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REACTIONS OF SULFUR-CONTAINING CARBANIONS WITH ETHYL 4-BROMOCROTONATE. A FACILE SYNTHESIS OF CYCLOPROPANECARBOXYLATES

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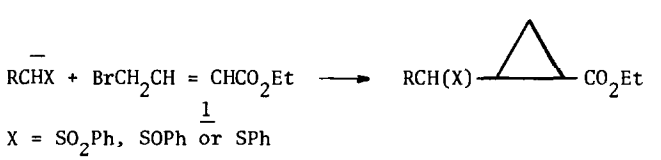
Abstract: Ethyl 4-bromocrotonate reacts as a Michael acceptor with carbanions derived from phenylsulfones and β-ester sulfides; the conjugated addition is followed by the displacement of Br^- affording various cyclopropanecarboxylates.

In reactions of sulfur-containing carbanions with α,β-unsaturated γ-bromoesters, the possibility of two processes can be envisaged: a) alkylation by a nucleophilic substitution reaction and b) an initial Michael addition of the carbanions to the α,β-unsaturated ester. Alkylation reactions of sulfur-containing carbanions by displacement on allyl halides occur readily[1] and an α-sulfonyl carbanion has been shown to react in this manner with an unsaturated bromoester.[2] Specifically, previously reported reactions of carbonyl-derived carbanions with ethyl 4-bromocrotonate occurred by way of nucleophilic substitution.[3]

The other process, involving conjugated addition and cyclopropanation, has also been reported[4] but it was limited to anion attack on 2-bromo-2-methylpropylidene malonate, in which the allylic site is hindered by alkyl disubstitution.

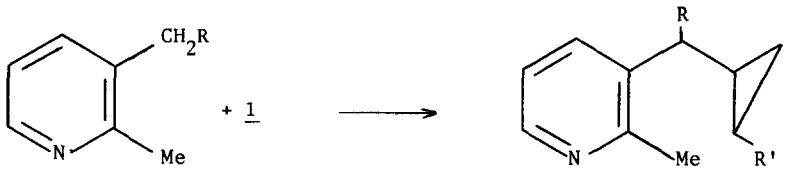
It is therefore of interest to report that some carbanions derived from α-phenylsulfones, sulfoxides and sulfides, in contrast to carbonyl-derived carbanions, can undergo exclusively a conjugated Michael addition with ethyl 4-bromocrotonate (1), with concomitant 1,3-displacement of the bromide ion, thus providing an efficient and simple synthesis of monosubstituted cyclopropanecarboxylates:



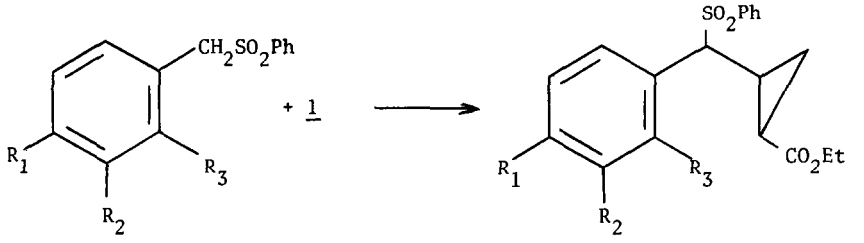
The mechanism of the reaction is possibly concerted: only negligible addition of the same donors occured when ethyl crotonate was used as an acceptor under analogous conditions.

The Table shows reactions of 1 with benzylic carbanions (or pyridine analogs) activated by an α-phenylsulfonyl group, the latter being more efficient than the corresponding sulfoxide (e.g., 3a versus 3b). The presence of a methyl substituent on the aromatic ring of the substrates, independent of location, was found to affect favorably the reactivity of the carbanions, as reflected in yields.[5] The obtained products were stereochemically homogeneous (t.l.c., mp , and ^{1}H NMR evidence), hence the Michael addition of the carbanions proceeds stereoselectively. With regard to cyclopropanes, the sterically favored trans-disubstitution was evidenced from the coupling constant values[6] of the corresponding vicinal ring protons in ^{1}H NMR (vide infra).

