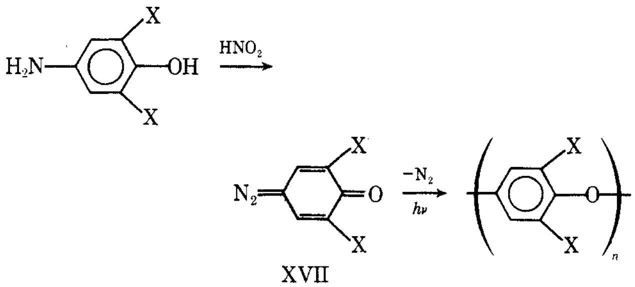
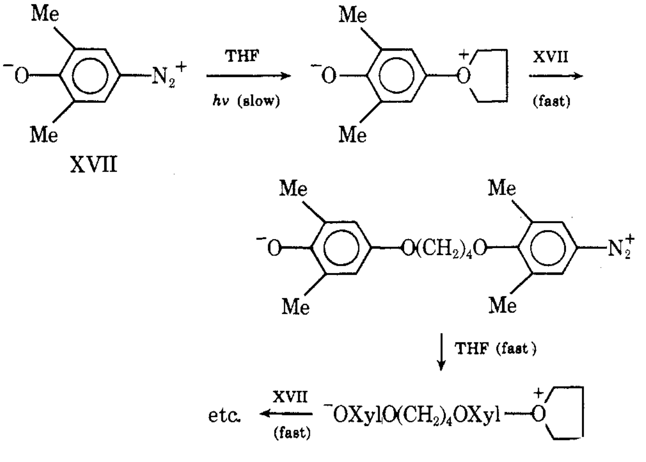


XVII

When this reaction was attempted with X = CH_3, no polymer was obtained, unless the reaction was carried out in THF or dioxane. Stille[53] and we[54] discovered concurrently and independently[55] that this polymerization involves incorporation of the cyclic ether solvent.

Scheme III does account for the regular alternating 1:1 polymer obtained. Most of the polymers obtained were low molecular weight, low melting, and soluble. Only a small amount (*ca.* 5%) of high-molecular-weight crystalline polymer was obtained, and that was deposited as a film on the glass surface of the reaction vessel.

Scheme III



In conclusion, while it is evident that much has been learned about reactions producing polyethers and important factors which affect them, there remain intriguing unanswered questions. Although there has been much speculation, it is not clear that we know in any detail the structural features of stereoselective and stereoelective coordination catalysts for epoxide polymerization.

For oxidative coupling of 2,6-xylenol, there has also been much speculation about the nature of the catalyst, but again there is much yet to be learned. In both cases, it seems clear that the central structural questions revolve around the nature of reactive groups coordinated around one or more metal atoms.

In the case of the polymerization of 4-bromo-2,6-xylenol, the free-radical chain-reaction hypothesis rests on relatively slender evidence. We are in the process of attempting to study the reaction under homogeneous conditions which may provide more substantial evidence for the mechanism involved.

I express my appreciation to the many coworkers who have been involved in our studies of polyethers. I also acknowledge the financial support of the General Tire and Rubber Company and of the U. S. Army Quartermaster Corps.

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(53) J. K. Stille, P. Cassidy, and L. Plummer, *J. Amer. Chem. Soc.*, 85, 1318 (1963).

(54) T. Kunitake and C. C. Price, *J. Amer. Chem. Soc.*, 85, 761 (1963).

(55) The last two references would have appeared together were it not for an oversight in editorial handling of the manuscripts.

Applications of Sodamide-Containing "Complex Bases" in Organic Synthesis

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Heterogeneous reactions, in which a solid substance reacts with something dissolved in a liquid solvent, often serve the chemist well. Yet they have idiosyncrasies, and may be a source of vexation.

It is sometimes found that a solid reactant will participate satisfactorily in such a reaction in one solvent but not in another which, *a priori*, would seem equally attractive. Sometimes seemingly minor changes in the solid reactant—such as changing the cation which accompanies a reactive anion, or adding some nonparticipating substance to the system—will be the means of converting failure to success.

In general terms, one can appreciate some of the factors that must be important in heterogeneous reactions. If the actual reaction occurs in the liquid phase, anything that alters the (slight) solubility of the solid reactant is of obvious importance. If reaction occurs at the surface of the solid phase, changing the ionic make-up of the solid reactant (if it is

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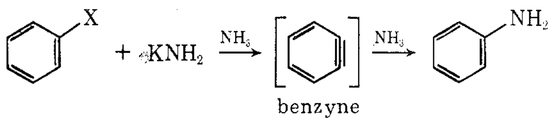
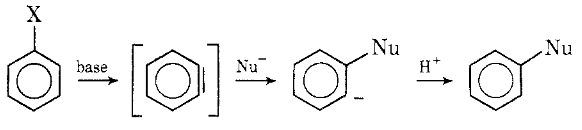
Scheme I



Scheme II



Nu$^-$ = nucleophile (it may be uncharged)

ionic) will in general change the structure of its surface and possibly its reactivity. The accumulation of insoluble reaction products on the solid surface may reduce the rate of solution of the solid reactant or block access of the dissolved to the solid reaction.

A few years ago we discovered that the reactivity of sodium amide with certain organic substrates in aprotic solvents is dramatically increased by admixture of some sodium alkoxides and related substances. Utilization of the resulting "complex base" reagents to effect various organic reactions opened gateways to hitherto inaccessible—or at least undiscovered—synthetic routes to some rather complex structures. These complex bases and the remarkable things they do are the subject of this Account.

