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Synthesis of 1,2-dihydro-2-oxo-4-quinolinyl phosphates from 2-acyl-benzoic acids

Xinhua He [a,†], Tharcilla Aglio [a], Jeffrey R. Deschamps [b], Rachita Rai [a], Fengtian Xue [a,*]

[a] Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 Penn Street, Baltimore, MD 21201, United States
[b] Naval Research Laboratory, Code 6930, 4555 Overlook Ave., Washington, DC 20375, United States

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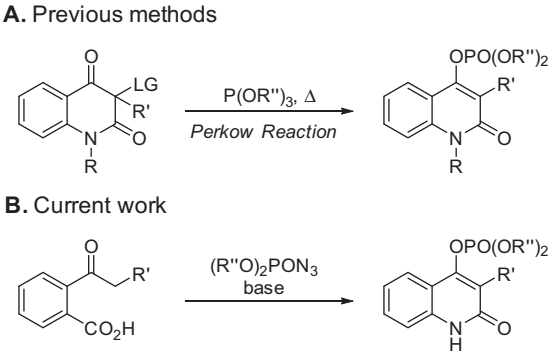
ABSTRACT

We report a facile synthesis of 1,2-dihydro-2-oxo-4-quinolinyl phosphates (**1a**–**l**) starting from 2-acyl-benzoic acids (**2a**–**l**) in the presence of phosphoryl azides via a one-pot cascade reaction involving a Curtius rearrangement, an intramolecular nucleophilic addition of the enol carbon to the isocyanate intermediate, and an addition-elimination of the enol oxygen to the phosphoryl azide. During the reaction three new bonds are formed under mild conditions to yield 1,2-dihydro-2-oxo-4-quinolinyl phosphates in modest yields.

The 1,2-dihydro-2-oxo-4-quinolinyl phosphate (DOQP) system has found broad application in different areas. Phosphoric ester are present in medicinally active synthetic therapeutic agents including antibacterial and antifungal agents,[1] and as ATP kinase inhibitors for the treatment of cancer.[2] The 3-carboxanilide derivatives of DOQP have been used as prodrugs of aromatic hydrocarbon receptor (AhR) activators for the treatment of autoimmune disorders such as multiple sclerosis (MS).[3] In addition, DOQP have been developed as phosphoryl transfer agents that can assist the transformation of AMP into ATP.[4] The quinolinone group of DOQP is a well-documented scaffold that is present in numerous biologically active molecules such as farnesyltransferase inhibitors,[5] β2 agonists,[6] 5TH antagonists,[7] and immunomodulators.[1b] Moreover, in the field of organic synthesis, enol phosphates are one of the most widely used starting materials for Suzuki–Miyaura cross-coupling.[8]

A common synthetic route to DOQP is via the Perkow reaction, in which the starting material α-halo ketones[9]or α-OTf ketones in a modified Perkow reaction,[10] is treated with a trialkyl phosphite ester to generate the enol phosphate product (Scheme 1). Although this method is widely used for the preparation of DOQP, it suffers from major drawbacks. First, the scope of the Perkow reaction is limited to trialkyl phosphite, therefore, compounds such as diphenyl phosphate cannot be synthesized using this method. Moreover, the preparation of starting material α-halo ketone **1** takes multiple steps. In the course of our research on novel PTP1B inhibitors for Type 2 diabetes (T2D), we performed a series of reactions intended to synthesize a collection of compounds based on a DOQP core.



Scheme 1. Synthetic methods to DOQP. (A) Perkow reaction and (B) current work.

Curtius rearrangement is widely used for the formation of isocyanate starting with acid azide.[11] The resulting isocyanate can react in situ with various nucleophiles such as amino groups or hydroxy groups to yield ureas and carbamates, respectively. Motivated by this cascade process, we hypothesize that when treated with an azide source (e.g., phosphoryl azide), 2-acyl-benzoic acid

* Corresponding author. Tel.: +1 410 706 8521.
E-mail address: fxue@rx.umaryland.edu (F. Xue).
† Current address: Beijing Institute of Pharmacology and Toxicology, 27 Taiping Road, Haidian District, Beijing 100850, United States.

