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# Synthesis of *n,n'*-biquinolines by a coupling reaction of bromoquinolines using organonickel(0) complexes

Yolanda Benito,* Laureano Canoira†‡ and J. Gonzalo Rodriguez*
*Departamento de Quimica, Universidad Autonoma de Madrid, Cantoblanco, 28049 Madrid, Spain
and †Visiting Research Fellow, Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, UK

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**Tris(triphenylphosphine)nickel(0) (A) and a zerovalent pyridine–nickel complex (B) have been used as reagents for the coupling reaction of 3-, 6- and 8-bromoquinolines: 3,3'-, 6-6'- and 8,8'-Biquinolines were obtained in quantitative yields when A was used as the coupling reagent. B gave always a mixture of the *n,n'*-biquinoline and substitution products. A mechanism can be outlined to explain the coupling reaction of bromoquinolines using zerovalent nickel complexes.**

**Keywords: Bromoquinolines, coupling reaction, biquinolines, tris(triphenylphosphine)nickel(0), pyridine–nickel complex.**

## INTRODUCTION

In previous papers,[1] we have reported the synthesis of heterocyclic compounds (indole, oxindole and 2-quinolone derivatives) from *N*-*β*-alkenyl-*o*-haloanilines and *N*-*β*-alkenyl-*o*-haloanilides, using zerovalent nickel complexes as cyclizing reagents. The coupling reaction of aromatic and benzylic halides to give biphenyl and bibenzyl derivatives, using organonickel(0) complexes,[2,3] is a well-established process.

In this paper, we now report the coupling reaction of heteroaromatic compounds such as bromoquinolines using organonickel(0) complexes to give a facile synthesis of biquinolines in quantitative yields. Some of the synthesized biquinolines could be useful ligands in the coordination and organometallic chemistry of transition metals[4] (Fig. 1).

‡Author to whom correspondence should be addressed. Present address: Departmento de Quimica C-I, Universidad Autonoma de Madrid, Cantoblanco, 28049 Madrid, Spain.

## EXPERIMENTAL

Melting points were measured in a hot-stage microscope and are uncorrected. The UV–visible spectra (UV) were obtained in a Shimadzu UV-240 instrument. The infrared spectra (IR) were recorded in a Perkin–Elmer 580B spectrophotometer and the $^1$H NMR spectra in a 200 MHz Bruker WH-200-SY (NMR). The mass spectra (MS) were obtained in a Hewlett–Packard 5985 GC MS system. Elemental analyses have been done with a Perkin–Elmer 240 elemental analyser. All the reactions were performed under an inert, oxygen-free atmosphere, using dried, deoxygenated solvents 3-Bromoquinoline **1** was purchased from Fluka and distilled before use. 6-Bromoquinoline[5] **2** and 8-bromoquinoline[6] **3** were prepared by the Skraup synthesis.

### Reaction of 3-, 6- and 8-bromoquinolines with tris(triphenylphosphine)nickel(0) (A): general procedure

Bis(triphenylphosphine) dichloronickel(II) [$NiCl_2(Ph_3P)_2$] (0.653 g, 1 mmol), triphenylphosphine (0.524 g 2 mmol) and zinc powder (0.065 g, 1 mmol) were placed in a previously dried flask. The flask was stopped with a septum-cap, evacuated and filled with oxygen-free nitrogen three times. Dried, deoxygenated dimethylformamide (DMF) (10 cm$^3$) was added

