JOC The Journal of Organic Chemistry

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$POCl_3$ Chlorination of 4-Quinazolones

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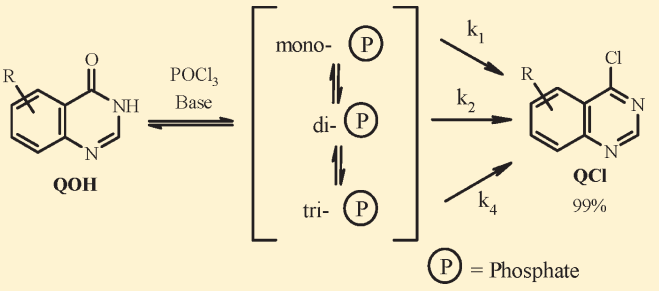
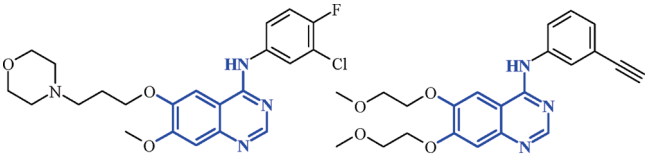
Supporting Information

ABSTRACT: The reaction of quinazolones with $POCl_3$ to form the corresponding chloroquinazolines occurs in two distinct stages, which can be separated through appropriate temperature control. An initial phosphorylation reaction occurs readily under basic conditions (R_3N, aq $pK_a > 9$) at $t < 25$ °C to give a variety of phosphorylated intermediates. Pseudodimer formation, arising from reaction between phosphorylated intermediates and unreacted quinazolone, is completely suppressed at these temperatures, *provided the system remains basic throughout the $POCl_3$ addition*. Clean turnover of phosphorylated quinazolones to the corresponding chloroquinazoline is then achieved by heating to 70−90 °C. (*N*)- and (*O*)-phosphorylated intermediates, involving multiple substitution at phosphorus, have been identified and their reactions monitored using a combination of ^1H, ^{31}P, and ^{19}F NMR. Kinetic analysis of the reaction profiles suggest that the various intermediates react with both Cl^- and $Cl_2P(O)O^-$, but product formation arises exclusively from reaction of (*O*)-phosphorylated intermediates with Cl^-. (*O*)- and (*N*)-phosphorylated intermediates equilibrate rapidly on the time scale of the reaction. A minimum of 1 molar equiv of $POCl_3$ is required for efficient conversion of the intermediates to product.



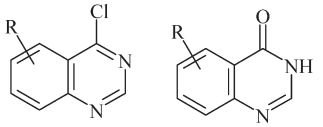
INTRODUCTION

Quinazolines are a common structural feature in a range of drugs for the treatment of cancer, such as Gefitinib, *N*-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine, **1**, and Erlotinib, *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine, **2**.[1]



1 **2**

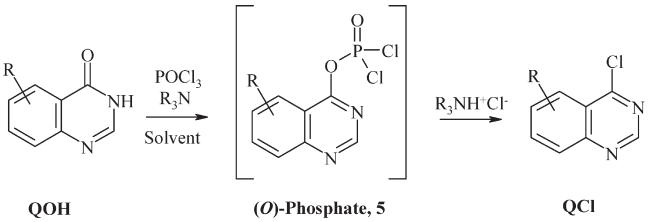
4-Chloroquinazolines, **3** (QCl), derived from the chlorination of the corresponding 4-quinazolone, **4** (QOH), are therefore synthetically valuable intermediates. Typically, (**3**) is not isolated as a solid but telescoped through to desired derivatives by reaction with a nucleophile (e.g., $ArNH_2$, ArOH/base).



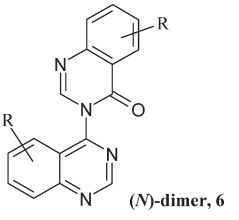
3 (QCl) **4** (QOH)

The chlorination of 4-quinazolones is well precedented[2] and is often effected by refluxing the 4-quinazolone in excess $POCl_3$ in the presence of a tertiary amine (Scheme 1). Evidence exists for the intermediacy of a dichloridophosphate, analogous to **5**, Scheme 1, in the chlorination of guanosine triacetate,[3] and such intermediates have also been postulated for the chlorination of 4-quinazolones and the related 4-pyrimidones.[4]

Scheme 1. Chlorination of 4-Quinazolones



The main problematic impurity arising during chlorination is "(*N*)-dimer" **6**, which results from the reaction between unphosphorylated quinazolone, QOH, and the phosphate intermediate, **5**.