It had been known since the pioneering work of Wittig[1] and especially since the masterful investigations of Roberts[2] that strong bases can effect the elimination of HX from halobenzenes to form benzyne[3,4] (Scheme I). Benzyne is the parent of a family of highly reactive intermediates known as arynes, or 1,2-dehydroarenes. The nature of the arynic triple bond is still under discussion.[3-5]

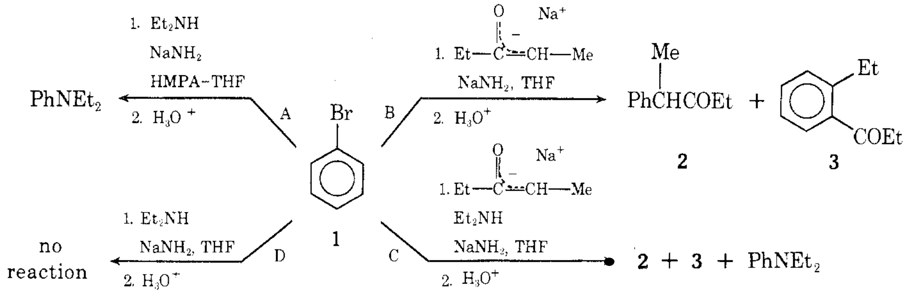
Characteristic reactions of arynes include their cycloaddition reactivity as dienophiles toward dienes and their capacity to add nucleophiles.[3,4] The sequence of base-induced elimination of HX and addition of nucleophile (Scheme II) constitutes a mechanism of aromatic nucleophilic substitution.

During a study of several intended arynic reactions in aprotic solvents,[6,7] we made some curious observations summarized in Scheme III.

Comparison of reactions B and D indicates that the generation of benzyne in THF depends upon the nature of the nucleophile to be condensed. Also, if diethylamine is present with the enolate ion (reaction C), it adds to benzyne to form diethylaniline, although this product was not obtained in THF in the absence of the enolate (reaction D).

We shall discuss later the mechanism of formation of ketones **2** and **3**.

Scheme III



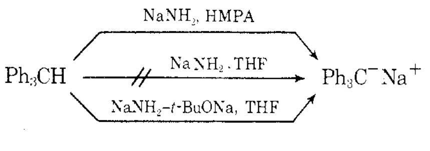
HMPA = hexamethylphosphotriamide; THF = tetrahydrofuran

After having verified that, under the specified conditions, the ketone enolate and NaNH$_2$, taken separately, do not react with bromobenzene, we concluded: (a) that in the presence of enolate ions the properties of NaNH$_2$ are modified; (b) that diethylamine, an uncharged nucleophile, does not have the same effect; and (c) that, insofar as condensation with diethylamine is concerned, the ketone enolate has an influence similar to that of HMPA, but has the disadvantage of being a competing nucleophile.

If these observations were more than fortuitous, they implied that association of NaNH$_2$ with a low-nucleophilicity sodium salt of an organic compound would enable condensation of Et$_2$NH with bromobenzene to occur in THF. Sodium *tert*-butoxide (*t*-BuONa) seemed to fit the specification; moreover, as an incidental advantage, it could be prepared *in situ*.

This was verified[7] by preparing in THF a mixture of NaNH$_2$ and *t*-BuONa by the action of *t*-BuOH on an excess of NaNH$_2$ and by demonstrating that it effects the condensation of Et$_2$NH with bromobenzene in quantitative yield and under remarkably mild conditions. This result led us to conclude that *t*-BuONa communicates to NaNH$_2$ in THF properties similar to those this amide has in the presence of HMPA. This was readily verified. Thus, Normant and Cuvigny[8] easily prepared tritylsodium in HMPA by reaction of NaNH$_2$ with triphenylmethane. This

Scheme IV



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(1) G. Wittig, G. Pieper, and G. Fuhrmann, *Ber. Deut. Chem. Ges.*, **73**, 1193 (1940).

(2) J. D. Roberts, H. E. Simmons, L. A. Carlsmith, and C. W. Vaughan, *J. Amer. Chem. Soc.*, **75**, 3290 (1953); J. D. Roberts, D. A. Semenow, H. E. Simmons, and L. A. Carlsmith, *ibid.*, **78**, 601 (1956).

(3) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Verlag Chemie, Weinheim/Bergstr., Germany, and Academic Press, New York, N. Y., 1967; H. G. Viehe, "Chemistry of Acetylenes," Marcel Dekker, New York, N. Y., 1969.

(4) G. Wittig, *Angew. Chem., Int. Ed. Engl.*, **4**, 731 (1965).

(5) P. Millie, L. Praud, and J. Serre, *Int. J. Quantum Chem.*, 187 (1971); O. L. Chapman, K. Mattes, C. L. Mc Intosh, J. Pacansky, G. V. Calder, and G. Orr, *J. Amer. Chem. Soc.*, **95**, 6134 (1973).

(6) P. Caubère and B. Loubinoux, *Bull. Soc. Chim. Fr.*, 3008 (1968).

(7) P. Caubère and B. Loubinoux, *Bull. Soc. Chim. Fr.*, 3857 (1968).

(8) T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 1872 (1965).

reaction can be obtained in THF only when $NaNH_2$–*t*-BuONa is used; see Scheme IV.

Interpretation of the Phenomenon

We supposed,[9] as a starting hypothesis, that certain sodium derivatives (activating compounds) somehow combine with $NaNH_2$ to form aggregates. We call these aggregates "complex bases" (see Scheme V).

Scheme V

$$NaNH_2\,(\text{solid}) + [(ZNa)_l\,(\text{solvent})] \rightleftharpoons [(NaNH_2)_m(ZNa)_n\,(\text{solvent})]$$

"complex base"

The role of the activating compound is apparently to "solubilize" $NaNH_2$, bringing it into solution in a complexed form. This has been confirmed by potentiometric measurements. $NaNH_2$ dissolves very slowly in solvents such as THF or DME (1,2-dimethoxyethane) giving solutions of extremely low concentration. However, addition of *t*-BuOH to suspensions of $NaNH_2$ in these solvents allows the maximum basicity to be attained much more quickly;[10] we cannot tell whether the concentration of *free* $NaNH_2$ is really increased.

We could foresee, and were able to verify,[9,11] that the properties of complex bases depend upon the ratio of $NaNH_2$ to activating compound and upon the solvent.

