UNSYMMETRICALLY *S*-SUBSTITUTED KETENE DITHIOACETALS

Alan R. Katritzky,* Zuoquan Wang, and Scott A. Henderson

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida, USA, 32611-7200

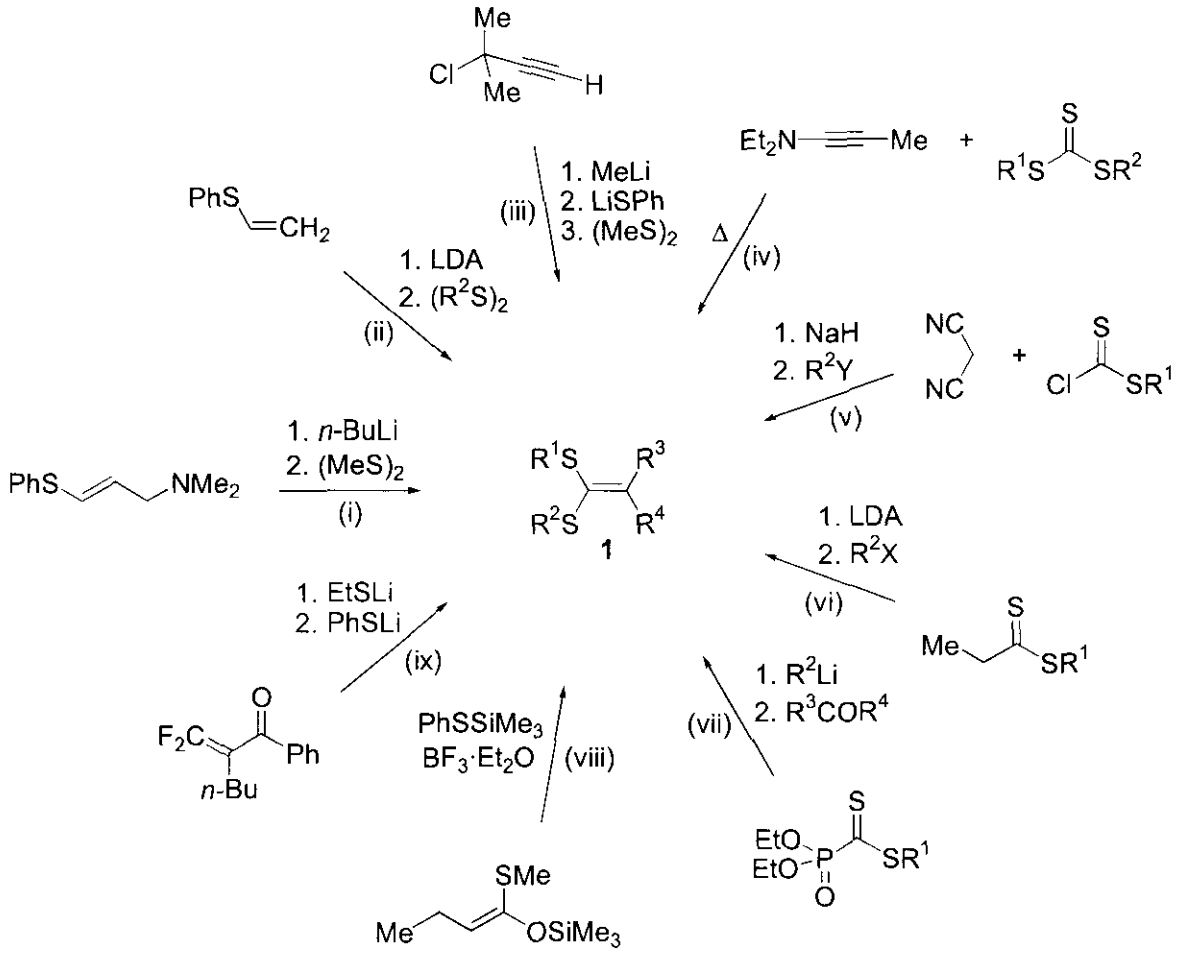
Abstract- A novel synthesis of unsymmetrically *S*-substituted ketene dithioacetals (**6a-e**) and (**7b-e**) *via* the benzotriazole derivatives (**5a-e**) is described.

