The detection of tricycloalkanes appears to be more definite with FI than with EB, since no data were reported in the latter case. The same is true of the indans and tetralins, whose presence in the sample was reported by some of the laboratories using EB mass spectrometers and not by others. The molecular weight distribution for the groups is given directly by the FI mass spectra.

To summarize, therefore, the analysis of high-boiling hydrocarbon mixtures containing many components by means of an FI mass spectrometer is much simpler if the sensitivity coefficients of the groups of substances are constant. Long calculations are avoided in the evaluation of the spectra, and it is unnecessary to solve extremely large matrix systems or to make allowance for the masking of fragments of heavier components by the lighter components. The detection of trace components in a mixture is more definite with FI than with EB; this observation is not confined to the high-boiling hydrocarbon mixtures discussed here.

Finally, it should be mentioned that *Wanless*[63,64] has constructed "FI metastable maps", which simplify the identification of isomers in hydrocarbon mixtures. On field ionization of apolar compounds, metastable fragments are formed almost exclusively from the molecular ions, and not from primary fragment ions. Accurate measurement of the apparent mass m^* of the metastable fragments ($m^* = m^2/M$, m = true mass of the fragment, M = mass of the molecular ion) allows the definite assignment of the metastable ions to the corresponding molecular ions with the aid of the tables (FI metastable maps). Isomers having the same mass number differ in the abundance distribution of the corresponding metastable ions. Thus a simple correlation is obtained between the structure of the compounds and the metastable ions, without the FI spectrum of mixtures being overloaded with fragment ions that can appear at the same mass number on electron bombardment despite the fact that they are formed from compounds having different molecular weights.

We are grateful to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Union Rheinische Braunkohlenkraftstoffe for their support of our work in this field.

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German version: Angew. Chem. *81*, 662 (1969)
Translated by Express Translation Service, London

[63] *G. G. Wanless* and *G. A. Glock jr.*, Analytic. Chem. *39*, 2 (1967).

[64] *G. G. Wanless*, Advances Spectroscopy Fuels Related Materials, in press.

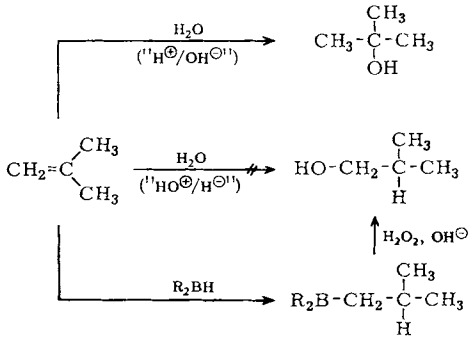
Methods and Possibilities of Nucleophilic Acylation[1]

By D. Seebach[*]

Nucleophilic acylation is the attachment of an $R-\overset{\ominus}{C}=O$ *group to an electrophilic center. A brief discussion of the advantages offered by acylations of this type in syntheses is followed by a description of the direct methods (reactions with acylmetal compounds) and the methods proceeding via "masked" acyl anions. The latter methods are based on the use of either metalated vinyl ether derivatives or carbanions derived from acetals. Organyllithiums of sulfur-stabilized carbanions are important reagents of this type.*

1. Introduction

The synthetic methods of organic chemistry have always been greatly enriched by the direct or indirect "reversal" of the mode of reaction of a reagent. Thus when water is added to unsymmetrically substituted double bonds, the OH group in the product is always attached to the carbon atom carrying the greater number of alkyl substituents (*Markownikoff*'s rule). A general method allowing the reverse mode of addition would require $HO^{\oplus}$ as an electrophile, the intermediate resulting from the primary attack by this species then being "neutralized" by an $H^{\ominus}$. This is not



Scheme 1.

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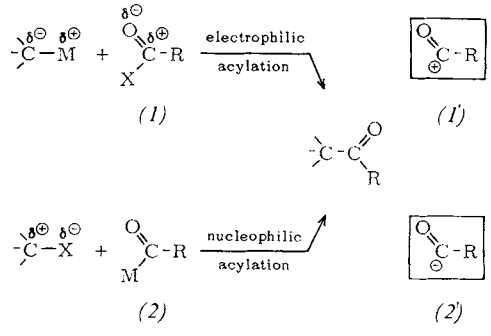
[1] A separate review of the dithiane method of nucleophilic acylation has already been published [84].

possible directly, but it can be achieved indirectly, according to *H. C. Brown*[2], by hydroboration.

In this reaction, if one considers only the starting materials and the final products, the mode of reaction of water is reversed. This may also be regarded as "symmetrization"[3] of the reactivity (Scheme 1).

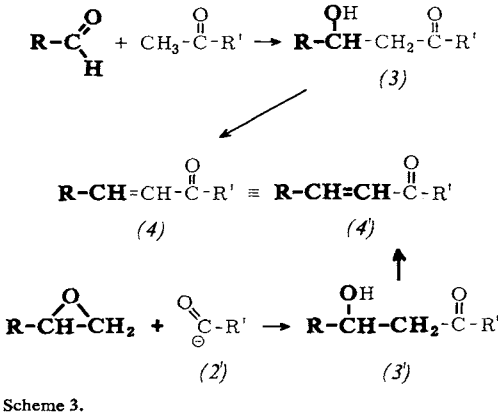
The present article is concerned with reversal of the mode of reaction of the carbonyl carbon atom. In reactions of conventional acylating agents *(1)*, X = halogen, OR, NR_2, *etc.* with carbanions[4], the



Scheme 2. M = metal.

acylating component used is formally (though not usually as a "true" intermediate) an acyl cation *(1')*, *i.e.* an electrophile. A nucleophilic acylation should then logically be the addition of an acyl anion *(2')* to a positively polarized C atom. The conventional acylating agents *(1)* are electrophiles, whereas a nucleophilic acylating agent *(2)* appears, at first sight at least, to be an impossibility. Acylating agents of both types should yield identical products [we cannot expect to be able to prepare novel carbonyl compounds with the aid of *(2)*], but the starting materials used may be entirely different (Scheme 2). Instead of a metal derivative having a negatively polarized C atom, a halide with a positively polarized C atom is used. The possibility of using different starting materials is illustrated in Scheme 3 for the preparation of an α,β-unsaturated ketone.

The aldol *(3)* can be prepared by the methods of classical carbonyl chemistry from an aldehyde and a

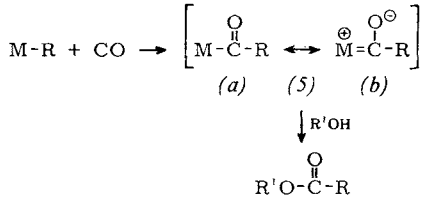


Scheme 3.

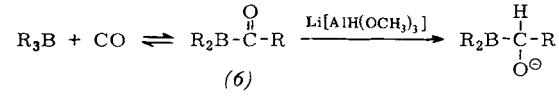
methyl ketone; we should be able to obtain the same aldol *(3')* from an epoxide by means of a nucleophilic acylating agent. Elimination of water leads to the identical α-β unsaturated ketones *(4)* and *(4')*. Since the epoxide is readily formed from the olefin, the formation of *(4')* corresponds in its final effect to the replacement of one of the hydrogen atoms on the less substituted C atom of the olefin by an acyl group. One starting compound is often predetermined in a synthesis, so the possibility of varying the building units ("synthons"[3]) can be of great value.

2. "Direct" Acylmetal Compounds *(2)*

The oldest known type of acylmetal compound is obtained by insertion of CO into metal-carbon bonds in which the metal is a transition metal of the group 6 to 8 triads[5]. Like the boryl ketones *(6)* obtained *e.g.* from boranes and carbon monoxide[6] or the silyl and germanyl ketones mentioned below, the acyl derivatives *(5)* which appear from the IR frequency to involve a contribution due to limiting structures *(5b)*, are generally not nucleophilic acylating agents. The transition metal compounds *(5)* react with alcohols



to form esters, and the boryl ketones *(6)* react with complex hydride to give alkoxides; the usual electrophilicity of the carbonyl carbon atom is thus evident in both types of compound. Nucleophilic acylations have, however, been observed with ionic compounds of the type *(5)* in which the acyl group is contained in an anion. Thus the reaction of tetracarbonylnickel with aryllithiums[7a,8a] leads to complex salts *(7)*



[2] *H. C. Brown*: Hydroboration. Benjamin, New York 1962.

[3] *E. J. Corey*, Pure appl. Chem. *14*, 19 (1967).

