Fuhrhop/Penzlin

Organic Synthesis

Concepts, Methods, Starting Materials

Jürgen Fuhrhop/Gustav Penzlin

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Preface

This book was written for the advanced chemistry student and for the research chemist. Its purpose is to convey knowledge about concepts, methods, starting materials, and target molecules that play important roles in modern organic syntheses. Moreover, it shows the application of this knowledge to retrosynthetic analysis and gives an introduction to the design of synthetic plans.

Important concepts are summarized at the beginning of each chapter. They include

- the synthon approach,
- systematic evaluation of the arrangement of functionality,
- strategies for achieving regio- and stereoselectivity in carbon-carbon bond formation and functional group conversions,
- strategies for enforcing thermodynamically unfavourable reactions, and
- retrosynthetic analysis.

The synthetic methods described were selected under the aspects of applicability, simplicity, and didactic value. Applicability implies that the method has been used in complex syntheses. Simplicity means that the method is not too time consuming. And didactic value is judged by some principles of selectivity control which we wanted to demonstrate.

Finally, a list of commercially available starting materials tells the synthetic chemist what industry can do for him, and a selection of complex synthetic procedures shows what he may aim for.

We should like to acknowledge the help and advice we have received from many students and colleagues, in particular Prof. Kevin Smith and Prof. A. Gossauer, who read the whole of the manuscript and made helpful suggestions. The "Lektorat Verlag Chemie" was giving us vigorous support throughout the time of writing and correcting. Above all we must thank our typist, Mrs. Jutta Fuhrhop, who has transferred difficult to read manuscripts to several intermediate and a final typescript with indulgence and great skill.

Berlin, in January 1983

Jürgen Fuhrhop
Gustav Penzlin

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Organic Synthesis

Errata

p. 1, 3rd paragraph, reaction equation should read:
$CH_3I + 2Li \rightarrow CH_3Li + LiI$

p. 4, 9th line from bottom should read:
-tional group (d^1 or a^1), ...

p. 14, 2nd line should read:
-etons, and allylic anions, $R_2C=CR-CR_2^-$, ...

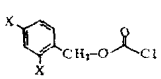
p. 29, lower paragraph, 1st line should read:
Another model considers the interactions of the phosphorus substituents, ...

p. 76, 5th line should read:
cleavage with alkaline H_2O_2

p. 150, 1st line of scheme is superfluous (see p. 149)

p. 186, 4th line should read:
natural products (C. G. Overberger, 1967, 1968; E. J. Corey, 1968 D; ...

p. 209, table 18, 4th column ("reagent"):
the mirror-image of the 2nd formula is shown.

correct formula: 

p. 287, 5th line from bottom, last words should read:
... a transition-state-like

p. 296, 2nd line from bottom should read:
chloromethylene Wittig reagents and subsequent thermal 18π-electrocyclization ...

p. 310, reference after Kuo, C. H., should read:
Kutney, J. P., 1977, in ApSimon, J. (ed.), *The Total Synthesis of Natural Products*, Vol. 3, p. 273, Wiley, New York

Contents

1 Synthons in the Synthesis of Carbon Chains and Carbocycles

Introduction and Summary

- *Most synthetic reactions, which produce carbon-carbon bonds, are polar: a negatively polarized ("electronegative") carbon atom (electron donor, d) of one reagent is combined with a positively polarized ("electropositive") carbon atom (electron acceptor, a) of another reagent. A new covalent carbon-carbon bond is formed.*

- *The formal carbanions and carbocations used as units in synthesis are called donor synthons and acceptor synthons. They are derived from reagents with functional groups.*

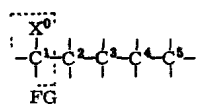
  Example:

  CH_3^- methyl donor synthon (from the reagent CH_3Li)
  CH_3^+ methyl acceptor synthon (from the reagent CH_3I)
  The combination (= synthetic reaction) of both synthons would yield ethane.

