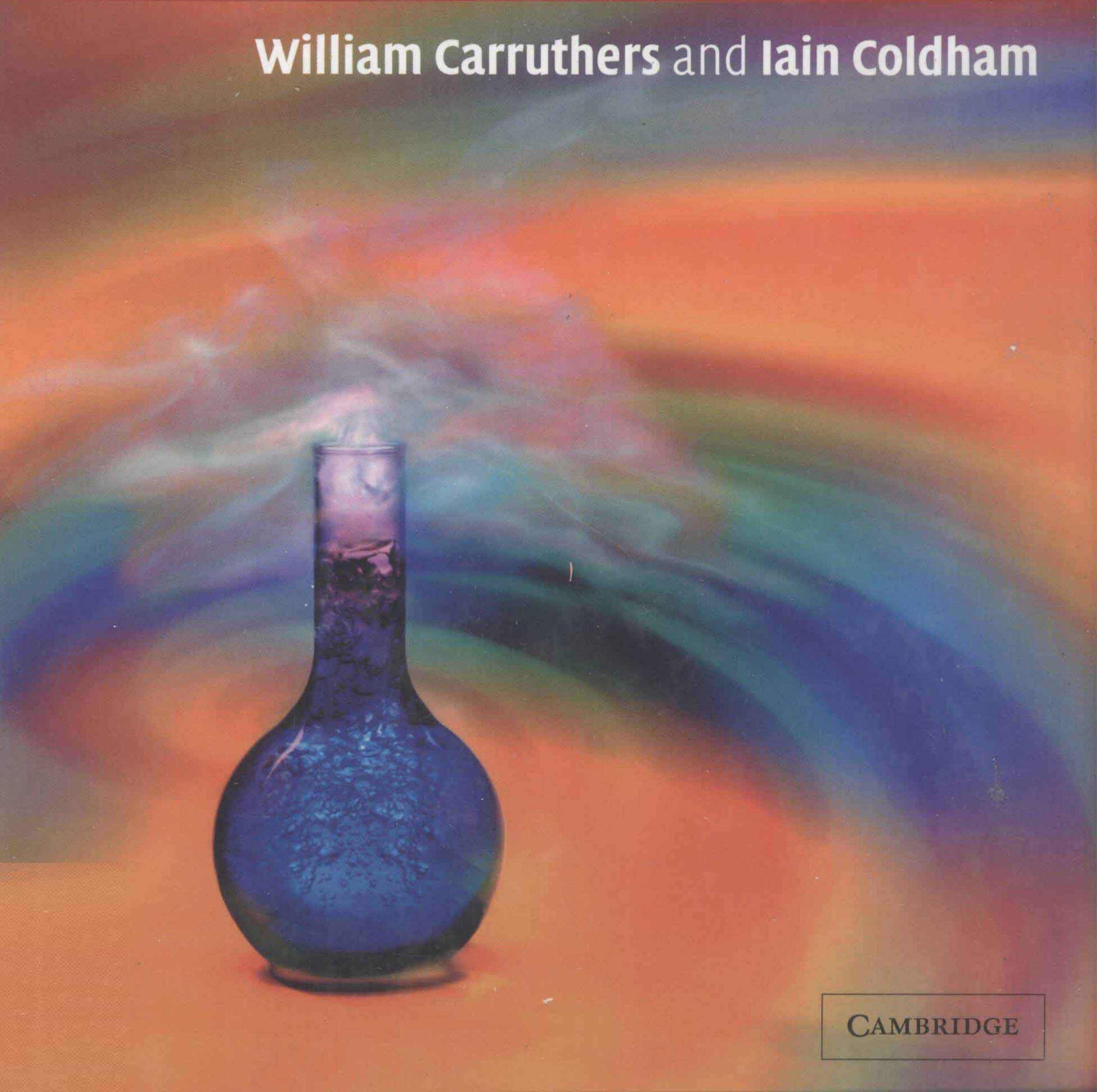
Fourth Edition

Modern Methods of Organic Synthesis

William Carruthers and **Iain Coldham**



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MODERN METHODS OF ORGANIC SYNTHESIS

The fourth edition of this well-known textbook discusses the key methods used in organic synthesis, showing the value and scope of these methods and how they are used in the synthesis of complex molecules. All the text from the third edition has been revised, to produce a modern account of traditional methods and an up-to-date description of recent advancements in synthetic chemistry. The textbook maintains a traditional and logical approach in detailing carbon–carbon bond formations, followed by a new chapter on the functionalization of alkenes and concluding with oxidation and reduction reactions. Reference style has been improved to include footnotes, allowing easy and rapid access to the primary literature. In addition, a selection of problems has been added at the end of each chapter, with answers at the end of the book. The book will be of significant interest to chemistry and biochemistry students at advanced undergraduate and graduate level, as well as to researchers in academia and industry who wish to familiarize themselves with modern synthetic methods.