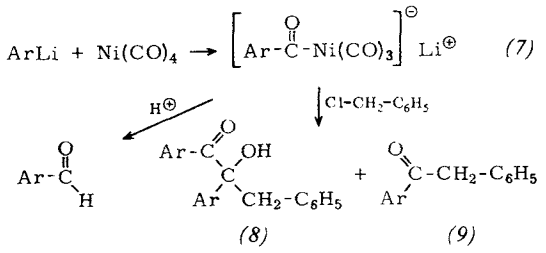
[4] Apart from Si- and Ge-acylation, the present article will be concerned only with C-acylation.

[5] *J. P. Candlin, K. A. Taylor*, and *D. T. Thompson*: Reactions of Transition-Metal Complexes. Elsevier, Amsterdam 1968, pp. 119 to 134; *J. Tsuji*, Accounts chem. Res. *2*, 144 (1969); cf. *T. Yukawa* and *S. Tsutsumi*, J. org. Chemistry *34*, 738 (1969).

[6] *H. C. Brown*, Accounts chem. Res. *2*, 65 (1969).

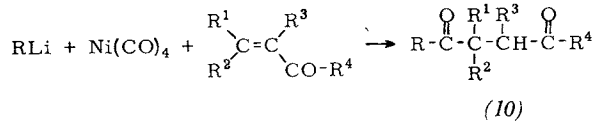
[7] a) *M. Ryang, S. Kwang-Myeong, Y. Sawa*, and *S. Tsutsumi*, J. organometallic Chem. *5*, 305 (1966); *Y. Sawa, I. Hishimoto, M. Ryang*, and *S. Tsutsumi*, J. org. Chemistry *33*, 2159 (1968) and other literature cited therein; b) *E. J. Corey* and *L. S. Hegedus*, J. Amer. chem. Soc., in press; c) *91*, 1233 (1969).

[8] a) Cf. Reaction of phenyllithium with hexacarbonyltungsen to give lithium benzoylpentacarbonyltungstate(0), *E. O. Fischer* and *A. Maasböl*, Angew. Chem. *76*, 645 (1964); Angew. Chem. internat. Edit. *3*, 580 (1964); Chem. Ber. *100*, 2445 (1967); b) *M. Schlosser*, Angew. Chem. *76*, 124 (1964); Angew. Chem. internat. Edit. *3*, 287 (1964) and literature cited therein; c) cf. also, Hg-derivatives: *D. Seyferth* and *R. J. Spohn*, J. Amer. chem. Soc. *91*, 3037 (1969).

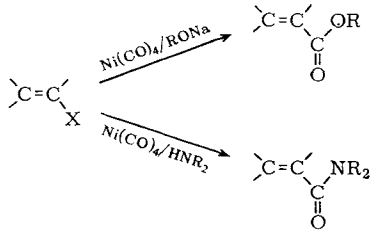


which give aldehydes on treatment with acid and react with benzyl chloride to form the α-hydroxy ketone *(8)* together with a little ketone *(9)*. The ketone *(9)* is the aroylation product of benzyl chloride, and the hydroxy ketone is probably the product of the nucleophilic acylation of the ketone *(9)*.

A useful application of reagents of this type was found by *Corey* and *Hegedus* [7b]. The reagents analogous to *(7)* that are formed in the reaction of methyl-, *n*-butyl-, or phenyllithium with tetracarbonylnickel add on in high yields to α,β-unsaturated carbonyl compounds in the 1,4-position, *i.e.* after the manner of a Michael addition; after hydrolysis, the 1,4-dioxo compounds *(10)* are isolated.

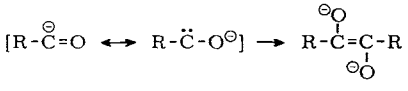


The alkoxycarbonylations and carbamoylations of vinyl halides with tetracarbonylnickel and alkoxides and amines [7c] are undoubtedly also mechanistically related.

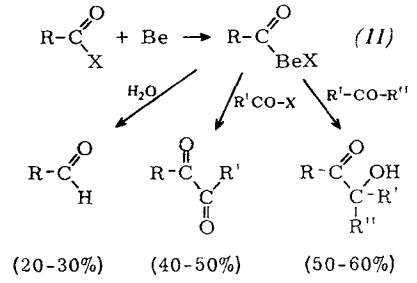


A benzoyl anion intermediate can possibly also be postulated in the reaction of phenyllithium, phenylsodium, or phenylmagnesium bromide with carbon monoxide [8b] to explain the formation of the products (benzhydryl phenyl ketone, benzoin, benzophenone, triphenylmethanol). The formation of benzoin leads to the conclusion that organometallic acylalkali metal compounds, the anions of which are carbenes in one of their limiting resonance structures, can dimerize to give dialkali metal salts of enediols, which are known from the acyloin reaction.

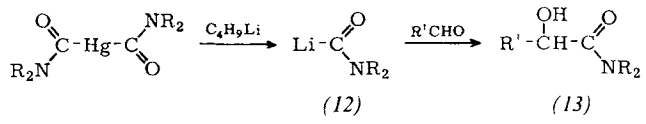
The problem of secondary reactions *e.g.* *(7)*→*(9)*→*(8)* can also arise in all *direct* nucleophilic acylations, since the *free* carbonyl derivatives formed in the reaction with electrophiles are themselves electrophiles.



Three years ago, *Lapkin et al.* [9] described the reaction of acyl chlorides, bromides and iodides with beryllium, which, like the formation of Grignard reagents, is exothermic. The resulting ether soluble beryllium derivatives are formulated as *(11)*, and exhibit the expected reactions of acyl anions. Thus hydrolysis leads to aldehydes, acylation to 1,2-diketones, and reaction with ketones to α-hydroxy ketones in the yields indicated. So far as we know, the range of application of these new reagents has not yet been investigated [10].

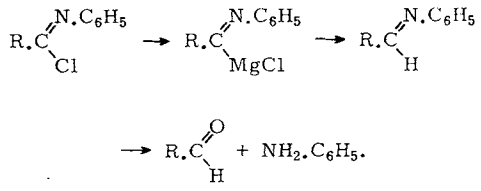


Schöllkopf and *Gerhart* [11] found only recently that treatment of bis(carbamoyl)mercury compounds with two moles of butyllithium yields products *(12)* that can effect nucleophilic carbamoylation; with aldehydes, for example, they form α-hydroxy amides *(13)*.



(11) and *(12)* are the simplest direct nucleophilic acylating agents known at present.

While seeking an aldehyde synthesis more than 60 years ago, *Staudinger* pointed out the possible synthetic value of acylmetal compounds [12]: "If acyl chlorides (bromides) could be converted into the corresponding *Grignard* compounds, this would provide a general method for the reduction of the COOH to the COH group, since the *Grignard* compounds should give aldehydes on cleavage with water:



This process cannot be achieved with acyl chlorides, but a similar reaction takes place with the *imidoyl*

[9] *I. I. Lapkin, G. Y. Anvarova,* and *T. N. Povarnitsyna,* Ž. obšč. Chim. *36*, 1952 (1966); J. gen. Chem. (USSR) (English transl.) *36*, 1945 (1966).

[10] The ease with which *(11)* can be prepared is evidently very strongly dependent on the purity of the metal used (cf. many Grignard reactions). We could not reach these yields with 98.5% beryllium powder; the reaction started only with difficulty.

[11] *U. Schöllkopf* and *F. Gerhart,* Angew. Chem. *79*, 819, 990 (1967); Angew. Chem. internat. Edit. *6*, 805, 970 (1967).

[12] *H. Staudinger,* Ber. dtsch. chem. Ges. *41*, 2217 (1908).

chlorides, since the *chlorine atom* in this case reacts with magnesium [13].

In this little-cited [14] article, *Staudinger* reported that *e.g. N*-phenylbenzimidoyl chloride reacts exothermally with magnesium in ether [15], and that benzylideneanilide can be isolated after hydrolysis; the latter can be readily converted into benzaldehyde. The Grignard compound of the imidoyl chloride would be a carbonyl analog of *(11)* and *(12)* [15].

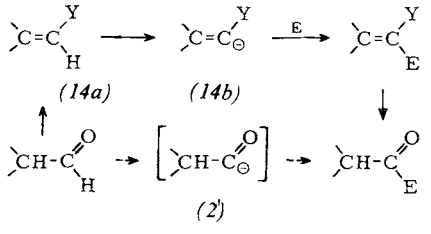
3. Possibilities of Indirect Nucleophilic Acylation

Carbanions (or more precisely organometallic compounds) of such a type that their products can be converted into carbonyl compounds by *hydrolysis*, will be referred to in this discussion as "masked" nucleophilic acylating agents. This requires removal of the hydrogen atom from the carbonyl carbon of an aldehyde, *i.e.* conversion of the aldehyde into its conjugate base.

