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STEREOSELECTIVE SYNTHESIS OF (E)-, (E,Z)- AND (E,E)-CONJUGATED DIENES VIA ALKYLATION OF 3-SULFOLENES AS KEY STEP

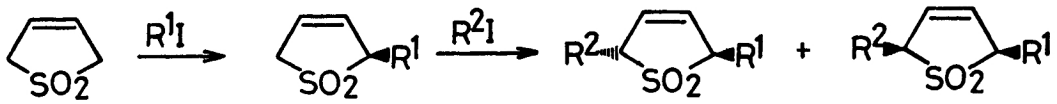
Sachiko YAMADA, Hideto OHSAWA, Takayoshi SUZUKI, and Hiroaki TAKAYAMA*
Faculty of Pharmaceutical Sciences, Teikyo University,
Sagamiko, Kanagawa 199-01

Stereoselective method for synthesizing (E)-, (E,Z)- and (E,E)-conjugated dienes via alkylation of 3-sulfolenes as key step is developed. Sex pheromones with (E)- and (E,E)-conjugated diene structures are synthesized with exclusively high stereoselectivity by applying the method.

2,5-Dihydrothiophene-1,1-dioxides (3-sulfolenes) have been utilized as versatile masked diene synthons in organic synthesis.[1] However structural modification of 3-sulfolenes, especially introduction of electrophiles to the α-position under basic conditions, is highly limited,[2] because 3-sulfolene α-carbanion is labile and undergoes ring opening before reacting with an electrophile.[3] Recently, Bloch et al.[4] deviced a method to obviate this difficulty where the double bond in 3-sulfolene is protected as a Diels-Alder adduct to prevent ring opening. During the studies of the chemistry of vitamin D, we found that sulfur dioxide adduct of vitamin D at the s-cis diene part can be alkylated at the position α to the SO_2 group in good yield when the labile sulfolene α-carbanion was generated in the presence of an alkylating agent.[5] We applied the method to alkylation of the parent 3-sulfolene and established, for the first time, a practical method for alkylating 3-sulfolenes including the first stereoselective method for synthesizing trans-2,5-disubstituted 3-sulfolenes. We also found a new highly stereoselective method for desulfonylating trans-2,5-disubstituted 3-sulfolenes to yield (E,E)-conjugated dienes in opposition to the symmetry rule.[6,7] Combination of the alkylation of 3-sulfolenes and stereoselective thermal desulfonylation of the substituted 3-sulfolenes provided novel stereoselective synthetic routes to (E), (E,Z)- and (E,E)-conjugated dienes.[8]

Alkylation of 3-sulfolenes was made successful by the following devices; i) to trap the labile sulfolene α-carbanion with an electrophile before it undergoes ring opening, the carbanion was generated in the presence of alkyl iodide, ii) the nature of the base was crucial and the use of lithium silylamide in the presence of HMPA as the cation trapping agent gave the best results, and iii) the base was added in one portion at low temperature (-78 °C) to obtain the maximum concentration of transient labile carbanion to react with the electrophile. The results are summarized in Table I. Alkylation of 3-sulfolene (1) gave 2-alkyl-3-sulfolenes (2) in 40-65% isolated yields based on the halide used. It is noteworthy that the alkylation of 2-substituted sulfolenes (2) proceeded with complete regio- and high (90-98%) stereoselectivity to yield trans-2,5-disubstituted 3-sulfolenes (3) (55-71% yield based on the sulfolenes used).[9] The results indicate that bulky base abstracts the least hindered and the most acidic proton at the 5-position located trans to the substitutent at C-2, and that the resulting carbanion reacts rapidly before inverting the stereochemistry.

Scheme 1.



1 2 3 4

2: R[1]
a: n-Bu
b: Me
c: Et
d: n-Hep
e: isoamyl
f: $(CH_2)_3COOBu^t$
g: $(CH_2)_8OTHP$
h: $(CH_2)_7OTHP$
i: Bz

3: R[1] R[2]
a: n-Bu n-Bu
b: n-Bu n-Hep
c: n-Hep Me
d: $(CH_2)_7OTHP$ Me

Table 1. Alkylation of 3-sulfolenes

entry	substrate	halide	base	molar ratio 1 or 2	halide	base	HMPA	product[a] (yield[b] %)
1	1	n-BuI	$(Me_3Si)_2NNa$	1.0	1.2	1.1	2.0	2a (28)
2	1	"	$(Me_3Si)_2NLi$	1.0	1.2	1.1	2.0	2a (42)
3	1	"	"	2.0	1.0	1.1	4.0	2a (65)
4	1	"	LDA			"		2a (27)
5	1	MeI	$(Me_3Si)_2NLi$			"		2b (46)
6	1	EtI	"			"		2c (55)
7	1	n-HePI	"			"		2d (65)
8	1	isoamyl-I	"			"		2e (61)
9	1	t-BuOOC$(CH_2)_3$I	"			"		2f (40)
10	1	THPO$(CH_2)_8$I	"			"		2g (50)
11	1	THPO$(CH_2)_7$I	"			"		2h (58)
12	1	BzI	"			"		2i (55)
13	2a	n-BuI	"	1.0	1.2	1.1	4.0	3a (58) 4a (1)
14	2a	n-HepI	"			"		3b (56) 4b (4)
15	2d	MeI	"	1.0	1.1	1.1	4.0	3c (71) 4c (9)
16	2h	MeI	"			"		3d (55) 4d (6)

a) All new compounds have satisfactory mass, IR, UV, ^1H NMR, and ^{13}C NMR spectra. b) Isolated yields based on the sulfolene in entry 1, 2, and entry 13-16, and those based on the halide in entry 3-12.