The structure of the aggregates, and therefore their properties, must be related to the nature of the activating compound. In other words, a complex base has its own properties, different from those of $NaNH_2$ and of the activating compound. The results described in this Account support this hypothesis.

Our observations may be compared with those previously made by Morton, Claff, and Collins[12] who showed that sodium alcoholates modify the properties of organosodium compounds. They postulated, in explanation, the formation of complexes between RNa and R^1ONa.

Nature of the Activating Compound

We studied the capability of compounds to activate $NaNH_2$ by testing the ability of mixtures of $NaNH_2$ with the compound under study to bring about formation of tritylsodium from triphenylmethane (see Scheme IV). Formation of tritylsodium was detected by adding CO_2 or benzyl chloride and isolating triphenylacetic acid or 1,1,1,2-tetraphenylethane.[9,11,13,14] It turns out that most ketone enolates, tertiary alcoholates, bis tertiary glycolates, and glycol monoether alcoholates[14] are good activating compounds. In particular, the sodium salt of diethylene glycol monoethyl ether, prepared *in situ,* enables the maximum basicity in THF[14] to be reached almost instantaneously. Its effect is comparable to that observed when heterobicyclics (cryptates[15]) are added to suspensions of $NaNH_2$ in DME[10]. Generally, secondary alcoholates and sodium salts of such compounds as thiophenol or acetonitrile are less efficient.[11]

It should be noted that the results described relate to a reaction involving the removal of a proton from a hydrocarbon and that the relative efficiency of activating compounds is determined only for reactions of that type.

In passing we note that Biehl and coworkers[16] have subsequently observed enhancement of the "basic power" of $NaNH_2$ in the presence of certain sodium salts in dimethylamine. However, the nature of activating compound used led these authors to conclude that only salts with a linear and resonating anion are good activating compounds. Their conclusion does not agree with our results.

Last, but not least, complex bases give the possibility of alkylating, in excellent yield, triphenylmethane as well as diphenylmethane in such low-polarity solvents as THF or DME.[11]

Use of Complex Bases in Arynic Chemistry

In comparison with many basic systems previously used, the complex bases $NaNH_2$–*t*-BuONa and $NaNH_2$–*t*-AmONa proved to be particularly efficient for carrying out arynic reactions (summarized in Scheme II). They enable condensations,[7,17] in THF media, under mild conditions and with very good yields, of aryl halides with sodium thiolates and secondary amines. Under these conditions, use of the lithium derivatives of amines[3] is not necessary. Moreover, use of these complex bases in THF has made possible wide use of aromatic fluorine compounds in arynic reactions.[18]

Most ketone enolates are good reagents for activating $NaNH_2$. Their nucleophilic power is only partly canceled by formation of the complex base aggregates.[9] It is therefore possible to carry out under mild conditions the condensation, *via* the aryne mechanism, of ketone enolates with halobenzenes in aprotic media (THF or DME).

The nature of the products obtained in aprotic media depends on experimental conditions and especially on the ketone from which the enolate is derived. However, all the products obtained are intelligible in terms of the intermediacy of anions **5**, **6**, and **7** (Scheme VI).

Investigations on cyclic ketone enolate condensations and on ring opening of alcohols derived from **6** (*vide infra*) led us to consider this general mechanism in which (a) **4** condenses with benzyne to yield **5** and/or **6** and (b) **5**, **6**, and **7** are equilibrated. The observed reactions are then very different than those described by Leake and Levine.[19] These authors only obtained phenyl ketones derived from **5**. This result is explained by the fact that they used liquid ammonia as solvent, while our reactions are performed in aprotic media.

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(9) P. Caubère and B. Loubinoux, *Bull. Soc. Chim. Fr.*, 2483 (1969).

(10) A. Caillet and D. Bauer, *J. d'Etude, Div. Chim. Anal. Org., Soc. Chim. Fr.* (Jan 1974).

(11) P. Caubère and G. Coudert, *Bull. Soc. Chim. Fr.*, 2234 (1971).

(12) A. A. Morton, C. E. Claff Jr., and F. W. Collins, *J. Org. Chem.*, 20, 428 (1955).

(13) G. Coudert, Thèse d'Etat, to be published.

(14) P. Caubère and G. Guillaumet, *J. d'Etude, Div. Chim. Anal. Org., Soc. Chim. Fr.* (Jan 1974).

(15) J. M. Lehn and J. P. Sauvage, *Chem. Commun.*, 440 (1971), and references cited therein.

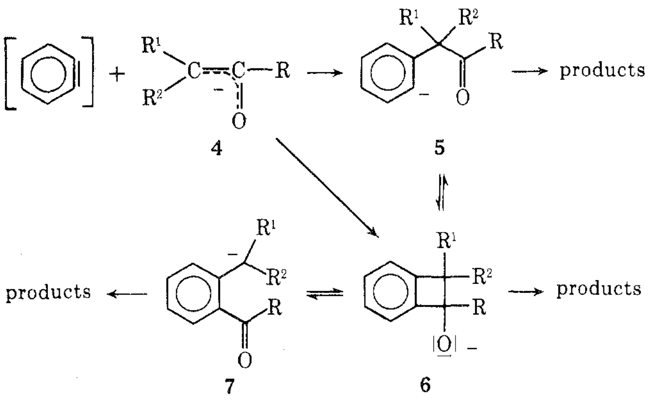
(16) E. R. Biehl, K. C. Hsu, and E. Nich, *J. Org. Chem.*, 35, 2454 (1970).

(17) P. Caubère and N. Derozier, *Bull. Soc. Chim. Fr.*, 1737 (1969).

(18) P. Caubère and M. F. Hochu, *Bull. Soc. Chim. Fr.*, 2854 (1969).

(19) W. W. Leake and R. Levine, *J. Amer. Chem. Soc.*, 81, 1169 (1959).

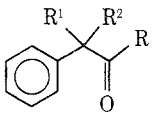
Scheme VI



Reactions of Arynes with Enolates from Aliphatic and Aryl Aliphatic Ketones

With ketones of this type, we have never obtained alcohols corresponding to anions 6.

