Oxidative Functionalization of the β-Carbon in α,β-Unsaturated Systems. Preparation of 3-Phenylthio Enones, Acrylates, and Other Vinyl Derivatives

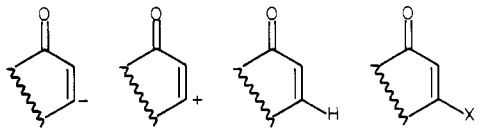
Peter Bakuzis* and Marinalva L. F. Bakuzis

Departamento de Quimica, Universidade de Brasilia, Brasilia, DF, 70.910 Brazil

Received April 1, 1980

The β-carbon of α,β-unsaturated ketones, esters, lactones, and nitriles can be oxidatively functionalized in a regiospecific manner in a simple sequence of reactions. Michael addition of thiophenol followed by oxidation with *N*-chlorosuccinimide gives chloro sulfides that readily lose HCl to give 3-phenylthio enones, acrylates, and other vinyl derivatives.

β-Acylvinyl anions **1** and cations **2** are important synthons, and consequently the preparation of their synthetic equivalents has received considerable attention recently.[1-3] While both of these synthons have been elaborated from precursors in high oxidation states (most commonly β-dicarbonyl compounds or their tautomeric equivalents) by addition of acyl halides to acetylene or of thiols to substituted acetylenes, processes beginning with α,β-unsaturated systems **3** are much rarer, particularly for the a[3]

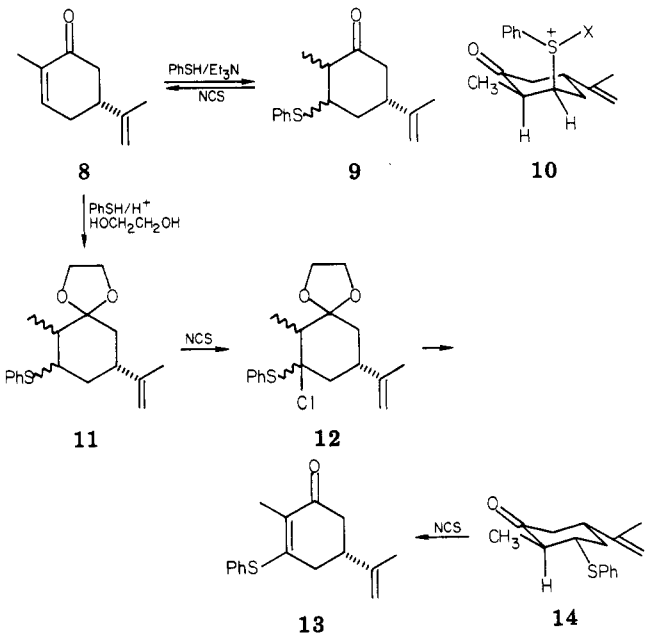


1 **2** **3** **4**

enone synthon **2**.[3] The commercial availability of many simple α,β-unsaturated carbonyl compounds together with the relative ease of regiospecific preparation of the more complex ones makes such processes synthetically attractive.

Since β-substituted enones **4** (X = OAc, OR, $OPO(OR)_2$, NR_2, SR, SAr, halide) have all been used as synthetic equivalents of cation **2**, we sought a process for transforming enones **3** into the desired **4** without involving a symmetrical intermediate (or a pair of rapidly equilibrating intermediates), thus preserving the regiochemistry associated with the original enone. Of the substituents X above, the sulfur ones should be the easiest to prepare since Michael additions of thiols to enones occur under very mild conditions,[4] and sulfides are readily oxidized with a variety of reagents[5,6] to give intermediates that should yield the desired enones **4**.

Scheme I



8 **9** **10** **11** **12** **13** **14**

Accordingly, a series of β-phenylthio ketones, esters, nitriles, and lactones was prepared by the NEt_3-catalyzed addition of thiophenol to the corresponding α,β-unsaturated compound in yields varying from 80% to 100% (see Table I). From prior experience[7] we expected that *N*-chlorosuccinimide (NCS) would oxidize the sulfides to give intermediate chloro sulfides, but in our first experiment on sulfide **5** (prepared from methyl vinyl ketone) we did

(1) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

(2) Piers, E.; Morton, H. E. *J. Org. Chem.* **1979**, *44*, 3437 and references cited therein. Drouin, J.; Leyendecker, F.; Julia, J. M. *Tetrahedron Lett.* **1965**, 4053. Iwai, K.; Kosugi, H.; Uda, H.; Kawai, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 242. Bryson, T. A.; Dordis, R. E.; Gammill, R. B. *Tetrahedron Lett.* **1978**, 743. Harding, K. E.; Tseng, C. *J. Org. Chem.* **1978**, *43*, 3974. Abdulla, R. E.; Fuhr, K. H. *Ibid.* **1978**, *43*, 4248. Hammond, M. L.; Mourino, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907. Sum, F. M.; Weiler, L. *Ibid.* **1979**, *101*, 4401. Cooper, G. K.; Dolby, L. L. *J. Org. Chem.* **1979**, *44*, 3414. Bradbury, R. H.; Gilchrist, T. L.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1979**, 528. Sum, F. W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431.

