REACTIONS OF QUINOLINE AND 4-CHLOROQUINOLINE 1-OXIDES WITH PHENOXYACETONITRILE, CHLOROMETHYLPHENYLSULFONE, AND METHYL-THIOMETHYL-p-TOLYLSULFONE[1]

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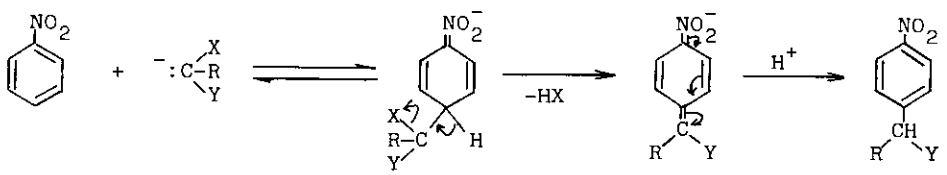
Abstract —— Quinoline and 4-chloroquinoline 1-oxides react with phenoxyacetonitrile (1) and chloromethylphenylsulfone (3) in KOH-DMSO and in t-BuOK-THF to give the respective vicarious nucleophilic substitution products, 2-cyanomethyl- (2a and 2b) and 2-phenylsulfonylmethylquinoline 1-oxides (4a and 4b). The reactions with methylthiomethyl-p-tolylsulfone (5) afford not only the vicarious nucleophilic substitution products (6a and 6b) but also the products by means of hydride elimination (7a and 7b).

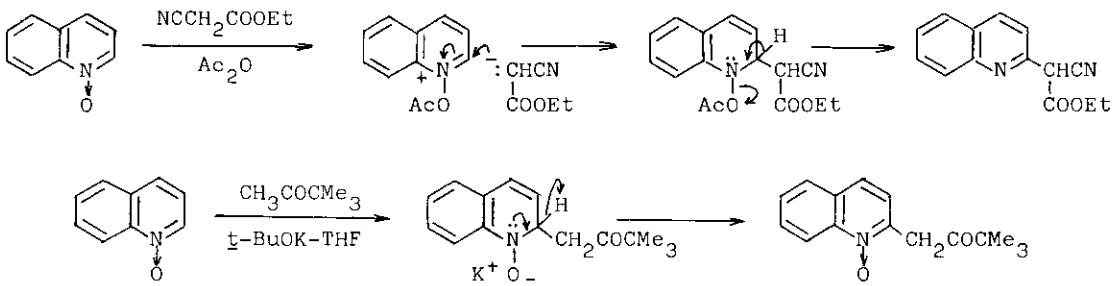
Makosza and coworkers have extensively studied the "vicarious" nucleophilic substitution of nitroarenes with some carbanions bearing leaving groups on the carbanionic center.[2] The reaction is now established to proceed by the following course as illustrated below by p-substitution.[2b]



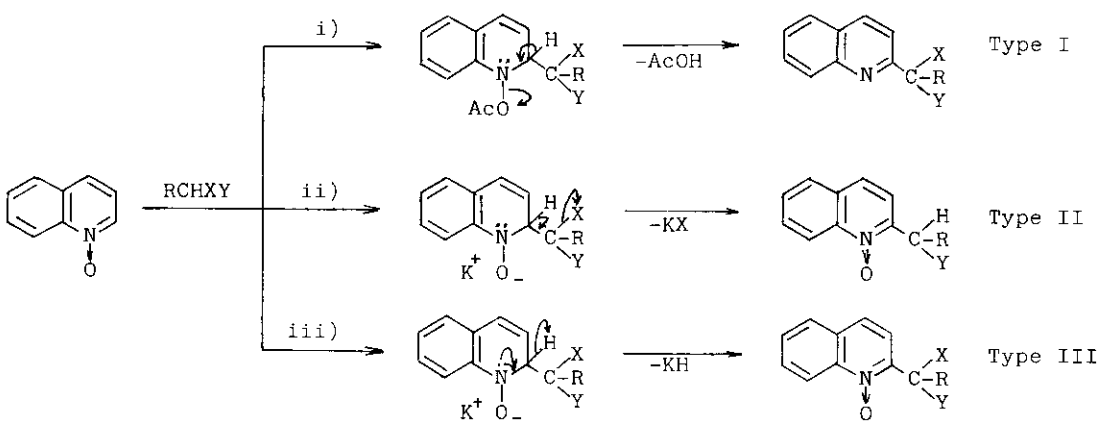
X: Leaving group, e.g., Cl, PhO, PhS, MeS etc.
Y: Carbanion stabilizing group, e.g., SO_2, CN, COOMe etc.

