REVIEWS

Quaternary Ammonium Compounds in Organic Synthesis

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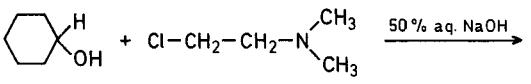
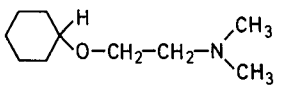
A survey of the use of quaternary ammonium compounds as reagents and as catalysts in homogeneous and two-phase systems is given. The use of solvents and the influence of the structure of the onium compounds on their reactivity is mentioned. A comparison with the corresponding uncatalysed systems is briefly made.

1. Substitution Reactions
2. Elimination Reactions
3. Addition Reactions
4. Generation of Carbenes
5. Deuterium Exchange
6. Oxidation of Olefins with Potassium Permanganate
7. Sodium Borohydride Reduction
8. Influence of the Structure of the Onium Compounds
9. The Use of Ion-Exchangers as Catalysts
10. The Use of Solvents
11. Conclusion

Es wird eine Zusammenfassung über die Verwendung quartärer Ammoniumverbindungen als Reagentien und Katalysatoren in homogenen und Zwei-Phasensystemen gegeben. Die Verwendung verschiedener Lösungsmittel und die Abhängigkeit der Reaktivität der Oniumverbindungen von ihrer Struktur werden beschrieben. Diese Systeme werden kurz mit den entsprechenden nichtkatalysierten System verglichen.

About twenty years ago Jarousse[1] described the following reaction in a two-phase system:





The possible catalytic effect of small amounts of N,N,N′,N′-tetramethylpiperazinium dichloride, formed during the reaction, was recognised. Furthermore, benzyl cyanide and cyclohexanol were successfully benzylated with triethylamine as hydrogen halide acceptor; the catalytic effect of small amounts of benzyltriethylammonium chloride was also demonstrated[1]. Recently Makosza has explored the scope of this reaction and proved its great synthetic value[2–19].

Starks[21] and Brändström[22–24] have also drawn attention to the particular importance of quaternary ammonium compounds in two-phase systems. These results have been a stimulus to a more general use of these catalysts in our laboratories.

1. Substitution Reactions

1.1. C-Alkylation

Hydrocarbons with a sufficiently acidic hydrogen can be conveniently alkylated by putting them in close contact with a concentrated aqueous solution of sodium hydroxide together with the alkylating halide and ~2% benzyltriethylammonium chloride. A survey is given in Table 1.

[1] M. J. Jarousse, *C. R. Acad. Sci., Paris, Ser. C.* **232**, 1424 (1951); *C.A.* **63**, 11371 (1965).

[2] Lodzkie Zaklady Farmaceutyczne „Polfa", *Neth. Appl.* 6, 412, 937 (1965).

Table 1. Catalytic Extractive C-Alkylation

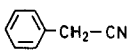
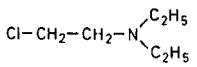
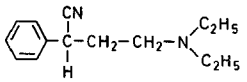
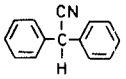
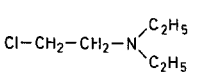
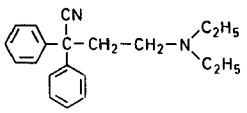
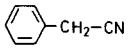
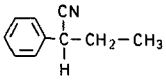
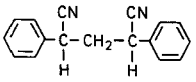
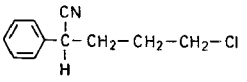
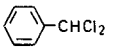
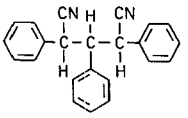
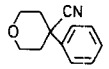
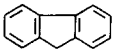
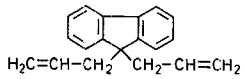
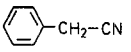
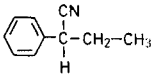
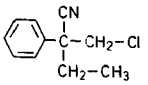
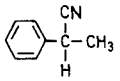
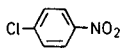
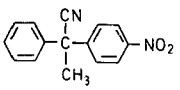
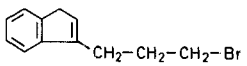
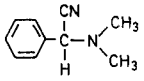
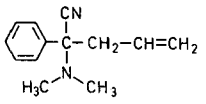
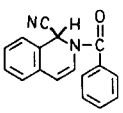
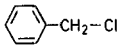
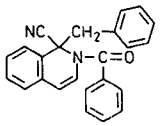
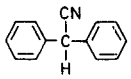
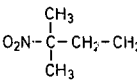
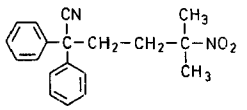
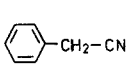
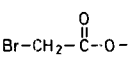
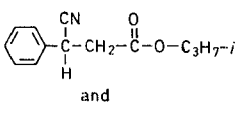
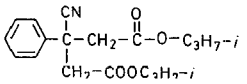
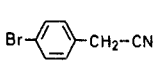
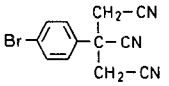
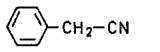
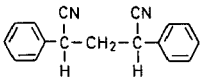
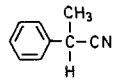
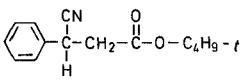
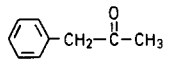
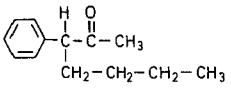
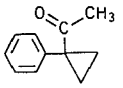
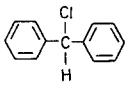
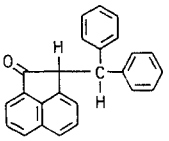
Substrate	Alkylating Agent	Product	Yield (%)	Reference
			76	2
			85	3
	C_2H_5-Cl		90	4
	H_2CCl_2		69	5
	$Cl-CH_2-CH_2-CH_2-Cl$		47	5
			93	5
	$Cl-CH_2-CH_2-O-CH_2-CH_2-Cl$		67	5
	$Cl-CH_2-CH=CH_2$		80	6
	$Cl-CH_2-CH_2-CH_2-CH_2-Cl$		?	7
	H_2CCl_2		67	8
			82	9
	$Br-CH_2-CH_2-CH_2-Br$		45	10
	$H_2C=CH-CH_2-Cl$		75	11
			78	12
			81	13
		 and 	?	14

Table 1, continued

Substrate	Alkylating Agent	Product	Yield (%)	Reference
	$Cl-CH_2-CN$		80	15
	$Cl-CH_2-O-CH_3$		87	16
	$Br-CH_2-\overset{O}{\overset{\|}{C}}-O-C_4H_9-t$		76	17
	$H_3C-CH_2-CH_2-CH_2-Br$		90	18
	$Br-CH_2-CH_2-Br$		54	18
			?	19

2-Ethyl-2-phenylbutyronitrile:
A mixture of 2-phenylbutyronitrile (0.1 mol), ethyl bromide (0.12 mol), benzyltriethylammonium chloride (0.001 mol), and 50% aqueous sodium hydroxide solution (40 ml) is stirred vigorously at 70° for 5 hr. The mixture is then diluted with water and the organic layer distilled; yield: 70%.

