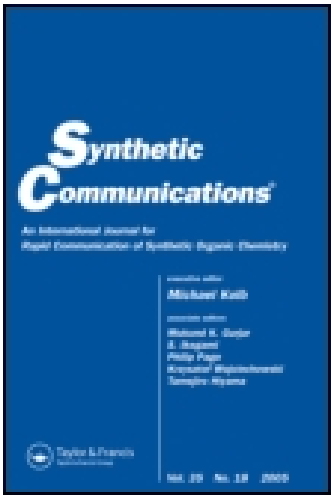

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Evelina Colacino [a], Hafid Benakki [a b], Farhate Guenoun [b], Jean Martinez [a] & Frédéric Lamaty [a]
[a] Institute of Biomolecules Max Mousseron, University of Montpellier, Montpellier, France
[b] My Ismail University, Faculty of Sciences, Meknès, Morocco
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Synthesis of Novel Pyrrolo-[3,2-c]quinolines via Iron-Catalyzed Cross-Coupling Reaction of Grignard Reagents

Evelina Colacino,[1] Hafid Benakki,[1,2] Farhate Guenoun,[2] Jean Martinez,[1] and Frédéric Lamaty[1]

[1]Institute of Biomolecules Max Mousseron, University of Montpellier, Montpellier, France

[2]My Ismaïl University, Faculty of Sciences, Meknès, Morocco

Abstract: Cross-coupling reaction of alkyl and aryl magnesium halides with 4-chloro-pyrrolo-[3,2-c]quinoline in the presence of a catalytic amount of iron salt is described. The reactions are completed in 30 min, resulting in moderate to excellent yields of 52–94% in a tetrahydrofuran (THF)–N-methylpyrrolidinone (NMP) solvent mixture.

Keywords: Cross-coupling, imidoyl chloride, iron catalysis, nitrogen heterocycles, organomagnesium reagents

Very few metal-catalyzed cross-coupling reactions of imidoyl chlorides have been studied, and most of the reported reactions require the use of expensive palladium or toxic nickel catalysts.[1] Despite their excellent compatibility with many functional groups, their high cost, toxicity, the need for ancillary ligands, extended reaction time, and elevated temperature are the most common disadvantages of their use. In contrast, $Fe(acac)_3$ as catalyst for cross-coupling reaction is very cheap, easily available, nontoxic, environmentally benign, and easy to handle (nonhygroscopic),

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Address correspondence to Frédéric Lamaty, Institut des Biomolécules Max Mousseron, UMR 5247 CNRS, Université Montpellier, 1 et Université Montpellier 2, Place Eugène Bataillon, 34095 Montpellier cedex 05, France. E-mail: frederic.lamaty@univ-montp2.fr

and the reactions are usually characterized by high rates under mild conditions.[2–7]

As a continuation of our ongoing studies of the development of novel routes for the synthesis of substituted pyrroles,[8–10] we decided to investigate the cross-coupling reaction between the 4-chloro-1*H*-pyrrolo-[3,2-c]quinoline **1**, synthesized as previously reported by us,[10] in the presence of alkyl and aryl Grignard reagents, catalyzed by an iron salt. No examples are described in the literature for the cross-coupling reaction between imidoyl chloride, confined in a pyrrolo-quinoline structure, and Grignard reagents in the presence of $Fe(acac)_3$ as catalyst.

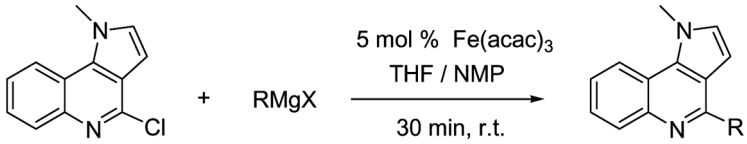
In a typical experiment, the imidoyl chloride **1** was reacted in the presence of $Fe(acac)_3$ (5 mol%) with different Grignard reagents in a 10:1 mixture of tetrahydrofuran (THF)/NMP at room temperature, leading to a new series of pyrrolo-[3,2-c]quinoline derivatives **2–7** (Scheme 1, Table 1). The results are summarized in Table 1.

Under iron-free reaction conditions, no reaction occurred, confirming the importance of iron catalyst in the rapid and high-yielding reactions. The kinetic study by thin-layer chromatography (TLC) and high performance liquid chromatography (HPLC) showed a completed reaction after only 30 min at room temperature. Our reaction conditions proved to be general for the formation of $C_{sp^2} - C_{sp^3}$ and $C_{sp^2} - C_{sp^2}$ bonds, and the *ortho*-substitution on the imidoyl chloride with the pyrrole ring does not affect the yield.

