Steric Limits to Ester Alkylation; Synthesis of Highly Hindered Esters *via* Hexamethylphosphoramide-favoured Enolization

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The steric limits to the alkylation of carboxylic esters by alkyl iodides with lithium di-isopropylamide as base in the presence of hexamethylphosphoramide have been investigated by using, with modifications, a method originally proposed by Schlessinger *et al.* The influence of hexamethylphosphoramide in promoting ester enolization, as opposed to its influence on the alkylation step, as previously reported, has been examined. The formation of αα-disubstituted from α-monosubstituted esters takes place in high yields and appears to be only slightly influenced by the nature of the alkylating agent (MeI, EtI, or $Pr^{i}I$). In contrast, the formation of ααα-trisubstituted for αα-disubstituted esters appears to be sensitive to the steric nature of the ester to be alkylated. Thus in the synthesis of tri- from mono-substituted esters the order of introduction of alkyl groups is critical. The failure of certain esters to react is interpreted as due to an inability to undergo enolization.

For some time we have been interested in the synthesis and properties of highly hindered ketones.[1-7] Their synthesis raises a number of problems; standard methods tend to give poor yields for even moderately hindered compounds. A bibliographic[8] analysis of available methods revealed that a route of choice to such compounds is the condensation of acid chlorides with organocuprates [reaction (i)].

$$RCO_2H \xrightarrow{SOCl_2} RCOCl + \begin{matrix} R'MgX \\ \text{or} \\ R'Li \end{matrix} \xrightarrow{CuX} RCOR' \quad \text{(i)}$$

Subsequent work has revealed this reaction to be extremely useful with bulky alkyl groups. However, it necessitates the prior synthesis of hindered carboxylic

[1] (*a*) J. E. Dubois and M. Boussu, *Tetrahedron*, 1973, **29**, 3943; (*b*) J. A. MacPhee, M. Boussu, and J. E. Dubois, *J.C.S. Perkin II*, 1974, 1525.

[2] (*a*) J. E. Dubois, A. Massat, and P. Guillaume, *J. Chim. phys.*, 1968, **65**, 729; (*b*) A. Massat and J. E. Dubois, *J. Mol. Structure*, 1969, **4**, 385; (*c*) J. E. Dubois, A. Massat, and P. Guillaume, *ibid.*, p. 403.

[3] J. E. Dubois and A. Cossé-Barbi, *Spectrochim. Acta*, 1972, **28A**, 523, 539, 561.

[4] J. E. Dubois, J. P. Doucet, and B. Tiffon, *J. Chim. phys.*, 1973, 805.

[5] J. E. Dubois and H. Herzog, *J.C.S. Chem. Comm.*, 1972, 932.

[6] G. Lepicard, J. Berthou, J. Delettré, A. Laurent, and J. P. Mornon, *Compt. rend.*, 1973, **276C**, 575.

[7] G. Lenfant, M. Chastrette, and J. E. Dubois, *J. Chromatog. Sci.*, 1971, **9**, 220.

[8] J. E. Dubois, F. Hennequin, and M. Boussu, *Bull. Soc. chim. France*, 1969, 3615.

acids. Conventional methods do not lead to satisfactory yields with hindered compounds. In view of the promising nature of recent work on the alkylation of esters by Schlessinger *et al.*[9] and the possibility of hydrolysing hindered esters under relatively mild conditions[10] in dimethyl sulphoxide–potassium t-butoxide, we investigated the former reaction in detail. Our aims were two-fold: to determine the steric limits to alkylation under conditions known to be favourable and to define improved conditions in order to extend its range of applicability.

EXPERIMENTAL

Reagents.—Methyl, ethyl, and isopropyl iodides were commercial reagents (Prolabo), from which iodine was removed by addition of mercury droplets; its formation was suppressed by storage in a cool dark place. Hexamethylphosphoramide (HMPA) was purified by treatment with sodium wire followed by distillation under reduced pressure. Tetrahydrofuran (THF) was treated with lithium aluminium hydride, then distilled on to molecular sieves (4 Å). Di-isopropylamine (Aldrich) was distilled from sodium hydroxide pellets before use.

Commercial 3,3-dimethylbutyric, isobutyric, and isovaleric acids were transformed into ethyl esters by the reaction of their sodium salts with ethyl iodide in hexamethylphosphoramide. Other ethyl esters used were prepared by the method described below.

