

Alkylation of β -Keto-ester Dianions with α -Chloroethers

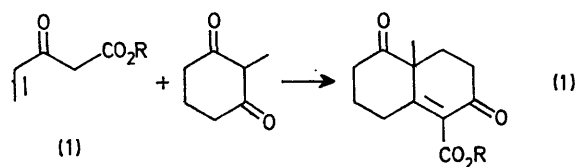
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Summary The dianion of β -keto-esters reacts with α -chloroethers to yield δ -alkoxy- β -keto-esters which are useful intermediates in annelation reactions.

SINCE the work of Nazarov and Zavyalov,¹ the usefulness of esters of 3-oxopent-4-enoic acid, such as (1), in Robinson-type annelation reactions with cyclic β -diketones [equation

(1)¹ and cyclic ketones,² and in Mannich reactions for the construction of piperidone rings,³ is well known. However, the tediousness and low overall yield of the classical synthesis of (1) were major deterrents to its general utility. More recently, alternative, and in some cases rather better,



routes to (1) and related compounds have been reported, some of which involved the dianion of methylacetoacetate.^{4,5} Subsequently, Heathcock and his co-workers found that ethyl 5-ethoxy-3-oxopentanoate (2), which is a precursor of (1), could be used directly in the annelation [equation (1)].⁶

We report a simple one-step synthesis of (2) and its methyl substituted derivatives which involves the alkylation of the dianion of β -keto-esters (3)⁵ with the α -chloroethers (4) [equation (2)]. The yields of the alkylated products (5) are given in the Table. This simple route to (5) gives

TABLE. Alkylation of the dianion (3) with the α -chloroethers (4).

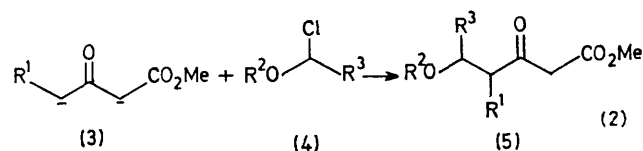
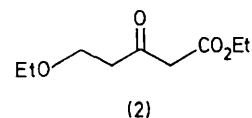
(3)	(4)		Yield of (5) (%) ^{a,b}			
	R ²	R ³	R ¹	R ²	R ³	
H	Me	H	H	Me	H	(65)
Me	Me	H	Me	Me	H	(87)
H	Me	Me	H	Me	Me	(89)
H	Et	Me	H	Et	Me	(73)

^a Yields shown are of isolated material. No attempt has been made yet to maximize yields. ^b New compounds were identified by spectroscopic data and, in some cases, by elemental analysis.

good yields and thus provides a range of δ -alkoxy- β -keto-esters for use in the Nazarov-Zavyalov annelation. In

addition, the ether derivatives (5) can be readily transformed in good yield into the corresponding δ -chloro- β -keto-esters on treatment with HCl in chloroform. These chlorides may also prove valuable in annelation reactions.⁷ Finally the ethers (5) are readily converted into the corresponding enones by acid-catalysed elimination of alcohol.

In a typical experiment, the dianion of methyl acetoacetate was generated as reported earlier⁵ using 0.27 g of a 57% mineral oil dispersion of sodium hydride [washed with tetrahydrofuran (THF) to remove the mineral oil], 0.58 g of methyl acetoacetate, and 2.4 ml of 2.2 M BuⁿLi, all in ca. 25 ml of dry THF at 0 °C. 0.54 g of α -chloroethyl ethyl



ether, prepared by passing HCl gas into a mixture of acetaldehyde and absolute ethanol,⁸ was added to the solution of the dianion and the mixture was stirred at -15 °C for 30 min. The mixture was then washed with NaHCO₃ and brine, dried over MgSO₄, and the solvents were removed under reduced pressure to yield 0.685 g (73%) of methyl 5-ethoxy-3-oxohexanoate.

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