TABLE II
PHYSICAL PROPERTIES OF SUBSTITUTED TRIFLUOROACETOPHENONES[a]

Substituent	Registry no.	Bp, °C (mm)	Mp,[b] °C	Ir, μ (C=O)	$n^{20}D$	^1H nmr[c]	^{19}F nmr[d]
p-NH_2	23516-79-2	113 (0.5)	94.5–95.5	5.93		7.9, 6.6 (d, 4 H) 4.50 (br s, 2 H)	71.03
m-NH_2	23516-80-5	82 (0.5)		5.85		7.3 (m, 4 H) 3.90 (s, 2 H)	71.54
p-$N(CH_3)_2$	2396-05-6		74–75[e]	5.94		7.9, 6.6 (d, 4 H) 3.04 (s, 6 H)	70.84
p-Cl[f]	321-37-9	84 (23)		5.80	1.4901	7.78 (A_2B_2, 4 H)	72.03
p-Br	16184-89-7	95 (4)		5.80	1.5141	7.77 (A_2B_2, 4 H)	72.02
p-I	23516-84-9	89 (1)		5.80	1.5589	7.80 (A_2B_2, 4 H)	72.01
p-CN	23516-85-0	71 (0.2)	53–55	5.80		8.08 (A_2B_2, 4 H)	72.19
m-I	23516-86-1	89 (3)		5.81	1.5431	8.1, 7.3 (m, 4 H)	72.04
m-CN	23568-85-6	71 (0.2)		5.79		7.95 (m, 4 H)[g]	72.07[g]

[a] All compounds gave satisfactory C, H, N analyses with the exception of *m*-NH_2 (slightly impure). [b] All melting points are corrected. [c] In δ, parts per million, downfield from TMS; $CDCl_3$ solvent. [d] In parts per million upfield from $CFCl_3$; $CDCl_3$ solvent. The three fluorines appeared as a singlet in all cases. [e] Lit.[7] mp 74.5–75.5°. [f] Also identified by comparison of ir spectra with an authentic sample.[2] [g] A small amount of DMSO-d_6 was added to dissolve all of the material.

This preparation of III is superior to the one reported,[7] since pure material can be obtained with a minimum of experimental difficulty.

The preparation of *m*-aminotrifluoroacetophenone (IV) was carried out by conventional means. That is, trifluoroacetophenone[2] was nitrated in the *meta* position according to the method of Stewart and Vander Linden,[8] and reduced to the amine with tin and hydrochloric acid.

Both II and IV were readily diazotized and used to prepare other substituted ketones. General procedures for such diazotization reactions (Sandmeyer reactions) have been described.[9] Table I indicates the ketones which were prepared from II or IV, the isolated yields, and reagents used. Table II lists the physical properties of all materials prepared.

Experimental Section

***p*-Aminotrifluoroacetophenone.**—Into a 1-l., three-necked flask equipped with a reflux condenser and gas inlet tube extending to the bottom of the flask were placed 61.6 g (0.32 mol) of *p*-fluorotrifluoroacetophenone (I)[2] and 200 ml of DMSO. The solution was stirred vigorously with a magnetic stirrer and heated to 135°. A large trap was inserted between the gas inlet tube and a tank of anhydrous ammonia, and ammonia was bubbled into the solution at a moderate rate for 24 hr. (The gas inlet tube had to be cleaned of solid formations several times during the reaction.) After cooling, the solution was poured into 1 l. of ice–water and stirred for several hours, and the dark precipitate was collected on a suction filter. The solid was air-dried and then melted and distilled under reduced pressure to yield 25.3 g (42%) of *p*-aminotrifluoroacetophenone (II).

***p*-Dimethylaminotrifluoroacetophenone.**—In the manner described previously, ammonia gas was bubbled into 57.5 g (0.30 mol) of *p*-fluorotrifluoroacetophenone (I) and 200 ml of DMF. The addition of ammonia continued for 12 hr while the reaction temperature was held at 150°. The mixture was cooled, poured over 1200 ml of water, and stirred overnight, and the precipitate was collected on a suction filter. The light green solid was recrystallized from a water–ethanol mixture. The crystals were dried over $CaSO_4$ at *ca.* 1-mm pressure. The yield was 36.2 g (55%).

