

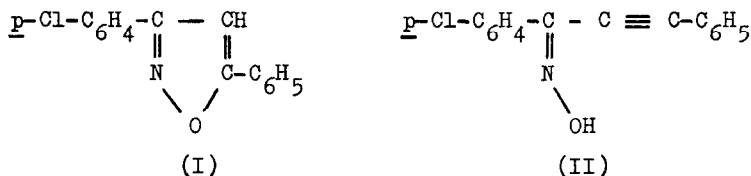
ISOXAZOLES FROM NITRILE OXIDES AND ARYLACETYLENES. THE ROLE OF THE  
 $\alpha$ -ACETYLENIC OXIME IN THE ISOXAZOLE SYNTHESIS FROM THE REACTION OF  
 p-CHLOROBENZONITRILE N-OXIDE WITH PHENYLACETYLENE

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Similarly to that recently reported (1) for other nitrile oxides, the reaction between p-chlorobenzonitrile N-oxide (2) and a tenfold molar excess of phenylacetylene in  $\text{CCl}_4$  affords (3) besides 3-(p-chlorophenyl)-5-phenylisoxazole (I), m.p. 176-177° (4) (80% yield), an open chain addition product in lower yield (16%) which has been identified as  $\alpha$ -acetylenic oxime (II).



The structure (II) is supported by spectroscopic evidence: major infrared bands ( $\text{cm.}^{-1}$ ) at 3580, 3300 (broad) (OH) and 2220 ( $\text{C}\equiv\text{C}$ ); the N.M.R. spectrum shows (deuteriochloroform) besides the resonance of the aromatic protons between 2.0 and 2.65 $\tau$ , a broad signal around 0.65 $\tau$  shifted by dilution or disappearing by addition of few drops of  $\text{D}_2\text{O}$ . Similar spectroscopic characteristics have been observed for other acetylenic oximes (1).

The oxime (II) may be carefully crystallized (5), m.p. 106-107° (from benzene-light petroleum) and stored unmodified for few days at room temperature. However in carbon tetrachloride solution at 45° a slow isomerization of this product to isoxazole (I), was observed. The reaction followed the first-order kinetic law ( $k_C = 1.32 \times 10^{-6} \text{ sec.}^{-1}$  in  $\text{CCl}_4$  at 45°) and appeared to be catalyzed by triethylamine but not affected by a considerable excess (53 moles) of the slightly basic (6) p-chlorobenzonitrile N-oxide.

Oxime (II) appeared more stable than expected on the basis of the behaviour reported (1) for similar compounds, but since it is observed to isomerize to

isoxazole (I), its role as a potential intermediate in the formation of (I) needs to be defined.

The reaction of p-chlorobenzonitrile N-oxide with phenylacetylene (7) was kinetically reexamined, runs being followed by quantitative infrared analysis of nitrile oxide ( $2290\text{ cm.}^{-1}$ ), isoxazole (I) ( $950\text{ cm.}^{-1}$ ) and acetylenic oxime (II) ( $3580\text{ cm.}^{-1}$ ). The molar ratio  $[\text{Is}]/[\text{Ox}]$  between (I) and (II) was calculated at various extents of conversion of nitrile oxide and found to be constant within the experimental error throughout each experiment (see Table)

T A B L E

Typical run for the reaction of p-chlorobenzonitrile N-oxide (0.00932 M) with phenylacetylene (0.157 M) in  $\text{CCl}_4$  at  $45 \pm 0.1^\circ$

time (sec.)...	63	120	180	245	330	425	510	600	725	840
$[\text{ArCNO}]$ ..... ( $10^3 \times \text{M}$ )	8.58	7.66	6.88	6.20	5.33	4.37	3.69	3.13	2.48	1.98
$[\text{Is}]/[\text{Ox}]$ .....	--	2.30	2.42	2.38	2.41	2.28	2.40	2.57	2.47	2.36

From the concentrations of reagents and products and from the over-all rate constant  $k_{\text{tot}}$  measured through the disappearance of nitrile oxide (7), the rate coefficients  $k_{\text{Is}}$  and  $k_{\text{Ox}}$  for the formation of isoxazole (I) and acetylenic oxime (II) respectively, were calculated. In  $\text{CCl}_4$  at  $45^\circ$  the following values ( $1.\text{ mole}^{-1}\text{ sec.}^{-1}$ ) were obtained:  $k_{\text{tot}} = 1.21 \times 10^{-2}$ ;  $k_{\text{Is}} = 8.98 \times 10^{-3}$ ;  $k_{\text{Ox}} = 3.76 \times 10^{-3}$ .

These results indicate that, at least in neutral medium, the isomerization of the acetylenic oxime (II) is consistently slower (3) than the formation of both isomers (I) and (II). If a detectable amount of isoxazole (I) were formed by isomerization of the oxime (II) while the reagents were disappearing, a variation of the molar ratio of the products should be observed. The data of the above Table show that this was not the case (9).

The over-all results reported here indicate that from the reaction of p-chlorobenzonitrile N-oxide and phenylacetylene two competing processes take place, one leading to isoxazole (I) and the other to acetylenic oxime (II). From kinetic evidence it may be safely deduced that under the conditions adopted here the amount of isoxazole (I) recovered from the reaction mixture immediately after the disappearance of p-chlorobenzonitrile N-oxide comes directly from the reagents, since the part of (I) formed through the acetylenic oxime (II) as intermediate is virtually negligible. For larger reaction times

or in the presence of basic catalysts, part of the isoxazole (I) is formed through the oxime (II).

We can conclude that for our system the one-step mechanism outlined (10) for the synthesis of isoxazoles (11) from nitrile oxides and acetylenes is predominant while the reagents are disappearing despite the existence of the acetylenic oxime (II) which requires large reaction times to act as a real intermediate in the formation of a further amount of (I). This result cannot be generalized. The relative extents of these competing paths leading to isoxazole (the direct one, and that via the acetylenic oxime) as a function of several factors (namely substituents and solvents) are under investigation in other cases. In fact it may be that kinetic data (7, 10a, 12) reported as further evidence for the one-step mechanism have to be reconsidered.

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3. The yields do not strictly reflect the relative rates of formation of (I) and (II) since a partial isomerization of (II) to (I) was observed during the working up of the reaction mixture.
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5. Satisfactory elemental analysis was obtained and impurities of (I) were not detected by thin-layer chromatography.
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8. Note that  $k_{tot}$ ,  $k_{Is}$  and  $k_{Ox}$  are second-order rate constants whereas  $k_C$  is first-order. However since the initial concentration of phenylacetylene was ca. 0.1 M for all set of experiments (tenfold excess with respect to nitrile oxide), the  $k_{Is}$  and  $k_{Ox}$  values in pseudo first-order terms are ca.  $9 \times 10^{-4} \text{sec.}^{-1}$  and  $4 \times 10^{-4} \text{sec.}^{-1}$  respectively, and therefore higher by 2-3 orders of magnitude than  $k_C$ .
9. It must be pointed out that the ratio  $[Is]/[Ox]$  is only apparently constant; since the isomerization of (II) to (I) is a fact, the ratio does change, but owing to the slowness of this reaction the variations are within the

experimental error.

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