As mentioned by Jarousse and also by Makosza, a reversed order of reactivity of alkylating halides is observed:

$$R-Cl > R-Br > R-J$$

The use of iodides requires stoichiometric amounts of quaternary ammonium chloride; iodide ions "poison" the catalyst.

The hard and soft acids and bases principle explains why quaternary ammonium iodides have no catalytic effect at all and why the corresponding ammonium fluorides should be the best ones[20]. Surprisingly, no fluorinated catalysts are found in the literature.

Different nucleophiles can be arranged in order of their increasing hardness:

$$J^{\ominus} < Br^{\ominus} < Cl^{\ominus} < OH^{\ominus} < F^{\ominus}$$

the hardness of the charged nucleophile $Nu^{\ominus}$ may be taken between $J^{\ominus}$ and $OH^{\ominus}$.

The mechanism of the catalytic process can be represented by a combination of ion-exchange and phase-transfer equilibria (Scheme **A**):

$$Nu-H + OH^{\ominus} \rightleftharpoons Nu^{\ominus} + H_2O$$

$$Nu^{\ominus} + \left[-\overset{|}{\underset{|}{N}}-\right]^{\oplus} Cl^{\ominus} \rightleftharpoons Nu^{\ominus}\left[-\overset{|}{\underset{|}{N}}-\right]^{\oplus} + Cl^{\ominus}$$

Nu = nucleophile

Scheme **A**

This is in full agreement with the concepts of "phase-transfer catalysis" and ion-pair extraction[22].

The negatively charged nucleophile is extracted by the positive ammonium ion into the organic phase, where the alkylation is taking place. The ion-pair extraction method developed by Brändström[22] is the uncatalysed counterpart: the anions are complexed with stoichiometric quantities of tetrabutyl ammonium ions.

Brändström properly called his method "Extractive Alkylation". His work and that of others is summarised in Tables 2 and 3.

[3] M. Makosza, B. Serafin, *Rocz. Chem.* **39**, 1799 (1965); *C.A.* **64**, 17475 (1966).
[4] M. Makosza, B. Serafin, *Rocz. Chem.* **39**, 1223 (1965); *C.A.* **64**, 12595 (1966).
[5] M. Makosza, B. Serafin, *Rocz. Chem.* **40**, 1647 (1966); *C.A.* **66**, 94792 (1967).
[6] M. Makosza, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **15**, 165 (1967).

Table 2. Stoichiometrie Extractive C-Alkylation

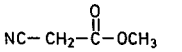
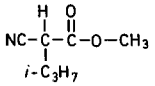
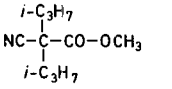
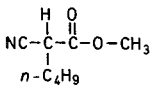
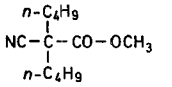
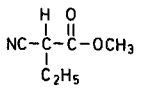
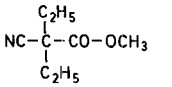
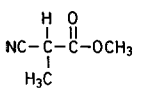
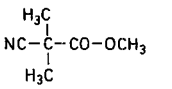
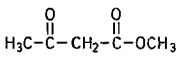
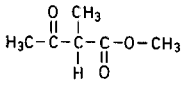
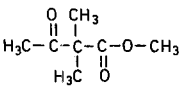
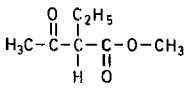
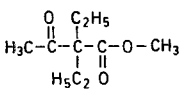
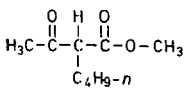
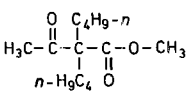
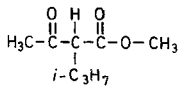
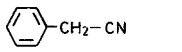
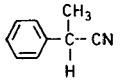
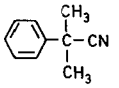
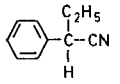
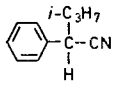
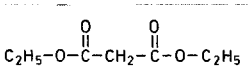
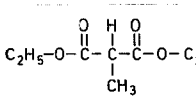
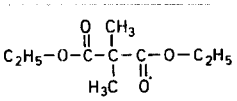
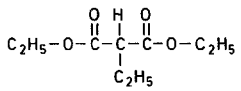
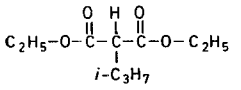
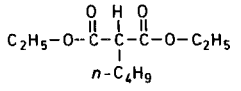
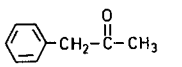
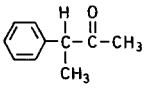
Substrate	Alkylating Agent	Mono-alkylated Product	Yield (%)	Di-alkylated Product	Yield (%)	Reference
	*i*-C_3H_7–J		94		3	24
	n-C_4H_9–J		86		7	24
	C_2H_5J		72		14	24
	H_3C–J		48		25	24
	H_3C–J		80		10	23
	C_2H_5–J		84		9	23
	n-C_4H_9–J		90		5	23
	i-C_3H_7–J		70[a]	—	–	23
	H_3C–J		72		14	26
	C_2H_5–J		90	—	–	26
	i-C_3H_7–J		75	—		26
	Br–$(CH_2)_4$–Br	—			97	26
	H_3C–J		86[c]		3[c]	26
	C_2H_5–J		88	–	–	26
	i-C_3H_7–J		45	–	–	26
	n-C_4H_9–J		85	–	–	26
	H_3C–J		92	–	–	26

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Table 2, continued

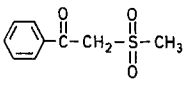
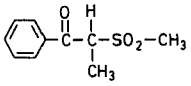
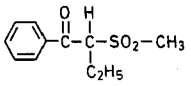
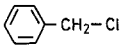
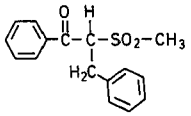
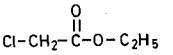
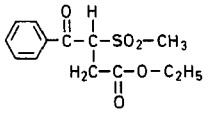
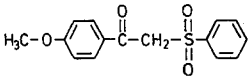
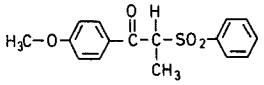
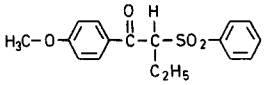
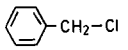
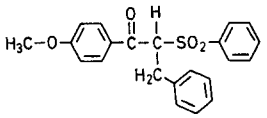
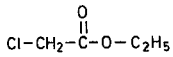
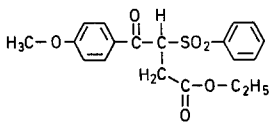
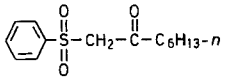
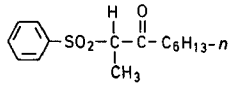
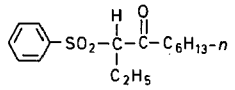
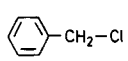
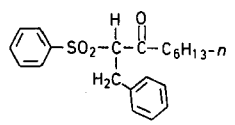
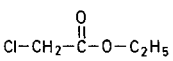
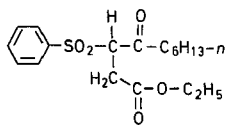
Substrate	Alkylating Agent	Mono-alkylated Product	Yield (%)	Di-alkylated Product	Yield (%)	Reference
	H_3C-J		81[b]	–	–	25
	C_2H_5-J		73	–	–	25
			65	–	–	25
			74	–	–	25
	H_3C-J		87	–	–	25
	C_2H_5-J		82	–	–	25
			74	–	–	25
			78	–	–	25
	H_3C-J		78	–	–	25
	C_2H_5-J		81	–	–	25
			67	–	–	25
			68	–	–	25

