Tetrahedron Letters 70 (2021) 153019

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Design, synthesis and cytotoxic evaluation of diphenyl(quinolin-8-yl) phosphine oxides

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ARTICLE INFO

Article history:
Received 26 January 2021
Revised 11 March 2021
Accepted 17 March 2021
Available online 23 March 2021

Keywords:
Povarov reaction
Aromatization
Quinolinylphosphine oxides
Antiproliferative effect

ABSTRACT

A new strategy is reported for the synthesis of quinolinylphosphine oxides *via* the Povarov reaction between phosphorous aldimines and acetylenes. Moreover, these compounds were studied for *in vitro* cytotoxicity on a human lung alveolus adenocarcinoma (A 549) cell line, demonstrating strong inhibition of cell growth.

Introduction

Cancer continues to be one of the leading causes of morbidity and mortality in the world [1]. Cancer is defined as a broad group of diseases which are characterized by the rapid multiplication of abnormal cells that extend beyond their usual boundaries and can invade adjacent parts of the body or spread to other organs, a process known as metastasis. One of the most lethal types of cancer is lung cancer [2].

Quinolines are important substrates widely used in biochemistry, the pharmaceutical industry and in the design of new materials [3]. In this regard, the Povarov reaction [4] represents an effective strategy for the synthesis of 6-membered nitrogen rings, many of which possess interesting biological properties [5,6]. Initially, the Povarov reaction described the involvement of aldimines in [4 + 2] cycloaddition reactions with electron-rich olefins in the presence of a Lewis acid catalyst, and subsequent tautomerization of the initial adduct into 1,2,3,4-tetrahydroquinoline derivatives (Scheme 1). Previously, our group reported a combined theoretical and experimental study of a Povarov type cycloaddition reaction, suggesting that the corresponding *endo*-adducts are obtained through an asynchronous concerted process, [7] favored by Lewis acid activation with $BF_3{\cdot}Et_2O$. Since then, we have prepared a number of heterocyclic compounds, with antiproliferative [8,9] and antileishmaniasic [10,11] activities using this methodology.

More recently, our research group developed this synthetic route with olefins for the first synthesis of a wide range of phosphino- and phosphine sulfide-1,2,3,4-tetrahydroquinolines and, after subsequent selective oxidation, the corresponding quinolines [12]. Moreover, these phosphorated compounds displayed interesting biological properties [13,14].

Herein, we report the direct synthesis of aromatic diphenyl (quinolin-8-yl)phosphine oxide derivatives *via* the Povarov reaction using acetylenes. Moreover, the *in vitro* cytotoxicity of these compounds on a human lung alveolus adenocarcinoma (A 549) cell line has been studied.

Results and discussion

The synthesis of quinolines **6** was carried out using a modification of the Povarov reaction, between phosphorous aldimines **3**, obtained by condensation between aniline **1** and aromatic aldehydes **2**, [13] and acetylenes **4** (Scheme 2). If acetylenic compounds are used as dienophiles in the Povarov reaction instead of olefins, diphenyl(quinolin-8-yl)phosphine oxides are directly obtained. The multicomponent approach between aniline **1**, [13] aromatic aldehydes **2** and acetylenes **4** cannot be considered, because of side-product formation due to coupling reactions between the acetylenes and aldehydes as indicated in previous work [15].

Firstly, the preparation of imines **3** was carried out *via* condensation of aniline **1** [13] with the corresponding aldehydes **2**, at reflux in the presence of molecular sieves (MS 4 Å) under an inert atmosphere (Scheme 2). The formation of imines **3** could be