INTRODUCTION

Symmetrical ketene dithioacetals (**1**) ($R^1 = R^2$) were first synthesised in 1919[1] and are now widely used in organic synthetic methodology because the double bond is susceptible to both nucleophilic and electrophilic attack due to the stabilising effect of the adjacent sulfur atoms.[2a-d] Schaumann and coworkers have used ketene dithioacetals, including unsymmetrically *S*-substituted, in the regioselective synthesis of functionalised cyclopropanes.[3] The preparations of ketene dithioacetals (**1**) have been reviewed,[4a,b] but the general routes apply only to symmetrical ketene dithioacetals. The literature describing the preparation of ketene dithioacetals (**1**) with different substituents on the sulfur atoms ($R^1 \neq R^2$) is fragmented and the following overview of available routes appears to be the only summary available.

Scheme 1 summarises the nine reported methods for the synthesis of unsymmetrically substituted ketene dithioacetals. They can be divided into four general approaches: 1. Electrophilic attack by disulfides on thioenolates: (i) α-Lithiation of vinyl sulfides followed by treatment with disulfides.[2a] This method generally lacks regioselectivity, but Fitt and Gschwend have used β-aminovinyl sulfides to direct lithiation exclusively α to the sulfur atom to prepare unsymmetrical ketene dithioacetals;[5] (ii) Lithiation of vinyl phenyl sulfide in the presence of a disulfide;[6] (iii) Treatment of 3-chloro-1-lithio-3-methylbutyne with lithium benzenethiolate followed by dimethyl disulfide gave an allene intermediate, which isomerises into the conjugated ketene dithioacetal;[7] 2. Ring opening of a cyclic intermediate: (iv) Elferink *et al.* prepared α-thionylketene dithioacetals from dithioesters and 1-(diethylamino)propyne;[8] 3. Treatment of dithioesters with electrophiles: (v) Base induced thioacylation of malonic acid derivatives

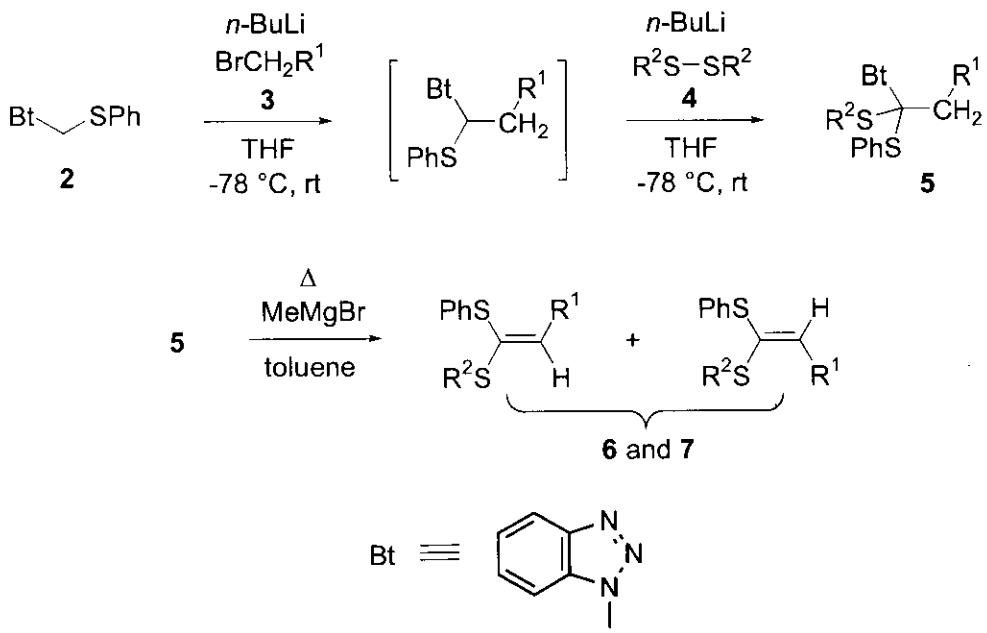
(*e.g.* malononitrile) with chlorodithioformate esters followed by alkylation of the intermediate thiolate anion;[9] (vi) Lithium *cis*-thioenolates, preferentially formed by deprotonation of dithiopropanoates with LDA, react with organo halides to selectively form *cis* unsymmetrical ketene dithioacetals;[10] (vii) Lithiation of phosphonodithioformates, accessible from dialkyl phosphites and carbon disulfide, and treatment with aldehydes or ketones gave unsymmetrical ketene dithioacetals as a mixture of *E* and *Z* isomers;[11] 4. Displacement of a leaving group with sulfur nucleophiles: (viii) Suitably substituted silyl enol ethers react with thiosilanes in the presence of boron trifluoroetherate to give unsymmetrical ketene dithioacetals;[12] (ix) Successive treatment of 2,2-difluorovinyl ketones with lithium ethanethiolate and lithium benzenethiolate gave unsymmetrical ketene dithioacetals as mixtures of *E* and *Z* isomers.[13]



