

THE REACTION OF QUINAZOLINE WITH AROMATIC COMPOUNDS
IN DILUTE SULFURIC ACID

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The reaction of quinazoline with aromatic compounds substituted by electron donating groups such as aniline, N-methyl-, N,N-dimethyl-aniline, phenol, anisole, and indole in dilute sulfuric acid was carried out. Thus, the corresponding 4-aryl-3,4-dihydroquinazoline (IIa - IIc) was obtained.

Some of the compounds (II) were converted into 4-aryl-quinazoline (IV) by the oxidation with potassium ferricyanide.

It has been reported by Albert et al. that water added across the N₃-C₄ bond of quinazoline (I) in dilute hydrochloric acid to form 3,4-dihydro-4-hydroxyquinazolinium cation.¹⁾ This fact might be owing to the increased nucleophilic reactivity of the 4-position of I caused by the formation of quinazolinium cation.

Because a similar reaction on I was expected to take place, we carried out the reaction of I with some aromatic compounds substituted by electron donating groups in dilute sulfuric acid, and

found that 4-aryl-3,4-dihydroquinazoline (II) was formed by the nucleophilic addition of aromatic rings across the N_3-C_4 bond of I.

Aromatic compounds (III) used in this reaction were as follows; aniline (IIIa), N-methyl- (IIIb), N,N-dimethyl-aniline (IIIc), phenol (IIId), anisole (IIIe), indole (IIIf), and 2-methylfuran (IIIg). Molar ratio of I to III was set at 1 : 1.1. A suitable reaction time for each was shown in Table 1, and the reaction was carried out at room temperature.

When a mixture of I and III in 2N sulfuric acid was allowed to stand at room temperature, 4-aryl-3,4-dihydroquinazoline (IIa - IIIf) was formed with varying yields.

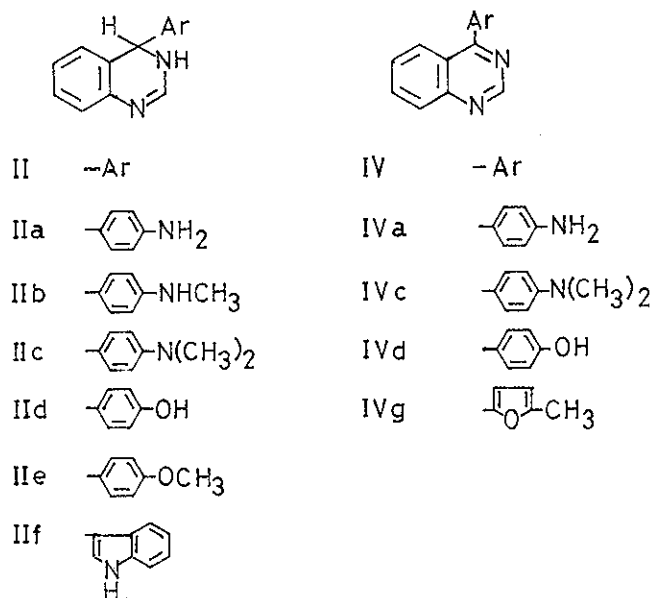


Chart 1

While a mixture of I and IIIg in 2N sulfuric acid / methanol

being allowed to stand for 30 days gave 4-(5-methyl-2-furyl)-quinazoline (IVg) in low yield, which was probably formed through an oxidation of 4-(5-methyl-2-furyl)-3,4-dihydroquinazoline (IIg) formed in the first step of the reaction.

