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PHASE TRANSFER CATALYSIS
AMINE CATALYZED ALKYLATION

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Abstract—Certain primary, secondary, and tertiary amines have been successfully employed as catalysts for the phase transfer catalytic alkylation of phenyl acetone. Studies strongly suggest that the alkylation is preceded by conversion of the amine catalyst into a quaternary ammonium salt.

Numerous compounds have been subjected to alkylation by phase transfer catalysis. Generally the reaction is conducted by stirring two liquid phases: an organic substrate, and 50% aqueous sodium hydroxide with a quaternary ammonium salt as a catalyst. This method has been employed for alkylation in indene,[1] fluorene,[2] ketones,[3] activated nitriles,[4] and aldehydes[5] to give mono and dialkyl products in good yield.

Isagawa[6] has reported the phase transfer catalytic generation of dichlorocarbene to be catalyzed by tertiary amines. Makosza[7] has suggested that the amine through reaction with chloroform forms an ammonium salt which in turn catalyzes the transfer of base to the organic phase of the mixture for the subsequent generation of dichlorocarbene. Attempts to employ tertiary amines as catalysts for other phase transfer reactions have been unsuccessful.[7,8] However, Hennis[9] found tertiary amines to be effective catalysts for the formation of carboxylic esters. The use of amines to catalyze the conversion of alkyl halides into alkyl cyanides has been recently reported.[10]

We have found the phase transfer alkylation of phenyl acetone with alkyl halides to be catalyzed by certain primary, secondary, and tertiary amines.

The catalytic activity of several amines was investigated with varying amounts of base. Results are shown in Table 1 for the reaction of phenyl acetone with ethyl bromide.

Several amines were not efficient catalysts. These include tribenzylamine, cyclohexylamine, s-butylamine, t-butylamine and aniline. In each case the carbon bonded to the nitrogen is either sterically crowded or bonded to an aromatic system. It is felt that either steric effects or decreased basicity, in the case of aromatic amines, is sufficient to suppress catalysis.

Presumably the amine must function as a nucleophile by reacting with the alkyl halide to yield an ammonium salt which is the true catalyst for the phase transfer reaction. Several bits of evidence seem to support this hypothesis. While the generation of dichlorocarbene is reported to be catalyzed only by tertiary amines,[6] we have found that reaction mixtures containing 50% sodium hydroxide, chloroform, cyclohexene, ethyl bromide, and a primary or secondary amine as catalyst, formed 7,7-dichloronorcarane in good yield upon stirring at room temperature. When ethyl bromide was replaced by n-butyl bromide, refluxing was required to achieve reaction.

It appears that the failure of phenyl acetonitrile to undergo butylation when catalyzed by tributylamine, as reported by Makosza,[7] was merely due to lack of salt formation. Using tributylamine as a catalyst we have noted an 87.3% yield of 2-phenylhexanenitrile for the alkylation of acetonitrile with n-butyl bromide when the reaction was conducted at 110°. Only a 4.3% yield was obtained at room temperature. When n-butyl bromide and catalyst, tributylamine, were refluxed for 3 hr prior to the addition of base and substrate, and the reaction was conducted at 110°, 2-phenylhexanenitrile was once again formed in 87.3% yield. When the catalyst and n-butyl bromide were refluxed 3 hr, cooled to room temperature and the reaction then allowed to proceed a 25.7% yield of 2-phenylhexanenitrile resulted. When the alkylations were conducted using tetrabutyl ammonium iodide as catalyst the room temperature reaction yielded 33.2% yield of product and the reaction at 110°C yielded 97.2% of 2-phenylhexanenitrile. No product was formed in absence of catalyst. These results are summarized in Table 2.

Alkylation of phenyl acetonitrile with ethyl bromide using tributylamine as catalyst yielded 33.5% of 2-phenyl butanenitrile. With tetrabutyl ammonium iodide 38.8% of product was formed. Both reactions were conducted at room temperature. Thus it seems that the key for

Table 1. Yields of 3-phenyl-2-pentanone[†]

Catalyst	I[*]	II[≠]
NONE	7%	9%
triethylamine	65%	93%
tributylamine	72%	100%
trihexylamine	71%	94%
1-methyl-4-piperidone	54%	83%
N-methyl piperidine	75%	93%
dipropylamine	74%	98%
diethylamine	55%	89%
dimethylamine	56%	80%
piperidine	69%	93%
n-hexylamine	68%	99%
n-butylamine	75%	97%
n-propylamine	50%	90%
2-ethoxyethylamine	70%	96%
cyclohexylamine	15%	27%
s-butylamine	10%	12%
t-butylamine	7%	9%
aniline	8%	10%

[*] Molar ratios based on phenyl acetone were as follows: bromide 1.77:1; potassium hydroxide in 50% aqueous solution 1.65:1; catalyst 0.047:1.

