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

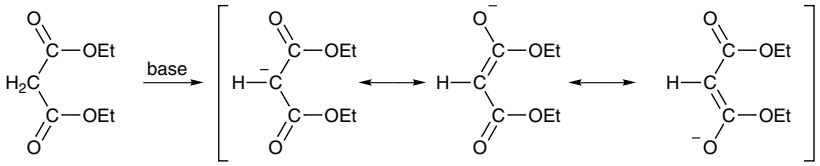
It is well known that carbonyl groups increase the acidity of the proton(s) adjacent (α-) to the carbonyl group. Table 1.1 shows the pK_a values for some unsaturated compounds and for some common solvents and reagents.

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 (pK_a ≈ 24). Acidity is increased slightly by electronegative substituents

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

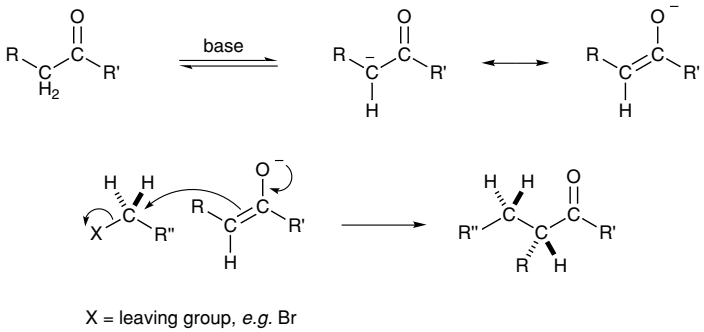
Compound	pK_a	Compound	pK_a
CH_3CO_2H	5	$C_6H_5COCH_3$	19
$CH_2(CN)CO_2Et$	9	CH_3COCH_3	20
$CH_2(COCH_3)_2$	9	CH_3CO_2Et	24
CH_3NO_2	10	CH_3CN	25
$CH_3COCH_2CO_2Et$	11	$((CH_3)_3Si)_2NH$	26
$CH_2(CO_2Et)_2$	13	$CH_3SO_2CH_3$	31
CH_3OH	16	CH_3SOCH_3	35
$(CH_3)_3COH$	19	$((CH_3)_2CH)_2NH$	36

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



(1.1)

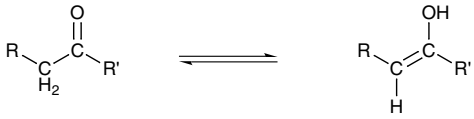
By far the most important activating group in synthesis is the carbonyl group. Removal of a proton from the α-carbon atom of a carbonyl compound with base gives the corresponding enolate anion. It is these enolate anions that are involved in many reactions of carbonyl compounds, such as the aldol condensation,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



(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.

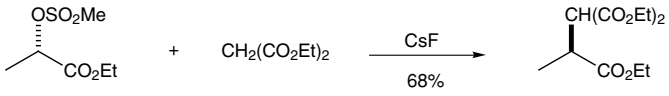
(1.4)

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

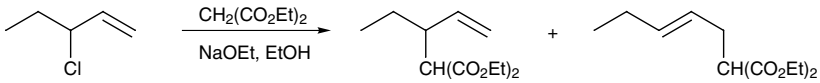
[1] H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers and R. W. DeNet, *J. Org. Chem.*, **26** (1961), 644; A. J. Parker, *Quart. Rev. Chem. Soc. Lond.*, **16** (1962), 163; M. Goto, K. Akimoto, K. Aoki, M. Shindo and K. Koga, *Tetrahedron Lett.*, **40** (1999), 8129.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

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]



(1.5)

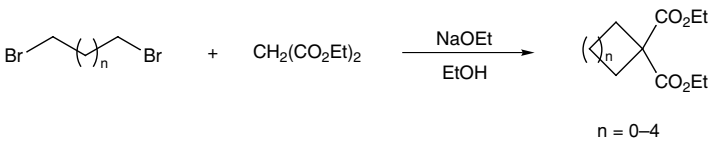
With secondary and tertiary allylic halides or sulfonates, reaction of an enolate anion may give mixtures of products formed by competing attack at the α- and γ-positions (1.6). Addition of the enolate anion to a π-allylpalladium complex provides an alternative method for allylation (see Section 1.2.4).



