Journal of the Korean Chemical Society
1994, *Vol. 38, No. 10*
Printed in the Republic of Korea

단 신

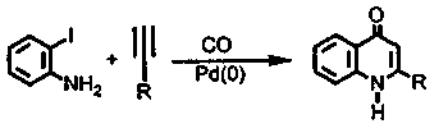
2-Phenyl-1,4-Dihydro-4-Oxoquinoline의 편리한 *N*-알킬화 반응

沈相赫* · 蔡信愛 · 李東燁 · 林鶴相 · V. N. Kalinin†
경북대학교 공과대학 공업화학과
(1994. 5. 17 접수)

Convenient *N*-Alkylation of 2-Phenyl-1,4-Dihydro-4-Oxoquinoline

Sang Chul Shim*, Shin Ae Chae, Dong Yub Lee, Hak Sang Lim, and V. N. Kalinin†
Department of Industrial Chemistry, Kyungpook National University, Taegu 702-701, Korea
†*Institute of Organoelement Compounds of Russian Academy of Science, Vavilov 28, Moscow, 1178/13*
(Received May 17, 1994)

Quinolones are an important synthetic class of biological active substances possessing antibacterial and anticancer properties[1]. A simple convenient synthesis of 2-substituted 1,4-dihydro-4-oxoquinolines (2-substituted quinolones) is known to be based on the Pd-catalyzed reaction of *o*-iodoaniline with terminal acetylenes under 20 atm of carbon monoxide (Eq. 1)[2].

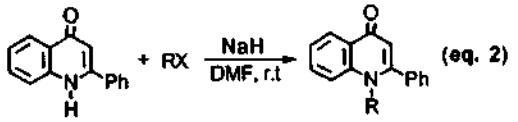


(eq. 1)

Structure-activity relationship studies seem to point out the antibacterial potency is greatly influenced by the steric bulk of the 1-substituents[3]. The general method used for the preparation of 1-substituted quinolones involves the alkylation of NH-group by alkyl halides to give 1-alkylated derivatives[4].

We have investigated the reaction of some alkyl halides with 2-phenyl-1,4-dihydro-4-oxoquinoline for the preparation of *N*-alkyl derivatives which are planned to be the key intermediate to quinoline antibacterial agents. Besides it was of interest to search a steric influence of aryl group in position 2 on the alkylation reaction.

The alkylation of 2-phenyl-1,4-dihydro-4-oxoquinoline was conducted in NaH-DMF system at room temperature for 3 hr (Eq. 2).



(eq. 2)

1 2

The alkylation reaction occurs rather fast and **1** disappears during 0.5~2 hr. The alkylation of **1** proceeds smoothly with primary halides such as methyl iodide, ethyl iodide, ethyl bromide, *n*-propyl iodide, allyl bromide, and benzyl bromide (run 1~4, 6, and 7) to give in 70~98% yields. Also secondary alkyl halide, *iso*-propyl iodide, gave

Table 1. Alkylation of 2-phenyl-1,4-dihydro-4-oxoquinoline[a]

Run	RX	Time (hr)	Product (R)	Isolated yield (%)
1	MeI	1	CH_3-	70
2	EtI	1	CH_3CH_2-	90
3	EtBr	2	CH_3CH_2-	80
4	*n*-PrI	1.5	$CH_3CH_2CH_2$-	88
5	*iso*-PrI	1.5	$(CH_3)_2CH_2$-	62
6	AllylBr	0.5	CH_3=CH-CH_1-	>98
7	BenzylBr	1	$C_6H_5CH_2$-	>98
8	*tert*-BuBr	2	$(CH_3)_3C$-	trace

[a]2-phenyl-1,4-dihydro-4-oxoquinoline (0.221 g, 1 mmol), NaH (0.025 g, 1.1 mmol), DMF 5 mℓ.

