PREPARATION OF 1,4-DIPHENYL-3-SUBSTITUTED ISOQUINOLINES

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Abstract —— The reaction of o-dibenzoylbenzene (1) with benzylamine (2a), m-(2b) and p-xylylendiamine (2c), n-butylamine (2d), ethylglycinate (2f) and aminoacetonitrile (2g) in the presence of basic catalysts afforded the corresponding 3-substituted 1,4-diphenylisoquinolines (3a-d,f,g, and i), while the reaction of 1 with ethanolamine (2e) gave a trace amount of 3-hydroxymethylisoquinoline (3e) and 1,3-diphenylisobenzofuran (4) in 25% yield.

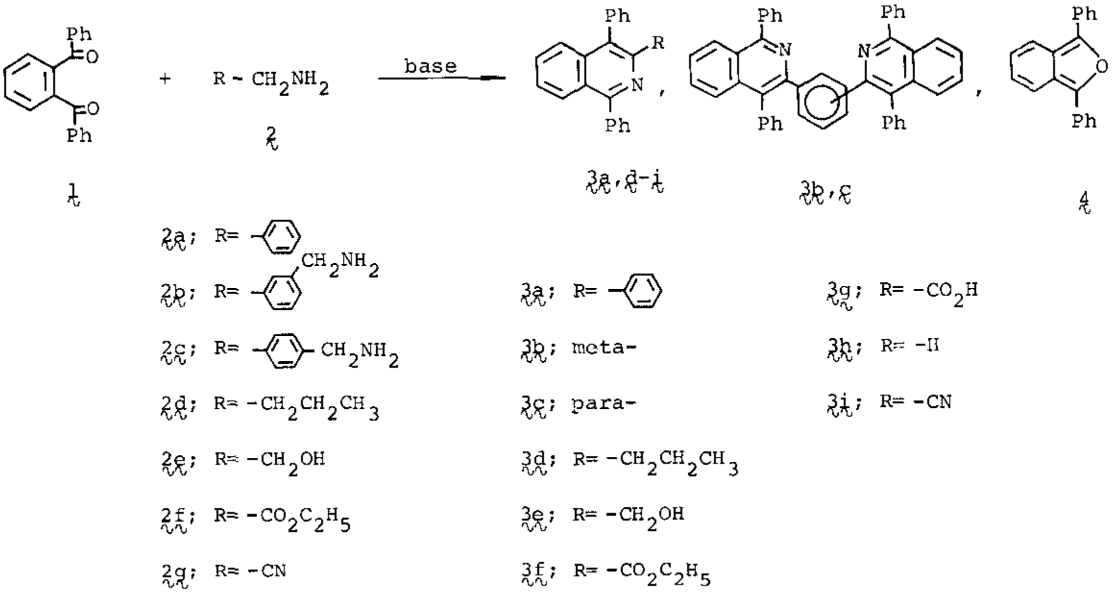
It has been previously reported[1)] that the reaction of 3,4-diaroyl-1,2,5-thia(oxa)diazoles with primary amines in the presence of 1,8-diazabicyclo[5.4.0]undecene (DBU) gave the corresponding 1,2,5-thia(oxa)diazolo[3,4-c]pyridines.

For the purpose of developing a new preparative method of isoquinolines, we investigated the reaction of o-dibenzoylbenzene(1)[2)] with a variety of primary amines (2a-g) in the presence of basic catalysts and the results are summarized in Table 1. The structures of the products were determined by their elemental analysis and spectral data, as well as some chemical conversions.

It took 24 hr for the reaction of 1 with 2a in refluxing toluene in the presence of DBU, while the reaction was completed in one hour in 10 mole % ethanolic potassium hydroxide solution and the expected 1,3,4-triphenylisoquinoline (3a)[3)] was easily isolated in an excellent yield by pouring the reaction mixture into a large amount of water.

Bis-isoquinolinobenzenes, 3b and 3c, were similarly prepared in good yields, respectively.

The reaction of 1 with 2d did not proceed under the influence of DBU and KOH.

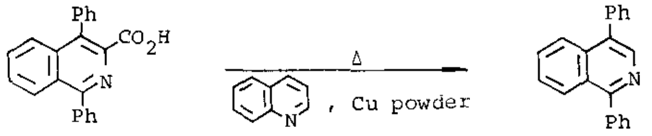


Scheme 1

It was needed a strong base such as t-BuOK in t-BuOH and a long reaction time to complete the reaction of 1 with 2d and 3-n-propyl-1,4-diphenylisoquinoline (3d) was obtained in 59% yield.

Only a trace amount of 3-hydroxymethyl-1,4-diphenylisoquinoline (3e) was isolated in the reaction with 2e and, interestingly, diphenylisobenzofuran (4)$^{4)}$ was obtained in 25% yield. The pathway of the formation of 4 will be briefly mentioned later.