(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.

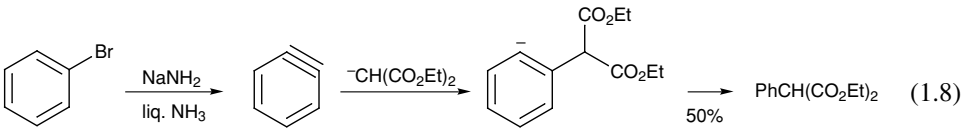
Dialkylation may, of course, be effected deliberately if required by carrying out two successive operations, by using either the same or a different alkylating agent in the two steps. Alkylation of dihalides provides a useful route to three- to seven-membered ring compounds (1.7). Non-cyclic products 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)

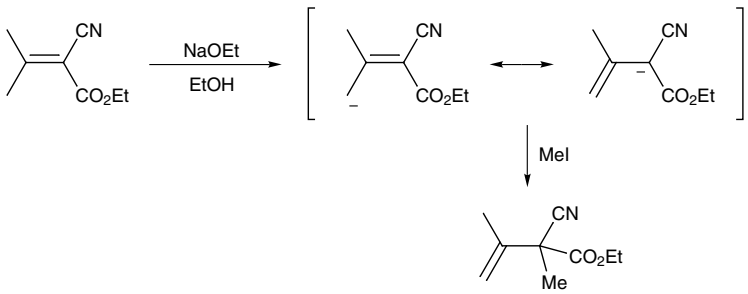
[4] O. Mitsunobu, *Synthesis* (1981), 1; J. Yu, J.-Y. Lai and J. R. Falck, *Synlett* (1995), 1127; T. Tsunoda, C. Nagino, M. Oguri and S. Itô, *Tetrahedron Lett.*, **37** (1996), 2459.
[5] T. Sato and J. Otera, *J. Org. Chem.*, **60** (1995), 2627.

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)

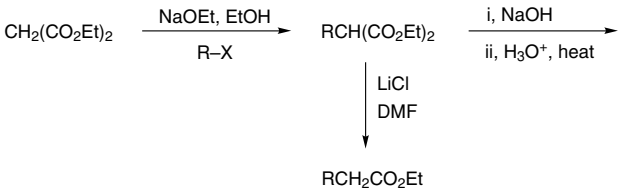
Enolate anions with extended conjugation can be formed by proton abstraction of α,β-unsaturated carbonyl compounds (1.9). Kinetically controlled alkylation of the delocalized anion takes place at the α-carbon atom to give the β,γ-unsaturated compound directly. A similar course is followed in the kinetically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

Alkylation of malonic esters and other active methylene compounds is useful in synthesis because the alkylated products can be subjected to hydrolysis and decarboxylation (1.10). Direct decarboxylation under neutral conditions with an alkali metal salt (e.g. lithium chloride) in a dipolar aprotic solvent (e.g. DMF) is a popular alternative method.[6]



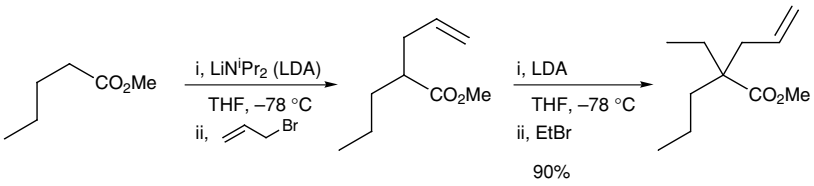
(1.10)

