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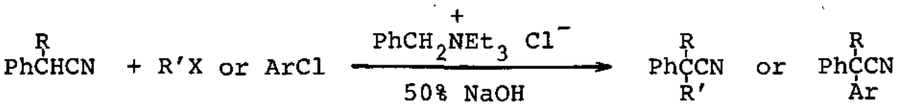
A PRELIMINARY STUDY ON PHASE-TRANSFER CATALYZED REACTION OF AROMATIC N-OXIDE DERIVATIVES. REACTION OF 4-CHLOROQUINOLINE 1-OXIDE WITH CARBANIONS

Masatomo Hamana, Fuminori Sato, Yoshio Kimura,
Makoto Nishikawa and Hiroshi Noda
Faculty of Pharmaceutical Sciences, Kyushu University
Maidashi, Higashi-ku, Fukuoka 812, Japan

A solution of 4-chloroquinoline 1-oxide (**1**) and α-phenylpropionitrile in benzene was treated with 50% sodium hydroxide and a catalytic amount of tetrabutylammonium bromide at 50° for 8 hr with vigorous stirring to produce 4-(α-cyano-α-phenyl)ethylquinoline 1-oxide in 72% yield. Reactions of **1** with butyl vinyl ether adducts of some aromatic aldehyde cyanohydrins under the same conditions gave, after hydrolysis with hot 10% hydrochloric acid, 4-aroylquinoline 1-oxides.

Recently much attention has been focussed on phase-transfer catalyzed reaction both for its theoretical interest and because of its practical synthetic value in various types of reactions[1]. As a preliminary study on phase-transfer catalyzed reaction of aromatic N-oxide derivatives, the reaction of 4-chloroquinoline 1-oxide (**1**) with α-phenylpropionitrile and butyl vinyl ether adducts of some aromatic aldehyde cyanohydrins was investigated.

Mokosza *et al*.[2] have described the successful alkylation and arylation of α-phenylalkylacetonitrile with alkyl halides and o- or p-nitrochlorobenzenes in the presence of 50% sodium hydroxide and a catalytic amount of benzyltriethylammonium chloride.

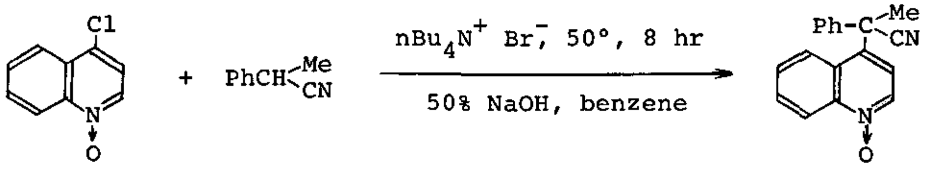


$$\overset{R}{PhCHCN} + R'X \text{ or } ArCl \xrightarrow[50\%\ NaOH]{PhCH_2\overset{+}{N}Et_3\ Cl^-} \overset{R}{\underset{R'}{PhCCN}} \text{ or } \overset{R}{\underset{Ar}{PhCCN}}$$

X: Cl or Br, R: H or alkyl
Ar: o- or p-nitrophenyl

At first, in order to explore the reactivity of 4-chloro-substituent of **1** toward phase-transfer catalyzed reaction with carbanions, the reaction of **1** with α-phenylpropionitrile (**2**) was carried out in a similar way as above. To a bezene solution (3 ml) of **1** (2 mmol) and **2** (2.2 mmol) was added tetrabutylammonium bromide (TBA) (0.1 mmol) and 50% sodium hydroxide (1.2 ml), and the reactants were vigorously stirred at 50° for 8 hr. The cooled reaction mixture was poured into water and extracted with dichloromethane to give 4-(α-cyano-α-phenyl)ethylquinoline 1-oxide (**3**), colorless pillars, mp 217~218° (EtOH), in 72% yield accompanied by 23% recovery of **1**; no formation of 4-quinolinol 1-oxide was noticed in spite of the use of excess alkaline solution.