When the reaction of 1 with 2f was carried out in the presence of DBU, the corresponding isoquinolinecarboxylate (3f) was obtained in 61% yield, while the reaction in 10 mole % ethanolic potassium hydroxide solution afforded the isoquinolinecarboxylic acid (3g), the hydrolyzed product of 3f, in 75% yield. The compound 3g was decarboxylated into 1,4-diphenylisoquinoline (3h)$^{3)}$ in 61% yield when heated at 230° for 3 hr in quinoline with copper powder. The reaction of 1 with 2g in t-BuOH in the presence of DBU gave 3-cyano-1,4-diphenylisoquinoline (3i) in a poor yield



3g

3h

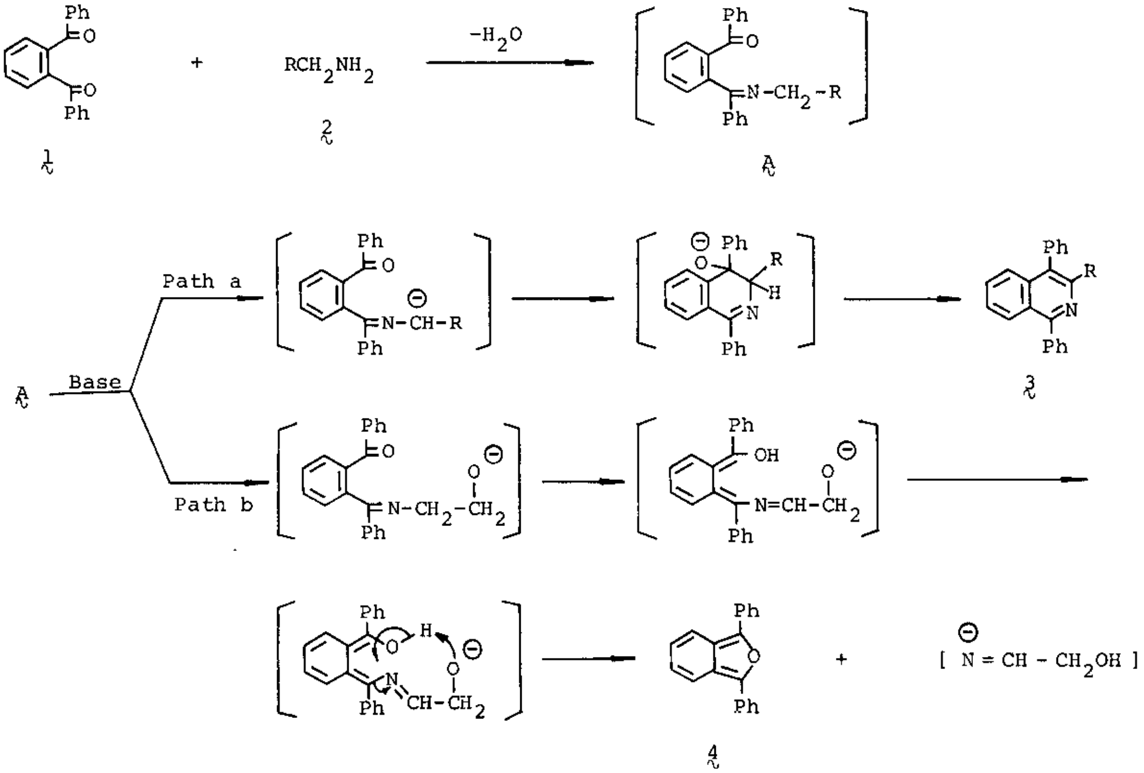
(18%) because of the instability of free aminoacetonitrile. Hydrolysis of **3i** in 50% sulfuric acid afforded **3g** in 91% yield.

The pathways of the formation of **3** and **4** are now tentatively considered as shown in Scheme 2; the reaction of **1** with **2** might afford the Schiff base **A** and isoquinolines (**3**) were supposed to be formed via a base-catalyzed condensation (pathway a), while the presence of hydroxy group in **2e** might cause the formation of **4** via the pathway b.

The reactions of other 1,2-dicarbonyl aromatics with primary amines are now in progress.

Table 1. The reaction of o-dibenzoylbenzene (**1**) with primary amines (**2a**-**g**).

Run	**2**	molar ratio **1** : **2**	Base	Solvent	Reaction time (hr)	Product (yield %)
1	**2a**	1 : 1.5	DBU	toluene	24	**2a** (96)
2	**2a**	1 : 0.75	KOH	ethanol	1	**2a** (91)
3	**2b**	1 : 0.75	DBU	toluene	24	**3b** (74)
4	**2b**	1 : 0.75	KOH	ethanol	1	**3b** (79)
5	**2c**	1 : 0.75	DBU	toluene	24	**3c** (72)
6	**2c**	1 : 10	KOH	ethanol	1	**3c** (95)
7	**2d**	1 : 10	t-BuOK	t-BuOH	72	**3d** (59)
8	**2d**	1 : 10	KOH	ethanol	48	——
9	**2d**	1 : 10	DBU	toluene	48	——
10	**2e**	1 : 10	t-BuOK	t-BuOH	48	**3e** (+), **4** (25), **1** (5)
11	**2e**	1 : 10	KOH	ethanol	48	**3e** (+), **4** (25), **1** (6)
12	**2f**	1 : 10	DBU	toluene	24	**3f** (61), **1** (7)
13	**2f**	1 : 10	KOH	ethanol	24	**3g** (81)
14	**2g**	1 : 10	DBU	n-BuOH	24	**3i** (14)



Scheme 2

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2) The compound 1 was easily obtained by the $Na_2Cr_2O_7$-AcOH oxidation of o-dibenzylbenzene.

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