Proton abstraction from a monofunctional carbonyl compound (aldehyde, ketone, ester, etc.) is more difficult than that from a 1,3-dicarbonyl compound. Table 1.1 illustrates that a methyl or methylene group which is activated by only one carbonyl or cyano group requires a stronger base than ethoxide or methoxide ion to convert it to the enolate anion in high enough concentration to be useful for subsequent alkylation. Alkali-metal salts of tertiary alcohols, such as tert-butanol, in the corresponding alcohol or an inert solvent, have been used with success, but suffer from the disadvantage that they are not sufficiently basic to convert the ketone completely into the enolate anion. This therefore allows the possibility of an aldol reaction between the anion and unchanged carbonyl compound. An alternative procedure is to use a much stronger base that will convert the compound completely into the anion. Traditional bases of this type are sodium and potassium amide or sodium hydride, in solvents such as diethyl ether, benzene, DME or DMF. The alkali-metal amides are often used in solution in liquid ammonia. Although these bases can convert ketones essentially quantitatively into their enolate anions, aldol reaction may again be a difficulty with these bases because of the insolubility of the reagents. Formation of the anion takes place only slowly in the heterogeneous reaction medium and both the ketone and the enolate ion are present at some stage. This difficulty does not arise with the lithium dialkylamides, such as lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (LTMP) or the alkali-metal salts of bis(trimethylsilyl)amine (LHMDS, NaHMDS and KHMDS), which are soluble in non-polar solvents. These bases are now the most commonly used reagents for the generation of enolates.

An example illustrating the intermolecular alkylation of an ester is given in Scheme 1.11. Intramolecular alkylations also take place readily in appropriate cases and reactions of this kind have been used widely in the synthesis of cyclic compounds. In such cases, the electrophilic centre generally approaches the enolate

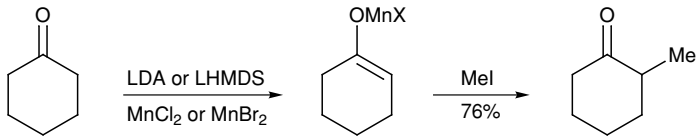
[6] A. P. Krapcho, *Synthesis* (1982), 805; 893.

from the less-hindered side and in a direction orthogonal to the plane of the enolate anion.



(1.11)

A common problem in the direct alkylation of ketones is the formation of di- and polyalkylated products. This difficulty can be avoided to some extent by adding a solution of the enolate in a polar co-ordinating solvent such as DME to a large excess of the alkylating agent. The enolate may therefore be consumed rapidly before equilibration with the alkylated ketone can take place. Nevertheless, formation of polysubstituted products is a serious problem in the direct alkylation of ketones and often results in decreased yields of the desired monoalkyl compound. An explanation for the presence of considerable amounts of polyalkylated product(s) is that enolates of alkylated ketones are less highly aggregated in solution and hence more reactive.[7] Some solutions to this problem use the additive dimethylzinc[8] or the manganese enolate of the ketone.[9] Good yields of the monoalkylated products have been obtained under these conditions (1.12).

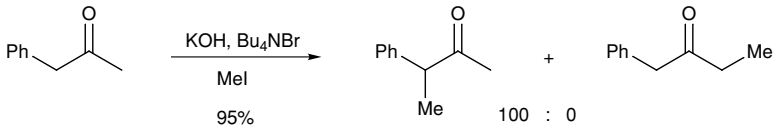


(1.12)

Alkylation of symmetrical ketones or of ketones that can enolize in one direction only can, of course, give just one mono-*C*-alkylated product. With unsymmetrical ketones, however, two different monoalkylated products may be formed by way of the two structurally isomeric enolate anions. If one of the isomeric enolate anions is stabilized by conjugation with another group, such as cyano, nitro or a carbonyl group, then only this stabilized anion is formed and alkylation takes place at the position activated by both groups. Even a phenyl or an alkenyl group provide sufficient stabilization of the resulting anion to direct substitution into the adjacent

