Some modern methods of organic synthesis

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SECOND EDITION

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Some modern methods of organic synthesis

Cambridge Texts in Chemistry and Biochemistry

Preface to the first edition

This book is addressed principally to advanced undergraduates and to graduates at the beginning of their research careers, and aims to bring to their notice some of the reactions used in modern organic syntheses. Clearly, the whole field of synthesis could not be covered in a book of this size, even in a cursory manner, and a selection has had to be made. This has been governed largely by consideration of the usefulness of the reactions, their versatility and, in some cases, their selectivity.

A large part of the book is concerned with reactions which lead to the formation of carbon–carbon single and double bonds. Some of the reactions discussed, such as the alkylation of ketones and the Diels–Alder reaction, are well established reactions whose scope and usefulness has increased with advancing knowledge. Others, such as those involving phosphorus ylids, organoboranes and new organometallic reagents derived from copper, nickel, and aluminium, have only recently been introduced and add powerfully to the resources available to the synthetic chemist. Other reactions discussed provide methods for the functionalisation of unactivated methyl and methylene groups through intramolecular attack by free radicals at unactivated carbon–hydrogen bonds. The final chapters of the book are concerned with the modification of functional groups by oxidation and reduction, and emphasise the scope and limitations of modern methods, particularly with regard to their selectivity.

Discussion of the various topics is not exhaustive. My object has been to bring out the salient features of each reaction rather than to provide a comprehensive account. In general, reaction mechanisms are not discussed except in so far as is necessary for an understanding of the course or stereochemistry of a reaction. In line with the general policy in the series references have been kept to a minimum. Relevant reviews are noted but, for the most part, references to the original literature are given only for points of outstanding interest and for very recent work. Particular reference is made here to the excellent book by H. O. House, *Modern Synthetic Reactions* which has been my guide at several points and on which I have tried to build, I fear all too inadequately.

I am indebted to my friend and colleague, Dr K. Schofield, for much helpful comment and careful advice which has greatly assisted me in writing the book.

W. CARRUTHERS

26 October 1970

Preface to the second edition

The general plan of this second edition follows that of the first edition, but the opportunity has been taken to bring the content up to date as far as possible. A considerable amount of new material has been included to take account of advances in knowledge and of new synthetic methods which have come into use since publication of the first edition. The increasing application of organic derivatives of sulphur, selenium and silicon in synthesis and improvements in the methods for selective alkylation of ketones and for reversing the polarity of functional groups ('umpolung') are among the subjects discussed more fully in this edition. To prevent the book from becoming too big, some material of less immediate interest which appeared in the first edition has been excised – it is hoped without detriment to the usefulness of the book. My aim, as before, has been to bring out the salient features of the reactions rather than to provide a comprehensive account. I have supported the discussion of new reactions by numerous references.

I am indebted to Dr I. Fleming for helpful correspondence about the reactions of organosilanes.

W. CARRUTHERS

January 1977

Nomenclature of olefins

Olefin configurations are expressed as *cis* or *trans*, using the priority rules formulated for the *E* (entgegen, *trans*) and *Z* (zusammen, *cis*) convention (Blackwood, Gladys, Loening, Petrarca and Rush, 1968).

Contents

1 Formation of carbon–carbon single bonds

In spite of the fundamental importance in organic synthesis of the formation of carbon–carbon single bonds there are comparatively few general methods available for effecting this process, and fewer still which proceed in good yield under mild conditions. Many of the most useful procedures involve carbanions, themselves derived from organometallic compounds, or from compounds containing 'activated' methyl or methylene groups. They include reactions which proceed by attack of the carbanion on a carbonyl or conjugated carbonyl group, as in the Grignard reaction, the aldol and Claisen ester condensations and the Michael reaction, and other reactions, with which this chapter will be largely concerned, which involve nucleophilic displacement at a saturated carbon atom, as in the alkylation of ketones and the coupling reactions of some organometallic compounds.

1.1. Alkylation: importance of enolate anions

It is well known that certain unsaturated groups attached to a saturated carbon atom render hydrogen atoms attached to that carbon relatively acidic, so that the compound can be converted into an anion on treatment with an appropriate base. Table 1.1, taken from House (1965), shows the pK_a values for some compounds of this type and for some common solvents and reagents.