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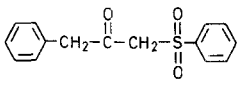
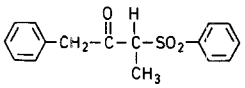
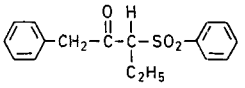
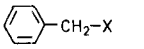
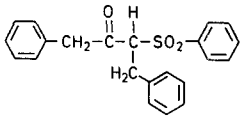
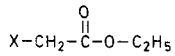
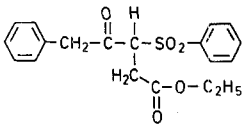
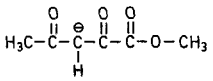
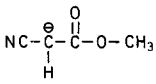
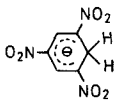
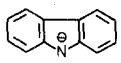
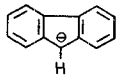
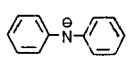
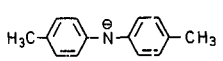
Table 2, continued

Substrate	Alkylating Agent	Mono-alkylated Product	Yield (%)	Di-alkylated Product	Yield (%)	Reference
	H_3C-J		86	–	–	25
	C_2H_5-J		76	–	–	25
			59 (X = Cl)	–	–	25
			75 (X = Br)	–	–	25
			30 (X = Cl)	–	–	25
			90 (X = Br)	–	–	25

[a] O-Alkylated product (~23%) is also obtained.
[b] This and the following figures refer to yields after crystallisation.
[c] The proper choice of the amount of catalyst and alkylating agent directs the reaction to mono- or di-substitution[26].

Table 3. Ammonium Complexes

No.	1:1 Complex Anion	Cation	m.p.	Yield (%)	Reference
1[a]		$[N(C_4H_9)_4]^{\oplus}$	140°	70	22
2[a]		$[N(C_4H_9)_4]^{\oplus}$	83°	70	24
3		$[N(CH_3)_4]^{\oplus}$	131–132°	86	27, 28
4[b]		$[NR_4]^{\oplus}$			29
5[b]		$[NR_4]^{\oplus}$			29, 30
6[b]	$(C_6H_5)_3C^{\ominus}$	$[NR_4]^{\oplus}$			29, 30
7		$[N(CH_3)_4]^{\oplus}$	75–80° (dec.)		31, 32
8		$[N(CH_3)_4]^{\oplus}$			31, 32
9		$[NIC_2H_5)_4]^{\oplus}$			32

[a] The complexes are alkylated.
[b] R = CH_3, C_3H_5, C_4H_9; used as catalysts in the polymerisation of propylene sulfide[29].

Methyl Acetopropanoate[23]:
Tetrabutylammonium hydrogen sulfate (0.1 mol) is added to a cooled solution of sodium hydroxide (0.2 mol) in water (75 ml). This mixture is then added to a stirred solution of methyl acetoacetate (0.1 mol) and methyl iodide (0.2 mol) in chloroform (75 ml). The reaction is exothermic and the mixture becomes neutral after a few minutes. The layers are separated and the solvent is evaporated; tetrabutylammonium iodide is precipitated by addition of ether and is then filtered off. Evaporation of the ether leaves the product; yield: 80% of mono- and ~10% of dimethylated product.

Sometimes the complexes of ammonium ions with organic anions can be isolated, others are prepared in solution (ether or liquid ammonia); a survey of some of the reactions is given in Table 3.

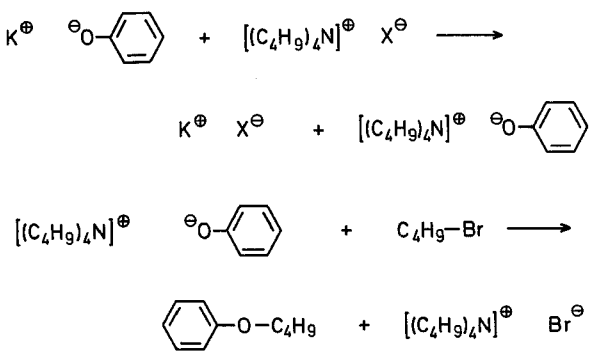
1.2. O-Alkylation

1.2.1. Alcohols

It is surprising that only Jarousse[1] describes the alkylation of alcohols; this is certainly a great area for further exploration. In this laboratory[33] O-alkylated products were detected during the reaction of benzyl alcohol, benzhydrol and cinnamyl alcohol with reactive halides such as cinnamyl chloride, benzyl chloride and aliphatic bromides under the conditions developed by Makosza.

1.2.2. Phenols

Alkylation of phenols can be realized with triethylamine, as a hydrogen halide acceptor and as a catalyst, owing to small amounts of quaternary compound formed during the reaction.
Ugelstad, Ellingsen, and Berge[34] described the synthesis of tetrabutylammonium phenoxide in dioxan, followed by alkylation with butyl bromide; (Scheme **B**) a 95% conversion is observed. These authors also mentioned the use of catalytic amounts of quaternary ammonium compounds.

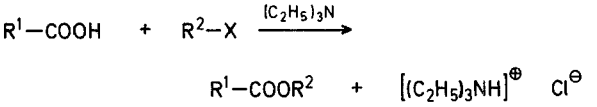


Scheme **B**

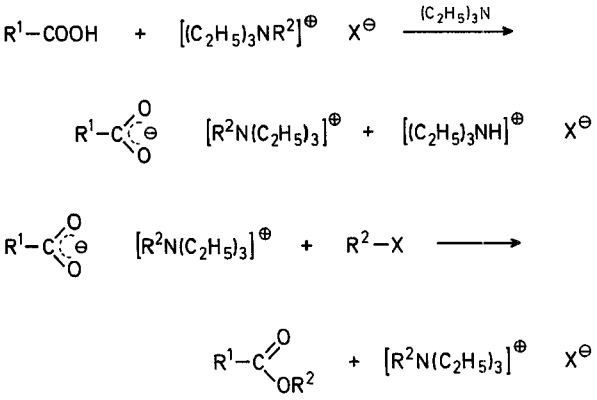
Benzyl Phenyl Ether[35]:
Benzyl chloride (0.4 mol), phenol (0.8 mol), and triethylamine (0.4 mol) are heated under reflux at 150–190° for 2 hr. The reaction mixture is then washed successively with water and dilute sodium hydroxide solution to remove unconverted phenol. The mixture is dried and then distilled; yield: 46%.

