Lateral functionalization of phosphonate quinolines

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Abstract: An efficient metalation-functionalization of diethylmethylphosphonate quinolines, at low-temperature, with suitable electrophiles in the presence of *n*-BuLi in THF, is described herein. It constitutes a general method for the synthesis of halogenophosphonoquinolines and vinylquinolines.

Keywords: methylphosphonate, quinoline, halogenophosphonoquinoline, vinylquinoline.

Résumé: L'application de la réaction de métallation-fonctionnalisation aux diéthyl méthylphosphonate quinolines en milieu *n*-BuLi/THF, à basse température et en présence d'électrophiles appropriés, est une méthode d'accès efficace et générale aux halogénophosphonoquinolines et aux vinylquinolines.

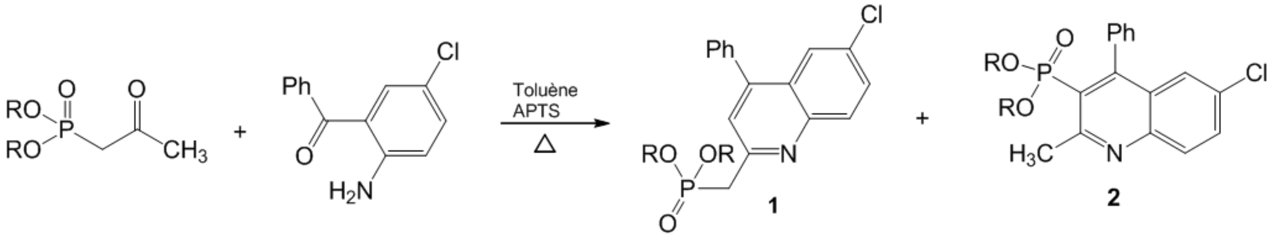
Mots clés: méthylphosphonate, quinoline, halogénoquinoline, vinylquinoline.

INTRODUCTION

Nitrogen containing organic compounds represent an important area of organic chemistry because of their biological significance [1]. In this context, numerous strategies for the preparation of nitrogenous compounds were mentioned in literature, in particular heterocyclic compounds [2]. Among various methods described, some of them were explored in our laboratory, such as hydrazones [3], phosphonoacetonitriles [4], imidates [5], thioamides [6] and phosphonohydrazines [7].

The elaborations described in this paper are realized in the continuity of those which we have already begun that are related to the synthesis of phosphonates quinolines[8]. Numerous examples of phosphonate-containing quinolines derivatives exhibit biological properties [9] as well as treatment of malaria or certain tumors[10].

On the basis of these elaborations, we aim to describe an efficient synthesis of variously halogenoquinolines and vinylquinolines using a lithiation-condensation reaction between func-



1a: R = CH_3; **1b**: R = CH_3-CH_2 ; **2a**: R = CH_3; **2b**: CH_3-CH_2

Scheme 1: Synthesis of quinolines **1** and **2**.

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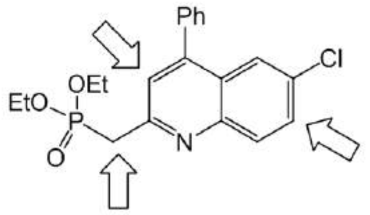


1b

Figure 1

tionalised quinolines and various electrophiles. Lithiations of the side chain establishes a very powerful synthetic tool in organic chemistry allowing the functionalization of the heterocycles and they intervene as key step in total syntheses of numerous natural products and physiologically active agents [11-17].

RESULTS AND DISCUSSION

The condensation of β-ketophosphonates on 2-amino-5-chlorobenzophenone, after refluxing with toluene in the presence of catalytic amount of PTSA, has afforded the phosphonates quinolines isomers **1** and **2** [8] (Scheme 1).

Among these quinolines, the diethyl(6-chloro-4 -phnylquinolin-2-yl)methylphosphonate **1b** has the particularity to present various sites susceptible to orient the metalation-reaction (formation of complexes with the nitrogen atom, cooperative effect of the oxygen, ortho-director effect of chlorine, …) (Fig. 1).

Among these three positions, the one that is positioned in α–position of the phosphonate group is enhanced by using *n*-BuLi. Consequently, we envisioned to check the metalation-condensation reaction of compound **1b** by using different electrophiles for the purpose of obtaining corresponded functionalized quinolines.