Alkylation Products.—The alkylation products, ethyl esters in all cases except one (an enol ether), were identified by their i.r. and n.m.r. spectra.

Synthetic Method.—The following general method was used for the reactions reported in Tables 1 and 2. To a

TABLE 1

Alkylation of α-monosubstituted esters; effect of the nature of the alkylating agent

$$R^1CH_2\cdot CO_2Et \xrightarrow{R^3I} R^1R^2CH\cdot CO_2Et$$

	R^1	R^2	Yield (%)
(1)	Bu^t	Me	99
(2)	Bu^t	Et	96
(3)	Bu^t	Pr^i	80
(4)	Pr^i	Me	95
(5)	Pr^i	Et	95
(6)	Pr^i	Pr^i	94

solution of di-isopropylamine (1.05 equiv.) in THF at 0 °C, 1.6M-butyl-lithium in pentane (1 equiv.) was added. After stirring for 10 min, the ester (0.7 equiv.) in THF at 0 °C was added slowly, and the mixture was stirred for 30 min. The temperature was then reduced to −78 °C and the alkyl iodide (1.10 equiv.) in THF containing HMPA (0.60 equiv.) was added. Stirring was continued for 2 h at −78 °C and the system was allowed to warm to room temperature (*ca.* 2 h). Work-up was performed by pouring the mixture onto ice, acidification, extraction, *etc.* Yields were determined by g.l.c. (internal standard).

The following modified method was used to prepare ethyl 2,2-di-isopropyl-3-methylbutyrate. To a solution of di-isopropylamine (3.15 equiv.) in 1 : 2 HMPA–THF at 0 °C, 1.6M-butyl-lithium in pentane (3 equiv.) was added. After stirring for 10 min, the ester (1 equiv.) in 1 : 2 HMPA–THF was added slowly, and the mixture was stirred at 0 °C for 2 h. Isopropyl iodide (3 equiv.) in THF was then added, giving an exothermic reaction, during which the mixture

TABLE 2

Alkylation of α-disubstituted esters; effect of the nature of the alkylating agent and the order of introducing alkyl groups

$$R^1R^2CH\cdot CO_2Et \xrightarrow{R^3I} R^1R^2R^3C\cdot CO_2Et$$

	R^1	R^2	R^3	Yield (%)
(7)	Me	Me	Pr^i	90
(8)	Pr^i	Me	Pr^i	99
(9)	Pr^i	Et	Pr^i	81
(10)	Pr^i	Pr^i	Me	10
(11)	Pr^i	Pr^i	Et	10
(12)	Pr^i	Pr^i	Pr^i	00
(13)	Bu^t	Me	Pr^i	94
(14)	Bu^t	Et	Et	78
(15)	Bu^t	Et	Pr^i	32
(16)	Bu^t	Pr^i	Me	00

was allowed to warm to ambient temperature. After stirring for 2 h, work-up was performed as above (overall yield 68%).

RESULTS AND DISCUSSION

The results reported in Tables 1 and 2 correspond to the reaction scheme (ii). Only alkyl iodides were used

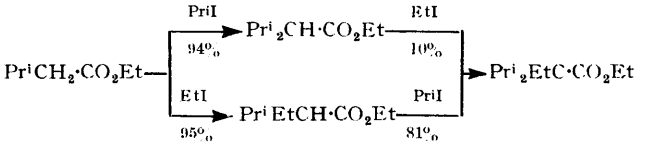
$$R^1R^2CH\cdot CO_2Et \xrightarrow{Pr^i_2NLi} R^1R^2C(Li^+)\text{–}C(=O)\text{–}OEt \xrightarrow{R^3I} R^1R^2R^3C\cdot CO_2Et \quad \text{(ii)}$$

as these have been shown to give the best yields. The conditions used cause formation of an enolate from an ethyl ester at 0 °C in the presence of a 30—100% excess of lithium di-isopropylamide; the alkylating agent is then added at −78 °C. In contrast to the findings of other workers,[9] we observed that in general there is only a slight reaction at this temperature; we therefore allowed the mixture to warm to room temperature before work-up in all cases. Under these conditions we did not find ester self-condensation to be a significant side reaction, probably because most of the esters used are sterically hindered. Table 1 shows that esters with tertiary α-carbon atoms can be prepared in high yields up to and including $Pr^i_2CH\cdot CO_2Et$ and $Bu^tPr^iCH\cdot CO_2Et$.

