NUCLEOPHILIC SUBSTITUTION OF 4-CHLOROQUINOLINE 1-OXIDE AND RELATED COMPOUNDS BY MEANS OF HYDRIDE ELIMINATION[1]

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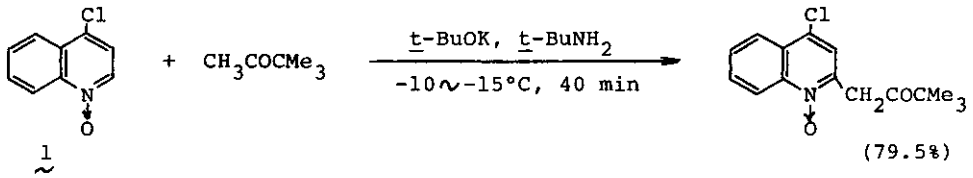
Abstract —— The reaction of 4-chloroquinoline 1-oxide (1) with pinacolone and t-BuOK in t-$BuNH_2$ at -10∼-15°C gives 4-chloro-2-pinacolylquinoline 1-oxide in good yield by means of hydride-elimination. Similar reactions of 1 with acetone, 2-butanone, acetophenone, and ethyl and t-butyl acetates occur when treated with t-BuOK or n-BuLi in t-$BuNH_2$ at -10∼-15°C, or t-BuOK, KNH_2 or $NaNH_2$ in liq NH_3 at -70°C. Reactions of this type proceed also with quinoline 1-oxide (2), 3-bromoquinoline 1-oxide (3), p-chloronitrobenzene (4) and nitrobenzene.

In order to examine the possibility of the nucleophilic substitution of 4-chloroquinoline 1-oxide (1) by means of $ArS_{RN}1$ mechanism[2], we tried the potassium tert-butoxide (t-BuOK)-catalyzed reaction of 1 with pinacolone in tert-butylamine (t-$BuNH_2$)[3], and found that 4-chloro-2-pinacolylquinoline 1-oxide was produced in high yield, without any participation of the 4-chloro substituent, contrary to our expectation. Thus, a suspension of pinacolone (2 equiv) and t-BuOK (2.5 equiv) in t-$BuNH_2$ was stirred at -10∼-15°C for 10 min. When 1 was added dropwise with stirring at the same temperature, the reaction mixture gradually turned orange, reddish orange and ultimately dark brown. After stirring was continued for 40 min, 4-chloro-2-pinacolylquinoline 1-oxide, pale yellow plates, mp 84-86°C, was obtained in 79.5% yield.



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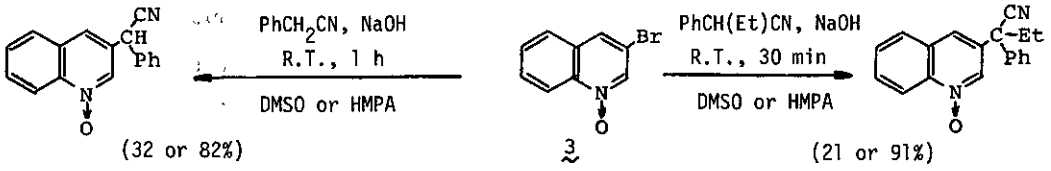
Some preliminary examinations revealed the following features: (1) the reaction proceeds smoothly with active methylene compounds of rather low acidity, but not with highly acidic ones such as ethyl cyanoacetate; (2) the reaction is not substantially interfered with radical and radical-anion scavengers (tetraphenylhydrazine and p-dinitrobenzene); (3) among bases so far examined, t-BuOK, n-BuLi, KNH_2 and $NaNH_2$ are highly effective, and the use of 2.5 equiv bases and 2 equiv active methylenes seems to be preferable; (4) t-$BuNH_2$ and liquid ammonia (liq NH_3) are fairly superior, as the reaction medium, to DMSO, HMPA and THF, which are also useful in a few cases. It was also found that quinoline 1-oxide (2) undergoes reactions of this type, although its reactivity is slightly lower as compared with 1.

The reaction time required in each case is considerably varied depending upon the nature of the reactants and the reaction conditions, however the proceeding of the reaction can be rather easily followed by the color-change and TLC-checking of the reaction mixture. Some representative reactions of 1 and 2 carried out under the following four conditions are listed in Table I[4]; condition (a): t-BuOK in t-$BuNH_2$ at -10~-15°C, (b): n-BuLi in t-$BuNH_2$ at -10~-15°C; (c) t-BuOK in liq NH_3 at -70°C, (d) KNH_2 or $NaNH_2$ in liq NH_3 at -70°C.

Previously, we reported that treatment of 3-bromoquinoline 1-oxide (3) with phenylacetonitriles in the presence of sodium hydroxide powder in DMSO or HMPA at room temperature affords the corresponding 3-substituted quinoline 1-oxides as exemplified below, and these reactions progress by $ArS_{RN}1$ mechanism[5].

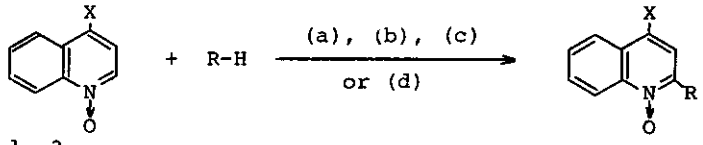


However, the reaction of 3 with active methylenes under the above-mentioned conditions resulted in the introduction of carbon-substituents into the 2-position in the same way as the cases of 1 and 2 (Table II).