This should be possible by two general methods.

3.1. Metalated Enol Derivatives

The aldehyde is converted into an enol derivative *(14a)*, which can be metalated to form *(14b)*. *(14b)* is a masked acyl anion, since reaction with an electrophile followed by hydrolysis converts it into a ketone, in which the hydrogen of the aldehyde is electrophilically substituted (dotted arrows). This method is

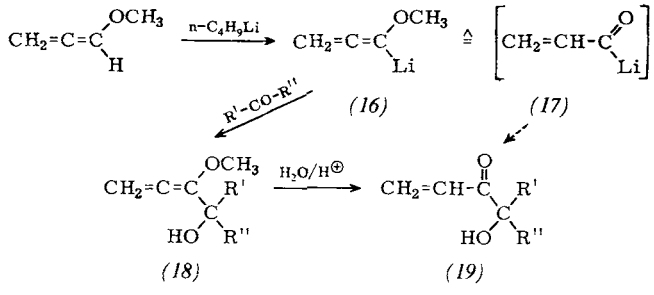


E = electrophile

of limited applicability, since the aldehyde must have at least *one* α-hydrogen atom; for example, nucleophilic benzoylation is not possible by this method because aryl aldehydes cannot be used. The metalation of *(14a)* is favored by anion-stabilizing groups Y. Oxygen rather destabilizes (see below) an α-carbanion, and only one derivative of an α-alkoxy carbanion has been preparatively obtained so far (CH_3-O-CH_2-Li [16]). Though sp^2-bound hydrogen is more acidic than sp^3-bound, enol ethers *(14a)*, Y = OR, can be metalated as indicated above only under very forcing conditions (amylsodium [17a], *tert*-butyllithium / *N,N,N′,N′*-tetramethylethylenediamine [17b]). Furan like thiophene (see below), is doubly metalated by amylsodium [to give *(15a)*] [18a]; *(15a)* is the masked succinyl dianion *(15b)*.

(15a) *(15b)*

The ease of metalation of alkyl allenyl ethers [18b] (readily obtainable from propargyl ethers) is particularly interesting; the lithium derivative *(16)* is obtained under "standard conditions" (ether/tetrahydrofuran, −20 °C).



Deuterolysis, alkylation, hydroxyalkylation, and thiolation lead to the expected products. The product *(18)* obtained by addition to a carbonyl compound is hydrolyzed to the hydroxy ketone *(19)* under very mild conditions (0 to 5 °C, 1 hour); the structure of *(19)* shows that *(16)* is a masked acyllithium derivative of acrolein [*(17)*] (see dotted arrow). *(16)* is the best of the known preparatively usable acylating agents, in that the "demasking" of the products [*e.g.* *(18)*→*(19)*] takes place under the mildest conditions. Replacement of the oxygen in enol ethers by sulfur [*(14a)*, *(14b)*, Y = SR] should lead to considerable stabilization of the vinyl anion.

There is no longer any doubt about the stabilizing effect of sulfur, even in the dicoordinate state, on adjacent anionic centers. On metalation of anisole and thioanisole with butyllithium, *Gilman* and *Webb* [19a] found that anisole exchanges an sp^2-bound ring proton α to the oxygen [→*(20)*], whereas thioanisole exchanges an sp^3-bound proton on the methyl group [→*(21)*].

[13] a) Recent attempts to prepare "acyl Grignard compounds" have also been unsuccessful (*A. Eschenmoser*, personal communication); b) reaction of benzoyl chloride with naphthalene-sodium followed by hydrolysis yields benzoin, the formation of which was explained as involving the intermediate formation of benzoylsodium [*W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *463*, 19 (1928)]; the reaction could, however, also proceed by a free-radical mechanism (see ketyls and the acyloin reaction).

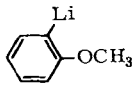
[14] *F. Runge*: Organometallverbindungen. Wissenschaftliche Verlagsgesellschaft, Stuttgart 1944, p. 490.

[15] No Mg-derivative of the imidoyl chloride is formed under the conditions used by *Staudinger* (ether/ethylacetate): on hydrolysis of the reaction product with D_2O we obtained exclusively non-deuterated (according to the ^{1}H-NMR spectrum) benzaldehyde (yield as given in [12]). On varying the reaction conditions (ether, THF; 20–65 °C) we could not detect more than 2% (theoretical) of aldehyde according to the given procedure in the absence of ethyl acetate.

[16] *U. Schöllkopf* and *H. Küppers*, Tetrahedron Letters *1964*, 1503.

[17] a) *R. Paul* and *S. Tchelitcheff*, C.R. hebd. Séances Acad. Sci. *235*, 1226 (1952); Bull. Soc. chim. France, Documentation *19*, 808 (1952); b) *U. Schöllkopf*, private communication, April 24, 1969.

[18] a) *A. A. Morton* and *C. E. Calff*, J. Amer. chem. Soc. *76*, 4935 (1954); b) *S. Hoff*, *L. Brandsma*, and *J. F. Arens*, Recueil Trav. chim. Pays-Bas *87*, 916, 1179 (1968).



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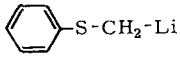

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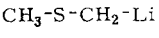
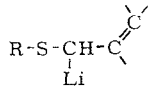


(22)

Amine-activated[21] *n*-butyllithium is necessary for the quantitative production of *(21)*[19b,c] and *(22)*[20] from the corresponding CH compounds, while the derivatives *(23)* of allyl thioethers[22,23], *(24)* of vinyl thioethers[22], *(25)* of thioacetals[19b,24], and *(26)* of orthotrithioformic esters[24–27] can be prepared with butyllithium in tetrahydrofuran. Since *(26)* is formed from tris(phenylthio)methane with trityllithium[26a], the pK_A value of this sulfur compound must be at least two orders of magnitude lower than that of triphenylmethane (pK_A value 28–32, depending on the scale[28]).



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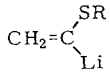

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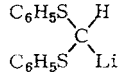

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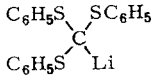

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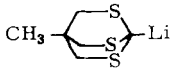

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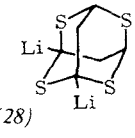
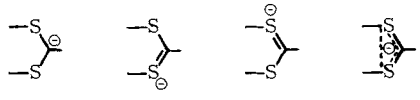


(28)

It is generally assumed that the stabilization of these anions results from overlap of the "anion orbital" with d shells of the sulfur[28–38]. This picture of d-orbital overlap is possibly too primitive[39], but it is certainly very useful. The looseness of the stereoelectronic requirements for stabilization can be seen from a comparison of the Li derivatives *(21)*–*(28)*. The central C atom in the anions of *(21)*–*(23)*, *(25)*, and *(26)* may be sp^2-hybridized, and p-d overlap then occurs, in *(24)* the $C^{\ominus}$ atom could be sp-hybridized (p-d overlap) or sp^2-hybridized (sp^2-d overlap) while in the anions of *(27)*[26a] and *(28)*[30c,41] the anionic C atom cannot be forced into coplanarity with the neighboring sulfur atoms. so that sp^3-d overlap should occur [cf. the trisulfone derived from *(27)*[42]]; the stabilization of α-sulfonyl carbanions may occur without the participation of d shells[43]. In the undissociated Li compounds *(21)*–*(28)* with the exception of *(24)*, stabilization is possible only by sp^3-d overlap[30c]. The metal atom and the medium used are of decisive importance in stability considerations.

To explain the results of D/H and T/H exchange experiments with thioacetals[33a] and orthotrithioformic esters[33] (see also Table 1), it was assumed[33a] that not only the identical limiting structures *(b)* and *(c)* (which are also decisive for monothiocarbanions), but also delocalization by "1,3-overlap" of the d orbitals of two or three sulfur atoms is involved as indicated in *(d)* for a dithiocarbanion. Dicoordinate selenium, the d shells of which have a higher energy level and should be more diffuse[38] than those of sulfur, also stabilizes carbanions[26d].



(a) (b) (c) (d)

Similar conclusions were drawn from the UV spectra[30c,33a,34,44,45] of thioacetals, where zwitterionic[44] or biradical[33a] excited states with delocalization (d) are assumed. Acceptor properties have also been ascribed to sulfur in the stabilization

[19] a) *H. Gilman* and *F. J. Webb*, J. Amer. chem. Soc. *62*, 987 (1940); *71*, 4062 (1949); b) *E. J. Corey* and *D. Seebach*, J. org. Chemistry *31*, 4097 (1966); c) see however: *D. A. Shirley* and *B. J. Reeves*, J. organometallic Chem. *16*, 1 (1969).