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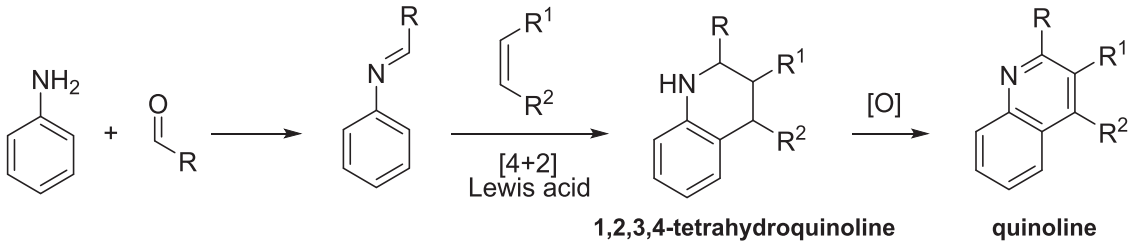
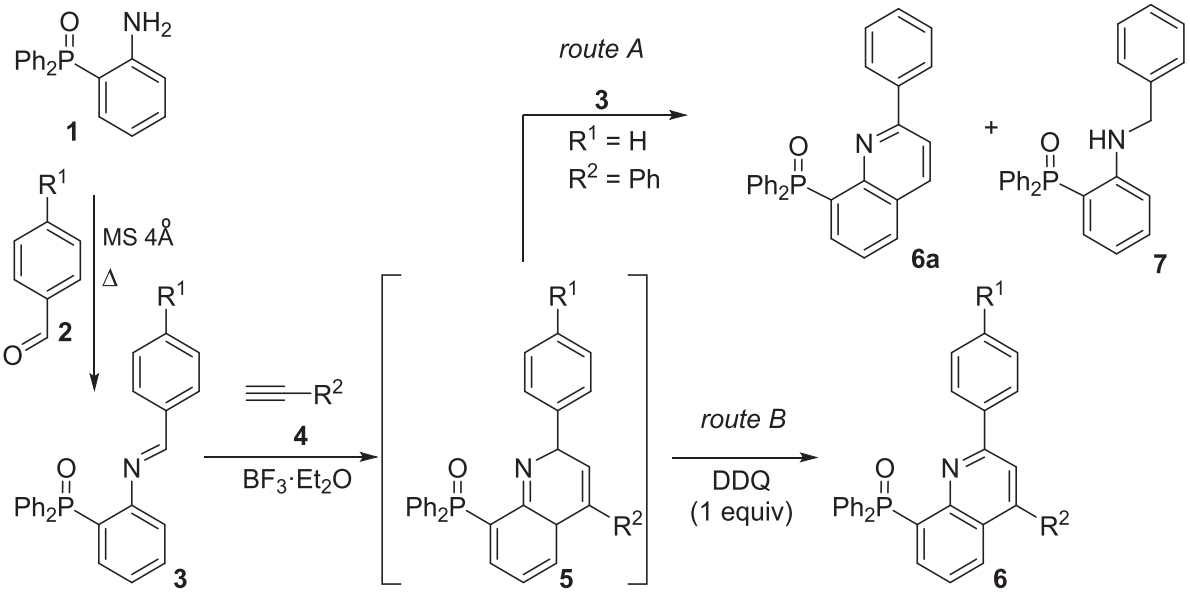
https://doi.org/10.1016/j.tetlet.2021.153019



Scheme 1. General scheme for the Povarov reaction.



Scheme 2. Synthesis of diphenyl(quinolin-8-yl)phosphine oxides **6** and amine **7**.

detected by NMR spectroscopy; however, in order to avoid hydrolysis, they were not purified and therefore used *in situ* for subsequent reactions.

Then, diphenyl(quinolin-8-yl)phosphine oxides **6** were prepared by the Povarov reaction between imines **3** and dienophiles **4**, in the presence of $BF_3{\cdot}Et_2O$ as the Lewis acid. In order to optimize the reaction conditions, the Povarov reaction between imine **3a** derived from benzaldehyde (R^1 = Ph) and phenylacetylene **4a** (R^2 = Ph) as the dienophile was studied (Scheme 2, route A).

Spectroscopic analysis of the crude reaction mixture showed the equimolecular formation of two compounds, quinoline **6a** and amine **7** (Scheme 2, route A, Table 1, entry 1) as determined

Table 1
Diphenyl(quinolin-8-yl)phosphine oxides **6** obtained by the Povarov reaction of aldimines **3** and acetylenes **4**, and subsequent treatment with 1 equiv. of DDQ.

