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HIGHLY STEREOSELECTIVE SYNTHESIS OF (2E,4E)-DIENAMIDES AND (2E,4E)-DIENOATES VIA A DOUBLE ELIMINATION REACTION

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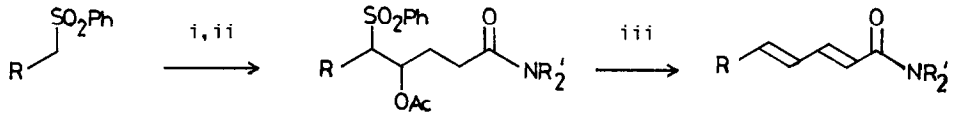
Summary: Highly stereoselective synthesis of (2E,4E)-dienamides and (2E,4E)-dienoates was achieved through a double elimination reaction of β-acetoxy sulfones.

(2E,4E)-Dienamides belong to an important class of compounds which show both physiologiacal and insecticidal activities.[1] (2E,4E)-Dienoates also are important key intermediates for various natural product syntheses.[2] There have appeared several synthetic methods[1,2] involving the Wittig reaction and the Knoevenagel condensation. Nevertheless, it is desirable to develop a more stereoselective and practical procedure for these compounds.

Recently, we have reported a novel synthetic method for polyenic and acetylenic compounds via a double elimination reaction of β-acetoxy sulfones employing t-BuOK as a base.[3] In our continuing study on this methodology, we have found that (2E,4E)-dienamides and (2E,4E)-dienoates are readily accessible in a high stereoselective manner. The outline of our method is illustrated in Scheme I, and the results are complied in Table 1.

Scheme I



1 3 4

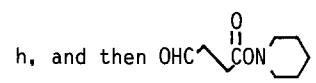
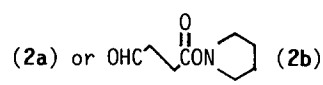
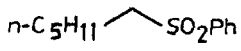
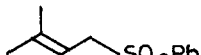
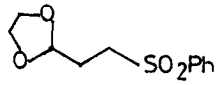
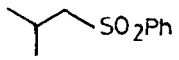
(i) n-BuLi, THF, -30 °C, 1 h, and then  (**2a**) or  (**2b**)
(ii) Ac_2O-pyridine
(iii) t-BuOK/t-BuOH, rt, 12 h

Table 1. Conversion of **1** to (2E,4E)-dienamides **4**

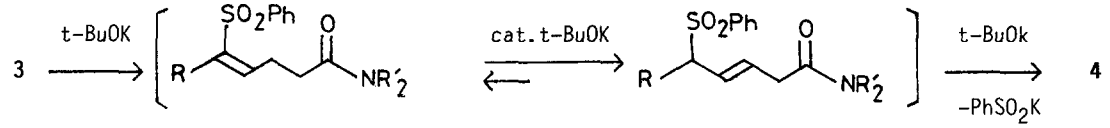
1	2	3(%)[a]	4(%)[b]	content of the (2E,4E) isomer (%)[c]
	**2a**	67	88	88
	2b	72	87	89
	**2a**	76	82	95
	2b	84	52	92
	**2a**	87	69	90
	**2b**	69	60	90

a) Isolated yields based on **1** after column chromatography (silica gel).

b) Yields based on **3**.

c) Deteremined by isolation with column chromatography.

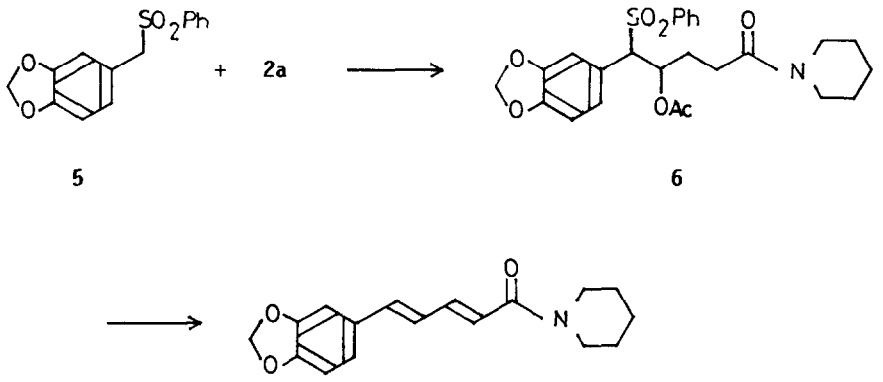
The notable features of the present method consist in (1) facile availability of the aldehydes **2**,[4] (2) mildness of the reaction conditions, and (3) high yields and stereoselectivity. The reaction mechanism can be rationalized as follows.[5]



The following procedure is representative. Sulfone **1** was lithiated by n-BuLi (1.2 eq) in THF at -30 °C for 1 h. Aldehyde **2** was added dropwise at -78 °C to this solution, and the reaction was continued at this temperature for 0.5 h. Treatment of the crude -hydroxy sulfone thus obtained with Ac_2O-Py provided the corresponding acetate **3** after column chromatography on silica gel. A solution of **3** (2.0 mmol) in t-BuOH (10 ml) was treated with t-BuOK (6.0 mmol)[6] at room temperature for 12 h. The product was found to be the (2E,4E)-dienamide **4** contaminated with a small amount of two stereoisomers (5-10%) whose stereochemistry has not been deteremined yet. Isolation of the pure compounds was performed with ease by column chromatography on neutral alumina.