1.2.3. Carboxylic Acids

The esterification of carboxylic acids by means of alkyl halides and triethylamine is a very useful and versatile reaction giving high yields. Here also triethylamine acts as the hydrogen halide acceptor and as a catalyst.



The mechanism of this reaction can be represented as shown in Scheme **C**[35,36]:



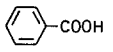
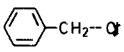
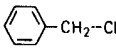
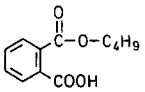
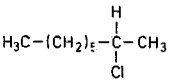
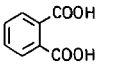
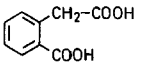
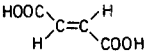
Scheme **C**

The catalytic effect of quaternary phosphonium and arsonium compounds has been mentioned[37]. The extensive work of Merker, Scott, and Mills[35,38] on the matter is summarised in Table 4.

---

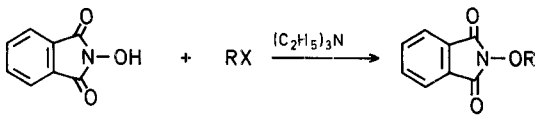
[23] A. Brändström, U. Junggren, *Acta Chem. Scand.* **23**, 2204 (1969).
[24] A. Brändström, U. Junggren, *Acta Chem. Scand.* **23**, 2203 (1969).
[25] B. Samuelsson, B. Lamm, *Acta Chem. Scand.* **25**, 1555 (1971).
[26] A. Brändström, U. Junggren, *Tetrahedron Lett.* **1972**, 473.
[27] R. P. Taylor, *Chem. Commun.* **1971**, 1463.
[28] L. A. Kaplan, A. R. Siedle, *J. Org. Chem.* **36**, 937 (1971).
[29] G. Tersac, S. Boileau, P. Sigwalt, *Bull. Soc. Chim. France* **1970**, 2537.
[30] G. Wittig, M. Heintzeler, M. H. Wetterling, *Liebigs Ann. Chem.* **557**, 201 (1947).
[31] W. Schlenk, J. Holtz, *Ber. dtsch. chem. Ges.* **49**, 603 (1916).
[32] W. L. Jolly, *J. Amer. Chem. Soc.* **77**, 4958 (1955).
[33] A. Verstraelen, W. Helsen, J. Dockx, Unpublished Results (1971).
[34] J. Ugelstad, T. Ellingsen, A. Berge, *Acta Chem. Scand.* **20**, 1593 (1966).
[35] R. L. Merker, M. J. Scott, *J. Org. Chem.* **26**, 5180 (1961).
[36] H. E. Hennis, L. R. Thompson, J. P. Long, *Ind. Eng. Chem. Prod. Res. Develop.* **7**, 96 (1968).
[37] Y. Yamashita, T. Shimamura, *Kogyo Kagaku Zasshi* **60**, 423 (1957); (English Translation).
[38] H. Mills, M. W. Farrar, O. J. Weinkauff, *Chem. & Ind.* **1962**, 2144.
[39] G. H. Hamor, D. M. Breslow, G. W. Fisch, *J. Pharm. Sci.* **59**, 1752 (1970).

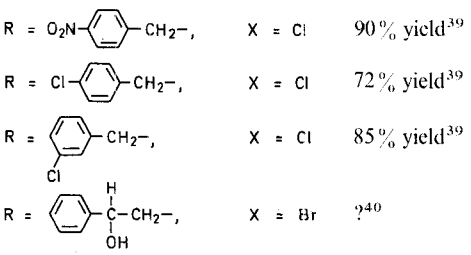
Table 4. Esterification of Carboxylic Acids

Acid	Alkyl Halide	Solvent	Temperature	Time	Yield (%)	Reference
		xylene	148–167°	4 hr	79	35
	n-C_6H_{13}–Cl	xylene	134–141°	11 hr	47	35
	t-C_4H_9–Br	without	63–88°	2 hr	12	38
H_3C–COOH		xylene	147°	2 hr	75	35
	H_2C=CH–CH_2–Cl	acetone	r.t.	1 week	35	35
	n-C_4H_9–Cl	without	91–138°	11 hr	90	38
	n-C_8H_{17}–Cl	without	136–139°	5 hr	84	38
		without	140–165°	28 hr	89	38
	H_2CCl_2	without	127–153°	12 hr	72	38
	Cl–CH_2–CH_2–Cl	without	130–150°	5 hr	91	38
	n-C_8H_{17}–Cl	without	150–160°	5.5 hr	98	38
	n-$C_{10}H_{21}$–Cl	without	145–150°	12 hr	87	38
	n-$C_{10}H_{21}$–Cl	without	121–181°	8 hr	74	38
n-C_9H_{19}–COOH	n-$C_{12}H_{25}$–Cl	without	140–165°	6 hr	82	38

1.2.4. N-Hydroxyphthalimides

Several alkylations are summarised in Scheme **D**. The mechanism can be described in the same way as represented in Scheme **C**.

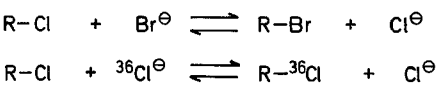




Scheme **D**

1.3. Halogen Exchange

The exchange reactions are catalysed by tricaprylmethylammonium chloride; for R = n-octyl, equilibrium is obtained after a 5 hr stirring period with an aqueous sodium chloride-^{36}Cl solution at 100°C. Alkyl chlorides can be converted to the corresponding bromides or vice versa, using at least two such exchanges with fresh sodium halide solution[21].



1.4. Preparation of Nitriles and Thiocyanates

The catalysts mentioned in the literature are benzyltrimethylammonium chloride[41] and hexadecyltributylphosphonium bromide[21].

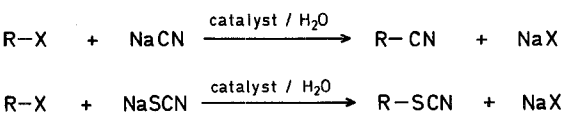


Table 5 shows some of these preparations.

[40] W. Kliegel, *Pharmazie* **25**, 525 (1970).
[41] N. Sugimoto, T. Fujita, N. Shigematsu, A. Ayada, *Chem. Pharm. Bull.* **20**, 427 (1962).
[42] B. Dobinson, G. E. Green, *Chem. & Ind.* **1972**, 214.
[43] F. Nerdel, J. Buddrus, G. Scherowsky, D. Klamann, M. Fligge, *Liebigs Ann. Chem.* **710**, 85 (1967).