Entry	Compound			Reaction conditions		Yield (%)[a]
		R^1	R^2	Solvent	T (°C)	
1	**6a**	H	Ph	toluene	111	30[b]
2	**6a**	H	Ph	$CHCl_3$	60	66
3	**6b**	F	Ph	$CHCl_3$	60	50
4	**6c**	CF_3	Ph	$CHCl_3$	60	68
5	**6d**	OCH_3	Ph	$CHCl_3$	60	58
6	**6e**	H	C_6H_4-4-OCH_3	$CHCl_3$	60	72
7	**6f**	CF_3	C_6H_4-4-OCH_3	$CHCl_3$	60	54
8	**6g**	H	$C_{10}H_6$-6-OCH_3	$CHCl_3$	60	85
9	**6h**	CF_3	$C_{10}H_6$-6-OCH_3	$CHCl_3$	60	73
10	**6i**	H	C_6H_4-4-F	$CHCl_3$	60	56
11	**6j**	F	C_6H_4-4-F	$CHCl_3$	60	68
12	**6k**	OCH_3	C_6H_4-4-F	$CHCl_3$	60	59
13	**6l**	H	C_6H_4-4-Me	$CHCl_3$	60	82
14	**6m**	F	C_6H_4-4-Me	$CHCl_3$	60	71

[a] Isolated yields of compound **6** from amine **1**.
[b] Without the addition of DDQ, a stoichiometric mixture of compounds **6** and **7** was obtained.

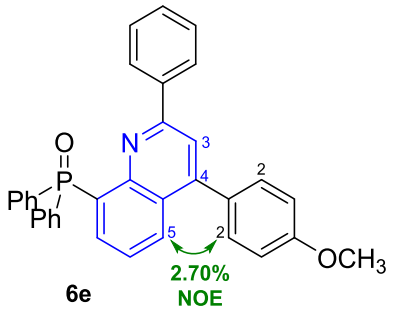


Fig. 1. NOESY-1D experiment for compound **6e**.

by ^{31}P NMR spectroscopy. The formation of quinoline **6** may be explained by a regioselective [4 + 2] cycloaddition between aldimine **3** and acetylenic compound **4** to give cycloadduct **5**, which subsequently undergoes oxidation to quinoline **6**, with the reduction of one equivalent of imine **3** to amine **7** (Scheme 2). To avoid the formation of by-product **7**, we postulated that the addition of an oxidant such as DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) would prevent imine **3** from acting as the hydrogen acceptor of dihydroquinoline **5**.

The desired diphenyl(quinolin-8-yl)phosphine oxides **6** were exclusively obtained in a regioselective manner *via* the reaction between imines **3** and acetylenes **4** in the presence of $BF_3{\cdot}Et_2O$ at reflux for 2 h, and subsequent oxidation in the presence of DDQ at reflux for 30 min (Scheme 2, route B, Table 1) [16]. The structures of compounds **6** were assigned by 1D and 2D NMR spectroscopy. The regiochemistry of the obtained compounds was supported by NOESY-1D experiments (Fig. 1, ESI). Difference experiments (NOE), between H-5 of the quinoline ring and H-2 of the *p*-methoxyphenyl substituent (2.7%) when H-5 was irradiated, are consistent with the formation of regioisomer **6** with the methoxyphenyl substituent at the 4 position of the quinoline ring instead of the formation of the other regioisomer with the substituent at position 3 of the quinoline ring.

The scope of the reaction was extended to the formation of diphenyl(quinolin-8-yl)phosphine oxides **6** containing electron-donating and electron-withdrawing groups, including fluorine and trifluoromethyl substituents on the aromatic ring. It should be noted that several recently approved drugs contain fluorine in their structure [17].

Table 2
Cytotoxic values of diphenyl(quinolin-8-yl)phosphine oxides **6** against the A 549 cell line.

