A Homologation of Aldehydes and Ketones *via* the Formation and the Subsequent Pummerer-type Ring Fission of 2-Methylsulfinyl-5,6-dihydro-*4H*-1,3,4-thiadiazine Derivatives

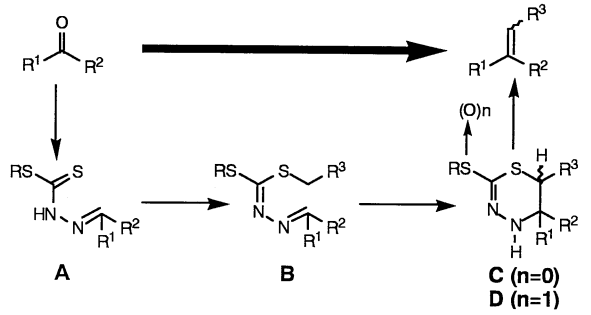
Kazuaki Shimada, Akihiro Otaki, Masaki Yanakawa, Shosuke Mabuchi, Naoya Yamakado, Takeshi Shimoguchi, Kazuya Inoue, Takashi Kagawa, Kazutoshi Shoji, and Yuji Takikawa*

Department of Applied Chemistry and Molecular Science, Faculty of Engineering, Iwate University, Morioka, Iwate 020

(Received June 22, 1995)

A two-carbon homologation of aldehydes and ketones was achieved by using a sequence involving the formation and the subsequent Pummerer-type ring fission of 5,6-dihydro-*4H*-1,3,4-thiadiazine rings possessing methylsulfinyl functionality at C-2.

Among the derivatives of multifunctionalized thiocarbamates, alkylidenehydrazonecarbodithioates have been widely studied as the synthetic precursors of 1,3,4-thiadiazine and 1,3,4-thiadiazole ring systems which exhibit various biological activities.[1] However, only slight attention has been concentrated to the intramolecular C-C bond formation of S,S-dialkylated derivatives **B** owing to the lack of the removal of heteroatoms from the ring-closure products **C**. During the course of our studies on the synthetic use of thiocarbonate derivatives, we have expected that the multifunctionalized hydrazones **B**, constructed from aldehydes or ketones, $NH_2NH_2{\cdot}H_2O$, CS_2, RX(CH_3I), and alkylating agents, would cause α-sulfenylcarbanion-induced ring-closure to give 5,6-dihydro-*4H*-1,3,4-thiadiazines **C**.[2] Furthermore, it was also expected that the subsequent removal of the heteroatoms of **C** or **D** would be carried out by eliminative ring fission[3] or [4+2]-type cycloreversion. In this paper, we would like to describe a procedure for the homologation of aldehydes and ketones including the formation and Pummerer-type ring fission of **C** as shown in Scheme 1.

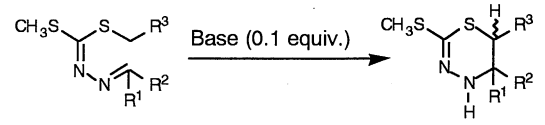


Scheme 1.

Methyl alkylidenehydrazonecarbodithioates **A** were easily prepared either by treating a benzene solution of methyl dithiocarbazate ($CH_3SCSNHNH_2$)[4] with 1 equiv. of aldehydes or ketones or by the sequential treatment of an ethanolic solution of aldehydes or ketones with $NH_2NH_2{\cdot}H_2O$, KOH, CS_2, and CH_3I. Subsequently, a solution of **A** was treated with a base (1.1 equiv. of KOH or NaH in EtOH or THF, respectively) and an alkylating agent ($BrCH_2CO_2Et$, $ClCH_2COMe$, $BrCH_2COPh$, and $BrCH_2CN$) to give **1** as the inseparable mixture of *syn* and *anti* isomers.[5]

Heating a THF or a benzene solution of **1** and a base (NaH or *t*-BuOK, 0.1 equiv.) for a few hours under a N_2 atmosphere afforded the ring-closure products **2** as a mixture of *cis* and*trans* isomers, and each isomer was separated by silica gel column chromatography. MS, IR, and ^1H NMR spectra of each isomer showed a similar pattern.[5] The relative stereochemistry of the isomers was confirmed by the J values between the H-5 and H-6 protons in the ^1H NMR spectra.[6] The treatment of a base with the solution of **1** possessing various substituents also gave the corresponding ring-closure products, 5,6-dihydro-*4H*-1,3,4-thiadiazines **2**, in good yields, and all results are shown in Table 1.