(3) Stotter, P. L.; Hill, K. A. *J. Org. Chem.* **1973**, *38*, 2576. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. Pelletier, S. W.; Djarmati, Z.; Lajsic, S. D.; Micôvič, I. V.; Yang, D. T. C. *Tetrahedron* **1975**, *31*, 1659. Gassman, P. G.; Partow, R. L. *J. Chem. Soc., Chem. Commun.* **1977**, 694. Ito, Y.; Hirao, F.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. Heck, R. H. *Acc. Chem. Res.* **1979**, *12*, 146. Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, 1133. Horino, H.; Inoue, N. *Ibid.* **1979**, 2403. Hayashi, Y.; Matsumotu, T.; Hyano, T.; Nishikawa, N.; Uemura, M.; Nishizwa, M.; Togami, M.; Sakan, T. *Ibid.* **1979**, 3311.

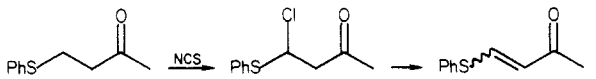
(4) Kuwajima, I.; Morofushi, T.; Nakamura, E. *Synthesis* **1976**, 602 and references cited therein.

(5) Isolated reports of oxidation of β-thioalkyl or aryl ketones have appeared in special cases. For chloranil: Hagio, K.; Yoneda, N. *Chem. Ind. (London)* **1974**, 494. For NCS: Chen, C. H.; Reynolds, G. A. *J. Org. Chem.* **1980**, *45*, 2449, 2453. For chlorine: Parham, W. E.; Bhavsan, M. D. *Ibid.* **1964**, *29*, 1575. For the "abnormal" Pummerer reaction: Corbet, J. P.; Benezra, C. *Can. J. Chem.* **1979**, *57*, 213. A conceptionally similar sequence utilizing iodobenzene dichloride as oxidant appeared after the original preparation of our manuscript: Bateson, J. H.; Roberts, P. M.; Smale, T. C.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1980**, 185.

(6) The "abnormal" Pummerer reaction has been used to prepare α-phenylthio enones: Oki, M.; Kobayashi, K. *Bull. Chem. Soc. Jpn.* **1970**, *45*, 1223; Monteiro, H. J.; Gemal, A. L. *Synthesis* **1975**, 437; Monteiro, H. J. *J. Org. Chem.* **1977**, *42*, 2324.

(7) Tuleen, D. L.; Stevens, T. B. *J. Org. Chem.* **1969**, *34*, 31. Paquette, L. A.; Klobucar, W. D.; Snow, R. A. *Synth. Commun.* **1976**, *6*, 575. Gassman, P. G.; Drewes, H. R. *J. Am. Chem. Soc.* **1978**, *100*, 7600 and references cited therein. Bakuzis, P.; Bakuzis, M. L. F.; Weingartner, T. F. *Tetrahedron Lett.* **1978**, 2371 and references cited therin.

0022-3263/81/1946-0235$01.00/0



5 6 7

not isolate the chloro sulfide 6 but rather the desired 7 as a 93/7 mixture of E/Z products. Subsequent experiments showed that 6 was indeed produced but that elimination of HCl was occurring at 25 °C as well, going to completion upon solvent removal. Similar results were encountered with the other keto sulfides and the sulfide produced from angelica lactone. The less acidic ester and nitrile sulfides gave fairly stable chloro sulfides, which were transformed into the vinyl sulfides upon treatment with NEt_3 at room temperature to give good to excellent yields of the desired products (see Table I).

In connection with the results shown in Table I, several comments are appropriate. Entry 4 shows that α-angelica lactone is a suitable precursor for Michael additions, a result which might not have been predicted[8] but has been confirmed independently.[9] While the sulfides derived from angelica lactone, cyclopentenone, and cyclohexenone (entries 4, 6, and 7), could be oxidized directly to the vinyl compounds, chlorination of the sulfide 9, derived from kinetic addition of thiophenol to carvone (8), gave a mixture of products in which carvone (8) predominated (Scheme I).

In analogy to the stereoselectivity observed upon thiophenol additions to 5-*tert*-butylcyclohex-2-enone,[10] the predominant isomer of sulfide 9 should have an axial phenylthio group. This assignment is supported by the ^1H NMR (CCl_4) spectrum of 9, the HCSPh peak appearing at δ 3.84 (m, w = 15 Hz) while in the corresponding equatorial phenylthio compound 14 (see below) the C-3 hydrogen appears as a very broad peak centered approximately at δ 3.2 (overlapping peaks did not permit accurate chemical shift or bandwidth assignments). Thus, the intermediate 10 (X = Cl), expected[11] to be formed upon oxidation of 9 with NCS under our reaction conditions, would be ideally set up for trans-diaxial elimination, competing with normal abstraction of the hydrogen α to the sulfur center. While we are unaware of direct literature precedent for this competition, eliminations (and/or substitutions) have been observed in sulfide systems that do not have α-hydrogens.[6,12] Since the most commonly used reagent for this transformation is a sulfenyl chloride, the phenylsulfenyl chloride eliminated from 10 (X = Cl) should react with a second molecule of 9 to give 10 (X = SPh), a species that once again is capable of giving carvone (8), this time by elimination of diphenyl disulfide. (Alternate explanations for the appearance of diphenyl disulfide, one of the products of the elimination reaction, can be imagined, but the reaction was not investigated further.)

On the basis of the above mechanistic speculation, two methods of avoiding the elimination reaction became obvious. The first solution required the protection of the carbonyl group of 9, a process that could be done by treating 9 with ethylene glycol in the usual manner. However, we found it more convenient to prepare the desired compound 11 directly from carvone (8) by an acid-catalyzed addition of thiophenol in the presence of ethylene glycol.[13,14] Oxidation of ketal 11, a mixture of isomers, followed by filtration and removal of the solvent, gave an oil which soon separated into two layers. Spectral analysis of this mixture showed that hydrolysis[15] of the ketal and elimination of HCl had occurred, giving 13 directly.

