Tetrahedron Vol. 36, pp. 775 to 777

0040-4020/80/0315-0775/$02.00/0

STERIC EFFECTS IN SYNTHESIS—STERIC LIMITS TO THE ALKYLATION OF NITRILES AND CARBOXYLIC ACIDS

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(*Received in UK* 17 *July* 1979)

Abstract—The steric limits to the alkylation of aliphatic nitriles and carboxylic acids have been investigated in some detail. For the experimental conditions considered (ionization by i-Pr_2NLi in THF followed by alkylation with RI/THF/HMPA) the most hindered nitriles R–CN and carboxylic acids R–CO_2H have the same secondary alkyl group R = tBuPr^{i}CH–, but different tertiary, i.e. R = t-BuPr^{i}EtC– or i-Pr_3C– for RCN and R = Et_2MeC for RCO_2H. A comparison of the relative merits of alkylation of esters, carboxylic acids, and nitriles is considered.

In recent years a great deal of attention has been turned to the synthesis and properties of highly hindered molecules.[1] The challenges represented by such compounds both at the purely synthetic as well as theoretical levels has provided a real stimulus and, to date, some significant progress has been made. One of the most promising techniques for preparing highly hindered structures is the alkylation of the conjugate bases of carbon acids; it is thus possible to prepare extremely hindered esters by the alkylation of the corresponding enolates.[2] The optimum conditions for the preparation of hindered esters have been previously investigated in this laboratory. In this article we extend this work to include the synthesis of hindered nitriles and carboxylic acids. We also examine and compare the relative merits of nitrile, ester, and carboxylic acid alkylation.

RESULTS AND DISCUSSION

The alkylation of nitriles is a classical reaction. Recent advances involving the use of HMPA as co-solvent and the development of weakly nucleophilic strong bases has revived interest in this technique. One important point is the demonstration of the feasibility of clean monoalkylation.[3] This is essential when one wishes to perform successive alkylations using different alkylating agents.

The complete reaction scheme may be written as follows:

$$RX^1 + Li \rightarrow RLi + LiX^1 \quad (1)$$

$$RLi + i\text{-}Pr_2NH \rightarrow i\text{-}Pr_2NLi + RH \quad (2)$$

$$i\text{-}Pr_2NLi + R^1R^2CHCN \rightarrow R^1R^2C(Li)CN + i\text{-}Pr_2NH \quad (3)$$

$$R^1R^2C(Li)CN + R^3X^2 \rightarrow R^1R^2R^3CCN + LiX^2. \quad (4)$$

It is seen that alkyl halides (RX^1 and R^3X^2) intervene in this scheme at two different stages and in the general case $R \neq R^3$. We have found it inadvisable to use an alkyl bromide for the formation of the akyllithium in step (1) since, if this reaction is incomplete, the alkyl bromide will react with the lithiated species produced in step (3). The alkylation reactivity sequence of alkyl halides is well-documented:[2] RI > RBr > RCl. For this reason it is recommended to use an alkyl chloride in step (1) and an alkyl iodide in step (3) to avoid undesirable alkylation products.

One of the probelms encountered in our previous study of ester alkylation[2] concerns the actual temperature at which the alkylation is carried out. To avoid the problem of ester self-condensation certain reactions were carried out at −78°. This is, of course not a problem for nitrile alkylation. It was also observed that, except for compounds of low steric hindrance, alkylation of ester enolates does not take place at this temperature. For this reason we begin this study by an examination of the effect of temperature variation on the alkylation of the relatively hindered nitrile i-Pr_2CHCN (E_S^U(i-Pr_2CH–) = −5.01) in order to optimise the yield with respect to this variable. Addition of nitrile to the base i-Pr_2NLi was carried out at 0° in all cases, followed by the addition of the appropriate alkyl iodides at the temperature specified in Table 1.

It is evident from Table 1 that alkylation yields at −50° are mediocre and similar for the alkyl iodides MeI, EtI i-PrI. At 0° the yields are remarkably improved and it is this temperature that is used for the remainder of this work.

In this study we consider the steric limits to the alkylation of nitriles in some detail. These results are given in Table 2.