Table 1. Reaction of I with III in Dilute Sulfuric Acid

Starting material		Reaction time (hr)	Product		
I	III		II	Yield (%)	mp (°C)
I	IIIa ^{a)}	48	IIa	quant.	217
I	IIIb ^{a)}	48	IIb	quant.	170
I	IIIc ^{a)}	48	IIc	quant.	184 - 185
I	IIId ^{b)}	12	IId	34.7	238
I	IIIe ^{b)}	30 days	IIe	38.9	141 - 142
I	IIIf ^{a)}	12	IIf	66.7	181 - 182
I	IIIg ^{b)}	30 days	IVg	2.5	74 - 75

The structures of II were indicated by their elemental analyses, and assigned on the bases of infrared (IR) and nuclear magnetic resonance (NMR) spectra as shown in Table 2. Moreover, the compound IIc was also prepared by the alkaline hydrolysis of 3-acetyl-4-[4-(N,N-dimethylaminophenyl)]-3,4-dihydroquinazoline (IIh), mp 188 - 189°, which was synthesized from the reaction between I and IIIc in acetic anhydride. The compound (IIe) was also prepared by the

a) : in 2N H₂SO₄ b) : in 2N H₂SO₄ / MeOH

Table 2. IR and NMR Spectra of II and IV

Compd.	IR ν_{max} KBr cm^{-1} -NH, -NH ₂ or -OH	NMR δ (ppm)			
		4-H ^s	-NH, -NH ₂ or -OH ^{bs}	Aromatic H ^m	Other H
IIa ^{a)}	3450, 3380, 3280, 3150	5.48	4.5 (3 x H)	6.5-7.3 (9 x H)	
IIb ^{a)}	3200, 3030	5.51	6.0 (2 x H)	6.4-7.2 (9 x H)	2.69 ^s (-NCH ₃)
IIc ^{a)}	3180	5.50	4.1 (1 x H)	6.5-7.1 (9 x H)	2.81 ^s (-N(CH ₃) ₂)
IId ^{a)}	3520, 3430	5.56	4.1 (2 x H)	6.6-7.2 (9 x H)	
IIe ^{b)}	3180	5.55	5.4 (1 x H)	6.4-7.4 (9 x H)	3.69 ^s (-OCH ₃)
IIIf ^{a)}	3400	5.92	5.7 (2 x H)	6.5-7.6 (10 x H)	
IVa ^{b)}	3400, 3310 3190		3.8 (2 x H)	6.5-7.8 (8 x H)	8.90 ^s (2-H)
IVc ^{b)}				7.1-8.3 (4 x H)	3.00 ^s (-N(CH ₃) ₂), 6.78 ^d , 7.70 ^d (2,3- 5,6-H, J: 8.5 Hz), 9.12 ^s (2-H)
IVd ^{c)}				7.9-8.2 (4 x H)	6.92 ^d , 7.60 ^d (2,3- 5,6-H, J: 8.4 Hz), 9.07 ^s (2-H)
IVg ^{b)}				7.1-8.3 (4 x H)	2.54 ^s (-CH ₃), 6.29 ^d , 7.45 ^d (3,4- H, J: 3.6 Hz), 9.25 ^s (2-H)

a): NMR in (CD₃)₂SO b): NMR in CDCl₃ c): NMR in CD₃OD

Grignard reaction of I with p-methoxyphenylmagnesium iodide.

Furthermore some of the compounds (II) so obtained, such as IIa, IIc, and IId, were converted into the corresponding 4-aryl-quinazoline (IVa, IVc, and IVd) by the oxidation with potassium ferricyanide in alkaline medium, although the yield was very low as shown in Table 3. And their IR and NMR spectra were in Table 2.

Table 3. Oxidation of II with Potassium Ferricyanide

Starting material II	Product		
	IV	Yield (%)	mp (°C)
IIa	IVa	20.4	189
IIc	IVc	12.9	110 - 112
IId	IVd	16.5	180 - 181

The reaction mentioned above provides one of the facile methods for the synthesis of 4-aryl-3,4-dihydroquinazoline (II) under the mild condition and by the simple procedure.

Although the formation of 4-aryl-3,4-dihydroquinazoline was found in the reaction of I with other aromatic compounds such as o-toluidine, o-anisidine, o-chloroaniline, o-phenylenediamine, o-, m-, and p-cresol, the detailed studies are now in progress.

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