While this type of reaction was not yet successfully effected with quinoline as well as pyridine 1-oxide, it was further disclosed that the reaction occurred with p-chloronitrobenzene (4) to give the o-substituted p-chloronitrobenzenes in moderate yields. In these cases, the use of 3 equiv active methylenes and 4 equiv bases was more preferable, and condition (c) was apparently most effective. Table

III shows some representative examples.

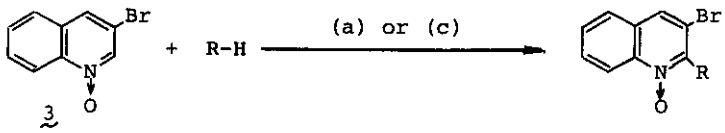
Table I. Reactions of 4-Chloroquinoline 1-Oxide (1) and Quinoline 1-Oxide (2) with Active Methylenes



1, 2

X	-R	Reaction Conditions	Products Yields (%)
Cl	$-CH_2COCH_3$	(c), 1 h	33.5
		(d), $NaNH_2$, 1 h	23.5
	$-CH_2COCMe_3$	(a), 40 min	79.5
		(b), 30 min	54.0
		(c), 2 h	89.8
		(d), KNH_2, 2 h	69.5
		(d), $NaNH_2$, 1 h	65.2
	$-CH(Me)COCH_3$	(c), 1 h	64.7
	$-CH_2COPh$	(a), 20 min	65.0
		(c), 2 h	41.6
		(d), KNH_2, 2 h	33.2
		(a), 50 min	41.0
		(c), 2 h	64.6
		(d), KNH_2, 1 h	51.3
	$-CH_2COOEt$	(a), 1 h	18.5
	$-CH_2COOCMe_3$	(a), 1 h	62.0
		(b), 1 h	67.0
		(d), KNH_2, 1 h	42.3
H	$-CH_2COCH_3$	(a), 2 h	37.4
		(d), KNH_2, 1 h	12.8
	$-CH_2COCMe_3$	(a), 2 h	81.0
		(b), 2 h	65.0
		(c), 2 h	47.3
	$-CH_2COPh$	(a), 1 h	65.0
		(c), 2 h	46.7
		(d), KNH_2, 2 h	16.2
	$-CH_2COOCMe_3$	(a), 2 h	34.0
		(b), 2 h	47.7
		(c), 2 h	40.4
	$-CH_2CN$	(a), 1 h	44.4
		(c), 2 h	25.9

Table II. Reactions of 3-Bromoquinoline 1-Oxide (3) with Active Methylenes



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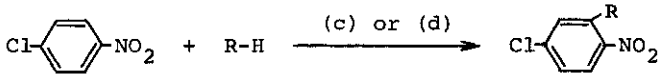
-R	Reaction Conditions	Products Yields (%)
$-CH_2COCH_3$	(a), 20 min	33.2
	(c), 30 min	83.0
$-CH_2COCMe_3$	(a), 40 min	43.4
$-CH_2COPh$	(a), 2 h	16.5
$-CH_2COOCMe_3$	(a), 30 min	16.0
	(c), 1 h	28.0

Table III. Reactions of p-Chloronitrobenzene (4) with Active Methylenes



4

-R	Reaction Conditions	Products Yields (%)
$-CH_2COCH_3$	(c), 2 h	24.9
	(c), 8 h	56.3
$-CH_2COCMe_3$	(c), 2.5 h	62.4
	(d), KNH_2, 4 h	43.9
$-CH_2COPh$	(c), 5 h	40.0
$-CH_2COOCMe_3$	(c), 1.5 h	10.5
	(c), 3 h	21.0
$-CH_2CN$	(c), 2.5 h	17.4
	(c), 6 h	22.0

Although an extensive study of the reaction of nitrobenzene itself has not been done yet, the reaction with acetone under condition (c) was recently found to give o- and p-acetonylnitrobenzene though in low yields of 15 and 5%, respectively.

These reactions should be considered as an aromatic nucleophilic substitution by means of the elimination of hydride anion. In this connection, the reaction of 1

with pinacolone under condition (a) was conducted in a stream of nitrogen, and it was found that 4-chloro-2-pinacolylquinoline 1-oxide was also formed though in somewhat lower yield of 36.4%. A similar result was observed in the reaction of 4 with pinacolone under condition (c). On the other hand, when a stream of oxygen was passed, at -70°C for 2 h, through a mixture of 4, acetone, t-BuOK and liq NH_3 [condition (c)], the yield of the product increased to 43%. Although the essential feature of the reaction has not been made clear, the combination of the base and the solvent seems to be the most important factor for the reaction to proceed smoothly.

Recently, Kienzle reported that treatment of nitroarenes with alkyl organometals at -30°C in ether, THF or n-hexane, followed by oxidation of products with bromine, DDQ or others, gave o- or/and p-alkylnitroarenes[6]. The reaction described above is conceivable to be different from the Kienzle's reaction in some details. Further studies are in progress to elucidate the reaction mechanism and extend the scope of the reaction under various conditions.

ACKNOWLEDGMENT

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REFERENCES AND NOTE

1. We wish to dedicate this paper to Emeritus Professor Kyosuke Tsuda on the occasion of his 75th birthday.
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