They have shown that this reaction is also applicable to some heteroaromatics, but pyridine or quinoline resists the reaction with chloromethylphenylsulfone.[3]

With respect to nucleophilic substitution of hydrogen in aromatic N-oxides with carbon nucleophiles, two types of reactions are of interest in relation to the above reaction. The first is the reaction with highly active methylenes in the presence of acylating agents giving the deoxygenated α- or/and γ-substitution products.[4] Another reaction proceeds with rather weakly acidic active methylenes in the presence of strong bases to give α-substituted N-oxides by means of hydride elimination.[5] The followings are the typical examples of reactions of quinoline 1-oxide.



Although pyridine and quinoline did not react with chloromethylphenylsulfone,[3] there is the possibility that some active aromatic N-oxides undergo the vicarious nucleophilic substitution with appropriate carbanions under suitable conditions. In fact, some aromatic N-oxides of naphthoid structure were found to react with methylsulfinyl carbanion to give the corresponding α-methyl N-oxides.[6,7] Therefore, three types may be conceivable for the reaction of aromatic N-oxides with active



i) Acylating agent, e.g., Ac_2O ii) Strong base, e.g., KOH-DMSO
iii) Strong base, e.g., t-BuOK-THF X: Leaving group

Chart 1

methylenes bearing leaving groups as formulated by quinoline 1-oxide in Chart 1.

In order to examine these possibilities, we have investigated reactions of quinoline 1-oxides with a number of active methylene compounds bearing leaving groups. This paper mainly deals with reactions of quinoline and 4-chloroquinoline 1-oxides with phenoxyacetonitrile, chloromethylphenylsulfone and methylthiomethyl-p-tolylsulfone in acetic anhydride (Ac_2O), in the presence of powdered potassium hydroxide in dimethylsulfoxide (KOH-DMSO) and in the presence of potassium tert-butoxide in tetrahydrofuran (t-BuOK-THF).

The reaction of quinoline 1-oxide (A) with phenoxyacetonitrile (1) in excess Ac_2O was first tried at 50 °C for 2 h or at room temperature for 1 week, but type I reaction did not occur, small amounts of carbostyril being formed besides the recovery of A. When excess powdered KOH (ca. 10 eq.) was added under ice-cooling to a solution of A and 1 (1.2 eq.) in DMSO, the reactants turned red after a few minutes and then dark red. The reaction mixture was stirred at room temperature for 1 h, and concentrated in vacuo, acidified with hydrochloric acid and extracted with chloroform. The extract was washed with saturated sodium chloride solution, and the product was purified by chromatography on silica gel with 1% MeOH-$CHCl_3$ to give 2-cyanomethylquinoline 1-oxide[4a] (2a) [pale yellow scales, mp 166-168° C (dec.) (EtOH)] in 32.4% yield. Thus it was revealed that a vicarious nucleophilic substitution, type II reaction, occurred. The reaction of A with 1 (2 eq.) in the presence of t-BuOK (2.4 eq.) in THF also proceeded at room temperature and gave 2a in 48.9% yield after the reaction for 2 h.

Quite similarly, 4-chloro-2-cyanomethylquinoline 1-oxide (2b) [colorless needles, mp 155-156 °C (dec.)(EtOH)] was produced in 49.3 and 37.8% yields from reactions of 4-chloroquinoline 1-oxide (B) with 1 in KOH-DMSO and t-BuOK-THF, respectively, the active 4-chloro substituent being not attacked at all.

Reactions using chloromethylphenylsulfone (3) as an active methylene also progressed in quite similar manners and afforded type II reaction products, 2-phenylsulfonylmethylquinoline 1-oxide (4a) [colorless needles, mp 164-165 °C (MeOH)] , and its 4-chloro derivative (4b) [colorless crystals, mp 228-230 °C (acetone-EtOH)], from reactions of A and B, respectively. While 4a was obtained in a poor yield of 9.7% in the reaction of A in KOH-DMSO, the other reactions proceeded in good to high yields.