Table 5. Preparation of Nitriles and Thiocyanates

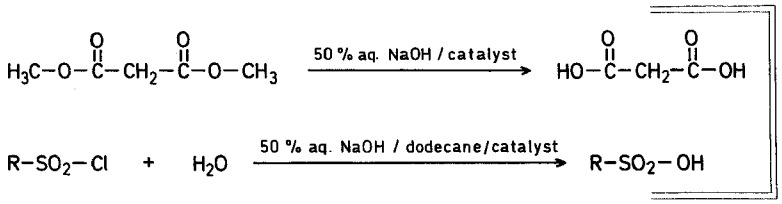
R	X	Nucleophile	Product	Catalyst	Reaction Time[a]	Reference
n-C_8H_{17}[b]	$H_3C-SO_2-O^{\ominus}$	$CN^{\ominus}$	n-C_8H_{17}-CN	1%[d]	20 min	21
n-C_8H_{17}	$Br^{\ominus}$	$CN^{\ominus}$	n-C_8H_{17}-CN	1%[d]	90 min	21
n-C_8H_{17}	$Cl^{\ominus}$	$CN^{\ominus}$	n-C_8H_{17}-CN	1%	300 min	21
n-C_8H_{17}	$Cl^{\ominus}$	$CN^{\ominus}$	n-C_8H_{17}-CN	5%	60 min	21
n-C_8H_{17}	$J^{\ominus}$	$CN^{\ominus}$	—	5%	ceased[e]	21
n-C_8H_{17}	$Tos^{\ominus}$	$CN^{\ominus}$	—	5%	ceased[e]	21
$C_6H_5-CH_2-$[c]	$Cl^{\ominus}$	$CN^{\ominus}$	$C_6H_5-CH_2-CN$	10%	60 min	41
$C_6H_5-CH_2-CH_2-$	$Br^{\ominus}$	$CN^{\ominus}$	$C_6H_5-CH_2-CH_2-CN$	10%	360 min	41
$C_6H_5-CH_2-$	$Cl^{\ominus}$	$SCN^{\ominus}$	$C_6H_5-CH_2-SCN$	10%	300 min	41

[a] Time to reach completion at about 100°C.
[b] With n-octyl reagent, hexadecyltributylphosphonium bromide is used as a catalyst.
[c] In the following cases, benzyltrimethylammonium chloride is used as a catalyst.
[d] With 5% catalyst the reaction becomes uncontrollable owing to violent boiling.
[e] Ceased after 5–30% completion.

***n*-Octyl Cyanide**[21]:
A mixture of an excess 1-chlorooctane (0.67 mol), sodium cyanide (0.2 mol) in water (25 ml), and hexadecyltributylphosphonium bromide (5 g) is heated rapidly to reflux temperature. After two hours the reaction is complete and the organic phase is distilled; yield: 95%.

1.5. Hydrolysis

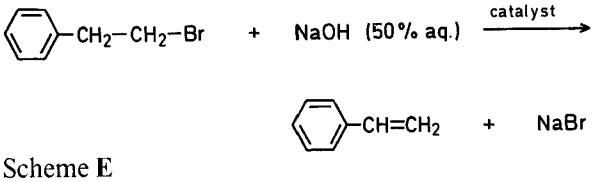
In the absence of catalyst no hydrolysis of dimethyl malonate is observed at room temperature. The hydrolysis starts exothermically and is complete in half an hour after addition of a small amount of quaternary ammonium catalyst. The hydrolysis of higher homologues such as methyl tetradecanoate stops after a 35% conversion. Coordination of the ammonium ion with the carboxylate ion destroys the catalytic effect. Sulfonyl chlorides are hydrolysed similarly; in a mixture of isomeric dodecanesulfonyl chlorides no reaction occurs. Addition of some catalyst starts the hydrolysis immediately. During the hydrolysis of n-octyl methanesulfonate a small amount of di-n-octyl ether is formed[21].



2. Elimination Reactions

In general, elimination is the most common side-reaction of nucleophilic substitution in an anhydrous environment, but it may also become an important side-reaction in aqueous media. Moreover, elimination reactions are catalysed by quaternary ammonium compounds[33].

The elimination of hydrogen bromide in the preparation of styrene from phenethyl bromide is catalysed by n-butyltriethylammonium chloride in a two phase system (Scheme **E**). At 90° the reaction is complete within 2 hr; in the absence of a catalyst only 1% styrene is formed.

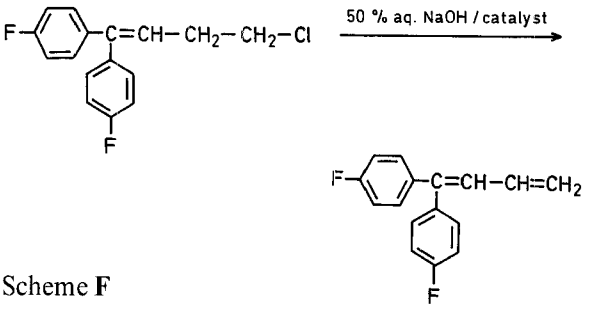


Scheme **E**

The catalysis of elimination reactions is further demonstrated in the preparation of 1,1-bis-(4-fluorophenyl)-1,3-butadiene (Scheme **F**); the corresponding butenyl chloride is stirred with aqueous sodium hydroxide at room temperature, with a catalytic amount of benzyltriethylammonium chloride; after 4 hrs a 60% conversion is obtained; in the absence of catalyst the conversion amounts to only 4%[33].

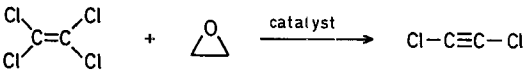
For the corresponding saturated butyl chloride no

elimination is observed under the conditions developed by Makosza[33].



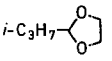
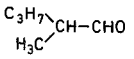
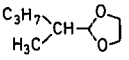
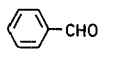
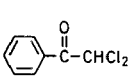
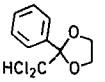
Scheme **F**

Recently, an elimination was described in homogeneous medium in the presence of ethylene oxide and a catalytic amount of a quaternary ammonium compound; the authors have drawn the attention of the explosion hazard during the catalytic formation of dichloroacetylene[42] (Scheme **G**). Ethylene oxide serves as strong base as shown below.



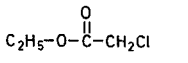
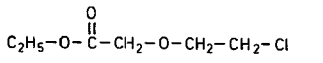
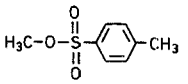
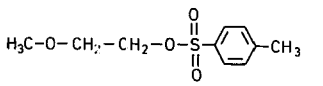
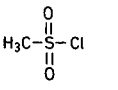
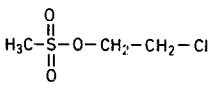
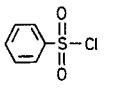
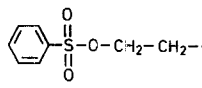
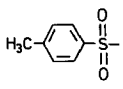
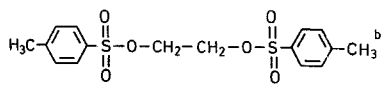
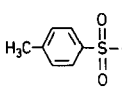
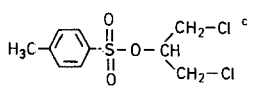
Scheme **G**

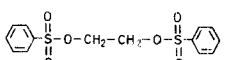
Table 6. Preparation of 1,3-Dioxolanes[43]

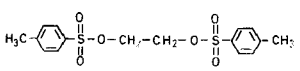
Carbonyl Compound	Reaction Product	Reaction Time	Temperature	Yield (%)
$(H_2CO)_x$		3 hr	110°	85
		2 hr 25 min	170°	12
$i\text{-}C_3H_7\text{-}CHO$		12 hr	125°	67
		24 hr	220°	81
		2 hr	170°	75
		1 hr	170°	21

2-Phenyl-1,3-dioxolane[43]**:**
Equimolar quantities of benzaldehyde and ethylene oxide are mixed with tetraethylammonium bromide (1 mol-equiv). The mixture is heated at 170° for 2 hr; distillation of the mixture yields the product; yield: 75%.