[20] *D. J. Peterson*, J. org. Chemistry *32*, 1717 (1967).

[21] *G. G. Eberhardt*, Organometallic Chem. Rev. *1*, 491 (1966); *G. G. Eberhardt* and *W. A. Butte*, J. org. Chemistry *29*, 2928 (1964).

[22] *E. J. Corey* and *B. W. Erickson*, unpublished results, 1967.

[23] *J. F. Biellmann* and *J. B. Ducep*, Tetrahedron Letters *1968*, 5629; *J. F. Biellmann*, private communication (May 16, 1969).

[24] *J. F. Arens*, *M. Fröling*, and *A. Fröling*, Recueil. Trav. chim. Pays-Bas *78*, 663 (1959); *A. Fröling* and *J. F. Arens*, *ibid. 81*, 1009 (1962).

[25] *J. Hine*, *R. P. Bayer*, and *G. G. Hammer*, J. Amer. chem. Soc. *84*, 1751 (1962).

[26] a) *D. Seebach*, Angew. Chem. *79*, 468 (1967); Angew. Chem. internat. Edit. *6*, 442 (1967); b) *D. Seebach*, Angew. Chem. *79*, 469 (1967); Angew. Chem. internat. Edit. *6*, 443 (1967); c) *D. Seebach* and *A. K. Beck*, J. Amer. chem. Soc. *91*, 1540 (1969); d) *D. Seebach* and *N. Peleties*, Angew. Chem. *81*, 465 (1969); Angew. Chem. internat. Edit. *8*, 450 (1969).

[27] *G. A. Wildschut*, *H. J. T. Bos*, *L. Brandsma*, and *J. F. Arens*, Mh. Chem. *98*, 1043 (1967).

[28] *D. J. Cram*: Fundamentals of Carbanion Chemistry. Academic Press, New York 1965.

[29] *D. S. Tarbell* and *M. A. MacCall*, J. Amer. chem. Soc. *74*, 48 (1952).

[30] a) *G. Cilento*, Chem. Reviews *60*, 147 (1960); b) *W. G. Salmond*, Quart. Rev. *22*, 253 (1968); c) *D. L. Coffen*, Rec. chem. Progr., in press.

[31] *A. B. Burg* in *N. Kharash*: Organic Sulfur Compounds. Pergamon Press, Oxford 1961, Vol. 1, p. 30.

[32] *C. C. Price* and *S. Oae*: Sulfur Bonding. Ronald Press, London 1962; see also *C. C. Price*, Chem. Engng. News *42*, No. 48, p. 58 (1964).

[33] a) *S. Oae*, *W. Tagaki*, and *A. Ohno*, Tetrahedron *20*, 417 (1964); b) *L. R. Slaugh* and *E. Bergmann*, J. org. Chemistry *26*, 3158 (1961); c) *R. Breslow* and *E. Mohacsi*, J. Amer. chem. Soc. *85*, 431 (1963).

[34] *H. H. Jaffé* and *M. Orchin*: Theory and Application of UV-Spectroscopy. Wiley, New York 1965, p. 466–507.

[35] *A. W. Johnson*: Ylid Chemistry. Academic Press, New York 1966.

[36] *H. A. Bent* in *N. Kharash*: Organic Sulfur Compounds. Pergamon Press, Oxford 1966, Vol. 2, p. 1.

[37] *R. Gleiter* and *R. Hoffmann*, Tetrahedron *24*, 5899 (1968), and private communication from *R. Hoffmann*.

[38] *D. P. Craig*, *A. Maccoll*, *R. S. Nyholm*, *L. E. Orgel*, and *L. E. Sutton*, J. chem. Soc. (London) *1954*, 332; *D. P. Craig* and *E. A. Magnusson*, *ibid. 1956*, 4895; *D. P. Craig*, Chem. Soc. (London), Special Publication No. 12, 343 (1958); *D. W. Cruickshank*, *B. C. Webster*, and *D. F. Mayers*, J. chem. Physics *40*, 3733 (1964).

[39] See the novel bonding models for hypervalent molecules [*J. I. Musher*, Angew. Chem. *81*, 68 (1969); Angew. Chem. internat. Edit. *8*, 54 (1969)] which no longer involve d shells; for more recent articles on hypervalent sulfur compounds, see *M. P. Cava* and *N. M. Pollack*, J. Amer. chem. Soc. *89*, 3639 (1967); *M. P. Cava*, *N. M. Pollack*, and *D. A. Repella*, *ibid. 89*, 3640 (1967); *R. H. Schlessinger* and *I. S. Ponticello*, *ibid. 89*, 3641 (1967); *M. Polk*, *M. Siskin*, and *C. C. Price*, *ibid. 91*, 1206 (1969); *B. M. Trost*, *R. LaRochelle*, and *R. C. Atkins*, *ibid. 91*, 2175 (1969); *M. P. Cava* and *G. E. M. Husbands*, J. Amer. chem. Soc. *91*, 3952 (1969); *J. M. Hoffman* and *R. H. Schlessinger*, *ibid. 91*, 3953 (1969); the stabilization of anions by sulfur is also "plausible" according to the concept of "soft and hard acids and bases" [40] (SHAB).

[40] *R. G. Pearson*, Science (Washington) *151*, 172 (1966); see also *B. Saville*, Angew. Chem. *79*, 966 (1967); Angew. Chem. internat. Edit. *6*, 928 (1967) and literature cited therein; *R. G. Pearson*, Chem. Engng. News *43*, No. 22, p. 90 (1965).

[41] *K. C. Bank* and *D. L. Coffen*, Chem. Commun. *1969*, 8.

[42] *W. v. E. Doering* and *L. K. Levi*, J. Amer. chem. Soc. *83*, 4100 (1961).

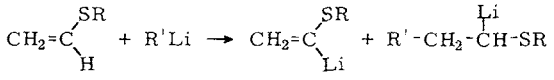
[43] *S. Wolfe*, *A. Rauk*, and *I. G. Csizmadia*, J. Amer. chem. Soc. *91*, 1567 (1969).

[44] *E. A. Fehnel* and *M. Carmack*, J. Amer. chem. Soc. *71*, 84 (1949).

[45] *E. E. Campaigne* and *G. F. Schaefer*, Bol. col. quim. Puerto Rico *9*, 25 (1952).

of sextet species (carbene[26b,26c], nitrene[37]). The mathematical description[30c,37,38,43] of the d orbitals, which are normally unoccupied ("absent"), is therefore difficult, since neither their extent nor their energy is adequately known, and these two quantities are of decisive importance to the result of calculations using the Hückel approximation.

According to this explanation, therefore, anions of the type *(14b)*, Y = SR, *e.g.* as Li derivatives *(24)*, should be much better reagents for nucleophilic acylations than the metalated enol ethers. A careful investigation of *(14)*, Y = SC_6H_5, SC_2H_5, and S-*tert*-C_4H_9, with R'Li = *n*-butyl-, *tert*-butyl- and phenyllithium as metalating agents showed that under optimum conditions only about 80% of the desired H/Li exchange to give *(24)* can be achieved[22]; the competing addition of the Li compounds to form *(29)*[22,46] could not be entirely suppressed. Difficulties of this nature appear to be reduced by the use of butyllithium "activated"

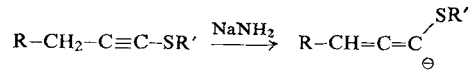


(14a), Y = SR *(24)* *(29)*

with *N,N,N',N'*-tetramethylethylenediamine or triethylenediamine (the basicity of the butyllithium in these complexes is increased at the expense of its nucleophilicity)[47]. The nucleophilicity of the vinyllithium *(24)*, R = C_6H_5, was found to be good; this compound reacts with D_2O, CO_2, CH_3I, aldehydes, and ketones to give the expected products in good yields[22,23]. Thiophene can be metalated to give a disodium compound of the type *(24)*[8b,18a] (see above in connection with furan). The acid hydrolysis[47b–47d] of thioenol ethers (see also Section 3.2.1) to carbonyl compounds proceeds particularly smoothly in the presence of $HgCl_2$[47a,62a].

Anions *(30)* of allenyl thioethers are obtained from alkynyl thioethers and sodamide in liquid ammonia[48,49], *i.e.* under conditions such that even the simple metal derivatives of thioenol ethers should be obtainable, since the nucleophilicity of NH_2 is much less than that of the lithium derivatives used, and the side reaction of addition should be suppressed.