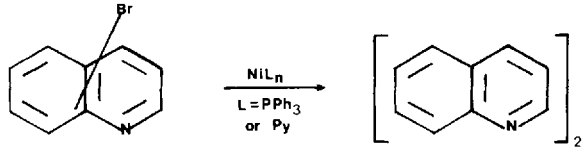
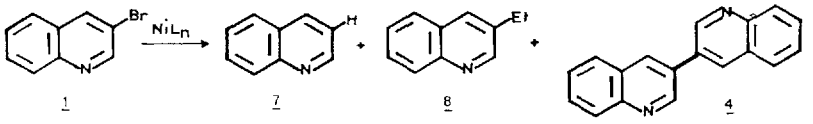
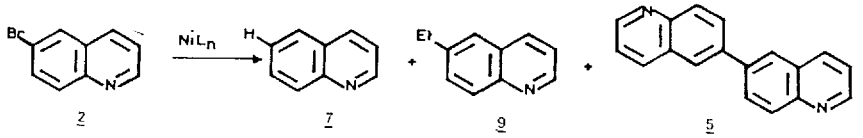
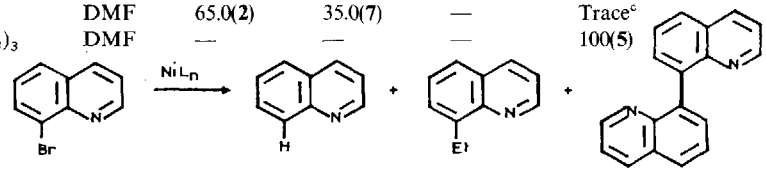



**Figure 1** Synthesis of *n'n*-biquinolines from *n*-bromoquinolines.

**Table 1** Synthesis of *n,n'*-biquinolines from *n*-bromoquinolines with zerovalent nickel complexes

| Complex | Solvent | Yield (%) *n*-Br | *n*-H | *n*-Et | *n,n'*- | *n*-Cl |
|---|---|---|---|---|---|---|
|  | | | | | | |
| 1 | | 7 | | 8 | 4 | |
| Ni–Py[a] | THF | 51.6(**1**) | 20.1(**7**) | 11.6(**8**) | 16.6(**4**) | |
| $Ni(PPh_3)_3$ | DMF | — | — | — | 100(**4**) | |
|  | | | | | | |
| 2 | | 7 | | 9 | 5 | |
| Ni–Py | THF | 16.8(**2**) | 14.0(**7**) | 38.1(**9**) | 31(**5**) | |
| Ni–Py[a] | DMF | 30.3(**2**) | 40.0(**7**) | — | — | 29.7 (**10**) |
| Ni–Py | DMF | 34.3(**2**) | 15.5(**7**) | 23.1(**9**) | — | |
| Ni–Py[b] | DMF | 65.0(**2**) | 35.0(**7**) | — | Trace[c] | |
| $Ni(PPh_3)_3$ | DMF | — | — | — | 100(**5**) | |
|  | | | | | | |
| 3 | | 7 | | | 6 | |
| Ni–Py | THF | 41.5(**3**) | 28.6(**7**) | — | 29.9(**6**) | |
| $Ni(PPh_3)_3$ | DMF | — | — | — | 100(**6**) | |

[a]The complex Ni–Py was prepared in diethyl ether and the reaction was carried out in DMF. [b]Prepared from $NiCl_2Py_2$/2Py/Zn in DMF. [c]Detected by GC MS techniques.

**Table 2** Analaytical data for the *n,n'*-biquinolines **4**, **5** and **6** and the quinolines **8**, **9** and **10**

| Compound | M.p. (°C) | Found (Required) (%) C | H | N |
|---|---|---|---|---|
| 3,3'-Biquinoline (**4**) | 259–260 (needles) | 84.1 (84.35) | 4.6 (4.72) | 11.2 (10.93) |
| 6,6'-Biquinoline (**5**) | 180–182 (plates) | 84.4 (84.35) | 4.8 (4.72) | 10.8 (10.93) |
| 8,8'-Biquinoline (**6**) | 205–207 (crystals) | 84.0 (84.35) | 4.9 (4.72) | 11.0 (10.93) |
| 3-Ethylquinoline (**8**)[9] | 199–200 (picrate) | 53.9 (52.85) | 3.8 (3.65) | 14.2 (14.5) |
| 6-Ethylquinoline (**9**)[10] | 205–206 (picrate) | 53.0 (52.85) | 3.24 (3.65) | 14.6 (14.5) |
| 6-Chloroquinoline (**10**)[8] | 40–41 | 66.0 (66.07) | 3.5 (3.7) | 21.7 (21.67) |