Table 7. Addition of Alkyl Halides to Ethylene Oxide[44]

R–X	R–O–CH_2–CH_2–X	Reaction Time	Temperature	Yield (%)
H_3C–J	H_3C–O–CH_2–CH_2–J	7 hr	180°	20
C_2H_5–Br	C_2H_5–O–CH_2–CH_2–Br	5 hr	210°	37
C_4H_9–Br	C_4H_9–O–CH_2–CH_2–Br	5.5 hr	230°	4
$t\text{-}C_4H_9$–Cl	$t\text{-}C_4H_9$–O–CH_2–CH_2–Cl	5 hr	170°	28
H_2C=CH–CH_2Cl	H_2C=CH–CH_2–O–CH_2–CH_2–Cl	5 hr	170°	14
H_2C=CH–CH_2–Br	H_2C=CH–CH_2–O–CH_2–CH_2–Br	5 hr	170°	59
		6 hr	150°	42
		5 hr	165°	47
		2 hr	150°	51
	 [a]	—	—	48
	 [b]	—	—	68
	 [c]	7 hr	150°	80

[a]  is also formed (25%).

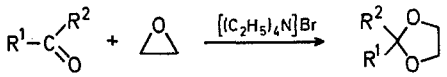
[b]  is formed as sole product.

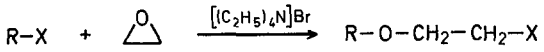
[c]  is used.

3. Addition Reactions

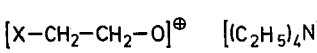
3.1. Addition to Ethylene Oxide

Nerdel et al.[43] described the use of tetraethylammonium bromide as catalyst in reactions with ethylene oxide.





In these reactions the intermediate tetraethylammonium haloethoxylate is formed; the haloethoxylate ion acts as a nucleophile.



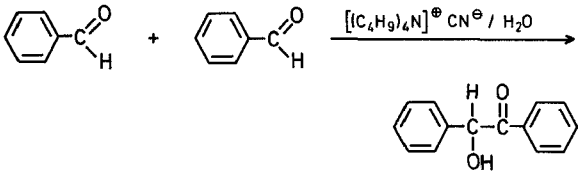
The reaction proceeds in homogeneous conditions and is completely comparable to the esterification of carboxylic acids mentioned above.

The results are summarised in Tables 6 and 7.

β,β-Dichloroisopropyl Tosylate[44]:
Equimolar quantities of p-toluenesulfonyl chloride and epichlorhydrin are mixed with tetraethylammonium bromide (1.5 mol%) and heated at 140–150° for 2 hr and then at 150–160° for a further 5 hr. The mixture is then allowed to cool and is crystallised from diisopropyl ether/petroleum ether (1:1); yield: 80%.

3.2. The Benzoin Condensation

The condensation of benzaldehyde to benzoin catalysed by cyanide ions is a well known reaction and is usually effected at 90 °C in a 50% methanol/water mixture as solvent; in water alone, sodium cyanide is ineffective and even after 20 hrs at room temperature no product is formed. Using tetrabutylammonium cyanide, however, the reaction is complete within one hour at room temperature[46].



It can be imagined, that the reaction with sodium cyanide can be catalysed by a quaternary ammonium bromide or chloride.

Benzoin[46]:
A mixture of benzaldehyde (25 ml), water (100 ml) and tetrabutylammonium cyanide (9g) is stirred at room temperature for 75 min.; the product is filtered off and dried; yield: 70%.

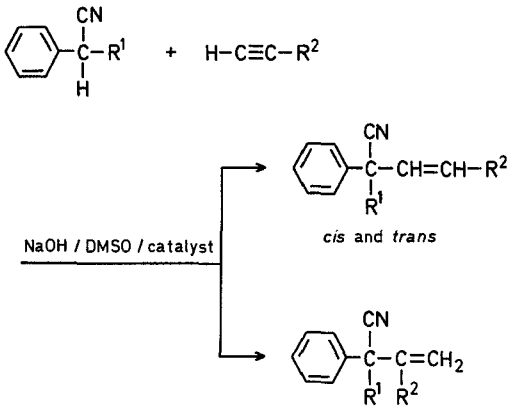
[44] D. Klamann, K. Ulm, P. Weyerstahl, F. Nerdel, *Liebigs Ann. Chem.* **710**, 71 (1967).

3.3. Activated Olefins

Triton B is a quaternary ammonium hydroxide and acts both as a strong base and as a catalyst. The mechanism of the reaction is similar to that described in reaction scheme **A**. All substrates with an active hydrogen atom such as alcohols, activated methylene compounds etc. can be alkylated similarly; this reaction is referred to as "Michael addition" and needs no further comment.

3.4. Alkynes

A reaction comparable with the Michael addition is the addition of alkylarylacetonitriles to acetylene and phenylacetylene; with the latter three isomers are possible as shown in Scheme **H**. Here, sodium hydroxide acts as a base and some dimethyl sulphoxide is added in order to ensure the dissolution of the components.



Scheme **H**

The reaction is also catalysed by triethylbenzylammonium chloride; diphenylacetylene and 1-hexyne fail to react. Similarly, no reaction occurs with diphenylacetonitrile[47].

2-Vinyl-2-phenylbutyronitrile[47]:
A mixture of 2-phenylbutyronitrile, sodium hydroxide, some dimethyl sulphoxide and a catalytic amount of triethylbenzylammonium chloride is saturated with acetylene. The reaction is exothermic. After completion of the reaction and work-up the product is obtained; yield: 80%.

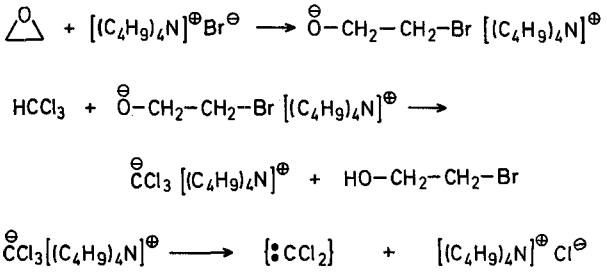
4. Generation of Carbenes

The literature covers many procedures for generation of carbenes[48]. The use of catalysts was not mentioned until recently the combined action of quaternary compounds with ethylene oxide was found[45]; this reaction takes place in a homogeneous anhydrous medium. All these methods require strictly anhydrous

conditions. However, a few years ago the generation of dichlorocarbene was described in a two-phase system[49]. From the viewpoint of large scale production the latter method seems to be most promising.