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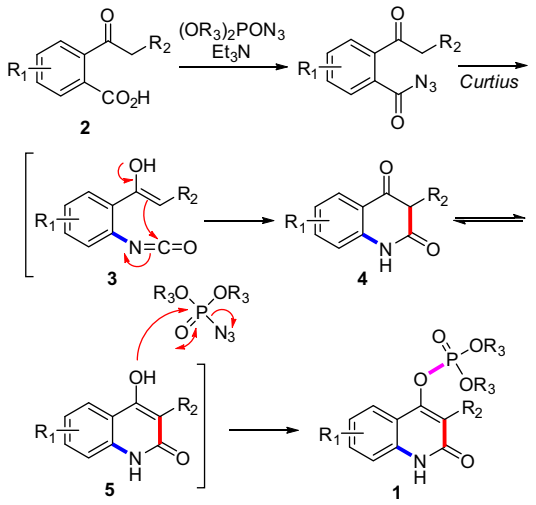
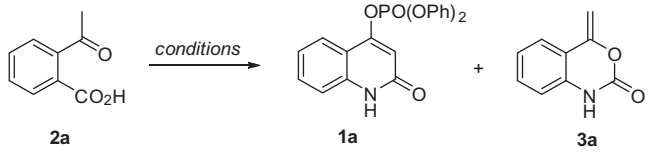


Scheme 2. Synthetic plan to aryl enol phosphates **1** from 2-acyl-benzoic acids **2**.

Table 1
Optimization of conditions for 2-hydroxyquinolin-4-yl diphenyl phosphate **1a**[a]



Entry	DPPA (equiv)	Solvent	Base[b]	*t* (°C)	Yield **1a**[c] (%)
1	2.0	Toluene	K_2CO_3	70	< 5
2	2.0	Toluene	Cs_2CO_3	70	< 5
3	2.0	Toluene	Et_3N	70	17
4	2.0	Toluene	DIPEA	70	16
5	2.0	Toluene	Pyridine	70	< 5
6	3.0	Toluene	Et_3N	70	18
7	2.0	DCM	Et_3N	70	15
8	2.0	$CDCl_3$	Et_3N	70	19
9	2.0	*t*-BuOH	Et_3N	70	< 5
10	2.0	THF	Et_3N	70	6
11	2.0	DCE	Et_3N	70	34
12	2.0	DCE	DIPEA	70	47
13	2.0	DCE	DMAP	70	< 5
14	2.0	DCE	Pyridine	70	< 5
15	2.0	DCE	K_2CO_3	70	< 5
16	2.0	DCE	Cs_2CO_3	70	< 5
17	2.0	DCE	DIPEA	40	14
19	2.0	DCE	DIPEA	90	46
20	2.0	DCE	DIPEA	110	26[d]
21	1.0	DCE	DIPEA	70	< 5

[a] The reaction was carried out in a pressure tube with 1.0 mmol of **2a**, 2.0 mmol of DPPA, and 2.0 mmol of base in 15 mL of solvent for overnight.
[b] K_2CO_3 = potassium carbonate, Cs_2CO_3 = cesium carbonate, Et_3N = triethylamine, DIPEA = diisopropyl ethylamine.
[c] Determined by ^1H NMR using pyridin-3-ylmethanol as an internal standard.
[d] TLC indicated a complicated reaction significant amount of side products was observed.

2 can undergo the Curtius rearrangement to generate isocyanate **3**, which cyclizes spontaneously in situ via the enol carbon atom to give intermediate **4**. Tautomerization of ketone **4** yields 4-hydroxyquinolinone **5**. The hydroxyl group of **5** attacks a second equiv of phosphoryl azide to generate aryl enol phosphate **1** (Scheme 2).

