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THE APPLICATION OF ULTRASOUND TO THE N-ALKYLATION OF AMINES USING PHASE TRANSFER CATALYSIS

R. Stephen Davidson,* Ali M. Patel and Ali Safdar,
(Department of Chemistry, The City University, Northampton Square,
London EC1V 0HB, U.K.)

and

David Thornthwaite
(Organic Chemicals Section, Unilever Research,
Port Sunlight, Merseyside, L62 4XN, U.K.)

The application of ultrasound to the N-alkylation of a variety of amines by alkyl halides under phase transfer conditions (polyethylene glycol methyl ether and alkylammonium compounds as catalysts) leads to a decrease in the time required to effect reaction.

The use of ultrasound in synthetic organic chemistry is growing. It has proved to be of benefit in the formation of Grignard reagents[1], in aiding the Barbier reaction[1] and in the coupling of acid chlorides[2] (silyl chlorides, aryl chlorides and aroyl chlorides) and in promoting the debromination of α-bromo ketones by mercury[3]. Cyclopropanation of alkenes using the Simmons-Smith[4] reagent occurs more readily when subjected to ultrasound. In all these heterogeneous reactions a factor of key importance is keeping the surface of the catalysing metal clean. The known ability of ultrasound to clean the surfaces of metals immersed in suitable fluids is attributed to the ultrasound causing the fluids to cavitate, thereby causing very efficient mixing.

We now wish to report upon the beneficial application of ultrasound to a phase transfer catalysis system. In a previous paper[5] we have shown that amines can be N-alkylated under phase transfer conditions which employ a solid/liquid reaction mixture. Many of these reactions take place at room temperature, but if high yields are to be obtained, long reaction times are required. When ultrasound is applied to these reactions high yields of products can be

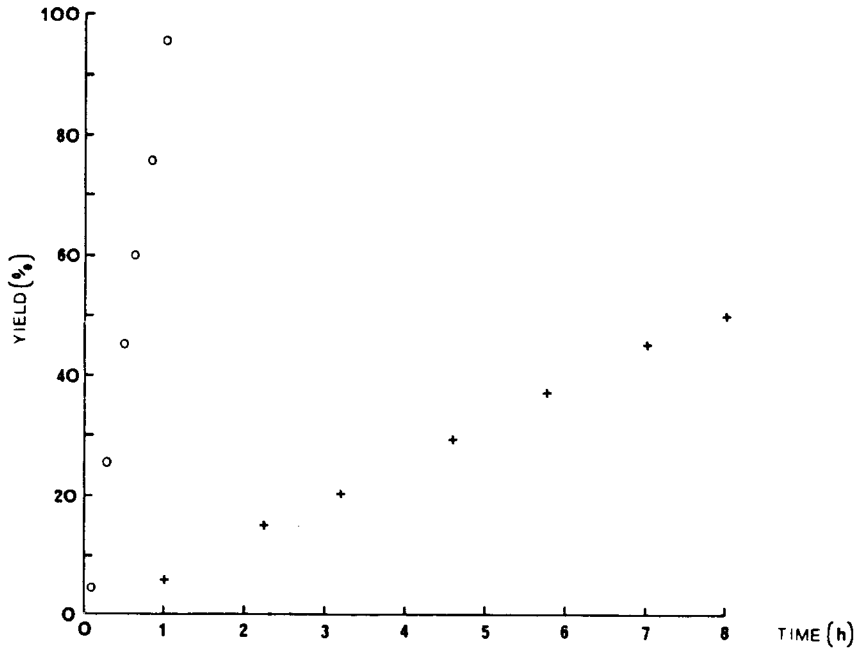
Yield of N-alkylated products from the reaction of amines with alkyl halides in toluene solution and in the presence of potassium hydroxide and phase transfer catalyst.

Compound	Alkylating Agent	Catalyst	Conditions	Reaction Time hr	% Yield of N-Alkylated Product
Indole	Iodomethane	PEG methyl ether	Stirred at 20°	5	60[a,b.]
"	"	"	Ultrasound	0.5	65[a,b.]
"	Benzyl bromide	"	Stirred at 20°	8	80[a,b.]
"	"	"	Ultrasound	2	95[a,b.]
"	1-Bromododecane	"	Stirred at room temp.	72	48[b,c.]
"	"	"	Ultrasound	1.3	60[a,b.]
"	"	Tetra-hexylammonium chloride	Ultrasound	1	92[a,b.]
"	"	Tetra-butylammonium nitrate	Stirred at 20°	3	19[a,b.]
"	"	"	Ultrasound	1.3	90[a,b.]
"	"	Tetra-butylammonium iodide	Ultrasound	0.8	73[a,b.]
Carbazole	Benzyl bromide	PEG methyl ether	Stirred at room temp.	8	50[a,b.]
"	"	"	Ultrasound	1	96[a,b.]
"	1-Bromododecane	Tetra-butylammonium	Ultrasound	3	84[a,b.]
Diphenylamine	"	Tetra-butyliodide	Ultrasound	0.8	58[a,b.]
"	Benzyl bromide	PEG methyl ether	Heated under reflux	48	70[a,b.]
"	"	"	Ultrasound	1	98[a,b.]

a) Yield determined by g.l.c. b) no reaction observed
in the absence of catalyst; c) yield determined by n.m.r.

obtained using reasonable reaction times. The results are summarised in the Table. For these, the reactions were monitored by g.l.c. in order to determine the optimal conditions. Ultrasound is known to cause rapid agitation and to ensure that the reactions are truly examples of phase transfer catalysed processes, they were run in the absence of the catalyst. Under these conditions, no reaction occurred. That the application of ultrasound accelerates the phase transfer reactions can be seen from the Figure.

RATE OF PRODUCT FORMATION IN THE REACTION OF BENZYLBROMIDE WITH CARBAZOLE (a) WITH STIRRING (+) AND (b) WITH THE APPLICATION OF ULTRASOUND (o)



During the process of sonication the temperature of the reaction gradually increases over a period of an hour to 50° and consequently some of the observed acceleration may, in part, be due to the effect of temperature. Based on previous experience[5] temperatures far in excess of 50° would be required to cause the observed degree of acceleration.

The results indicate that many heterogeneous reactions may benefit by the application of ultrasound.

Typical procedure - Synthesis of N-(Dodecyl)indole

To a solution of polyethylene glycol methyl ether (MW 350, 20 mmole) in dry toluene (50 ml), potassium hydroxide (80 mmole, fine powder), indole (20 mmole) and 1-bromododecane (20 mmole) were added. Ultrasound (Dawe Instruments ultrasonic cleaning bath containing an aqueous detergent solution)) was applied to the reaction mixture (1.3h.). Addition of water followed by the usual isolation procedures and distillation gave N-(1-dodecyl)indole (3.4g 60%) b.p. 90-100°C, 2.5 mmHg, identity confirmed by ^{1}H n.m.r. and gl.c.-m.s.

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