ELECTROPHILIC REACTION OF QUINOLINE 1-OXIDE THROUGH BASE-INDUCED DEPROTONATION

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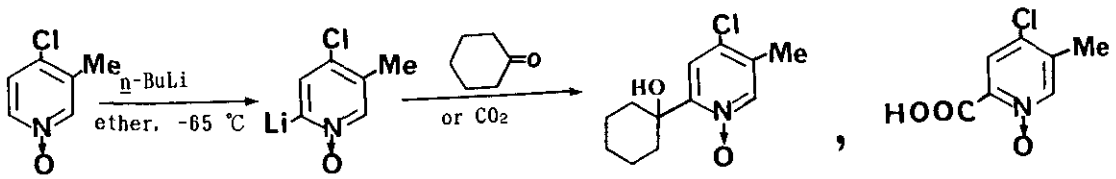
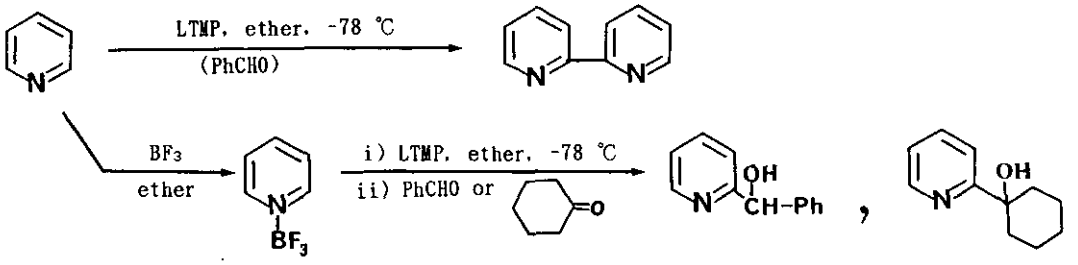
Abstract Lithiation of quinoline 1-oxide-BF_3 complex (3) with LTMP and TMEDA in ether at -78℃ followed by treatment with benzaldehyde or cyclohexanone affords the corresponding 2-substituted derivatives (4, 5 or 6), while the reaction of quinoline 1-oxide (1) itself under the same conditions results in the formation of 2,2'-biquinoline 1-oxide (2).

Since 1967, Abramovitch and co-workers have developed the alkylation and acylation of pyridine 1-oxides which involve base-induced α-proton abstraction followed by treatment with an appropriate electrophile as exemplified below.[1]



Recently, Ohta et al. applied this reaction to some 2,5-disubstituted pyrazine 1-oxides and disclosed that the reaction proceeded most effectively in tetrahydrofuran at -78℃ in the presence of lithium 2,2,6,6-tetramethylpiperidide (LTMP) and N,N,N',N'-tetramethylethylenediamine (TMEDA) to give the corresponding 6-substitution products.[2]

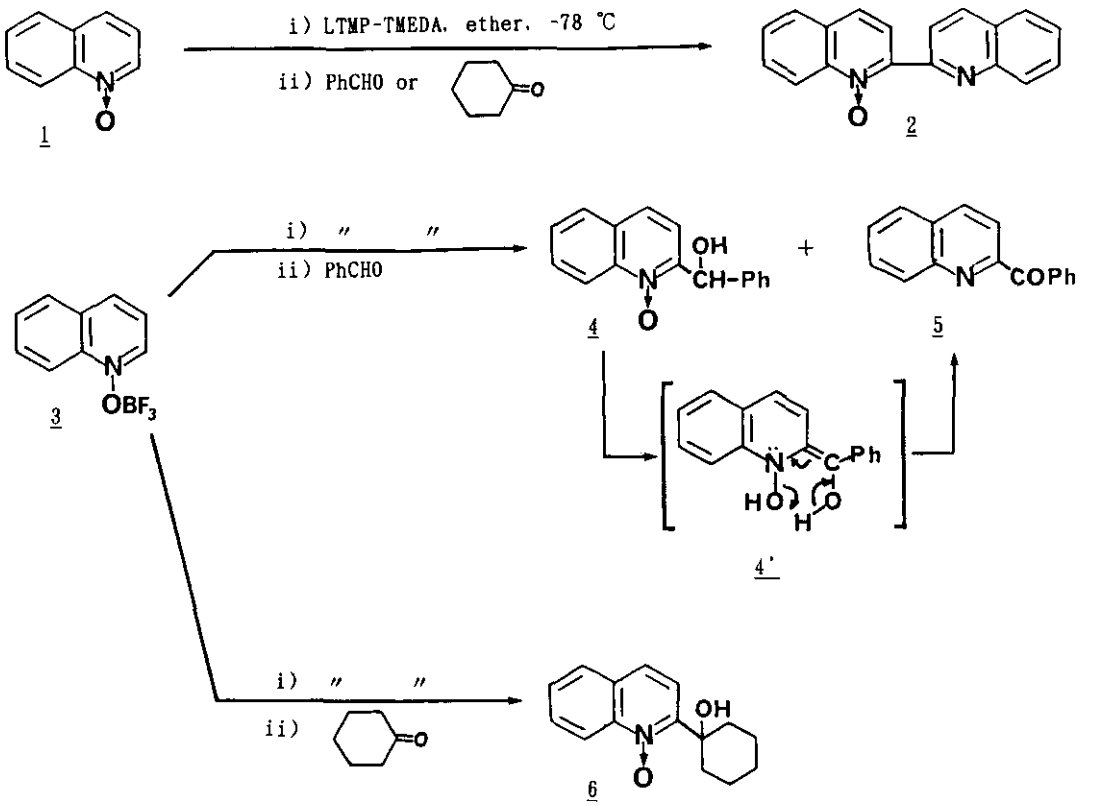
On the other hand, Kessar and others reported that treatment of pyridine-boron trifluoride (BF_3) complex with LTMP in ether at -78℃ followed by adding benzaldehyde or cyclohexanone gave the corresponding 2-pyridinemethanol derivatives, while only 2,2'-bipyridine was formed in the reaction of pyridine itself.[3]