Scheme 1

DISCUSSION

We now report that unsymmetrically *S*-substituted ketene dithioacetals (**6a-e**) and (**7b-e**) are advantageously synthesised *via* the benzotriazole derivative (**5a-e**) (Scheme 2). Sequential lithiation of 1-(phenylthiomethyl)benzotriazole (**2**) and subsequent addition of electrophiles – bromide (**3a-e**) and disulfide (**4a-c**) – gave the benzotriazole derivative (**5a-e**) in good yields (Table 1). The ability of benzotriazole to assist α-deprotonation is well documented.[14] Methylmagnesium bromide in toluene at reflux acts as a base to remove the β-proton of the benzotriazole derivative (**5a-e**) which is accompanied by loss of the benzotriazolyl moiety to give ketene dithioacetals as approximately 1:1 mixtures of the respective *E* and *Z* isomers (**6a-e**) and (**7b-e**). The two α-thioether groups activate the benzotriazolyl group towards this ionisation.[14] The isomers were separated by column chromatography and are listed in Table 2 in order of elution. Attempts to determine the configuration of (**6b**) and (**7b**) by NOE experiments were unsuccessful. When ketene dithioacetal (**6b**) was irradiated at 6.2 ppm (olefinic proton) the only observed NOE effect was at 3.1 ppm (*i*-Pr proton). No NOE effects were observed when ketene dithioacetal (**6b**) was irradiated at 7.2 ppm (aromatic protons) or at 2.7 ppm (methylene protons adjacent to sulfur atom). Similar results were obtained with ketene dithioacetal (**7b**).



Scheme 2

Table 1. Preparation of benzotriazole derivatives (**5a-e**)

Compound (**5**)	R^1	R^2	Found (required) C	H	N	mp (°C)	Yield (%)[a]
5a	C_7H_{15}	Ph	70.52 (70.24)	7.09 (6.77)	9.43 (9.10)	65-67	76
5b	*i*-Pr	C_8H_{17}	68.31 (67.98)	8.27 (7.99)	9.72 (9.51)	oil	76
5c	C_7H_{15}	*i*-Pr	67.32 (67.40)	8.01 (7.78)	10.02 (9.83)	93-95	71
5d	$CH(OEt)_2$	*i*-Pr		unstable[b]		oil	60
5e	*i*-Pr	*i*-Pr	64.78 (64.65)	6.96 (6.78)	11.43 (11.31)	79-81	80

[a] Isolated yield; [b] On standing compound (**5d**) decomposes into ketene dithioacetal (**6d**) and (**7d**).

