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# Michael Reactions of α-Phenylthio and α-Phenylsulfinyl Crotonic Esters with Cyclic Enones

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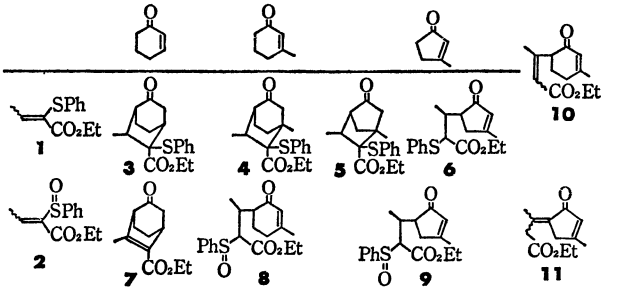
**Synopsis.** The Michael reactivities of ethyl α-phenylthio- and α-phenylsulfinylcrotonates with 2-cyclohexenone, 3-methyl-2-cyclohexenone, and 3-methyl-2-cyclopentenone have been investigated.

In connection with the study of α-phenylthio or α-phenylsulfinyl α,β-unsaturated esters[1] for synthetic utility, we have examined the reactivities of ethyl α-phenylthiocrotonate **1** and ethyl α-phenylsulfinylcrotonate **2** to cyclic enones as the Michael acceptor and addend.[2]

Compound **1** easily underwent the sequential Michael additions with the enolates of 2-cyclohexenone and 3-methyl-2-cyclohexenone, generated by treatment with lithium diisopropylamide in the presence of HMPA, to give the bicyclo[2.2.2]octane derivatives **3** and **4** in 70 and 77% yields, respectively.[3] (Table 1).

TABLE 1. MICHAEL ADDITION PRODUCTS OF **1** AND **2** WITH CYCLIC ENONES*




* All the products except **7** were mixtures of diastereoisomers.

In the reactions the addition of HMPA was essential, since an intractable mixture was produced when the reaction of **1** with 2-cyclohexenone was conducted in the absence of HMPA. On the other hand, in the reaction with 3-methyl-2-cyclopentenone the double Michael product **5** was the minor component (17%), the major one (58%) being the first Michael adduct **6**. Such a difference in the second Michael addition process between the six and five membered enones may be attributed to the difference of ring strain in the enolates of the bicyclo[2.2.2]octanone system in **4** and bicyclo[2.2.1]heptanone one in **5**; in the latter the ring-opened enolate, the first Michael adduct, appears to be more favorable in the equilibrium condition.

The sequential Michael addition was also observed in the reaction of **2** with 2-cyclohexenone, accompanied by desulfenylation during the work-up, giving rise to the bicyclo[2.2.2]octene derivative **7**. The reaction of **2** with 3-methyl-2-cyclohexenone and 3-methyl-2-cyclopentenone afforded only the first Michael adducts **8** and **9** in low yields. Failure for the second Michael additions of **8** and **9** would be ascribed to the stability of the anion, $-\bar{C}(SOPh)COOEt$, and the steric effect of the ring methyl group.

The structures of **3**, **8**, and **9** were further confirmed by transformation into the desulfenylated compounds **7**, **10**, and **11**, respectively.

## Experimental

IR spectra were taken on a Hitachi EPI-S2 spectrophotometer using $CCl_4$ as a solvent. NMR spectra were obtained on a JEOL C-60HL instrument using TMS as an internal standard and $CCl_4$ as a solvent. The results are given in terms of the δ scale, the values of ester ethyl and phenyl protons except **1** and **2** being omitted. Analytical samples were purified by evaporative distillation and bath temperatures are given as the boiling points. Elemental analyses were carried out in the microanalytical laboratory of this institute.