Table 2 shows that esters containing hindered quaternary α-carbon atoms, with $Bu^tPr^iEtC\cdot CO_2Et$ and $Pr^i_3C\cdot CO_2Et$ representing the structural limits, can be prepared, but the order of introducing the alkyl groups is very important. Scheme 1 illustrates the synthesis of $Pr^i_2EtC\cdot CO_2Et$ from $Pr^iCH_2\cdot CO_2Et$ by reactions with EtI and Pr^iI, or *vice versa*. The overall yield for the upper alkylation pathway (isopropylation followed by

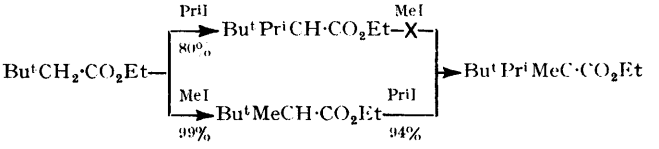
[9] R. J. Creege, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 2425.
[10] F. C. Chang and N. F. Wood, *Tetrahedron Letters*, 1964, 2969.

ethylation) is only 9.4%, whereas the lower one (ethylation followed by isopropylation) has an overall yield of



SCHEME 1

77%. The synthesis of $Bu^tPr^iMeCCO_2Et$ (Scheme 2) demonstrates this effect in a more striking manner: the upper pathway (isopropylation followed by methylation) is not realizable since the methylation step does not take place, whereas the lower pathway (methylation followed by isopropylation) results in an overall yield of 93%.



SCHEME 2

This observation is counter to what one would expect. The alkylation of ketones [11] with sodium amide as base does, in fact, give the opposite result, *i.e.* it is preferable to introduce the more bulky group in the early stages and the less bulky one in the final stages. Our observation permits the optimization of procedures for the alkylation of esters. However, when there is no possibility of reducing the ' crowded ' nature of the intermediate ester by a judicious choice of precursor, as is the case for $Bu^tPr^i_2CCO_2Et$ and $Pr^i_3CCO_2Et$, the reaction becomes unrealizable under the above-mentioned conditions. In this case improvements are needed.

The low reactivity of hindered esters to alkylation may be due to the inability of the ester to form an enolate, to the lack of reactivity of the enolate formed owing to steric effects, or to a combination of these effects. The results in Table 1 show that, other things being equal, the alkylation of an ester with a secondary α-carbon atom is relatively insensitive to changes in the alkylating agent from Me to Et and Pr^i.

To gain some insight into this problem and to extend the range of application of this reaction to more hindered compounds, experiments were carried out in which hexamethylphosphoramide was added during the enolization step. The isopropylation of $Pr^i_2CH·CO_2Et$ was investigated under these modified conditions since this compound is difficult to alkylate by the general method (expts. 10—12). Isopropylation of this compound can be achieved in 42% yield by conducting the enolization in 1 : 2 HMPA–THF at 0 °C. The yield is further improved to 68% if the temperature is not maintained at 0 °C during addition of the alkylating agent (the reaction is exothermic). This synthesis represents an improvement in both facility and yield over that previously reported.[12] This result demonstrates that addition of HMPA during the enolization step is necessary in the case of $Pr^i_2CHCO_2Et$, and that steric hindrance to alkylation is of relatively minor importance.

Methylation of $Bu^tPr^iCH·CO_2Et$ under the same conditions that resulted in 68% isopropylation of $Pr^i_2CHCO_2Et$ gave 80% *O*-alkylation, showing that enolization does take place. Attempts with $Bu^t_2CH·CO_2Et$ gave only unchanged starting material. Even under such forcing conditions, enolization does not take place, as found also by Newman [12] for reaction in liquid ammonia in the case of the 1,1-diethylpropyl ester.

The fact that enolization appears to be sensitive to the steric properties of the ester is easily understood when one considers that the base Pr^i_2NLi is bulky; this could disfavour formation of enolate from a sufficiently hindered ester. The use of a bulky base is necessary to prevent formation of an amide by attack on the carbonyl group.

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[11] J. E. Dubois and A. Panaye, unpublished results.
[12] M. S. Newman and T. Fukunaga, *J. Amer. Chem. Soc.*, 1963, **85**, 1176.