When the ketone used has methylene groups both α and α' (diethyl and diisobutyl ketones), two ketonic products of types 8 and 9 are isolated after hydrolysis. They are derived from anions 5 and 7, respectively. The relative amounts of 8 and 9 depend upon experimental conditions; thus, 9/8 increases with increasing temperature and decreasing solvent polarity. It is possible, for instance, to direct the reaction toward the formation of mixtures rich in 9.[6,20] If the ketones have at least two substituents α and α' (diisopropyl and isopropyl *tert*-butyl ketones), ketonic products of type 8 are not observed. On the other hand, besides ketones of type 9, three further types of products, namely, 10, 11, and 12, are formed from 7 (see Scheme VII).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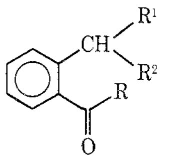
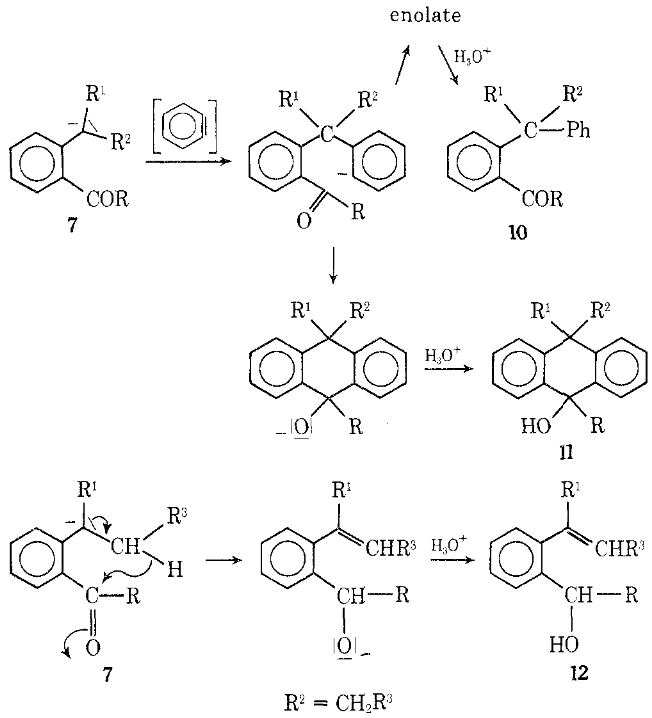

9

With aryl aliphatic ketones (PhCOCHMe$_2$, PhCOC$_6$H$_{11}$) the only isolated products are alcohols of type 12, anthrones of type 13 (Scheme VIII), and, in the case of phenyl isopropyl ketone, anthranol of type 11.[21] The mechanism of Scheme VIII is similar to that proposed by Burley and Young[22] for certain reactions of BuLi with β-substituted styrenes.

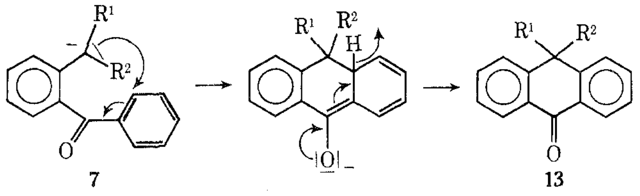
With some ketones, if the reaction temperature is too high, cleavage of the Haller–Bauer type is observed.[21,23] The latter may have some unexpected consequences. Thus, methyl cyclopropyl ketone normally leads to ketonic products of types 8 and 9 at low temperatures (*ca.* −20 to 0°). At higher temperatures (*ca.* 45°) the amide 15 and a benzylic anion are formed. The latter condenses with ketone 9 (R^1 = R^2 = H; R = cyclopropyl) to give 14 in 60% yield.[20]

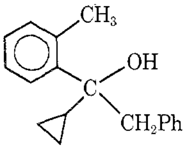
The reactions exposed above may be extended to substituted arynes. However, the reactions are feasible for purposes of synthesis only if the substituent has a strong directing effect so that nucleophiles attack almost exclusively to one terminus of the aryne "triple" bond. In that case, one avoids the formation of too large a number of products.[24]

Scheme VII



Scheme VIII

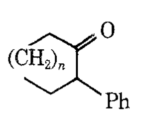



14


15

Reactions of Arynes with Enolates from Alicyclic Ketones and Benzocyclenones

The products formed by condensation of enolates from alicyclic ketones with benzyne have formulas of the types 16, 17, and 18.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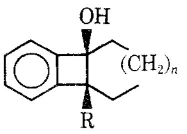
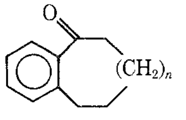

17


18

A remarkable feature of these reactions is the formation of alcohols of type 17.[25-28] However, they

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(20) P. Caubère and G. Guillaumet, *Bull. Soc. Chim. Fr.*, 4643 (1972).

(21) P. Caubère and G. Guillaumet, *Bull. Soc. Chim. Fr.*, 4649 (1972).

(22) J. N. Burley and R. N. Young, *J. Chem. Soc. C*, 3780 (1971).

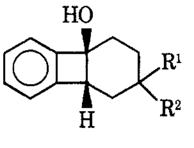
(23) C. L. Bumgardner and K. G. Mc Daniel, *J. Amer. Chem. Soc.*, 91, 6821 (1969), and references cited therein.

(24) P. Caubère and G. Guillaumet, *C. R. Acad. Sci., Ser. C*, 275, 463 (1972).

(25) P. Caubère, N. Derozier, and B. Loubinoux, *Bull. Soc. Chim. Fr.*, 302 (1971).

only have been obtained when n = 1–3 (in appropriate conditions, better yields are respectively 20,[26] 45,[25] and 95%[25]).

