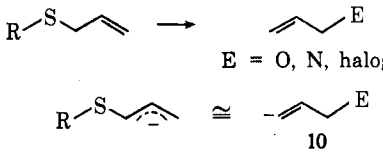
Conclusions

Through our own work as well as that of others, there now exist efficient means for the allylic interchange of sulfur with other atoms such as oxygen, nitrogen,[42] and halogen[35a] (eq 6). Consequently, the synthetic applications of anion equivalents such as **10** may be considerably expanded beyond the examples included in this Account.

During the last few years the number of new innovations in synthetic organic chemistry that have involved the use of the sulfur atom has been quite exciting.[43] Throughout much of this work sulfur-stabilized carbanions have played a prominent role. In this regard the future use of sulfur derivatives of 2-mercapto-1-methylimidazole in reagent design appears quite promising.



(6)

10

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(42) P. A. Brisco, F. Challenger, and P. S. Duckworth, *J. Chem. Soc.*, 1755 (1956).
(43) E. Block, *J. Chem. Educ.*, 48, 814 (1971).

Base-Catalyzed Carbon–Carbon Addition of Hydrocarbons and of Related Compounds

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Acid-catalyzed conversions of hydrocarbons have been widely studied and reported in the chemical literature.[1] Many important petrochemical processes involve catalysis by acids. In contrast, the use of bases as catalysts for hydrocarbon reactions has received until recently relatively little attention, except for the conversion of conjugated dienes and styrenes to high molecular compounds using alkali metals as catalysts.[2]

The discovery that sodium in the presence of small amounts of organosodium compounds, produced *in situ* or deposited on alumina, acts as an effective catalyst for double bond isomerization of alkenes and cyclenes[3] triggered much research in this field.[2] It was subsequently discovered that base-catalyzed isomerization of olefins may proceed in homogeneous solutions using lithium ethylenediamine in ethylenediamine[4] or potassium *tert*-butoxide (*t*-BuOK) in dimethyl sulfoxide (DMSO).[5]

Since base-catalyzed isomerization of olefins has been adequately reviewed,[6] the present Account is limited to the title subject only. However it omits reactions leading to the formation of macromolecules.

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Base-catalyzed carbon–carbon addition reactions are of synthetic interest because they afford hydrocarbons and related compounds in good yields by a simple one-step procedure. These reactions are made possible by the fact that hydrocarbons and related compounds having a benzylic or allylic hydrogen are carbon acids, having a pK_a of about 35 to 37; they can donate a proton to a base and thus become carbanions.[7] These carbanions can add to olefinic hydrocarbons. The steps involved in the catalytic chain reactions are illustrated by the following set of equations, using toluene and ethylene as reactants, and sodium as catalyst:[8]

$$\text{Promoter} + \text{Na} \longrightarrow \text{B}^-\text{Na}^+ \quad (1)$$

Initiation

$$\text{C}_6\text{H}_5\text{CH}_3 + \text{B}^-\text{Na}^+ \rightleftharpoons \text{C}_6\text{H}_5\text{CH}_2^-\text{Na}^+ + \text{BH} \quad (2)$$

Addition

$$\text{C}_6\text{H}_5\text{CH}_2^-\text{Na}^+ + \text{CH}_2{=}\text{CH}_2 \rightleftharpoons \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2^-\text{Na}^+ \quad (3)$$

Propagation

$$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2^-\text{Na}^+ \ \text{C}_6\text{H}_5\text{CH}_3 \longrightarrow \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_3 + \text{C}_6\text{H}_5\text{CH}_2^-\text{Na}^+ \quad (4)$$

(1) "Friedel-Crafts and Related Reactions," Vol. I-IV, G. A. Olah, Ed., Interscience, New York, N. Y., 1965.
(2) H. Pines and L. A. Schaap, *Advan. Catal. Relat. Subj.*, 12, 117 (1960).
(3) (a) H. Pines, J. A. Vesely, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, 77, 347 (1955); (b) H. Pines and H. E. Eschinazi, *ibid.*, 77, 6314 (1955); 78, 1178, 5950 (1956); (c) H. Pines and W. O. Haag, *J. Org. Chem.*, 23, 328 (1958).
(4) L. Reggel, S. Friedman, and I. Wender, *J. Org. Chem.*, 23, 1136 (1958).
(5) A. Schriesheim, J. E. Hofmann, and C. A. Rowe, *J. Amer. Chem. Soc.*, 83, 3731 (1961).
(6) A. J. Hubert and H. Reimlinger, *Synthesis*, 3, 97 (1969) (review).
(7) For general discussion of carbon acids see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965.

Step 2, chain initiation, involves the metalation of toluene by an organosodium compound. Since the action of sodium on the reactants does not produce organosodium compounds, a "promoter" is added to accomplish it. *o*-Chlorotoluene and anthracene were found to be effective "promoters" since they readily react with sodium to form benzylsodium[9] and disodium anthracene,[10] respectively. The "promoters" also facilitate the dispersion of sodium into a very fine black powder which can form additional organosodium compounds as the reactions progress.

Step 3, the addition reaction, is energetically the least favorable step as it involves the formation of an anion lacking resonance stabilization from a resonance-stabilized benzylic anion. However, once the anion adduct is produced it is instantaneously and irreversibly protonated by the benzylic hydrogen of the toluene present. The facility with which addition occurs depends to a great degree on the olefin used. Addition of benzyl anion to propene requires more drastic conditions than to ethylene, due both to steric and to inductive effects. The addition reaction is greatly facilitated when conjugated alkadienes or styrenes are used as olefins since the anion adducts formed are resonance stabilized by conjugation with a double bond and benzene ring, respectively.

The ease of addition to olefins depends also on the acidity of the alkylarenes used in the reaction. 4-Methylpyridine, having a pK_a of about 29 at −40°,[11] adds to isoprene at room temperature in the presence of *t*-BuOK in DMSO. Toluene, however, having a much higher pK_a[7] does not add to isoprene in the presence of this catalyst.

