CHEMISTRY LETTERS, pp. 785-788, 1979. Published by the Chemical Society of Japan

METHYL 3-LITHIO-2-METHYL-3-PHENYLTHIO-2-PROPENOATE AS A ZWITTERIONIC THREE-CARBON ADDEND; REACTIONS WITH CARBONYL COMPOUNDS

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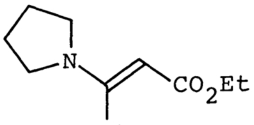
With α,β-enoates and aldehydes, methyl 3-lithio-2-methyl-3-phenylthio-2-propenoate undergoes addition and cyclization yielding functionalized cyclopentenones and butenolides, respectively. Reaction with acyl chlorides gives γ-keto-α,β-enoates.

Recent work by Schmidt and Talbiersky[1] concerning the reactions of ethyl β-lithio-β-(1-pyrrolidinyl)acrylate (1) with carbonyl compounds leading to functionally substituted cyclopentenones and butenolides prompts us to report similar results of our independent work using methyl 3-lithio-2-methyl-3-phenylthio-2-propenoate (3) as a zwitterionic three-carbon addend 4.[2]



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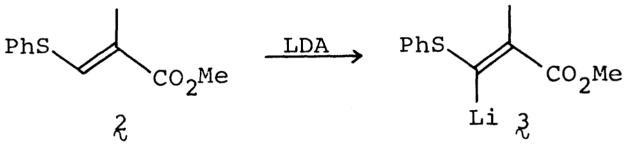

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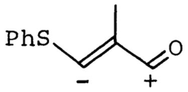

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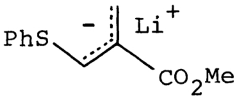

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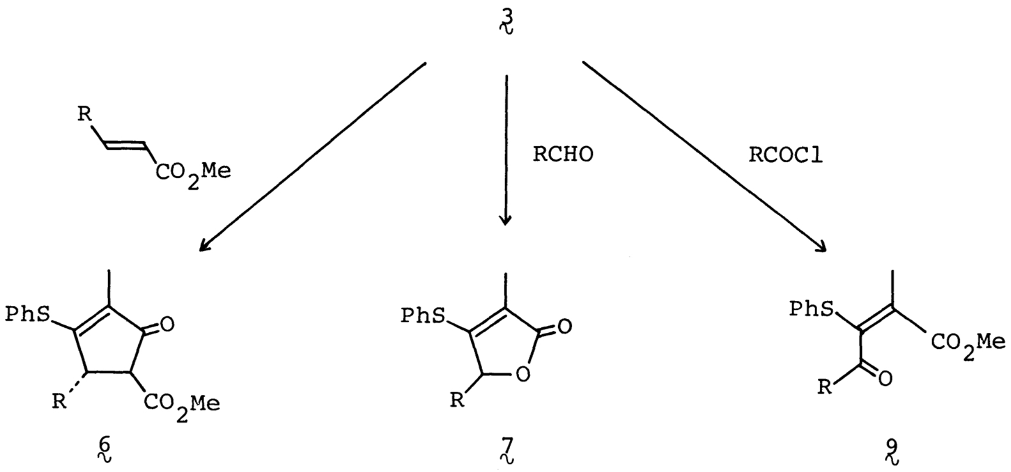
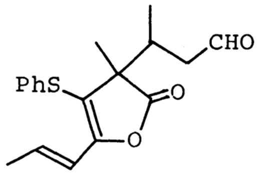
Upon treatment with 1.2 equiv of lithium diisopropylamide (LDA) at -80°C, methyl 2-methyl-3-phenylthio-2-propenoate (2)[3,4] produced quantitatively the relatively stable[7] vinylic carbanion 3; there was no indication for the formation of the allyl carbanion 5.[8,9] Reaction of the carbanion 3 with α,β-unsaturated esters at -70 ∿ -15°C (or 0°C) gave functionalized cyclopentenones 6 in moderate yields (Table 1). None of the products derived from the allyl carbanion 5 was observed. In the reaction with 2-hexenoate, the use of methyl 2-hexenoate gave an extremely low yield of the product (see Table 1). The reason was unresolved. Assignment of the trans configuration of the substituents, R and CO$_2$Me groups, in 6b-d follows from the method of formation and from the small coupling constants (2∿3 Hz)[10] between two adjacent methine protons.

The carbanion 3 also reacted with aldehydes to give functionalized butenolides





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[2(5*H*)-furanones] **7**. As shown in Table 1, in contrast to the reaction with α,β-enoates, inverse addition procedure (Method B) at low temperature, -80 ∿ -60°C, was essential to optimize the yields of the products **7**. It was found that, in the case of crotonaldehyde, the butenolide **7d** generated simultaneously the corresponding allyl carbanion by the action of **3**,[11] which further reacted with crotonaldehyde giving the by-product **8**. This result, combined with a considerable recovery of the starting propenoate **2** from the reactions, the carbanion **3** seems to be a weak nucleophile, rather in some cases abstracting a proton from the substrates. In fact, **3** did not react with ketones; only aldol condensation of a ketone itself was observed.

The carbanion **3** was acylated with acyl chlorides to yield γ-keto-α,β-enoates **9**. In this case, the normal addition procedure (Method A) gave the good results. The low yield of **9a** from propionyl chloride is presumably due to competitive dehydrochlorination.

