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SYNTHETIC APPLICATIONS OF HOMOGENEOUS BASE-CATALYZED ADDITIONS OF AROMATIC ALKYLHETEROCYCLICS TO CONJUGATED HYDROCARBONS

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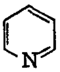
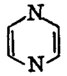
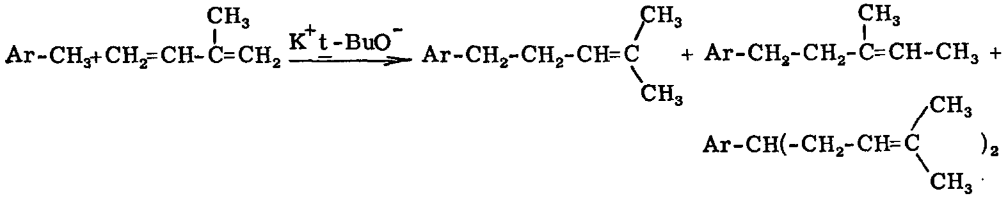
We wish to report a catalytic synthetic method for the preparation of heterocyclic aromatic addition compounds in homogeneous media. We have found it possible to alkenylate a large number of heterocyclic compounds in significant quantities. The reaction of a conjugated diene with a compound of the type Ar-CH_3(Ar =  ,  , ) produces the addition products in good yields. The following scheme indicates the two monoaddition and one diaddition products obtained when isoprene is the olefin used:

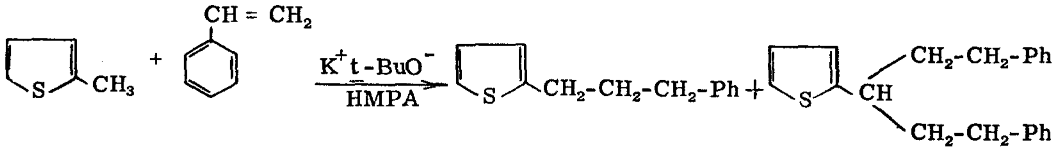


$$Ar\text{-}CH_3 + CH_2{=}CH\text{-}\overset{CH_3}{\overset{|}{C}}{=}CH_2 \xrightarrow{K^+t\text{-}BuO^-} Ar\text{-}CH_2\text{-}CH_2\text{-}CH{=}\underset{CH_3}{\overset{CH_3}{C}} + Ar\text{-}CH_2\text{-}CH_2\text{-}\overset{CH_3}{\overset{|}{C}}{=}CH\text{-}CH_3 + Ar\text{-}CH(\text{-}CH_2\text{-}CH{=}\underset{CH_3}{\overset{CH_3}{C}})_2$$

Under optimum conditions some of the reactions have been found to give nearly quantitative yields of the desired compounds with only trace amounts of side reaction products. The best solvents for these reactions were found to be the dipolar solvents dimethylsulfoxide and hexamethylphosphoramide.

There have been previous examples indicating that dipolar aprotic solvents enhance the rate of base-catalyzed reactions.[1] However, in this particular type of solvent-catalyst system there has been reported only one preliminary account of the condensation of conjugated olefins with compounds of the general structure x-CH_3, x= nitro, nitrile, or carbonyl.[2] To date, the wide range of compounds that are susceptible to this type of addition reaction has not been reported, although the reactions are easily carried out and appear to be a valuable synthetic tool.

Table I lists some of the compounds that have been observed to undergo reaction. These reactions seem to be generally applicable, even for the more sensitive heterocyclic compounds which undergo decomposition in the quasi-homogeneous system of catalytic amounts of metallic sodium or potassium dispersed in a substrate medium.[3,4] One notable example is the reaction of 2-methylthiophene with styrene to give the two products shown:



The other reactions unique to this system are the additions of β-picoline to styrene and of 2-methylpyrazine to isoprene. The reaction rate and products varied with the reactants involved; while the condensation of 2-methylthiophene with styrene was a fairly slow reaction accompanied by some minor side products, the reaction of some γ-alkyl pyridines with isoprene gave quantitative conversion of the pyridine in a short time, and was accompanied by almost undetectable amounts of side reaction products. Other olefins used include piperylene, α-methylstyrene, β-methylstyrene and butadiene. The addition of these olefins proceeded in the same manner as that of isoprene and styrene to give analogous products.