Entry	Compound	R^1	R^2	IC_{50} (μM)[a]
1	chlorambucil			72.78 ± 2.30
2	cisplatin			28.1
3	**6a**	H	Ph	1.21 ± 0.68[b]
4	**6b**	F	Ph	2.26 ± 0.21[b]
5	**6c**	CF_3	Ph	1.03 ± 0.16[b]
6	**6d**	OCH_3	Ph	nd
7	**6e**	H	C_6H_4-4-OCH_3	1.59 ± 0.39
8	**6f**	CF_3	C_6H_4-4-OCH_3	1.93 ± 0.30
9	**6g**	H	$C_{10}H_6$-6-OCH_3	1.37 ± 0.52
10	**6h**	CF_3	$C_{10}H_6$-6-OCH_3	2.02 ± 0.14
11	**6i**	H	C_6H_4-4-F	2.59 ± 0.77
12	**6j**	F	C_6H_4-4-F	3.82 ± 0.42[b]
13	**6k**	OCH_3	C_6H_4-4-F	nd
14	**6l**	H	C_6H_4-4-Me	0.11 ± 0.01[b]
15	**6m**	F	C_6H_4-4-Me	2.64 ± 0.43

[a] Concentration corresponding to 50% growth inhibition.[b] IC_{50} previously reported.[13] nd: Not determined.

The antiproliferative activity of quinolines **6** was evaluated *in vitro* using alveolar adenocarcinoma cells (A 549), by means of a colorimetric assay with CCK −8 (Cell Counting Kit-8).

As shown in Table 2, quinolines **6** show antiproliferative activity in the culture of lung alveolar adenocarcinoma cells (A549). The antiproliferative activity of these compounds against A549 cells is much higher than the reference anticancer agents chlorambucil [18] (Table 2, entry 1) or cisplatin [19] (Table 2, entry 2).

In summary, the one-pot synthesis of diphenyl(quinolin-8-yl) phosphine oxide derivatives containing a phosphine oxide substituent can be achieved *via* the Povarov reaction of phosphorated anilines, aldehydes, and acetylenes. The [4 + 2]-cycloaddition reaction of imines **3** with acetylenes **4** represents an excellent synthetic strategy for the preparation of phosphorated quinolines with regioselective control. Initially, an equimolecular mixture of quinoline **6** and (2-(benzylamino)phenyl)diphenylphosphine oxide by-product **7** was obtained. However, the use of DDQ as an oxidant proved to be essential to avoid formation of by-product **7**. This approach therefore offers a new strategy for the straightforward preparation of hybrid phosphorated quinolines, which have potential as antiproliferative agents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Financial support from the *Ministerio de Ciencia, Innovación y Universidades (MCIU), Agencia Estatal de Investigación (AEI) y Fondo Europeo de Desarrollo Regional (FEDER; RTI2018-101818-B-I00, UE)* and by *Gobierno Vasco, Universidad del País Vasco (GV, IT 992-16; UPV)* is gratefully acknowledged. Technical support provided by *IZO-SGI, SGIker (UPV/EHU, MICINN, GV/EJ, ERDF and ESF)* is gratefully acknowledged. AS thanks the Basque Government for a formation contract.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153019.

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[16] To a solution of (2-aminophenyl)diphenylphosphine oxide (2 mmol, 0.587 g) in CHCl3 (10 mL) with molecular sieves (4Å) was added the corresponding aldehyde (2 mmol). The mixture was stirred under nitrogen at reflux for 12 h to give the corresponding aldimine 3. Then to this solution were added the corresponding acetylene 4 (2 mmol) and BF3·Et2O (2.4 mmol, 0.3 mL), and the mixture was stirred at reflux for 2 h. Then DDQ was added (2 mmol, 0.454 g) and the reaction was stirred at reflux for 30 minutes. The reaction mixture was washed with a 2 M aqueous solution of NaOH (25 mL) and water (25 mL), extracted with dichloromethane (2 × 25 mL), and dried over anhydrous MgSO4. Removal of the solvent under vacuum afforded an oil that was purified by silica gel flash column chromatography using a gradient elution of 10−40% ethyl acetate in hexane to afford products 6.
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