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SYNTHESIS OF 2- AND 4-BROMOQUINOLINES WITH A NEW BROMINATING REAGENT, PBr_3-DMF

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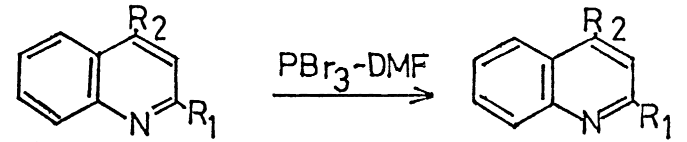
A congener of 2- and 4-bromoquinolines was synthesized in good yields from the corresponding methoxyquinolines using a new brominating reagent, PBr_3-DMF, under the quite mild conditions. The new reagent seems to be useful in organic synthesis, especially in bromination of the complex molecules.

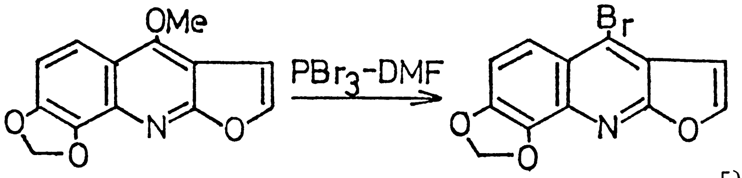
We wish to report here a facile synthesis of 2- and 4-bromoquinolines from the corresponding methoxyquinolines using a new bromination reagent, PBr_3-DMF (N,N-dimethylformamide). The new reagent readily replaces under moderate conditions the methoxyl groups attached at 2- and 4-positions of quinoline ring with bromine atoms. By this method, bromoquinolines and their congeners are synthesized in good yields as shown in Table 1. Hitherto, 2- and 4-bromoquinolines have been synthesized$^{1)}$ from the corresponding quinolones with a wide variety of brominating reagents such as phosphorous tribromide, phosphorous pentabromide, or phosphorous oxybromide. Although these bromination reagents have considerable synthetic value, they suffer some disadvantages. For example, the reaction mixture was usually heated under refluxing of the brominating reagent for the completion of the reaction, and liberates HBr, by which the reaction solution becomes strongly acidic. Because of these disadvantages, they are difficultly applicable to the compounds susceptible to heat or acid. Our new synthetic method used 2- and 4-methoxyquinolines as starting materials and the complex of phosphorous tribromide with DMF as a brominating reagent. The reaction proceeded smoothly at the moderate temperature of 60-80°C, and no evolution of HBr was observed during the reaction. Thus, the bromination condition was quite mild. The new reagent seems to be useful in organic synthesis, especially in bromination of complex molecules. The structure of the reagent is not clear, but it may be an iminium salt, speculated from the proposed structure of the Vilsmeier reagent and its analogous adducts.$^{2)}$

A typical procedure was as follows:

Fifty milligrams of 2-methoxy-4-methylquinoline <u>3</u> was dissolved in dry DMF (1.0 ml). To the stirred solution, phosphorous tribromide (0.10 ml) was added at 0°C. The reaction proceeded exothermic and the resulting mixture was solidified partially at room temperature. The sludgy reaction mixture$^{3)}$ was stirred under protection of moisture at 60°C for 90 minutes and then 80°C for 60 minutes. The reaction product was poured onto a mixture of crushed ice (10 g) and 1N sodium hydroxide (50 ml). The aqueous mixture was extracted with three 50 ml portions of ether. The organic layer was washed twice with 50 ml portions of brine. After drying (anhyd. Na_2SO_4) and evaporating the solvent, the residual yellow solid mass gave on recrystallization (CH_2Cl_2-MeOH) 2-brmo-4-methylquinoline <u>10</u>, 58.4 mg (mp 197-198°C).

Table 1. Bromination of 2- and 4-Methoxyquinolines



				Isolated Yields(%)	Reaction Condition
R_1=OMe, R_2=H	1	R_1=Br, R_2=H	8	78	a)
R_1=H, R_2=OMe	2	R_1=H, R_2=Br	9	68	a)
R_1=OMe, R_2=Me	3	R_1=Br, R_2=Me	10	76	a)
R_1=R_2=OMe	4	R_1=R_2=Br	11	44	a)
R_1=Cl, R_2=OMe	5	R_1=R_2=Br	11	$77^{4)}$	a)
R_1=OMe, R_2=Cl	6	R_1=R_2=Br	11	87	a)
R_1=OMe, R_2=Cl	6	R_1=Br, R_2=Cl	12	16	b)
 Kokusagine	7		$13^{5)}$	90	a)

a) The typical procedure described above.

b) To the stirred solution of 6 (34 mg) in dry DMF (1 ml), phosphorous tribromide (0.025 ml) was introduced at 0°C and the reaction mixture was stirred at 60°C for 5 hours. After the usual work up, the crude product (15 mg) was purified by TLC on silica-gel giving 7 mg of 12, mp 85.5-86°C (from aq. MeOH), PMR δ 7.4-8.2(5H,m), MS (m/e) 245(M^++4), 243(M^++2), 241(M^+), 208(M^++2-Cl), 206(M^+-Cl), 164(M^++2-Br), 162(M^+-Br), 127(M^+-Cl-Br), 126.

References and Notes

(1) Leo A. Paquette, "Principles of Modern Heterocyclic Chemistry," W.A.Benjamin, Inc., New York, Amsterdam, 1968, p. 252, and its references cited therein.

(2) R.R. Koganty, M.B. Shambhu, and G.A. Digenis, Tetrahedron Letters, 4511 (1973).

(3) If desired, an addition of one more milliliter of dry DMF is recommended for efficient stirring.

(4) 2-Chloro-4-methoxyquinoline 5 gave, under the milder condition (50°C, 90 minutes) than the typical procedure, 2-bromo-4-methoxyquinoline 14 (27%) with unreacted 5, based on the analysis with GC-MS. Under the condition at 60°C for 150 minutes, the yield of 14 increased to 52%. 14; MS (m/e) 239(M^++2), 237(M^+), 158(M^+-Br), 143(M^+-Br-Me), 113. It is interesting that bromine substitution at the 2-position of quinoline ring took place in preference to the 4-position occupied by a methoxyl group.

(5) Mp 197-198°C (from CH_2Cl_2-MeOH), PMR δ 6.48(2H,s), 7.07(1H,d,J=2.8Hz), 7.50(1H,d,J=9.5Hz), 7.99(1H,d,J=2.8Hz), 8.05(1H,d,J=9.5Hz), MS (m/e) 293(M^++2), 291(M^+), UV λ_{max}^{EtOH} nm (ε) 213(22,200), 264(67,900), 287(sh.), 325(sh.), 375(4,000).

* PMR spectra were recorded on a JEOL MH-100 spectrometer at 100 MHz in $CDCl_3$, using TMS as an internal standard.

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