We have applied the present method to synthesis of piperine (**7**).[7] Scheme II illustrates the outline of our approach. Sulfone **5**,[8] readily available from piperonal, was coupled with

Scheme II



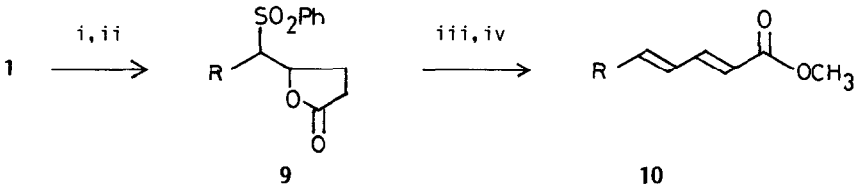
5 6

piperine(7)

the aldhyde **2a** in the predescribed manner affording the acetate **6** in 66% yield. The acetate **6** was subjected to the double elimination reaction to give piperine (**7**) with good stereocontrol (90% E,E isomer based on ^{1} NMR) in 77% yield: mp 130-131 °C (lit.[9] 129-130 °C).

Next, synthesis of (2E,4E)-dienoates was realized from the sulfone **1** and the aldehyde **8** as shown in Scheme III. The lithiated sulfone was treated with **8**[10] in THF at -78 °C for 5 min to give a hydroxy sulfone. Subjection of this compound to the double elimination reaction resulted in unsatisfactory yield and stereochemical outcome. The drawback was overcome by converting the β-hydroxy sulfone to the lactone **9** with a catalytic amount of p-toluenesulfonic acid in refluxing benzene. Then, the double elimination reaction of **9** was found to proceed successfully by employing t-BuOK (3.0 eq) in t-BuOH at room temperature for 12 h. The desired (2E,4E)-dienoates **10** were obtained as a majar product after treatment with diazomethane. The results are summarized in Table 2.

scheme III

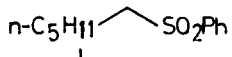
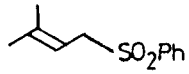
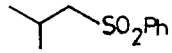
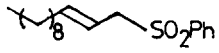


9 10

(i) n-BuLi, THF, -30 °C, 1 h, and then $OHCCH_2CH_2CO_2Et$ (**8**), -78 °C, 5 min
(ii) cat. p-TsOH, benzene, reflux, 4 h (iii) t-BuOK, t-BuOH, rt, 12 h (iv) CH_2N_2

Acknowledgement: Thanks are due to Dr. S. Tsuboi of Okayama University for providing us with ^{1}H and ^{13}C NMR spectral data of piperine.

Table 2. Conversion of **1** to (2E,4E)-Dienoates **10**

1	**9**(%)	**10**(%)	content of the (2E,4E) isomer(%)
	63	70	90
	82	53	90
	70	64	94
	68	67	77

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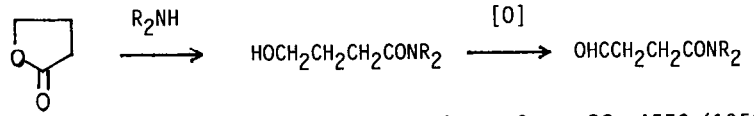
(1) (a) F. Bohlmann, M. Ganzer, M. Kruger, and E. Nordhoff, Tetrahedron, **39**, 123 (1983). (b) S. Tsuboi, Y. Nooda, and A. Takeda, J. Org. Chem., **49**, 1204 (1984), and references cited therein.

(2) (a) T. Sakai, K. Seko, A. Tsuji, M. Utaka, and A. Takeda, J. Org. Chem., **47**, 1101 (1982). (b) B. M. Trost, M. Lautens, and B. Peterson, Tetrahedron Lett., **24**, 4525 (1983).

(3) T. Mandai, T. Yanagi, K. Araki, Y. Morisaki, M. Kawada, and J. Otera, J. Am. Chem. Soc., **106**, 3670 (1984).

(4) Aldehydes **2a** and **2b** were prepared in 70% and 52% overall yields as follows:



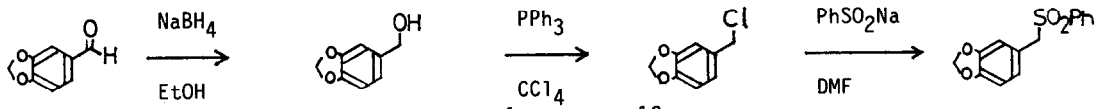
cf: N. H. Cromwell and K. F. Cook, J. Am. Chem. Soc., **80**, 4573 (1958); J. B. Jones and J. M. Young, Can. J. Chem., **44**, 1059 (1966); A. J. Macuso, S. L. Huang, and D. Swern, J. Org. Chem., **43**, 2480 (1978).

(5) Base-catalyzed equilibrium between vinyl and allyl sulfones was well established: D. E. O'Connor and W. I. Lyness, J. Am. Chem. Soc., **86** 3840 (1964).

(6) t-BuOK was used as a t-BuOH solution (0.5 mol/l).

(7) (a) E. Wenkert, D. W. Cochran, E. W. Hagaman, R. B. Lewis, and F. M. Schell, J. Am. Chem. Soc., **93**, 6721 (1971). (b) S. Tsuboi and A. Takeda, Tetrahedron Lett., 1043 (1979).

(8) Prepared in 74% overall yield by the following procedure.



(9) S. Tsuboi, private communication. The ^{1}H NMR and ^{13}C NMR data were identical with those of the authentic sample.

(10) Prepared in 50% yield according to the known method: E. J. Corey and M. Mehrotra, J. Am. Chem. Soc., **106**, 3384 (1984).

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