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An efficient HCCP-mediated direct amination of quinazolin-4(3*H*)-ones

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ABSTRACT

An efficient direct amination of quinazolin-4(3*H*)-ones has been developed. Treatment of quinazolin-4(3*H*)-ones with HCCP, DIPEA, and *N*-contained nucleophiles in acetonitrile could be able to form the corresponding 4-aminoquinazoline derivatives. Under the optimal reaction conditions, the amination products were achieved in good yields.

1. Introduction

Nitrogen-containing heterocycles are present in a variety of biologically active compounds that can be used in a wide range of therapeutic areas.[1] Quinazoline derivatives are an important class of nitrogen-containing heterocycles, which display a wide variety of biological activities, such as anticonvulsant, antihypertensive, vasodilator, antiinflammatory, antibiosis, fibrinogen receptor antagonistic, and nanomolar Hedgehog antagonistic.[2] Among the family of quinazolines, 4-aminoquinazolines have been received particular interests because of their potential pharmacological activity.[3] For example, three drugs Gefitnib (Iressa), Erlotinib (Tarceva), and Lapatinib (Tykerb), derived from 4-aminoquinazolines, have been approved and marketed for non-small-cell lung cancer treatment (Fig. 1).[4]

4-Aminoquinazolines are usually synthesized from acid- or base-mediated amination of electron-deficient 4-chloroquinazolines via S_NAr substitution.[5] Alternatively, Tasler's group have reported a Pd-catalyzed Buchwald–Hartwig amination reaction to prepare the corresponding 4-aminoquinazolines from 4-chloroquinazolines.[6a] Very recently, we have also described a Pd-catalyzed selective amination of 4-chloroquinazolines with bifunctional amines.[6b] Both methods employ the same starting material 4-chloroquinazolines.[3–6] The common method for preparation of 4-chloroquinazolines is the chlorination of quinazolin-4(3*H*)-ones, which often require harsh and acidic conditions with $SOCl_2$, $POCl_3$, PCl_5 or their combinations as the chlorination reagents. However, these reagents are not environmentally benign, and the reaction conditions may cause destruction of some functional groups. In addition, many 4-chloroquinazoline derivatives are moisture sensitive and their purification and storage require special treatment.

In order to avoid the use of chlorination reagents and an individual activation step of the quinazolin-4(3*H*)-ones, a direct amination of quinazolin-4(3*H*)-ones via in situ activation is highly desirable for the synthesis of 4-aminoquinazoline derivatives. Phosphonium compounds, such as benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluorophosphate (BOP) and its analogues (i.e., BroP, PyBOP, PyBroP), are efficient coupling reagents for amide bond formation between a carboxylic acid and an amine under mild conditions.[7] In recent years, they have also been successfully employed in the one-step aminations of cyclic amides and ureas.[8–13] Successful results have also been obtained in BOP-mediated direct amination of quinazolin-4(3*H*)-ones.[11b,c] In fact, when quinazolin-4(3*H*)-ones are treated with BOP in the presence of a base, a phosphonium intermediate **1** possessing an active C–O–P fragment is readily formed (Fig. 2), which subsequently undergoes S_NAr substitution with a reactive amine nucleophile to give the desired product.[11a–c,14] Unfortunately, BOP and its analogues are expensive, moreover, utilization of BOP generates end product HMPA, a highly carcinogenic chemical. We hoped that a less expensive and readily available activating reagent can be used as the BOP surrogate. The mechanism of the BOP-involved activation indicates that a compound, which can react with quinazolin-4(3*H*)-ones to form the active C–O–P fragment, could be considered to serve as this role. Hexachlorocyclotriphosphazene ($Cl_6N_3P_3$, HCCP), a bulky flame-retardant polyphosphazenes,[15] could be a good candidate. We assumed that quinazolin-4(3*H*)-ones can convert to

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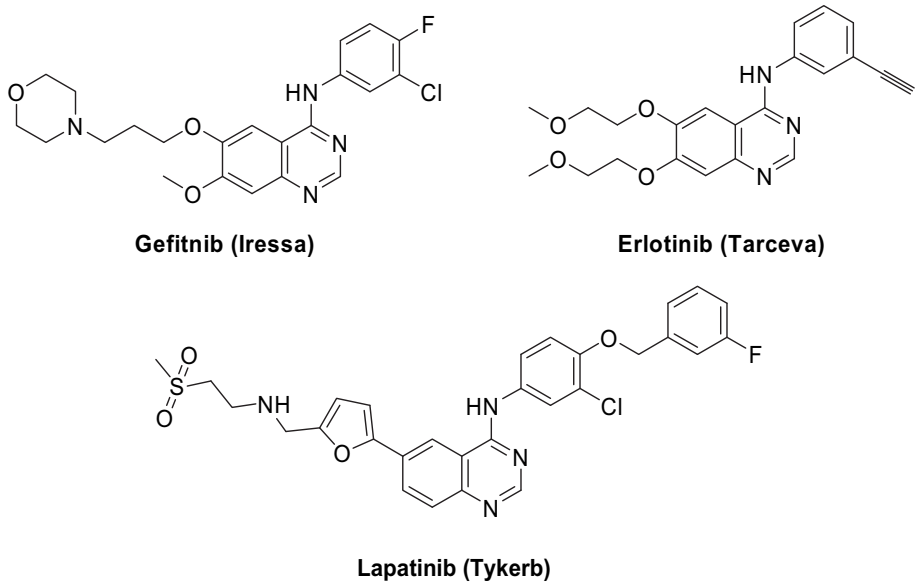


Fig. 1. The structures of commercialized 4-aminoquinazoline derivatives.