Of the alkali metals, potassium is a more effective catalyst than sodium, while lithium has only limited applications as catalyst. Unlike sodium, potassium does not require a "promoter" as it may react with the reactants to form organopotassium compounds. Unlike sodium, potassium also catalyzes certain cyclialkylation reactions, and thus provides new methods for the synthesis of a variety of cyclic compounds.

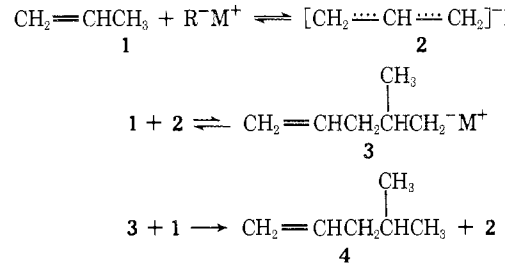
The application of base-catalyzed reactions to the synthesis of a broad spectrum of compounds is summarized below.

Oligomerization of Olefins

Alkenes. The oligomerization of olefins by bases was first reported in 1956 using simple olefins or olefin pairs in the presence of sodium as catalyst, and anthracene as a chain initiator.[12] The olefins used were ethene, propene, isobutylene, and cyclohexene.

The dimerization of propene at about 210° in the presence of potassium or cesium yielded 4-methyl-1-pentene as the predominant dimer.[13] The dimerization proceeds through an initial formation of an organoalkali compound, followed by metalation of the propene.

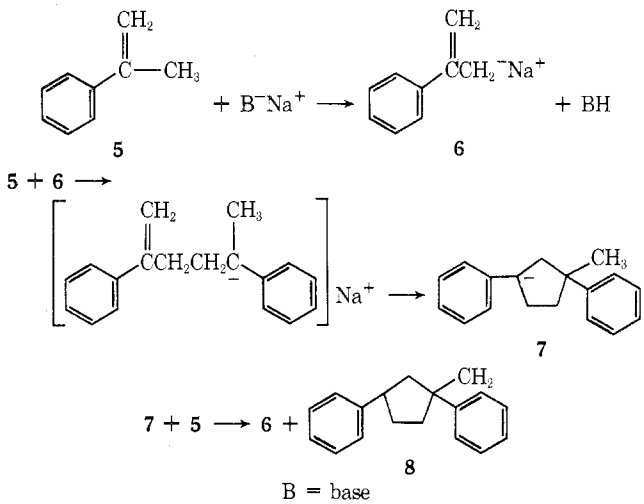
Chain initiation can be attributed to the addition



of alkali metals to the anthracene to form an anion radical which can then lead to mono- or dianion.[14] It has been suggested that in the presence of potassium at 200° the anion could also be produced by direct addition of the alkali metal to propene to form an intermediate anion radical.[13]

The dimerization of propene in a flow system over supported potassium or sodium on graphite or potassium carbonate, at 150° and under pressure, gave good yields of dimers, and the copolymerization of ethene with propene on supported alkali metal catalysts gave 92% *n*-pentenes.[15]

α-Methylstyrene. α-Methylstyrene (**5**) on refluxing in the presence of sodium–benzylsodium formed a cyclic dimer, **8**, in 32% yield.[16]



Reaction of Alkylaromatic Hydrocarbons with Olefins

The base-catalyzed reaction of alkylaromatics with olefins is unique in that it allows the size of the alkyl group of an arylalkane to be increased. Arylalkanes suitable for this reaction are those which contain a benzylic hydrogen. The olefins most useful for this reaction are ethene, propene, conjugated alkadienes, and styrene and its derivatives, such as α- and β-methylstyrene. Sodium and potassium are very effective catalysts. Sodium usually requires the presence of a "promoter" or a chain precursor to initiate the reaction. The presence of promoters is not required in those cases where the substrate reacts readily with the metal to form organo alkali metal compounds. Reviews on this subject have been published.[2,17,18]

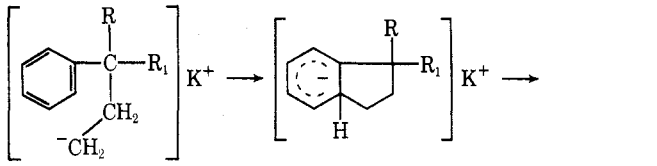
Ethylation of Alkylbenzenes. The ethylation proceeds at 150 to 200° with ethene pressure ranging

(8) H. Pines, J. A. Vesely, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **77**, 554 (1955).
(9) H. Gilman and H. A. Pacewitz, *J. Amer. Chem. Soc.*, **62**, 673 (1940).
(10) For general discussion of sodium anthracene complexes see K. Tamaru, *Advan. Catal. Relat. Subj.*, **20**, 327 (1969).
(11) J. A. Zoltewicz and L. S. Helmick, *J. Org. Chem.*, **38**, 658 (1973).
(12) V. Mark and H. Pines, *J. Amer. Chem. Soc.*, **78**, 5946 (1956).
(13) A. W. Shaw, C. W. Bittner, W. V. Bush, and G. Holzman, *J. Org. Chem.*, **30**, 3286 (1965).
(14) E. deBoer, *Advan. Organometal. Chem.*, **2**, 115 (1964).
(15) J. K. Hambling, *Chem. Brit.*, **5**, 354 (1969).
(16) M. Kolobielski and H. Pines, *J. Amer. Chem. Soc.*, **79**, 5820 (1957).
(17) G. G. Eberhardt, *Organometal. Chem. Rev.*, **1**, 491 (1966).
(18) H. Pines, *Synthesis*, in press.

from 1 to 70 atm. The reaction involves the replacement of benzylic hydrogens by ethyl groups, *i.e.*, toluene forms *n*-propylbenzene as the primary product of reaction. Further ethylation produces 3-phenylpentane and 3-ethyl-3-phenylpropane.[8]

This reaction can also be extended to the ethylation to cycloalkylbenzenes, indan, and tetrahydronaphthalenes.