To test our hypothesis, in initial studies 2-acetylbenzoic acid (**2a**) was chosen as the starting material to optimize the reaction conditions for the formation of 2-hydroxyquinolin-4-yl diphenyl phosphate (**1a**) in the presence of 2 equiv of diphenyl phosphoryl azide (DPPA, Table 1). Using inorganic bases K_2CO_3 (entry 1) and Cs_2CO_3 (entry 2), no obvious formation of compound **1a** can be detected. However when tertiary amines triethylamine (Et_3N, entry 3) or diisopropylethylamine (DIPEA, entry 4) were used, we were able to isolate the desired product **1a** with 17% and 16% yields, respectively, along with small amounts of 4-methylene-1,4-dihydro-2*H*-benzo[*d*][1,3]oxazin-2-one **3a**. It is noted that compound **3a** decomposed as a solution in deuterated chloroform ($CDCl_3$). No obvious reaction was observed when pyridine was used as the base (entry 5). An additional equivalence of DPPA was not beneficial for the reaction (entry 6). After screening solvents for the reaction (entries 7–11), we found that the 1,2-dichloroethane (DCE) gave the highest yields (entry 11). Next, we kept the solvent of the reaction as DCE and re-visited the base used in the reaction (entries 12–16). We found that DIPEA gave the highest yield for reactions in DCE (entry 12). The reaction temperature was also studied (entries 17–19). It turned out that the original choice of 70 °C was optimal for the formation of compound **1a**. We noticed that at 110 °C a much more complex reaction was achieved with less compound **1a** formed (entry 20). When one equivalence of DPPA was used (entry 21), 4-hydroxyquinolin-2(1*H*)-one (**4** in Scheme 2) was isolated as the major product.[12]

Next we studied the scope of the reaction using the optimized conditions (Table 2). When 2-propionylbenzoic acid (**2b**) was treated with two equiv of DPPA at 70 °C for 12 h, the desired quinolinyl phosphate **1b** was isolated in modest yields in both toluene (entry 1) and DCE (entry 2). The chemical structure of compound **1b** has been confirmed by single crystal X-ray analysis (Fig. 1). Decreased yields were observed when 2-pentanoylbenzoic acid (**2c**) was used as the starting material (entries 3 and 4), which is likely due to the unfavorable steric effect of the propyl group at the R_2 position of **2c**. The synthesis of starting material **2c** has been reported previously.[13] Effects of substitution on the phenyl ring have also been studied (entries 5–12). When 2-acetyl-3-chlorobenzoic acid (**2d**)[13] and 2-acetyl-3-methylbenzoic acid (**2e**)[13] were used as the starting material, low yields were obtained for reactions in both toluene and DCE (entries 5–8). The low yields are likely due to the steric hindrance of the 3-chloro or 3-methyl groups during the nucleophilic addition of the enol intermediate to the second equivalence of DPPA. Increased yields were achieved when the substituent on the phenyl ring moved further from the enol group (entries 9–12), with the formation of compounds **1f** and **1g** in modest yields. Other phosphoryl azides have also been used in the study (entries 13–22). 2-Propionylbenzoic acid reacted in the presence of diethyl phosphoryl azide[14] (DEPA) to give compound **1h** in modest yields (entries 13 and 14). When compounds **2a** and **2b** were treated with 2-azido-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide,[14] the desired product **1i** and **1j** were isolated in modest yields, respectively (entries 15–18). Similarly modest yields were obtained when phenyl substituted starting materials **2f** and **2g** were treated with 2-azido-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (entries 19–22). The overall isolated yields of the listed reactions were not high, however, considering the complexity of the three-step cascade reaction and the mild reaction condition involved to perform the reaction, the current method represents a practical alternative method for the preparation of DOQP.

In summary, we have disclosed a practical method to synthesize DOQP starting from readily available starting material 2-acyl-benzoic acids. The reaction proceeds smoothly in various azide sources at 70 °C to give a collection of DOQP derivatives in modest yields.