BILL CARRUTHERS was born in Glasgow. He won a bursary to Glasgow University, where he graduated with a first-class honours degree in 1946 and a Ph.D. in 1949. He moved to Exeter in 1956, working first for the Medical Research Council and then, from 1968, as a lecturer then senior lecturer at the Department of Chemistry in the University of Exeter. He died in April 1990, just a few months before he was due to retire.

IAIN COLDHAM was born in Sandbach, Cheshire. He graduated from the University of Cambridge with a first-class honours degree in 1986 and a Ph.D. in 1989. After postdoctoral studies at the University of Texas, Austin, he moved in 1991 to the University of Exeter as a lecturer then senior lecturer. He is currently Reader at the Department of Chemistry in the University of Sheffield and specializes in organic synthesis.

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*

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Reactions which has been my guide at several points and on which I have tried to build, I feel 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.

26 October 1970

Preface to the fourth edition

Some Modern Methods of Organic Synthesis was originally written by Dr W. (Bill) Carruthers, and three popular editions were published that have helped many students of advanced organic chemistry. Unfortunately, Dr Carruthers died in 1990, just prior to his retirement. As his successor at the University of Exeter, it was appropriate that I should take on the task of preparing the fourth edition of this text. In honour of Dr Carruthers, a similar format to previous editions has been taken, although of course the book has been completely re-written and brought up-to-date (through 2003) to take account of the many advances in the subject since the third edition was published. As in previous editions, the text begins with descriptions of some of the most important methods for the formation of carbon–carbon bonds, including the use of enolates and organometallic compounds for carbon–carbon single-bond formation (Chapter 1), methods for carbon–carbon double-bond formation (Chapter 2), pericyclic reactions (Chapter 3), radicals and carbenes (Chapter 4). There has been some re-organization of material and emphasis has been placed on reactions that are useful, high yielding or selective for organic synthesis. For example, Chapter 1 has been expanded to include some of the most popular and contemporary reactions using main-group and transition-metal chemistry (rather than placing reactions of organoboron and silicon compounds into a separate chapter). A new chapter describing the functionalization of alkenes has been devised, covering reactions such as hydroboration, epoxidation and dihydroxylation (Chapter 5). The book concludes with examples of pertinent oxidation (Chapter 6) and reduction (Chapter 7) reactions that are used widely in organic synthesis. The opportunity has been taken to add some problems at the end of each chapter, with answers at the end of the book. References have been compiled as footnotes on each relevant page for ease of use.

In common with the previous editions, the book is addressed principally to advanced undergraduates and to graduates at the beginning of their research careers. My aim has been to bring out the salient features of the reactions and reagents rather than to provide a comprehensive account. Reaction mechanisms are not normally discussed, except where necessary for an understanding of the course or stereochemistry of a reaction. My hope is that the book will find widespread use as a helpful learning and reference aid for synthetic chemists, and that it will be a fitting legacy to Dr Carruthers.

The majority of the text was written at the University of Exeter before my move to the University of Sheffield and I would like to acknowledge the encouragement and help of the staff at Exeter.

Part of one chapter was written while I was a Visiting Professor at the University of Miami, and I am grateful to Professor Bob Gawley for hosting my visit. My thanks extend to various people who have proof-read parts of the text, including Chris Moody, Mike Shipman, Mark Wood, Alison Franklin, Joe Harrity, Steve Pih and Ben Dobson. Finally, I would like to thank my family for their patience during the writing of this book.

I. Coldham
January 2004

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1

Formation of carbon–carbon single bonds

The formation of carbon–carbon single bonds is of fundamental importance in organic synthesis. As a result, there is an ever-growing number of methods available for carbon–carbon bond formation. Many of the most useful procedures involve the addition of organometallic species or enolates to electrophiles, as in the Grignard reaction, the aldol reaction, the Michael reaction, alkylation reactions and coupling reactions. Significant advances in both main-group and transition-metal-mediated carbon–carbon bond-forming reactions have been made over the past decade. Such reactions, which have been finding useful application, are discussed in this chapter. The formation of carbon–carbon single bonds by pericyclic or radical reactions are discussed in chapters 3 and 4.

