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β-SULFINYL ENONES, SYNTHONS FOR TERPENOID SYNTHESIS

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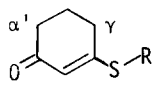
Vinylogous thioesters (1 and analogous structures) are common synthetic intermediates being useful not only as protecting groups but also as sources of other functional groups and substituents.[2] Reported herein is an additional usage of these systems, via the



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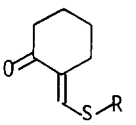

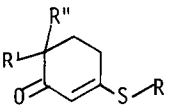

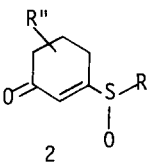

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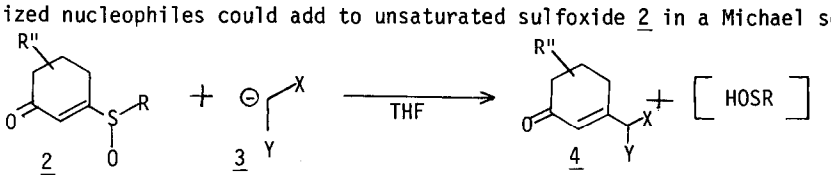
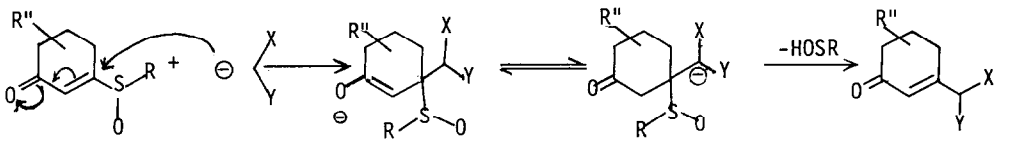
sulfoxide, for formation of new carbon-carbon, carbon-oxygen and carbon-nitrogen bonds. In earlier studies we have utilized the vinylogous thioesters as α'-alkylating substrates[3] and as sources for new β-vinyl carbon-carbon bond formation within the limit that replacement of sulfur was through a copper [Cu(I)] catalyzed 1,4-addition-elimination reaction with organometallic reagents (alkyllithium and Grignards).[4] More stabilized anions, i.e. malonates, fail to displace sulfur limiting the utility of sulfur α'-alkylations. Attempts to activate vinylogous thioesters for 1,4-addition-elimination through intermediates such as sulfonium salt formation failed due to the propensity of these vinylogous thioesters to O-alkylate ($Et_3O^{\oplus}BF_4^{\ominus}$, CH_3OSO_2F) and then dealkylate on addition of nucleophiles.[5] We now report that the sulfoxide unit, in β-sulfinyl enone 2, formed from vinylogous thioesters 1, ($NaIO_4$/aq MeOH),[6] undergoes facile 1,4-addition of stabilized anions and enolates (3,Table below) at room temperature with elimination of the sulfoxide substituent to form β-substituted enones 4 in excellent yields. In principal these stabilized nucleophiles could add to unsaturated sulfoxide 2 in a Michael sense



2 3 4

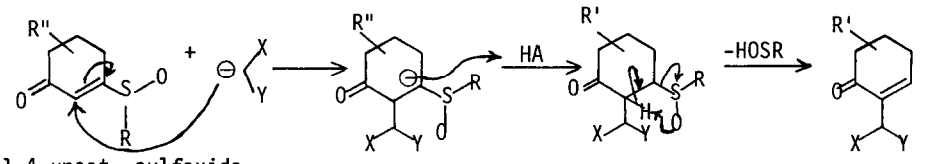
in two ways (path a or b). Products from the alternative addition process (path b) have not been isolated and identified although other minor products (5-10%) are observed.

Path a:



1,4-unsat. carbonyl addition

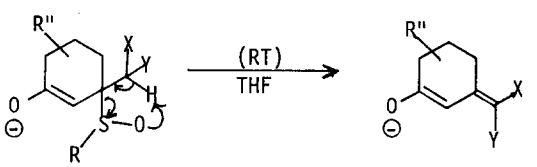
Path b:



1,4-unsat. sulfoxide addition

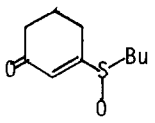
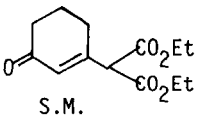
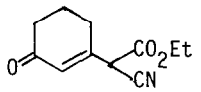
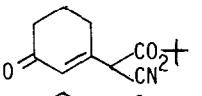
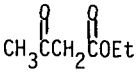
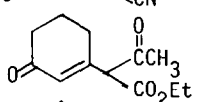
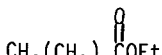
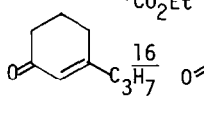
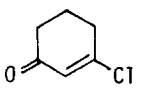
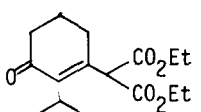
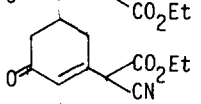
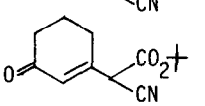
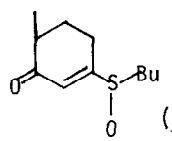
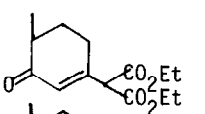
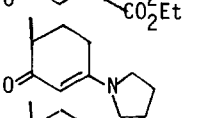
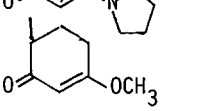
Where R"=H in 2, an alternate synthetic route to 4 from the 3-chloro-2-cyclohexenone[7] ($Na^{+-}CHXY$ displacement) and the above described process are comparable in yields and reaction conditions.

The smooth loss of the β-sulfinyl group is presumably attributable to (1) a steric factor (at the β-site) that may hinder 1,4 attack but should accelerate ejection of the β-sulfinyl group, (2) the availability of acidic hydrogens allowing the initial 1,4-adduct to lose sulfinic acid (RT) and perhaps most important (3) the highly stabilized nature of the resulting enolate product after loss of HOSR. These observations

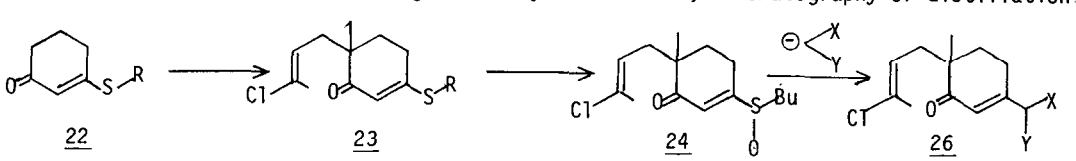


emanate from the fact that dimethyl methylmalonate fails to add (1,4) to 5, (probably due to steric hindrance and lack of acidic hydrogens) and that enolates of simple ester 15 formed adducts 16 and 17 (loss of sulfoxide group) in low yield.[14] Further, the best yields of product are obtained when excess malonate is used presumably acting as a proton source.

In a typical experiment the sodium enolate of the activated ester [1 eq. NaH, two equivalents ester] in THF is treated with β-sulfinyl enone (1 eq.) and the resulting

ENONE	ESTER	BASE	PRODUCT(S)	YIELD[13]
 (5)	 (6)	NaOMe NaH NaOEt	 (7)	78% 72% 75%
	 (8)	NaH	S.M.	-
	 (9)	NaH	 (10)	89%
	 (11)	NaH	 (12)	83%
	 (13)	NaH	 (14)	54%
	 (15)	NaH	 16 17	10%
 (18)	 (6)	NaH	 (7)	85%
	 (9)	NaH	 (10)	97.8%
	 (11)	NaH	 (12)	Quant.[8]
 (19)	 (6)	NaH	 (25)	70%[12]
	-		 (20)	79.4%
	-	NaOMe		94%

mixture stirred at RT for 15 hr. After the addition of water, the products were isolated by acid-base-organic solvent partitioning and recrystallization, chromatography or distillation.



22 23 24 26

Usage of this technique can present strategic advantages. Vinylogous thioester 22 is cleanly alkylated[3] with a range of agents at the α'-site, once or twice, to afford an unsymmetrical cyclic enone equivalent 23.[11,12] Through sulfoxide 24, the β-site of the system can be regioselectively substituted with enolate anions forming a range of synthons for natural products. Further β-cyanomethylcyclohexenones, are readily available from these sulfoxides (eq 5) and t-butyl cyanoacetate (11) via decarboxylation (TsOH/toluene/Δ).[8,9] Finally, other nucleophiles such as alkoxides and amines undergo the same 1,4-addition-elimination (THF, RT, 6 hr)[10] to regioselectively form vinylogous ester 21 or enamino ketone 20 from β-sulfinyl enones. This latter point could be quite important with respect to synthetic chemistry and further aspects of this chemistry will be forthcoming.

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1. To whom correspondence is to be addressed, A. P. Sloan Fellow 1977-1979.
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10. Structures of vinylogous amides and esters previously prepared, see reference 5.
11. R. B. Gammill, T. A. Bryson, Syn. Commun., 6(3), 209 (1976).
12. Dianion alkylation of compounds 7 and 10 were attempted with respect to formation of 25 and the analogous nitrile with only low yield conversions realized. Sulfur (α') alkylations and sulfoxide displacement was a vastly superior way of forming compounds like 25 from 1,3-cyclohexanedione.
13. All compounds exhibited satisfactory nmr, ir, uv, chromatography and mass spectral (or CH analysis) analytical data.
14. Other bases such as LDA and alkoxides were used; all showed low yields due to exchange, hydrolysis, decarboxylation, and/or formation of alkoxy enone.