Table 2. Characterization of 1-alkyl-2-phenyl-1,4-dihydro-4-oxoquinoline

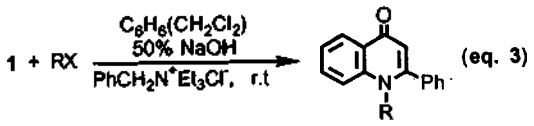
Run	R	mp.	Mass spectra
1	Me	60~62℃	235(M^+), 234, 220, 207, 206, 77, 76
2	Et	96~97℃	249(M^+), 234, 220, 206, 165, 77, 76
3	*n*-Pr	81~82℃	263(M^+), 248, 234, 220, 165, 77, 76, 43
4	*iso*-Pr	94~95℃	263(M^+), 221, 220, 165, 77, 76, 43
5	Allyl	75~76℃	261(M^+), 260, 247, 246, 165, 77, 76, 41
6	Benzyl	107~108℃	311(M^+), 220, 192, 191, 77, 76

Run	Elemental analyses (%) C	H	N	^{1}H NMR (δ, CCl_4)
1	81.70 (81.75)	5.53 (5.52)	5.96 (5.58)	4.17(s, 3H), 7.20(s, 1H), 7.42~8.25(m, 9H)
2	81.93 (81.94)	6.02 (6.02)	5.62 (5.48)	1.61~1.68(t, 3H), 4.30~4.43(t), 7.19(s, 1H), 48~8.26(m, 9H)
3	82.13 (82.20)	6.46 (6.52)	5.32 (5.32)	1.11~1.18(t, 3H), 1.90~2.08(m, 2H), 4.18~4.24(t, 2H), 7.14(s, 1H), 7.40~8.24(m, 9H)
4	82.13 (81.59)	6.46 (6.54)	5.32 (5.08)	1.50(d, 6H), 4.87~4.96(m, 1H), 7.14(s, 1H), 7.45~8.23(m, 9H)
5	82.76 (82.20)	5.75 (5.71)	5.36 (5.02)	4.89(d, 2H), 5.42~.565(d. 2H), 6.16~6.30(m, 1H), 7.21(1H), 7.41~8.31(m, 9H)
6	84.89 (84.15)	5.47 (5.14)	4.50 (4.38)	5.42(s, 2H), 7.29(s, 1H), 7.44~8.34(m, 14H)

( ): analytical value.

in 62% yield (run 5), while the reaction with tertiary alkyl halide, *tert*-butyl bromide, gave the unsatisfied result (run 8).

We also invesgated alkylation reaction of **1** with benzyl-, allyl- and ethyl bromide using phase transfer catalyst. However, the yields of *N*-alkyl derivatives were too low. This is clue to a very slow solubility of 1 in C_6H_6 and CH_2Cl_2 (Eq. 3).



(eq. 3)

R : benzyl(18%)
: allyl(20%)
: ethyl(10%)

The following general procedure was used; To the DMF (5 m*l*) solution of sodium hydride (0.046 g of the 55% oil suspension which was washed with hexane three times: 1.1 mmol) 2-phenyl-4-quinolone **1** (0.221 g, 1 mmol) was added. To the resulting mixture the 1.3 mmol of alkyl halide was added and stirred at room temperature under nitrogen atmosphere. The reaction mixture was poured into cold water. The extraction with ether and subsequent work up of the extract gave almost pure **2**. Further purification was performed by preparative TLC using silica gel (eluant: $CHCl_3$/MeOH=20/1).

Table 2 shows chemical and physical data of 1-substituted 2-phenyl-1,4-dihydro-4-oxoquinolines. These values were well same with known quinolones.

ACKNOWLEDGEMENT

This work was supported by the Organic Chemistry Research Center-the Korea Science & Engineering Foundation and by the Basic Science Research Institute Program, Ministry of Education of Korea (BSRI-94-3408).

REFERENCES

1. (a) Lesher, G. Y.; Froelich, E. J.; Gruett, M. D.; Bailey, J. H.; Brundage, R. P. *J. Med. Chem.* **1962**, *5*, 1063. (b) Aimi, A.; Nishimura, M.; Miwa, A.; Hoshino, H.; Sakai, S.; Haginiwa, J. *ibid.* **1990**, *31*, 5169.
2. (a) Torii, S.; Okumoto, H.; Xu, L. H. *Tetrahedron Lett.* **1991**, *33*, 237. (b) Kalinin, V. N.; Shostakovsky, M. V.; Ponomay, A. B. *Tetrahedron Lett.* **1992**, *33*, 373.
3. Albrecht, R. *Prog. Drug. Res.* **1977**, *21*, 9.
4. All compounds were fully characterized by ^{1}H-NMR, IR and mass-spectra of products are given in *Table* 2.