6H_5	*trans*-**1a**	98 (**2a**, 89:11)							
CH_3	H	**1b**	40 (**2b**) [g]	*t*-BuOK	Benzene	24 (**3b**) [e]	Al-Hg [f]	Et_2O-EtOH	18 (**4b**)	0
i-C_3H_7	H	**1c**	quant. (**2c**) [g]	*t*-BuOK	Benzene	83 (**3c**) [e]	Al-Hg [f]	Et_2O-EtOH	48 (**4c**)	0
	H	*cis*-**1d**	70 (**2d**, 61:39)	NaH	THF	94 (**3d**) [e]	Al-Hg [f]	Et_2O-EtOH	32 (**4d**)	0
H		*trans*-**1d**	79 (**2d**, 71:29)	NaH	THF					
H		*trans*-**1e**	87 (**2e**, 68:32)	NaH	THF	74 (**3e**) [c]	Al-Hg [f]	Et_2O-EtOH	73 (**4e**)	0
	H	**1f** [h]	90 (**2f**, 3:1)	NaH	THF	79 (**3f**) [i]	Al-Hg [f, j]	Et_2O-EtOH	77 (**4f**)	0
-$(CH_2)_5$-		**1g**	99 (**2g**)	*t*-BuOK	Benzene	87 (**3g**)	Al-Hg [f]	Et_2O-EtOH	0	39 (**5g**)

[a] Isolated yields. [b] A benzene solution of **1** was treated with 1.5 molar amount of $(CF_3CO)_2O$ and an excess amount of Et_3N at room temperature. [c] Determined by integration of the ^1H NMR spectra of the mixture of **2**. [d] A THF or a benzene solution of **2** was treated with 1.2 molar amount of NaH or *t*-BuOK at 0 °C for 30 min. [e] Single geometrical isomer of **3**. [f] An ether-ethanol (3:1) solution of **3** was treated with an excess amount of aluminium amalgam (Al-Hg)[6] at room temperature. [g] The ratios of the isomers were not determined. [h] The mixture of stereoisomers (about 10:3:1:1, estimated from integration of the ^1H NMR signals of the mixture) was used for the substrate. [i] A 3:2 mixture of **3f**. [j] A crude mixture was submitted to desulfurization owing to the unstability of **3f**.

Table 2. One-Pot Conversion of **2** to 6-Alkylidene-*4H*-1,3,4-thiadiazin-5-ones (**6**)



Substrate **2**	Base	Solvent	Temp / °C	Time / h	Yield of **6** /% (major:minor) [a,b]
2a	*t*-BuOK	Benzene	R.T.	0.5	87 (**6a**, >10:1)
2d	NaH	THF	R.T.	0.5	72 (**6d**, >10:1)
2e	NaH	THF	R.T.	0.5	59 (**6e**, 5:1)

[a] Determined by the integration of the ^1H NMR spectra of the geometrical mixture of **6**. [b] The geometry of the double bonds of the major isomers of **6** was not determined in all cases.

References and Notes

1 a) K. Shimada, A. Otaki, M. Yanakawa, S. Mabuchi, N. Yamakado, T. Shimoguchi, K. Inoue, T. Kagawa, K. Shoji, and Y. Takikawa, *Chem. Lett.*, **1995**, 925. b) K. Shimada, A. Otaki, M. Yanakawa, S. Mabuchi, N. Yamakado, T. Shimoguchi, K. Inoue, T. Kagawa, K. Shoji, and Y. Takikawa, *Bull. Chem. Soc. Jpn.*, **69**, 1043 (1996), and the references cited therein.

2 a) F. Babudri, S. Florio, G. Indelicati, and G. Trapani, *J. Org. Chem.*, **48**, 4082 (1983). b) F. Babudri, S. Florio, A. Reho, and G. Trapani, *J. Chem. Soc., Perkin Trans 1*, **1984**, 1949.

3 M. Busch and M. Starke, *J. Prakt. Chem.*, **93**, 59 (1916).

4 The physical data of **2**, **3**, and **6** are available as supplementary materials.

5 The geometry of the double bond of major-**3a** was supposed to be *E*, because the signal of the vinyl proton revealed the significant downfield shift (δ=8.30 ppm) in the ^1H NMR spectrum of major-**3a** comparing with that of minor-**3a** (δ=7.0-7.5 ppm).

6 H. Wislicenum and L. Kaufmann, *Ber.*, **28**, 1323 (1895).

7 The coupling constants between the vinyl protons (C-2 and C-3 positions) of **4d** and **4e** in the ^1H NMR spectra are *J*=15.0 -16.0 Hz, respectively.

8 For example, the singlet signals of the vinyl protons of major- and minor-**6a** revealed at δ=7.88 ppm and δ=6.97 ppm, respectively, in the ^1H NMR spectrum of the mixture of **6a**.