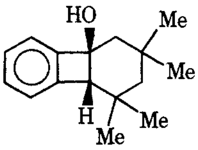
We have particularly studied condensations with enolates from cyclohexanones and thus worked out a method for preparation of the novel alcohols of types **19**, **20**, and **21**.[25,27] These benzocyclobutenols, although synthesized in basic media, are unstable with bases. Indeed, when treated with $NaNH_2$ or NaH, they are quickly opened to give the corresponding ketones **16** and/or **18**.[29,30] This apparent contradiction finds explanation in the postulate that, during the condensation, the cation stays near the oxygen atom, increasing by coordination the stability of the alcoholates. This postulate was supported by studies of the effects of the enolates of several cations on benzocylobutenols formation.[28] This result led us to propose the direct formation of **6** (see Scheme VI) from **4** and benzyne, simultaneously with formation of **5**. The stability of such alcoholates also depends on the size of the saturated ring.[28]



19

$R^1 = R^2 = H$, Me

$R^1 = H$; $R^2 = Me$; *t*-Bu



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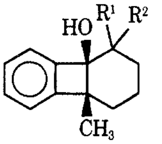


21

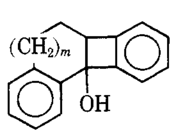
$R^1 = R^2 = H$, Me

$R^1 = H$; $R^2 = Me$

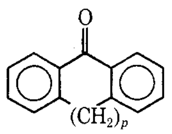
The way in which benzycyclobutenols open by action of bases depends on the size of the saturated ring, on the substituents, and on the solvent. Thus, alcohols **21** always lead to the corresponding ketones **16** in 80–90% yields.[30] On the other hand, **17** (n = 3, R = Me) is converted into a benzocyclenone with 80% yield.[31] Finally, in the cases of alcohols **19** and **20**, other things being equal, HMPA strongly favors the formation of benzocyclenones of type **18** at the expense of ketones of type **16**; in all cases, the overall yields reach 70 to 90%.

By taking these factors into account, we have worked out a general method for access to benzocyclenones **18** with $1 \leq n \leq 12$.[24]

Benzyne also readily adds the enolates from benzocyclenones. If ketones **18** (n = 0, 1) are employed, these reactions are good methods of synthesis of **22** (60–85% yield)[27] and, by ring opening of the latter, of **23** (90% yield).[30]

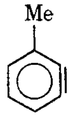


22, m = 1, 2

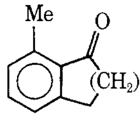


23, p = 3, 4

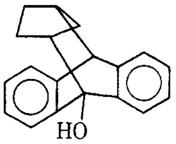
Condensation of enolates from alicyclic ketones with **24** (generated from *o*-bromotoluene) showed the sensitivity of these reactions to steric hindrance. Attack on the meta position is preponderant. This property enabled the facile synthesis of benzocyclenones **25**, which are difficultly accessible by other means, in 25–35% yield.[32]



24



25, n = 3–6



26

The addition to benzyne of the enolate from norcamphor leads, in only one step, to alcohol **26** in 85% yield.[33] Its formation is easily explained by the mechanism sketched above for reactions of enolates from aliphatic ketones.

Scope and Limitations

Yields from arynic reactions carried out in the presence of complex bases—nucleophilic or not—are generally good. When these condensations lead to mixtures (as with most ketone enolates), separation of the products is sometimes difficult. This disadvantage is offset by the simplicity of methods which lead in one or two steps from simple starting substances to products not accessible, or difficult to obtain, in other ways.

Furthermore, observations on reactions of enolates from α,β-unsaturated ketones[34] indicate that these nucleophiles react according to mechanisms quite similar to those described above. These reactions provide interesting means of access to various substituted naphthalenes and tetralones. Somewhat similar studies have been reported by Sammes and Wallace.[35]

Use of Complex Bases in Cycloalkyne and 1,2-Cycloalkadiene Chemistry

The intermediacy of strained cycloalkynes and 1,2-cycloalkadienes[3] in certain reactions was proven long ago.[36] Reactions of 1-halocycloalkenes with base and nucleophiles often occur by the elimination–addition mechanism of Scheme IX.[37]

n must be small enough for intermediates **28** and **29** to be highly reactive with nucleophiles. This field of chemistry still raises much interest.[38] We were

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(26) P. Caubère, G. Guillaumet, and M. S. Mourad, *Tetrahedron*, **28**, 95 (1972).

(27) P. Caubère, M. S. Mourad, and G. Guillaumet, *Tetrahedron*, **29**, 1843 (1973).

(28) P. Caubère, G. Guillaumet, and M. S. Mourad, *Tetrahedron*, **29**, 1857 (1973).

(29) P. Caubère, G. Guillaumet, and M. S. Mourad, *Tetrahedron Lett.*, 4673 (1971).

(30) P. Caubère, M. S. Mourad, and G. Guillaumet, *Tetrahedron*, **29**, 1851 (1973).

(31) M. S. Mourad, Thèse d'Etat, to be published (CNRS No. A.O. 9673).

(32) P. Caubère, G. Guillaumet, and M. S. Mourad, *Bull. Soc. Chim. Fr.*, 3493 (1973).

(33) P. Caubère, M. S. Mourad, and D. Canet, *Tetrahedron Lett.*, 2221 (1973).

(34) J. J. Brunet, M. Essiz, and P. Caubère, *Tetrahedron Lett.*, 871 (1974).

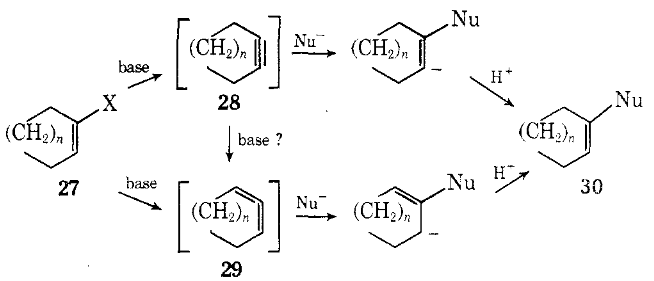
(35) P. G. Sammes and T. W. Wallace, *J. Chem. Soc., Chem. Commun.*, 524 (1973).