Lithium anthracene is less active for ethylation of toluene than sodium anthracene,[19] while potassium also catalyzes cyclialkylation reaction, resulting in the formation of indans.[20] The ratio of indans to monoalkylbenzenes formed depends on the extent of substitution on the α carbon of the arylalkane; it increases from toluene, 2%, to ethylbenzene, 14%, and to isopropylbenzene, 49%. The following mechanism was proposed for the cyclialkylation reaction.



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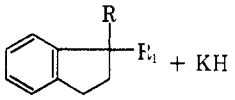
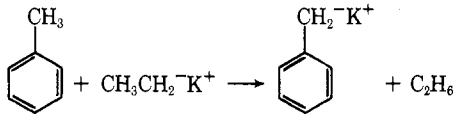


$$CH_2{=}CH_2 + KH \longrightarrow CH_3CH_2^-K^+$$

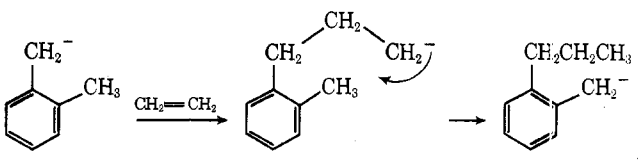
11



Potassium hydride–butyllithium or potassium metal–butyllithium seem to be more effective catalysts for cycliethylation reaction than potassium anthracene.[21] The role of lithium was explained by its coordinative ability to assist in the concerted reaction of the hydride abstraction from the aromatic nucleus.

The relative rates of ethylation of alkylbenzene using sodium anthracene as a catalyst is given in Table I.[20]

The relative rates of reactions of dialkylbenzenes are not easily explained. The presence of *p*-alkyl substitution causes a large decrease in rate, whereas *o*-xylene, which should have the same inductive effects as *p*-xylene, reacts thrice as fast as this rapid reaction of *o*-xylene was attributed to intramolecular transmetalation between the carbanion adduct with ethylene and the remaining methyl group. It was

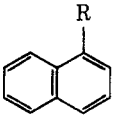


also observed that α-hydrogen in *o*-xylene is exchanged twice as fast as in *p*-xylene by lithium cyclohexylamide, and this was attributed to an entropy effect.[22]

Ethylation of Alkylnaphthalenes. Sodium in the presence of *o*-chlorotoluene promoter is a selective catalyst for the ethylation of alkylnaphthalenes under pressure and at 175–200°.[23] With 1-methylnaphthalene, propyl- (**10**) and pentylnaphthalene (**11**) are the only products formed. Only on prolonged stirring and heating a small amount of **12** is produced.

Table I
The Relative Rates of Reaction of Arenes with Ethene

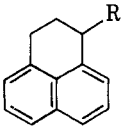
Hydrocarbon	Relative rate, toluene = 1
Ethylbenzene	2.8
n-Propylbenzene	1.2
Isopropylbenzene	1.9
sec-Butylbenzene	0.57
Indan	1.35
o-Xylene	1.9
m-Xylene	1.6
p-Xylene	0.62
p-Cymene	0.75
p-*tert*-Butyltoluene	0.21



9, R = CH_3
10, R = $CH_2CH_2CH_3$
11, R = $CH(C_2H_5)_2$
12, R = $C(C_2H_5)_3$

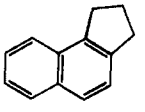
2-Methylnaphthalene, on the other hand, readily forms 3-*tert*-heptylnaphthalene.

Potassium-catalyzed ethylation of alkylanaphthalenes proceeds at 90–160°. The product from this reaction is complex and, besides the normal side-chain ethylation, cyclialkylation and nuclear alkylation also occur. From 1-methylnaphthalene cyclialkylated products **13** and **14** are obtained.

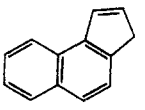


13, R = H
14, R = C_2H_5

2-Methylnaphthalene forms cyclialkylated compounds **15** and **16**.



15



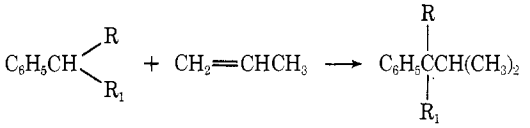
16

Propylation of Alkylbenzenes. The reaction of alkylbenzenes with propene is slower than that with ethene and requires temperatures of 230–280° to make it proceed satisfactorily in the presence of sodium[24,25] and 150° in the presence of potassium.[25] With lithium the alkylation is sluggish even at 300°.

The main product of side-chain propylation of tol-

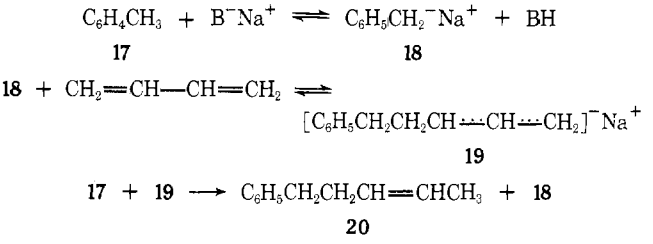
(19) L. A. Schaap and H. Pines, *J. Amer. Chem. Soc.*, **79**, 4967 (1957).
(20) H. Pines and L. A. Schaap, *J. Amer. Chem. Soc.*, **80**, 3076 (1958).
(21) G. G. Eberhardt, *J. Org. Chem.*, **29**, 643 (1964).
(22) (a) A. Streitwieser, Jr., and H. F. Koch, *J. Amer. Chem. Soc.*, 86, 404 (1964); (b) A. Streitwieser, Jr., J. R. Murdoch, G. Häffinger, and C. J. Chang, *ibid.*, **95**, 4248 (1973).
(23) B. Stipanović and H. Pines, *J. Org. Chem.*, **34**, 2106 (1969).
(24) H. Pines and V. Mark, *J. Amer. Chem. Soc.*, **78**, 4316 (1956).
(25) R. M. Schramm and G. E. Langlois, *J. Amer. Chem. Soc.*, **82**, 4912 (1960).

uene was isobutylbenzene. *n*-Butylbenzene in amounts ranging from 6 to 16% was also found in the alkylate fraction. The formation of the more stable primary anion intermediate is probably responsible for the predominance of isobutylbenzene. Higher alkylaromatics also react with propene to give the corresponding monoadducts. The reaction is accompanied by dimerization of propene to 2-methylpentenes.