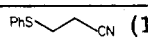
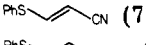
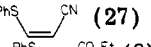
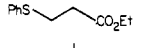
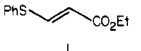
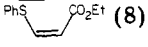
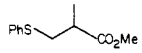
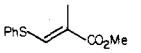
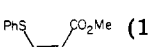
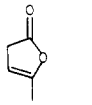
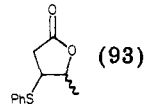
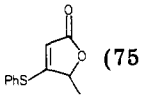
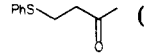
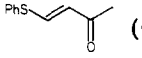
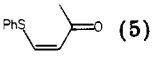
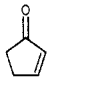
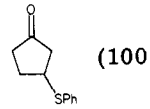
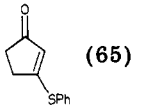
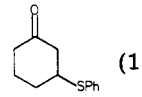
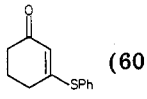
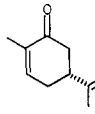
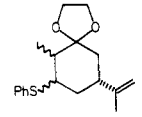
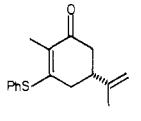
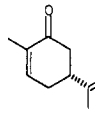
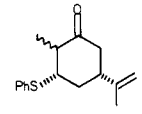
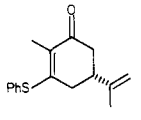
While the desired preparation of 13 could be carried out by the above sequence, the overall yield from carvone (8) was only moderate. Treatment of carvone with thiophenol in the presence of triethylamine[16] (neat) for 4 days at room temperature gave a crude product mixture in which the compound 14 with the equatorial sulfide group predominated. Oxidation of this mixture with NCS in benzene of CCl_4 gave only moderate yields of 13, while good yields could be obtained in the more basic solvent diethyl ether (but at the expense of long reaction times). By using a 2:1 mixture of benzene and diethyl ether, a good yield of 13 was obtained (68% overall, from carvone).

We have also briefly examined the preparation of two simple vinyl sulfides not activated by electron-withdrawing groups. Thus (phenylthio)ethane and (phenylthio)octane were oxidized by NCS, and the resulting chloro sulfides were refluxed in pyridine to give phenyl vinyl sulfide and 1-(phenylthio)-1-octene in 57% and 84% isolated yields, respectively.[17]

The 3-phenylthio enones, acrylates, etc. shown in Table I are highly functionalized, and several of them have already been used as synthons for important transformations. For instance, the vinyl sulfides of entries 3, 6, and 7 have been used in Danishefsky's cyclohexadienone synthesis,[18] the vinyl sulfide of entry 3, via its surprisingly stable vinyl anion, served as a starting material for lactone and cyclopentenone synthesis,[19] and vinyl sulfides analogous to that in entry 5 were used in the preparation of α,β- and $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes.[20] Other transformations are anticipated, particularly since several new methods of preparing β-phenylthio ketones, esters, and lactones have appeared recently,[21] and the vinyl sulfide functional group is begining to show synthetic promise in a variety of reactions.[22]

(8) Ducher, S.; Michet, A. *Bull. Soc. Chim. Fr.* **1973**, 1037.
(9) Shono, T.; Matsumura, Y.; Kashimura, S.; Kyutoku, H. *Tetrahedron Lett.* **1978**, 2807.
(10) Chamberlain, P.; Whitman, G. H. *J. Chem. Soc., Perkin Trans. 2* **1972**, 130.
(11) Vilsmaier, E.; Schutz, J.; Zimmerer, S. *Chem. Ber.* **1979**, *112*, 2231.
(12) Moore, C. G.; Porter, M. *Tetrahedron* **1960**, *9*, 58. Yoshino, H.; Kuwazoe, Y.; Taguch, T. *Synthesis* **1974**, 713. Wilson, G. E., Jr.; Huang, M.-G. *J. Org. Chem.* **1976**, *41*, 966. Yoshioka, M.; Kikkawa, I.; Tsuji, T.; Nishitani, Y.; Mori, S.; Okada, K.; Murakami, M.; Matsubura, F.; Yamaguchi, M.; Nagata, W. *Tetrahedron Lett.* **1979**, 4287. Gordon, E. M.; Chang, H. W.; Cimarusti, C. M.; Toeplitz, B.; Gougotas, J. Z. *J. Am. Chem. Soc.* **1980**, *102*, 1690.
(13) The acid-catalyzed addition of excess thiophenol to α,β-unsaturated compounds has been described and leads to tris(phenylthio)alkanes: Cohen, T.; Mura, A. J., Jr.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R. *J. Org. Chem.* **1976**, *41*, 3218.
(14) Ethylene glycol under acidic conditions has been used to "trap" the product of Michael addition of amines, amides, bromides, and sulfinic acids: Bryson, T. A.; Wilson, C. A. *Synth. Commun.* **1976**, *6*, 521; Buchi, G.; Wuest, H. *J. Org. Chem.* **1969**, *34*, 1121; Janssen, C. G. M.; van Lier, P. M.; Buck, H. M.; Godefroi, E. F. *Ibid.* **1979**, *44*, 4199. Methanol "locked" the product of another nitrogen nucleophile: Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152.
(15) Similar in situ hydrolyses of ketals have been observed: Boeckman, R. K.; Blum, D. M. *J. Org. Chem.* **1974**, *39*, 3307.
(16) Cohen, T.; Matz, J. R. *J. Org. Chem.* **1979**, *44*, 4816.
(17) (Phenylthio)cyclohexane was also oxidized with NCS to give the expected eliminated product, (phenylthio)cyclohexene. However, yields were variable (up to 65% by ^1H NMR analysis), and the product mixtures were difficult to purify.
(18) Danishefsky, S.; Harayama, T.; Singh, R. K *J. Am. Chem. Soc.* **1979**, *101*, 7008.
(19) Isobe, K.; Fuse, M.; Kosugi, H.; Hagiwara, H.; Uda, H. *Chem. Lett.* **1979**, 785.
(20) Akiyama, S.; Nakatsuji, S.; Hamamura, T.; Kataoka, M.; Nakagawa, M. *Tetrahedron Lett.* **1979**, 2809.
(21) Miller, R. D.; McKean, D. R. *Tetrahedron Lett.* **1979**, 583, 1003. Peterson, J.; Fleming, I. *Ibid.* **1979**, 2179 and references therein. Watanabe, M.; Shirai, K.; Kumamoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3318. Shono, T.; Matsumura, Y.; Kashimura, S.; Hatanaka, K. *J. Am. Chem. Soc.* **1979**, *101*, 4752. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron* **1980**, *21*, 361.