- *The change of a donor reagent into an acceptor reagent and vice versa is called "umpolung" (= dipole inversion).*

  Example:
  (a) (d)
  $CH_3I + 2\,Li \rightarrow CH_3CH_3Li + LiI$

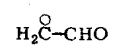
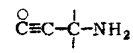
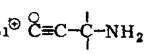
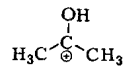
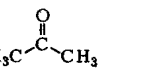
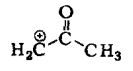
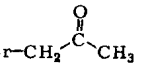
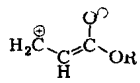
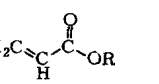
- *Synthons are numbered according to the relative positions of a functional group (FG) and the reactive carbon atom.*



X = hetero atom
FG = functional group

If the carbon atom C-1 of the functional group itself is reacting, one has a d^1- or a^1-synthon. If the carbon atom C-2 next to the functional group (the α-carbon atom) is the reaction centre, we call it a d^2- or a^2-synthon. If the β-carbon atom C-3 is the reactive one, we assign d^3 or a^3 to the corresponding synthon, etc. Alkyl synthons without functional groups are called alkylating synthons. The electronegative hetero atom of the functional group may also form covalent bonds with acceptor synthons. In such cases we speak of d^0-synthons.

Examples

synthon type	example	reagent	functional group
d^0	$CH_3S^{\ominus}$	CH_3SH	
d^1	$^{\ominus}C{\equiv}N$	K^+CN^-	$-C{\equiv}N$
d^2		CH_3CHO	$-CHO$
d^3			
alkyl d		$LiCH_3$	–
a^0	$^{\oplus}P(CH_3)_2$	$(CH_3)_2P{-}Cl$	$-P(CH_3)_2$
a^1			
a^2			
a^3			
alkyl a		$(CH_3)_3S^{\oplus}\ Br^{\ominus}$	–

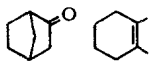
- *The combination of two reagents corresponding to one d-synthon and one a-synthon under appropriate conditions yields an additional carbon-carbon bond (exception: d^0-synthons) The following obvious rules apply to the arrangement of functionality in the product ("target molecule").*

reacting synthons:	products:
alkyl a + alkyl d	*non-functional*
alkyl a + d^1, alkyl d + a^1	*monofunctional*
a^1 + d^1	*1,2-difunctional*
a^1 + d^2, a^2 + d^1	*1,3-difunctional*
a^1 + d^3, a^2 + d^2, a^3 + d^1	*1,4-difunctional*
and so on.	

Examples for arrangements of functionality

non-functional products  $n\text{-}C_{100}H_{202}$

monofunctional products

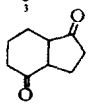


difunctional products

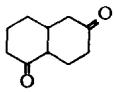
1,3-difunctional*)

1,4-difunctional*)

1,4-difunctional*)



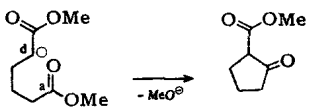
1,4- or 1,5-difunctional



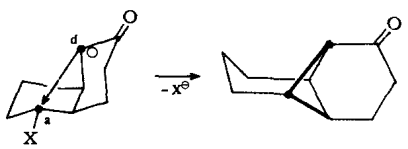
1,5-difunctional

- *If the target molecule is polyfunctional, the synthons must contain more than one functional group.*
- *If an open-chain organic molecule contains an electron acceptor* **and** *an electron donor site, two carbon atoms may be combined intramolecularly. This corresponds to the synthesis of a monocyclic compound.*

Example



- *Intramolecular reactions of electron donor and acceptor sites in cyclic starting materials produce spirocyclic, fused, or bridged polycyclic compounds.*



- *Chapter 1 first describes some common synthons and corresponding reagents. Emphasis is on regioselective carbanion formation. In the second part some typical synthetic*

* The ends of C—C multiple bonds are defined as the centers of functionality

procedures in the following order of "arrangements of functionality in the target molecule" are given:

- *non-functional (=saturated), open-chain hydrocarbons;*
- *monofunctional (=unsaturated), open-chain hydrocarbons;*
- *hydrocarbons by special coupling reactions;*
- *monofunctional, open-chain C,H,O-compounds (in the order of rising oxidation number);*
- *difunctional open-chain C,H,O-compounds (in the order 1,2-; 1,3-; 1,4-; and 1,5-difunctional);*
- *cyclic hydrocarbons and C,H,O-compounds (in the order 3-, 4-, 5-, and 6-membered rings);*
- *1,6-difunctional C,H,O-compounds by cleavage reactions;*
- *bridged carbocycles.*

General problems with synthetic organic reactions are discussed together with some practical solutions for specific examples. These problems include

- *regio- and stereoselectivity by exploitation of the substrates' stereochemistry (p. 20, 22, 26) and differentiated nucleophilicity (p. 24f., 41, 53ff.)*
- *regioselectivity by reversible addition of activating groups (p. 40, 83)*
- *selectivity in competitive cyclization, polymerization, and dialkylation reactions (p. 23, 25)*
- *overcome of sterical hindrance (p. 33ff., 79) and of unfavorable entropy effects (p. 23, 40f., and 50f)*

"Synthons" are defined as units which can be joined to (organic) molecules by known or conceivable synthetic operations (E.J. Corey, 1967A). A synthon may be as simple as a methyl anion or as complex as a steroid enolate anion. Since most synthetic reactions are polar, a synthon usually contains a nucleophilic electron donor centre (d) or an electrophilic electron acceptor centre (a). Synthons for the synthesis of carbon compounds are produced from organic reagents which contain functional groups such as C—Br, C=C, C=O, C=N etc. The reactive site of the synthon may now either be on carbon atom C^1, which is part of the functional group d^1 or a^1), or on remote carbon atoms C^n (d^nor a^n; $n \geq 2$). Important donor and acceptor synthons will be described in the order of increasing distance between the functional group and the polar, reactive carbon atom. Hetero atoms of functional groups are, with rare exceptions, electron donors (d^0)

1.1 Electron Donors (Nucleophiles)

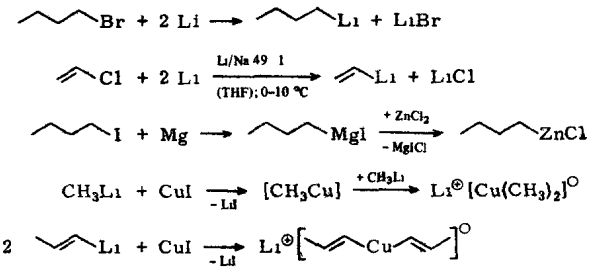
1.1.1 Alkylating and d^1-Synthons

Carbanions are negatively charged organic species with an even number of electrons and the charge mainly concentrated on a carbon atom. In alkyl, alkenyl, and alkynyl anions all of the nonbonding electrons are localized on carbon atoms and these anions are particularly reac-

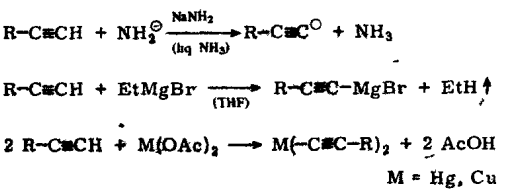
tive. The ease of carbanion formation increases in the same order as the s-character of the CH bond: C—CH < C=CH < C≡CH. Saturated alkyl anions are less stable when the carbon atom is highly substituted: tertiary < secondary < primary.

Alkyl, aryl, and alkenyl carbanions are usually produced from the corresponding halides by metal-halogen exchange).* Halides at sp^3-hybridized carbon atoms are more reactive than at sp^2-hybridized carbon atoms (for an example see p. 20). An ionic carbon-metal bond (e.g. C—Na, C—Li, or C—Mg) may subsequently be replaced by a more covalent carbon-metal bond (e.g. C—Cu) by metal-metal interchange. The metal ion may be strongly associated with the carbanion centre and modify its behaviour. However, carbanion chemistry and the chemistry of organometallic compounds, especially of lithium, magnesium, sodium, and potassium (M. Schlosser, 1973) are closely related. Their chemical reactions are similar. Synthetic chemistry, however, takes advantage of two important distinctions: lithium forms more covalent structures than other alkali metals (p. 11f., 22) and carbanions with a "soft" copper(I) counterion tend to be highly nucleophilic (p. 20f. and p. 35f.).