***m*-Aminotrifluoroacetophenone.**—Into a 1-l., three-necked flask equipped with a reflux condenser and magnetic stirrer were placed 36.0 g (0.30 g-atom) of tin granules and 34.0 g (0.16 mol) of *m*-nitrotrifluoroacetophenone,[8] bp 131° (10 mm) [lit. bp 113° (12 mm)]. The mixture was stirred vigorously while 350 ml of concentrated hydrochloric acid was added in three portions. The reaction was moderated with a water bath. After the addition was completed, the solution was refluxed for 1 hr, cooled, and neutralized with aqueous sodium bicarbonate. The mixture was extracted twice with 200-ml portions of ether, and the extracts were washed with water. The ether was evaporated and the residue was distilled under reduced pressure to yield 11.5 g (39%) of *m*-aminotrifluoroacetophenone. Glpc analysis indicated 95% purity.

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Base-Catalyzed Reactions. XXXVIII.[1] Selected Lithium-Catalyzed Reactions of 4-Alkylpyridines with Olefins

WAYNE M. STALICK[2] AND HERMAN PINES

Ipatieff High Pressure and Catalytic Laboratory, Department of Chemistry, Northwestern University, Evanston, Illinois 60201

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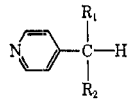
In previous papers of this series it was reported that sodium and potassium are catalysts for the side-chain alkylation,[3] aralkylation,[4] and alkenylation[5] of alkyl aromatics. It was also reported that potassium cat-

(1) (a) For paper XXXVII, see W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 422 (1970). (b) Paper IX of the series Alkylation of Heteroaromatics. (c) For part VIII see ref 1a.
(2) Taken in part from the Ph.D. thesis of W. M. Stalick, Northwestern University, Aug 1969.
(3) H. Pines and L. A. Schaap, *Advan. Catal.*, **12**, 117 (1960).
(4) (a) H. Pines and D. Wunderlich, *J. Amer. Chem. Soc.*, **80**, 6001 (1958); (b) H. Pines and J. Shabtai, *J. Org. Chem.*, **26**, 4220 (1961); (c) J. Shabtai, E. M. Lewicki, and H. Pines, *ibid.*, **27**, 2618 (1962).
(5) H. Pines and N. C. Sih, *ibid.*, **30**, 280 (1965).

TABLE I

EFFECT OF CHANGING CATALYST ON PRODUCT RATIO AND CONVERSION



Expt no.	R_1	R_2	Catalyst	Temp, °C	Reaction time, hr	% conversion[a]	Products, % — Monoaddition — I[b]	Monoaddition — II[c]	Diaddition — I[d]	Diaddition — II[e]	Diaddition — III[f]
1	CH_3	CH_3	K	20–25	2.5	75	58	42			
2	CH_3	CH_3	Na	20–25	2.0	84	77	23			
3	CH_3	CH_3	Li	20–25	>12.0	60	91	9			
4	H	CH_3	K	0–25	2.5	100[g]	39	32	14	15	Trace
5	H	CH_3	Na	20–25	2.5	96[h]	44	21	20	14	1
6	H	CH_3	Li	20–25	>15.0	98	75	18	5	2	Trace
7	H	H	K	20–25	1.5	51	13	9	38	32	8
8	H	H	Na	20–25	2.0	56	35	22	43		
9	H	H	Li	70	3.0	54	32	18	50		
10	H	H	*n*-BuLi	20–25	5.0	~95[i]	44	27	39		

[a] Per cent conversion is based on alkylpyridine reacted. [b] Tail addition compound. [c] Head addition compound. [d] Di-tail addition compound. [e] Head and tail addition compound. [f] Di-head addition compound. [g] After 1 hr at 0° the conversion was 70% and after 2 hr 93%. [h] After 1 hr at 23° the conversion was 66%. [i] Per cent conversion is based on isoprene for this experiment.

TABLE II

SIDE-CHAIN ETHYLATION OF 4-ETHYLPYRIDINE

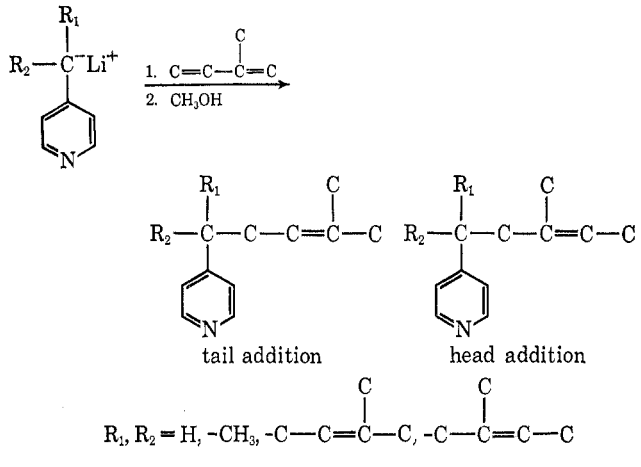
Expt no.	Catalyst	Temp, °C	Reaction time, hr	Max[a] *P*, atm	Min[a] *P*, atm	% yield	Mono-addition	Di-addition
1[b]	Na	150	5	28	10	58	100	
2	Li	150	15	45	45	0		
3	Li	185	12	105	74	49	86	14