Lithiation was realized within THF by the action of *n*-BuLi (2M) on quinoline **1b**. The *in-situ* prepared carbanion is reacted subsequently with various electrophiles such as tetrabromomethane, hexachloroethane, iodine and deuterium chloride leads to quinolines **3a-d** after hydrolysis (Scheme 2).

We note in particular that a difference in reactivity of the electrophiles employed was observed under the same deprotonation-metalation conditions. We have therefore established the optimized conditions to each electrophile for the purpose of achieve the finest conversion rates of compound **1b**.

In table I, the optimal conditions for the synthesis of products **3a-d** are presented.

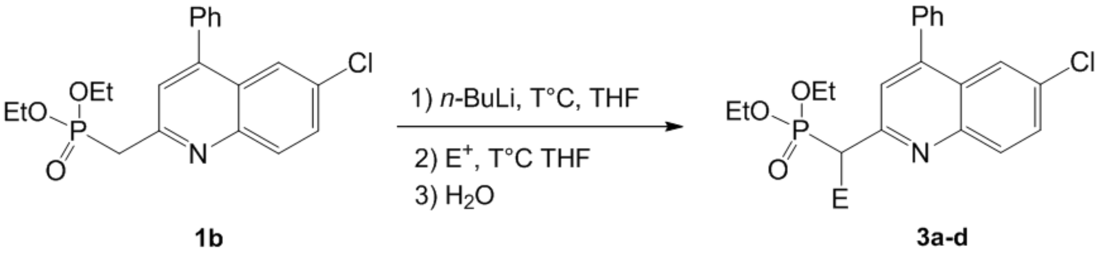
In ^{1}H NMR formation of quinolines **3a-d** is confirmed through disappearance of relative doublet of protons CH_2 in α of P=O (δ = 3.61 ppm, $^2J_{PH}$ = 21.0 Hz) and appearance of relative doublet of CH-P around 5ppm, with a coupling constant $^2J_{PH}$ around 12 Hz.

We have also used this protocol to the metallation-fonctionnalisation of quinoline **1b** in the presence of numerous aldehydes. This Wittig-Horner reaction [18-20] leads after cleavage of the phosphonate moieties to vinylquinolines **4a-d** (Scheme 3).

The reaction started with a deprotonation of carbone in α position of the phosphonate group by using *n*-BuLi to give carbanion which reacts with the aldehyde. Oxaphosphetane intermediate is formed then rearranged to provide corresponding alkene (Scheme 4).

In table II, the vinylquinolines **4a-d** synthesized, as well as yields and reaction time are presented.

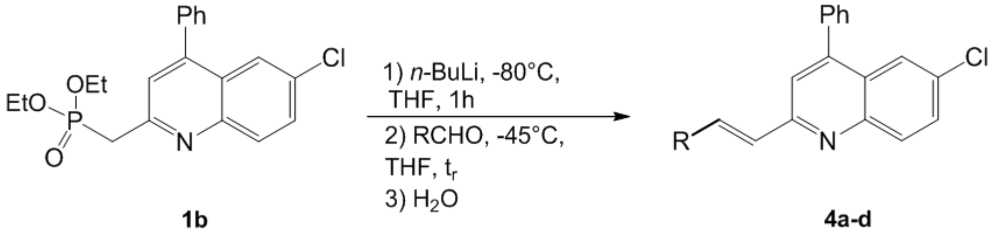
We note in Particular that quinolines **4a-d** is exclusively formed with a unique configuration. In this case, coupling constants $^3J_{H-H}$ (12 Hz) permitted the unambiguous assignment of the *E* stereochemistry to alkene **4d**. As mentioned in literature, Wittig-Horner reaction is often



