Tetrahedron Letters No. 39, pp 3753 - 3756.
©Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/0922-3753$02.00/0

THE EFFECT OF PHASE TRANSFER CATALYSTS ON THE REIMER-TIEMANN REACTION

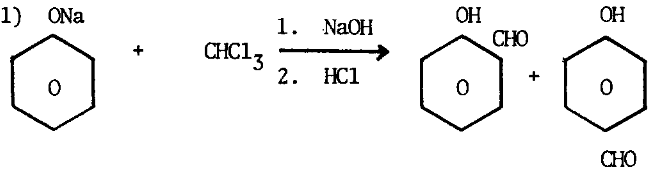
Yoel Sasson* and Minda Yonovich
Casali Institute of Applied Chemistry, The Hebrew University of Jerusalem
Jerusalem, Israel

Abstract: Quaternary ammonium salts were found inactive as phase transfer catalysts in the Reimer-Tiemann reaction. Tertiary amines, on the other hand, proved to have significant effect on the process.

The generation of dichlorocarbene by action of bases on chloroform in a two-phase system is greatly enhanced in the presence of quaternary ammonium salts. This phenomenon, originally reported by Makosza,(1) is of significant synthetic importance in various reactions of dichlorocarbene intermediates namely: addition to C=C bonds(2,3), insertion to C-H bonds(4) and conversion of amides, primary amines and secondary amines to nitriles(5) isocyanides(6) and formamides (7) respectively.

A well-known dichlorocarbene reaction is the Reimer-Tiemann (R-T) process (eq. 1)(8).

(1)



The reaction is carried out in a two-phase system. The reported yields are 20-35% of salicylaldehyde and 8-10% of 4-hydroxybenzaldehyde. The R-T reaction is apparently an interfacial process which takes place at the water-chloroform interphase. (In a series of experiments we have found that the yield of the reaction linearly depends on the mixing rate of the system).

Similarly to other dichlorocarbene reactions we have attempted to improve the efficiency of the process by addition of various ammonium salts to the reaction mixtures. We have expected to extract the hydroxide and the phenoxide ions (eqs 2,3) into the organic phase and thus obtain both the dichlorocarbene generation and the electrophilic attack of the carbene on the phenolate ion in this phase.

$$(2) \quad R_4\overset{+-}{NX} + NaOPh \rightleftharpoons R_4\overset{+\ -}{N\ OPh} + NaX$$

$$(3) \quad R_4\overset{+-}{NX} + NaOH \rightleftharpoons R_4\overset{+\ -}{N\ OH} + NaX$$

Several experiments in which quaternary ammonium salts were added to the reaction mixture have shown practically no change in the conversions and the yields. Typical phase transfer agents we have tried were tetrabutylammonium bromide, tetrabutylammonium hydrogen sulfate and benzyltriethyl ammonium chloride. Minor increase in the conversion (5%) was observed, however, when the added ammonium salt was a surface active agent, e.g., hexadecyltrimethylammonium bromide.

The lack of activity is attributed to the large difference between the equilibrium constants of reactions 2 and 3. In separate experiments we have found that it is practically impossible to extract hydroxide ion as tetralkyl ammonium hydroxide to an organic phase in the presence of phenoxide ion. The catalysts in the above experiments are thus completely converted to phenoxide salts and no hydroxide is transferred to the chloroform phase. The phenoxide ion is too weak a base for generation of dichlorocarbene and thus no catalytic effect is observed. Even addition of stoichiometric quantities of triethylbenzylammonium chloride did not improve the yields.

It is interesting to note that when we have used preprepared tetrabutylammonium hydroxide, in a mixture of sodium phenolate and chloroform at 50° for 1 hour, we obtained 24.3% 4-hydroxybenzaldehyde and only 10.5% of salicyaldehyde(9). When the same treatment was applied on tetrabutylammonium phenoxide and tetrabutylammonium hydroxide in chloroform, an unexpected product, namely butylphenyl ether was isolated in quantitative yield(10). It is therefore obvious that even if both the hydroxide and the phenoxide were extracted into the organic phase the result could not be normal R-T reaction.

Since it is known that simple tertiary amines can also catalyze dichlorocarbene reactions[12,13) we have added various aliphatic tertiary amines to R-T reaction mixtures. The results are given in the table. The yield of salicylaldehyde has increased significantly in the presence of the tertiary amines. The effect on the yield of 4-hydroxybenzaldehyde was smaller.

We suggest that while quaternary ammonium salts can extract and activate only one substrate the tertiary amines can simultaneously activate both the phenoxide ion and the dichlorocarbene. The following sequence of steps is probably involved in the mechanism of the catalytic reaction:

a) Generation of dichlorocarbene in the water chloroform interphase (4)

$$(4)\quad CHCl_3 \xrightarrow{OH^-} :CCl_2 + H_2O + Cl^-$$

b) Reaction of dichlorocarbene with the tertiary amine followed by attack of another chloroform molecule and generation of additional dichlorocarbene(13) (5).