[a] Maximum and minimum pressures at the reaction temperature. [b] Results taken from previous work; see footnote 15.

alyzed the cyclization of alkenylbenzenes while sodium gave only double-bond isomerization and lithium was inert,[6] indicating a marked difference in the catalysts. A similar trend was noticed in the cyclialkylation reaction of alkylbenzenes with olefins.[7] The use of lithium as a catalyst for the side-chain alkylation of toluene with ethylene[8] and propylene[9] has been reported, but the reactions had to be made at temperatures of 230–320°, and the yields of the side-chain alkylated products were very low. Owing to low yields and relatively high temperature, the products from the side-chain alkylation could be ascribed to a thermal[10] rather than to a catalytic reaction.

Since 2- and 4-alkylpyridines are more reactive than the corresponding alkylbenzenes, it was possible to carry out side-chain alkenylation and aralkylation reactions using conjugated dienes or styrenes[11] as olefins at room temperature or lower in the presence of sodium or potassium catalysts. The possible use of lithium as a catalyst for addition of 4-alkylpyridines to olefins was thus reinvestigated.

As in the case of potassium and sodium we now report that a catalytic amount of lithium metal can be dispersed in a 4-alkylpyridine medium to give the corresponding anions of 4-picoline, 4-ethylpyridine, and 4-isopropylpyridine. The reaction of 4-alkylpyridine with isoprene proceeds as follows.



The rates of addition for the lithium-catalyzed reactions are slower than for sodium and potassium (Table I). Previous studies indicated that sodium-catalyzed reactions were more selective, giving a larger amount of tail-addition product, than reactions catalyzed by potassium.[12] Table I reveals that the trend is continued, with lithium being the most selective of the three catalysts. This is best illustrated in expt 1–3 using 4-isopropylpyridine as the alkylpyridine, because in these experiments the absence of diaddition products permits a more quantitative estimation of the stereospecificity of the addition reaction.

The reaction was also tried using an *n*-butyllithium catalyst without any solvent, and expt 10 (Table I) shows that this reaction proceeds in a manner compara-

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(10) H. Pines and J. T. Arrigo, *ibid.*, **79**, 4958 (1957).
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(12) (a) H. Pines and J. Oszczapowicz, *ibid.*, **32**, 3183 (1967); (b) W. M. Stalick and H. Pines, *ibid.*, **35**, 415 (1970).

ble with the others. This is in contrast to the ring alkylation noted by other workers when *n*-butyllithium was used to metalate 4-picoline in ether.[13] The side-chain alkenylation of 4-alkylpyridines with isoprene in the presence of lithium gave no indication of polymerization, although lithium was reported to be highly stereoselective when used to polymerize isoprene in hydrocarbon solvents.[14]

The sodium-catalyzed addition of 4-ethylpyridine to ethylene has been studied in these laboratories.[15] Lithium-catalyzed reactions required longer reaction times and higher temperatures to get yields comparable with those obtained with sodium (Table II). In expt 2, under conditions for which sodium is known to catalyze the addition of ethylene, a lithium catalyst failed to yield any product.

Experimental Section[16]

Reagents.—4-Picoline and 4-ethylpyridine were obtained from Reilly Tar and Chemical Co. 4-Isopropylpyridine was purchased from Pfaltz and Bauer, Inc. The alkylpyridines were distilled, dried over Linde 5A Molecular Sieves, and redistilled immediately before use. Isoprene (Aldrich) was distilled before use and ethylene (Matheson) was used directly from the tank. Regular grade lithium metal (A. D. MacKay Inc.) was used.