While the reaction of A with methylthiomethyl-p-tolylsulfone (5) in KOH-DMSO gave

only 2-p-tolylsulfonylmethylquinoline 1-oxide (6a) [colorless needles, mp 172-173°C (EtOH)] in a poor yield of 3.5%, the reaction in t-BuOK-THF afforded 2-(methylthio-p-tolylsulfonyl)methylquinoline 1-oxide (7a) [colorless needles, mp 165-167°C (dec.) (EtOH)] in 16.1% yield in addition to 6a (23.6%). Apparently, 7a is the product by type III reaction; the separation of 6a and 7a was easily effected by chromatography on silica gel with 0.2% MeOH-$CHCl_3$ with earlier elution of 7a. Reactions of B with 5 in KOH-DMSO and in t-BuOK-THF gave the both type products, 6b [coloeless needles, mp 200-202°C (dec.) (EtOH)] and 7b [colorless needles, mp 166-168°C (dec.) (EtOH)]. In these ceses, the amounts of 7b (9.1 and 27.4%) were always larger than those of 6b (trace and 9.1%), though the total yields were not so good. These results are given in Chart 2. The structures of products were established by the elemental analyses, the ms, ir and nmr spectroscopies.

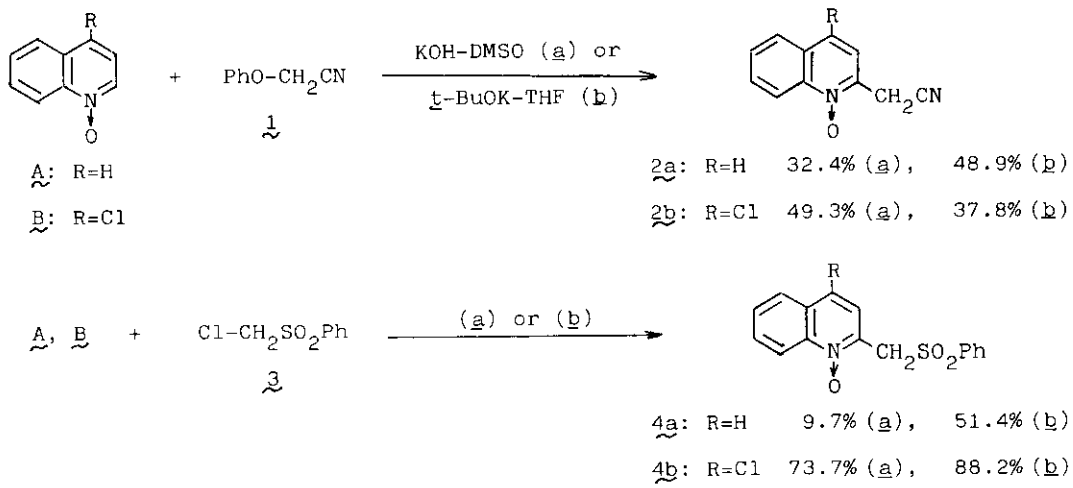
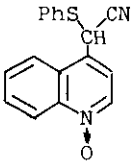


Chart 2

Reactions of A and B with chloroacetonitrile and phenylthioacetonitrile were also attempted, but neither type II nor type III reaction took place. However, treatment of B with phenylthioacetonitrile at room temperature in NaOH-DMSO caused the nucleophilic displacement of the 4-chloro substituent to give 4-(cyanophenylthio)methylquinoline 1-oxide (8) [pale yellow prisms, mp 131-133 °C (acetone-hexane)] in 47.8% yield.



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Thus, it has been revealed that quinoline 1-oxides are able to undergo type II and type III reactions upon treatment with some rather weakly acidic active methylenes bearing leaving groups in the presence of bases. The ease and the course of the reaction must largely depend on the nature of active methylenes and on reaction conditions. Further studies on these aspects are now in progress.

REFERENCES AND NOTE

1. We wish to dedicate this paper to Professor Dr. G. Stork on the occasion of his 65th birthday.
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