TABLE



		mp (°C)	Yield (%)
2a; R=SO_2Ph	3a; R'=CO_2Et	107	75
2b; R=SOPh	3b; R'=CO_2Et	129-131	53
	4a; R'=CH_2OH		

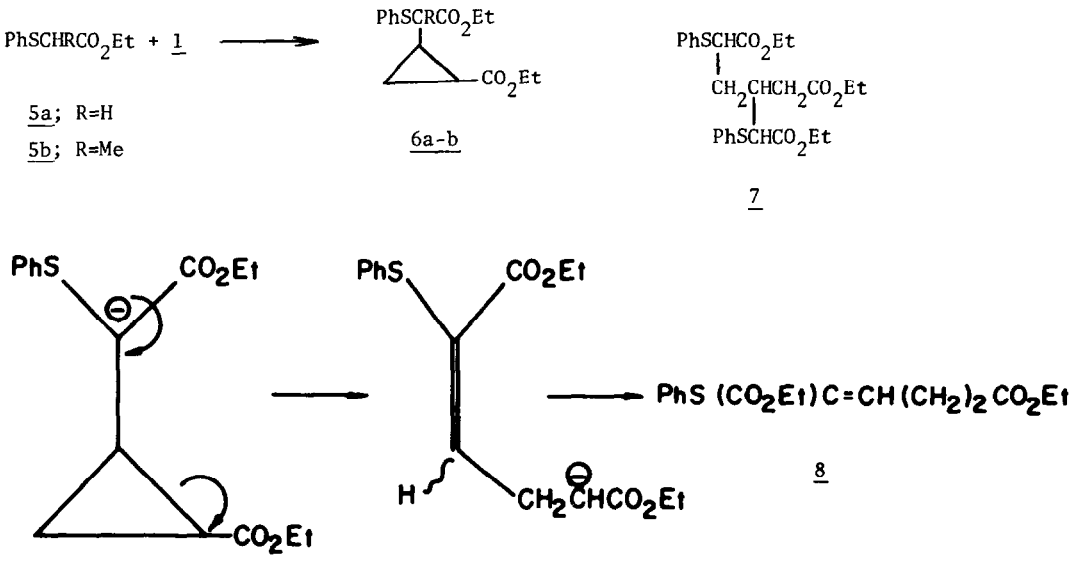


	mp (°C)	Yield (%)
2c; R_1=R_2=R_3=H	3c;	116-118	61
2d; R_1=Me; R_2=R_3=H	3d;	138-140	78
2e; R_2=Me; R_1=R_3=H	3e;	103-104	72
2f; R_3=Me; R_1=R_2=H	3f;	130-131	77

The experimental procedure for 2a-b consisted in adding the compound (1 mmol) in tetrahydrofuran (THF, 2 ml) and tetramethylethylenediamine (TMEDA, 2 mmol) to a solution of lithium diisopropylamide (LDA, 2 mmol in 2 ml THF) at -78°C under argon. The stirred reaction mixture was allowed to warm to -20°C during 1 h, then cooled again to -78°C and ester 1 (1.2 mmol in 2 ml THF) was added. The reaction was quenched (NH_4Cl solution) after 1 h at -50°C. Compound 3a (column purification), showed m/e 359 (M^+), 314, 218; ^{1}H NMR ($CDCl_3$): δ 0.91-1.02 (m, 1H), 1.16 (t, 3H), 1.29-1.46 (m, 2H), 2.13-2.26 (m, 1H), 2.32

(s, 3H), 3.73 (d, 1H, J=10 Hz), 4.04 (q, 2H), 7.10-8.48 (m,8H). Reduction of 3a ($LiAlH_4$, ether, 0°C) gave the alcohol 4a, mp 152°C, in which the unmasked cyclopropane protons at δ 0.53-0.88 (m, 3H), 1.25-1.62 (m, 1H) could be decoupled by double irradiation: J=3.2 Hz for vicinal ring methine protons. Modification[7] of the experimental procedure for compounds 2c-f was motivated by the enhanced formation and reactivity of carbanions from aromatic substrates.