The following procedure for the reaction of isobutyraldehyde is representative. To a solution of lithium diisopropylamide (1.8 mmol) in anhydrous THF (1 ml) and hexane (1.22 ml) was added dropwise a solution of methyl 2-methyl-3-phenylthio-2-propenoate (**2**) (312 mg, 1.5 mmol) in anhydrous THF (5 ml) at -80°C under N_2, and the mixture was stirred at -80°C for 45 min. This solution was added dropwise to a solution of isobutyraldehyde (216 mg, 3 mmol) in anhydrous THF (12 ml) at -80°C through a long injection needle (a connecting end was cut off.) by applying the pressure of N_2. The reaction mixture was stirred at -80 ∿ -62°C for 3 h. An aqueous saturated solution of ammonium chloride and then dilute hydrochloric acid were added, and the product was extracted with ether twice. The combined extracts were washed with water and brine, and evaporated to dryness. The residue (402 mg) was chromatographed twice on preparative tlc of silica gel using 4:1 and then 9:1

Table 1. Reaction of the carbanion 3 with carbonyl compounds.

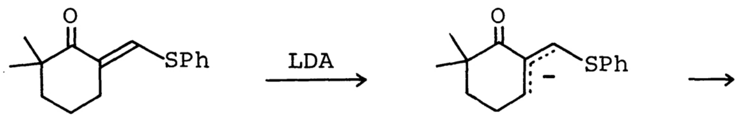
Carbonyl compound	Method[a]	Product[b]	R	Yield, %[c]
$CH_2=CHCO_2Me$	A	6a	H	31 (56)
	B			41 (76)
$CH_3CH=CHCO_2Me$	A	6b[d]	CH_3	39 (45)
	B			37 (81)
$C_3H_7CH=CHCO_2Et$[e]	A	6c[d] (Et ester)	C_3H_7	26
$PhCH=CHCO_2Me$	A	6d[d]	Ph	36 (62)
	B			45 (62)
$CH_3CH_2CH_2CHO$	B	7a	C_3H_7	69 (85)
$(CH_3)_2CHCHO$	A	7b	$(CH_3)_2CH$	37 (81)
	B			60 (76)
PhCHO	A	7c	Ph	19
	B			55 (82)
$CH_3CH=CHCHO$	A	8		23 (49)
	B	7d	$CH_3CH=CH$	18 (42)
		8		13
CH_3CH_2COCl	A	9a	CH_3CH_2	20 (52)
$(CH_3)_2CHCOCl$	A	9b	$(CH_3)_2CH$	47 (83)
	B			12 (30)
$(CH_3)_3CCOCl$	A	9c	$(CH_3)_3C$	72 (100)
PhCOCl	B	9d	Ph	32 (100)

[a] Method A (normal addition): A solution of the carbonyl compound was added to a solution of 3. Method B (inverse addition): A solution of 3 was added to a solution of the carbonyl compound. [b] Satisfactory spectral and analytical data were obtained. [c] Isolated yield. Yields in parentheses are based on 2 consumed. [d] A single stereoisomer. [e] Yield of the methyl ester corresponding to 6c: 4% (32%) from the methyl ester by Method B.

petroleum ether – ether as eluants to yield the butenolide 7b (223 mg, 60%) along with the recovery of 2 (62 mg, 20%); b.p. 90–100°C (bath temp)/0.8 mmHg.

References and Notes

1) R. R. Schmidt and J. Talbiersky, Angew. Chem., 90, 220 (1978); Angew. Chem., Int. Ed. Engl., 17, 204 (1978), and references for the related pyrrolidinylvinyl carbanions cited therein.
2) For a review of the carbanions of vinyl sulfides, see B. -T. Gröbel and D. Seebach, Synthesis, 357 (1977).
3) L. Legrand and N. Lozac'h, Bull. Soc. Chim. Fr., 953 (1958); N. Lozac'h, L. Legrand, and N. Bignebat, ibid., 3247 (1964); S. Danishefsky, R. K. Singh, and T. Harayama, J. Am. Chem. Soc., 99, 5810 (1977).
4) Compound **2** was shown to be the E-isomer from the downfield position (δ 7.43) of the vinyl hydrogen[5] and from the large downfield shift of the vinyl methyl (δ 1.92 ⟶ 2.28) upon conversion of **2** into the sulfoxide derivative.[6]
5) (a) A. Hassner and T. C. Mead, Tetrahedron, 20, 2201 (1964); (b) J. P. Marino and Wm. B. Mesbergen, J. Am. Chem. Soc., 96, 4050 (1974).
6) S. Yamagiwa, N. Hoshi, H. Sato, H. Kosugi, and H. Uda, J. Chem. Soc., Perkin Trans. 1, 214 (1978).
7) The carbanion **3** was shown to be stable at room temperature for several hours.
8) Complete hydrogen–deuterium interchange at the vinylic position of **2** retaining the geometry through the carbanion **3** was observed.
9) It was reported that the reaction of a cyclic ketone derivative **i** gave only the product through the allyl carbanion **ii**.[5b]



i **ii**

10) S. Forsén, B. Gestblom, R. A. Hoffman, and S. Rodmar, J. Mol. Spectroscopy, 21, 372 (1966); see also S. Sternhell, Quart. Rev., 23, 236 (1969).
11) Formation of the allyl carbanion from **7d** by **3** was confirmed by a separate experiment.

(Received May 7, 1979)