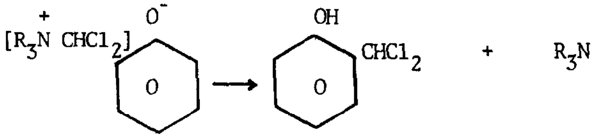
$$(5)\quad \ddot{C}Cl_2 + R_3N \longrightarrow R_3\overset{+}{N}\overset{-}{C}Cl_2 \xrightarrow{CHCl_3} [R_3\overset{+}{N}\,CHCl_2]\,\overset{-}{C}Cl_3 \longrightarrow [R_3\overset{+}{N}\,CHCl_2]\,\overset{-}{Cl} + :CCl_2$$

c) Anion exchange of the quaternary chloride salt with phenoxide (6):

$$(6)\quad [R_3\overset{+}{N}\,CHCl_2]\,\overset{-}{Cl} \xrightarrow{\overset{-}{OPh}} [R_3\overset{+}{N}\,CHCl_2]\,\overset{-}{OPh}$$

d) Intramolecular rearrangement of the phenoxide salt to yield mainly ortho alkylated phenol and the original tertiary amine (7). This proposed step is similar in nature to the well-known Sommelet rearrangement (14).

(7)



The dichloro product is eventually hydrolyzed to yield salicyaldehyde.

TABLE

The effect of tertiary amines on the yield of R - T reaction(a)

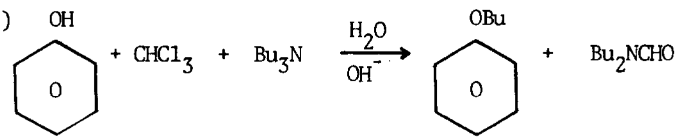
Exp.	Catalyst	Salicylaldehyde (%) (b)	4-hydroxybenzaldehyde (%) (b)
1	none	26.0	4.1
2	$(n\text{-}C_4H_9)_3N$	64.5	5.8
3	$(n\text{-}C_6H_{13})_3N$	53.4	5.2
4	$(n\text{-}C_8H_{17})_3N$	49.0	3.9

(a) Reaction conditions: 0.05 mole phenol. 0.3 mole chloroform, 10^{-3} mole catalyst, 50 ml. benzene, 0.3 mole sodium hydroxide 50% solution in water. Magnetic stirring at 60° for 25 min. Hydrolysis with 50 ml. 10% hydrochloric acid.

(b) GLC analysis using 6 ft. 10% carbowax 20M on chromosorb W column.

Additional support for the existence of the intermediate formed in eq. [6] can be found in the fact that when 4-tertbutylphenol was formylated under the above conditions additional products were isolated from the mixture. When the formylation was carried out in the presence of tributylamine those side products were n-butyl-4-tertbutylphenyl ether and N,N-di-n-butylformamide which are formed according to the following:

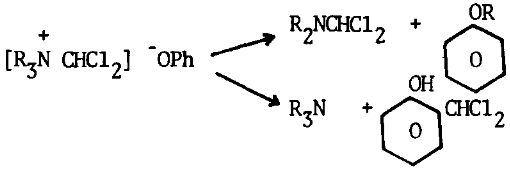
(8)



We observed that this route can be the major reaction when the amine is present in stoichiometric quantities. The course of the reaction is also strongly dependent on the solvent, temperature, mixing rate, concentration and structure of the reactants(10).

The ether and the aldehyde are apparently formed from the same specie obtained in eq. [6] which decompose in two competing routes both via intramolecular nucleophilic attack of the phenoxide group, eq. [8].

(8)



Detailed studies of the system are now in progress.

REFERENCES

(1) M. Makosza and M. Wawrzyniewicz, Tetrahedron Lett., 4659 (1969).

(2) C.G. Joshi, N. Singh and L.M. Pande, Tetrahedron Lett., 1461 (1972).

(3) E.V. Dehmlow, Tetrahedron Lett., 91 (1976).

(4) E.V. Dehmlow, Tetrahedron 27, 4071 (1971).

(5) T. Saraie, T. Ishiguro, K. Kawashima dn K. Morita, Tetrahadron Lett., 2121 (1973).

(6) W.P. Weber and G.W. Gokel, Tetrahedron Lett., 1637 (1972).

(7) M. Makosza and A. Kacprowicz, Rocz. Chem. 49 1627 (1975).

(8) H. Wynberg, Chem. Rev., 60, 169 (1960).

(9) O. Brady and J. Jakobovitz, J. Chem. Soc., 767 (1950).

(10) Y. Sasson and M. Yonovich, to be published.

(11) W.P. Reeves and R.G. Hilbrich, Tetrahedron, 32, 2235 (1976).

(12) K. Isagawa, Y. Kimura and S. Kwon, J. Org. Chem., 39, 3171 (1974).

(13) M. Makosza, A. Kacprowicz and M. Fedorynsky, Tetrahedron Lett., 2119 (1975).

(14) S.W. Kantor and C.R. Hauser, J. Am. Chem. Soc., 73, 4122 (1951).

(Received in UK 2 July 1979)