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A CONVENIENT ONE FLASK PROCEDURE FOR ESTER ALKYLATION

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During the course of several syntheses, we have had occasion to face the tactical necessity of alkylating ester residues. This type of transformation has classically been accomplished using malonic esters but experience has shown the yields of these reactions to be quite variable.[1] Rathke and coworkers have recently reported what appeared to us to be a promising approach to the problem of ester alkylation.[2] These authors described the generation in THF solution of some simple lithium ester enolates using lithium isopropylcyclohexylamide as the base. Alkylation was then carried out at 0° by adding the enolate solution to a 50% excess of the alkylating agent dissolved in DMSO. Although ingenious, Rathke's method struck us as having some potential preparative drawbacks. For example, the apparent requirement of adding the ester enolate to the alkylating solution could become critical when dealing with a temperature sensitive enolate, especially on a large scale. Furthermore, the use of a 50% excess of alkylating agent might be disadvantageous if the alkylating species were the valuable reaction component.

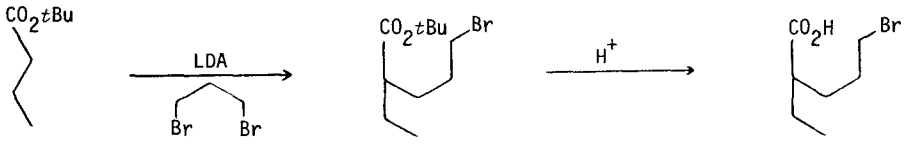
We now wish to report a significantly more convenient one-flask experimental procedure for the high yield alkylation of ester enolates at low temperature using a wide variety of alkylating agents under nearly theoretical stoichiometric conditions. This procedure consists simply of adding a given ester (1 equivalent, neat or as a solid) to a 1 molar THF solution containing 1

equivalent of lithium diisopropylamide (LDA)[3] at -78°, allowing the ester enolate to form (-78°) over a period of 20 to 40 minutes, and then adding at -78° the desired alkylating agent (1.0 to 1.2 equivalents) dissolved in hexamethylphosphoramide (0.3 equivalents).[4] A summary of some typical results using methyl butyrate is given in the table.

TABLE

Ester	Alkylating Agent	R	Product	Yield,[5] %
Methyl Butyrate	CH_3CH_2Br	CH_3CH_2-	$CH_3CH_2CH(R)CO_2CH_3$	92%
Methyl Butyrate	CH_3CH_2I	CH_3CH_2-	$CH_3CH_2CH(R)CO_2CH_3$	96%
Methyl Butyrate	$(CH_3)_2CHBr$	$(CH_3)_2CH$-	$CH_3CH_2CH(R)CO_2CH_3$	88%
Methyl Butyrate	$(CH_3)_2CHI$	$(CH_3)_2CH$-	$CH_3CH_2CH(R)CO_2CH_3$	96%
Methyl Butyrate	$Br(CH_2)_3Br$	$Br(CH_2)$-	$CH_3CH_2CH(R)CO_2CH_3$	90%
Methyl Butyrate	$CH_2=CHCH_2Br$	$CH_2=CHCH_2$-	$CH_3CH_2CH(R)CO_2CH_3$	97%
Methyl Butyrate	HC CCH_2Br	HC CCH_2-	$CH_3CH_2CH(R)CO_2CH_3$	89%
Methyl Butyrate	CH_3OCH_2Cl	CH_3OCH_2-	$CH_3CH_2CH(R)CO_2CH_3$	98%

With the exception of methyl acetate, we have not found ester self-condensation under these reaction conditions to be competitive with alkylation.[6] Both primary bromides and iodides may be used without difficulty but secondary iodides have a clear advantage over their corresponding bromides in that reaction times are longer for the latter reagents. Difunctional alkylating agents such as 1,3-dibromopropane undergo only monoalkylation providing a very convenient synthesis of δ-bromo esters of acids. The δ-bromo acid I, for example, can be obtained from *t*-butyl butyrate in two steps (88% overall yield) both on small and large scales using this method whereas the corresponding malonate elaboration is much less satisfactory.[7]