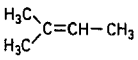
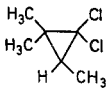
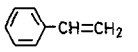
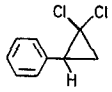
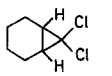
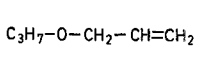
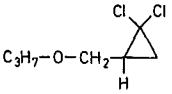
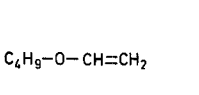
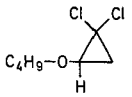
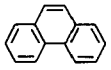
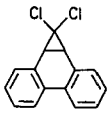
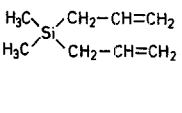
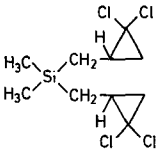
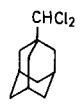
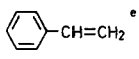
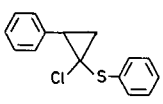
4.1. Generation in a Homogeneous System

Nucleophilic cleavage of ethylene oxide by bromide ions generates the strong base necessary to form the trichloromethyl carbanion[45] as shown in Scheme I.



Scheme I

Table 8. Halocarbene Reactions

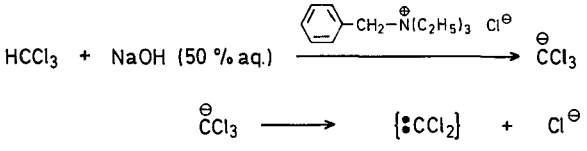
Substrate	Reaction Product	Method[a]	Yield (%)	Reference
		1	60	49
		1	80	49
		1 1[b] 2	72 98 79	49 50 51
		1	64	49
		1	71	49
 [c]	 [c]	2	67	52
		1	84	50
		1	79	50
		1	77	50
		1	54[d]	53
 [e]		1	63	54

[a] Method 1 represents the conditions developed by Makosza; Method 2 indicates the ethylene oxide method in homogeneous medium. In method 1, benzyltriethylammonium chloride and in method 2, tetrabutylammonium chloride are used.
[b] Cetyltrimethylammonium chloride is used as catalyst.
[c] Dichlorofluoromethane is used.
[d] Yield is 91% based on adamantane consumed.
[e] Dichloromethyl phenyl sulfide is used.

7,7-Dichlorononcarane[45]:
A mixture of chloroform (0.25 mol), cyclohexene (0.2 mol), ethylene oxide (0.6 mol) and a catalytic amount of tetrabutylammonium bromide is heated at 170° for 5 hr. Distillation of the reaction mixture gives the product; yield: 79%.

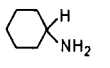
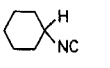
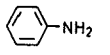
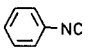
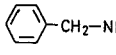
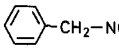
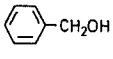
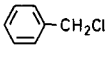
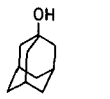
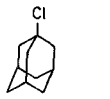
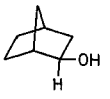
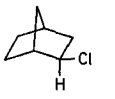
4.2. Generation in a Two-Phase System

Generation of a dichlorcarbene species in a catalytic two-phase system seems to be the method of choice for the preparation of dichlorocyclopropanes[49]. The dichlorocarbene, generated at the interface of the two phases, should be extracted into the organic layer before it can be hydrolysed. Since the discovery of this method and its application to the dichlorocyclopropane preparation[49], several papers appeared dealing with this matter; the use of a long chain quaternary ammonium compound seems to improve the yield[50].

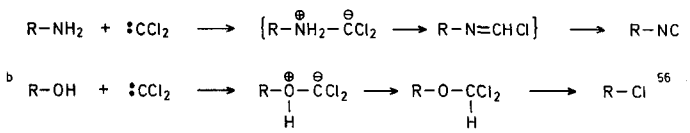


Several applications of the dichlorocarbene species generated in heterogeneous (method 1) or homogeneous (method 2) media are collected in Tables 8 and 9.

Table 9. Preparation of Isocyanides from Amines[a] and Chlorides from Alcohols[b] by Dichlorocarbene Reactions

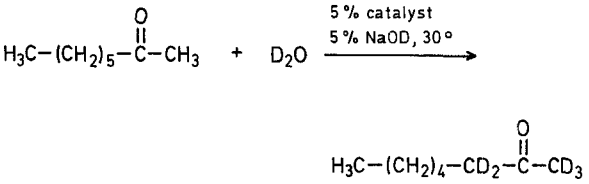
Substrate	Reaction Product	Yield (%)	Reference
n-C_4H_9–NH_2	n-C_4H_9–NC	60	55
n-$C_{12}H_{25}$–NH_2	n-$C_{12}H_{25}$–NC	41	55
		48	55
		57	55
		55	55
		90	56
		94	56
		90	56

[a] Hoffman carbylamine reaction



5. Deuterium Exchange

A deuterium exchange reaction is conveniently illustrated with 2-octanone (Scheme **J**). In the absence of the quaternary ammonium catalyst less then 5% exchange takes place after 3 hours at 30°C.

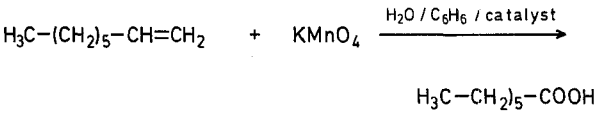


Scheme **J**

2-Octanone-1,3-d_5[21]:
A solution of 5% sodium hydroxide-OD in deuterium oxide is mixed with 5% tricaprylmethylammonium chloride in 2-octanone at 30 °C. The equilibration is complete after ½ hr; two of these exchange reactions are sufficient to replace more than 99% of the active hydrogens by deuterium (10:1 ratio of deuterium oxide per active hydrogen in each exchange).

6. Oxidations of Olefins with Potassium Permanganate

The reaction is illustrated by the oxidation of 1-octene, Scheme **K**[21]. No reaction is observed in the absence of catalyst; the added quaternary ammonium compound acts as a carrier of the permanganate anion from the aqueous phase to the organic phase where it can react with the olefin.



Scheme **K**

Nonanoic Acid[21]:
1-Decene (0.2 mol) is added to a stirred mixture of benzene (50 ml), tricaprylmethylammonium chloride (0.01 mol), potassium permanganate (0.8 mol) and water (100 ml) at such a rate, that the temperature is maintained at 40 °C (½ hr). After stirring for an additional ½ hr the excess permanganate is destroyed with sodium sulfite solution, the mixture is filtered and the filtrate is acidified with dilute hydrochloric acid. The benzene solution is extracted with 10% aqueous sodium hydroxide solution (100 ml) and the alkaline phase is then acidified with hydrochloric acid and extracted with ether (100 ml). Evaporation of the ether leaves the acid; yield: 91%.

