A Convenient Access to Biquinoline Carbaldehydes using Nickel-Phosphine Complex-Mediated Homocoupling of Haloquinoline Carbaldehydes in One-Pot Reaction

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Abstract: The homocoupling of 2-chloro-carbaldehyde derivatives gave the corresponding 2,2'-biquinolines by using the *in situ* generated reactive reagent $\text{Ni}[(\text{PPh}_3)_4]$. Several new 2-chloro-3-(1,3 dioxalan-2yl) quinoline derivatives are synthesized and structurally characterized. The overall structures of biquinoline derivatives are not planar.

Keywords: 2-Chloroquinoline carbaldehyde, Homocoupling, One-pot reaction, 2,2'-Biquinoline derivatives.

Introduction

There is growing interest in the chemistry of biquinoline compounds due to the possibility of their use in high performance heterocyclic ladder polymers¹, as ligands for the preparation of metal complexes bearing biological activities, such as antibacterial, antifungal, antimalarial and antitumor properties and as hydrogenation catalysts²⁻⁴. Even though there are several synthetic methods of biquinoline derivatives cited in the literature⁵, most of them suffer from some drawbacks such as low yields due to the formation of by-products, the use of highly reactive coupling reagents and competitive reductions from the presence of protonic sources^{6,7}.

To overcome these difficulties, we describe herein an efficient one-pot synthesis of some new biquinoline carbaldehyde derivatives which consists of the homocoupling of haloquinolines mediated by nickel-phosphine complexes. This method is based on the procedure described by Tiecco *et al.*⁸, which uses the *in situ* generated nickel(0) complex.

To surmount the well known competitive reduction of aldehyde function and haloheterocycles by $\text{Zn}(0)$ in the presence of a proton source such as water⁶, we protected the aldehyde function using ethylene glycol in the presence of montmorillonite (K10)⁹. The amount

of zinc dust was added in portions to a solution of PPh_3 and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ in DMF at 70°C under argon followed by the addition of the protected 2-chloroquinoline carbaldehyde **2** (Scheme 1).

Scheme 1

Experimental

^1H NMR spectra were recorded on a BRUKER AC spectrometer (200 or 300 MHz) using CDCl_3 . Chemical shifts are reported in parts of million (ppm) relative to TMS (0.0) as internal standard and coupling constant (J) is reported in hertz (Hz). ^{13}C NMR spectra were recorded on a BRUKER AC spectrometer (75 or 50 MHz). High resolution mass spectral analysis (HR-MS) were performed by CMPO (the Centre regional de Mesure de Physique de l'Ouest, Rennes, France) on a ZabSpecTOF (LSIMS, 4KV) and presented as m/e (relative intensity, assignment).

Zinc powder was washed successively with diluted hydrochloride acid, water, ethanol, acetone and diethyl ether and dried under reduced pressure. Anhydrous DMF was purified to remove traces of HCN ¹⁰. All other reagents were commercially available and were purified or used as such.

The 2-chloroquinoline carbaldehyde derivatives (**2**), from which the present synthesis is initiated, were prepared from the corresponding acetanilide using the method reported by Meth-Cohn¹¹ (Scheme 2).

Scheme 2

General procedure for the synthesis of biquinoline derivatives

Zinc dust (127 mg, 1.92 mmol) was added in portions to a stirred deep blue solution of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (428 mg, 1.8 mmol) and triphenylphosphine (1.9 g, 7.2 mmol) in degassed DMF (20 mL) at 70°C under argon. The resulting mixture was stirred for 1 h, the time necessary for $\text{Ni}(0)$ formation (red-brown color). 2-Chloro-3-(1,3 dioxalan-2yl) quinoline derivative (1.8 mmol) dissolved in degassed DMF (10 mL) was added drop wise and the mixture was stirred for a further 3 h. Upon cooling to room temperature, the reaction mixture was poured into a dilute ammonia solution (5%, 30 mL), the resulting solution was extracted with $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (3×100 mL, 2/1) and evaporated. The residue obtained was dissolved in CH_2Cl_2 (60 mL), washed with water (4×20 mL) and the combined organic layers were extracted with a saturated solution of NaCl (40 mL), dried over anhydrous MgSO_4 and then concentrated to give the crude product which was purified by column chromatography on silica gel using ethyl acetate / pentane (1/1) as eluent to afford the corresponding biquinoline derivative in pure state.

All compounds obtained according to this protocol were characterized and identified by NMR, mass spectra and elemental analysis. The results are summarised in Table 1.

Table 1. Ni[(PPh₃)₄] catalyzed synthesis of biquinoline derivatives

Biquinoline 3 ^a	R ₁	R ₂	Yield ^b %
3a	H	H	53
3b	H	OMe	60
3c	OMe	OMe	56
3d	Me	Me	65

^aThe products were characterized by their mass, ¹H, ¹³C NMR and elemental analysis ^bYield based on the amount of starting compound employed and calculated from the amount of product isolated by column chromatography.