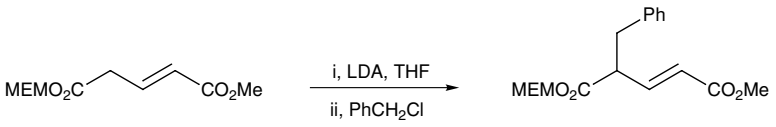
[7] A. Streitwieser, Y. J. Kim, and D. Z. R. Wang, *Org. Lett*., **3** (2001), 2599.
[8] Y. Morita, M. Suzuki and R. Noyori, *J. Org. Chem*., **54** (1989), 1785.
[9] M. T. Reetz and H. Haning, *Tetrahedron Lett*., **34** (1993), 7395; G. Cahiez, B. Figadère and P. Cléry, *Tetrahedron Lett*., **35** (1994), 3065; G. Cahiez, K. Chau and P. Cléry, *Tetrahedron Lett*., **35** (1994), 3069; G. Cahiez, F. Chau and B. Blanchot, *Org. Synth*., **76** (1999), 239.

position (1.13).[10]



(1.13)

Sometimes, specific lithium enolates of unsymmetrical carbonyl compounds are formed because of chelation of the lithium atom with a suitably placed substituent. For example, lithiation and alkylation of the mixed ester **1** took place α- to the MEM ester group, presumably as a result of intramolecular chelation of the lithium atom with the ethereal oxygen atom (1.14).[11]



(1.14)

1

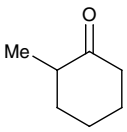
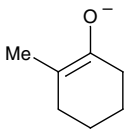
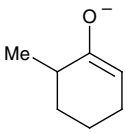
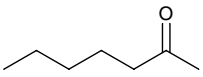
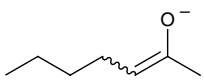
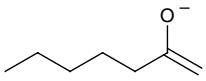
MEM = $CH_3OCH_2CH_2OCH_2$–

Alkylation of unsymmetrical ketones bearing α-alkyl substituents generally leads to mixtures containing both α-alkylated products. The relative amount of the two products depends on the structure of the ketone and may also be influenced by experimental factors, such as the nature of the cation and the solvent (see Table 1.2). In the presence of the ketone or a protic solvent, equilibration of the two enolate anions can take place. Therefore, if the enolate is prepared by slow addition of the base to the ketone, or if an excess of the ketone remains after the addition of base is complete, the equilibrium mixture of enolate anions is obtained, containing predominantly the more-substituted enolate. Slow addition of the ketone to an excess of a strong base in an aprotic solvent, on the other hand, leads to the kinetic mixture of enolates; under these conditions the ketone is converted completely into the anion and equilibration does not occur.

The composition of mixtures of enolates formed under kinetic conditions differs from that of mixtures formed under equilibrium conditions. The more-acidic, often less-hindered, α-proton is removed more rapidly by the base (e.g. LDA), resulting in the less-substituted enolate under kinetic conditions. Under thermodynamic conditions, the more-substituted enolate normally predominates. Mixtures of both structurally isomeric enolates are generally obtained and mixtures of products result on alkylation. Di- and trialkylated products may also be formed and it is not always

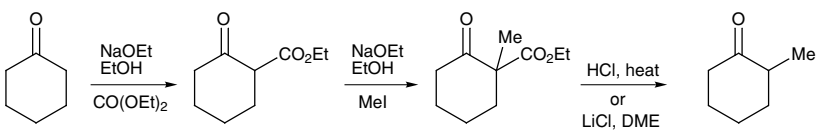
[10] A. Aranda, A. Díaz, E. Díez-Barra, A. de la Hoz, A. Moreno and P. Sánchez-Verdú, *J. Chem. Soc., Perkin Trans. 1* (1992), 2427.
[11] M. T. Cox, D. W. Heaton and J. Horbury, *J. Chem. Soc., Chem. Commun*. (1980), 799.