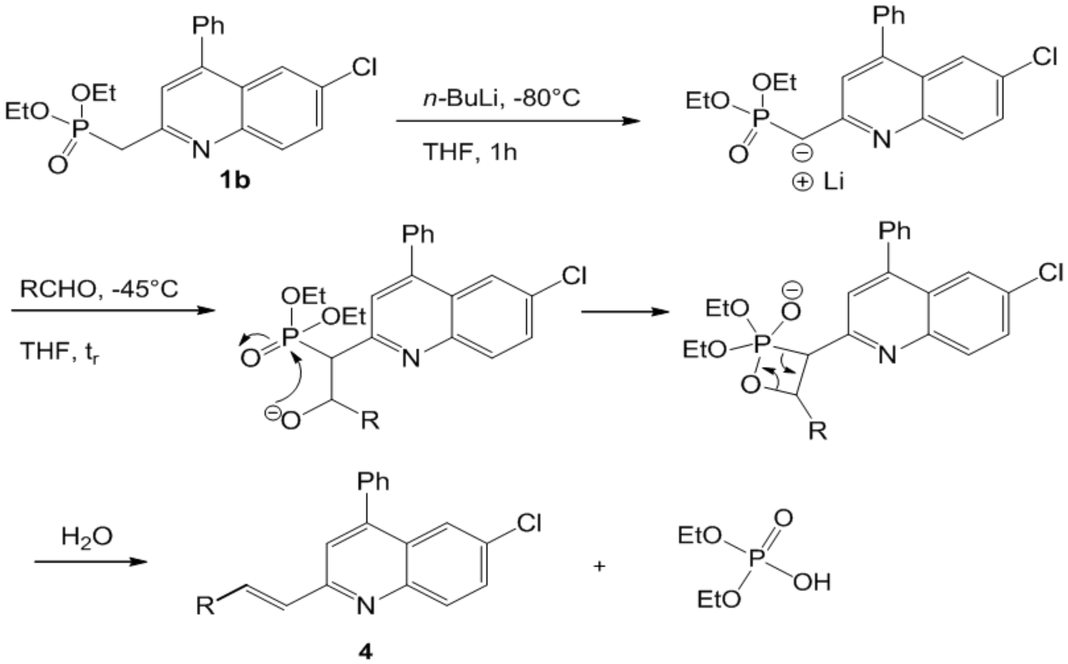
Scheme 2: Quinolines **3** Synthesis.

Table I: Synthesis conditions of quinolines **3a-d.**

Compound	**3a**	**3b**	**3c**	**3d**
n-BuLi (equiv)	1	1	3	1,2
Metalation Temperature (°C)	-80	-80	-45	-80
Metallation duration(h)	2	2	1	2
Electrophile (E^+)	CBr_4	I_2	C_2Cl_6	DCl/D_2O
Electrophile (equiv)	1	1	3	20
TrappingTemperature of E^+ (°C)	-80	-80	-45	-45
Trapping Duration (h)	1	1	2	2
Conversion rate(%)	94	76	71	100
yields (%)	67	61	55	89

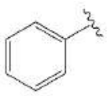
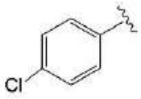
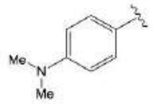
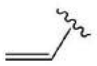


Scheme 3: Vinylquinolines **4a-d** synthesis



Scheme 4: Proposed mechanism for the formation of vinylquinolines **4a-d.**

Table II: Vinylquinolines **4a-d** synthesis

Compound 4	**4a**	**4b**	**4c**	**4d**
R				
yields (%)	91	90	86	87
Reaction times (min)	30	60	60	60

characterized by selectivity and leads majority or exclusively to alkene with *E* configuration [21-22].

In view of these findings, we concluded that all synthesized vinylquinolines **4** have also *E* configuration.

CONCLUSION

We described in this paper the metallation-fonctionnalisation reaction of diethylmethylphosphonate quinoline **1b** which allowed the formation of halogenophosphonoquinolines. We have also showed that the application of the Wittig-Horner reaction to phosphonate quinoline **1b** is an efficient method for the synthesis of vinylqinolines.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Brüker AC 300 spectrometer, with $CDCl_3$ as solvent and TMS (for ^{1}H NMR) or H_3PO_4 (for ^{31}P) as internal standards. Coupling constants are expressed in Hz. Chemical shifts are expressed in ppm. The following abbreviations are used: s (singlet), t (triplet), q (quadruplet), m (multiplet) and qp (quintuplet).

Melting points are expressed in Celsius degrees and calculated with Büchi apparatus.

HRMS spectra were recorded on a Brüker microTOF-Q spectrometer.

1. Procedure for the preparation of diethylmethyl phosphonatequinoline 1b

A solution of 0.03 mol of β-ketophosphonate, 0.03 mol of 2-amino-5-chlorobenzophenone, 100 mL of toluene and 0.0006 mole of paratoluene sulfonic acid was refluxed during 36 h using Dean Stark apparatus. After cooling, solvent was evaporated and the crude product was purified by column chromatography on silica gel 60 (eluent: 88/12 ether/ethanol).