Table I. Preparation of 3-Phenylthio Enones, Acrylates, and Other Vinyl Derivatives

entry	ene	sulfide (% isolated yield)	vinyl sulfide (% isolated yield)[a]
1		 (100)	 (73),  (27)
2		 (100)	 (86),  (8)
3		 (80)	 (70),  (15)
4		 (93)	 (75)
5		 (86)	 (69),  (5)
6		 (100)	 (65)
7		 (100)	 (60)
8		 (69)	 (64)
9		 (100)	 (68)

[a] *E/Z* mixtures were not separated but were determined by ^{1}H NMR and/or GLC analysis.

Experimental Section

All reactions were preformed under an atmosphere of argon. ^{1}H NMR spectra were taken on a Varian A-60D instrument with tetramethylsilane as an internal standard. GLC analyses were conducted on a $^1/_8$ in. × 6 ft aluminum column packed with 10% silicone DCC 550 on 60/70 Chrom W,Reg with a flow rate of 30 mL/min.

Preparation of Sulfides. In general, the sulfides were prepared by triethylamine-catalyzed additions of thiophenol to the α,β-unsaturated compound in either $CHCl_3$ or CCl_4. Representative examples of experimental details are presented below.

3-(Phenylthio)cyclopentanone. To a solution of 1.64 g (20.0 mmol) of 2-cyclopentenone and 2.22 g (20.1 mmol) of thiophenol in 4 mL of $CHCl_3$ at 0 °C was added 0.1 mL of triethylamine. The cooling bath was removed, and the solution was stirred at room temperature for 2 h, diluted with ether, and washed twice with 5% aqueous NaOH, H_2O, and saturated NaCl solution. After the mixture was dried over Na_2SO_4, the solvent was removed to give 3.84 g (100% yield) of 3-(phenylthio)cyclopentanone. An analytical sample was prepared by bulb to bulb distillation: IR (neat) 1760 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.65–2.85 (m, 6 H), 3.60–4.07 (m, 1 H), 7.0–7.6 (m, 5 H); mass spectrum calcd for $C_{11}H_{12}OS$ (M) *m/e* 192.0609, found *m/e* 192.0661.

4-(Phenylthio)-5-methyl-3,4-dihydro-2(5*H*)-furanone. To a solution of 2.0 g (20.0 mmol) of α-angelica lactone (Aldrich, 98%) and 2.46 g (22.3 mmol) of thiophenol in 10 mL of CCl_4 at 0 °C was added 0.15 mL of triethylamine. After the cooling bath was removed, the solution was stirred at room temperature for 2 h and then elaborated as above to give 4.16 g of crude product, purified by chromatography on silica gel with elution with benzene to give 3.89 g (93%) of 4-(phenylthio)-5-methyl-3,4-dihydro-2-(5*H*)-furanone:[9] IR (neat) 1790 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.38 (d, 3 H, J = 6.0 Hz), 2.1–3.15 (m, 2 H), 3.27–3.73 (m, 1 H), 4.0–4.6 (m, 1 H), 7.16–7.64 (m, 5 H); GLC (225 °C) and ^{1}H NMR (PhH) spectroscopy indicated a 92/8 ratio of products, presumably trans and cis isomers, respectively.

Addition of Thiophenol to Carvone in the Presence of Ethylene Glycol. A mixture of 3.00 g (20.0 mmol) of *l*-carvone (Aldrich, freshly distilled), 2.5 g (40.3 mmol) of ethylene glycol, 2.60 g (23.7 mmol) of thiophenol, and 70 mg of *p*-TsOH in 50 mL of PhH was refluxed under Dean–Stark conditions for 10 h (after 2.5 h, an additional 50 mg of *p*-TsOH was added). The solution was cooled and washed with dilute NaOH solution, H_2O, and saturated NaCl solution. After the mixture was dried over Na_2SO_4, the solvent was removed to give 6.44 g of crude product. Chromatography on 150 g of silica gel, upon elution with 2:1 petroleum ether/PhH to 100% PhH, gave 4.19 g (69%) of a mixture of diastereomeric sulfides **11**. An analytical sample was prepared by crystallization from 95% EtOH: mp 88–96 °C; IR (KBr) 1650 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.13 (d, 3 H, J = 6.5 Hz), 1.69 (s, 3 H), 1.3–3.15 (m, 6 H), 3.2–3.65 (m, 1 H), 3.65–4.15 (m, 4 H), 4.7 (s, 2 H), 7.0–7.6 (m, 5 H). Anal. Calcd for $C_{18}H_{24}O_2S$: C, 71.01; H, 7.95. Found: C, 70.82; H, 7.86.