*Ethyl α-Phenylthio- and α-Phenylsulfinylcrotonates* ***1*** *and* ***2***. Ethyl α-phenylsulfinylbutyrate (3.07 g, 12.8 mmol) was prepared by the reaction of ethyl α-bromobutyrate with sodium thiophenolate followed by oxidation with $NaIO_4$ in the usual manner. To this was added dropwise trifluoroacetic anhydride (4.2 g, 20 mmol) with stirring and ice-cooling (the Pummerer rearrangement and subsequent elimination of trifluoroacetic acid took place). The mixture was stirred at room temperature for 1.5 hr and then evaporated to dryness *in vacuo*. The residual liquid was dissolved in ether, passed through Woelm neutral alumina activity III, and freed from ether to give spectroscopically single ethyl α-phenylthiocrotonate **1** (2.34 g, 82%): bp 120—130 °C (3.5 mmHg, large scale distillation caused decomposition to produce a considerable amount of a substance with lower-boiling point, reducing the yield of **1**, *ca.* 52%); IR 1730, 1620 $cm^{-1}$; NMR 1.02 (3H, t, $J$=7.5), 2.05 (3H, d, $J$=6.8), 4.05 (2H, q, $J$=7.5), 7.15—7.50 (5H, m), 7.45 (1H, q, $J$=6.8); Anal. Found: C, 65.11; H, 6.62%. Calcd for $C_{12}H_{14}O_2S$: C, 64.85; H, 6.35%. The geometry of the double bond has not been determined.

Ethyl α-phenylsulfinylcrotonate **2** was prepared from **1** by oxidation with an equivalent amount of *m*-chloroperbenzoic acid in $CH_2Cl_2$ (0 °C, 10 min) in the usual manner and purified by chromatography on $SiO_2$. Yield: 67%. IR 1720, 1627 $cm^{-1}$; NMR 1.07 (3H, t, $J$=7.5), 2.26 (3H, d, $J$=7.5), 4.06 (2H, q, $J$=7.5), 7.25—7.80 (6H, q and m).

*General Procedure for Michael Reactions of* ***1*** *and* ***2*** *with Cyclic Enones.* To a solution of lithium diisopropylamide (1.20—1.30 mmol) in anhydrous THF (2 ml) and ether (1 ml) was added dropwise at −60 °C a solution of a cyclic enone (1.00 mmol) and then a solution of HMPA (1.00 mmol) in anhydrous THF (2 ml each). After being stirred at −60 °C for 1 hr, the solution was cooled at −75 °C and a solution of **1** or **2** (1.10 mmol) in anhydrous THF (2 ml)

was added. The operation was carried out under nitrogen. The progress of the reaction was followed by tlc. The reaction mixture was stirred at an appropriate temperature for an appropriate time, and then acidified with dil. HCl and thoroughly extracted with $CH_2Cl_2$. The extract was washed with saturated salt solution, dried, and freed from the solvent. The product was separated by preparative tlc on $SiO_2$ with 1 : 1 petroleum ether-ether for **3**—**6** and with 1 : 10 or ether alone for **8** and **9**. The reaction conditions (temperature and time) and the yields of products are shown for each case.

*Ethyl 3-Methyl-5-oxo-2-(phenylthio)bicyclo*[2.2.2]*octane-2-carboxylate* ***3*** *and its Conversion into* ***7***. Reaction conditions: −75——55 °C for 2 hr. Yield: 70%. IR 1725 (br.) $cm^{-1}$; NMR 0.80—1.50 (6H, complex d and t), 1.50—3.20 (9H, m).

To a cold solution of **3** (230 mg, 0.72 mmol) in $CH_2Cl_2$ (4 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (85%, 147 mg, 0.72 mmol) in $CH_2Cl_2$ (4 ml), and the mixture was stirred at 0 °C for 30 min. Aqueous saturated $NaHSO_3$ was added and the water layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with saturated $NaHCO_3$ and salt solution, dried, and evaporated. The residue was dissolved in toluene (5 ml) and heated under reflux for 30 min. Evaporation of toluene, followed by preparative tlc of the residue ($SiO_2$, 2 : 1 petroleum ether-ether) afforded **7** (41 mg, 27%): bp 120 °C (4 mmHg); IR 1725, 1700, 1632 $cm^{-1}$; NMR 1.50—3.37 (8H, m), 2.23 (3H, s); Anal. Found: C, 69.31; H, 7.63%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H. 7.74%.

*Ethyl 1,3-Dimethyl-5-oxo-2-(phenylthio)bicyclo*[2.2.2]*octane-2-carboxylate* ***4*** *and Desulfurization.* Reaction conditions: −75——50 °C for 1.5 hr. Yield: 77%. Bp 120—130 °C (5 mmHg); IR 1725 (br) $cm^{-1}$; NMR 0.80—1.45 (9H, complex s, d, and t), 1.50—3.50 (8H, m); Anal. Found: C, 68.80; H, 7.28%. Calcd for $C_{19}H_{24}O_3S$: C, 68.65; H, 7.28%.