General Procedure for Alkenylation Reactions.—The catalyst was prepared by dispersion of 15×10^{-4} g-atom of freshly cut alkali metal under predried *n*-pentane into 0.03 mol of 4-ethylpyridine or 4-isopropylpyridine for 5–10 hr to ensure complete dispersion. The reactions were performed under a slow stream of dry nitrogen in a three-necked flask equipped with reflux condenser, a rubber septum through which additions and withdrawals could be made with a syringe, and a specially designed high-speed stirrer. The active catalyst was a brown-black pseudohomogeneous solution. Isoprene (0.03–0.09 mol) was then added by a syringe to the catalyst solution, and the reaction carried out at room temperature. Samples were withdrawn periodically during the reaction, decomposed with methanol, and analyzed by vpc. At the conclusion of the reaction, the catalyst was decomposed with methanol. It was not possible to disperse lithium in 4-picoline at room temperature; so in this case the 4-picoline was heated to 130° and stirred for 3 hr before all of the lithium was dispersed. The catalyst solution was cooled and isoprepene added when the mixture was at 70°. The reaction was then followed as described above.

Ethylation of 4-Ethylpyridine.—The dispersion of lithium metal was carried out as described for the isoprene reactions. The lithium–4-ethylpyridine catalyst solution was transferred to a 100-ml-capacity Magne-Dash agitated autoclave. The autoclave was sealed, and after flushing with nitrogen it was charged with 40–70 atm of ethylene and heated to the desired temperature (see Table II). Stirring was started and continued for 8–12 hr until the pressure finished dropping. The stirring was then stopped and the autoclave removed from the heating jacket and allowed to cool. After the pressure was released, a few milliliters of methanol was added to the reaction mixture to decompose the organolithium compounds. The crude reaction mixture was then analyzed by vpc.

***n*-Butyllithium-Catalyzed Reactions.**—In a drybox 0.05 mol of 4-picoline was placed in a 30-dram vial, and 0.0025 mol of *n*-butyllithium (Alfa, 90% in hydrocarbon) was slowly added. An exothermic reaction occurred, giving a dark brown solution like that obtained when lithium metal was dispersed in the 4-alkylpyridines. A rubber septum was inserted and the catalyst solution was removed to the laboratory where the reactions were carried out at room temperature. Isoprene (0.015 mol) was then injected through the septum, and samples were removed with a syringe at various intervals, decomposed with methanol, and analyzed by vpc.

Registry No.—4-Isopropylpyridine, 696-30-0; 4-ethylpyridine, 536-75-4; 4-picoline, 108-89-4.

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(16) All compounds were identified by comparison with authentic samples from our laboratories.

Solvent Effects in the Base-Catalyzed Cyclization of 5-Chloro-2-pentanone

RICHARD A. BARTSCH AND DAVID M. COOK[1]

Department of Chemistry, Washington State University, Pullman, Washington 99163

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Cyclization of γ-substituted ketones is an important synthetic route to cyclopropylcarbonyl compounds.[2] The base-catalyzed cyclization of 5-halo-2-pentanones to cyclopropyl methyl ketones is well known.[3,4] The analogous formation of cyclopentanone, though conceivable, is not observed. It has been proposed that the preferred cyclization to a three-membered ring is due to solvation.[5] A high degree of solvation of the enolate anion produced by abstraction of the methyl proton would hinder intramolecular displacement, whereas only slight solvation of the enolate anion formed by removal of the methylene proton would be anticipated and intramolecular substitution would be more facile. If this is correct, the relative amounts of cyclopropyl methyl ketone and cyclopentanone should be strongly influenced by the anion-solvating properties of the reaction medium.

Successful cyclization of 5-halo-2-pentanones has been reported only with potassium or sodium hydroxide in water. Other base–solvent systems gave little or no yield of cyclopropyl methyl ketone.[4,6] Thus, only limited information is available concerning the effect of solvent.

Using gas–liquid partition chromatography (glpc), the cyclization of 5-chloro-2-pentanone in a number of base–solvent systems has been examined. Reaction of 5-chloro-2-pentanone with an excess of base produced the yields of cyclopropyl methyl ketone recorded in Table I. Although an estimated 0.2% yield of cyclopentanone would have been detected, no cyclization to form the five-membered ring was observed.

The results presented in Table I demonstrate that essentially quantitative cyclization of 5-chloro-2-pentanone to cyclopropyl methyl ketone can be induced by a variety of base–solvent systems. In view of the preferred cyclization to a three-membered ring even with wide variation of the anion-solvating capacity of the solvent, the solvation proposal is clearly inapplicable to this system. However, the results do not allow for

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(6) Reference 4 reports reaction of 5-chloro-2-pentanone with $LiNH_2$–Et_2O produces only traces of cyclopropyl methyl ketone. However, a 44% yield of 1-acetyl-2-methylcyclopropane is cited in the sodamide-catalyzed cyclization of 5-chloro-2-hexanone in ether.[7]
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