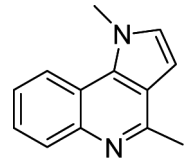
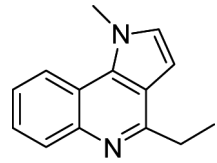
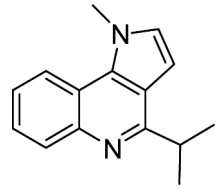
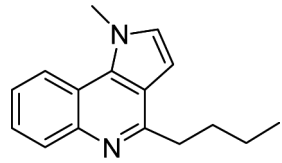
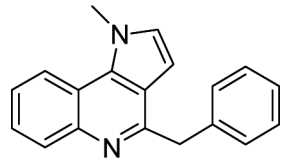
The analysis of the crude products by HPLC and liquid chromatography–mass spectrometry (LC-MS) showed the formation of the expected products along with some by-products, according to four main secondary reactions responsible for the moderate yield obtained in some cases: (i) dehalogenation reaction of imidoyl chloride **1** to afford the corresponding unsubstituted imine (entries 2–6); (ii) hydrolysis of the imine function in **1** to afford the corresponding cyclic amide[10] (entries 1–3); (iii) homocoupling of imidoyl chloride **1** (entry 7); and (iv) the oxidative dimerization of the Grignard reagents.[3]

For alkyl Grignard reagents (entries 1–4, Table 1), independent of the nature of halogen atom (RMgX, X = I, Br, Cl), the cross coupling products **2–5** were obtained in moderate to good yields. Contrary to previous reports on the reactivity of the secondary alkyl Grignard, for which [Fe(salen)Cl][2,3] should be used to achieve the cross-coupling reaction, in our case a good yield of product **4** could be obtained in the presence of $Fe(acac)_3$. With the more sterically demanding 2-methyl-2-phenylpropylmagnesium chloride (entry 8), coupling with imidoyl chloride **1** was unsuccessful, and the unreacted substrate **1** was recovered. When the less hindered substrate benzylmagnesium chloride (entry 5) was used, the cross-coupling product **6** was obtained in a satisfactory yield.

Table 1. Cross-coupling product of imidoyl chloride **1** in the presence of RMgX

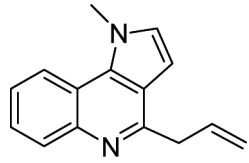
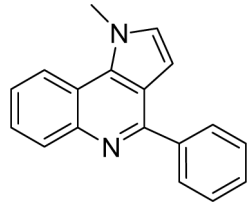


1 **2-9**

Entry	RMgX	Product		Yield (%)[a]
1	MeMgI		**2**	52
2	EtMgBr		**3**	74
3	*i*-PrMgCl		**4**	86
4	BuMgCl		**5**	64
5	$PhCH_2MgCl$		**6**	60

(*Continued*)

Table 1. Continued

Entry	RMgX	Product		Yield (%)[a]
6	$CH_2{=}CHCH_2MgBr$		**7**	Traces
7	PhMgCl		**8**	94[b]
8	$(CH_3)_2CH(Ph)MgCl$	–	**9**	0

[a]Isolated yield after purification on column chromatography;
[b]The product was recovered by crystallization from CH_2Cl_2.

Only traces of product **7** (entry 6) were obtained in the presence of allyl magnesium bromide, and the result could not be improved by adding some more catalyst (10% mol), extending the reaction time (up to 24 h), adding an excess of Grignard reagent, or heating the mixture up to 60°C, classically or under microwave activation. In all cases, unreacted **1** was recovered.

To our great satisfaction, the aryl–aryl bond formation was successful when phenyl magnesium chloride was coupled with imidoyl chloride **1**, affording compound **8** in a very high yield (entry 7). In this case, the catalytic decomposition of the Grignard reagent[11–13] to afford biphenyl in the presence of transition-metal salts and aryl halides acting as oxidizing agents is diminished. This is may be due to the lower oxidizing power of the pyrrolo-quinoline aromatic system, showing that the reaction is applicable to π-electron-deficient heterocycles,[3,5] associated with a stabilization of frontier orbital energy, which allow the reaction to proceed.

In conclusion, we have shown that the developed conditions are quite general and mild for the formation of $C_{sp^2} - C_{sp^3}$ and $C_{sp^2} - C_{sp^2}$ bonds, affording differently substituted pyrrolo-quinoline derivatives, which are useful scaffolds for medicinal chemistry.[14,15]