However, no comparable studies are reported on the quinoline 1-oxide series. This communication deals with some of our observations obtained from the preliminary examination of the electrophilic substitution of quinoline 1-oxide through base-induced deprotonation.

The reaction of quinoline 1-oxide (1) with benzaldehyde was first attempted using LTMP and TMEDA as the deprotonating agent. When 1 was sucessively treated with LTMP-TMEDA (1.2 equiv.) for 1.5 h and benzaldehyde (1.2 equiv.) for 2 h in ether at -78℃, then the reaction mixture was allowed to reach room temperature (overnight), 2,2'-biquinoline 1-oxide[4] (2) was isolated as a sole product in 70% yield without participation of benzaldehyde. Subsequently we tried the reaction of quinoline 1-oxide-BF_3 complex[5] (3) under the same conditions and obtained 2-(α-hydroxybenzyl)quinoline 1-oxide[6] (4) and 2-benzoylquinoline[7] (5) in 12 and 22% yields, respectively. The formation of 5 may be rationalized by the course[8] via the anhydro base (4') from 4.

The reaction using cyclohexanone as an electrophile also followed the same pattern. The reaction of 1 gave only 2, and 2-(1-hydroxycyclohexyl)quinoline 1-oxide[9] (6) was formed in the reaction of 3 though in a small yield of 11%. These results are quite unexpected ones, demonstrating that quinoline 1-oxide behaves in the same manner as pyridine in the electrophilic substitution through deprotonation. Although detailed examination of the reaction conditions, such as the reaction temperature, time and the natures of base, solvent and electrophile, was not carried out, it seems likely that this type of reaction would proceed much more difficultly in the quinoline 1-oxide series as compared with pyridine 1-oxide series. But it was found that derivation of 1 to its BF_3 complex (3) apparently facilitates this type of electrophilic substitution.



Further work is in progress to make clear the essential features of this electrophilic reaction and extend its scope by using appropriate adducts of N-oxide such as BF_3 complex and acyl adducts.

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6. Compound 4 : mp 151-152 ℃, Anal. Calcd for $C_{15}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.62; H, 5.15; N, 5.64. ^{1}H-Nmr($CDCl_3$)δ : 5.80(1H, br s, OH), 6.32(1H, s, H-C-OH), 7.12(1H, d, J=8.3Hz, Ar-H), 7.30-7.40(3H, m, Ar-H), 7.51-7.54(2H, m, Ar-H), 7.61-7.65(2H, m, Ar-H), 7.75-7.82(2H, m, Ar-H), 8.73(1H, d, J=8.8Hz, Ar-H). ^{13}C-Nmr($CDCl_3$)δ : 72.70(d, H-C-OH), 119.38(d, Ar), 120.51(d, Ar), 126.80(d, Ar), 126.97(d, Ar), 128.04(d, Ar), 128.18(d, Ar), 128.58(d, Ar), 128.61(d, Ar), 129.35(s, Ar), 130.90(d, Ar), 139.33(s, Ar), 141.32(s, Ar), 149.36(s, Ar).

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9. Compound 6: mp 135-136 ℃, Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.06; H, 7.18; N, 5.83. ^{1}H-Nmr($CDCl_3$)δ : 1.26-1.37(1H, m, cyclohexyl-H) , 1.62-1.81(5H, m, cyclohexyl-H) , 1.96-2.07(2H, m, cyclohexyl-H) , 2.42(2H, d, J=12Hz, cyclohexyl-H) , 7.47(1H, d, J=9.3Hz, Ar-H), 7.62-7.66(1H, m, Ar-H), 7.77-7.86(3H, m, Ar-H), 8.76(1H, d, J=8.8Hz, Ar-H). ^{13}C-Nmr($CDCl_3$)δ : 21.36(t, cyclohexyl-C) , 25.93(t, cyclohexyl-C) , 34.55(t, cyclohexyl-C) , 73.19(s, -C-OH), 118.63(d, Ar), 119.53(d, Ar), 127.53(d, Ar), 127.84(d, Ar), 128.39(d, Ar), 129.06(s, Ar), 131.01(d, Ar), 141.86(s, Ar), 152.20(s, Ar).

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