**Table 3** UV-visible, infrared and MS data for the *n,n'*-biquinolines **4**, **5** and **6**

| Spectrum | | Compound **4** | **5** | **6** |
|---|---|---|---|---|
| UV–VIS (EtOH) | $\lambda_1(\varepsilon_1)$ | 325(3408sh) | 325(1458sh) | 325(1086) |
| $\lambda$ (nm) | $\lambda_2(\varepsilon_2)$ | 330(3725) | 330(1655) | — |
| IR ($CHCl_3$) | | 1635 | 1635 | 1635 |
| $\bar{\nu}$ ($cm^{-1}$) | | 1615 | 1620 | 1590 |
| | | 1570 | 1585/1570 | 1580/1565 |
| MS(70 eV) | $M^+$ | 256(100) | 256(100) | 256(65) |
| | $M^+-1$ | 255(33) | 255(37) | 255(100) |
| | 227 | 7 | 10 | 11 |
| | 200 | 6 | 5 | 4 |
| | 128 | 4 | 6 | 13 |
| | 114 | 3 | 6 | 13 |
| | 100 | 5 | 5 | 7 |

**Table 4** $^1$H NMR data for the *n,n'*-biquinolines **4**, **5** and **6** ($\delta$ ppm, *J* Hz)[a]

| | Compound | | |
|---|---|---|---|
| | **4** | **5** | **6** |
| H2, H2' | 9.30 | 8.95 | 8.78 |
| H3, H3' | — | 7.46 | 7.36 |
| H4, H4' | 8.48 | 8.10 | 8.22 |
| H5, H5' | 7.96 | 8.13 | 7.91 |
| H6, H6' | 7.64 | — | 7.66 |
| H7, H7' | 7.64 | 8.25 | 7.80 |
| H8, H8' | 8.20 | 8.25 | — |
| *J*2,3;*J*2',3' | — | 4.25 | 4.20 |
| *J*2,4;*J*2',4' | 2.27 | 1.7 | 1.83 |
| *J*3,4;*J*3',4' | — | 8.30 | 8.26 |
| *J*5,6;*J*5',6' | 8.07 | — | 8.02 |
| *J*5,7;*J*5',7' | — | 1.61 | 1.67 |
| *J*5,8;*J*5',8' | — | — | — |
| *J*6,7;*J*6',7' | 6.92 | — | 7.10 |
| *J*6,8;*J*6',8' | — | — | — |
| *J*7,8;*J*7',8' | 8.49 | 8.21 | — |

[a]Integrated intensities for the signals of the protons in the $^1$H NMR spectra of the biquinolines were as expected for these compounds.

with a syringe, and the flask was warmed at 50°C for 1 h. The initial blue solution becomes deep green and later a red–brown slurry of tris(triphenylphosphine)nickel(0) ($Ni(PPh_3)_3$)[7] (**A**) was formed. The bromoquinoline (0.208 g, 1 mmol) was added in dried DMF (5 cm$^3$), and the mixture was stirred at 50°C for 24 h. Afterwards, the flask was cooled in an ice bath and a saturated ammonium chloride solution was added with stirring. A solid precipitated, which was filtered, dissolved in ethyl acetate (25 cm$^3$) and extracted with three 10 cm$^3$ portions of a 5% solution of hydrochloric acid. This aqueous layer was decanted and made basic with a 5% sodium hydroxide solution until pH 9 was achieved. The biquinoline precipitated as a white solid, which was recovered by filtration, dried under vacuum and recrystallized from dichloromethane–hexane (3:1) (5 cm$^3$) upon cooling at −20°C. The physical and spectral data for the biquinoline products **4**, **5** and **6** are given in Tables 2, 3 and 4.