Table 2. Preparation of ketene dithioacetals (**6a-e**) and (**7b-e**)

Compounds (**6**) and (7)[b]	R^1	R^2	Found (required) C		H		Yield (%)[a]
6a	C_7H_{15}	Ph	73.70	(73.63)	7.80	(7.65)	88
6b	*i*-Pr	C_8H_{17}	70.92	(70.75)	9.75	(9.37)	48
7b	*i*-Pr	C_8H_{17}	70.37	(70.75)	9.48	(9.37)	42
6c	C_7H_{15}	*i*-Pr	70.44	(70.07)	9.46	(9.15)	55
7c	C_7H_{15}	*i*-Pr	70.05	(70.07)	9.54	(9.15)	37
6d	CHO	*i*-Pr	60.17	(60.47)	6.15	(5.92)	44
7d	CHO	*i*-Pr	60.16	(60.47)	5.99	(5.92)	17
6e	*i*-Pr	*i*-Pr	66.96	(66.61)	8.23	(7.99)	45
7e	*i*-Pr	*i*-Pr	66.78	(66.61)	8.19	(7.99)	29

[a] Isolated yield; [b] Compounds listed in order of elution from column. Configuration was not assigned.

CONCLUSION

Previous methods of preparing unsymmetrically *S*-substituted ketene dithioacetals are either limited to specific substituents (Scheme 1: methods i-vi and ix) or the starting material is not readily available (Scheme 1: methods vii and viii). The method described here is general for the preparation of unsymmetrically *S*-substituted ketene dithioacetals and offers an alternative procedure to previously published methods.

EXPERIMENTAL

Melting points were determined on a hot stage apparatus and are uncorrected. NMR spectra were obtained in chloroform-*d* and chemical shift values are reported as δ downfield from tetramethylsilane as an internal standard for ^{1}H (300 MHz) and chloroform-*d* as the internal standard for ^{13}C (75 MHz).

THF and toluene were distilled under nitrogen immediately prior to use from a solution containing sodium/benzophenone. Column chromatography was carried out on MCB silica gel (230-400 mesh). Other chemicals were used as obtained from commercial sources.

1-(Phenylthiomethyl)benzotriazole (**2**) was prepared by the literature method.[15]

General Method for Preparation of Benzotriazole Derivatives (5a-e). *n*-Butyllithium (8.3 mmol) was added to a solution of 1-(phenylthiomethyl)benzotriazole (**2**) (2.0 g, 8.3 mmol) in THF (30 mL) at -78 °C and stirred for 15 min under nitrogen. Bromide (**3**) (8.3 mmol) was added and the mixture stirred at -78 °C for 2 h before warming to rt. The mixture was cooled to -78 °C, *n*-butyllithium (8.3 mmol) added, followed by disulfide (**4**) (8.3 mmol), and stirred for 8 h. On warming to rt the mixture was quenched with water (50 mL) and extracted with ether (3 x 50 mL). The combined extracts were dried (anhyd. $MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 30:1) to give the benzotriazole derivative (**5**).

1-Benzotriazolyl-1,1-di(phenylthio)-1-nonane (**5a**): ^{1}H-NMR δ: 0.93 (t, J = 6.6 Hz, 3H), 1.18-1.45 (m, 10H), 2.02-2.18 (m, 2H), 2.47 (m, 2H), 6.80 (d, J = 7.4 Hz, 4H), 7.07 (t, J = 7.7 Hz, 4H), 7.24 (t, J = 7.4 Hz, 2H), 7.48 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 8,64 (d, J = 8.2 Hz, 1H); ^{13}C-NMR δ: 14.0, 22.6, 24.5, 28.9, 29.1, 29.5, 31.8, 36.2, 85.1, 116.0, 119.9, 124.2, 126.7, 128.9, 129.0, 129.8, 132.3, 135.3, 146.7.