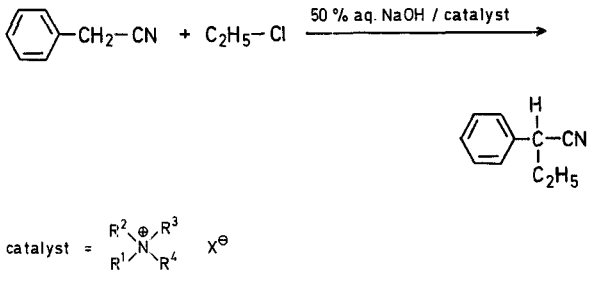
7. Sodium Borohydride Reduction

2-Octanone (50% solution in benzene) can be reduced to the corresponding alcohol with a sodium boro-

hydride solution in 2*N* aqueous sodium hydroxide; the reaction rate is about twenty times higher in the presence of a quaternary ammonium compound as catalyst. However, the reaction is still slow and does not offer any advantage over routine reductions[21]. Long chain quaternary ammonium borohydrides are commercially available and can be used in solvents not suitable for conventional reductions[57].

8. Influence of the Structure of the Onium Compounds

Makosza has found a different catalytic activity for different quaternary ammonium halides in the ethylation of benzyl cyanide, see Scheme **M**[58]. The results are summarised in Table 10.



Scheme **M**

These results encouraged us to explore additional structure-reactivity phenomena. We therefore investigated, under the conditions used by Makosza, the conversion of phenethyl bromide to styrene by using different catalysts[33]. The results are summarised in Table 11.

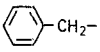
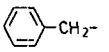
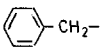
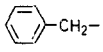
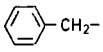
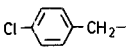
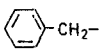
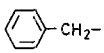
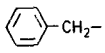
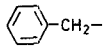
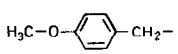
Table 11. Influence of Chain-Length on Catalyst Activity

$H_3C-(CH_2)_n-\overset{\oplus}{N}(C_2H_5)_3\ Br^{\ominus}$

n	% Styrene[a]
1	3
2	7.2
3	12
4	50
5	53
6	45.5
7	43.7
9	42.2
11	38.3

[a] Reaction temperature: 60 ; the figures give G.L.C.-surface percentages.

Table 10. Influence of the Structure of the Catalyst on the Ethylation of Benzyl Cyanide (Scheme **M**)

R^1	R^2	R^3	R^4	X	% Ethylation[a]
C_3H_5	$-CH_2-CH-CH_2-CH_2-CH_2-$			Cl	5.4
C_3H_7	C_3H_7	C_3H_7	C_3H_5	Cl	6
C_2H_5	C_2H_5	C_2H_5		Cl	8
C_2H_5	C_2H_5			Cl	15
C_2H_5	C_2H_5	C_2H_5	C_3H_5	Cl	23
H_3C	H_3C	H_3C		Cl	32
C_2H_5	C_2H_5	C_2H_5		Br	35
C_2H_5	C_2H_5	C_2H_5		Cl	38
H_3C	H_3C	C_2H_5		Cl	40
H_3C	C_2H_5	C_3H_7		Cl	43
C_3H_7	C_3H_7	C_3H_7		Cl	43
C_2H_5	C_3H_7	C_3H_7		Cl	44
H_3C	C_2H_5	C_2H_5		Cl	45
C_2H_5	C_2H_5	C_4H_9		Cl	45
C_2H_5	C_2H_5	C_2H_5		Cl	50
C_2H_5	C_2H_5	C_2H_5	C_2H_5	Cl	51
C_2H_5	C_2H_5	C_2H_5		Cl	54

[a] Determination of $Cl^{\ominus}$ ions.

Long-chain alkyl groups increased the solubility in the organic phase. The same correlation between chain-length and reactivity was found in the methanesulfonation of the acetylcholinesterase reaction centre.

With *n*-alkyltrimethylammonium bromide as a catalyst, a peak activity[59] was found for n=4.

$H_3C-(CH_2)_n-\overset{\oplus}{N}(CH_3)_3\ Br^{\ominus}$

In the reaction of ethylene oxide and chloroform for the generation of dichlorocarbene, tetrabutylphosphonium bromide and tetrabutylarsonium bromide were found to be as active as tetrabutylammonium bromide[60]. A proper choice of catalyst is also determined by its stability under the reaction conditions; obviously catalysts forming stable emulsions are to be avoided[21].

9. The Use of Ion Exchangers as Catalysts

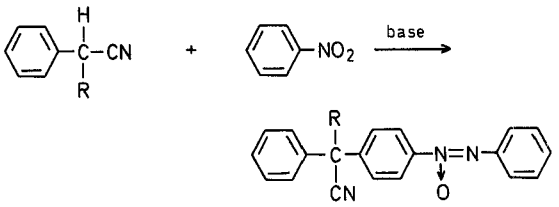
The use of ion exchangers in organic synthesis is described in an excellent review[61]. Amberlite IRA 400 and IRA 410 were found to be effective in the benzoin condensation[62] and the alkylation of ethyl cyanoacetate[63]. Amberlite IRA 400 proved to be effective in the benzylation of phenylacetonitrile[41]. Use of Dowex 21 was mentioned in the preparation of carbenes with ethylene oxide and their use in a continuous process was suggested[60]. Obviously "Makosza type" systems closely resemble those of "Liquid Ion Exchangers".

10. The Use of Solvents

For extractive alkylation, chloroform and dichloromethane are recommended as solvents[24]. The extraction and the alkylation can be done separately by evaporation of the chloroform and dissolution of the residue in ethyl acetate, the solvent of choice for the alkylation[25].

For the "Makosza type" alkylations it is recommendable to work without a solvent; if substrate and alkylating agent are solids at the reaction temperature, it is desirable to use solvents such as tetrahydrofuran, dimethyl sulfoxide, dioxan, or pyridine[58].

Alcohols and nitrobenzene as solvents have an inhibitory effect[64]; nitrobenzene can react with the substrate as shown below in Scheme N.



Scheme N

In general, a solvent suitable for cation solvation will enhance the effective concentration of the anion thereby favouring the reaction. A proper choice of solvents will diminish the number of side reactions e.g. hydrolysis or elimination of the alkylating agent.

In heterogeneous systems, both phase-transfer and chemical equilibria have to be taken into account as the influence of the former may even be rate determining for the overall process. This mass-transport from one phase to the other is undoubtedly influenced by the nature of the solvent, whose effect is difficult to predict.

11. Conclusions

It is obvious that in a heterogeneous system a close contact must be maintained between the two phases. It is therefore worthwhile to point out the surface activity of most of the quaternary ammonium compounds, which in fact are cationic detergents.

There are numerous papers discussing the catalytic effect of micelles of cationic detergents on enzymatic reactions[65]. Recently they have been used as catalysts in nucleophilic substitution reactions[66].

A systematic comparison with existing methods is beyond the scope of this review. However it is obvious that in many cases the catalytic method is superior, giving high yields and eliminating expensive

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solvents and dangerous reagents such as sodamide. This review is intended to draw the attention to the synthetic value of these "onium" compounds and to their strongly related mechanisms of catalysis.

Many aspects of their use, both theoretical and practical, remain to be explored.

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