1b: Diethyl(6-chloro-4-phenylquinolin-2-yl) methylphosphonate

Mp°C = 95; Yields = 23%; ^{1}H NMR: δ = 1.28 (t, 6H, $^3J_{HH}$ = 6.0 Hz, $2\underline{CH_3}$-CH_2-O-P); 3.61 (d, 2H, $^2J_{PH}$ = 21.0 Hz, P-$\underline{CH_2}$-C=N-); 4.15 (qp, 4H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, $2CH_3$-$\underline{CH_2}$-O-P); 7.47-7.86 (m, 9H, H_{arom}); ^{31}P NMR: δ =24.7ppm; ^{13}C NMR: (J_{CP} in Hz) δ = 16.3 ($^3J_{CP}$ = 6.2 Hz, CH_3); 37.5 (J_{CP} = 133.5 Hz, -CH_2-P); 62.3 ($^2J_{CP}$ = 6.7 Hz, -$\underline{CH_2}$-CH_3); 123.1-148.0 (C_{arom}); 153.3 ($^2J_{CP}$ = 7.5 Hz, C=N).

2. Procedure for the preparation of deuterio- and halogenoquinolines 3

To a solution of diethyl (6-chloro-4-phenylquinolin-2-yl) methylphosphonate **1b** (0.5 mmol) in anhydrous THF (10 mL) was added dropwise *n*-BuLi ($N_{equivB-}$) at temperature T_1 and under nitrogen atmosphere. After 2 h of stirring at temperature T_1, $N_{equivE+}$ of electrophile in anhydrous THF (5 mL) was added dropwise at temperature T_2. After t_r of stirring at temperature T_2, the hydrolysis was performed with H_2O (15 mL). The aqueous layer was then extracted twice with ethyl acetate (2 x 20 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on silica gel 60 (eluent: ethyl acetate).

3a : Bromo-diethyl(6-chloro-4-phenylquinolin-2-yl)methylphosphonate

Viscous oil; ^{1}H NMR: δ = 1.12 (t, 3H, $^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}$-CH_2-O-P); 1.26 (t, 3H, $^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}$-CH_2-O-P); 4.05 (q, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3-$\underline{CH_2}$-O-P); 4.20 (q, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3-$\underline{CH_2}$-O-P); 5.17 (d, 1H, $^2J_{PH}$ = 12.0 Hz, P-$\underline{CH}$-Br); 7.43-8.00 (m, 9H, H_{arom}); ^{31}P NMR: δ = 15.3ppm; ^{13}C NMR: (J_{CP} in Hz) δ = 15.4 (CH_3);

43.5 (J_{CP} = 149.3 Hz, -CH-Br); 63.4 ($^2J_{CP}$ = 3.5 Hz, -$\underline{CH_2}$-CH_3); 121.5-147.9 (C_{arom}); 153.5 (C=N); HRMS calcd for $C_{20}H_{20}BrClNNaO_3P$ $(M+Na)^+$: 491.9924; found: 491.9931.

3b : Iodo-diethyl(6-chloro-4-phenylquinolin-2-yl) methylphosphonate

Viscous oil; ^{1}H NMR: δ = 1.13 (t, 3H, $^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}$-CH_2-O-P); 1.24 (t, 3H, $^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}$-CH_2-O-P); 4.11 (q, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3-$\underline{CH_2}$-O-P); 4.27 (q, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3-$\underline{CH_2}$-O-P); 5.24 (d, 1H, $^2J_{PH}$ = 12.0 Hz, P-$\underline{CH}$-I); 7.69-8.12 (m, 9H, H_{arom}); ^{31}P NMR: δ = 19.1ppm ^{13}C NMR: (J_{CP} in Hz) δ =16.2 (CH_3); 32.2 (J_{CP} = 93.8 Hz, -CH-I); 63.0 ($^2J_{CP}$ = 3.6 Hz, -$\underline{CH_2}$-CH_3); 121.4-143.5 (C_{arom}); 158.1 (C=N).