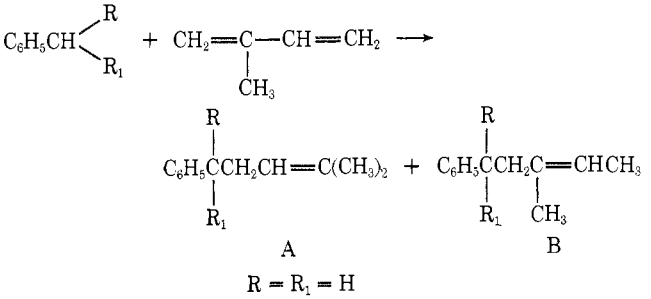
R = H, R_1 = H
R = H, R_1 = CH_3
R = CH_3, R_1 = CH_3
R = H, R_1 = C_6H_5

Alkenylation of Alkylbenzenes. The reaction of toluene with conjugated alkadienes was first reported in 1928.[26] Although the alkenylation reaction proceeds in the absence of added chain initiators, the presence of *o*-chlorotoluene in the preparation of the catalyst facilitates the reaction and eliminates the induction time necessary to initiate the reaction. The mechanism of alkenylation is similar to that described for the side-chain ethylation of alkylaromatics, and can be illustrated as follows.



The alkenylation reaction proceeds at 100° or below. Good yields, 80–91%, of monobutenylated alkylbenzenes were obtained from toluene, *o*- and *p*-xylenes, and ethylbenzene by contacting an excess of the alkylbenzenes with butadiene in the presence of a catalyst composed of 2.5% sodium or potassium deposited on calcium oxide.[27]

The pentenylation of alkylbenzenes with isoprene was carried out at 135° using dispersed sodium or potassium as catalysts.[28] Two monoadducts were obtained, A and B, with a ratio of A:B ranging from 2 to 3. The predominance of monoadduct A can be attributed to the greater stability of the intermediate monoadduct anions which are resonance stabilized.



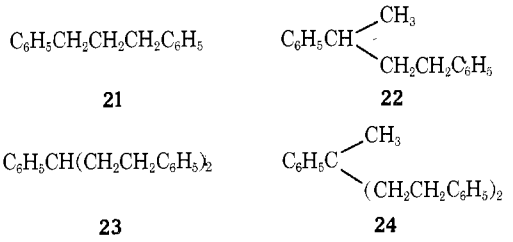
R = R_1 = H
R = H, R_1 = CH_3
R = R_1 = CH_3

In A the charge resides on primary and secondary carbon atoms and in B on primary and tertiary carbon atoms.

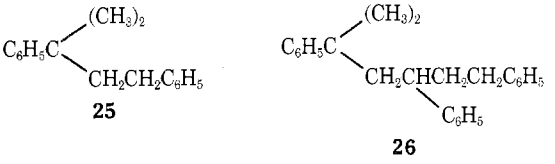
In the presence of a catalyst composed of sodium naphthalene in tetrahydrofuran solvent, the pentenylation of alkylbenzenes with isoprene occurs at 20°.[29] The yield of alkenylated product was 80% with toluene, and 40–50% with ethylbenzene, isopropylbenzene, and tetralin, with type A product also predominating.

Aralkylation of Alkylbenzenes. The aralkylation of alkylbenzenes with styrene and α- and β-substituted styrene has been studied in the presence of sodium and potassium. Mono- and diadducts have been produced in relatively good yields, depending upon experimental conditions and the structure of hydrocarbon used. The reaction proceeds with great ease at 100–120°, owing to the stabilization by the benzene ring of the intermediate anion adduct formed in the reaction.

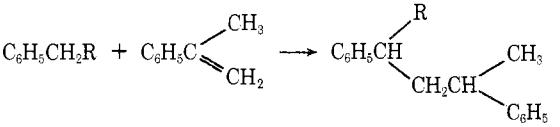
Toluene and ethylbenzene react with styrene in the presence of sodium and a chain initiator to form monoadducts **21** and **22** and diadducts **23** and **24**, respectively.[30]



Isopropylbenzene produces with styrene monoadduct **25** and diadduct **26**.



α-Methylstyrene reacts readily with *n*-alkylbenzenes at 100–105° in the presence of dispersed potassium to form 1,3-diphenylalkanes in yields ranging from 73 to 82%.[31]



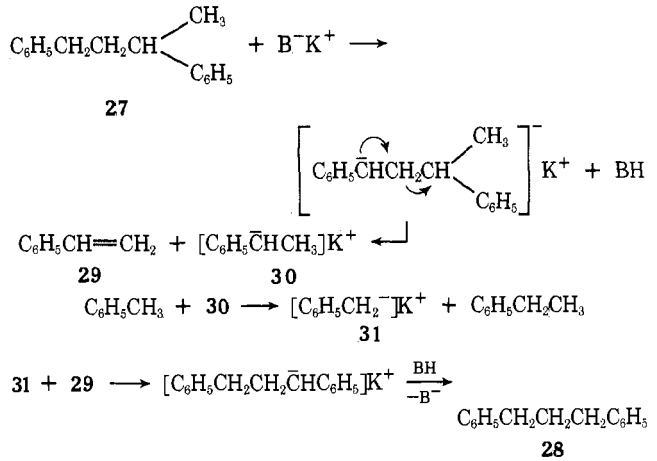
R = H, CH_3, and C_2H_5

On longer contact time, 5 hr *vs.* 2 hr, the monoadduct **27** produces ethylbenzene and **28**.