Spectral data for all the compounds

[3,3-Bis[1,3]dioxalan-2-yl]-2,2'-biquinoline (**3a**)

¹H NMR (CDCl₃): δ (ppm) = 8.60 (s, 2H, *H*₄), 8.17 (s, 2H, *H*₅), 7.96 (d, 2H, *H*₈), 7.79 (d, 2H, *H*₇), 7.62 (d, 2H, *H*₆), 6.41 (s, 2H, *CH*), 3.94 (m, 8H, *CH*₂); ¹³C NMR(CDCl₃): δ (ppm) = 157.4, 147.6, 135.4, 131.4, 130.5, 129.7, 128.5, 127.7, 127.5, 101.2, 65.4; HR-MS.FAB⁺ (*m/z*) 400.14231 ([M⁺] (calc.: 400.1423). Elemental analysis (%) for C₂₄H₂₀N₂O₄: C (71.99), H (5.03), N (7.00), Calc.: C (72.05), H (5.12), N (6.70). Yellow-brown solid.

[3,3-Bis[1,3]dioxalan-2-yl]-7,7'-dimethoxy[2,2']biquinoline (**3b**)

¹H NMR (CDCl₃): δ (ppm) = 8.5 (s, 2H, *H*₄), 7.83 (d, 2H, *H*₅), 7.5 (s, 2H, *H*₈), 7.26 (d, 2H, *H*₆), 6.25 (s, 2H, *CH*), 4.02 (m, 4H, *CH*₂), 3.96 (s, 6H, OCH₃), 3.85 (m, 4H, *CH*₂); ¹³C NMR (CDCl₃, 75MHz, ppm): δ = 161.6, 152.6, 146.1, 135.1, 129.4, 128.9, 122.9, 120.8, 107.7, 101.3, 65.5, 56.0; HR-MS.FAB⁺ (*m/z*) 460.16344 ([M⁺] (calc.: 460.1612); Elemental analysis (%) for C₂₆H₂₄N₂O₆: C (67.82), H (5.25), N (6.08), Calc.: C (68.04), H (5.65), N (5.88). White solid.

[3,3-Bis[1,3]dioxalan-2-yl]-6,7,6',7'-tetramethoxy-[2,2']biquinoline (**3c**)

¹H NMR (CDCl₃): δ (ppm) = 8.43 (s, 2H, *H*₄), 7.50 (s, 2H, *H*₅), 7.18 (s, 2H, *H*₈), 6.19 (s, 2H, *CH*), 4.07 (s, 6H, OCH₃), 4.04 (s, 6H, OCH₃), 3.91 (m, 8H, *CH*₂); ¹³C NMR(CDCl₃): δ (ppm) = 155.2, 153.4, 150.5, 144.8, 133.6, 129.3, 123.35, 108.4, 105.6, 101.4, 65.5, 56.5; Elemental analysis (%) for C₂₈H₂₈N₂O₈, C (64.61), H (5.42), N (5.38), (calc.: C (64.67), H (5.55), N (5.52); HR-MS.FAB⁺ (*m/z*) 520.18457 ([M⁺] (calc.: 520.1831). White solid.

[3,3-Bis[1,3]dioxalan-2-yl]-6,7,6',7'-tetramethyl-[2,2']biquinoline (**3d**)

¹H NMR (CDCl₃): δ (ppm) = 8.45 (s, 2H, *H*₄), 7.91 (s, 2H, *H*₈), 7.66 (s, 2H, *H*₅), 6.29 (s, 2H, *CH*), 4.19–4.08 (m, 8H, *CH*₂), 2.48 (s, 12H, *CH*₃); ¹³C NMR (CDCl₃): δ (ppm) = 156.6, 146.7, 140.8, 137.3, 134.4, 130.4, 129.1, 127.6, 126.2, 101.4, 65.4, 20.9, 20.5. White shiny crystals.

Furthermore, the crystal structure of **3d** was determined (Figure 1).

Figure 1. The crystal structure of **3d**

Results and Discussion

We would like to disclose here our preliminary results using the *in situ* generated Ni(0) complex, $[(PPh_3)_4Ni]$, for the preparation of some 2,2'-biquinoline derivatives (**3**).

After some exploratory experiments, we determined that the best results to produce **3** were achieved on adding zinc dust (1.92 mmol) to a solution of nickel(II) chloride hexahydrate (1.8 mmol) and triphenylphosphine (7.2 mmol) in degassed dimethylformamide (20 mL) under argon at 70 °C followed by the addition of 2-chloro-3-(1.3 dioxalan-2yl) quinoline derivative (1.8 mmol). The method seems to be generally applicable, thus substituted 2-chloro-3-(1.3 dioxalan-2yl) quinoline underwent the homocoupling to afford the corresponding biquinolines under the above described conditions.

In summary, the present method for the synthesis of 2,2'-biquinoline-carbaldehydes has overcome some difficulties by using the modified procedure of Tiecco *et al.*⁸.

Conclusion

In conclusion, we have synthesized and characterised some new biquinoline carbaldehyde derivatives by using the modified procedure of Tiecco *et al.*⁸ in which a stoichiometric amount of a nickel coupling reagent was used. The generation of $[(PPh_3)_4Ni]^0$ was conducted by the Zn(0) reduction of $NiCl_2 \cdot 6H_2O$ in the presence of PPh_3 .

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