EXPERIMENTAL

General

All reagents were purchased from Aldrich Chemical Co. and used without further purification. ^{1}H and ^{13}C NMR analyses were performed with Bruker Avance DPX 200-MHz, Bruker Avance AM 300-MHz or Bruker AC 400-MHz instruments, reported in parts per million (ppm), and calibrated using residual undeuterated solvents as an internal reference. Data are reported as br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet, and coupling constant(s) are in Hertz (Hz). Mass spectra (electrospray ionization mode, ESI-MS) were recorded on a Platform II (Micromass, Manchester, U.K.) quadrupole mass spectrometer fitted with an electrospray interface. The mass spectrometer was calibrated in the positive- and negative-ion ESI mode. The samples were dissolved in H_2O/CH_3CN (50/50 v/v). Fast atom bombardment (FAB) mass spectra and HRMS (high-resolution mass spectrum) were recorded on a Jeol JMS DX300-S × 102 instrument in positive mode using NBA (3-nitrobenzylalcool) or GT (mixture of glycerol/thioglycerol 50/50 v/v) as matrix. Infrared (IR) spectra were recorded by diffuse reflectance or by transmittance in KBr salt plates on a Nicolet Avatar 330FT-IR instrument. Data are reported according their group absorption regions as s = strong, m = medium, and w = weak. Analytical high-performance liquid chromatography (HPLC) was performed on a Waters Millenium 717 instrument equipped with autosampler and a variable-wavelength diode detector using a Chromolith RP18 column (50 × 4.6 mm) [flow 5 mL/min, linear gradient CH_3CN in water 0–100% (+0.1% TFA)] in 4.5 min.

Representative Experimental Procedure for the Iron-Catalyzed Synthesis of Compounds 2–8

A flame-dried flask was charged under nitrogen with 4-chloro-1H-pyrrolo-[3,2-c]quinoline **1**[7] (0.093 mmol, 20 mg), $Fe(acac)_3$ (0.05 mol, 1.64 mg), and THF/NMP 10:1 v/v (2.2 mL). A solution of the Grignard reagent (2.0 M in THF, 0.1 mL, 0.186 mmol) was added via syringe to the solution, and the resulting mixture was stirred for 30 min at room temperature. Then, the reaction mixture was diluted with Et_2O (10 mL) and carefully quenched upon addition of sat. NH_4Cl (5 mL). The organic phase was washed with water (2 × 10 mL) and with sat. NaCl (1 × 10 mL). The organic phase was dried on $MgSO_4$, filtered, and evaporated. The crude was purified by column chromatography (compounds **3–6**; eluent is

given in brackets for each compound) or by hot recrystallization (compounds **2** and **8**).

Data

1,4-Dimethyl-1*H*-pyrrolo[3,2-c]quinoline (**2**)

Hot crystallization from *n*-pentane afforded 9.39 mg (52% yield) of compound **2**. Product decomposes at temperatures greater than 200°C. ^{1}H NMR ($CDCl_3$, Me_4Si) δ (ppm): 3.23 (s, 3H), 4.34 (s, 3H), 6.92 (d, $J = 3.2$ Hz, 1H), 7.29 (d, $J = 3.2$ Hz, 1H), 7.67–7.76 (m, 2H), 8.39 (d, $J = 8.2$ Hz, 1H), 8.97 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ (ppm) 17.77, 38.56, 104.84, 116.63, 120.40, 120.77, 122.98, 128.08, 129.56, 133.37, 134.97, 135.74, 152.41; ESI-MS m/z 197.2 $[M+H]^+$. HRMS calcd. for $C_{13}H_{13}N_2$ 197.1082; found 197.1079.

4-Ethyl-1-methyl-1*h*-Pyrrolo[3,2-c]quinoline (**3**)

Purification of the crude by column chromatography [cyclohexane/Et_2O: linear gradient 100/0–30/70 v/v) afforded 14 mg (74% yield) of **3**. Mp 84–88°C; ^{1}H NMR ($CDCl_3$, Me_4Si) δ (ppm): 1.38–1.43 (t, $J = 7.5$ Hz, 3H), 3.13–3.2 (q, $J = 7.5$ Hz, 4H), 4.22 (s, 3H). 6.67 (d, $J = 2.9$ Hz, 1H), 7.03 (d, $J = 2.9$ Hz, 1H), 7.44–7.56 (m, 2H), 8.18 (d, $J = 7.4$ Hz, 1H), 8.30 (d, $J = 8.0$ Hz, 1H); ^{1}H NMR [$(CD_3)_2CO$, Me_4Si] δ (ppm): 8.35 (dd, $J = 6.8$ and 1.5 Hz, 1H), 7.97 (dd, $J = 6.8$ and 1.5 Hz, 1H), 7.49–7.31 (m, 2H), 7.17 (d, $J = 3.1$ Hz, 1H), 6.62 (d, $J = 3.1$ Hz, 1H), 4.15 (s, 3H), 3.03 (q, $J = 7.3$ Hz, 2H), 1.29 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ (ppm): 13.78, 29.69, 38.02, 101.79, 118.23, 120.19, 120.76, 125.00, 126.30, 129.42, 134.14, 159.35; ^{13}C NMR [$(CD_3)_2CO$, Me_4Si] δ (ppm): 136.18, 132.4 (2C), 132.0, 128.6, 128.2, 127.3, 127.2, 124.3, 123.6, 122.9, 121.1, 39.9, 15.1. ESI-MS m/z 211.1 $[M+H]^+$ HRMS calcd. for $C_{14}H_{15}N_2$ 211.1235; found 211.1238.