Preparation of Vinyl Sulfides. Chlorinations of the sulfides could be done in a variety of solvents, e.g., CCl_4 (purified by acid wash),[23] $CHCl_3$, or CH_2Cl_2, but for most cases, we found PhH to be most convenient. Generally, in the case of the more acidic compounds (ketones), elimination of HCl was spontaneous, but even in these cases, slightly higher yields were obtained by the addition of NEt_3 *after* chlorination. Representative examples of the experimental details are presented below.

3-(Phenylthio)propenonitrile (*E*/*Z* Mixture). To a solution of 302 mg (1.85 mmol) of 3-(phenylthio)propanonitrile[24] in 3 mL of PhH and cooled with an ice–water bath was added 272 mg (2.04 mmol) of *N*-chlorosuccinimide (NCS), and the suspension was stirred for 3 h, the temperature slowly rising to 25 °C. The reaction mixture was cooled with an ice–water bath, 0.77 mL of NEt_3 in 3 mL of of PhH was added, and stirring was continued for an additional 4 h, the temperature slowly rising to 25 °C. After being diluted with Et_2O and washed with 10% HCl, H_2O, and saturated NaCl, the organic phase was dried over Na_2SO_4 and

(22) Saddler, J. C.; Conrad, P. C.; Fuchs, P. L. *Tetrahedron Lett.* **1978**, 5079. Okamura, H.; Miura, M.; Takei, H. *Ibid.* **1979**, 43. Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637. Trost, B. M.; Tanigawa, Y. *J. Am. Chem. Soc.* **1979**, *101*, 4413, 4743 and references cited therein.

(23) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1977**, *42*, 2362.

(24) Ricci, A.; Danieli, R.; Pirazzini, G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1069.

the solvent removed to give 298 mg (100%) of 2-(phenylthio)-propenonitrile:[25] IR (neat) 2250, 1570 cm^{-1}; ^1H NMR (CCl_4) δ 4.98 (d, 1 H, J = 16 Hz, E isomer), 5.35 (d, 1 H, J = 10 Hz, Z isomer), 7.38 (d, 1 H, J = 16 Hz, E isomer), 7.15–7.47 (m, 5 H); GLC (180 °C) and ^1H NMR spectroscopy indicated an E/Z ratio of 73:27.

Ethyl 3-(phenylthio)propenoate (E/Z Mixture)[26] was prepared from ethyl 3-(phenylthio)propionate[27] as above (base treatment of the chloro sulfide was extended to 16 h) in 94% yield (after chromatography on silica gel with a 1:2 PhH/petroleum ether mixture): IR (neat) 1710, 1585, 1575 cm^{-1}; ^1H NMR (CCl_4) δ 5.65 (d, 1 H, J = 15 Hz, E isomer), 5.85 (d, 1 H, J = 10 Hz, Z isomer), 7.21 (d, 1 H, J = 10 Hz, Z isomer), 7.4 (m, 5 H), 7.73 (d, 1 H, J = 15 Hz, E isomer); GLC (210 °C) indicated an E/Z ratio of 91/9.

Methyl 2-Methyl-3-(phenylthio)propenoate (E/Z Mixture). A mixture of 1.05 g (5.0 mmol) of methyl 2-methyl-3-(phenylthio)propionate,[28] 0.70 g (5.2 mmol) of NCS, and 10 mL of CCl_4 was stirred at 0 °C for 2 h and filtered, and the filtrate was evaporated. The residue refluxed for 1.5 h with 0.8 mL of NEt_3 in 10 mL of $CHCl_3$ and then allowed to stand overnight. The solution was poured into 75 mL of PhH, the resulting suspension was filtered, and the filtrate was evaporated to give 1.06 g of crude product. Chromatography on 50 g of silica gel, upon elution with 1:1 petroleum ether/PhH, gave 0.903 g (85%) of methyl 2-methyl-3-(phenylthio)propenoate:[18,19] IR ($CHCl_3$) 1710, 1590, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (br s, 3 H), 3.68 (s, 3 H, E isomer), 3.77 (s, 3 H, Z isomer), 6.95 (q, 1 H, J = 1 Hz, Z isomer), 7.1–7.55 (m, 5 H), 7.63 (m, 1 H); GLC (190 °C) and ^1H NMR spectroscopy indicated an 82/18 ratio of E/Z product, contaminated with 2% of starting sulfide.

4-(Phenylthio)-3-buten-2-one (E/Z Mixture).[29] This compound was prepared from 4-(phenylthio)-2-butanone[4,30] as above in 74% yield (after chromatography on silica gel with a 1:2 petroleum ether/PhH mixture): IR (KBr) 1660, 1550 cm^{-1}; ^1H NMR (CCl_4) δ 2.08 (s, 3 H), 6.0 (d, 1 H, J = 15.5 Hz, E isomer), 6.3 (d, 1 H, J = 9.5 Hz, Z isomer), 7.4 (m, 5 H), 7.63 (d, 1 H, J = 15.5 Hz, E isomer); GLC (195 °C) indicated an E/Z ratio of 93/7. ^1H NMR spectra (CCl_4) taken of a reaction run at 25 °C for 1.25 h in CCl_4 (after filtration but without removal of solvent) showed an ~1:1 mixture of eliminated product **7** and chloro sulfide **6**: δ 2.12 (s, 3 H), 3.07 (d, J = 6.5 Hz, 2 H), 5.58 (t, J = 6.5 Hz, 1 H), 7.0–7.6 (m, 5 H).