Structure assignment of **3** is based on the satisfactory elemental analysis [$C_{18}H_{14}ON_2$], the mass spectrum [m/e: 274(M^+)],

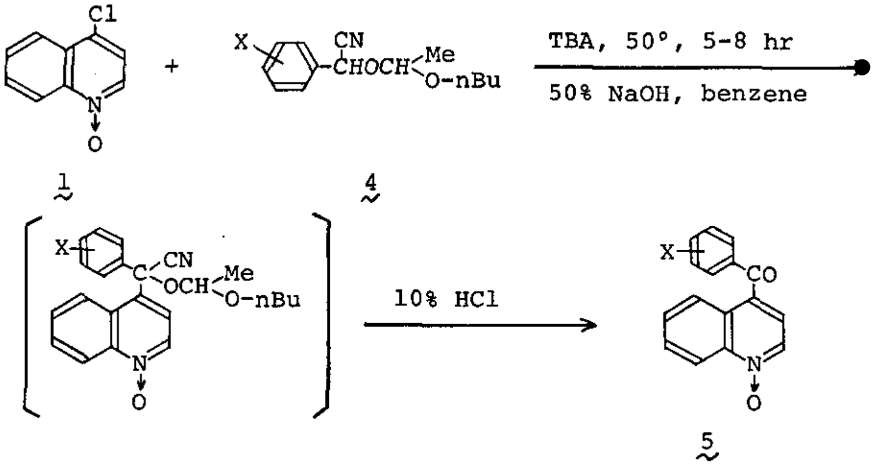


1 **2** **3**

the IR spectrum [ν_{max}^{KBr} cm^{-1}: 2230 (C≡N), 1240 (N-O)] and the NMR spectrum [δ($CDCl_3$): 2.20 (3H, s, CH_3), 8.60 (1H, d, J=6.5 Hz, C_2-H), 8.81 (1H, d, J=9.0 Hz, C_8-H), 7.20-7.90 (9H, m, aromatic protons)].

Subsequently, reactions using butyl vinyl ether adducts of aromatic aldehyde cyanohydrins (**4**) as active methines were examined. A solution of **1** and α-(α-butoxyethoxy)phenylacetonitrile (**4a**)[3] in benzene was treated with TBA and 50% sodium hydroxide under the same conditions as the reaction of **1** with **2**. Since the product obtained on treatment of the reactants with water followed by extraction with dichloromethane was rather difficult to crystallize, it was hydrolyzed with hot 10% hydrochloric acid to 4-benzoylquinoline 1-oxide (**5a**)[4], colorless scales, mp 77.5-79° [EtOH-H_2O (1:1)]. This compound had an empirical formula, $C_{16}H_{11}O_2N\cdot 1/4\,H_2O$, and its mass spectrum showed the parent peak at m/e 249 and the IR spectrum exhibited a carbonyl band at 1665 cm^{-1}.

Further some substituted benzaldehyde derivatives were applied to **1** under the same conditions followed by hydrochloric acid hydrolysis of products, giving the corresponding 4-aroylquinoline 1-oxides (**5b**-**5f**) as shown below.



4a-f	Appearance	5a-f		Recov.
		mp (C°)	Yield (%)	1 (%)
a) X=H	colorless scales	77.5-79	72	15
b) X=p-Cl	colorless needles	132.5-134	60	30
c) X=p-CN	yellow prisms	181-182	41	47
d) X=p-Me	colorless needles	53.5-54.5	38	39
e) X=p-OMe	colorless needles	62-62.5	48	42
f) X=o-Cl	pale yellow needles	168-171	40	34

All compounds 5 showed a carbonyl band in their IR spectra around 1650 cm^{-1} and their elemental analyses, the mass and NMR spectra agreeded with respective structures. Although yields were not necessarily satisfactory in some cases because of lack of elucidation of the optimum conditions for each reaction, the above reaction is apparently promising for the preparation of 4-aroylquinoline 1-oxides and analogous heteroaromatic derivatives.

These results suggest that the above-mentioned procedure is a fairly promising method for the preparation of 4-carbon-substituted derivatives of aromatic N-oxides. This is particularly significant in view of the fact that the introduction of carbon-substituents into the 4-position of pyridine and quinoline rings can be attended only with great difficulties[5]. For instance, the reaction of acyl-adducts of their N-oxides with nucleophilic carbon compounds is a useful means for the introduction of carbon-substituents into the 2-position but the 4-substitution cannot be effected by this reaction except for few cases[6], and 4-halogen or 4-nitro group of pyridine, quinoline and their N-oxides stoutly resist nucleophilic displacement with carbanions in spite of facile exchange with other anions such as alkoxy, aryloxy, alkylthio, amino and halide ones[5].

Further work is in progress in our laboratory in order to widen the scope of this type of reaction varying heteroaromatic derivative as well as nucleophile.

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