Table 2 shows that the very crowded structures i-Pr_3CCN and t-BuPr^{i}EtCCN may be prepared in 70 and 36% yields respectively while the compound t-$BuPr_2^iCCN$ is inaccessible. It was found that N alkylation becomes increasingly favoured with respect to C alkylation as a function of increasing steric hindrance. For example, for Runs 5 and 8 (Table 2), 23% and 52% of N alkylated products were observed. Thus, the alkylation of nitriles appears to be a useful method for preparing highly crowded structures. It is at least as effective as the alkylation of carboxylic esters[2a] with however a noteworthy difference. Runs 3 and 4 show that methylation and ethylation of i-Pr_2CHCN are quantitative reactions. On the other hand, the methylation and ethylation of i-Pr_2CHCO_2Et result in only 10% yields. The "overall' reaction yield becomes quantitative if the order of alk-

Table 1. Effect of temperature on alkylation yields $i\text{-Pr}_2\text{CHCN} \xrightarrow[(2)\ \text{RI}]{(1)\ i\text{-Pr}_2\text{NLi}} i\text{-Pr}_3\text{C-CN}$

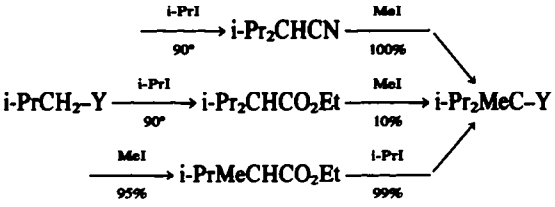
RI	T	Yield (%)
Me	-50°	31
	-5°	97
	0°	100
Et	-50°	31
	-5°	97
	0°	97
i-Pr	-50°	40
	-5°	50
	0°	70

Table 2. Steric limits in the alkylation of nitriles $R^1R^2CHCN \xrightarrow{R^3I} R^1R^2R^3CCN$

Run No	R^1	R^2	$-E_S'(R^1R^2CH-)$	R^3	$-E_S'(R^1R^2R^3C-)$	Yield (%)
1	H	H	0	2i-Pr	5.01	80
2	t-Bu	H	1.63	i-Pr	6.53	60
3	i-Pr	i-Pr	5.01	Me	7.38	100
4	i-Pr	i-Pr	5.01	Et	7.38	97
5	i-Pr	i-Pr	5.01	i-Pr	6.73	70
6	t-Bu	i-Pr	6.53	Me	7.56	50
7	t-Bu	i-Pr	6.53	Et	6.62	36
8	t-Bu	i-Pr	6.53	i-Pr	-	00

Appropriate E_S' values taken from Ref. 1*a*].

ylation is altered: methylation of $i\text{-PrCH}_2\text{CO}_2\text{Et}$ followed by iso-propylation, as follows:



In Table 2 we give the steric parameters[1a] E_S' for the alkyl groups of the nitrile to be alkylated R^1R^2CHCN, as well as that of the alkylation product, $R^1R^2R^3CCN$. This enables us to see the effect of increasing steric hindrance on the two important steps of the reaction, i.e. the ionization step (eqn 3) and the alkylation step (eqn 4). It is evident that the steric effect on the ionization step is slight. Even in the case of run No. 8 where no C-alkylated product is formed the isolation of 52% of N-alkylated product shows that ionization does occur. The alkylation step is more sensitive to the steric effect as may be seen from the last three entries in Table 2. In the alkylation of esters,[2a] on the other hand, the enolization step is more sensitive to the steric effect than in the case of nitriles and it is for this reason that the order of introduction of alkyl groups is so important, as seen above.

The alkylation of carboxylic acids has received some attention[4] but since the steric limits have not been clearly defined we decided to investigate this point. When a carboxylic acid is the object of synthesis direct alkylation avoids the esterification and hydrolysis steps. We have turned our attention directly to rather hindered di- and tri-alkylated structures since the preparation of slightly hindered acids is well-documented. These results are given in Table 3.

It is immediately evident that even relatively hindered disubstituted acetic acids (e.g. $t\text{-BuPr}^i\text{CHCO}_2\text{H}$) may be prepared by direct alkylation of the carboxylic acids. Tri-substituted acids, with the exception of $i\text{-PrMe}_2\text{CCO}_2\text{H}$, are not accessible by this method. Of course, such slightly hindered tri-substituted structrues as $\text{EtMe}_2\text{CCO}_2\text{H}$ and $\text{Me}_3\text{CCO}_2\text{H}$ may be prepared in quantitative yields (see Run 12) but these compounds are available commercially. This method, however, would be particularly useful for the preparation of labelled compounds.