β-Methyl-, β-ethyl-, and β-isopropylstyrenes react with toluene at 110° in the presence of potassium to form the corresponding 1,3-diphenyl-2-alkylpropanes in 60–95% yield.[32]

β,β-Dimethylstyrene fails to react with toluene, but instead undergoes hydrodimerization to form **32**. This is a noncatalytic reaction and it is stoichiometrically related to the amount of potassium present.[33]

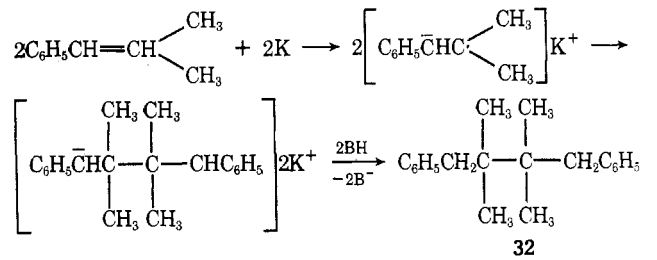
(26) F. Hoffman and A. Michael, U. S. Patent 2,448,641.
(27) G. G. Eberhardt and J. J. Peterson, *J. Org. Chem.*, **30**, 82 (1965).
(28) H. Pines and N. C. Sih, *J. Org. Chem.*, **30**, 280 (1965).
(29) S. Watanabe, K. Suga, and T. Fujita, *Synthesis*, **3**, 375 (1971).
(30) H. Pines and D. Wunderlich, *J. Amer. Chem. Soc.*, **80**, 6001 (1958).
(31) J. Shabtai and H. Pines, *J. Org. Chem.*, **26**, 4225 (1961).
(32) J. Shabtai, E. M. Lewicki, and H. Pines, *J. Org. Chem.*, **27**, 2618 (1962).



27 29 30 31 28

B^-K^+ and BH = an anion or a hydrocarbon containing a benzylic hydrogen

Its formation can be explained by the dimerization of anion radical produced through the addition of potassium to the styrene.



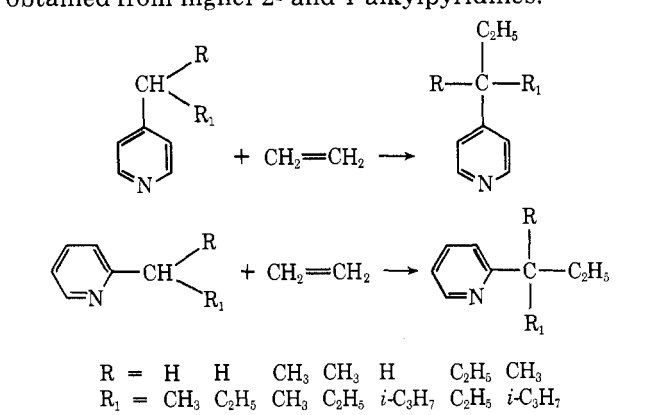
32

Reaction of Alkylpyridines with Olefins

The picolyl hydrogens of 2- and 4-alkylpyridines are more acidic than the corresponding benzylic hydrogens. For that reason, the reactions of alkylpyridines with olefins occur under mild conditions, and with conjugated dienes, styrenes, and vinylpyridines at below room temperatures. The mechanism of side-chain addition of olefins to alkylpyridines is very similar to that described for alkylbenzenes.

2- and 4-Alkylpyridines with Ethene. 4-Alkylpyridines undergo reaction with ethene under pressure at 140–150° in the presence of sodium.[34,35] With 2-alkylpyridines higher temperatures and the use of anthracene as promoter are required. 2- and 4-methylpyridines form the corresponding 2-*n*-propyl- and (3-pentyl)-2- and 4-pyridines.

Yields of 86–94% of monoethylated products are obtained from higher 2- and 4-alkylpyridines.[36]

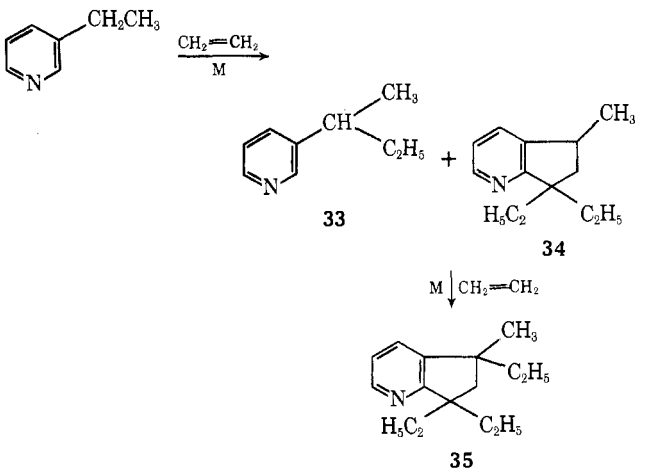


R =	H	H	CH_3	CH_3	H	C_2H_5	CH_3
R_1 =	CH_3	C_2H_5	CH_3	C_2H_5	*i*-C_3H_7	C_2H_5	*i*-C_3H_7

(33) J. Shabtai and H. Pines, *J. Org. Chem.*, **29**, 2408 (1964).
(34) E. Profft and F. Schneider, *Arch. Pharm.*, **289**, 99 (1955).
(35) H. Pines and D. Wunderlich, *J. Amer. Chem. Soc.*, **81**, 2568 (1959).

