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Enolate Alkylation with Bromomethyl Sulphides: Synthesis of α-Methylene Ketones and Carboxylic Acids

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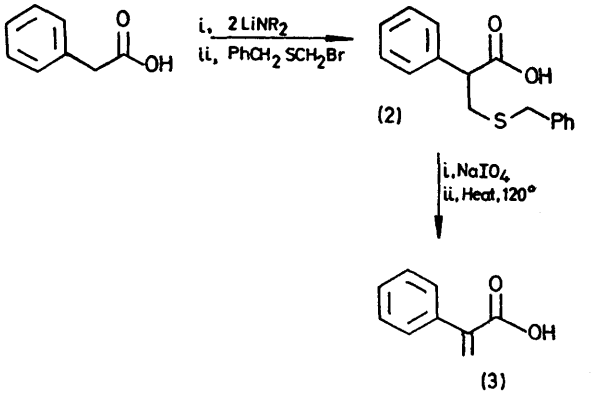
Summary Alkylation of ketone and carboxylate enolates with benzyl bromomethyl sulphide, followed by sulphoxide elimination, gives α-methylene ketones and carboxylic acids.

Synthetic methods for the introduction of methylene groups α to carbonyl groups have involved reactions of carbonyl compounds with formaldehyde[1] or formaldehyde equivalents such as Mannich reagents.[2] The necessary eliminations, either thermal, or acid- or base-catalysed often require vigorous conditions which sometimes result in the destruction of sensitive olefinic products. The successful use of selenoxide[3,4] and sulphoxide[5] eliminations for the synthesis of αβ-unsaturated carbonyl compounds led us to examine the utility of these reactions for the introduction of methylene groups. We report here our results on the use of bromomethyl sulphides[6] as formaldehyde equivalents.



Benzylbromomethyl sulphide (**1**), prepared in 72% yield by reaction of formaldehyde, phenylmethanethiol, and HBr, reacts with ketone and carboxylate enolates to give monoalkylated materials. Typical conditions involve addition of (**1**) to the lithium enolate of phenylacetic acid (prepared using 2 equiv. of $LiNPr^i_2$) in dimethoxyethane and stirring at 0° for 0·5 h. The sulphide (**2**), m.p. 103—104°, was isolated in 80% yield. Oxidation with sodium metaperiodate gave the corresponding sulphoxide, which underwent thermal elimination in refluxing toluene (1·5 h) to 2-phenyl-

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Table. **Preparation of α-methylene carbonyl compounds**

	Sulphide	Yield (%)	Olefin	Yield (%)
$PhCH_2CO_2H$	**(2)**	80	**(3)**	84
Lauric acid	$Me[CH_2]_9CH(CH_2SCH_2Ph)CO_2H$	61	$Me[CH_2]_9CH(:CH)CO_2H$	73
Propiophenone[a]	$PhCOCH(CH_2SCH_2Ph)Me$	60	$PhCOCH(:CH)Me$	86
Cyclo-octanone[a]	2-benzylthiomethylcyclo-octanone	51	2-methylenecyclo-octanone	62

[a] LiI (1 mol. equiv.) was added during the alkylation.

acrylic acid (**3**). The Table lists several other systems on which we have successfully carried out this sequence (conditions have not been optimized).

Ester and lactone enolates are not alkylated in useful yield under the above conditions, or under other conditions reported to give high yields of alkylated products with alkyl bromides and iodides.[7] The sulphide (**1**) is the best of several reagents we have examined. With aryl bromomethyl and benzyl chloromethyl sulphides alkylation of enolates does not compete effectively with side reactions. The more ready thermal elimination of selenoxides[8] *vs.* sulphoxides has led us to examine the utility of benzyl bromomethyl selenide for this reaction. Preliminary results indicate that this reagent is a less reactive alkylating agent than (**1**), and attempted alkylation of enolates has failed.

It should be possible to extend the synthetic utility of bromomethyl sulphide alkylations by using the intermediate sulphides for storing an *exo*-methylene function while carrying out reactions at the carbonyl function or in other parts of the molecule.[9]

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