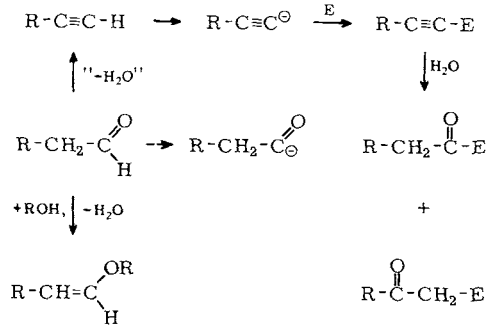
It should in principle also be worth considering the use of compounds containing halogens, such as $CH_2{=}CClLi$[50a]. However, the low stability of such carbenoids and the great resistance of the products to



(30)

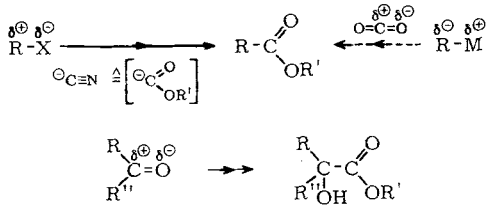
hydrolysis [cf. Cl_3CH with $(CH_3O)_3CH$, $R{-}CCl_2R'$ with $R{-}C(OCH_3)_2{-}R'$, or $CH_2{=}CRCl$ with $CH_2{=}CR(OR)$] have so far prevented their use as nucleophilic acylating agents.

The enol ether-like group of masked acylmetals also includes acetylides. The products of their reaction with electrophiles give carbonyl compounds on *hydrolysis* (addition of water catalyzed by Hg(II) salts). However, the direction of the addition of water cannot usually be controlled[51a]. The reaction yields two isomeric carbonyl compounds, only one of which may be regarded as an acylated electrophile (scheme 4).



Scheme 4. E = electrophile

A well known indirect nucleophilic carboxylating agent, the counterpart of carbon dioxide (dotted arrow in Scheme 5) is the cyanide ion[51b], with the aid of which an ROOC group can be introduced into an



Scheme 5.

electrophilic center. The relatively drastic conditions of the complete acidic or alkaline hydrolysis to the acid stage may be a disadvantage in the synthesis of sensitive compounds (cf. Section 3.2.2).

3.2. Metal Derivatives of Acetals and Related Compounds

3.2.1. Principle and Possible Reagents

In addition to enol derivatives *(14a)*, acetal-like derivatives *(31)* of aldehydes should also be suitable for the production of masked acyl anions *(32)*. The descrip-

[46] *W. E. Parham* and *R. F. Motter*, J. Amer. chem. Soc. *81*, 2146 (1959); *W. E. Parham, M. A. Kalnins*, and *D. R. Theissen*, J. org. Chemistry *27*, 2698 (1962).

[47] a) *J. H. S. Weiland* and *J. F. Arens*, Recueil. Trav. chim. Pays-Bas *79*, 1293 (1960); b) *M. Green*, J. chem. Soc. (London) *1963*, 1324; c) *B. S. Kupin* and *A. A. Petrov*, Ž. org. Chim. *3*, 975 (1967); Chem. Abstr. *67*, 99786 (1967); d) *T. Mukaiyama, S. Fukuyama*, and *T. Kumamoto*, Tetrahedron Letters *1968*, 3787.

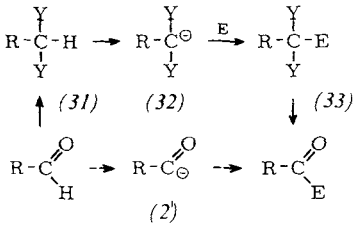
[48] *J. F. Arens et al.*, Recueil Trav. chim. Pays-Bas *80*, 244 (1961); *82*, 1040 (1963); *85*, 580 (1966); *87*, 97 (1968).

[49] *L. Brandsma, C. Jonker*, and *M. H. Berg*, Recueil Trav. chim. Pays-Bas *84*, 560 (1965).

[50] a) *G. Köbrich*, Angew. Chem. *79*, 15 (1967); Angew. Chem. internat. Edit. *6*, 41 (1967) and literature cited therein; b) *P. Blumbergs* and *M. P. LaMontagne*, 157th ACS-Meeting *1969*, ORGN No. 40; c) *G. Köbrich* and *W. Werner*, Tetrahedron Letters *1969*, 2181.

[51] a) *E. g. G. Stork* and *R. Borch*, J. Amer. chem. Soc. *86*, 935 (1964); b) see also the new, extremely reactive aluminum cyanide reagents, *W. Nagata, M. Yoshioka, S. Hari*, and *T. Okumura*, Tetrahedron Letters *1962*, 461; *1966*, 847, 1913

tion "acetal-like" is applied here to derivatives *(31)* and *(33)* that can be converted into the free carbonyl compounds by hydrolysis. Like the vinyl anions *(14b)*,



E = electrophile

anions *(32)* (*i.e.* conjugate bases of aldehydes) should be able to act as acylating agents. They appear less suitable at first sight, since *(32)* is a trisubstituted carbanion, the nucleophilicity of which may be low because of steric hindrance, but whose basicity may be high for the same reason. R could also be a group linked *via* a trisubstituted C atom or an aromatic ring in this case. The restriction on the use of metalated enol ether derivatives (Section 3.1), *i.e.* that the aldehyde must have at least one α-hydrogen atom, is not valid here.

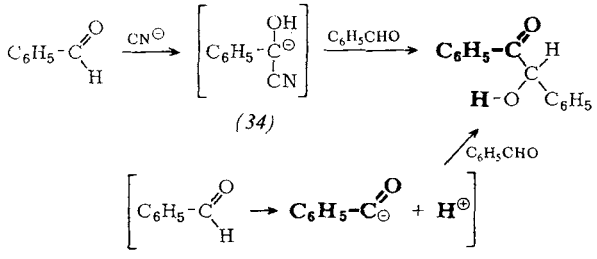
The conversion of an aldehyde *via (31)*, *(32)*, and *(33)* into a ketone (dotted arrows) would, according to the definition in Section 1, be a "reversible symmetrization" of the mode of reaction of the carbonyl group. The electrophilic carbonyl C atom of the aldehyde has become nucleophilic in *(32)*, and after reaction with an electrophile, the electrophilic carbonyl C atom can be restored by hydrolysis of the product *(33)*.

We impose the following requirement for a generally applicable masked nucleophilic acylating agent of the type *(32)*. The groups Y must be such that

1. *(31)* is preparatively readily obtainable.
2. the conversion into the anion *(32)* proceeds easily and quantitatively,
3. the anion is not so stable that it no longer exhibits high reactivity,
4. the carbanionic center is subject to a minimum of hindrance,
5. no carbenoid decomposition [*(32)* → R–C̈–Y + Y⊖] or other rearrangements occur, and
6. the hydrolysis of the reaction products *(33)* can be carried out under the mildest possible, and also the most specific possible conditions.

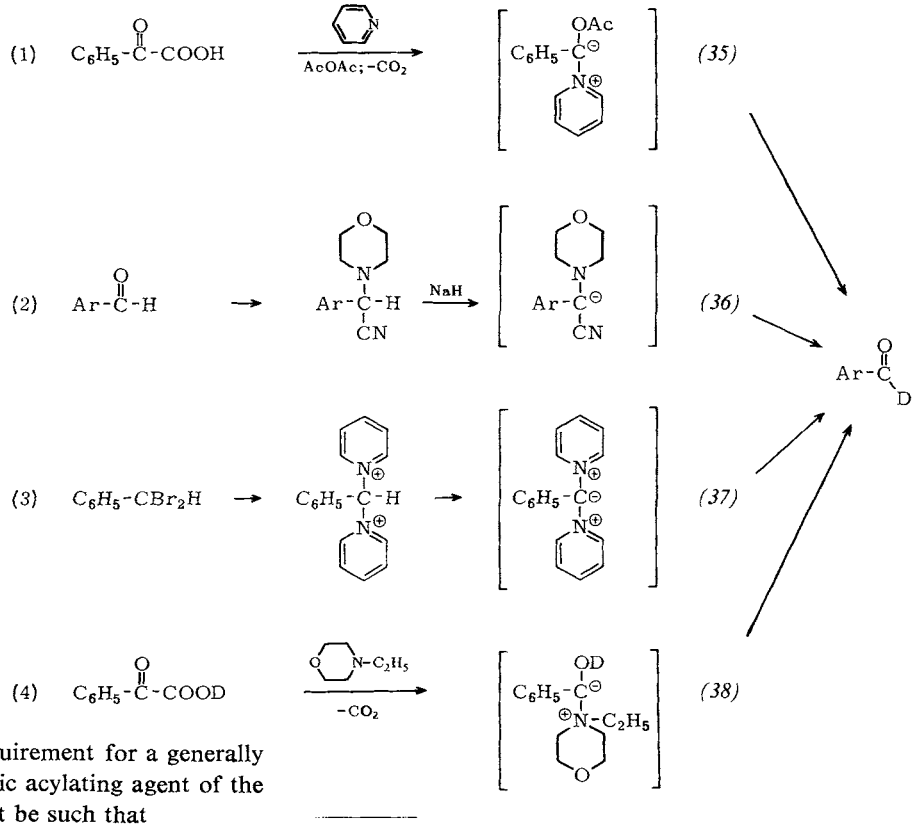
With so many conditions to be satisfied, compromises seem inevitable.