The relative ethylation of 4-alkylpyridines is 3.5 to 7.0 times greater than that of 2-alkylpyridines, and is associated with greater acidity of the 4 over the 2 isomers.[37] The relative rates of ethylation of 4-alkylpyridines closely parallel the rates obtained with alkylbenzenes (Table I). The rate of ethylation of 4-ethylpyridine is 5.5 greater than that of 4-methylpyridine, while the rate of ethylation of 4-isopropylpyridine is about the same as that of 4-ethylpyridine.[36] It seems that two or more factors are involved in the rate of ethylation: stability and/or concentration of the picolyl anions, and steric effects to the addition of the anions to ethylene.

3-Alkylpyridines with Ethene. The reaction between ethene and 3-alkylpyridines in the presence of alkali metals is much more complicated than similar reactions made with the corresponding 2 and 4 isomers.[38,39] The two primary products from the reaction of 3-ethylpyridine with ethene in the presence of either sodium or potassium are 3-*sec*-butylpyridine (**33**) and cyclic compound **34.** Further ethylation occurs with a longer reaction time to form **35.**



33 34 35

M = Na or K

2- and 4-Alkylpyridine with Olefins, Diolefins, Styrenes, and Vinylpyridines. The reaction of alkylpyridines with isoprene, styrenes, and vinylpyridines occurs at 0–25°, and that with propene takes place at 140°. The yields of adducts are high, and the compounds formed are those predicted from similar reactions made with alkylbenzenes (Table II[39-45]).

The relative rate of alkenylation of 4-alkylpyridines with either butadiene or isoprene is about 8 to 20 times greater than that of 4-methylpyridine, and therefore the alkenylation of 4-methylpyridine is always accompanied by dialkenylation.[42,46]

The reaction of 1,3-pentadienes with alkylpyridines is of special interest because the dienes exist in cis and trans configuration.[47] The monopentylated

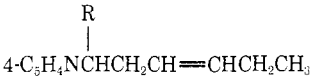
(36) H. Pines and B. Notari, *J. Amer. Chem. Soc.*, **82**, 2209 (1960).
(37) W. N. White and D. Lazdins, *J. Org. Chem.*, **34**, 2756 (1969).
(38) H. Pines and S. V. Kannan, *Chem. Commun.*, 1360 (1969).
(39) S. V. Kannan and H. Pines, *J. Org. Chem.*, **36**, 2304 (1971).
(40) H. Pines and B. Notari, *J. Amer. Chem. Soc.*, **82**, 2209 (1960).
(41) Y. I. Chumakov and V. M. Ledovskikh, *Ukr. Khim. Zh.*, **31**, 506 (1965).
(42) H. Pines and J. Oszczapowicz, *J. Org. Chem.*, **32**, 3183 (1967).
(43) W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 415 (1970).
(44) H. Pines and N. E. Sartoris, *J. Org. Chem.*, **34**, 2113 (1969).
(45) N. E. Sartoris and H. Pines, *J. Org. Chem.*, **34**, 2119 (1969).
(46) W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 422 (1970).
(47) J. Oszczapowicz and H. Pines, *J. Org. Chem.*, **37**, 2799 (1972).

Table II
Reaction of Alkylpyridines with Olefins in the Presence of Sodium

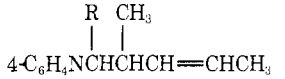
Alkylpyridine (PR) taken; R =	Olefins	Temp. °C	Compounds formed	Yield, %	Reference
4-PC—C	C=C—C	150	4-PC—C(C—C)C	74	40
2-PC—C—C	C=C—C	150	2-PC—C—C(C—C)C	80	40
2-PC[a]	C=C—C=C	~150	2-PC—C—C=C—C	53	41
			2-PC(C—C=C—C)$_2$	45	
			2-PC(C—C=C—C)$_3$	2	
3-PC—C[a]	C=C—C=C	60	3-PC—C(C—C=C—C)	78	39
			3-PC—C(C—C=C—C)$_2$	22	
4-PC—C—C	C=C—C=C	0–5	4-PC—C—C(C—C=C—C)	92	42
4-PC—C	C=C—C=C(C)	25	4-PC—C(C—C=C—C)C	65	43
			4-PC—C(C—C=C—C)C	35	
3-P—C	C=C—C=C(C)	80	3-PC—C—C=C—C(C)	75	39
			3-PC—C—C=C—C(C)	25	
2-PC	C_6H_5C=C	55	2-PC—C—CC_6H_5	69	44
			2-PC(C—CC_6H_5)$_2$	26	
4-PC	C_6H_5C=C	0	4-PC—C—CC_6H_5	40	44
			4-PC(C—CC_6H_5)$_2$	42	
			4-PC(C—CC_6H_5)$_3$	13	
4-PC—C(C)	C_6H_5C=C(C)	0	4-PC—C(C)—CC_6H_5(C)	86	44
2-PC—C	C_6H_5C=C—C	0–5	2-PC—C(C)—CC_6H_5(C)	99	44
4-PC—C	C_6H_5C=C—C		4-PC—C(C)—CC_6H_5(C)	99	44
2-PC	2-PC=C		2-PC—C—CP-2	70	45
			2-PC(C—CP—2)$_2$	21	
2-PC	4-PC=C		2-PC—C—CP-4	84	45

[a] Molar ratio alkylpyridine: butadiene = 1:1.

product from the reaction with *cis*-1,3-pentadiene consists of over 80% of straight-chain compounds (**36**), while with the trans isomer forms over 80% branched chain alkenylpyridines (**37**).