Thermolytic desulfonylation (octane, reflux) of trans-2,5-disubstituted sulfolenes (3) (Table 2. entry 1) thus synthesized gave exclusively (E,Z)-dienes (5) as previously reported.[7] Reductive desulfonylation[10] of 3 was found to give only the (E,Z)-dienes in accord with the symmetry rule

(entry 2 and 5). However it was found that stereoselectivity of the thermolysis of trans-2,5-disubstituted 3-sulfolenes (3) was dramatically changed by carrying out the reaction in a protic solvent in the presence of basic reagents and that (E,E)-dienes (6) are obtained exclusively in opposition to the symmetry rule. Thus, thermolysis (95% EtOH, 125 °C) of 3a in the presence of K_2CO_3 (entry 3) or KOH (entry 4) gave exclusively (E,E)-dodecadiene (6a). The effect of the basic reagents on the stereochemical consequence of the desulfonylation of 3 can be rationalized by intermediary formation of the cis-2,5-disubstituted 3-sulfolene (4) in the reaction, namely under a basic protic medium the trans isomer (3) equilibrates with the cis isomer (4) which in turn rapidly extrudes sulfur dioxide in the suprafacial manner to afford the (E,E)-diene (6).[11] The isomerization of trans-2,5-disubstituted 3-sulfolene (3a) to the cis isomer (4a) was demonstrated under a basic protic medium (0.5% KOH in MeOH) at lower temperature (50 °C), after 30-min equilibration the ratio of 3a and 4a being 1:1.4.[12]

Scheme 2.