A saturated alkyl group does not exhibit functionality. It is not a d^1-synthon, because the functional groups, e.g. halide or metal ions, are lost in the course of the reaction. It functions as an alkyl synthon. Alkenyl anions (R. West, 1961) on the other hand, constitute $d^{1,2}$-synthons, because the C=C group remains in the product and may be subject to further synthetic operations.



Alkynyl anions are more stable ($pK_a \approx 22$) than the more saturated alkyl or alkenyl anions ($pK_a \approx 40$-45). They may be obtained directly from terminal acetylenes by treatment with strong base, e.g. sodium amide (pK_a of $NH_3 \approx 35$). Frequently magnesium acetylides are made in proton-metal exchange reactions with more reactive Grignard reagents. Copper and mercury acetylides are formed directly from the corresponding metal acetats and acetylenes under neutral conditions (G.E. Coates, 1977; R.P. Houghton, 1979).



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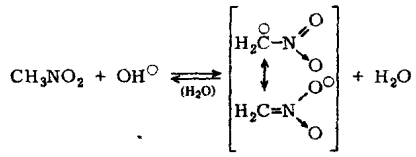
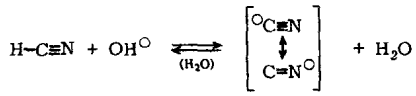
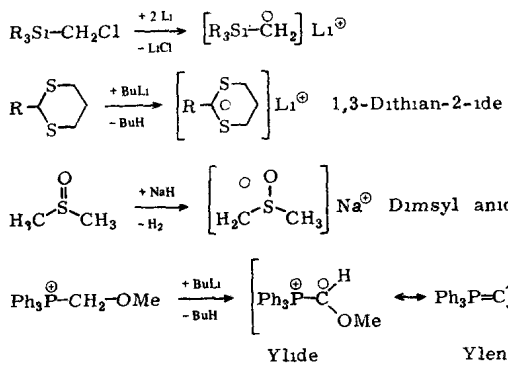
* For several standard procedures no references are given. They can be easily located in M Fieser and L.F. Fieser, Reagents for Organic Synthesis, Vol 1, Wiley, N.Y , 1967 or standard textbooks.

There exist a number of d^1-synthons, which are stabilized by the delocalization of the electron pair into orbitals of hetero atoms, although the nucleophilic centre remains at the carbon atom. From nitroalkanes anions may be formed in aqueous solutions (e.g. CH_3NO_2: pK_a = 10.2). Nitromethane and -ethane anions are particularly useful in synthesis. The cyanide anion is also a classical d^1-synthon (HCN: pK_a = 9.1).