### Reaction of 3-, 6- and 8-bromoquinolines with a pyridine-nickel complex (B): general procedure

In a previously dried flask were placed anhydrous bis(acetylacetonate)nickel(II) (0.256 g, 1 mmol) and dried pyridine (0.39 g, 5 mmol, 0.4 cm$^3$) in dried THF (25 cm$^3$). The flask was surrounded with an ice–ammonium chloride bath, and triethylaluminium (0.34 g, 3 mmol, 0.84 cm$^3$ of a 50% solution in toluene) was added under an inert atmosphere. The mixture was left to reach room temperature and later, the bromoquinoline (0.208 g, 1 mmol) was added in dried tetrahydrofuran THF (5 cm$^3$) and the whole warmed at reflux temperature overnight. Afterwards, a saturated ammonium chloride solution (50 cm$^3$) was added with cooling in an ice–ammonium chloride bath, and the aqueous layer was extracted with three 20 cm$^3$ portions of diethyl ether. Solvent was removed under reduced pressure, and the crude product was purified by chromatography on silica gel using as the eluent variable ratios of *n*-hexane–diethyl ether (6:1 at the beginning of the chromatography and 3:1 and 1:1 later). The physical and spectral data of the 6-chloroquinoline[8] and 3-[9] and 6-ethylquinoline[10] products are in good agreement with previously reported data (see Table 2).

The reaction of 6-bromoquinoline with the pyridine–nickel(0) complex has also been performed in dried dimethylformamide following this same experimental procedure.

### Reaction of 6-bromoquinoline with the system $NiCl_2(Py)_2$/2Py/Zn(Py = pyridine)

The reaction of 6-bromoquinoline (**2**) with the system $NiCl_2(Py)_2$/2Py/Zn in DMF has been carried out following the same experimental procedure reported above for the reaction of bromoquinolines with tris(triphenylphosphine)-nickel(0), but using bis(pyridine) dichloronickel as the starting divalent nickel complex and pyridine as ligand. The starting bromoquinoline **2** was recovered in 65% yield, and quinoline was isolated in 35% yield. Traces of the 6,6'-biquinoline derivative were only detected by GC MS techniques.

## RESULTS AND DISCUSSION

The starting compounds 6-bromoquinoline and 8-bromoquinoline were synthesized in high yields (83% and 84% respectively) by the Skraup synthesis.

Tris(triphenylphosphine)nickel(0) (**A**) was prepared from bis(triphenylphosphine)dichloronickel(II) and triphenylphosphine with metallic zinc as reducing agent, in DMF as solvent. The zerovalent pyridine–nickel complex was prepared from bis(acetylacetonate)nickel(II) and pyridine with triethylaluminium as the reducing agent, and THF as solvent.

The reaction of the bromoquinolines **1**, **2** and **3** with the zerovalent nickel complexes is summarized in Table 1.

The reaction of 3-bromoquinoline with tris(triphenylphosphine)nickel(0) (**A**), in DMF as solvent, gave 3,3'-biquinoline (**4**) in quantitative yield. 3,3'-Biquinoline was easily isolated from the crude material by extraction with 5% hydrochloric acid solution, and reprecipitation from the aqueous solution by basification with 5% sodium hydroxide solution, and it was recrystallized from dichloromethane–hexane.

The reaction of 3-bromoquinoline **1**, with the zerovalent pyridine–nickel complex **B**, in THF as solvent, gave only a 16.6% yield of the 3,3'-biquinoline and left a 51.6% yield of unreacted starting material **1**. Quinoline (**7**) (20.1%) and 3-ethylquinoline (**8**) (11.6%) were also isolated, resulting from the attack of hydride (**7**) and ethyl (**8**) anions respectively on the $\pi$-arylnickel intermediate complex. The formation of these side-products lowered the yield of the 3,3'-biquinoline, and the isolation of the reaction products required in this case the use of a chromatographic column of silica-gel.

