Method for the Synthesis of 4-Substituted Acetoacetates

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Summary Ethyl 4-bromo-3-oxobutyrate can be converted with sodium hydride into the enolate salt and nucleophilic substitutions can thereafter be carried out at the 4-carbon atom.

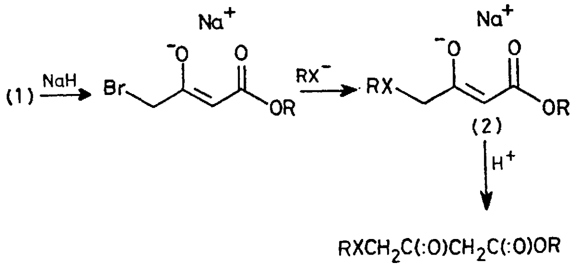
METHODS for alkylating or acylating the 2-carbon atom of ethyl acetoacetate are fundamental reactions of organic chemistry. The products are essential to a remarkably large number of syntheses.[1]

In connection with another problem we required examples of 4-substituted acetoacetates.[2] There is, however, a paucity of literature information on such compounds; this reflects the fact that the high acidity of the 2-position dominates acetoacetate chemistry. Ideal precursors for 4-substituted acetoacetates would be the 4-bromo-derivatives (**1**), which are obtained on bromination of alkyl acetoacetates in the presence of hydrogen bromide [equation (1)].[3] However, nucleophilic substitution of bromide in (**1**) almost always fails on using reasonably basic nucleophiles

$$\mathrm{MeC(:O)CH_2C(:O)OR} \xrightarrow{\mathrm{Br_2}} \underset{(\mathbf{1})}{\mathrm{BrCH_2C(:O)CH_2C(:O)OR}} + \mathrm{HBr} \qquad (1)$$

owing to competing deprotonation at the 2-position. There is, however, a brief report in the patent literature on the preparation of 4-alkoxy and 4-phenoxy acetoacetates using (**1**) (Cl instead of Br) and $>$ 2 equiv. of alkoxide in dimethyl sulphoxide.[4] Also a few 4-thio-derivatives have been prepared by substitution on (**1**) by less basic and more nucleophilic thiolate anions.[5]

We have developed a method for carrying out nucleophilic substitutions, even with strongly basic nucleophiles, on the 4-carbon atom of (**1**). With sodium hydride (**1**) can be converted into the chelate (**2**) (not isolated) without detectable amounts of self-condensation; nucleophilic substitution at the 4-carbon atom of (**2**) can then be carried out smoothly and on acidification 4-substituted acetoacetates are obtained in excellent yield [equation (2)]. The procedure for synthesis of ethyl 4-methoxy-3-oxobutyrate is representative.



(2)

Sodium hydride (10 mmol, washed × 3 with pentane under N_2) was suspended in freshly distilled dimethoxyethane (DME) (40 ml). After cooling to −30 °C (**1**) (10 mmol) dissolved in DME (10 ml) was added dropwise and stirring was continued for 10 min to give a solution of (**2**). A suspension of sodium methoxide (10 mmol) in DME (40 ml), made by treatment of methanol with sodium hydride, was added to (**2**) and the resulting mixture was then refluxed for 15 h. Work-up with dilute hydrochloric acid, extraction, and drying ($MgSO_4$) afforded, after distillation, 63% of pure ethyl 4-methoxy-3-oxobutyrate. No methoxy-ester formed through ester interchange was detected.

Further examples are in the Table. All products were characterized by their spectra and molecular compositions were determined from exact mass spectral measurements. Only the lower molecular weight products could be distilled without decomposition.

Only secondary amines have given good yields of substitution products; products from primary amines appear to undergo further condensations under the reaction conditions and this problem has not yet been overcome. The formation of new carbon–carbon bonds at the 4-position (last entry, Table) opens the route to particularly attractive synthetic intermediates.

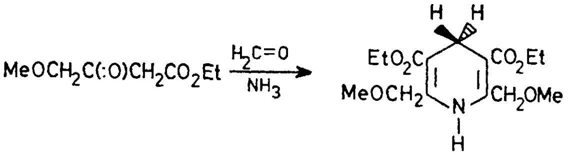
TABLE

$$\mathrm{RX^-} + \mathrm{BrCH_2C(:O)\bar{C}HC(:O)OEt} \twoheadrightarrow \mathrm{RXCH_2C(:O)CH_2C(:O)OEt}$$

RX	Solvent	% Yield
MeO	DME	63
$\mathrm{Pr^iO}$	"	73
$\mathrm{Bu^tO}$	"	61
PhO	"	79
PhS[b]	"	75
$\mathrm{PhCH_2S}$[b]	"	86
$\mathrm{Bu^tS}$[b]	"	94
Ph(Me)N[c]	Tetrahydrofuran	70
N≡C	$\mathrm{Me_2SO}$–DME	81

[a] All reactions at 85 °C for 15 h unless otherwise noted. % Yields are of isolated products. [b] With thiols, direct reaction with (**1**) without conversion into (**2**) proceeds equally well. [c] Prepared by deprotonation of PhNHMe with 1 equiv. of $\mathrm{Bu^nLi}$. Reaction at 64 °C for 15 h.

Further work on the synthetic applications of these compounds is in progress. One interesting application is shown in equation (3).



(3)

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