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SYNTHESIS OF 2,2'-BIQUINOLINES FROM *o*-ISOCYANOSTYRENES

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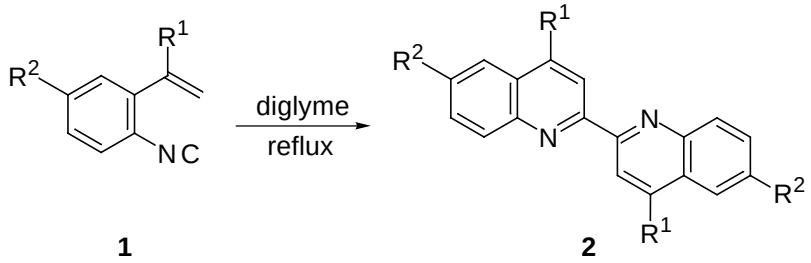
Abstract- The heating of *o*-isocyanostyrenes (**1**) in diglyme at reflux temperature for 2 h afforded the corresponding 2,2'-biquinolines (**2**) *via* a coupling/electrocyclic reaction in fair-to-good yields.

Extensive studies on the synthesis utilizing metal complexes having a 2,2'-biquinoline ligand as a catalyst have recently been reported.[1] A number of elegant methods have been reported to prepare this class of compounds.[2] However, little is known about the simple general synthesis of substituted 2,2'-biquinolines. Recent work in our laboratory demonstrated that *o*-isocyanostyrenes were oxidized with *m*CPBA to *o*-isocyanatostyrenes, which underwent electrocyclic reaction to give quinolin-2(1*H*)-ones in good yields.[3] We have found that 4,4'-disubstituted 2,2'-biquinolines (**2**) can be obtained simply by heating *o*-isocyanostyrenes (**1**) in diglyme at reflux temperature.

The starting isocyanides (**1**) were prepared as follows. Treatment of *o*-aminostyrenes, which were commercially available or readily prepared using the procedure by Smith and Livinghouse[4] or Bell *et al.*,[5] with formic acid in refluxing toluene gave the corresponding formamide, which were then dehydrated with phosphorous oxychloride in the presence of triethylamine in THF to give **1** in high overall yields. While these isocyanides appeared to be somewhat unstable, most of them could be purified by column chromatography on silica gel and storable for prolonged periods at refrigerator temperature.

The transformation of **1** into 2,2'-biquinolines (**2**) was carried out as outlined in Scheme 1. The results are given in the Table, which indicates that the yields of the products are fair-to-good. The progress of the reactions could be readily monitored by IR spectral measurement. The characteristic absorption band of isocyanide group (ν *ca.* 2120 cm^{-1}) disappeared during about 2 h heating. The reactions also proceeded smoothly in other solvents, such as *p*-cymene, mesitylene, or xylene, but did not proceed to any appreciable extent in refluxing toluene. For example, the reaction of **1d** in refluxing toluene gave only 30 %



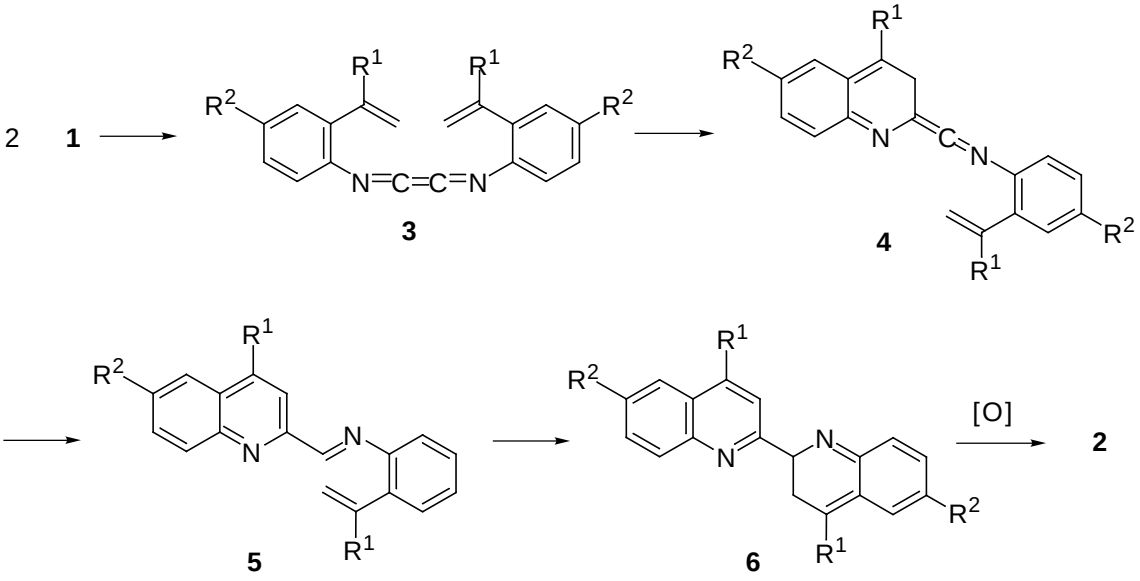
1 **2**

Scheme 1.