The reaction of 6-bromoquinoline **2** with tris(triphenylphosphine)nickel(0), in DMF as solvent, gave also the 6,6'-biquinoline **5** in quantitative yield, and the crude product was purified in the same way to obtain the crystalline 6,6'-biquinoline.

The reaction of 6-bromoquinoline **2** with the zerovalent pyridine–nickel complex was carried out under different reaction conditions, with the aim of improving the yield in 6,6'-biquinoline **5**. When the reaction was carried out in THF, the 6,6'-biquinoline **5** was obtained in a 31% yield, and the starting material **2** was recovered in a 16.8% yield. Quinoline **7** (14.0%) and 6-ethylquinoline **9** (38.1%) were isolated as side-products resulting from the attack of hydride (**7**) and ethyl (**9**) anions respectively on the $\pi$-organonickel intermediate complex.

In another experiment, the zerovalent pyridine–nickel complex (**B**) was prepared in diethyl ether; this solvent was removed under vacuum at room temperature, the complex was dissolved in DMF and the reaction with **2** was carried out at 50°C for 24 h. The 6,6'-biquinoline **5** was not detected, and the starting material was recovered in 30.3% yield. Quinoline **7** (40%) and 6-chloroquinoline (**10**) (29.7%) were isolated; these arose by substitution of the bromine atom by hydride (**7**) and chloride (**10**) anion attack respectively, on the $\pi$-organonickel complex. The formation of the compound **10** showed how the $\pi$-intermediate complex is present here until the end of the reaction, since the chloride anion came from the aqueous ammonium chloride used as hydrolysing reagent.

DMF was also used as solvent to prepare the pyridine–nickel(0) complex **B** and to carry out the reaction with 6-bromoquinoline. In this case, 6,6'-biquinoline was not detected, and **2** was recovered in a 34.3% yield. Quinoline **7** (15.5%) and 6-ethylquinoline (**9**) (23.1%) were isolated as side-products.

In an attempt to reproduce the experimental behaviour of tris(triphenylphosphine)nickel(0), (**A**), the pyridine–nickel(0) complex **B** was prepared from bis(pyridine) dichloronickel(II) and pyridine with metallic zinc as reducing agent, and DMF as solvent. 6-Bromoquinoline (**2**) was stirred with the resulting brown slurry at 50°C for 24 h, but 6,6'-biquinoline **5** could only be detected by GC MS techniques. 6-Bromoquinoline was recovered in 65% yield and quinoline **7** was isolated in 35% yield.

These results show that DMF is not an adequate solvent for the coupling reaction of 6-bromoquinoline using the zerovalent pyridine–nickel complex **B**.

The reaction of 8-bromoquinoline **3** with tris(triphenylphosphine)nickel(0) gave 8,8'-biquinoline (**6**) in quantitative yield, and this was purified by the same extraction method.

The reaction of 8-bromoquinoline (**3**) with the pyridine–nickel(0) complex, in THF as solvent gave 8,8'-biquinoline in 29.9% yield. 8-Bromoquinoline was recovered in 41.5% yield and quinoline **7** was isolated in 28.6% yield. 8-Ethylquinoline was not detected and we think that, in this case, the larger ethyl anion (with respect to hydride or chloride) cannot approach the 8-position of the 8-bromoquinoline $\pi$-intermediate complex, by electronic repulsion with the lone electron pair on the heterocyclic nitrogen. Smaller hydride and chloride anions can approach this position in alternative ways, avoiding the electronic repulsion from the lone electron pair.