The oldest known reaction involving "masked" acyl anions of the type *(32)* is the preparation of benzoins from aromatic aldehydes [52], as illustrated in Scheme 6



Scheme 6.

for benzaldehyde. The decisive intermediate in this reaction is assumed to be an anion *(34)*, which adds onto an aldehyde molecule. The final product is formally the result of addition of a benzoyl anion and a

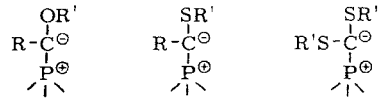


[52] *M. S. Ide* and *J. S. Buck*, Org. Reactions *4*, 269 (1948); cf. also *S. M. McElvain*, *ibid. 4*, 256 (1948).

proton to benzaldehyde; *(34)* is mechanistically equivalent to an acyl anion. The reaction is applicable only to aldehydes having no α-hydrogen atoms (otherwise the aldol reaction competes); attempts to prepare mixed acyloins must be expected to yield mixtures of products. Quantitative production of anions such as *(34)* is not possible.

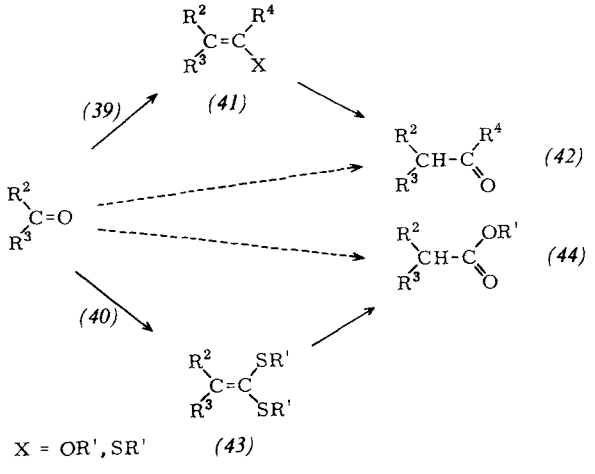
Several methods for the preparation of deuterated aromatic aldehydes have been published in recent years. Intermediates *(35)–(38)* resembling *(34)* were postulated or prepared in every case [eqs. (1)–(4)]. To prove occurrence of these intermediates, they were allowed to react with D_2O, or deuterated starting materials were used; deuterated aldehydes were formed [53–56]. The compounds *(35)–(38)* cannot be used as generally applicable reagents for the introduction of acyl groups, since they are not formed in high concentrations and/or they exhibit strong steric hindrance [for example, *(37)* is of the triarylmethyl type], *i.e.* they do not satisfy the above conditions; even the acylation of $D^{\oplus}$ has so far been preparatively developed for several examples only by the reaction described in eq. (2) [54].

Alkoxy-(alkylthio-) *(39)* and dialkylthiomethylene phosphoranes *(40)* are also nucleophilic acylating or carboxylating



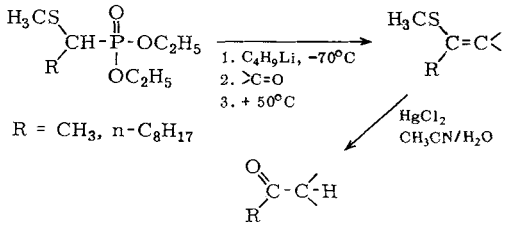
(39a) *(39b)* *(40)*

reagents in a certain sense. Reaction with carbonyl compounds leads in the one case to enol ethers (thioenol ethers), *(41)* [47d,57–59], and in the other case, which has so far been observed only with the sulfur derivatives *(40)*, to ketene thioacetals *(43)* [26b,60–62]. The hydrolysis [47,62a,84] yields the carbonyl compounds *(42)* and *(44)*. In the final effect (dotted arrows), the only respect in which these reactions differ from the nucleophilic acylations is in the absence of the α-hydroxyl group in the final product; the oxygen atom is removed with the phosphorus in the olefination step.

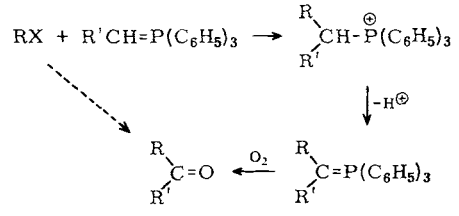


X = OR', SR' *(43)*

A more recent application of this principle, using phosphonates [62a] is shown in the following Scheme.

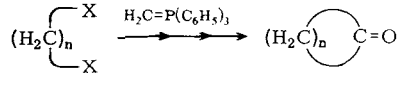


If one considers only the overall reaction in Scheme 7 (dotted arrow), the reaction sequence shown here is also a nucleophilic acylation [35].

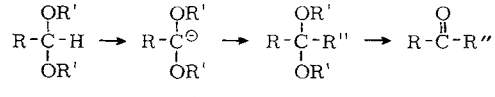


Scheme 7.

However, the final product, *i.e.* the free carbonyl compound, is formed by an oxidative process in this case. Cyclanones can be prepared in good yields by this method [63] (cf. below, dithiane method [82,84]).



Since the acetal grouping is readily hydrolyzed, an anion *(45)* would be a welcome masked acylating agent, the products of which would also satisfy the condition that the free carbonyl group should be easily obtainable under mild and specific conditions by hydrolysis. It is well known that acetals are stable in alkaline solution, but can be readily hydrolyzed with acids. As was mentioned in connection with the



(45)

[53] *T. Cohen* and *I. H. Song*, J. Amer. chem. Soc. *87*, 3780 (1965).

[54] *D. J. Bennett*, *G. W. Kirby*, and *V. A. Moss*, Chem. Commun. *1967*, 218.

[55] *R. A. Olofson* and *D. M. Zimmerman*, J. Amer. chem. Soc. *89*, 5057 (1967).

[56] *J. C. Craig* and *L. R. Kray*, J. org. Chemistry *33*, 871 (1968).

[57] *S. G. Levine*, J. Amer. chem. Soc. *80*, 6150 (1958); *G. Wittig* and *E. Knauss*, Angew. Chem. *71*, 127 (1959).

[58] For a summary see [35].

[59] See also halogeno- and dihalogenomethylene phosphoranes, *e.g. A. J. Speziale*, *K. W. Ratts*, and *D. E. Bissing*, Org. Syntheses *45*, 33 (1965), and [35].

[60] The reaction proceeds only with aldehydes. Triphenylphosphorane: *D. M. Lemal* and *E. H. Bannit*, Tetrahedron Letters *1964*, 245. Trimethoxyphosphorane [61]: *E. J. Corey* and *G. Märkl*, *ibid.* 1967, 3201.

[61] The ylid $(CH_3O)_3P=C(SC_6H_5)_2$ is obtained from $(C_6H_5S)_3SLi$ [26] and trimethyl phosphite, and derivatives *(43)*, $R^3 = H$, $R' = C_6H_5$, can be prepared in this way [62b].

[62] a) *E. J. Corey* and *J. I. Shulman*, unpublished results, 1969; b) *D. Seebach* and *H.-D. Herrmann*, unpublished results.