1-Benzotriazolyl-3-methyl-1-octylthio-1-phenylthiobutane (**5b**): ^{1}H-NMR δ: 0.72-0.90 (m, 6H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.02-1.40 (m, 12H), 2.14-2.22 (m, 1H), 2.30-2.41 (m, 1H), 2.43-2.57 (m, 2H), 2.58-2.70 (m, 1H), 6.94 (d, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.37 (d, *J* = 8.3 Hz, 1H); ^{13}C-NMR δ: 13.9, 22.4, 23.8, 23.9, 25.0, 27.5, 28.7, 30.4, 31.5, 44.9, 84.3, 114.9, 119.8, 124.0, 126.6, 128.5, 129.4, 129.6, 132.0, 135.7, 146.7.

1-Benzotriazolyl-1-isopropylthio-1-phenylthiononane (**5c**): ^{1}H-NMR δ: 0.67 (d, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 6.6 Hz, 3H), 1.05-1.50 (m, 13H), 1.85-2.10 (m, 2H), 2.45-2.65 (m, 1H), 2.66-2.88 (m, 2H), 6.75 (d, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 8.48 (d, *J* = 8.3 Hz, 1H); ^{13}C-NMR δ: 14.1, 22.6, 23.5, 24.1, 24.7, 29.0, 29.2, 29.6, 31.8, 36.2, 36.6, 83.4, 115.9, 119.8, 124.2, 126.5, 128.8, 129.0, 129.9, 132.3, 135.6, 146.8.

1-Benzotriazolyl-1-isopropylthio-1-phenylthiopropanal diethyl acetal (**5d**): ^{1}H-NMR δ: 0.53 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 3.14-3.22 (m, 2H), 3.23-3.34 (m, 1H), 3.58-3.85 (m, 4H), 5.40 (t, *J* = 3.3 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 2H), 7.03 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 8.48 (d, *J* = 8.3 Hz, 1H); ^{13}C-NMR δ: 15.2, 22.9, 23.0, 36.4, 41.4, 59.9, 61.7, 81.2, 100.3, 116.0, 119.7, 124.1, 126.5, 128.2, 128.6, 130.0, 132.2, 136.5, 146.7.

1-Benzotriazolyl-1-isopropylthio-3-methyl-1-phenylthiobutane (**5e**): ^{1}H-NMR δ: 0.72 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 2.40-2.58 (m, 1H), 2.59-2.77 (m, 2H), 2.85-3.01 (m, 1H), 6.93 (d, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 7.0 Hz, 2H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.3 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 8.40 (d, *J* = 8.3 Hz, 1H); ^{13}C-NMR δ: 23.3, 23.5, 24.1, 24.4, 25.1, 36.6, 45.0, 84.2, 115.7, 119.8, 124.2, 126.6, 128.7, 129.6, 129.7, 132.5, 135.4, 146.8.

General Method for Preparation of Ketene Dithioacetals (6a-e) and (7b-e). Methylmagnesium bromide (5.6 mmol) was added dropwise to a solution of benzotriazole derivative (**5**) (2.8 mmol) in toluene (40 mL) and heated at reflux for 5 h, under nitrogen. On cooling the mixture was poured onto ice-water (40 g) and extracted with ether (3 x 50 mL). The combined extracts were washed with ammonium chloride solution (20%, 30 mL), sodium hydroxide solution (5%, 30 mL), and dried (anhyd. $MgSO_4$). The solvent was removed under reduced pressure and the crude product purified by column chromatography (hexane) to give ketene dithioacetals (**6**) and (**7**).

1,1-Di(phenylthio)-1-nonene (**6a**): ^{1}H-NMR δ: 0.88 (t, J = 6.4 Hz, 3H), 1.17-1.38 (m, 8H), 1.38-1.50 (m, 2H), 2.43 (q, J = 7.4 Hz, 2H), 6.39 (t, J = 7.4 Hz, 1H), 7.13-7.35 (m, 10H); ^{13}C-NMR δ: 14.1, 22.6, 29.0, 29.2, 31.3, 31.8, 126.6, 127.1, 128.6, 128.6 (overlapped), 128.7, 130.3, 131.2, 134.5, 134.5 (overlapped), 145.0.