The oxidative addition of aryl halides to

nickel(0) phosphine complexes, which has been extensively studied by Kochi,[11] affords *trans*-arylnickel(II) halides (path *a*), and paramagnetic nickel(I) halides (path *b*), perhaps by involvement of a $\pi$-complex, before the formation of the intermediate paramagnetic ion pair (*c*) (Scheme, step [1]). The above aryl halide oxidative addition to nickel(0) complexes is related to an Ullman-type coupling of aryl halides in the presence of nickel(0) complexes. Kochi has shown that this is a radical-chain process involving intermediate nickel(I) and nickel(III) aryl complexes. The key step is the oxidative addition of an aryl halide to an intermediate nickel(I) complex (step [ii]). Aryl exchange between nickel (III) and nickel(II) gives a nickel (III) diaryl (step [iii]). Reductive elimination affords the biaryl and regenerates nickel(I) (step [iv]). Free aryl radicals appear not to be involved, because we did not isolate any products coming from radical side-reactions. The existence of a $\pi$-arene complex was proposed as an intermediate before the formation of the paramagnetic ion pair, and this could explain the formation of the side-products by nucleophilic attack of ethyl, hydride and chloride anion on this $\pi$-arene complex.

The coupling reaction of bromoquinolines to give *n,n'*-biquinolines using $Ni(PPh_3)_3$ is a useful synthetic method, since the yields of the dimeric products were quantitative, no side-products were detected and the starting materials were not expensive. 2,2'-Biquinoline, which is a commercial ligand in coordination chemistry, could be also prepared in this way. Moreover, the method could be applied to the chemical modification of polyvinylquinolines prepared in our laboratory,[12] by attachment of different functional groups to the quinoline moieties, by a coupling reaction using $Ni(PPh_3)_3$. *n,n'*-Bipyridines could be prepared by this method using $Ni(PPh_3)_3$ as the coupling reagent and bromo- or chloro-pyridines as starting materials, since the reactivity of pyridines is very similar to that of the quinolines. We intend to extend this coupling reaction to the synthesis of C–C linked bipyrazoles, bisimidazoles and bisindoles. We have not yet attempted to use this reaction scheme for the polymerization of dibromoquinolines to prepare polyquinolines, although, looking at the mechanism proposed by Kochi, it would be reasonable to take into account this possibility.

## CONCLUSIONS

The reaction of 3-, 6- and 8-bromoquinolines with tris(triphenylphosphine)nickel(0), in DMF as solvent, provides a useful synthetic method towards *n,n'*-biquinolines in quantitative yield. The lack of basic side-products allows an easy procedure for the purification of the synthesized *n,n'*-biquinolines.

$$NiL_3 + ArX \rightarrow \underset{(c)}{[N^{+\cdot}L_3\,Ar^{-\cdot}X]} \begin{cases} \xrightarrow{\text{Path } a} ArNi(II)XL_2 + L \\ \xrightarrow{\text{Path } b} XNi(I)L_3 + Ar\cdot \end{cases} \quad [i]$$

$$Ni(I)X + ArX \rightarrow ArNi(III)X_2 \quad [ii]$$

$$ArNi(III)X_2 + ArNi(II)X \rightarrow Ar{-}\underset{\displaystyle Ar}{\underset{|}{Ni(III)X}} + NiX_2 \quad [iii]$$

$$Ar{-}\underset{\displaystyle Ar}{\underset{|}{Ni(III)X}} \rightarrow Ar{-}Ar + Ni(I)X \quad [iv]$$

$$L = PR_3,\ Ar = \text{quinoline},\ X = Br$$

N.B. The nickel(0) complexes are designated in the text and above, but it should be noted that all work described here was carried out in the solution phase, where equilibria between $NiL_3$ and $NiL_2$ occur. Hence we refer here to $NiL_3$ where $L = PPh_3$ and Py.

**Scheme 1**

The reaction of the bromoquinolines with the zerovalent pyridine–nickel complex, in THF as solvent, gives acceptable yields in *n,n'*-biquinolines when the bromine atom is in the homoaromatic ring, and lower yields when it is on the heteroaromatic ring. The starting *n*-bromoquinoline was always recovered, and side-products such as quinoline and *n*-ethylquinoline were formed in variable yields. In these cases, the presence of different basic products obliges a chromatographic separation. DMF proved not to be a useful reaction solvent for this nickel complex, although an interesting substitution product (**10**) was isolated when DMF was used as the solvent in this reaction.

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