3-(Phenylthio)-2-cyclopentenone.[18] This compound was prepared as above from 3-(phenylthio)cyclopentanone, described above, in 65% yield (after chromatography on silica gel with a 1% EtOH/PhH mixture): IR (neat) 1695, 1555 cm^{-1}; ^1H NMR (CCl_4) δ 2.2–2.85 (m, 4 H), 5.57 (t, J = 1 Hz, 1 H), 7.3–7.75 (m, 5 H).

3-(Phenylthio)-2-cyclohexenone[18] was prepared as above from 3-(phenylthio)cyclohexanone[10,30] in 60% yield (after chromatography on silica gel with a 1% EtOH/PhH mixture): IR (neat) 1660, 1575 cm^{-1}; ^1H NMR (CCl_4) δ 2.3–2.6 (m, 6 H), 5.40 (t, J = 1 Hz, 1 H), 7.15–7.7 (m, 5 H).

3-(Phenylthio)-5-methyl-2(5*H*)-furanone was prepared as above from 4-(phenylthio)-5-methyl-3,4-dihydro-2(5*H*)-furanone, described above, in 75% yield (after chromatography on silica gel with a 1:1 PhH/petroleum ether mixture): IR ($CHCl_3$) 1750, 1570 cm^{-1}; ^1H NMR (CCl_4) δ 1.50 (d, 3 H, J = 7 Hz), 5.05 (qd, 1 H, J_q = 7 Hz, J_d = 1.5 Hz), 5.23 (d, 1 H, J = 1.5 Hz), 7.52 (m, 5 H). Anal. Calcd for $C_{11}H_{20}O_2S$: C, 64.05; H, 4.89. Found: C, 63.92; H, 4.99.

2-Methyl-5-(2-propenyl)-3-(phenylthio)-2-cyclohexenone (13). Procedure A. A mixture of 304 mg (1.0 mmol) of sulfide **11**, 190 mg (1.4 mmol) of NCS, and 5 mL of CCl_4 was stirred for 6 h at 0 °C. After warming to room temperature, the suspension was filtered and the solvent removed on a Rotovac to give a homogeneous oil which separated into two phases over a period of several minutes. Chromatography on silica gel with 1:2 petroleum ether/PhH gave 165 mg (64%) of enone. An analytical sample was prepared by cold-finger distillation (220 °C bath; 0.2 mm): IR (neat) 1660, 1575 cm^{-1}; ^1H NMR (CCl_4) δ 1.57 (br s, 3 H), 1.92 (m, 3 H), 2.0–2.9 (m, 5 H), 2.5–2.85 (m, 2 H), 7.43 (m, 5 H); mass spectrum calcd for $C_{16}H_{18}OS$ (M) m/e 258.1078, found m/e 258.1026.

Procedure B. A mixture of 3.04 g (20.0 mmol) of carvone (**8**), 2.30 g (20.9 mmol) of thiophenol, and 0.5 mL of triethylamine was stirred at room temperature for 4 days. The reaction mixture was diluted with ether, washed with dilute NaOH, twice with H_2O, and once with saturated NaCl solution, and dried over Na_2SO_4. Removal of solvent gave 5.34 g of crude product as a mixture of isomers in which the equatorial sulfide **14** predominated: IR (neat) 1708 cm^{-1}; ^1H NMR (CCl_4) δ 1.27 (d, J = 6.5 Hz, 3 H), 1.64 (m, 3 H), 1.72–3.45 (m, 7 H), 4.73 (m, 2 H), 7.35 (m, 5 H). Integration of the peak appearing at δ 3.84 (m, w = 15 Hz), presumably corrsponding to the axial sulfide isomer, against the other absorptions indicated a 5:1 equatorial to axial sulfide ratio.

A mixture of 237 mg of the crude sulfide product (corresponding to 0.888 mmol of carvone) and 146 mg (1.10 mmol) of NCS in 5.0 mL of benzene and 2.5 mL of ether was stirred at room temperature for 7 h. After filtration and solvent removal, the residue was triturated with CCl_4 and refiltered, and the solvent was removed to give 240 mg of crude product. Chromatography on 30 g of silica gel with benzene gave 10 mg of **14** and 155 mg of **13** (68% yield based on carvone).

(Phenylthio)ethene. A mixture of 5.5 g (50 mmol) of thiophenol, 6.0 g (55 mmol) of ethyl bromide, 2.2 g (55 mmol) of NaOH, 2.0 mL of tetrabutylammonium hydroxide (40% in methanol), 20 mL of H_2O, and 30 mL of PhH was stirred overnight at room temperature. The organic phase was separated, washed with dilute NaOH and H_2O, and dried over Na_2SO_4. After removal of the solvent, the residue was distilled to give 6.48 g (94%) of (phenylthio)ethane, bp 79–80 °C (1.25 mm). A mixture of 2.76 g (20.0 mmol) of this sulfide, 2.80 g (21.0 mmol) of NCS, and 30 mL of CCl_4 was stirred at room temperature for 3 h. After the resulting suspension was filtered, the solvent was removed on a Rotovac, and the residue was refluxed in 10 mL of pyridine for 0.5 h. After cooling, the mixture was diluted with petroleum ether, and the organic phase was washed two times with H_2O, once with dilute aqueous HCl, and once with saturated NaCl solution and dried over Na_2SO_4. Removal of the solvent on a Rotovac gave 2.00 g of crude product, which was distilled to give 1.54 g (57%) of (phenylthio)ethene:[31] bp 44–45 °C (0.3 mm); IR (neat) 1580 cm^{-1}; ^1H NMR (CCl_4) δ 5.25 (d, 1 H, J = 17 Hz), 5.27 (d, 1 H, J = 9.5 Hz), 6.5 (dd, 1 H, J = 17, 9.5 Hz), 7.0–7.55 (m, 5 H).