Table 1. Preparation of 5,6-dihydro-*4H*-1,3,4-thiadiazines (**2**)



1 **2**

Substrate			Base	Solvent	Temp	Time	Yield [a,b]
R^1	R^2	R^3			/°C	/h	/%
Ph	H	CO_2Et	NaH	benzene	55	4	72 (**2a**) [c]
Ph	H	CO_2Et	NaH	THF	reflux	3	89 (**2a**) [d]
Ph	H	$COCH_3$	NaH	benzene	65	4	89 (**2b**) [e]
Ph	H	COPh	NaH	benzene	65	4	82 (**2c**) [f]
Ph	H	CN	*t*-BuOK	benzene	reflux	1	93 (**2d**) [g]
i-Pr	H	CO_2Et	NaH	benzene	65	4	97 (**2e**) [h]
-$(CH_2)_5$-		CO_2Et	*t*-BuOK	benzene	reflux	1	75 (**2f**)
Ph	CH_3	CO_2Et	*t*-BuOK	benzene	reflux	3	trace (**2g**)[i]

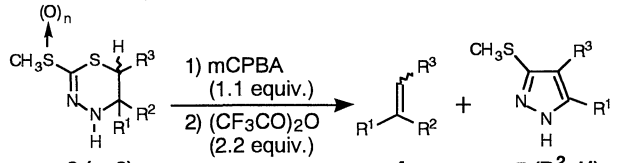
[a] Combined yields. [b] The ratio of *cis*-**2**:*trans*-**2** was determined by the integration of the ^1H NMR spectra of the crude products. [c] *cis*-**2a**:*trans*-**2a**=98:2. [d] *cis*-**2a**:*trans*-**2a**=7:93. [e] *cis*-**2b**:*trans*-**2b**=5:95. [f] *cis*-**2c**:*trans*-**2c**=0:100. [g] *cis*-**2d**:*trans*-**2d**=5:95, [h] *cis*-**2e**:*trans*-**2e**=15:85. [i] The starting material **1g** was recovered.

Interestingly, treatment of **1a**(R^1=Ph, R^2=H, R^3=CO_2Et) with a base under the mild reaction condition (0.1 equiv. of NaH in benzene at 55 °C) afforded *cis*-**2a** predominantly. On the other hand, *trans*-**2a** was mainly obtained when **1a** was treated with a base at higher temperature. Base-induced equilibration was also observed by treating a solution of *cis*-**2a** with a catalytic amount of NaH or *t*-BuOK under the higher temperature. The use of tertiary amines (Et_3N or DBU) in place of NaH or *t*-BuOK was ineffective for the ring-closure of **1**. These results suggested that the intramolecular complexation of the metal enolates of **5** with the nitrogen atom of hydrazone moiety promotes the approaching of two reaction sites of **5** in the primary stage, and the *cis* isomers were formed as the primary ring-closure products.

Treating of a CH_2Cl_2 solution of *cis*-**2** or *trans*-**2** with mCPBA(1.1 equiv.) at 0 °C afforded sulfoxides **3** in high yields as an inseparable mixture of diastereomers on the sulfur atoms. All physical data and the elemental analysis data were consistent with the structures of **3**.[5] The significant downfield shift of the methyl signal of trans-**3a** in both ^1H NMR and ^{13}C NMR spectra suggested that **3** possessed methylsulfinyl groups at C-2 position in all cases.

