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 halogénoquinolines 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-

\[ \text{Scheme 1: Synthesis of quinolines 1 and 2.} \]

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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-phenylquinolin-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 1H NMR formation of quinolines 3a-d is confirmed through disappearance of relative doublet of protons CH2 in α of P=O (δ = 3.61 ppm, 2JPH = 21.0 Hz) and appearance of relative doublet of CH-P around 5 ppm, with a coupling constant 3JPH 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 carbene 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 3JH-H (12 Hz) permitted the unambiguous assignment of the E stereochemistry to alkene 4d. As mentioned in literature, Wittig-Horner reaction is often
Table 1: Synthesis conditions of quinolines 3a-d.

<table>
<thead>
<tr>
<th>Compound</th>
<th>3a</th>
<th>3b</th>
<th>3c</th>
<th>3d</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-BuLi (equiv)</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1,2</td>
</tr>
<tr>
<td>Metalation Temperature (°C)</td>
<td>-80</td>
<td>-80</td>
<td>-45</td>
<td>-80</td>
</tr>
<tr>
<td>Metalation duration (h)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Electrophile (E⁺)</td>
<td>CBr₄</td>
<td>I₂</td>
<td>C₂Cl₆</td>
<td>DCl/D₂O</td>
</tr>
<tr>
<td>Electrophile (equiv)</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Trapping Temperature of E⁺ (°C)</td>
<td>-80</td>
<td>-80</td>
<td>-45</td>
<td>-45</td>
</tr>
<tr>
<td>Trapping Duration (h)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Conversion rate (%)</td>
<td>94</td>
<td>76</td>
<td>71</td>
<td>100</td>
</tr>
<tr>
<td>yields (%)</td>
<td>67</td>
<td>61</td>
<td>55</td>
<td>89</td>
</tr>
</tbody>
</table>

Scheme 3: Vinylquinolines 4a-d synthesis

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

### EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker AC 300 spectrometer, with CDCl₃ as solvent and TMS (for ¹H NMR) or H₂PO₄ (for ³¹P) 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 Bruker microTOF-Q spectrometer.

#### 1. Procedure for the preparation of diethylmethyl phosphonatequinoine 1b

A solution of 0.03 mol of β-ketophosphate, 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).

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

<table>
<thead>
<tr>
<th>Compound 4</th>
<th>4a</th>
<th>4b</th>
<th>4c</th>
<th>4d</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td><img src="Image" alt="Structure" /></td>
<td><img src="Image" alt="Structure" /></td>
<td><img src="Image" alt="Structure" /></td>
<td><img src="Image" alt="Structure" /></td>
</tr>
<tr>
<td>yields (%)</td>
<td>91</td>
<td>90</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>Reaction times (min)</td>
<td>30</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

1b: Diethyl(6-chloro-4-phenylquinolin-2-yl)methylphosphonate
Mp°C = 95; Yields = 23%; ¹H NMR: δ = 1.28 (t, 6H, ³J_HH = 6.0 Hz, 2CH₃-CH₂-O-P); 3.61 (d, 2H, ²J_PH = 21.0 Hz, P-CH₂-C=N-); 4.15 (q, 4H, ³J_HH = 3.0 Hz, ²J_PH = 6.0 Hz, 2CH₃-CH₂-O-P); 7.42-7.86 (m, 9H, H_arom); ³¹P NMR: δ = 24.7 ppm; ¹³C NMR: (JC_P in Hz) δ = 16.3 (JC_P = 6.2 Hz, CH₃); 37.5 (JC_P = 133.5 Hz, -CH₂-P); 62.3 (JC_P = 6.7 Hz, -CH₂-CH₃); 123.1-148.0 (C_arom); 153.3 (JC_P = 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_equiv- ) at temperature T₁ and under nitrogen atmosphere. After 2 h of stirring at temperature T₂, the hydrolysis was performed with H₂O (15 mL). The aqueous layer was then extracted twice with ethyl acetate (2 x 20 mL). After drying (MgSO₄), 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; ¹H NMR: δ = 1.12 (t, 3H, ³J_HH = 6.0 Hz, CH₃-CH₂-O-P); 1.26 (t, 3H, ³J_HH = 6.0 Hz, CH₃-CH₂-O-P); 4.05 (q, 2H, ²J_PH = 3.0 Hz, CH₃-CH₂-O-P); 4.20 (q, 2H, ²J_PH = 6.0 Hz, CH₃-CH₂-O-P); 5.17 (d, 1H, ²J_PH = 12.0 Hz, P-CH₂-Br); 7.43-8.00 (m, 9H, H_arom); ³¹P NMR: δ = 15.3 ppm; ¹³C NMR: (JC_P in Hz) δ = 15.4 (CH₃);
with H₂O (15 mL). The aqueous layer was then filtered and solvent evaporation, the crude product was purified by column chromatography on silica gel 60 (eluents: 7/3 ether/petroleum ether).

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 equiv.) was added dropwise in anhydrous THF (5 mL) at -45°C. After t₀ of stirring, the hydrolysis was performed with H₂O (15 mL). The aqueous layer was then extracted twice with ethyl acetate (2 × 20 mL). After drying (MgSO₄), filtration and solvent evaporation, the crude product was purified by column chromatography on silica gel 60 (eluents: 7/3 ether/petroleum ether).

REFERENCES
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