[≠] Ratio of base increased to 3.3:1.

[†] Yields were determined by gas chromatography using decane as an internal standard. The product was identified by spectral methods.

Table 2. Alkylation of phenyl acetonitrile with n-butyl bromide

Catalyst	Reaction temp.	% yield
tributylamine	25°C	4.3%
tributylamine	110°	87.3%
tetrabutyl ammonium iodide	25°	25.7%
tetrabutyl ammonium iodide	110°	97.2%
none	25°	0%
none	110°	4.2%
tributylamine and n-butyl bromide refluxed	25°	25.7%
tributylamine and n-butyl bromide refluxed	110°	87.3%

successful catalysis by an amine is sufficient conditions for *in situ* salt formation.

Another factor which seems to affect the catalytic efficiency of amines is the solubility of the amine in the aqueous layer. Small amines being highly water soluble do not readily encounter the alkyl halide and are not converted into quaternary salts thus these compounds are poor catalysts for alkylation.

Comparative experiments were run with double and quadruple amounts of catalyst. As indicated by Table 3, the reactions containing the larger amounts of catalyst initially proceeded quite rapidly. However, after 5 hr there was no significant yield difference.

Thus it appears that with low catalyst concentration initial salt formation is slowed. Once this induction period is over then the reaction proceeds readily and the final yield of product is essentially independent of catalyst concentration.

Additional evidence for such an induction period is noted in Figs. 1 and 2.

The plots represent the alkylation of phenyl acetone by ethyl bromide at room temperature with varying catalytic conditions. In Fig. 1, Curve A, the tributylamine and ethyl bromide were added simultaneously with other reactants. Curve B represents the reaction in which tributylamine and ethyl bromide were stirred for 3 hr prior to the introduction of the other reactants. The reaction with tributyl ethyl ammonium bromide, the salt presumed to be formed, is represented by Curve C. It should be noted that the induction period of Curve A is eliminated by the stirring of the amine with alkyl halide as shown in Curve B. Thus the similarity of Curves B and C also seems to indicate that the alkyl halide and amine are forming the salt prior to the alkylation of the phenyl acetone.

In the reactions depicted in Fig. 2, n-butylamine rather than tributylamine was employed as a catalyst. All other conditions are identical to those described in Fig. 1. In Curve D all reactants were added simultaneously, and in Curve E the n-butylamine and ethyl bromide were stirred for 3 hr prior to introduction of the other reactants. The long induction period of Curve D is not surprising as the primary amine must be converted into quaternary ammonium salts prior to the alkylation reactions.

Preliminary results employing solid potassium hydroxide instead of the usual 50% aqueous solution gave superior yields of alkylation products. These results were obtained with either ammonium salts or amines as catalysts. However, appreciable amounts of dialkylation products were detected (5–10%). In reactions conducted with the aqueous base the amount of dialkylated product was always less than 1%. Further work is underway in an effort to obtain improved yields of dialkylated products.

Table 3. Catalysis by varying amounts of dipropylamine

Moles of catalyst	% yield 1 hr	3 hr	5 hr	8 hr
0.000712	10.7	60.4	73.7	79.1
0.001424	16.5	62.0	74.8	77.2
0.002848	32.6	65.1	73.3	78.9

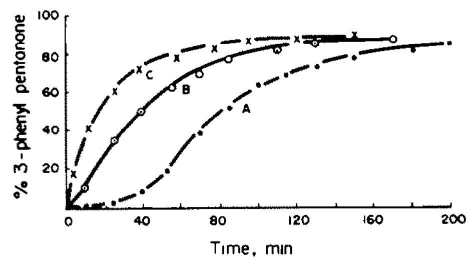

Fig. 1. Yield vs time study of formation of 3-phenyl-2-pentanone. A and B indicate tributylamine as catalyst; C indicates tributyl ethyl ammonium bromide as catalyst.

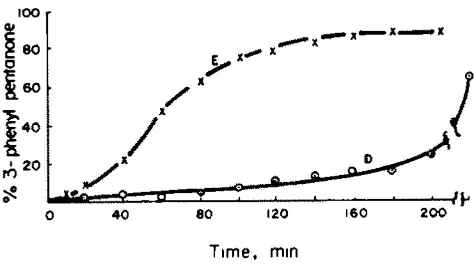

Fig. 2. Yield vs time studies of the formation of 3-phenyl-2-pentanone catalyzed by n-butyl amine.