Overview

The families of aliphatic esters, acids, and nitriles whose alkylations are discussed above have the same degree of oxidation and so are formally dependent on the possibility of transforming the functionality with which it is associated. Carboxylic acids and esters are versatile in this regard since, by a variety of well-known reactions, they may be changed into ketones, alcohols, hydrocarbons, amides, etc. with great facility.[6] The cyano function is more resistant to transformation. Structures more hindered than $i\text{-Pr}_2\text{CHCN}$ ($i\text{-Pr}_2\text{CH-}$, $E_S' = -5.01$) are not readily hydrolysed by available methods. High pressure catalytic hydrogenation of the nitriles, even the most hindered, gives excellent yields of primary amines which may then be transformed into other compounds. A recent publication shows,[7] for example, how primary

Table 3. Steric limits in the alkylation of carboxylic acids $R^1R^2CHCO_2H \xrightarrow{R^3I} R^1R^2R^3CCO_2H$

Run No	R^1	R^2	$-E_S'(R^1R^2CH-)$	R^3	$-E_S'(R^1R^2R^3C-)$	Yield (%)
9	i-Pr	H	0.93	i-Pr	5.01	90
10	t-Bu	H	1.63	Me	3.21	70
11	t-Bu	H	1.63	i-Pr	6.53	40
12	Me	Me	0.48	i-Pr	3.54	97
13	Et	Et	2.00	Me	3.63†	11
14	i-Pr	i-Pr	5.01	Me	7.38	0
15	i-Pr	Me	1.92†	i-Pr	7.38	0
16	t-Bu	Me	3.21	i-Pr	7.56	0

†Estimated E_S' values[5].

amines may be converted into alkyl fluorides. Oxidation of these amines by conventional methods yields the corresponding nitriles and, in some cases, a variety of fragmentation products.[8] It has been shown, however, that primary amines may be oxidized to aldehydes via the N-(2,4-di-nitrophenyl) derivative[9] but the steric limits to this reaction remain to be investigated. Thus it appears that the readily obtainable hindered nitriles do not provide a convenient access to carboxylic acids and their derivatives. They do provide an entry into primary amines and the compounds obtainable therefrom. The use of nitrile, ester, or carboxylic acid alkylation depends on the particular synthetic probelm at hand.

Generally speaking, it may be stated that the ease of alkylation of the three families considered in this article is in the order: nitrile > carboxylic ester > carboxylic acid. This does not mean that only the most efficient reaction is of synthetic interest. For example, the syntheses of $i\text{-}Pr_2CHCO_2H$ and $i\text{-}PrMe_2CCO_2H$ are most conveniently carried out by direct alkylation with i-PrI on the commercially available acids $i\text{-}PrCH_2CO_2H$ and Me_2CHCO_2H rather than ester or nitrile alkylation. The preparation of more crowded structures would require alkylation of the more reactive nitriles or esters. The present article along with the preceding one dealing with ester alkylation[1a] contains sufficient information to enable a careful analysis of *synthetic strategy* before undertaking the synthesis of a hindered compound.

EXPERIMENTAL[10]

The entire series of operations was conducted under an inert atmosphere.

Preparation of organolithium. To Li cut in small pieces, in dry ether, was added n-BuCl, also in dry ether (1.5N) over a period of 30 min. The reaction began spontaneously and refluxed, during the period of addition.

Amide formation. To di-isopropylamine, slightly in excess (5–10%), diluted once in THF at 0°, the ethereal soln of n-BuLi was added slowly.

Enolization. To lithium di-isopropylamide soln at 0°, in excess (30–100%), the nitrile or carboxylic acid diluted three times in THF was added slowly. Stirring was continued for 30 min after completion of addition.

Alkylation. The alkyl iodide along with HMPA (0.5 mole per mole RI) was added dropwise at 0°. After stirring for 2 hr the temp was allowed to rise to *ca* 20° followed by pouring onto ice, acidification with dil H_2SO_4, extraction, and work up.

The compounds, nitriles and carboxylic acids, were characterised by their NMR and IR spectra in all cases and present no points of special interest in the present context.

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[10]The experimental part was carried out with the assistance of Jacques Pantigny to whom the authors are extremely grateful.