(36) F. Scardiglia and J. D. Roberts, *Tetrahedron*, **1**, 343 (1957); L. K. Montgomery and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 4750 (1960); G. Wittig and A. Krebs, *Ber.*, **94**, 3260 (1961); L. K. Montgomery, F. Scardiglia, and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 1917 (1965); G. Wittig and P. Fritze, *Angew. Chem., Int. Ed. Engl.*, **5**, 846 (1966); L. K. Montgomery and L. E. Applegate, *J. Amer. Chem. Soc.*, **89**, 2952 (1967).

(37) A. T. Bottini and W. Schear, *J. Amer. Chem. Soc.*, **87**, 5802 (1965); L. K. Montgomery, A. O. Clouse, A. M. Crelier, and L. E. Applegate, *J. Amer. Chem. Soc.*, **89**, 3453 (1967); L. K. Montgomery and L. E. Applegate, *ibid.*, **89**, 5305 (1967).

(38) P. Mohanakrishnan, S. R. Trayal, R. Viadyanathaswamy, and D. Devaprabhakara, *Tetrahedron Lett.*, 2871 (1972); A. T. Bottini, F. P. Corson, R. Fitzgerald, and K. A. Frost II, *Tetrahedron*, **28**, 4883 (1972), and references cited therein; A. T. Bottini, K. A. Frost II, B. R. Anderson, and

Scheme IX



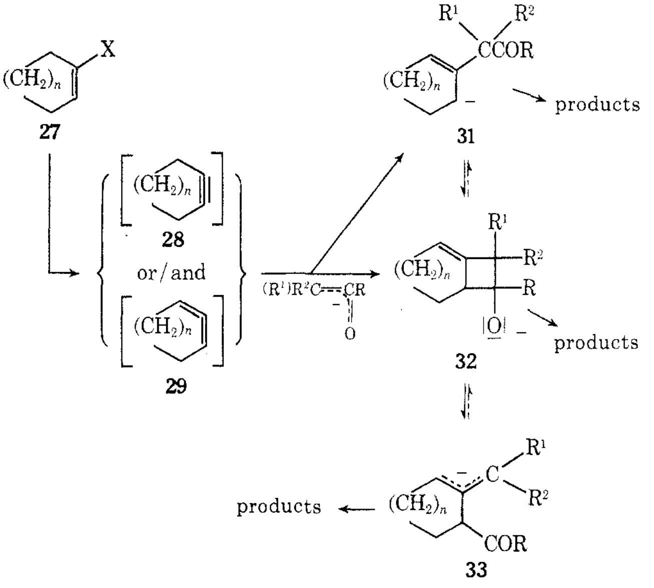
especially interested in the cases where $n = 2$ and 3 because no general method for performing the reactions of Scheme IX had been described. The use of complex bases enables these reactions to be performed readily. Thus condensations of secondary amines, sodium thiolates, tritylsodium, and sodiophenylacetonitrile with **27** ($n = 2$, X = Cl) in the presence of $NaNH_2$-t-BuONa, in THF media, lead to the expected substitution products **30**.[39,40] The conditions are mild (30–35°), and the yields are fairly good (37–80%, depending on the nucleophile).

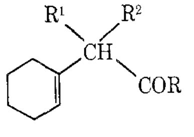
A study of substituted chlorocyclohexenes showed that the first step of these condensations involves cyclohexyne **28** ($n = 2$).[41]

With 1-halocycloheptenes **27** ($n = 3$, X = Cl, Br), condensations with secondary amines are also feasible;[42] yields are nevertheless slightly smaller than when $n = 2$. The mechanism is in this case much more complex and certainly involves cycloheptyne **28** ($n = 3$) and 1,2-cycloheptadiene **29** ($n = 3$).[43]

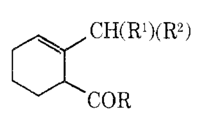
Use of complex bases comprising $NaNH_2$ and a nucleophilic enolate leads to interesting results. The proposed condensation mechanisms (Scheme X) are similar to those described for the arynic series. For $n = 2$, and when the condensed carbonyl derivative is aliphatic or alicyclic, anions **31** and **33** evolve toward the formation of enolates, the nature of which depends upon the starting ketone and experimental conditions. The solvent plays a particularly important part.[44,45] By hydrolysis these enolates lead to ketones **34–36**. In fact, these reactions constitute, in general, good means for access to ketones of type **36** (40% yield) and to some of type **34** (25% yield).

Scheme X

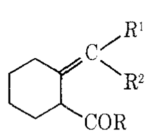




34

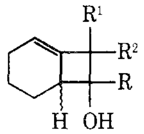


35

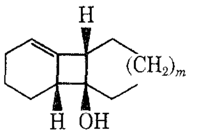


36

Noteworthy is the great stability of the alcoholates **32** in comparison with those observed in the aromatic series. Thus it is possible to synthesize alcohols of type **37** (25% yield) as well as **38** (55% yield).[44,45]



37

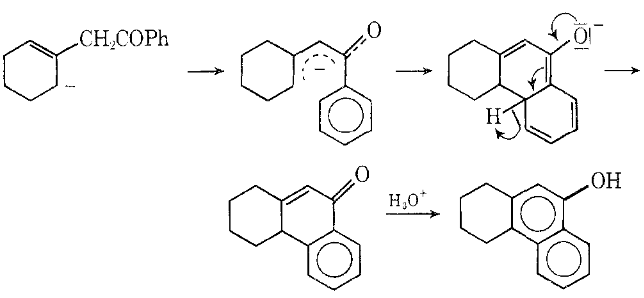


38, m = 2–4

However, **38** could not be obtained for $m > 4$.[46] The stereochemistry of the alcohols depends upon substituents in the case of **37**, whereas it is always cis, around the four-membered ring, in the case of **38**, as indicated.