Table. Preparation of 4,4'-disubstituted 2,2'-biquinolines **2**

Entry	Starting isocyanide **1**	Product **2** (Yield/%)[a]
1	**1a** (R^1 = Ph, R^2 = H)	**2a** (66)
2	**1b** (R^1 = *o*-Tol, R^2 = H)	**2b** (68)
3	**1c** (R^1 = 4-$MeOC_6H_4$, R^2 = H)	**2c** (52)
4	**1d** (R^1 = Me, R^2 = H)	**2d** (75)
5	**1e** (R^1 = Ph, R^2 = Cl)	**2e** (62)

[a] Yields are based on **1** and isolated products after recrystallization.



Scheme 2.

yield of the desired product (**2d**) after 12 h heating.

The following procedure is typical for the preparation of 4,4'-disubstituted 2,2'-biquinolines (**2**). A solution of 1-isocyano-2-(1-phenylethenyl)benzene (**1a**) (0.39 g, 1.9 mmol) in diglyme (19 mL) was heated at

reflux temperature for 2 h, when the IR spectral analysis of the mixture did not reveal presence of any isocyano compounds. The resulting mixture was allowed to cool to room temperature to give yellow precipitate, which was collected by filtration. The solid was recrystallized from chloroform to give pure **2a** (0.26 g, 66%): mp 371 ˚C (lit.,[6] 362 ˚C).[7]

Although we have no evidence for the intermediaries of the present reaction, a possible pathway leading to the formation of biquinolines (**2**) from isocyanides (**1**) may be illustrated in Scheme 2. Coupling of two isocyanides on their isocyano carbon gives the dimeric intermediate (**3**).[8] This then undergoes electrocyclization[9] to give the keteneimine intermediate (**4**). Isomerization of **4** to form a quinoline ring, giving the intermediate (**5**), is followed by the second electrocyclic reaction to yield the dihydrobiquinoline derivative (**6**), which is oxidized with oxygen probably contaminated in the reaction mixture to lead to the biquinoline product (**2**).

As a limitation of the present reaction, it should be noted that similar heating of 1-isocyano-2-[(*E*)-2-phenyl-1-methylethenyl]benzene gave an intractable mixture of products, from which only a trace amount of the expected biquinoline derivative was detected. This result indicates that 3,3'-disubstituted 2,2'-biquinolines cannot be obtained under the present conditions. This may be due to the strained hindrance of the transition state of electrocyclic intermediate such as **3** and/or **5**.

In summary, we have shown that the reaction described here offers a convenient method for the preparation of 4,4'-disubstituted 2,2'-biquinolines. The method is not only of simple manipulations, but also efficient because of the ready availability of the starting materials. A study on the synthesis of heterocycle-fused 2, 2'-bipyridine derivatives is currently under way in our laboratory.

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7. **2b:** mp 322 ˚C ($CHCl_3$); IR (KBr disk) 1604, 1588, 758 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.12 (6H, s), 7.3–7.55 (12H, m), 7.71 (2H, ddd, *J* = 8.2, 6.6, 1.6 Hz), 8.22 (2H, d, *J* = 8.2 Hz), 8.81 (2H, s); MS *m/z* 436 (M^+, 64), 435 (100). Anal. Calcd for $C_{32}H_{24}N_2$: C, 88.04; H, 5.54; N, 6.42. Found: C, 87.94; H, 5.42; N, 6.21. **2c:** mp 324–325 ˚C ($CHCl_3$); IR (KBr disk) 1608, 1590, 1248 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.94 (6H, s), 7.11 (4H, d, *J* = 8.6 Hz),7.52 (2H, t, *J* = 8.2 Hz), 7.60 (4H, d, *J* = 8.6 Hz), 7.74 (2H, t, *J* = 8.2 Hz), 8.01 (2H, d, *J* = 8.2 Hz), 8.26 (2H, d, *J* = 8.2 Hz), 8.81 (2H, s); MS *m/z* 468 (M^+, 100). Anal. Calcd for $C_{32}H_{24}N_2O_2$: C, 82.03; H, 5.16; N, 5.98. Found: C, 82.02; H, 5.16; N, 6.00. **2d:** mp 289 ˚C ($CHCl_3$) (lit.,[10] 285–287 ˚C). **2e:** mp 385–386 ˚C ($CHCl_3$); IR (KBr disk) 1604, 1588, 699 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.55–7.7 (12H, m), 7.92 (2H, d, *J* = 2.3 Hz), 8.17 (2H, d, *J* = 8.9 Hz), 8.82 (2H, s); MS *m/z* 476 (M^+, 37), 475 (49), 203 (100). Anal. Calcd for $C_{30}H_{18}Cl_2N_2$: C, 75.48; H, 3.80; N, 5.87. Found: C, 75.49; H, 3.83; N, 5.85.

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