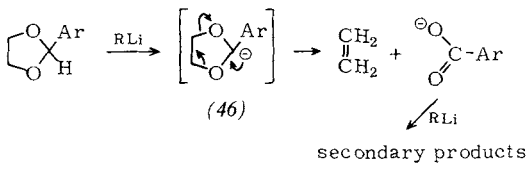
[63] *A. Monden*, Liebigs Ann. Chem. *603*, 115 (1957); *H. J. Bestmann* and *H. Häberlein*, Z. Naturforsch. *17b*, 787 (1962); *P. T. Keough* and *M. Grayson*, J. org. Chemistry *29*, 631 (1964); *K. V. Scherer* and *R. S. Lunt*, *ibid. 30*, 3215 (1965); *H. J. Bestmann* and *E. Kranz*, Chem. Ber. *102*, 1802 (1969).

metalated enol ether derivatives, however, α-alkoxy and α-aryloxy carbanions are not generally obtainable; the ether oxygen does not stabilize negative charges, whereas it is an excellent stabilizer for carbonium ions. Aryloxy carbanions can undergo Wittig rearrangement [64]. The only simple alkoxy carbanion derivative

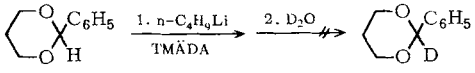
that can be obtained preparatively is methoxymethyllithium, which was mentioned earlier [16]. No dialkoxy carbanions of the type *(45)* have been obtained as yet.

As is known from H-isotope exchange experiments [33] (see also Table 1) and from conductivity measurements [24], the kinetic and thermodynamic acidity [28] of aldehyde acetals is so low that it cannot be measured directly; it has been shown by indirect methods that the kinetic acidity of an α-alkoxy proton (>CH–OR) is about six orders of magnitude lower than that of an α-alkylthio proton (>CH–SR) [33]. This tells us nothing about the thermodynamic stability of corresponding carbanions. Attempts to metalate dialkoxyacetals with strong bases have either been unsuccessful or led to cleavage of the compound used. Thus when organolithium compounds and 2-aryldioxolanes are brought together at room temperature in ether, an exothermic reaction occurs; the products indicate that this reaction proceeds *via* an anion *(46)*. As indicated in eq. (5),

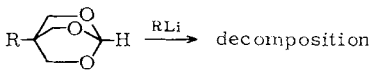
(5)



(6)

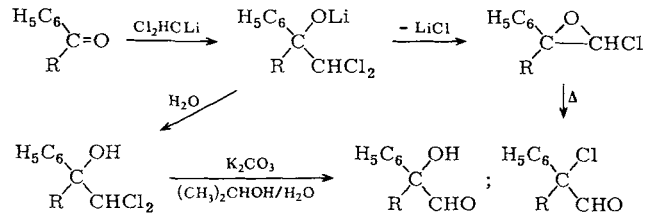


(7)



this decomposes into ethylene and arenecarboxylate [65] (cf. the olefin synthesis described by *Corey* and *Winter* [66]). Even in experiments with 2-phenyl-1,3-dioxane [eq. (6)], the anion of which cannot "fragment" in this way, with the very effective metalating agent *n*-butyllithium/*N,N,N',N'*-tetramethylethylenediamine [21], in tetrahydrofuran at −78 to +20 °C it was not possible to detect an anion, which should be stabilized, like *(46)*, as a benzyl-like carbanion by conjugation with the aromatic system [62b]. (Under the same conditions, toluene is metalated to give benzyllithium [21,67]; the kinetic acidification due to an α-phenyl group is about ten times as large as that due to an α-ethylthio group [33a].) The orthoformic acid derivative [eq. (7)] also failed to give a directly detectable anion, but decomposed with butyllithium in ether *via* carbenes or carbenoids [65a]. Thus, in none of these cases can the desired metalated acetals or ortho esters be produced under conditions such that they are still stable.

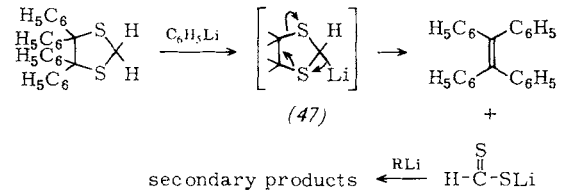
The use of chloro- and bromocarbenoids [50] ($R-CCl_2-Li$, $R-CBr_2-Li$) as masked acyllithium compounds is somewhat limited, the reasons being the same as in the case of vinyl halogenocarbenoids (see Section 3.1). Only recently has it been shown [50b,c] that arylketones can be converted into α-hydroxy- and α-chloroaldehydes by dichloromethyllithium, which is stable at temperatures below −90 °C:



In view of the observations described in Section 3.1 on the stabilization of carbanions by adjacent dicoordinate sulfur [see Li derivatives of the anions *(21)* to *(28)*,] it is not surprising that preparatively useful reagents of the type *(32)* have been found among the thioacetals [68]. [The methylene groups in corresponding "diphosphinoacetals", *e.g.* bis(diphenylphosphino)-methane $(C_6H_5)_2P-CH_2-P(C_6H_5)_2$, appear to be much more active than those in thioacetals [69,70]; nothing is known about the possibility of using metalated derivatives *(32)*, Y = PR_2, for nucleophilic acylation.]

Schönberg et al. [71] were probably the first to produce a dithiomethyllithium compound *(47)* when they treated tetraphenyl-1,3-dithiolane in ether with phenyllithium [eq. (8)]. They observed the olefin formation discovered much later for dioxolanes [eq. (5)].

(8)



[64] *G. Wittig*, Angew. Chem. *66*, 10 (1954); see also [28], pp. 230–233.

[65] a) *K. D. Berlin* and *B. S. Rathore*, Tetrahedron Letters *1964*, 2547; *K. D. Berlin, B. S. Rathore*, and *M. Peterson*, J. org. Chemistry *30*, 226 (1965); b) *P. S. Wharton, G. A. Hiegel*, and *S. Ramaswami, ibid. 29*, 2441 (1964).

[66] *E. J. Corey* and *R. A. E. Winter*, J. Amer. chem. Soc. *85*, 2677 (1963); *E. J. Corey, F. A. Carey*, and *R. A. E. Winter, ibid. 87*, 934 (1965); *E. J. Corey* and *J. I. Shulman*, Tetrahedron Letters *1968*, 3655.

[67] Cf. also [19b, 20] and *J. F. Eastham* and *G. W. Gibson*, J. Amer. chem. Soc. *85*, 2171 (1963); *C. G. Screttas* and *J. F. Eastham, ibid. 87*, 3276 (1965); *88*, 5668 (1966); *M. Schlosser*, J. organometallic Chem. *8*, 9 (1967).

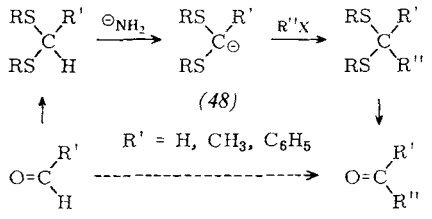
[68] *E. J. Corey* and *D. Seebach*, Angew. Chem. *77*, 1134, 1135 (1965); Angew. Chem. internat. Edit. *4*, 1035, 1037 (1965).

[69] *K. Issleib* and *S. Häusler*, Chem. Ber. *94*, 113 (1961).

[70] *D. J. Peterson*, J. organometallic. Chem. *8*, 199 (1967) and literature cited therein.

[71] *A. Schönberg, D. Černik*, and *W. Urban*, Chem. Ber. *64*, 2577 (1931).

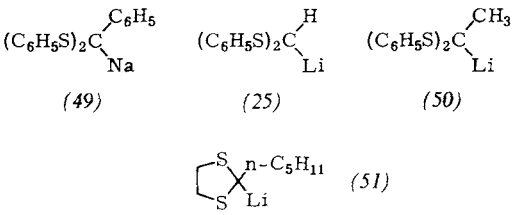
In 1959 and 1962, *Arens* and *Fröling*[24] described the preparation of solutions containing alkali metal derivatives of dithio carbanions *(48)*. Treatment of open-chain aldehyde thioacetals in liquid ammonia with alkali metal amides yields colored solutions, and ketone thioacetal can be obtained on addition of an alkali metal halide. The authors recognized the significance of the reaction sequence as a novel method for the preparation of higher aldehydes from formaldehyde (R′ = H) and of ketones from aldehydes (dotted arrow in Scheme 8). They also found, however, that this method is of limited application, and no further investigations were carried out. The limitations of the method were that (i) only thioacetals of formaldehyde, acetaldehyde, and benzaldehyde could be metalated in this way, (ii) to obtain good yields it was necessary



Scheme 8.

to use excess amide, and hence also excess halide, (iii) only the anion of formaldehyde bis(phenylthio)acetal *(48)*, R = C_6H_5, R′ = H, reacted (in moderate yields) with carbonyl compounds, (iv) very reactive electrophiles, such as acyl chlorides, cannot be used in the medium in question, and (v) the hydrolysis of thioacetals, *i.e.* the last step of the cycle, is generally believed to be difficult[72].