3-Methyl-1-octylthio-1-phenylthio-1-butene (**6b**): ^{1}H-NMR δ: 0.90 (t, J = 6.6 Hz, 3H), 1.06 (d, J = 6.6 Hz, 6H), 1.16-1.40 (m, 10H), 1.45-1.60 (m, 2H), 2.70 (t, J = 7.2 Hz, 2H), 2.95-3.15 (m, 1H), 6.18 (d, J = 9.3 Hz, 1H), 7.15-7.45 (m, 5H); ^{13}C-NMR δ: 14.1, 22.3, 22.6, 28.6, 29.1, 29.2, 29.8, 30.4, 31.8, 32.7, 126.4, 126.7, 128.8, 129.3, 135.5, 151.4.

3-Methyl-1-octylthio-1-phenylthio-1-butene (**7b**): ^{1}H-NMR δ: 0.88 (t, J = 6.5 Hz, 3H), 1.02 (d, J = 6.7 Hz, 6H), 1.12-1.40 (m, 10H), 1.43-1.60 (m, 2H), 2.64 (t, J = 7.5 Hz, 2H), 3.00-3.16 (m, 1H), 6.10 (d, J = 9.3 Hz, 1H), 7.15-7.40 (m, 5H); ^{13}C-NMR δ: 14.1, 22.6, 28.7, 28.9, 29.1, 30.7, 31.8, 32.9, 126.0, 126.1, 128.7, 129.0, 135.2, 149.1.

1-Isopropylthio-1-phenylthio-1-nonene (**6c**): ^{1}H-NMR δ: 0.89 (t, J = 6.3 Hz, 3H), 1.10-1.45 (m, 16H), 2.37 (q, J = 7.2 Hz, 2H), 3.39 (septet, J = 6.7 Hz, 1H), 6.27 (t, J = 7.2 Hz, 1H), 7.15-7.39 (m, 5H); ^{13}C-NMR δ: 14.1, 22.6, 22.9, 29.0, 29.1, 29.2, 31.0, 31.8, 36.8, 126.6, 128.8, 128.9, 130.1, 135.3, 144.5.

1-Isopropylthio-1-phenylthio-1-nonene (**7c**): ^{1}H-NMR δ: 0.87 (t, J = 6.9 Hz, 3H), 1.10-1.49 (m, 16H), 2.40 (q, J = 7.2 Hz, 2H), 3.26 (septet, J = 6.7 Hz, 1H), 6.37 (t, J = 7.2 Hz, 1H), 7.13-7.37 (m, 5H); ^{13}C-NMR δ: 14.1, 22.5, 22.6, 29.1, 29.2, 31.2, 31.8, 36.3, 126.1, 128.0, 128.7, 129.3, 135.1, 144.9.

1-Isopropylthio-1-phenylthio-2-propenal (**6d**): ^{1}H-NMR δ: 1.41 (d, J = 6.8 Hz, 6H), 3.81 (septet, J = 6.8 Hz, 1H), 5.81 (d, J = 7.2 Hz, 1H), 7.39-7.53 (m, 5H), 9.97 (d, J = 7.2 Hz, 1H); ^{13}C-NMR δ: 23.0, 39.5, 127.8, 129.0, 130.0, 130.3, 135.0, 164.7, 188.3.

1-Isopropylthio-1-phenylthio-2-propenal (**7d**): ^{1}H-NMR δ: 1.29 (d, J = 6.9 Hz, 6H), 3.41 (septet, J = 6.8 Hz, 1H), 6.26 (d, J = 6.9 Hz, 1H), 7.32-7.42 (m, 5H), 10.11 (d, J = 6.9 Hz, 1H); ^{13}C-NMR δ: 21.9, 37.8, 125.3, 128.8, 129.0, 129.2, 132.8, 164.7, 187.5.