(*N*)-dimer, **6**

Received: November 19, 2010
Published: February 04, 2011

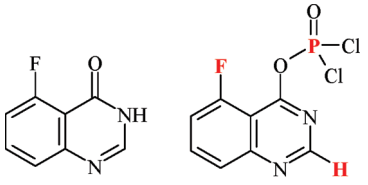
Table 1. Typical ^{31}P NMR Shifts for Phosphorus-Containing Species[a]

species[b]	$POCl_3$	(O)	(*N,O*)	$Cl_2P(O)O^-$	(*O,O*)	(*N,O,O*)	(*O,O,O*)[c]
δ_P/ppm	+4.5 very broad s	−0.2 s	−0.9 d, 2 Hz	−7.5 broad s	−10.4 s	−14.1 d, 3 Hz	−25 s
$D/10^{-10}m^2\ s^{-1}$	17.9	10.9	7.9	7.6	7.9	7.0	7.0

[a] 20 °C, PhF + d_5-PhF lock. [b] Abbreviations: (*O*) = monosubstituted, (*O*)-linked phosphate, (*N,O*) = disubstituted, (*N*)- and (*O*)-linked phosphate, etc.; see text. [c] Low abundance (<1%), tentative assignment only.

The minimization of the reaction of **5** with QOH relative to that with Cl^- is, therefore, important for the success of the synthetic procedure. A process of "hot inverse addition", whereby a slurry of (highly insoluble) QOH is added slowly to an excess of $POCl_3/R_3N$ at 75−95 °C, can achieve significant reductions in dimer formation. The process is, however, operationally difficult, especially at larger scale, as it depends upon rapid mixing and good dispersion of the QOH slurry as it is added, making addition time critical and sensitive to scale/reactor geometry. Overall yields by this procedure are also typically relatively modest (~70%). A much preferred option would be the direct addition of $POCl_3$ under conditions such that the reaction outcome is not sensitive to the addition time. In order to achieve this, a greater understanding of the nature and reactivity of the reaction intermediates is required.

We report here a detailed kinetic and mechanistic study of the chlorination of quinazolones. 5-Fluoroquinazolin-4(3*H*)-one, **7**, in chlorobenzene was chosen for kinetic studies for two reasons: first, the intermediates and product are soluble, and, second, the presence of the spin-active "reporter" nuclei ^{19}F, along with ^{31}P and the clearly resolved ^{1}H signal from the H-2 proton of the pyrimidine ring (δ ~9 ppm), allows convenient and comprehensive monitoring by NMR of the reactant, product, and intermediates. The simple monophosphorylated 5-fluoroquinazolin-4-yl dichloridophosphate, **8**, for example, contains all three nuclei. General conclusions from this study have been confirmed for several additional quinazolones.

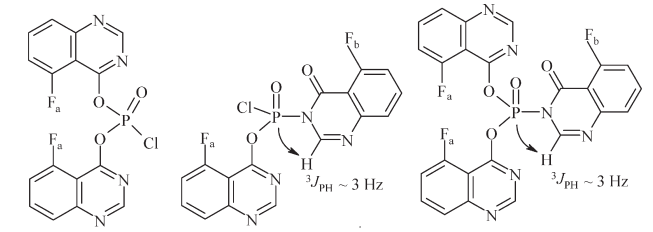


7 **(*O*)-Phosphate, 8**

Since the quinazolones are ambident nucleophiles (O and N) and $POCl_3$ possesses three reactive P−Cl bonds, multiple intermediates might be expected. A subset of these possible intermediates is indeed observed. We show, furthermore, that the phosphorylation reactions occur much more rapidly than the subsequent conversion of the various intermediates to product. This can be used to advantage in designing a robust and efficient synthetic process.

RESULTS AND DISCUSSION

Identification of Intermediates. The significant intermediate species observed were the (*O*)-phosphate **8**, the disubstituted phosphates bis(5-fluoroquinazolin-4-yl) chloridophosphate, **9**, and 5-fluoroquinazolin-4-yl (5-fluoro-4-oxoquinazolin-3(4*H*)-yl)-phosphonochloridate, **10**, and the trisubstituted phosphate bis-(5-fluoroquinazolin-4-yl) (5-fluoro-4-oxoquinazolin-3(4*H*)-yl)-phosphonate, **11**. In **10** and **11**, nonequivalent fluorines are identified by subscripts *a* and *b*.