Trans-**3a** was then subjected to the heating (125 °C for 26h in a sealed tube) to give an olefinic compound (*E*-**4a**) in rather low

Table 2. Preparation and Ring Cleavage of 2-Methylsulfinyl-5,6-dihydro-*4H*-1,3,4-thiadiazines (**3**) [a, b]



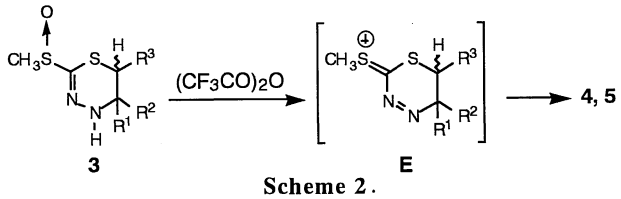
2 (n=0)
3 (n=1)

4

5 (R^2=H)

Substrate				Yield / % [c]	Yield / % [c]	
R^1	R^2	R^3	**2**	**3** [d]	**4**	**5**
Ph	H	CO_2Et	*trans*-**2a**	84	64 (*E*-**4a**)	20(**5a**)
Ph	H	CO_2Et	*cis*-**2a**	61	58 (*Z*-**4a**) [e]	- [f]
Ph	H	$COCH_3$	*trans*-**2b**	78	81 (*E*-**4b**)	- [f]
Ph	H	COPh	*trans*-**2c**	96	63 (*E*-**4c**)	- [f]
Ph	H	CN	*trans*-**2d**	96	0 (*E*-**4d**) [g]	- [f]
i-Pr	H	CO_2Et	*trans*-**2e**	78	50 (*E*-**4e**)	- [f]
-$(CH_2)_5$-		CO_2Et	**2f**	68	60 (**4f**)	-

[a] A CH_2Cl_2 solution of **2** was treated with mCPBA(1.1 equiv.) at -78 °C for 1h. [b] A CH_2Cl_2 solution of **3** was treated with $(CF_3CO)_2O$ (2.2 equiv.) at -78 °C for 1h. [c] Isolated yields. [d] Combined yields of the diastereomers. [e] *E*-**4a** was also obtained in 7% yield along with *Z*-**4a**. [f] Not isolated. [g] Complex mixture.



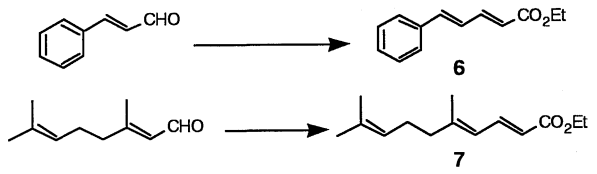
3 **E**

Scheme 2.

yield (30%) along with the deoxygenated product (*trans*-**2a**, 50%). Improved results were obtained by adding BF_3•OEt_2(1 equiv.) to the benzene solution of *trans*-**3a** (80 °C, 1h) to give *E*-**4a** in 40% yield, and furthermore, treatment of a CH_2Cl_2 solution of *trans*-**3a** with $(CF_3CO)_2O$ (2.2 equiv.) at -78 °C afforded *E*-**4a** in 64% yield besides pyrazole **5a**(20%)[1j,5] and various unidentified compounds. The use of $(CH_3CO)_2O$ in place of $(CF_3CO)_2O$ was ineffective at all for the reaction even at room temperature.[7] The treatment of sulfoxides **3** possessing various substituents with $(CF_3CO)_2O$ also gave similar olefinic products **4** in modest yields, and all results of the reactions were shown in Table 2.

It is noteworthy that the geometry of the double bond of product **4a** was *E* exclusively when *trans*-**3a** was treated with $(CF_3CO)_2O$, and *Z*-**4a** was also mainly obtained by treating *cis*-**3a** with $(CF_3CO)_2O$ under the same reaction condition. These results suggested that the olefinic products **4** were afforded through the regioselective fragmentation of 2-methylsulfinyl-5,6-dihydro-*4H*-1,3,4-thiadiazines **3**. It was supposed that the Pummerer-type intermediates **E** were initially generated by the reaction of sulfoxides **3** with $(CF_3CO)_2O$, and thus, these results suggested that the olefinic products **4** were afforded by the stereoeselective ring fission of **E**. However, all attempts to trap or detect the intermediates of the reaction were unsuccessful, and the products containing sulfur atoms originated from **3** were not found at all in the crude reaction mixture. The formation of pyrazole derivative **5a** was also explained by the mechanism including the sulfur extrusion[8,9] from **E**.