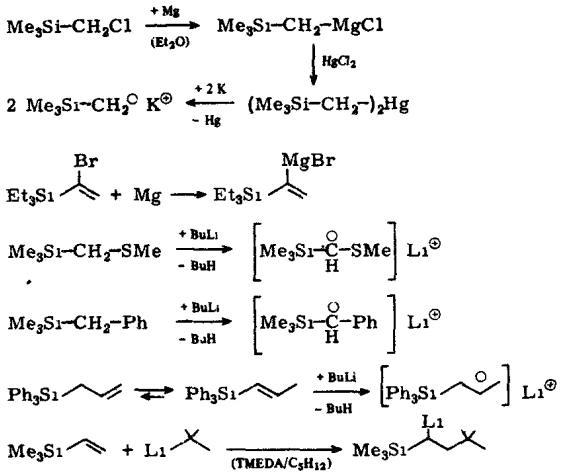




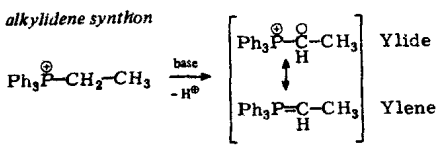
More recent developments are based on the finding, that *the d-orbitals of silicon, sulfur, phosphorus and certain transition metals may also stabilize a negative charge on a carbon atom* This is probably caused by a partial transfer of electron density from the carbanion into empty low-energy d-orbitals of the hetero atom ("backbonding") or by the formation of "ylides", in which a positively charged "onium centre" is adjacent to the carbanion and stabilization occurs by "ylene" formation.



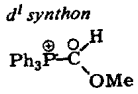
Silylated carbanions are available from the corresponding silylated alkyl chlorides by Grignard techniques. The repulsive interaction between the electropositive silicon and metal atoms leads to particularly loose carbon-metal bonds, and metal-metal interchange is possible under a variety of conditions. If the silylated carbon atom carries a phenyl group, a sulfur atom, or a second silicon atom, deprotonation is also possible. It occurs with strong bases or with butyllithium. Allylic silanes are also deprotonated by butyllithium and form anions, in which the negative charge is delocalized over three carbon atoms Vinyl silanes, however, tend to undergo nucleophilic additions to metal organyls. The negative charge of the resulting saturated anion is generally localized on the carbon atom adjacent to silicon (I. Fleming, 1979).



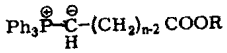
Alkyl groups adjacent to a phosphorus atom in quaternary phosphonium salts lose a proton when treated with base. An ylide is formed, which is stabilized by (d-p) π-bonding or "ylene" formation. The strength of base required depends on the substituents on the carbon atom, which is to be deprotonated. The more these substituents are able to stabilize an adjacent negative charge, the more stable and the less reactive will the ylide be. Since the phosphorus atom is removed at the end of most synthetic operations, phosphorus ylides may, depending on the substituents, behave as non-functional (= alkyl) synthons or as d^1, d^2, ...d^n-synthons. Carbanions derived from phosphonic acids are also frequently used in synthesis (B.J. Walker, 1972; J.I.G. Cadogan, 1979).



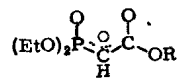
d^1 synthon



d^n synthon

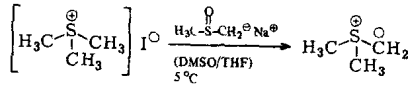


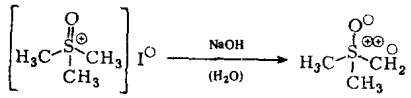
d^2 synthon



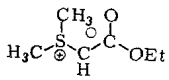
Sulfur ylides contain a carbanion, which is stabilized by an adjacent positively-charged sulfur. Ylides derived from alkylsulfonium salts are usually generated and utilized at low temperatures. Oxosulfonium ylides are, however, stable near room temperature. The most common method of ylide formation is deprotonation of a sulfonium salt. What has been said

about the applicability of phosphonium ylide synthons is also true for their sulfur analogues: in principle they may serve to introduce all kinds of substituents So far they have mostly served as nonfunctional and d^2-synthons (B.M Trost, 1975, A)

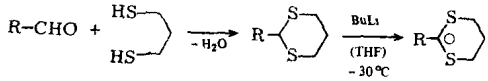




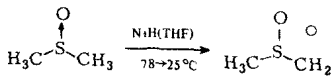
d^2 synthon



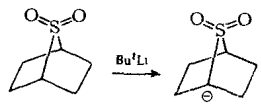
The carbanions derived from thioacetals, however, are typical d^1-synthons. Most frequently used are 1,3-dithianes and C^{α}-silylated thioethers (see p 33; D. Seebach, 1969, 1973; B.-T Gröbel, 1974, 1977). In these derivatives the proton is removed by butyllithium in THF.