1.1 Main-group chemistry

1.1.1 Alkylation of enolates and enamines

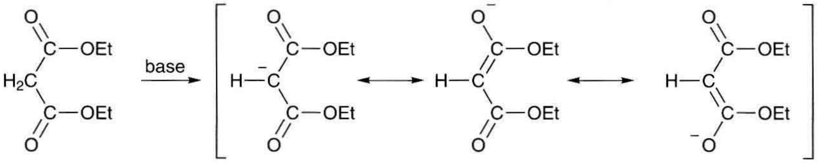
It is well known that carbonyl groups increase the acidity of the proton(s) adjacent (α-) to the carbonyl group. Table 1.1 shows the pK_a values for some unsaturated compounds and for some common solvents and reagents.

The acidity of the C—H bonds in these compounds is caused by a combination of the inductive electron-withdrawing effect of the unsaturated groups and the resonance stabilization of the anion formed by removal of a proton (1.1). Not all groups are equally effective in ‘activating’ a neighbouring CH; nitro is the most powerful of the common groups, with the series following the approximate order $NO_2 > COR > SO_2R > CO_2R > CN > C_6H_5$. Two activating groups reinforce each other; for example, diethyl malonate has a lower pK_a (≈ 13) than ethyl acetate (p$K_a \approx 24$). Acidity is increased slightly by electronegative substituents

Table 1.1. *Approximate acidities of some activated compounds and common reagents*

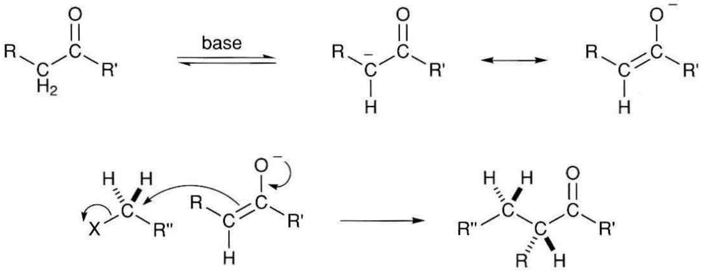
Compound	pK_a	Compound	pK_a
$\mathrm{CH_3CO_2}\mathit{H}$	5	$\mathrm{C_6H_5CO}\mathit{CH_3}$	19
$\mathit{CH_2}\mathrm{(CN)CO_2Et}$	9	$\mathrm{CH_3CO}\mathit{CH_3}$	20
$\mathit{CH_2}\mathrm{(COCH_3)_2}$	9	$\mathit{CH_3}\mathrm{CO_2Et}$	24
$\mathit{CH_3}\mathrm{NO_2}$	10	$\mathit{CH_3}\mathrm{CN}$	25
$\mathrm{CH_3CO}\mathit{CH_2}\mathrm{CO_2Et}$	11	$\mathrm{((CH_3)_3Si)_2N}\mathit{H}$	26
$\mathit{CH_2}\mathrm{(CO_2Et)_2}$	13	$\mathrm{CH_3SO_2}\mathit{CH_3}$	31
$\mathrm{CH_3O}\mathit{H}$	16	$\mathrm{CH_3SO}\mathit{CH_3}$	35
$\mathrm{(CH_3)_3CO}\mathit{H}$	19	$\mathrm{((CH_3)_2CH)_2N}\mathit{H}$	36

(e.g. sulfide) and decreased by alkyl groups.



(1.1)

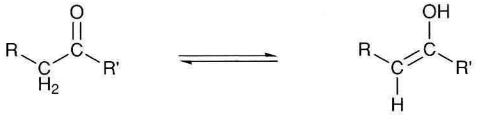
By far the most important activating group in synthesis is the carbonyl group. Removal of a proton from the α-carbon atom of a carbonyl compound with base gives the corresponding enolate anion. It is these enolate anions that are involved in many reactions of carbonyl compounds, such as the aldol condensation, and in bimolecular nucleophilic displacements (alkylations, as depicted in Scheme 1.2).