(*O,O*)-Phosphate 9 **(*N,O*)-Phosphate, 10** **(*N,O,O*)-Phosphate, 11**

Identification of the species was achieved by a combination of methods. Initially, the *degree of substitution* was determined by the relative apparent diffusion coefficients of the various species determined using ^{1}H, ^{19}F, and ^{31}P pulsed field gradient stimulated echo NMR experiments as listed in Table 1.[5] Figure 1 shows a pseudo-2D (DOSY) representation of a typical ^{31}P diffusion experiment. The apparent diffusion coefficient (D) is a measure of the approximate molecular weight and so for example, as seen in Table 1, the disubstituted species, (***N,O***) and (***O,O***) have the same coefficient, which is significantly larger than that seen for the trisubstituted (***N,O,O***) and (***O,O,O***) species. The spectral assignments were subsequently confirmed by correlation of intensity changes with time between ^{31}P, ^{1}H, and ^{19}F NMR signals as the reaction occurred. A typical set of ^{31}P NMR spectra obtained during a reaction are shown in Figure 2. *Substitution isomerism*, involving various (*O*)-linked and (*N*)-linked phosphates, as in (***N,O***) and (***N,O,O***), **10** and **11**, respectively, was confirmed by the presence of nonequivalent fluorines in mixed phosphates and different coupling patterns: $^3J_{PH}$ coupling of ~3 Hz was characteristic of (*N*)-linked phosphates, whereas there was no coupling for *O*-linked phosphates, $^5J_{PH} = 0$. ^{31}P NMR for the various phosphorus-containing species are listed in Table 1.

Inorganic Phosphate. At the completion of the reaction in typical aromatic solvents, such as chlorobenzene or anisole, the exclusive stoichiometric phosphorus-containing byproduct is $Cl_2P(O)O^-$, which coexists in solution with the excess $POCl_3$. There was no measurable tendency for formation of diphosphoryl chloride via the substitution reaction, eq 1, to occur, although it is a known product of partially hydrolyzed $POCl_3$.[6] Rather, at longer reaction times, there is a gradual tendency for $Cl_2P(O)O^-$ to disproportionate, eq 2, giving the corresponding (nonsymmetrical) trichloropyrophosphate: ^{31}P NMR δ (ppm) −8 (d, J_{PP} = 40 Hz) and −16 (d, J_{PP} = 40 Hz). We assume that the lack of reaction between $Cl_2P(O)O^-$ and $POCl_3$ in these solvents is a result of an unfavorable equilibrium, as the rate of reaction in the forward