In sulfoxides and sulfones an adjacent CH group is also deprotonated by strong bases. If one considers the sulfinyl (—SO—) or sulfonyl ($—SO_2—$) groups to be functional groups, then these carbanions are d^1-synthons It will be shown later (p. 48 and 60ff.), that these anions may either serve as nonfunctional, d^1-, d^2- or d^3-synthons

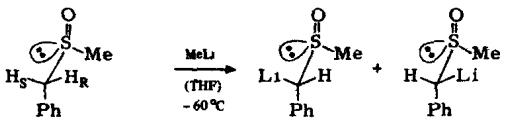


Dimsyl anion

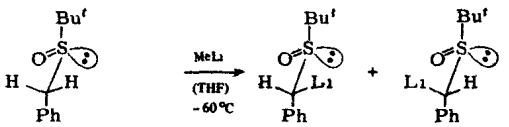


The large sulfur atom is a preferred reaction site in synthetic intermediates to introduce chirality into a carbon compound. Thermal equilibrations of chiral sulfoxides are slow, and carbanions with lithium or sodium as counterions on a chiral carbon atom adjacent to a sulfoxide group maintain their chirality. The benzylic proton of chiral sulfoxides is removed stereoselectively by strong bases The largest groups prefer the *anti* conformation, e g phenyl and oxygen in the first example, phenyl and *tert*-butyl in the second Deprotonation occurs at the methylene group on the least hindered site adjacent to the unshared electron pair of the sulfur atom (R.R Fraser, 1972; F Montanari, 1975).

In cyclic sulfoxides the diastereomeric product ratio is even higher, and the chirality of the sulfur atom has been efficiently transferred to the carbon atom in synthesis

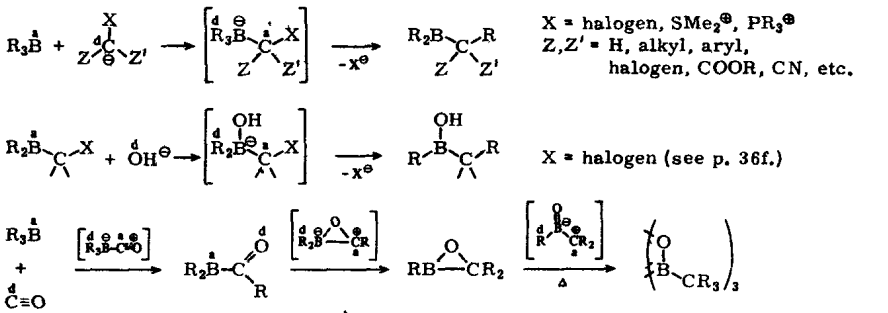


(S)-(+) benzyl methyl sulfoxide — (S,S) 94% — (R,S) 6%



(R)-(+) benzyl t-butyl sulfoxide — (R,R) ~100% — (S,R) ~0%

A final remark concerns the triorganylboranes, BR_3. These are electron-deficient Lewis acids and function therefore as acceptor synthons (a^0). If the boron atom is combined with an electron donor, it becomes negatively charged, and its carbon substituents now behave like carbanions. Rearrangement brings about neutralization of the boron atom and is energetically favored. A new C—C bond is formed in high yield, if an electron-accepting centre is present at an adjacent site (H.C. Brown, 1975; see pp. 21, 36f., and 44f.).



1.1.2 d^2-Synthons

C—H bonds are polarized by attached unsaturated carbon substituents. Such groups "activate" the neighbouring CH_3, CH_2, or CH groups in the following order: $CR{=}NR_2^+ >$ COR > CN > COOR > CR=NR > Ph > $CR{=}CR_2$. Two activating substituents reinforce each other.

1,3-Dioxo compounds are deprotonated at C-2 and C-4 by two equivalents of strong bases (e.g. LDA or BuLi). *Carbon atom C-4 of those dianions is much more nucleophilic than the less basic center C-2* (Hauser's rule; C.R. Hauser, 1958; K.G. Hampton, 1965). The formation of some typical d^2-synthons and their pK_a values are given below.