A mixture of **4** (102 mg), Raney-Ni (pest, 0.5 ml), and acetone (3 ml) was heated under reflux for 20 min. The reaction mixture was passed through $SiO_2$ and evaporated. The residue was purified by preparative tlc ($SiO_2$, 1 : 1 petroleum ether-ether) to give ethyl 1,3-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate (**4**, PhS group = H) (33 mg, 42%): IR 1730 (br.) $cm^{-1}$; NMR 0.90—1.15 (6H, s and d), 1.40—3.00 (9H, m). Attempt to apply oxidation-desulfenylation procedure to **4** failed.

*Ethyl 1,3-Dimethyl-5-oxo-2-(phenylthio)bicyclo*[2.2.1]*heptane-2-carboxylate* ***5*** *and Ethyl α-Phenylthio-β-(2-oxo-4-methyl-3-cyclopentenyl)butyrate* ***6***. Reaction conditions: −75——70 °C for 30 min. Yield: 17% for **5** and 58% for **6**. **5**: bp 110—120 °C (2.5 mmHg); IR 1755, 1725 $cm^{-1}$; NMR 1.35 (3H, d, $J$=7.5) 1.62 (3H, s), 1.19—2.40 (5H, m), 2.99 (1H, m); Anal. Found: C, 67.95; H, 7.16%. Calcd for $C_{18}H_{22}O_3S$: C, 67.91; H, 6.97%. **6**: bp 130—140 °C (3 mmHg); IR 1725, 1693, 1627 $cm^{-1}$; NMR 0.74—1.35 (6H, complex d and t), 2.05 (3H, br. s), 1.50—3.90 (5H, m), 5.83 (1H, br.); Anal. Found: C, 67.86; H, 6.92%. Calcd for $C_{18}H_{22}O_3S$: C, 67.91; H, 6.97%.

When the reaction mixture was warmed up above −50 °C, **6** was the sole product.

*Ethyl 3-Methyl-5-oxobicyclo*[2.2.2]*oct-2-ene-2-carboxylate* ***7***. Reaction conditions: −75 °C for 1 hr and 20 °C for 1.5 hr. Yield: 48%. The IR and NMR spectra were identical with those of the sample derived from **3**.

*Ethyl α-Phenylsulfinyl-β-(2-oxo-4-methyl-3-cyclohexenyl)butyrate* ***8*** *and Pyrolysis.* Reaction conditions: −60—20 °C for 4 hr. Yield: 46%. IR 1730, 1670 $cm^{-1}$; NMR 0.75—1.42 (6H, complex d and t), 1.93 (3H, br. s), 1.80—4.42 (7H, m), 5.83 (1H, br.)

Pyrolysis of **8** in toluene was carried out in the same manner as described above to give ethyl β-(2-oxo-4-methyl-3-cyclohexenyl)crotonate **10** (70% yield): bp 120—130 °C (5 mmHg): IR 1715, 1670, 1640 $cm^{-1}$; NMR 1.96 (3H, s), 2.08 (3H, s), 1.78—3.10 (5H, m), 5.58—5.90 (2H, br.); Anal. Found: C, 70.51; H, 8.34%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%.

*Ethyl α-Phenylsulfinyl-β-(2-oxo-4-methyl-3-cyclopentenyl)butyrate* ***9*** *and Pyrolysis.* Reaction conditions: −60—20 °C for 2 hr. Yield: 23%. IR 1730, 1695, 1625 $cm^{-1}$; NMR 0.73—1.32 (6H, complex d and t), 2.16 (3H, br. s), 2.30—4.30 (5H, m), 5.92 (1H, br.).

Pyrolysis of **9** in toluene was carried out in the same manner as described above to give ethyl β-(2-oxo-4-methyl-3-cyclopentylidene)butyrate **11** (73% yield): bp 110—120 °C (5 mmHg); IR 1735, 1693, 1650, 1625 $cm^{-1}$; NMR 1.85 (3H, s), 2.10 (3H, s), 3.10 (2H, br. s), 3.87 (2H, s), 6.00 (1H, br. s); Anal. Found: C, 68.98; H, 7.40%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

## References

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