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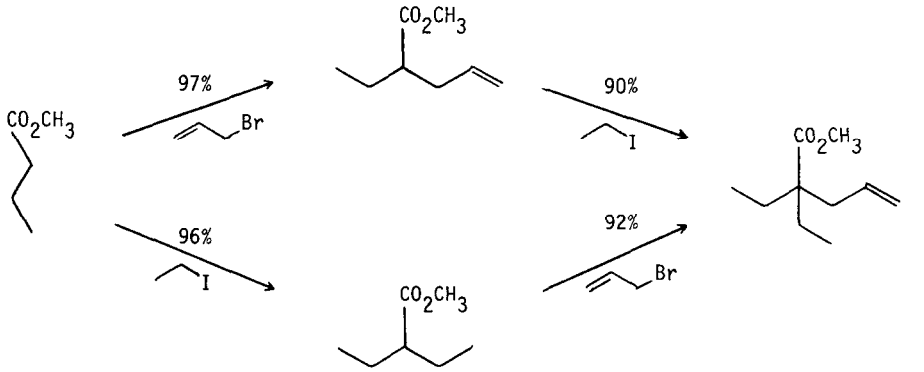
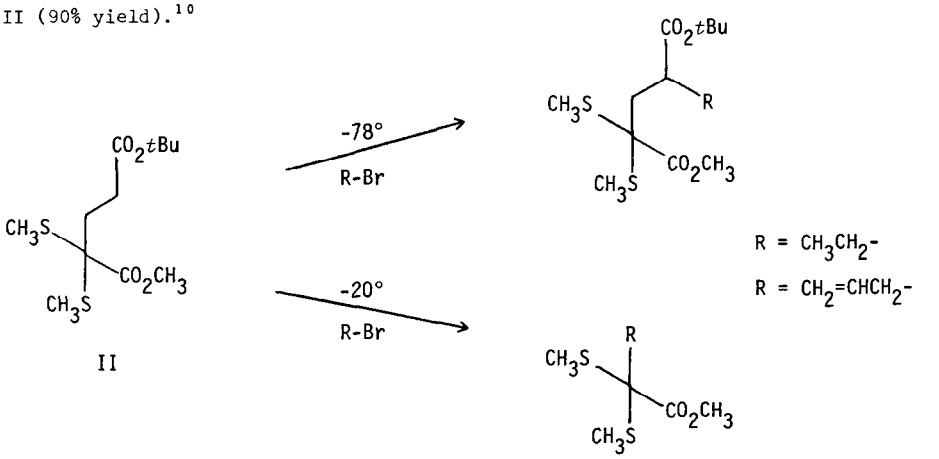
It is also easily possible to construct esters with quaternary α carbon atoms and a representative sequence is shown below.[8] We have found it useful although not always necessary to use a full equivalent of hexamethylphosphoramide to facilitate the second alkylation step (-78°).



The low temperature aspect of these alkylation experiments has proven to be especially important in cases where β-elimination can occur from the initial ester enolate. For example, the lithium enolate formed from the diester II[9] (1 equivalent of LDA) is stable indefinately at -78° and will undergo high yield alkylation (90 to 95%, 1.2 equivalents of alkylating agent, 0.3 equivalents of hexamethylphosphoramide) at this temperature. If, however, the temperature of the alkylation step is raised to -20°, very rapid β-elimination occurs and the product isolated is the ester III (90% yield).[10]



In summary, the simple high yield alkylation procedure described herein is clearly applicable to a wide variety of esters and alkylating agents. These alkylations are convenient to carry out both on a small and large scale. Further, they are usually compatible with nearly ideal stoichiometry, an aspect of particular importance in organic synthesis.

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REFERENCES

1. For a recent summary of β-dicarbonyl alkylation reactions, see "Modern Synthetic Reactions," 2 ed., H. O. House, W. A. Benjamin, Inc., Menlo Park, California, 1972, Chapter 9.
2. M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971).
3. Lithium diisopropylamide was prepared by treatment of diisopropylamine with *n*-butyllithium at 4° for 15 minutes. This reagent when properly prepared is colorless to faintly yellow. Distinctly yellow solutions of lithium diisopropylamide are not satisfactory for these reactions.
4. The use of hexamethylphosphoramide is not required for most alkylating agents but its use does permit the alkylating reagent usually to be employed on an equal equivalence basis.
5. The yields given are for isolated products and are based on the amount of ester used. All compounds exhibited satisfactory spectral and physical properties.
6. High yield alkylations can be realized with *t*-butyl acetate under these conditions.
7. E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, **87**, 1580 (1965).
8. A variety of other alkylating agent combinations can be used in these reactions. However, it is necessary to introduce difunctional reagents such as 1,3-dibromopropane or chloromethyl methyl ether in the second step.
9. A novel preparation of II and similar compounds will be reported shortly.
10. The product III is also formed in high yield from II using the reaction conditions reported in reference 2.