The acidity of the C—H bonds in these compounds is due to a combination of the inductive electron-withdrawing effect of the unsaturated groups and resonance stabilisation of the anion formed by removal of a proton (1.1). Not all groups are equally effective in 'activating' a neighbouring CH_2 or CH_3; nitro is the most powerful of the common groups and thereafter the series follows the approximate order $—NO_2 > —COR > —SO_2R > —CO_2R > —CN > —C_6H_5$. Two activating groups reinforce each other, as can be seen by comparing diethyl malonate

TABLE 1.1 *Approximate acidities of active methylene compounds and other common reagents*

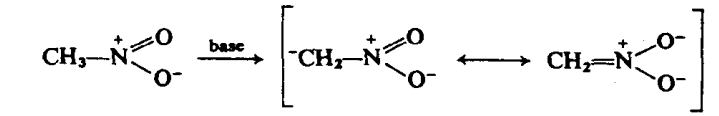
Compound	pK_a	Compound	pK_a
$CH_3CO_2\underline{H}$	5	$C_6H_5COC\underline{H}_3$	19
$C\underline{H}_2(CN)CO_2C_2H_5$	9	$CH_3COC\underline{H}_3$	20
$C\underline{H}_2(CO.CH_3)_2$	9	$C\underline{H}_3SO_2C\underline{H}_3$	~23
$C\underline{H}_3NO_2$	10	$C\underline{H}_3CO_2C_2H_5$	~24
$CH_3COC\underline{H}_2CO_2C_2H_5$	11	$CH_3\underline{CO}_2^-$	~24
$C\underline{H}_2(CO_2C_2H_5)_2$	13	$C\underline{H}_3CN$	~25
$CH_3O\underline{H}$	16	$C_6H_5N\underline{H}_2$	~30
$C_2H_5O\underline{H}$	18	$(C_6H_5)_3C\underline{H}$	~40
$(CH_3)_3CO\underline{H}$	19	$C\underline{H}_3SOC\underline{H}_3$	~40

(Acidic hydrogen atoms are underlined)

H. O. House, *Modern synthetic reactions*, copyright 1972, W. A. Benjamin, Inc., Menlo Park, California.

($pK_a \approx 13$) with ethyl acetate ($pK_a \approx 24$). Acidity is also increased slightly by electron-withdrawing substituents, and decreased by alkyl groups, so that diethyl methylmalonate, for example, has a slightly less acidic C—H group than diethyl malonate itself.

By far the most important activating groups in synthesis are the carbonyl and carboxylic ester groups. Removal of a proton from the



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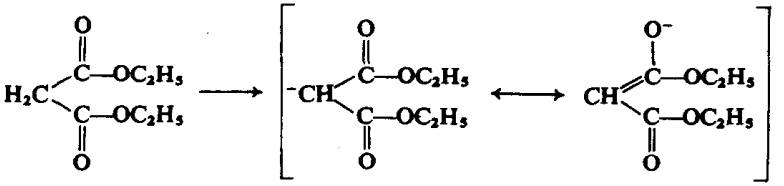
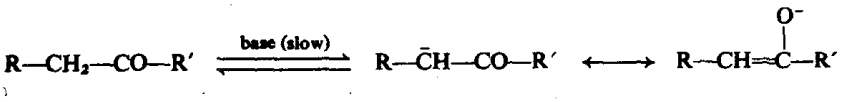
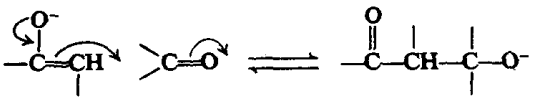


α-carbon atom of a carbonyl compound with base gives the corresponding enolate anion, and it is these anions which are involved in base-catalysed condensation reactions of carbonyl compounds, such as the aldol condensation, and in bimolecular nucleophilic displacements (alkylations) (1.2). The enolate anions must be distinguished from the enols themselves, which are always present in equilibrium with the





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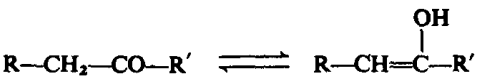


(1.3)

carbonyl compound in presence of acidic or basic catalysts (1.3). The enols are concerned in certain acid-catalysed condensations of carbonyl compounds. Most monoketones and esters contain only small amounts of enol (<1 per cent) at equilibrium, but with 1,2- and 1,3-dicarbonyl compounds much higher amounts of enol (>50 per cent) may be present.