36, R = H or CH_3



37, R = H or CH_3

The aralkylation of alkylpyridines with β-methylstyrenes proceeds noticeably slower than the corresponding reactions with styrene and α-methylstyrene, and *trans*-β-methylstyrene reacts much faster than the cis isomer.[44]

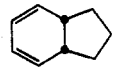
Intramolecular Cyclization Reactions

Octatrienes (1,3,6 and 1,3,7) undergo cyclization at room temperature in the presence of piperidinosodium to form a mixture of methylcycloheptadienes.[48] Potassium hydride catalyzes cyclization of 1,3- and 1,5-cyclooctadienes at 190° to form 84–94% of **38**.[49]

(48) E. A. Zuech, D. L. Crain, and R. F. Kleinschmidt, *J. Org. Chem.*, **33**, 771 (1968).
(49) L. Slaugh, *J. Org. Chem.*, **32**, 108 (1967).

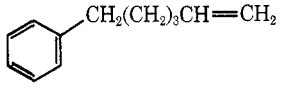
38

1,4,7-Cyclononatriene undergoes in the presence of potassium *tert*-butoxide in dimethyl sulfoxide double bond migration with ultimate cycloisomerization to form **39**.[50]

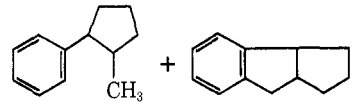


39

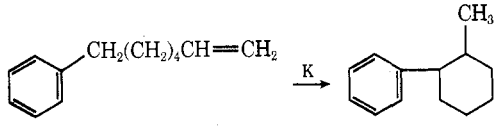
ω-Phenylalkenes **40** and **41** undergo cyclization and cyclialkylation at 185° in the presence of either potassium or cesium, and *o*-chlorotoluene promoter.[51] In the presence of sodium, however, only double bond migration occurs.



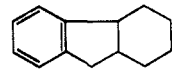
40



cis and trans 66% 12%

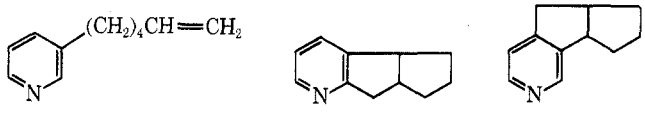


41 cis and trans 76%



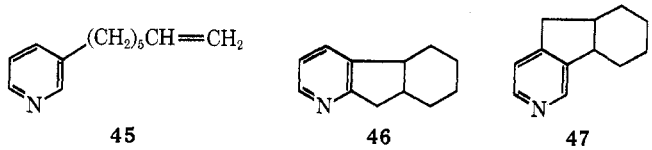
7%

6-(3-Pyridyl)-1-hexene (**42**) in the presence of either sodium or potassium forms **43** and **44** in good yields. **43** is the preferred tricyclic compound.[52]



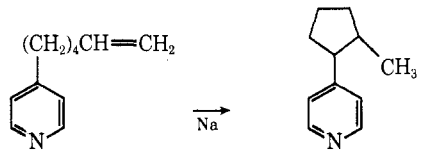
42 43 44

3-(6-Heptenyl)pyridine (**45**) undergoes a set of reactions analogous to **42**; tricyclic compounds **46** and **47** are produced.

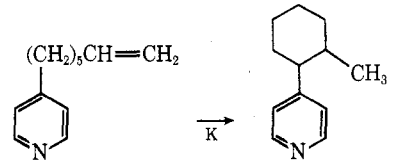


45 46 47

ω-(4-Pyridyl)alkenes **48** and **49** in the presence of either sodium or potassium undergo only monocyclization to form **50** and **51** with yields of over 80%.[52]



48 **50**, 87% trans, 13% *cis*



49 **51**, ~100% trans

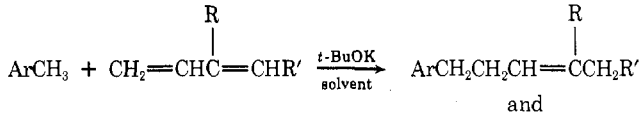
Table III
Effect of Solvents on Reaction Rate and Product Ratio of 4-Isopropylpyridine with Isoprene[a]

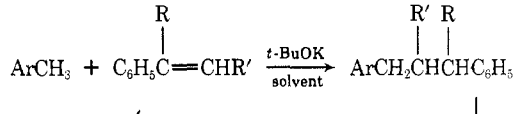
Solvent[b]	$t_{1/2}$, min	Rate constant[c] × 10^5 sec^{-1}	Product,[e] % head addition	tail addition
DMSO	1.15	1010	59	41
HMPA	1.89	612	41	59
NM-2-P[d]	32.8	35.2	52	48
DMF	70.7	16.4	54	46
TMSO	240	4.8	51	49
TMU	250	4.7	51	49
THF, *p*-dioxane, DME	>1000			

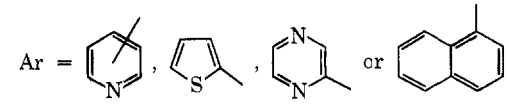
[a] Concentration of reagents 4-isopropylpyridine 4.8 *M* and isoprene 0.6 *M*; potassium *tert*-butoxide concentration 0.45 *M*. [b] DMSO, dimethyl sulfoxide; HMPA, hexamethylphosphoramide; NM-2-P, *N*-methyl-2-pyrrolidone; DMF, dimethylformamide; TMSO, tetramethylene sulfoxide; TMU, tetramethylurea; THF, tetrahydrofuran; DME, dimethoxyethane. [c] The pseudo-first-order rate constants were determined at 20°. [d] The alkylpyridine used was 4-ethylpyridine. [e] Head adduct: $CH_3C(4\text{-py})RCH_2C(CH_3)=CHCH_3$; tail adduct: $CH_3C(4\text{-py})RCH_2CH=C(CH_3)_2$; R = H or CH_3.

Homogeneous Carbon–Carbon Addition Reactions

The use of aprotic solvents promotes anionic reactions of very weak organic acids under mild conditions. A variety of alkylaromatic compounds undergo alkenylation and aralkylation in a homogeneous solvent–*t*-BuOK system.[53,54] The reactions can be represented by the following equations.