X = leaving group, *e.g.* Br

(1.2)

Enolate anions should be distinguished from enols, which are always present in equilibrium with the carbonyl compound (1.3). Most monoketones and esters contain only small amounts of enol (<1%) at equilibrium, but with 1,2- and 1,3-dicarbonyl compounds much higher amounts of enol (>50%) may be present. In the presence of a protic acid, ketones may be converted largely into the enol form, implicated in many acid-catalysed reactions of carbonyl compounds.



(1.3)

Table 1.1 illustrates the relatively high acidity of compounds in which a C—H bond is activated by two or more carbonyl (or cyano) groups. It is therefore possible to use a comparatively weak base, such as a solution of sodium ethoxide in ethanol, in order to form the required enolate anion. An equilibrium is set up, as illustrated in Scheme 1.4, in which the conjugate acid of the base (BH) must be a weaker acid than the active methylene compound. Another procedure for preparing the enolate of an active methylene compound is to use sodium hydride (or finely divided sodium or potassium metal) in tetrahydrofuran (THF), diethyl ether (Et_2O) or benzene. The metal salt of the enolate is formed irreversibly with evolution of hydrogen gas. β-Diketones can often be converted into their enolates with alkali-metal hydroxides or carbonates in aqueous alcohol or acetone.

$$CH_2(CO_2Et)_2 \quad + \quad B^- \rightleftharpoons {}^-CH(CO_2Et)_2 \quad + \quad BH \tag{1.4}$$

Much faster alkylation of enolate anions can often be achieved in dimethylformamide (DMF), dimethylsulfoxide (DMSO) or 1,2-dimethoxyethane (DME) than in the usual protic solvents. The presence of hexamethylphosphoramide (HMPA) or a triamine or tetramine can also enhance the rate of alkylation. This is thought to be because of the fact that these solvents or additives solvate the cation, but not the enolate, thereby separating the cation–enolate ion pair. This leaves a relatively free enolate ion, which would be expected to be a more reactive nucleophile than the ion pair.[1] Reactions with aqueous alkali as base are often improved in the presence of a phase-transfer catalyst such as a tetra-alkylammonium salt.[2]

Alkylation of enolate anions is achieved readily with alkyl halides or other alkylating agents.[3] 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 elimination. It is sometimes advantageous to proceed by way of the toluene-*p*-sulfonate, methanesulfonate or trifluoromethanesulfonate rather than a halide. The sulfonates are excellent alkylating agents and can usually be obtained from the alcohol in a pure condition more readily than the corresponding halides. Primary and secondary alcohols can be used as alkylating agents under Mitsunobu conditions.[4] Epoxides have also been used, generally reacting at the less substituted carbon atom. Attack of the enolate anion on the alkylating agent takes place by an S_N2 pathway and thus results in inversion of configuration at the carbon atom of the alkylating agent (1.5).[5]

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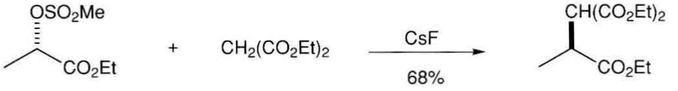
[1] H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers and R. W. DeNet, *J. Org. Chem.*, **26** (1961), 644; A. J. Parker, *Quart. Rev. Chem. Soc. Lond.*, **16** (1962), 163; M. Goto, K. Akimoto, K. Aoki, M. Shindo and K. Koga, *Tetrahedron Lett.*, **40** (1999), 8129.

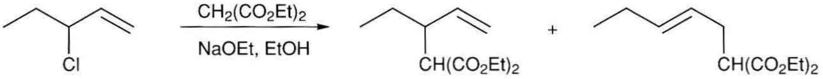
[2] M. Makosza and A. Jonczyk, *Org. Synth.*, **55** (1976), 91.

[3] D. Caine, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, vol. 3 (Oxford: Pergamon Press, 1991), p. 1.



(1.5)

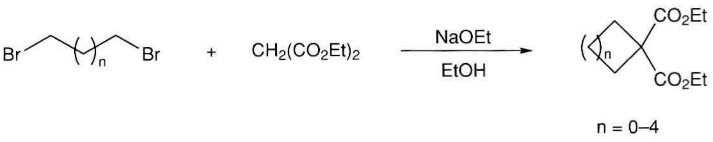
With secondary and tertiary allylic halides or sulfonates, reaction of an enolate anion may give mixtures of products formed by competing attack at the α- and γ-positions (1.6). Addition of the enolate anion to a π-allylpalladium complex provides an alternative method for allylation (see Section 1.2.4).