Table 1.2. *Composition of enolate anions generated from the ketone and a base*

Ketone	Base (conditions)	Enolate anion composition (%)	
			
	LDA, DME, −78 °C (kinetic control)	1	99
	Ph_3CLi, DME, −78 °C (kinetic control)	9	91
	Ph_3CLi, DME (equilibrium control)	90	10
	t-BuOK, t-BuOH (equilibrium control)	93	7
			
	LDA, THF, −78 °C (kinetic control)	0	100
	Ph_3CLi, DME (equilibrium control)	87	13

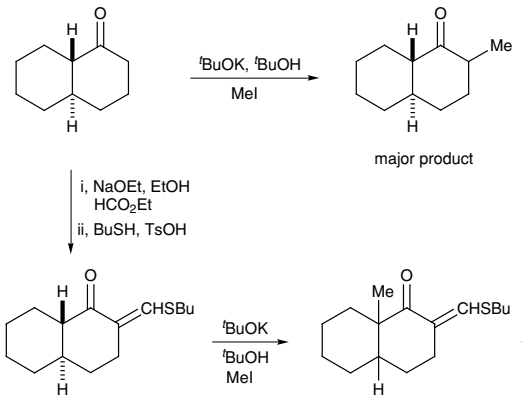
easy to isolate the pure monoalkylated compound. This is a serious problem in synthesis as it results in the loss of valuable starting materials.

A number of methods have been used to improve selectivity in the alkylation of unsymmetrical ketones and to reduce the amount of polyalkylation. One procedure is to introduce temporarily an activating group at one of the α-positions to stabilize the corresponding enolate anion; this group is removed after the alkylation. Common activating groups used for this purpose are ester groups. For example, 2-methylcyclohexanone can be prepared from cyclohexanone as shown in Scheme 1.15. The 2-ethoxycarbonyl derivative is obtained from the ketone by reaction with diethyl carbonate (or by reaction with diethyl oxalate followed by decarbonylation). Conversion to the enolate anion with a base such as sodium ethoxide takes place exclusively at the doubly activated position. Methylation with iodomethane and removal of the β-ketoester group with acid gives 2-methylcyclohexanone, free from polyalkylated products.



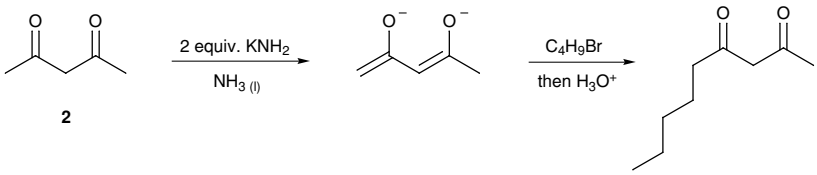
(1.15)

Another technique is to block one of the α-positions by introduction of a removable substituent which *prevents* formation of the corresponding enolate. Selective alkylation can be performed after acylation with ethyl formate and transformation of the resulting formyl (or hydroxymethylene) substituent into a group that is stable to base, such as an enamine, an enol ether or an enol thioether. An example of this procedure is shown in Scheme 1.16, in the preparation of 9-methyl-1-decalone from *trans*-1-decalone. Direct alkylation of this compound gives mainly the 2-alkyl derivative, whereas blocking the 2-position allows the formation of the required 9-alkyl-1-decalone (as a mixture of *cis* and *trans* isomers).



(1.16)

Alkylation of a 1,3-dicarbonyl compound at a 'flanking' methyl or methylene group instead of at the doubly activated C-2 position does not usually take place to any significant extent. It can be accomplished selectively and in good yield, however, by way of the corresponding *dianion*, itself prepared from the dicarbonyl compound and two equivalents of a suitable strong base. For example, 2,4-pentanedione **2** is converted into 2,4-nonanedione by reaction at the more-reactive, less-resonance-stabilized carbanion (1.17).[12]



2

(1.17)

With unsymmetrical dicarbonyl compounds that could give rise to two different dianions, it is found that in most cases only one is formed and a single product results on alkylation. Thus, with 2,4-hexanedione alkylation at the methyl group greatly predominates over that at the methylene group, and 2-acetylcyclohexanone and 2-acetylcyclopentanone are both alkylated exclusively at the methyl group. In general, the ease of alkylation follows the order $C_6H_5CH_2 > CH_3 > CH_2$.

[12] T. M. Harris and C. M. Harris, *Org. Reactions*, **17** (1969), 155.