R, R' = H or CH_3

The rate of reaction is greatly influenced by the type of solvents used[54] (Table III). The results are in agreement with the data obtained for the isomerization of olefins,[55,56] but the results are in contradic-

(50) J. W. H. Wathley and S. Winstein, *J. Amer. Chem. Soc.*, **85**, 3715 (1963).
(51) H. Pines, N. C. Sih, and E. Lewicki, *J. Org. Chem.*, **30**, 1457 (1965).
(52) H. Pines, S. V. Kannan, and W. M. Stalick, *J. Org. Chem.*, **36**, 2308 (1971).
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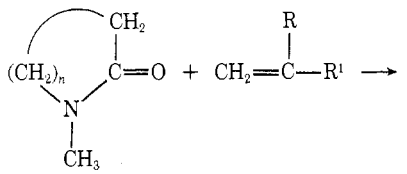
(54) H. Pines, W. M. Stalick, T. G. Holford, J. Golab, H. Lazar, and J. Simonik, *J. Org. Chem.*, **36**, 2299 (1971).
(55) S. Bank, A. Schriesheim, and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **87**, 3244 (1965).

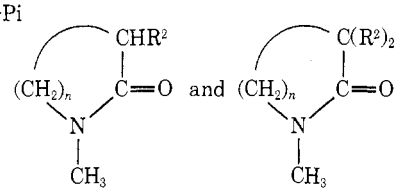
tion with the findings that HMPA is the best dipolar aprotic solvent.[57] A similar solvent effect was encountered in the addition of styrenes to alkylpyridines.[54]

Base-Catalyzed Carbon–Carbon Addition of "Aprotic Solvents"

In the course of an attempt to aralkylate 3-ethylpyridine with styrene using *t*-BuOK as catalyst in "aprotic" solvent *N*-methyl-2-pyrrolidone (NM-2-P), it was found that the solvent itself enters reaction.[58] A similar type of reaction occurred with *N*-methyl-2-piperidone (NM-2-Pi). The general scope of the reaction is represented by



$n = 2$ = NM-2-P
$n = 3$ = NM-2-Pi



R = H; R^1 = CH=CH_2; R^2 = CH_2CH=$CHCH_3$
R = H; R^1 = $C(CH_3)$=CH_2; R^2 = $CH_2CH_2CH(CH_3)_2$, $CH_2CH(CH_3)C_2H_5$ (after hydrogenation)
R = H; R^1 = C_6H_5; R^2 = $CH_2CH_2C_6H_5$
R = H; R^1 = $Si(CH_3)_3$; R^2 = $CH_2CH_2Si(CH_3)_3$
R = CH_3; R^1 = C_6H_5; R^2 = $CH_2CH(CH_3)C_6H_5$

(56) A. Schriesheim, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14**, D9 (1969).
(57) J. J. Delpuech, *Tetrahedron Lett.*, 2111 (1965).
(58) H. Pines, S. V. Kannan, and J. Simonik, *J. Org. Chem.*, **36**, 2311 (1971).

The addition reaction takes place at room temperature. In the case of less reactive olefins, such as α-methylstyrene or trimethylvinylsilane, it is essential to carry out the reaction in dimethyl sulfoxide. The yield of products, based on the olefins charged, was about 100%. NM-2-Pi reacts about twice as fast as NM-2-P.

Although DMSO is used extensively as an aprotic solvent, the hydrogens in DMSO are quite labile.[5,59,60] Dimethyl sulfoxide under the influence of base can react with a variety of conjugated dienic hydrocarbons,[61] arylalkenes,[62] and aromatic and heteroaromatic ring compounds.[61,63,64] The net result of these reactions is the formation of methylated analogs of the starting hydrocarbons.

The methylation reactions can be explained by a mechanism using butadiene as an example.[61]

$$CH_3SOCH_3 + t\text{-}BuO^-K^+ \rightleftharpoons \underset{\mathbf{52}}{CH_3SOCH_2^-K^+} + t\text{-}BuOH$$

$$\mathbf{52} + CH_2{=}CHCH{=}CH_2 \rightleftharpoons \underset{\mathbf{53}}{[CH_3SOCH_2CH_2CH{\cdots}CH{\cdots}CH_2]^-K^+}$$

$$\mathbf{53} + BH \longrightarrow \underset{\mathbf{54}}{CH_2SOCH_2CH_2CH{=}CHCH_3} + B^-K^+$$

$$\mathbf{54} + B^- \longrightarrow CH_3SOCH_2\bar{C}HCH{=}CHCH_3 + BH$$

$$CH_3SOCH_2\bar{C}HCH{=}CHCH_3 \longrightarrow CH_3SO^- + CH_2{=}CHCH{=}CHCH_3$$

I wish to thank the collaborators listed in the references for their invaluable contribution to the progress and development of the work.

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(60) C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, **89**, 2960 (1967), and references therein.
(61) P. A. Argabright, J. E. Hofmann, and A Schriesheim, *J. Org. Chem.*, **30**, 3233 (1965).
(62) M. Feldman, S. Danischefsky, and R. Levine, *J. Org. Chem.*, **31**, 4322 (1966).
(63) G. A. Russell and S. A. Weiner, *J. Org. Chem.*, **31**, 248 (1966).
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Protein Interactions with Small Molecules

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Binding of a small molecule by a protein is the pivotal step in a host of biological functions. One of the earliest recognized, and now most familiar, of such interactions is the uptake of O_2 by hemoglobin, where binding inaugurates the transport of molecular oxygen throughout the vascular system. It has been increasingly realized that similar interactions appear at all stages in biochemical and physiological functions, from the cellular level to the organismic.

From a biochemical viewpoint our perception of the molecular nature of these interactions is sharpened if we categorize them in terms of the conformational accommodation that plays a dominant role in the functioning of the protein–small molecule complex (Figure 1).[1] In some situations the conformational adaptation of the protein (Figure 1A) is the

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