1-Isopropylthio-3-methyl-1-phenylthio-1-butene (**6e**): ^{1}H-NMR δ: 1.01 (d, J = 6.7 Hz, 6H), 1.21 (d, J = 6.8 Hz, 6H), 2.94-3.13 (m, 1H), 3.38 (septet, J = 6.8 Hz, 1H), 6.12 (d, J = 9.3 Hz, 1H), 7.15-7.40 (m, 5H); ^{13}C-NMR δ: 22.3, 22.9, 30.3, 36.6, 126.6, 126.9, 128.8, 129.9, 135.2, 151.5.

1-Isopropylthio-3-methyl-1-phenylthio-1-butene (**7e**): ^{1}H-NMR δ: 1.03 (d, J = 6.7 Hz, 6H), 1.18 (d, J = 6.8 Hz, 6H), 2.98-3.15 (m, 1H), 3.25 (septet, J = 6.6 Hz, 1H), 6.19 (d, J = 9.3 Hz, 1H), 7.15-7.38 (m, 5H); ^{13}C-NMR δ: 22.4, 22.6, 30.7, 36.3, 125.9, 126.2, 128.7, 129.3, 135.1, 151.8.

REFERENCES

1. E. Freund, *Ber.*, 1919, **52**, 542.
2. (a) B.-T. Gröbel and D. Seebach, *Synthesis,* 1977, 357. (b) M. Mikolajczyk, S. Grzejszczak, A. Zatorski, B. Mlotkowska, H. Gross, and B. Costisella, *Tetrahedron,* 1978, **34**, 3081. (c) G. C. Barrett, 'Comprehensive Organic Chemistry', Vol. 3, ed. by D. N. Jones, Pergamon Press, New York, 1979, pp. 3-20 and pp. 33-53. (d) G. N. Sheldrake, 'Comprehensive Organic Functional Group Transformations', Vol. 4, ed. by G. W. Kirby, Pergamon Press, New York, 1995, pp. 842-853.
3. E. Schaumann, C. Friese, and C. Spanka, *Synthesis,* 1986, 1035.
4. (a) M. Kolb, 'The Chemistry of Ketenes, Allenes and Related Compounds', Part 2, ed. by S. Patai, Wiley, Chichester, 1980, p. 669. (b) M. Kolb, *Synthesis*, 1990, 171.
5. J. J. Fitt and H. W. Gschwend, *J. Org. Chem.,* 1979, **44**, 303.
6. B. Harirchian and P. Magnus, *J. Chem. Soc. (Chem. Comm.),* 1977, 522.
7. J.-C. Clinet and S. Julia, *J. Chem. Res. (S),* 1978, 125.
8. V. H. M. Elferink, R. G. Visser, and H. J. T. Bos, *Recl, J. Royal Neth. Chem. Soc.,* 1981, **100**, 414
9. N. H. Nilsson, *Tetrahedron,* 1974, **30**, 3181
10. P. Beslin and Y. Vallee, *Tetrahedron,* 1985, **41**, 2691.
11. A. Bulpin, S. Masson, and A. Sene, *Tetrahedron Lett.,* 1989, **30**, 3415.
12. A. Degl'Innocenti, P. Ulivi, A. Capperucci, A. Mordini, G. Reginato, and A. Ricci, *Synlett,* 1992, 499.
13. J. Ichikawa, M. Kobayashi, N. Yokota, Y. Noda, and T. Minami, *Tetrahedron,* 1994, **50**, 11637.
14. A. R. Katritzky, X. Lan, Z. J. Yang, and O. V. Denisko, *Chem. Rev.* 1997, in press
15. A. R. Katritzky, S. Rachwal, K., C. Caster, F. Mahni, K. W. Law, and O. Rubio, *J. Chem. Soc., Perkin Trans. 1,* 1987, 781.

Received, 5th November, 1997