EXPERIMENTAL

Isolated products were identified on a Varian EM-360 NMR Spectrometer with TMS as internal standard. Infra-red spectra were obtained in CCl_4 using a Perkin–Elmer Model 700 Spectrophotometer. Gas chromatographic analysis were done on a Varian Aerograph Model 90-P3 gas chromatograph with a 5 × ¼ in. 20% SE 30 60/80 Chromosorb W column.

General alkylation procedures

1. Into a 25 ml Erlenmeyer flask was placed 3.78×10^{-2} moles of phenyl acetone, 6.7×10^{-2} moles of EtBr, 5 ml of 50% KOH aq, and 1.78×10^{-3} moles of catalyst. The mixture was stirred at room temp. for 5 hr, acidified with 10% H_2SO_4. The aqueous and organic layers were separated, the aqueous soln was extracted with ether. The combined organic material was dried with $MgSO_4$ and the ether and remaining EtBr was removed. Yields were obtained by gas chromatograph analysis. Yields using this procedure are listed in Table 1, column I.

2. An alternative to the above procedure employed 10 ml and 50% KOH aq and stirring for 3 hr. Yields using this procedure are in Table 1, column II.

Carbene generation

1. To a 125 Erlenmeyer flask was added 9.87×10^{-2} moles cyclohexene, 3.12×10^{-1} moles chloroform, 5.5×10^{-2} moles of EtBr, 20 ml of 50% KOH aq, and 2.61×10^{-3} moles of n-butylamine. The mixture was stirred at room temp. for 4 hr, then made acidic with 10% H_2SO_4. The organic and aqueous layers were separated, extracted with ether, and dried with $MgSO_4$. These were then analyzed for 7,7-dichloronorcarane by gas chromatography. Other primary and secondary amines were run in the same manner.

2. n-BuBr may be substituted for EtBr in the above procedure.

However, to obtain substantial yields the reaction must be refluxed at 110° for 4 hr. Work up is the same as above.

Alkylations of benzyl cyanide by n-butyl bromide

In all of the following alkylations, 3.78×10^{-2} moles of benzyl cyanide, 6.7×10^{-2} moles of n-BuBr, 10 ml of 50% KOH aq, and 1.78×10^{-3} moles of catalyst were used. Upon completion of the given stirring times the mixture was made acidic by 10% H_2SO_4, separated and extracted with ether. It was then dried and analyzed by gas chromatography. These reactions are summarized in Table 2.

1. Tri-butylamine and n-BuBr were stirred at room temp. for 3 hr, then the other reactants were added and this mixture was refluxed at 110° for 3 hr. Yield of 2-phenylhexanenitrile was 87.3%.
2. Tri-butylamine and n-BuBr were stirred at room temp. for 3 hr, then other reactants were added. The mixture was then stirred at room temp. for 3 hr. Yield of 2-phenylhexanenitrile was 4.3%.
3. Tri-butylamine and n-BuBr were stirred at 110° for 3 hr and then the other reactants were added. The mixture was stirred for 3 hr at 110°. Yield of 2-phenyl-hexanenitrile was 87.3%.
4. Tri-butylamine and n-BuBr were stirred at 110° for 3 hr and then the other reactants were added. The mixture was stirred at room temp. for 3 hr. Yield of 2-phenylhexanenitrile was 25.7%.
5. Tetrabutyl ammonium iodide was used as catalyst with 3 hr stirring at room temp. Yield of 2-phenyl-hexanenitrile was 33.2%.
6. Tetrabutyl ammonium iodide was used as catalyst with 3 hr stirring at 110°. Yield of 2-phenyl-hexanenitrile was 97.2%.
7. EtBr was substituted for n-BuBr. (a) Tributylamine as catalyst with stirring at room temp for 3 hr. Yield of 2-phenylhexanenitrile was 33.5%. (b) Tetrabutyl ammonium iodide as catalyst with stirring at room temp. for 3 hr. Yield of 2-phenylhexanenitrile was 38.8%.

Yield versus time studies

In these studies the procedure was the same as that of the general alkylations 1, except that at intervals small samples were withdrawn from the mixture and analyzed by gas chromatography. These reactions are illustrated in Figs. 1 and 2, where the yield of 3-phenyl-2-pentanone is plotted vs time.

1(a). Tributylamine, EtBr and other reactants added simultaneously. (b) Tributylamine and EtBr stirred for 3 hr at room temp. and then the other reactants were added and time studies begun. (c) Tributylethyl ammonium bromide was added simultaneously with all other reactants.

2(a) n-Butylamine and EtBr were added simultaneously with other reactants. (b) n-Butylamine and EtBr were stirred for 3 hr at room temp. before the other reactants were added and time studies begun.

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