Furthermore, we attempted the homologation of cinnamic aldehyde and geranial by using this sequence shown above.[5] However, the final step of the sequence afforded the corresponding α,β,γ,δ-unsaturated esters (**6** and **7**) in low yields (20% and 28%, respectively).



In conclusion, we have found a novel formation and the Pummerer-type ring fission of 2-methylsulfinyl-5,6-dihydro-*4H*-1,3,4-thiadiazines. Further attempts to trap the reaction intermediates **E** as well as the synthetic applications of the sequence are in progress in our laboratory.

References and Notes

1 a) R. Andreasch, *Monatsh.*, **27**, 1211 (1906). b) S. M. Losanitch, *J. Chem. Soc.*, **119**, 763 (1921). c) P. K. Bose, *Quart. J. Ind. Chem. Soc.*, **3**, 197 (1926). d) J. Sandström, *Arkiv. Kemi.*, **7**, 249 (1952). e) J. Sandström, *Arkiv. Kemi.*, **4**, 297(1952). f) R. A. Mathes, *J. Org. Chem.*, **17**, 877 (1952). g) R. Hull, *J. Chem. Soc.*, **1952**, 2959. h) H. Beyer, W. Lässig, and E. Bulka, *Chem. Ber.*, **87**, 1385 (1954). i) T. Sato and M. Ohta, *Yakugaku Zasshi*, **77**, 771 (1957). j) J. Sandström, *Acta Chem. Scand.*, **16**, 2395 (1962). k) D. L. Trepanier, W. Reifschneider, W. Shumaker, and D. S. Tharpe, *J. Org. Chem.*, **30**, 2228 (1965). l) D. L. Trepanier and P. E. Krieger, *J. Heterocycl. Chem.*, **4**, 254 (1967). m) Y. Usui and T. Yamano, *Yakugaku Zasshi*, **89**, 689 (1969). n) Y. Usui and T. Yamano, *Yakugaku Zasshi*, **89**, 699 (1969), o) J. Beger, C. Thilemann, and P. D. Thong, *J. Prakt. Chem.*, **321**, 959 (1979). p) S. Kubota, Y. Ueda, K. Fujikane, K. Toyooka, and M. Shibuya, *J. Org. Chem.*, **45**, 1473 (1980). q) S. H. Askari, S. F. Moss, and D. R. Taylor, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 360. r) S. Kubota, K. Toyooka, J. Ikeda, N. Yamamoto, and M. Shibuya, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 967. s) Y. Nakayama and Y. Sanemitsu, *J. Org. Chem.*, **49**, 1703 (1984). t) Y. Nakayama and Y. Sanemitsu, *Synthesis*, **1984**, 771. u) S. V. Usol'tseva, G. P. Andronnikova, S. L. Nikolaeva, A. T. Lebedev, and V. A. Shevyrin, *Khim. Gelerotsikl. Soedin.*, **1991**, 554. v) W. Hanefeld and M. Schlitzer, *Arch. Pharm.*, **326**, 249 (1993).

2 D. M. Evans, D. R. Taylor, and M. Myers, *J. Chem. Soc., Chem. Commun.*, **1984**, 1444.

3 F. Babudri, S. Florio, A. Reho, and G. Trapani, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1949, and the references cited therein.

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

5 Supplementary materials containing the physical data of the compounds **1**-**5** and the precursors of **6** and **7** are available.

6 For example, the J value of H-5 and H-6 of *trans*-**2a** was 9 Hz. On the other hand, that of *cis*-**2a** was 3 Hz.

7 The treatment of a benzene solution of *trans*-**3a** with $(CF_3CO)_2O$ in the presence of an excess amount of Et_3N gave a complicated mixture, in which **4a** was not found at all.

8 R. R. Schmidt, *Angew. Chem.*, **87**, 603 (1975), and the references cited therein.

9 W. D. Pfeiffer, E. Bulka, and R. Miethchen, *Z. Chem.*, **27**, 296 (1987), and the references cited therein.