The formation of the enolate anion results from an equilibrium reaction between the carbonyl compound and the base. A competing equilibrium involves the enolate anion and the solvent. Thus, with diethyl malonate in solvent SolH in presence of base B^-, we have

$$\begin{aligned} CH_2(CO_2C_2H_5)_2 + B^- &\rightleftharpoons {}^-CH(CO_2C_2H_5)_2 + BH \\ {}^-CH(CO_2C_2H_5)_2 + SolH &\rightleftharpoons CH_2(CO_2C_2H_5)_2 + Sol^-, \end{aligned} \tag{1.4}$$

and to ensure an adequate concentration of the enolate anion at equilibrium clearly both the solvent and the conjugate acid of the base must be much weaker acids than the active methylene compound. The correct choice of base and solvent is thus of great importance if the subsequent alkylation, or other, reaction is to be successful. Reactions must normally be effected under anhydrous conditions since water is a much stronger acid than the usual activated methylene compounds and, if present, would instantly protonate any carbanion produced. Another point of importance is that the solvent must not be a much stronger acid than the conjugate acid of the base, otherwise the equilibrium

$$B^- + SolH \rightleftharpoons BH + Sol^- \tag{1.5}$$

will lie too far to the right and lower the concentration of B^-. For example, sodamide can be used as base in liquid ammonia or in benzene, but, obviously, not in ethanol. Base–solvent combinations commonly

used to convert active methylene compounds into the corresponding anions include sodium methoxide, sodium ethoxide and sodium or potassium t-butoxide in solution in the corresponding alcohol, or as suspensions in ether, benzene or dimethoxyethane. Potassium t-butoxide is a particularly useful reagent, since it is a poor nucleophile and its solutions in different solvents have widely different basic strengths; it is most active in solution in dry dimethyl sulphoxide (Pearson and Buehler, 1974). Metallic sodium or potassium, or sodium hydride, in suspension in benzene, ether or dimethoxyethane, sodamide in suspension in an inert solvent or in solution in liquid ammonia, and solutions of sodium or potassium triphenylmethyl in ether or benzene are also widely used with the less 'active' compounds.

Recently the lithium salts of secondary amines, particularly lithium diisopropylamide and lithium 2,2,6,6-tetramethylpiperidide have been finding increasing application (see Olofson and Dougherty, 1973). These amide bases are non-nucleophilic and have the advantage that they are soluble in non-polar, even hydrocarbon, solvents. The insolubility of the bases listed above, in such solvents, seriously limits their usefulness.

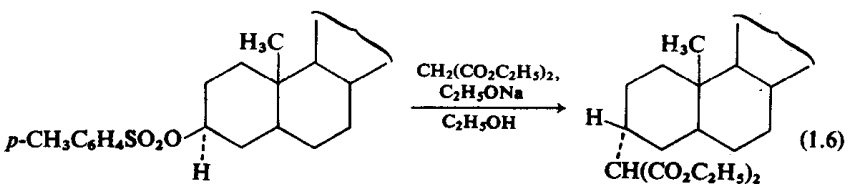
1.2. Alkylation of relatively acidic methylene groups

In order to effect a reasonably rapid reaction it is, of course, necessary to have a high concentration of the appropriate carbanion. Because of their relatively high acidity (see Table 1.1) compounds in which a C—H bond is activated by a nitro group or by two or more carbonyl, ester or cyano groups can be converted largely into their anions with an anhydrous alcoholic solution of a metal alkoxide, such as sodium ethoxide or potassium t-butoxide. An alternative procedure is to prepare the enolate in benzene or ether, using finely divided sodium or potassium metal or sodium hydride, which react irreversibly with compounds containing active methylene groups with formation of the metal salt and evolution of hydrogen. β-Diketones can often be converted into their enolates with alkali metal hydroxides or carbonates in aqueous alcohol or acetone.

Much faster alkylation of enolate anions can often be achieved in dimethylformamide, dimethyl sulphoxide, 1,2-dimethoxyethane or hexamethylphosphoramide than in the usual protic solvents. This appears to be due to the fact that the former solvents do not solvate the enolate anion and thus do not diminish its reactivity as a nucleophile.