4-Isopropyl-1-methyl-1*H*-pyrrolo[3,2-c]quinoline (**4**)

Purification of the crude by column chromatography [cyclohexane/Et_2O: linear gradient 100/0–80/20 v/v) afforded 18 mg (86% yield) of **4**. ^{1}H NMR ($CDCl_3$, Me_4Si) δ (ppm): 1.44 (d, $J = 6.9$ Hz, 6H), 3.52–3.61 (m, 1H), 8.38 (s, 3H), 6.69 (d, $J = 2.5$ Hz, 1H), 7.00 (d, $J = 2.5$ Hz, 1H), 7.41–7.54 (m, 2H), 8.19 (d, $J = 6.7$ Hz, 1H), 8.27 (d, $J = 8.00$ Hz, 1H);

^{13}C NMR ($CDCl_3$, Me_4Si) δ (ppm): 22.69, 29.70, 38.08, 118.13, 120.13, 121.22, 125.08, 126.33, 129.43, 131.40, 134.31, 162.42; ESI-MS m/z 225.1 $[M+H]^+$.

4-Butyl-1-methyl-1*H*-pyrrolo[3,2-c]quinoline (**5**)

Purification of the crude by column chromatography [cyclohexane/Et_2O: linear gradient 100/0–80/20 v/v) afforded 14 mg (64% yield) of compound **5**. Mp 80–82°C; ^{1}H NMR ($CDCl_3$, Me_4Si) δ (ppm): 0.85–0.96 (t, $J = 3.0$ Hz, 3H), 1.38–1.49 (m, 2H), 1.80–1.86 (m, 2H), 3.1 (t, $J = 8.0$ Hz, 2H), 4.22 (s, 3H), 6.65 (d, $J = 3.7$ Hz, 1H); 7.01 (d, $J = 3.7$ Hz, Hz, 1H), 7.42–7.55 (m, 2H), 8.13 (d, $J = 8.2$ Hz, 1H), 8.30 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ (ppm): 14.26, 23.27, 32.05, 36.63, 38.21, 101.98, 118.48, 120.38, 121.46, 125.00, 126.32, 129.40, 134.19, 158.76; ESI-MS m/z 239.0 $[M+H]^+$. HRMS calcd. for $C_{16}H_{19}N_2$ 239.1545; found 239.1548.

4-Benzyl-1-methyl-1*H*-pyrrolo[3,2-c]quinoline (**6**)

Purification of the crude by column chromatography [cyclohexane/Et_2O: linear gradient 100/0–60/40 v/v) afforded 15 mg (60% yield) of compound **6**. Mp 68–70°C; ^{1}H NMR ($CDCl_3$, Me_4Si) δ (ppm): 4.17 (s, 3H), 4.5 (s, 2H), 6.52 (d, $J = 3.0$ Hz, 1H), 7.01 (d, $J = 3.0$ Hz, 1H), 7.06–7.11 (m, 3H), 7.15–7.19 (m, 2H), 7.45–7.58 (m, 2H), 8.22 (d, $J = 7.9$ Hz, 1H), 8.30 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ (ppm): 42.72, 53.42, 102.38, 118.31, 120.22, 121.24, 125.42, 126.28, 126.51, 128.17, 128.43, 128.93, 129.34, 129.75, 129.95, 134.52, 139.05, 155.86, ESI-MS m/z 273.2 $[M+H]^+$. HRMS calcd. for $C_{19}H_{17}N_2$ 273.1393; found 273.1392.

1-Methyl-4-phenyl-1*H*-pyrrolo[3,2-c]quinoline (**8**)

Hot crystallization from CH_2Cl_2 afforded 22.3 mg (94% yield) of compound **8**. Mp 124–126°C; ^{1}H NMR ($CDCl_3$, Me_4Si) δ (ppm): 4.25 (s, 3H), 6.78 (d, $J = 3.1$ Hz, 1H), 7.23 (d, $J = 3.1$ Hz, 1H), 7.40–7.61 (m, 5H), 7.97 (d, $J = 2.9$ Hz, 2H), 8.34 (d, $J = 2.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ (ppm): 38.2, 102.4, 118.3, 120.2, 120.4, 125.3, 126.3, 128.8, 129.1, 129.7, 130.7, 134.9, 140,7, 144.7, 154.7; ESI-MS m/z 259.19 $[M+H]^+$. HRMS calcd. for $C_{18}H_{15}N_2$ 259.1235; found 259.1238.

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