The similarity of reactivity between cycloalkynes–1,2-cycloalkadienes and benzyne is particularly apparent in reactions with enolates from aryl alkyl ketones. Thus with acetophenone enolate one obtains ketone **36** ($R^1 = R^2 = H$; R = Ph) in 25% yield and 1,2,3,4-tetrahydrophenanthrol **39** in 30% yield (Scheme XI).[47] On the other hand, the enolate from phenyl isopropyl ketone leads to **36** ($R^1 = R^2 =$ Me; R = Ph), **37** ($R^1 = R^2 =$ Me; R = Ph), and **40** in 30, 10, and 40% yields, respectively (Scheme XII).[47] The extent of these cyclizations depends upon the solvent. They are favored by HMPA.

Scheme XI



The results obtained with 1-halocycloheptenes **27** ($n = 3$) are quite similar to those just described. The

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V. Dev, *Tetrahedron*, **29**, 1975 (1973), and references cited therein; P. K. Freeman and T. A. Hardy, *Tetrahedron Lett.*, 3317 (1973); A. T. Bottini and B. Anderson, *Tetrahedron Lett.*, 3321 (1973).

(39) P. Caubère and J. J. Brunet, *Tetrahedron Lett.*, 3323 (1969); P. Caubère and J. J. Brunet, *Bull. Soc. Chim. Fr.*, 2418 (1970).

(40) J. J. Brunet, Thèse d'Etat, University Nancy, 1972 (CNRS No. A.O. 6670).

(41) P. Caubère and J. J. Brunet, *Tetrahedron*, **27**, 3515 (1971).

(42) J. J. Brunet, B. Fixari, and P. Caubère, *C. R. Acad. Sci., Ser. C*, **276**, 1045 (1973).

(43) J. J. Brunet, B. Fixari, and P. Caubère, *Tetrahedron*, in press.

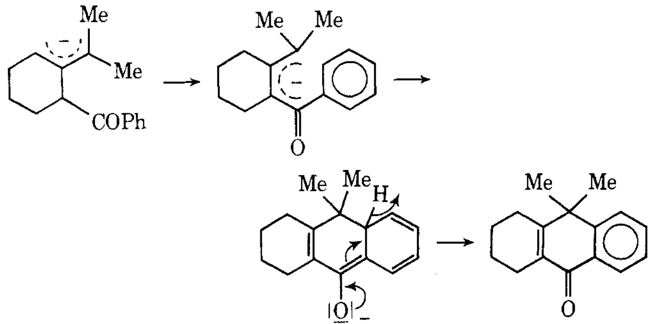
(44) P. Caubère and J. J. Brunet, *Tetrahedron*, **28**, 4835 (1972).

(45) P. Caubère and J. J. Brunet, *Tetrahedron*, **28**, 4847 (1972).

(46) J. J. Brunet, B. Fixari, and P. Caubère, *Tetrahedron*, **30**, 1237 (1974); J. J. Brunet, B. Fixari, and P. Caubère, *Tetrahedron*, **30**, 1245 (1974).

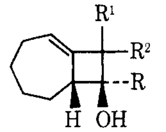
(47) P. Caubère and J. J. Brunet, *Tetrahedron*, **28**, 4859 (1972).

Scheme XII

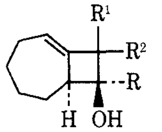


40

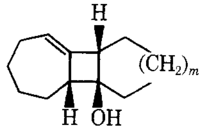
main difference is that the methylenecyclobutanols, produced in 40 to 50% yields, exist in two isomeric forms, **41a** and **41b**, or **42a** and **42b**.[42,46] As a whole,



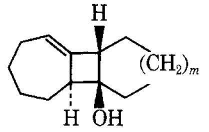
41a



41b



42a



42b

they are, as alcoholates, more stable than their analogs **37** and **38**; furthermore, the alcohols **42a** (or their alcoholates) are more stable than their isomers **42b**.

This particular stability makes it possible to obtain methylenecyclobutanols, whatever the starting ketone and, particularly, whatever the magnitude of m.[46]

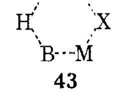
Scope and Limitations

The overall yields from these reactions are often good, although they sometimes are smaller than those reached in arynic chemistry. When there is a simultaneous formation of several products, it is possible, by varying the experimental conditions, to direct, more or less selectively, the course of the condensation.

In this case, too, the simplicity of the methods involved, with respect to the complexity of the structures they lead to, makes these reactions interesting from the point of view of synthesis.

Use of Complex Bases in Syn Eliminations

It seemed to us that the facility with which the above exposed elimination–addition reactions occur was due, not only to the strength of the complex bases, but also to the fact that the aggregates which constitute them have a structure suitable for the formation of a transition state of type **43**, proposed by Sicher and Zavada[48] to explain some syn eliminations.



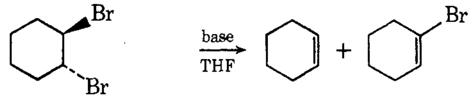
43

If this supposition were true, the use of complex bases should make it possible to perform some syn eliminations inaccessible with usual bases. Moreover, we might expect that all complex bases would not be equally efficient inasmuch as the structure of the aggregates would change from one activating compound to another.

We chose to study elimination from *trans*-1,2-dibromocyclohexane. It is general experience[49] that this halogen derivative, on being treated with bases, leads only with great difficulty to 1-bromocyclohexene (the yields are low and tedious purifications are required to obtain a pure product[50]).

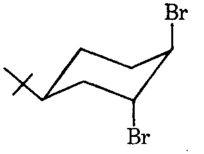
Scheme XIII gathers the results obtained[51,52] with several complex bases. The influence of the structure of the complex base is obvious. It is clear that the observed syn elimination reaction does not depend upon the strength of the complex base, which varies, as a function of the activating compound, in the sense[9,14] $Et(OCH_2CH_2)_2ONa \gg t\text{-}AmONa > t\text{-}BuONa \gg C_6H_{11}ONa$.