3c : Chloro-diethyl(6-chloro-4-phenylquinolin-2-yl)methylphosphonate

Viscous oil; ^{1}H NMR: δ = 1.09 (t, 3H, $^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}$-CH_2-O-P); 1.21 (t, 3H, $^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}$-CH_2-O-P); 3.95 (q, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3-$\underline{CH_2}$-O-P); 4.16 (q, 2H, $^3J_{HH}$ = $^3J_{PH}$ = 6.0 Hz, CH_3-$\underline{CH_2}$-O-P); 5.09 (d, 1H, $^2J_{PH}$ = 12.0 Hz, P-$\underline{CH}$-Cl); 7.59-8.04 (m, 9H, H_{arom}); ^{31}P NMR: δ = 14.7ppm; ^{13}C NMR: (J_{CP} in Hz) δ = 16.3 (CH_3); 47.2 (J_{CP} = 100.7 Hz, -CH-Cl); 62.9 ($^2J_{CP}$ = 4.3 Hz, -$\underline{CH_2}$-CH_3); 120.6-149.0 (C_{arom}); 156.1 (C=N).

3d : Deuterio-diethyl (6-chloro-4-phenylquinolein-2-yl) methylphosphonate

Mp°C = 117-119; ^{1}H NMR: δ =0.84 (t, 6H, $^3J_{HH}$= 6.0 Hz, 2$\underline{CH_3}$-CH_2-O-P); 3.30 (qp, 4H, $^3J_{HH}$= $^3J_{PH}$ = 6.0 Hz, 2CH_3-$\underline{CH_2}$-O-P); 4.00 (m, 1H, P-$\underline{CH}$-D); 7.07-7.70 (m, 9H, H_{arom}); ^{31}P NMR: δ = 23.6ppm; ^{13}C NMR: (J_{CP} in Hz) δ =17.4 (CH_3); 57.3 (J_{CP} = 67.3 Hz, -CH-D); 62.5 ($^2J_{CP}$ = 6.8 Hz, -$\underline{CH_2}$-CH_3); 123.0-148.5 (C_{arom}); 152.7 ($^2J_{CP}$ = 8.3 Hz; C=N).

3. Procedure for the preparation of vinylquinolines 4

To a solution of diethyl (6-chloro-4-phenylquinolin-2-yl) methylphosphonate **1b** (0.5 mmol) in anhydrous THF (10 mL) was added dropwise *n*-BuLi 2M (0.6 mmol, 1.2 equiv) at -80° C and under nitrogen atmosphere. After 1 h of stirring, electrophile (0.5 mmol, 1 équiv.) was added dropwise in anhydrous THF (5 mL) at -45° C. After t_r of stirring, the hydrolysis was performed with H_2O (15 mL). The aqueous layer was then extracted twice with ethyl acetate (2 x 20 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on silica gel 60 (eluent: 7/3 ether/petroleum ether).

4a : 6-Chloro-4-phenyl-2-styrylquinoline

Yellow oil; ^{1}H NMR: δ = 6.90-8.00 (m, 16H, H_{arom} -$H_{ethylenic}$); ^{13}C NMR: δ = 120.3-148.0 (C_{arom} -$C_{ethylenic}$); 158.6 (C=N).

4b : 6-Chloro-2-(4-chlorostyryl)-4-phenylquinoline

Yellow oil; ^{1}H NMR: 6.80-7.99 (m, 15H, H_{arom} -$H_{ethylenic}$); ^{13}C NMR: δ = 118.7-147.1 (C_{arom} -$C_{ethylenic}$); 154.2 (C=N).

4c : 4-(2-(6-Chloro-4-phenylquinolin-2-yl)vinyl)-N-N-dimethylaniline

Yellow oil; ^{1}H NMR: δ = 2.98 (s, 6H, -$\underline{CH_3}$-N); 6.71-7.95 (m, 15H, H_{arom} -$H_{ethylenic}$) ^{13}C NMR: δ = 39.8 (-N-CH_3); 118.5-149.2 (C_{arom} -$C_{ethylenic}$); 161.1 (C=N).

4d : 2-(Buta-1,3-dienyl)-6-chloro-4-phenylquinoline

Yellow oil; ^{1}H NMR: δ = 5.25 (d, 1H, J_{HH}= 12.0 Hz, CH_2=$\underline{CH}$-); 5.41 (d, 1H, J_{HH}= 12.0 Hz, CH_2=$\underline{CH}$-); 6.47-7.96 (m, 12H, H_{arom} -$H_{ethylenic}$); ^{13}C NMR: δ = 119.2-146.8 (C_{arom} -$C_{ethylenic}$); 154.5 (C=N).

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