1-(Phenylthio)octene. A mixture of 2.22 g (10.0 mmol) of 1-(phenylthio)octane,[32] 1.40 g (10.5 mmol) of NCS, and 50 mL of CCl_4 was refluxed for 40 min. After the mixture was cooled and filtered and the solvent removed, the crude residue was refluxed for 1 h with 20 mL of pyridine. A workup as above gave 1.28 g of crude product which was purified by chromatography on 50 g of silica gel by elution with petroleum ether to give 1.85 g (84%) of a mixture of (*E*)- and (*Z*)-1-(phenylthio)-1-octene.[9]

Acknowledgment. We thank Professor Baker for mass spectral determinations and H. Martins of CETEC for elemental analysis. The partial support of this work by CNPq and CAPES is greatfully acknowledged.

Registry No. **5**, 6110-01-6; (*E*)-**7**, 33944-98-8; (*Z*)-**7**, 33944-97-7; **8**, 99-49-0; **9**, 75717-28-1; **11**, 75717-29-2; **13**, 75717-30-5; **14**, 75717-31-6; 2-propenenitrile, 107-13-1; ethyl 2-propenoate, 140-88-5; ethyl 2-methyl-2-propenoate, 97-63-2; 5-methyl-2(3*H*)-furanone, 591-12-8; 3-buten-2-one, 78-94-4; 2-cyclopenten-1-one, 930-30-3; 2-cyclohexen-1-one, 930-68-7; 3-(phenylthio)propanenitrile, 3055-87-6; ethyl 3-(phenylthio)propanoate, 60805-64-3; methyl 2-methyl-3-(phenyl-

(25) Gundermann, K. D.; Roehl, E. *Justus Liebigs Ann. Chem.* **1974**, 1661.
(26) Liu, Y. C.; Wang, H. K.; Chu, S. C. *Hua Hsueh Hsueh Pao* **1964**, *30*, 283; *Chem. Abstr.* **1964**, *61*, 11865*h*.
(27) Iwai, K.; Kosugi, H.; Miyazaki, A.; Uda, H. *Synth. Commun.* **1976**, *6*, 357.
(28) Georges, G.; Rouvier, E.; Musso, J.; Cambon, A.; Fellous, R. *Bull. Soc. Chim. Fr.* **1972**, 4622.
(29) Prilezhaeva, E. N.; Mikhelashivili, I. L.; Bogdanov. V. S.; Vasilév, G. S. *Dokl. Vses. Konf. Khim. Atsetilena* **1972**, *1*, 525; *Chem. Abstr.* **1973**, *79*, 17699.
(30) Chang, Y.-H.; Pinnick, H. W. *J. Org. Chem.* **1978**, *43*, 373.
(31) Hopkins, P. H.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1209.
(32) Bakuzis, P.; Bakuzis, M. L. F.; Fortes, C. C.; Santos, R. *J. Org. Chem.* **1976**, *41*, 3261.

thio)propanoate, 777-80-0; *cis*-dihydro-5-methyl-4-(phenylthio)-2-(3*H*)-furanone, 75717-32-7; *trans*-dihydro-5-methyl-4-(phenylthio)-2(3*H*)-furanone, 75717-33-8; 3-(phenylthio)cyclopentanone, 75717-34-9; 3-(phenylthio)cyclohexanone, 35155-84-1; (*E*)-3-(phenylthio)-2-propenenitrile, 2974-75-6; (*Z*)-3-(phenylthio)-2-propenenitrile, 2974-76-7; ethyl (*E*)-3-(phenylthio)-2-propenoate, 75717-35-0; ethyl (*Z*)-3-(phenylthio)-2-propenoate, 75717-36-1; methyl (*E*)-2-methyl-3-(phenylthio)-2-propenoate, 71847-74-0; methyl (*Z*)-2-methyl-3-(phenylthio)-2-propenoate, 66349-63-1; 5-methyl-4-(phenylthio)-2-(5*H*)-furanone, 75717-37-2; 3-(phenylthio)-2-cyclopenten-1-one, 75717-38-3; 3-(phenylthio)-2-cyclohexen-1-one, 75717-39-4; thiophenol, 108-98-5; ethyl bromide, 74-96-4; (phenylthio)ethane, 622-38-8; (phenylthio)ethene, 1822-73-7; 1-(phenylthio)octane, 13910-16-2; (*E*)-1-(phenylthio)-1-octene, 75717-40-7; (*Z*)-1-(phenylthio)-1-octene, 75717-41-8; (phenylthio)cyclohexane, 7570-92-5; (phenylthio)cyclohexene, 4922-47-8.

