Stereochemical Control of the Interfacial Darzens Condensation[1]

By Andrzej Jończyk, Andrzej Kwast, and Mieczysław Makosza
(*Institute of Organic Chemistry and Technology, Technical University,* 00-662 *Warsaw, Koszykowa* 75, *Poland*)

Summary The condensation of α-chlorophenylacetonitrile (**1**) with benzaldehyde (**2**) carried out in the presence of 50% aq. NaOH and a quaternary ammonium catalyst gives *trans*-2,3-diphenylglycidonitrile, while without the catalyst, the *cis*-isomer predominates; in the latter case the reaction proceeds at the interface.

The catalytic, two-phase system[2,3] (50% aq. NaOH–quaternary ammonium salt–organic solvent) is now widely used in organic synthesis involving carbanions and carbenes. However, there are still many uncertainties concerning the mechanism, particularly the site where the reactions proceed. It is believed[2] that the abstraction of a proton, which is the initial step of the multi-step carbanionic reaction, takes place at the interface. The lipophilic cation introduced with the catalyst then transports the carbanions into the organic phase (as an ion-pair with the quarternary ammonium cation), where all further reactions take place. There are many arguments in favour of this, based mainly on the fact that some reactions proceed in this system even in the absence of a catalyst.[4] Because of the mutual insolubility of the two phases, it is believed that such reactions proceed at the interface.

The most interesting independent evidence for the interfacial processes seems to be the possibility of stereochemical control. Here we report that the stereochemistry of the Darzens reaction is, in some cases, controlled by the site of the reaction.

Thus, the condensation of the chloronitrile (**1**) with benzaldehyde (**2**) conducted in benzene in the presence of 50% aq. NaOH solution and benzyltriethylammonium chloride (BTEA) as catalyst results in formation of *trans*-2,3-diphenylglycidonitrile (*trans/cis ca.* 9). The same result was obtained when catalytic amounts of dibenzo-18-crown-6, instead of BTEA were used. In contrast, when this reaction was carried out without a quaternary ammonium salt the *cis*-isomer of the glycidonitrile was the predominant product (*trans/cis ca.* 0·5) (Table).

Table[a]

Solvent	Base	Ratio of *cis* to *trans* Without catalyst	 With catalyst
Benzene	50% aq. NaOH	52:48	11:89[b]
Benzene	50% aq. NaOH	68:32[c]	8:92[c]
Benzene	Solid KOH	59:41	10:90
Benzene	17% aq. NaOH	6:94	2:98
CCl_4	50% aq. NaOH	55:45	15:85
Me_2SO	50% aq. NaOH	5:95	—

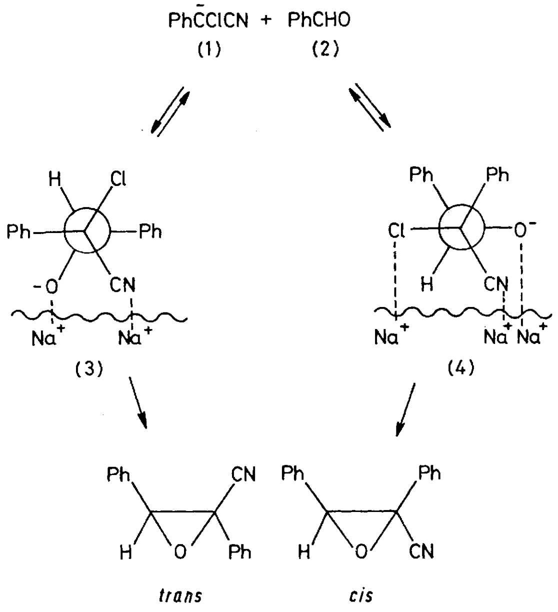
[a] Conditions: 1·0 M solutions of (**1**) and (**2**), except where noted, 5 mole % of BTEA, with stirring at 20 °C. [b] A similar result was obtained in the presence of 5 mole % of dibenzo-18-crown-6. [c] 0·3 M solutions of (**1**) and (**2**); a similar ratio of products was obtained in more dilute solutions.

The reason for this seems to be as follows. The cyclization step is slow compared to the rather fast, reversible formation of the intermediate aldol condensation products.[5]

The transition state for the cyclization of both halogenohydrin anions (**3**) and (**4**) requires that the $-O^-$ and $-Cl$ substituents should be *anti* to each other. When the halogenohydrin anions accompanied by quaternary ammonium cations (or Na^+ ions complexed by the crown ether) react in the organic phase, the Ph–Ph interactions in (**4**) increase the energy of the transition state, so (**3**) cyclizes faster. However when the halogenohydrin anions are located at the phase boundary, the interactions of the $-O^-$, $-Cl$, and $-CN$ substituents with Na^+ located at the surface of the aqueous phase (Scheme) considerably decrease the energy of the transition state of (**4**) for cyclization. As a consequence, in spite of the unfavourable Ph–Ph interaction, (**4**) cyclizes faster.

The results of other non-catalytic reactions are in line with the above explanation. Thus, the *cis*-isomer predominated when the reaction was carried out in the presence of solid KOH. When dilute, instead of conc. aq. NaOH solutions were used, these interfacial effects were no longer observed, because of the strong solvation of Na^+ ions by water molecules. In the case of Me_2SO, Na^+ cations, being strongly solvated, are soluble in the organic phase; the situation is similar to that described for the catalytic reactions (Table).

This phenomenon was observed only in those Darzens condensations where the cyclization step is slow compared to the fast, reversible formation of the halogenohydrin anions. In fact, we have not observed these effects with the two-phase condensation of chloroacetonitrile or α-chloropropiononitrile with carbonyl compounds. From the literature,[6] the cyclization step in this case is faster than the rather slow and irreversible formation of the halogenohydrin anion.



Scheme

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[1] For previous paper in the series, 'Reactions of Organic Anions,' see A. Jończyk, J. Włostowska, and M. Makosza, *Bull. Soc. chim. belges*, submitted for publication.

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