Some of the percent conversions listed in Table I represent data from earlier runs in which the reactants were not purified as is necessary for optimum yields. Also it was found that product ratios could be varied depending upon the amount of olefin used. For example, in the reaction of γ-picoline with isoprene it was found that an isoprene/picoline ratio of 2.0 to 2.5 gave a 96% yield of the diaddition product, $\gamma\text{-}C_4H_5NCH(CH_2CH{=}C(CH_3)CH_3)_2$, thus providing a convenient synthesis of this compound. Monoaddition products could be separated from diaddition products by vacuum distillation. If styrene is the olefin reacted, only one monoaddition and one diaddition product can be formed. If, however, isoprene is used the two monoaddition products were separated by gas chromatography. Only one diaddition product is formed, although three are theoretically possible.

All of the needed reactants and solvents were distilled immediately before use. The catalyst solutions were prepared in a dry box and then removed to the laboratory, where the general reaction procedure followed was similar to that of Schriesheim and co-workers for the isomerization of olefins.[6] The samples from these reactions were quenched with methanol and analyzed for products by the use of gas chromatography. Identifications were made by I. R., N. M. R., and elemental analysis. Larger quantities of material could be prepared with only slight variations in procedure.

TABLE I

Reactions of Alkylaromatic Compounds with Conjugated Olefins in Various Potassium *tert*-Butoxide Solutions

Solvent[a]	Substrate[b]	Olefin[c]	Percent Conversion[d]	Number of Products[e] Mono addition	Di-addition	Product Ratio[f] Mono/Di
HMPA[g]	γ-Picoline	Isoprene	83	2	1	1.00
HMPA	γ-Isopropylpyridine	Isoprene	100	2	-	-
HMPA	1-Methylnapthalene	Styrene	26	1	-	-
HMPA	α-Ethylpyridine	Isoprene	20	1	-	-
HMPA	γ-Picoline	Styrene	70	1	1	0.67
HMPA	2-Methylthiophene	Styrene	10	1	1	1.00
HMPA	β-Picoline	Styrene	46	1	1	0.77
DMSO[h]	γ-Ethylpyridine	Isoprene	90	1	2	0.83

[a] Potassium *tert*-butoxide catalyst concentration varied from 0.5 to 0.7 molar. [b] Molarity of substrate varied from 3 to 10 molar. [c] Olefin molarity ranged from 3 to 15 molar. [d] Conversion percentages are approximate, as they are based on only one observation in each case. [e] Monoaddition and diaddition refer to the addition of one or two olefin units to a single substrate unit. Structures of products are given in the text. [f] It was possible to control the ratio of products by varying the concentration of olefin used. [g] Hexamethylphosphoramide. [h] Dimethylsulfoxide.

A unique feature of this reaction is that no isomerization of the double bond was observed in the products isolated. Also, these homogeneous reactions now permit kinetic studies to be made on a wide variety of compounds in order to determine the detailed mechanism of side-chain alkylation reactions.[5] The solvent plays an important role in determining the rate of the addition reactions. Studies in progress indicate that the pseudo first-order alkenylation of γ-isopropylpyridine with isoprene proceeds fastest in dimethylsulfoxide. In this solvent a 50% conversion to products ($t_{\frac{1}{2}}$) has been observed to occur in approximately one minute at 20° C. Other solvents have been found to support the reaction with the following half-lives: hexamethylphosphoramide, $t_{\frac{1}{2}} \simeq 30$ minutes; and dimethylformamide, $t_{\frac{1}{2}} \simeq 65$ minutes. In tetramethylurea and tetramethylenesulfoxide however, the rate of reaction appears to be slower than in any of the solvents listed above.[7] Thus through the proper selection of a solvent, it is possible to control these reactions to produce the desired products at the optimum rate. Work is now in progress on measuring the rates of reaction when the olefin and substrates are varied, and on increasing the scope of this type of reaction to make it a synthetically useful route for an even larger range of weakly acidic compounds.

REFERENCES

1. D. J. Cram, Fundamentals of Carbanion Chemistry, p 32-33, and references contained therein. Academic Press, New York (1965).
2. J. E. Hofmann and A. Schriesheim, Preprints, Division of Petroleum Chemistry, 153rd National Meeting of The American Chemical Society, Miami Beach, Florida, March 1967, p. 161.
3. H. Pines and J. Oszczapowicz, J. Org. Chem., **32**, 3183 (1967).
4. H. Pines, W. Stalick, B. Stipanovic, and N. Sartoris, unpublished results from this laboratory.
5. For general references see H. Pines and L. A. Schaap Advances in Catalysis, **12**, 117 (1960).
6. S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Naslund, J. Am. Chem. Soc., **89**, 6897 (1967), and references contained therein.
7. Reaction rate studies were performed by Thomas G. Holford.