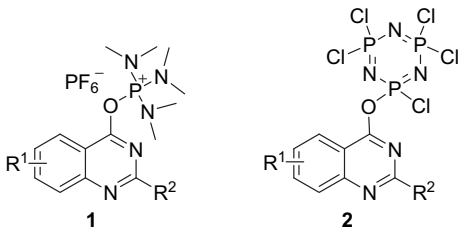


Fig. 2. Active phosphonium intermediates.

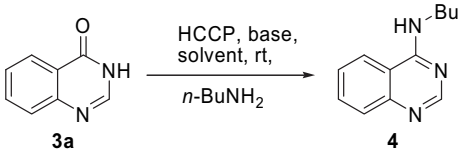
the above-mentioned active C–O–P fragment with HCCP (**2**, Fig. 2) or its analogues, since the Cl–P bond of HCCP can react with hydroxyl group, and thus promote direct amination.

2. Results and discussion

Our initial experiments proved that HCCP can promote the direct amination of quinazolin-4(3*H*)-one (**3a**) with *n*-butylamine. Thus, **3a** and *n*-butylamine were used as the model system for investigating the effects and amounts of solvent, base, and HCCP (Table 1). Although DBU was an efficient base in the BOP-mediated amination,[11b,c] it proved not to be the best in our case (entry 1). Diisopropylethylamine (DIPEA) was found to be most effective in comparison with others (entry 4). Inorganic bases K_2CO_3 and Cs_2CO_3 could also be employed (entries 5 and 6).

Previously, we hypothesized that the phosphonium intermediate **2** or its analogues was the crucial intermediate for the current direct amination. If this intermediate **2** or its analogues could be confirmed or separated, it would be beneficial to understand the reaction mechanism and further optimize reaction conditions. In a designed experiment, a mixture of **3a** (1 equiv), HCCP (1 equiv) and DIPEA (6.0 equiv) in acetonitrile was stirred for 1 h at room temperature. TLC showed that **3a** was completely converted to a new compound, which was relatively stable and readily isolable by flash chromatographic separation. Structural analyses confirmed that this compound was the desired phosphonium intermediate **2a** (R^1=R^2=H).[16] Decrease of the amount of HCCP from 1.0 to 0.8 equiv resulted in a loss of the yield (entry 7). By TLC monitoring, the experiment with 0.8 equiv of HCCP showed that **3a** could not be completely converted into the active intermediate **2a** even after prolonging the activation time to 12 h. These

Table 1
HCCP-mediated direct amination of **3a** with *n*-butylamine[a]



Entry	Base	Solvent	Yield[b] (%)
1	DBU	MeCN	70
2	DABCO	MeCN	74
3	TEA	MeCN	75
4	DIPEA	MeCN	90
5	K_2CO_3	MeCN	82
6	Cs_2CO_3	MeCN	81
7	DIPEA	MeCN	76[c]
8	DIPEA	THF	32
9	DIPEA	DMF	41
10	DIPEA	DCM	39
11	DIPEA	NMP	53
12	DIPEA	1,4-Dioxane	10
13	DIPEA	MeCN	65[d]
14	DIPEA	MeCN	89[e]

[a] Conditions: **3a** (0.5 mmol), HCCP (1.0 equiv), base (6.0 equiv), solvent (2 mL), rt, activation time (1 h), then *n*-$BuNH_2$ (6.0 equiv), 16 h.
[b] Isolated yield after chromatographic purification.
[c] HCCP (0.8 equiv).
[d] *n*-$BuNH_2$ (4.0 equiv).
[e] DIPEA (5.0 equiv).

results indicated that only one Cl–P bond in all six Cl–P bonds of an HCCP molecule could react with one **3a** molecule to form **2a** at room temperature. Thus, we proposed the mechanism of HCCP-mediated direct amination of **3a** as follows:(1) tautomerization of **3a** to 4-hydroxyquinazoline in the presence of DIPEA; (2) activation of 4-hydroxyquinazoline with HCCP generating the high reactive intermediate **2a**; (3) nucleophilic attack of *n*-butylamine to **2a** forming the product **4**.

Results in Table 1 showed the solvent can greatly affect the HCCP-mediated amination, and acetonitrile was found to be the most suitable solvent (entries 4, 8–12). When nucleophile *n*-butylamine attacked **2a**, two competitive S_NAr substitutions are both present either on C–O bond or P–Cl bond. This could explain that only 65% yield of **4** was obtained when decreasing the amount of *n*-$BuNH_2$ from 6.0 equiv (entry 4) to 4.0 equiv (entry 13). On the other hand,