Selective γ Alkylation of Copper Enolates Derived from α,β-Unsaturated Acids: Factors Affecting Scope and Regio- and Stereoselectivity

Patricia M. Savu and John A. Katzenellenbogen*

The Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

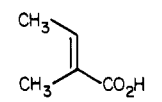
Received June 11, 1980

Copper dienolates derived from α,β-unsaturated acids undergo alkylation at the γ-carbon with high regioselectivity. A systematic investigation has been made of several factors that affect the γ-alkylation process of the dienolate derived tiglic acid (1): alterations in the nature of the counterion, in the stoichiometry of cuprous ion, and in the nature of the electrophile. Compared to allylic electrophiles, nonallylic electrophiles react with copper dienolates sluggishly and with little selectivity for the γ-carbon; vinylic epoxides, however, are particularly good alkylating agents. They undergo allylic transposition and react at the γ-carbon of the dienolate with high selectivity (70–90%), generating an allylic unit that forms part of a 1,5-diene skeleton oxygenated at both ends. Tiglic (1) and crotonic (3) acids react with vinylic epoxides to form a 1,5-diene with entirely *E* stereochemistry at the 2,3 double bond, while senecioic acid (2) forms a 1,5-diene with mostly *Z* stereochemistry at the 2,3 double bond. Geometry at the 6,7 double bond depends both on the α,β-unsaturated acid used and on the structure of the epoxide. With allylic electrophiles under direct (S_N2) attack, stereochemical analysis showed that some isomerization occurs around the 6,7 double bond (derived from the electrophile). Addition of cuprous ion to the lithium dianion of 2-hexenoic acid (17) was found to enhance the regioselectivity of γ alkylation, but a subsequent Michael addition reaction limits the potential of γ alkylation in this system.

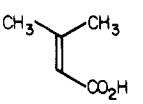
One approach to the synthesis of isoprenoid 1,5-polyolefins is the coupling of two allylic units containing the appropriate olefinic stereochemistry; this is, in fact, the basis of linear terpenoid biosynthesis. Complications develop in the chemical adaptation of this approach that involves the displacement of an allylic electrophile by an allylic nucleophile: allylic electrophiles can undergo S_N2 or S_N2' attack, and their geometrical integrity is not assured;[1] the nucelophile is an ambident anion and its olefinic stereochemistry is subject to ready isomer equilibration.[2]

A number of successful strategies to 1,5-diene synthesis by allylic–allylic coupling involve the alkylation of a charge-stabilized allylic organometallic reagent with an allylic electrophile. Groups such as sulfone,[3-5] sulfoxide,[6] sulfide,[7,8] carbonyl,[9] or alkylphosphonium bromide[10] have been used to stabilize allylic anions and direct alkylation α to themselves. The stabilizing group can be reductively cleaved with double bond transposition[4,6,8] or without[3,10] to yield a 1,5-diene. One problem encountered with this approach is that product mixtures are often obtained in the reductive cleavage step. In some cases (allylic ethers and thioethers) alkylation occurs at the site γ to the stabilizing group.[11-14]

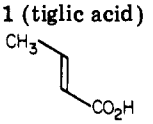
Chart I. Structures of α,β-Unsaturated Acids



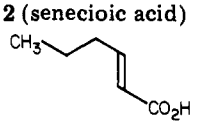
1 (tiglic acid)



2 (senecioic acid)



3 (crotonic acid)



4 (2-hexenoic acid)

Theoretically, carbonyl-stabilized allylic anions (i.e., dienolates derived from α,β-unsaturated carbonyl compounds) are capable of this type of γ alkylation. A major advantage of the use of such carbonyl-stabilized precursors is that a natural oxygenation pattern (at the chain terminus) is maintained, whether elongation of the isoprene chain proceeds from tail to head or vice versa. Unfortunately, the anions derived from most α,β-unsaturated ketones,[15] aldehydes,[16] and aldimines[17] have been found to alkylate predominantly at the α-carbon, although certain

(1) MacKenzie, K.; DeWolf, R. H.; Young, W. G. In "The Chemistry of Alkenes"; Patai, S., Ed., Interscience: New York, 1964; pp 436–453, 681–738.
(2) Hutchinson, D. A.; Beck, K. R.; Benkeser, R. A.; Grutzner, J. B. *J. Am. Chem. Soc.* **1973**, *95*, 7075 and references cited therein.
(3) Grieco, P. A.; Masaki, Y. *J. Org. Chem.* **1974**, *39*, 2135.
(4) Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 123.
(5) (a) Lansbury, P. T.; Erwin, R. W. *Tetrahedron Lett.* **1978**, *2675*. (b) Lansbury, P. T.; Erwin, R. W.; Jeffrey, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1602.
(6) Nederlof, P. J. R.; Moolenaar, M. J.; de Waard, F. R.; Huisman, H. O. *Tetrahedron Lett.* **1976**, 3175.
(7) Bielmann, J. F.; Ducep, J. B. *Tetrahedron Lett.* **1969**, 3707.
(8) Brownbridge, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1131.
(9) Carlson, R. M.; Oyler, A. R. *J. Org. Chem.* **1976**, *41*, 4065.
(10) Axelrod, E. H.; Milne, G. M.; Van Tamelen, E. E. *J. Am. Chem. Soc.* **1970**, *92*, 2139.
(11) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560.
(12) Still, W. C., Macdonald, T. L. *J. Am. Chem. Soc.* **1974**, *96*, 5561.
(13) Barsanti, P.; Calò, V.; Lopez, L.; Marchese, G.; Naso, F.; Pesce, G. *J. Chem. Soc., Chem. Commun.* **1978**, 1085.
(14) Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 7926.
(15) Zimmerman, H. E. "Molecular Rearrangements"; de Mayo, P., Ed.; Interscience: New York, 1963; p 345.
(16) deGraaf, S. A. G.; Oosterhoff, P. E. R.; Van der Gen, A. *Tetrahedron Lett.* **1974**, 1653.
(17) Takabe, K.; Katagiri, T.; Tanaka, J. *Tetrahedron Lett.* **1972**, 4097.

0022-3263/81/1946-0239$01.00/0