(1.6)

A difficulty sometimes encountered in the alkylation of active methylene compounds is the formation of unwanted dialkylated products. During the alkylation of the sodium salt of diethylmalonate, the monoalkyl derivative formed initially is in equilibrium with its anion. 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 diethylmalonate itself, to a very low value. However, replacement of ethanol by an inert solvent favours dialkylation. Dialkylation also becomes a more serious problem with the more acidic cyanoacetic esters and in alkylations with very reactive electrophiles such as allyl or benzyl halides or sulfonates.

Dialkylation may, of course, be effected deliberately if required by carrying out two successive operations, by using either the same or a different alkylating agent in the two steps. Alkylation of dihalides provides a useful route to three- to seven-membered ring compounds (1.7). Non-cyclic products are formed at the same time by competing intermolecular reactions and conditions have to be chosen carefully to suppress their formation (for example, by using high dilution).



(1.7)

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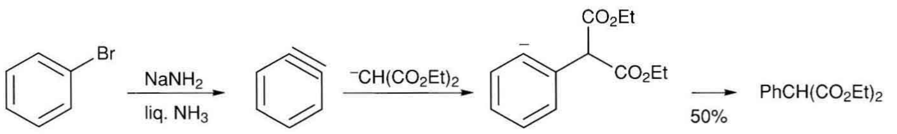
[4] O. Mitsunobu, *Synthesis* (1981), 1; J. Yu, J.-Y. Lai and J. R. Falck, *Synlett* (1995), 1127; T. Tsunoda, C. Nagino, M. Oguri and S. Itô, *Tetrahedron Lett.*, **37** (1996), 2459.

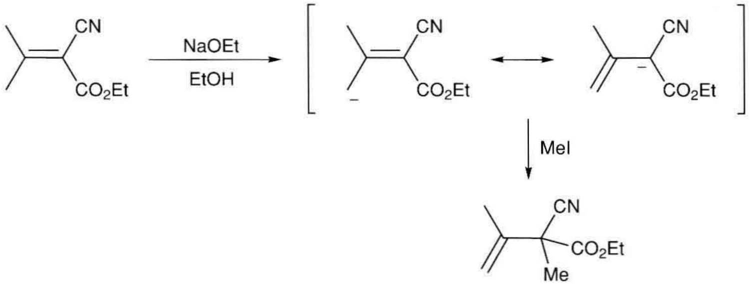
[5] T. Sato and J. Otera, *J. Org. Chem.*, **60** (1995), 2627.

Under ordinary conditions, aryl or alkenyl halides do not react with enolate anions, although reaction can occur with aryl halides bearing strongly electronegative substituents in the *ortho* and *para* positions. 2,4-Dinitrochlorobenzene, for example, with ethyl cyanoacetate gives ethyl (2,4-dinitrophenyl)cyanoacetate (90%) by an addition–elimination pathway. Unactivated aryl halides may react with enolates under more vigorous conditions, particularly sodium amide in liquid ammonia. Under these conditions, the reaction of bromobenzene with diethylmalonate, for example, takes place by an elimination–addition sequence in which benzyne is an intermediate (1.8).



(1.8)

Enolate anions with extended conjugation can be formed by proton abstraction of α,β-unsaturated carbonyl compounds (1.9). Kinetically controlled alkylation of the delocalized anion takes place at the α-carbon atom to give the β,γ-unsaturated compound directly. A similar course is followed in the kinetically controlled protonation of such anions.



(1.9)

A wasteful side reaction which sometimes occurs in the alkylation of 1,3-dicarbonyl compounds is the formation of the *O*-alkylated product. For example, reaction of the sodium salt of cyclohexan-1,3-dione with butyl bromide gives the *O*-alkylated product (37%) and only 15% of the *C*-alkylated 2-butylcyclohexan-1,3-dione. In general, however, *O*-alkylation competes significantly with *C*-alkylation only with reactive methylene compounds in which the equilibrium concentration of enol is relatively high (as in 1,3-dicarbonyl compounds). The extent of *C*- versus *O*-alkylation for a particular 1,3-dicarbonyl compound depends on the choice of cation, solvent and electrophile. Cations (such as Li^+) that are more covalently bound to the enolate oxygen atom or soft electrophiles (such as alkyl halides) favour *C*-alkylation, whereas cations such as K^+ or hard electrophiles (such as alkyl sulfonates) favour *O*-alkylation.

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