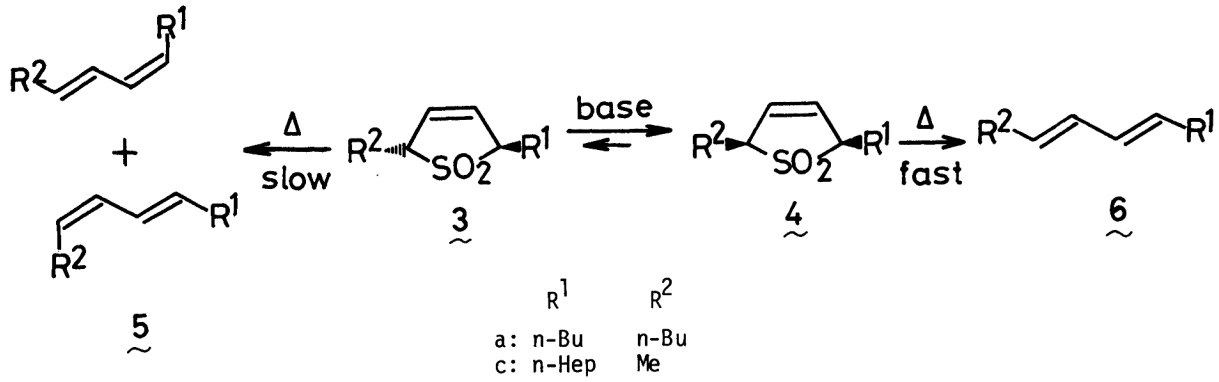


Table 2. Desulfonylation of 3

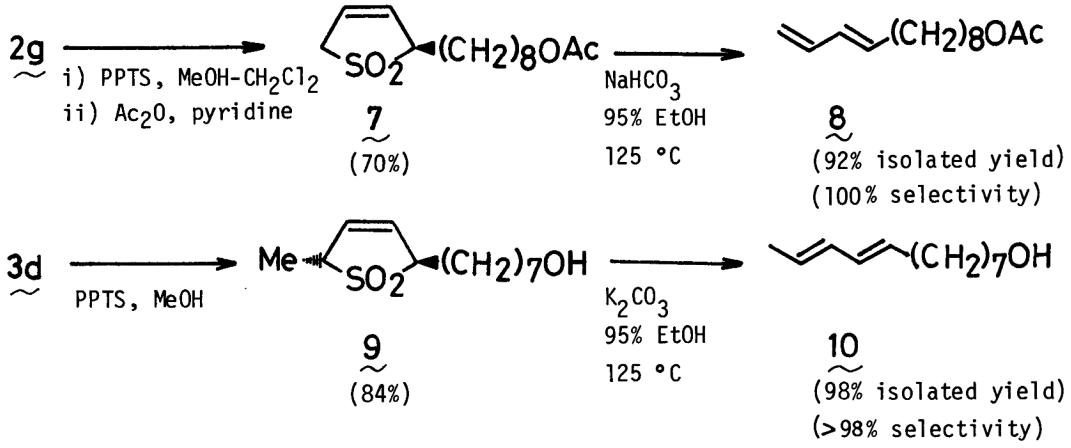
entry	substrate	conditions	products[a] 5 : 6[b]	total yield %[c]
1	3a	octane, reflux, Ar bubbling	97 : 3	92
2	3a	LAH, Et_2O, reflux	100 : 0	91
3	3a	K_2CO_3 (2 equiv.), 95% EtOH, 125 °C[d]	1 : 99	96
4	3a	KOH (2 equiv.), 95% EtOH, 125 °C[d]	0 : 100	90
5	3c	LAH, Et_2O, reflux	100 : 0	90
6	3c	K_2CO_3 (2 equiv.), 95% EtOH, 125 °C[d]	0 : 100	96

a) The structure of 5 and 6 was confirmed by mass, UV, ^1H NMR, and ^{13}C NMR spectra. b) Determined by GC analysis. c) Isolated yields. d) Carried out in a sealed tube.

Since it has been known that 2-alkyl-3-sulfolenes give only (E)-conjugated dienes by thermolysis,[7d] we have now established novel stereoselective synthetic routes to (E)-, (E,Z)- and (E,E)-conjugated dienes.

Applying the methodology, (E)-9,11-dodecadien-1-yl acetate (8), a sex pheromone of the red ballworm moth,[13] and (E,E)-8,10-dodecadienol (10), a sex pheromone of the codling moth,[14] were synthesized conveniently and stereoselectively (Scheme 3).[15]

Scheme 3.



References

1) S. F. Martin, S. R. Desai, G. W. Phillips, and A. C. Miller, J. Am. Chem. Soc., 102, 3294 (1980); H. F. Schmitthenner and S. M. Weinreb., J. Org. Chem., 45, 3372 (1980), and references cited therein.
2) Practical method for alkylating 3-sulfolenes has not been known except for those of stabilized derivatives fused to aromatic ring. W. Oppolzer, D. A. Roberts, T. G. C. Bird, Helv. Chim. Acta, 62, 2017 (1979); K. C. Nicolaou, W. E. Barnette, and P. Ma, J. Org. Chem., 45, 1463 (1980); V. M. Berestovitskaya, E. M. Speranskii, R. V. Perekalin, and E. M. Trukhin, Zh. Org. Khim., 10, 1783, (1974); R. P. Welcher, J. Org. Chem., 28, 1712 (1963).
3) R. C. Krug, J. A. Rigney, and G. R. Tichelaar, J. Org. Chem., 27, 1305 (1962).
4) R. Bloch and J. Abecassis, Tetrahedron Lett., 23, 3277 (1982); 24, 1247 (1983).
5) S. Yamada, T. Suzuki, and H. Takayama, Tetrahedron Lett., 22, 3085 (1981).
6) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie-Academic Press.
7) a) W. L. Mock, J. Am. Chem. Soc., 88, 2857 (1966); b) W. L. Mock, ibid., 97, 3666 (1975); c) S. D. McGregor and D. M. Lemal, ibid., 88, 2858 (1966); d) N. S. Isaacs and A. A. R. Laila, J. Chem. Soc., Perkin Trans. 2, 1976, 1470.
8) Preliminary results of this work were presented at 4th International Conference on Organic Synthesis, Tokyo, August 1982, Abstr. p. 208, and 9th Symposium on Progress in Organic Reactions and Synthesis, Hiroshima, November 1982, Abstr. pp. 103-106.
9) The stereochemical assignments of 2,5-disubstituted sulfolenes are based on the fact that on treatment with bromine in CCl_4 the major (trans) isomer of 2,5-dibutyl-3-sulfolene (3a) gave two dibromides whereas the minor (cis) isomer (4a) afforded a single dibromide.
10) Y. Gaoni, Tetrahedron Lett., 1977, 947.
11) It has been known that cis-2,5-dimethyl-3-sulfolene predominates over the corresponding trans isomer at an equilibrium and that the rate of the desulfonylation is faster in the cis isomer than in the trans isomer.[7a]
12) In addition to the two isomers (3a and 4a), 2,5-dibutyl-2-sulfolene was observed in the reaction.
13) B. F. Nesbitt, P. S. Beevor, R. A. Cole, R. Lester, and R. G. Poppi, Tetrahedron Lett., 1973, 4669.
14) W. Roelofs, A. Comeau, A. Hill, and G. Milicevic, Science, 174, 297 (1971).
15) The structure of 8 and 10 was confirmed by spectral analysis and the homogeneity of these compounds was based on the GC and ^{13}C NMR spectral analysis.

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