Truce and *Roberts*[73] who concluded from literature references[71,74] that phenyllithium and *n*-butyllithium cleave thiacetals, prepared the sodium derivative *(49)* of benzaldehyde bis(phenylthio)acetal in dimethylformamide with the aid of sodium hydride; *(49)* could

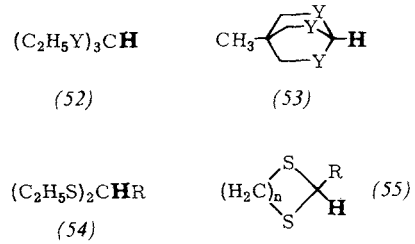


be alkylated and acylated. They obtained sulfur-free products by hydrolysis and desulfurization (Raney Ni or $NiCl_2/NaBH_4$). *Normant* and *Cuvigny*[75] obtained the Na derivative *(49)* with NaH in hexamethylphosphoric triamide (HMPT), whereas other thioacetals are cleaved by sodamide in this solvent. *n*-Butyllithium in tetrahydrofuran gives excellent results in the preparation of bis(phenylthio)methyllithium *(25)* from the CH_2 compound[19b]; however, this simple method fails in attempts to obtain *(50)* by metalation of the corresponding acetaldehyde derivative. Under these conditions, thioacetals having a dithiolane structure give the same results as were obtained by *Schönberg*, *i.e.* *(51)* decomposes[76] under the conditions of its formation (−20 °C) [cf. eqs. (5) and (8)].

3.2.2. Dithiane and Trithiane Method

Though the relative acidities (as was mentioned, kinetic acidities often give no reliable information on the thermodynamic stabilities of the metal derivatives or their anions) listed in Table 1 gave no reason to expect any very pronounced difference between open-chain and six-membered ring thioacetals [cf. *(54b)* with *(55e)*], *Corey* and *Seebach*[68,76] found that the 1,3-dithianes *(55)*, $n = 3$, occupy a special place.

Table 1. Relative rates of D/H or T/H exchange for acetals, thioacetals, orthoformic esters, and trithioorthoformic esters with K *tert*.-butoxide in *tert*.-butanol [33a]. **H** = D or T.



Compound	Y	*n*	R	Relative rate
(52a)	O			[a]
(52b)	S			1.5×10^4
(53a)	O			[a]
(53b)	S			1.8×10^7
(54a)			H	40
(54b)			C_2H_5	1
(55a)		2	H	515
(55b)		2	C_2H_5	20
(55c)		3	H	215
(55d)		3	CH_3	0.4
(55e)		3	C_2H_5	1.5
(55f)		3	$(CH_3)_2CH$	1.3
(55g)		3	$(CH_3)_3C$	1.2
(55h)		4	C_2H_5	5.4

[a] No exchange in 20 hours at 110—140 °C.

Under the conditions mentioned above (tetrahydrofuran, *n*-butyllithium, −20 °C, 1–5 hours), many dithianes *(56)* with a wide range of groups R can be quantitatively metalated to give the 1,3-dithian-2-yllithium compounds *(57)*, which are stable below 0 °C. The reagents *(57)* exhibit good nucleophilic properties, and the products of their reactions with electrophiles can be hydrolyzed under mild conditions. s-Trithian-2-yllithium compounds *(58)* can also be used[76–78].

[72] *L. F. Fieser* and *M. Fieser*: Organische Chemie. Verlag Chemie, Weinheim 1965, p. 525.

[73] *W. E. Truce* and *F. E. Roberts*, J. org. Chemistry *28*, 961 (1963).

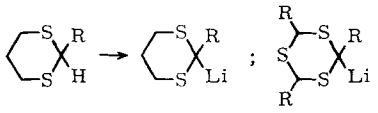
[74] *E. E. Reid*: Organic Chemistry of Bivalent Sulfur. Vol. III, Chem. Publishing Co., New York 1960, p. 332.

[75] *H. Normant* and *T. Cuvigny*, Bull. Soc. chim. France *1965*, 1881.

[76] *E. J. Corey* and *D. Seebach*, unpublished results, 1965/1966.

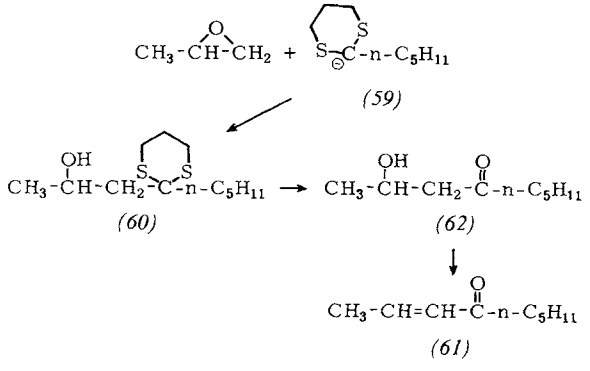
[77] *D. Seebach* and *D. Steinmüller*, Angew. Chem. *80*, 617 (1968); Angew. Chem. internat. Edit. *7*, 619 (1968).

[78] *D. N. Crouse* and *D. Seebach*, Chem. Ber. *101*, 3113 (1968).

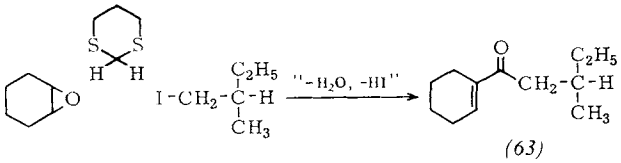


(56) (57) (58)

The dithiane method is the most extensively studied of all the nucleophilic acylation methods. It has proved successful in the preparation of 1-deuterated aldehydes [79], silyl and germanyl ketones [80], optically active aldehydes and ketones [77,81], and cyclic carbonyl compounds and hydrocarbons [82], as well as in the most prolific prostaglandin synthesis known at present [83]. One advantage is the chemical stability of the dithianyl protective group for the carbonyl group under various conditions, so that reactions on the C-2 substituents of the dithiane or trithiane system with the reaction products of *(57)* and *(58)* can be carried out. The free carbonyl compound is obtained, when desired, by hydrolysis. Since a comprehensive review of the chemistry of 1,3-dithian-2-yllithium compounds is at present being published [84], we shall merely demonstrate their application to the preparation of aldols and α,β-unsaturated carbonyl compounds as mentioned in the introduction [68,76,77].



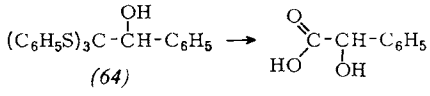
The Li compounds *(57)* add onto epoxides in high yields; the *n*-hexanal derivative *(59)* and propylene oxide give the dithiane derivative *(60)* of an aldol (90%). Hydrolysis with mercuric chloride/mercuric oxide yields the free aldol *(62)* (90%), which is then dehydrated to obtain the aldol condensation product *(61)* (85%). [The mild and extremely specific hydrolysis does not lead directly to the dehydrated product *(61)*!] The aldehyde from which the thioacetal *(56)* is derived is not required for the preparation of a dithianyllithium *(57)*. For example, successive reaction of unsubstituted dithiane [82] with (*S*)-(+)-1-iodo-2-methylbutane and 1,2-epoxycyclohexane in a single reaction



(63)

vessel, followed by hydrolysis and dehydration leads to the optically active ketone *(63)* in an overall yield of 40% from simple starting materials.

Metalated orthotrithioformic esters, *e.g* *(26)* and *(27)* can be used in a similar manner for nucleophilic carboxylation. Hydrolysis of the product *(64)* obtained from *(26)* and benzaldehyde to mandelic acid can be achieved merely by stirring a solution in acetone in the presence of mercuric salts at room temperature [26a]



(64)

The requirements listed above for a "good" masked nucleophilic acylating agent are only incompletely satisfied by the trithiocarbanion derivatives. Unlike the Li dithianes, these compounds tend to undergo carbenoid decomposition [24–27].

The above outline of the methods of nucleophilic acylation is intended to direct the attention of synthetic chemists toward this variant of carbonyl chemistry, which permits the use of little-noticed "short cuts" in syntheses. For this reason, the development of new methods and the extension of the known principles of nucleophilic acylation should not be neglected.

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[82] *D. Seebach, N. R. Jones*, and *E. J. Corey*, J. org. Chemistry *33*, 300 (1968); *T. Hylton* and *V. Boekelheide*, J. Amer. chem. Soc. *90*, 6887 (1968).

[83] *E. J. Corey et al.*, J. Amer. chem. Soc. *90*, 3245, 5947 (1968); *91*, 535 (1969).

[84] *D. Seebach*, Synthesis, in press.