Scheme XIII

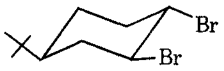


$NaNH_2$-*t*-BuONa	36%	50–55%
$NaNH_2$-*t*-AmONa	50%	30%
$NaNH_2$-$C_6H_{11}ONa$	40%	30%
$NaNH_2$-$Et(OCH_2CH_2)ONa$	60%	15%

Despite the trans-diaxial disposition of the halogens, **44** leads to 20% of 1- and 2-bromo-4-*tert*-butylcyclohexenes; 70% of *tert*-butylcyclohexene is formed at the same time.[52]



44



45

The same reaction, carried out with a known mixture **44** + **45** (derivative **45** can be prepared in the pure state only with great difficulty), indicated that **45** is transformed practically quantitatively into bromocyclohexene derivatives. It should be noted that cyclohexyl *trans*-1,2-bis(*p*-toluenesulfonate) does not undergo syn elimination with complex bases.[52]

From our point of view, the facts that these reactions so strongly depend on the composition of the complex base (and not on its strength) and on the nature of the leaving group are consistent with a transition state of type **43**.

Scope and Limitations

Complex bases partially resolve the problem of effecting syn elimination from *trans*-1,2-dibromocyclo-

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(48) J. Sicher, *Angew. Chem., Int. Ed. Engl.*, **11**, 200 (1972), and references cited therein.

(49) N. A. Le Bel, *Advan. Alicycl. Chem.*, **3**, 195 (1971).

(50) P. Maitte, *Bull. Soc. Chim. Fr.*, 499 (1959), and references cited therein.

(51) P. Caubère and G. Coudert, *J. Chem. Soc., Chem. Commun.*, 1289 (1972).

(52) G. Guillaumet, V. Lemmel, G. Coudert, and P. Caubère, *Tetrahedron*, **30**, 1289 (1974).

hexanes, but their effectiveness seems, at the present time, to be limited to these and closely related substrates. Their use does enable the yield in transformation of *trans*-1,2-dibromocycloheptane into 1-bromocycloheptene[52] to be greatly improved (90%).

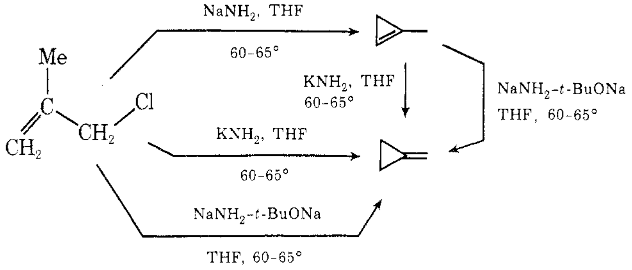
Moreover, it is possible to prepare readily cyclooctyne from *trans*-1,2-dibromocyclooctane.[53] The yields are only fair (30%), but the isolation of the acetylenic derivative in pure state does not require any special purification steps. Finally, reactions of *trans*-2-alkylstyrenes with Br_2 and then with $NaNH_2$–*t*-BuONa led to mixtures containing 40% of the expected alkylphenylacetylenes.[54] This synthesis, studied previously by Davis and Ansari,[55] had never given acetylenic compounds with conventional basic systems.

In fact, the most serious limitation of complex bases for use in these reactions is their isomerizing power; that we are not yet able to control sufficiently.

Use of the Complex Base $NaNH_2$–*t*-BuONa in the Synthesis of Methylenecyclopropane

$NaNH_2$–*t*-BuONa may advantageously replace KNH_2[11] in the synthesis of methylenecyclopropane (Scheme XIV), worked out by Koster, Arora, and Binger.[56] The chief advantage of the complex base is its simplicity of use which gives the possibility of working readily with large quantities; this reaction was used by Conia and Salün[57] in their synthesis of cyclobutanone.

Scheme XIV



Conclusion

The studies described above show that complex bases comprising $NaNH_2$ and an activating compound are interesting reagents for synthesis both because they provide access to otherwise difficultly accessible structures and because they are easy to use.

The principle of activation is not limited to $NaNH_2$ nor even to modification of basic power. Indeed, we have shown that the reducing properties of NaH can be increased considerably by the use of sodium alcoholates.[58]

We must point out that, in all the activation phenomena we have discovered, both entities constituting the aggregates have the same cation, contrary to what is found, for instance, in the activation of organolithium compounds by *t*-BuOK.[59]

From a general point of view, study of the "synergy" of two reagents upon formation of "mixed" aggregates

$$n\text{X-M} + m\text{Y-M} \longrightarrow [(\text{XM})_x(\text{YM})_y]$$

is an interesting field of research. There is promise that new reagents for synthesis may be found. Also, this phenomenon gives some possibility of resolving problems of nonreactivity in heterogeneous media, as some of the experiments described above already indicate.

Finally, such synergistic effects pose problems of physical interpretation. What is the nature of the entity which actually reacts?

I express my sincere appreciation to my coworkers, who are named in the references. I am grateful to them for their experimental and intellectual contributions to our work. I thank the Centre National de la Recherche Scientifique and the Délégation Générale à la Recherche Scientifique et Technique (Comité ASCO) for financial support.

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(53) P. Caubère and G. Coudert, *Bull. Soc. Chim. Fr.*, 3067 (1973).

(54) P. Caubère and G. Coudert, *Tetrahedron*, 28, 5635 (1972).

(55) D. D. Davis and G. G. Ansari, *J. Org. Chem.*, 35, 4285 (1970).

(56) R. Koster, S. Arora, and P. Binger, *Angew. Chem., Int. Ed. Engl.*, 8, 205 (1969).

(57) J. R. Salaün and J. M. Conia, *Chem. Commun.*, 1579 (1971).

(58) J. Moreau and P. Caubère, *Tetrahedron*, 27, 5741 (1971), and references cited therein.

(59) M. Schlosser, *J. Organometal. Chem.*, 8, 9 (1967); W. J. Trepka, J. A. Favre, and R. J. Sonnefeld, *J. Organometal. Chem.*, 55, 221 (1973), and references cited therein.