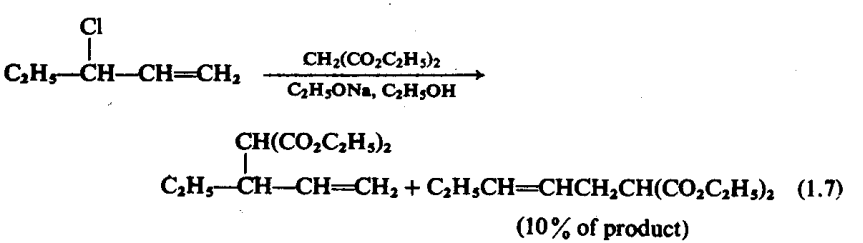
At the same time they are able to solvate the cation, separating it from the cation–enolate ion pair and leaving a relatively free enolate ion which would be expected to be a more reactive nucleophile than the ion pair (Parker, 1962). Reactions effected with aqueous alkali as base are often improved in the presence of a phase-transfer catalyst such as a tetra-alkylammonium salt (cf. Makosza and Jończyk, 1976).

Alkylation of enolate anions is readily effected with alkyl halides or other alkylating agents. Both primary and secondary alkyl, allyl or benzyl halides may be used successfully, but with tertiary halides poor yields of alkylated product often result because of competing dehydrohalogenation of the halide. It is often advantageous to proceed by way of the toluene-*p*-sulphonate or methanesulphonate rather than a halide. The sulphonates are excellent alkylating agents, and can usually be obtained from the alcohol in a pure condition more readily than the corresponding halides. Epoxides have also been used as alkylating agents, generally reacting at the less substituted carbon atom. Attack of the enolate anion on the alkylating agent takes place by a bimolecular nucleophilic displacement (S_N2) process and thus results in inversion of configuration at the carbon atom of the alkylating agent.



(1.6)

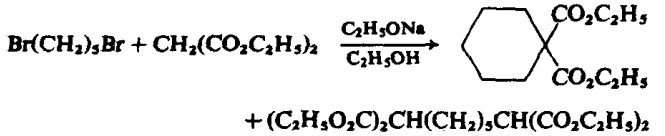
With secondary and tertiary allylic halides or sulphonates, reaction of an enolate anion may give mixtures of products formed by competing attack at the α- and γ-positions (1.7).



(1.7)

Alkylation of active methylene compounds with $\alpha\omega$-polymethylene dihalides, and intramolecular alkylation of ω-haloalkylmalonic esters provides a useful method for synthesising three- to seven-membered

rings. Non-cyclic products are frequently formed at the same time by competing intermolecular reactions and conditions have to be carefully chosen to suppress their formation (1.8).



$$+ (C_2H_5O_2C)_2CH(CH_2)_5CH(CO_2C_2H_5)_2 \qquad (1.8)$$

A difficulty sometimes encountered in the alkylation of active methylene compounds is the formation of unwanted dialkylated products. During the alkylation of diethyl sodiomalonate, the monoalkyl derivative formed initially is in equilibrium with its anion as indicated in the first equation of (1.9). In ethanol solution, dialkylation does not take place to any appreciable extent because ethanol is sufficiently acidic to reduce the concentration of the anion of the alkyl derivative, but not that of the more acidic diethyl malonate itself, to a very low value.

$$RCH(CO_2C_2H_5)_2 + \bar{C}H(CO_2C_2H_5)_2 \rightleftharpoons R\bar{C}(CO_2C_2H_5)_2 + CH_2(CO_2C_2H_5)_2 \qquad (1.9)$$

$$R\bar{C}(CO_2C_2H_5)_2 + C_2H_5OH \rightleftharpoons RCH(CO_2C_2H_5)_2 + C_2H_5O^-$$

However, replacement of ethanol by an inert solvent favours dialkylation, and dialkylation also becomes a more serious problem with the more acidic alkylcyanoacetic esters, and in alkylations with very reactive compounds such as allyl or benzyl halides or sulphonates. It has been said that alkylation of β-dicarbonyl compounds by reaction of the thallium(I) salts with an alkyl iodide or bromide, leads to high yields of monoalkylated product without any dialkylation, but this has been questioned (Hooz and Smith, 1972). Dialkylation may, of course, be effected deliberately if required by carrying out two successive operations, using either the same or a different alkylating agent in the two steps. It is often found that active methylene compounds with a secondary or tertiary alkyl substituent in the position adjacent to the activating group undergo further alkylation only with difficulty. This is partly due to increased steric hindrance to approach of the base for proton abstraction and partly, in the case of carbonyl compounds at any rate, to steric interference with the attainment of a transition state for proton removal that allows continuous overlap of the *p*-orbitals concerned (1.10). This difficulty may be overcome by use of a stronger base in a less acidic