Similar donor reactivity has been exhibited by the β-ester sulfides 5a-b, of increased acidity. The reaction results of the latter with 1 were however found to be dependent on the base by which the carbanions were generated: use of LDA under shown above conditions afforded from 5a mainly a mixture of 6a and 7 (1:2 ratio), whereas the use of lithium dicyclohexylamide as base under slightly modified conditions[8] afforded only 6a (64% isolated yield) and 6b (74%), respectively. Diester 6a showed m/e 308 (M^+), 262, 235, ^1H NMR (270 MHz, $CDCl_3$): δ 0.97-1.10 (m, 1H), 1.20 (t, 3H, J=7 Hz), 1.26 (t, 3H, J=7 Hz), 1.25-1.28 (m, 1H), 1.59-1.66 (m, 1H, -C-CH-CO_2Et, on irradiation centered at 1.10 collapses to d, J=4.8 Hz),[9] 1.72-1.89 (m, 1H, -CH-CH-SPh), 3.13 (d, 1H, -CH-SPh, J=10 Hz), 4.02-4.22 (dq, J=7 Hz), 7.07-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 173, 171, (C=O of esters). The formation of 6a-b represents a versatile route to cyclopropanecarboxylates functionalized in the side chain, via mild reductive desulfurization of β-carbonyl sulfides[10] or elimination of the corresponding sulfoxides.[11]



If the reaction mixture containing 6a is allowed to warm up to 0°C (20-30 min) instead of quenching at -60°C, a quantitative conversion of 6a to diester 8 takes place. A single isomer of undetermined configuration was obtained: m/e 308 (M^+), ^1H NMR (270 MHz, $CDCl_3$) δ 1.06, (3H, t, J=7 Hz), 1.25 (3H, t, J=7 Hz), 2.49 (t, 2H, J=7 Hz, when hv at 2.81, collapses to s), 2.81

(dt overlapped to q, J=7 Hz, when hv at 7.32, collapses to t), 4.09 (dq, 4H, J=7 Hz), 7.09-7.26 (m, 5H) and 7.32 (t, 1H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ 172 and 165; IR (film): ν_{CO} 1718 and 1731 cm^{-1} This conversion, which occurs probably by proton abstraction from 6a followed by ring opening to 8, represents an interesting and novel intramolecular nucleophilic cleavage of a monoactivated cyclopropane which is not part of a strained ring system.[12]

Acknowledgement. The authors are grateful to Mr. M. Grunberg for the NMR spectroscopic work.

References and Notes

1. See e.g., E. Block, "Reactions of organosulfur compounds", Academic Press, 1978, p. 57 ff.
2. K. Uneyama and S. Torii. Tetrahedron Lett., 443 (1967); for similar reactivity of other anions see e.g., M. Julia and D. Arnould, Bull.Soc.Chim.France, 743 (1973); H. Ishii and I. Ishikawa, Tetrahedron Lett., 4189 (1973).
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4. P. Kolsaker and H.J. Storesund, Chem.Commun., 357 (1972); R. Verhé, N. De Kimpe, L. De Buick, D. Courtheyn and N. Schamp, Bull.Soc.Chim.Belg., 86, 55 (1977); J. Kristensen, I. Thomsen and S.O. Lawesson, Bull.Soc.Chim.Belg., 87, 721 (1978).
5. The methyl group effect is more drastic in the substrate with the electron-withdrawing pyridine ring: absence of the C-2 methyl in 2a resulted in negligible addition yields.
6. See e.g., G. Kyriakakou, M.C. Roux-Schmitt and J. Seyden-Penne, Tetrahedron, 31, 1883 (1975); K.B. Wiberg, D.E. Barth and P.H. Schertler, J.Org.Chem., 38, 378 (1973).
7. A smaller excess of LDA (1.5 equiv) was used. Ester 1 was added at -78°C after stirring the reaction mixture for 30 min at -65°C. The reaction was then continued for 30 min and quenched at -60°C.
8. A ratio of 1:1:1 of base, 5a-b and TMEDA equiv was used. After addition of the sulfide at -78°C, the reaction mixture was allowed to warm up during 1 h to -20°C, then cooled to -78°C, 1.5 equiv of 1 was added and the reaction was quenched after 1 h stirring at -60°C.
9. This value agrees with the trans stereochemistry of cyclopropane substituents in 6a (ref 6).
10. See e.g., B.M. Trost, H.C. Arndt, P.E. Strege, T.R. Verhoeven, Tetrahedron Lett., 3477 (1976)
11. See e.g., B.M. Trost and K.K. Leung, Tetrahedron Lett., 4197 (1975).
12. For references see S. Danishevsky, Accounts Chem.Res., 12, 66 (1979); For ring opening of monoactivated cyclopropanes by intermolecular attack see A.B. Smith III and R.M. Scarborough Jr., Tetrahedron Lett., 1649 (1978); W.E. Truce and L. B. Lindy, J.Org.Chem., 26, 1643 (1961).

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