dx.doi.org/10.1021/jo102262k |*J. Org. Chem.* 2011, 76, 1653–1661

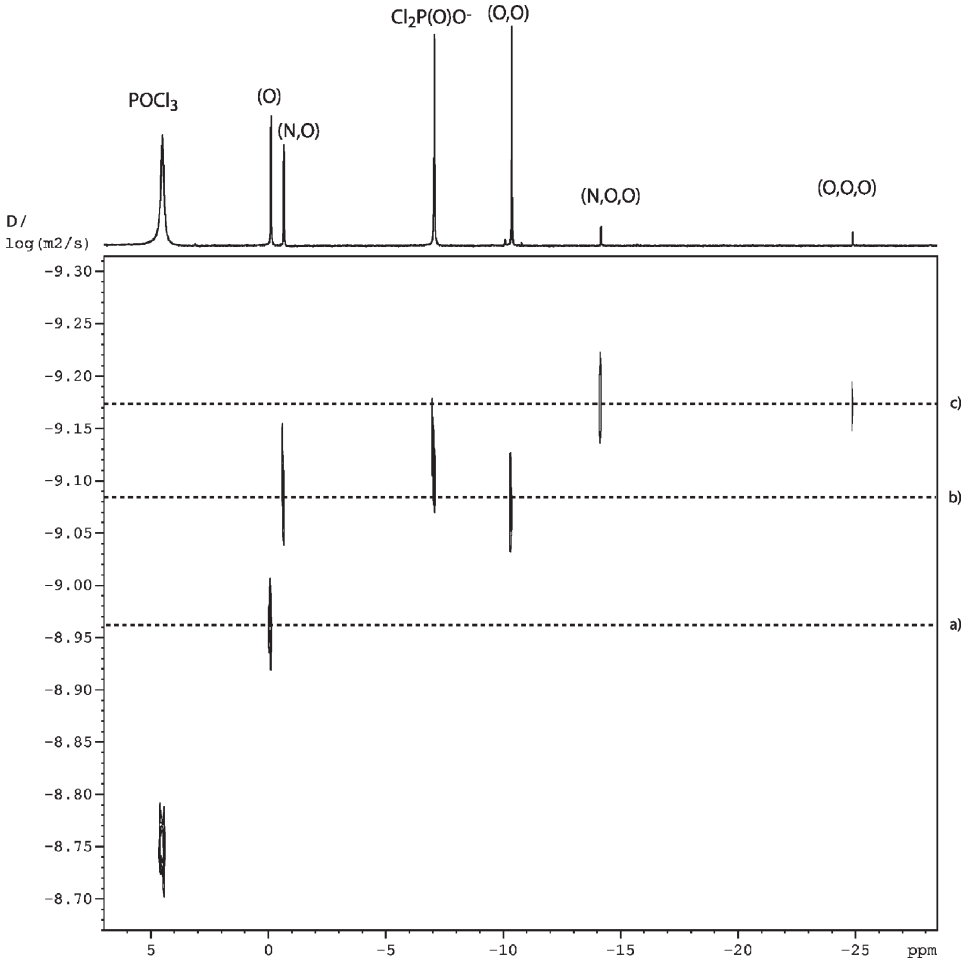
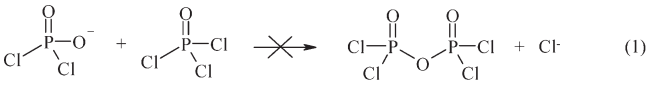
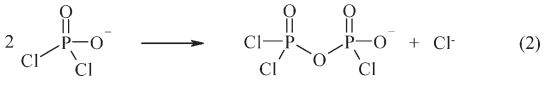


Figure 1. ^{31}P DOSY spectrum of species in Table 1 under the same experimental conditions. A pulse field gradient stimulated echo experiment with bipolar gradient was used. To generate diffusion-weighted data, eight increments were acquired with increasing gradient strength. Data was fitted to a single exponential; Bruker TopSpin software was used to generate the pseudo-2D plot. The dotted line represents the diffusion coefficient for (a) monosubstituted, (b) disubstituted, and (c) trisubstituted species.

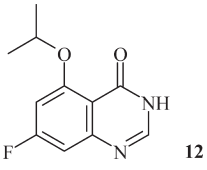
direction for eq 1 might be expected be greater than that of eq 2.





Phosphorylation Reaction. Preliminary studies showed that in the presence of a strong base, such as diisopropylethylamine (aq pK_a = 11),[7] phosphorylation to give the intermediate Phosphates (e.g., **8**−**11**) is essentially complete after 30 min at 20 °C. Furthermore, at this temperature all other reactions are slow. This means that direct addition of $POCl_3$ can be performed at <25 °C to give *only* assorted phosphate intermediates, without forming the dimer **6** impurity (<0.5%).

The phosphorylation reactions are strongly exothermic and are particularly convenient for a calorimetric investigation. Quantitative details of the reaction were explored calorimetrically with the substrate 7-fluoro-5-isopropoxyquinazolin-4(3*H*)-one, **12**, in chlorobenzene with various added bases.



12

The work was carried out in an Omnical Ultralow Super CRC calorimeter, using an external circulating bath (Presto bath with Baysilone KT3 oil) to maintain the reaction temperature at 20 °C. $POCl_3$ was added to a mixture of the substrate and base rapidly in a single portion ("dump-charge"), and the power output was recorded every 15 s. Samples were taken for NMR analysis when the power output had returned to baseline level. The progressive and total heat output was calculated by integration of the heat-output curve, using baseline-to-baseline extrapolation in MS Excel. Typical heat-output profiles and the corresponding $-\Delta H$ values are included in Figure 3. They show that the heat output, and hence the reaction, is largely (>98%) complete after 30−40 min. ^{31}P and ^{19}F NMR analysis of the resulting reaction mixtures confirmed complete conversion

dx.doi.org/10.1021/jo102262k |*J. Org. Chem.* 2011, 76, 1653–1661

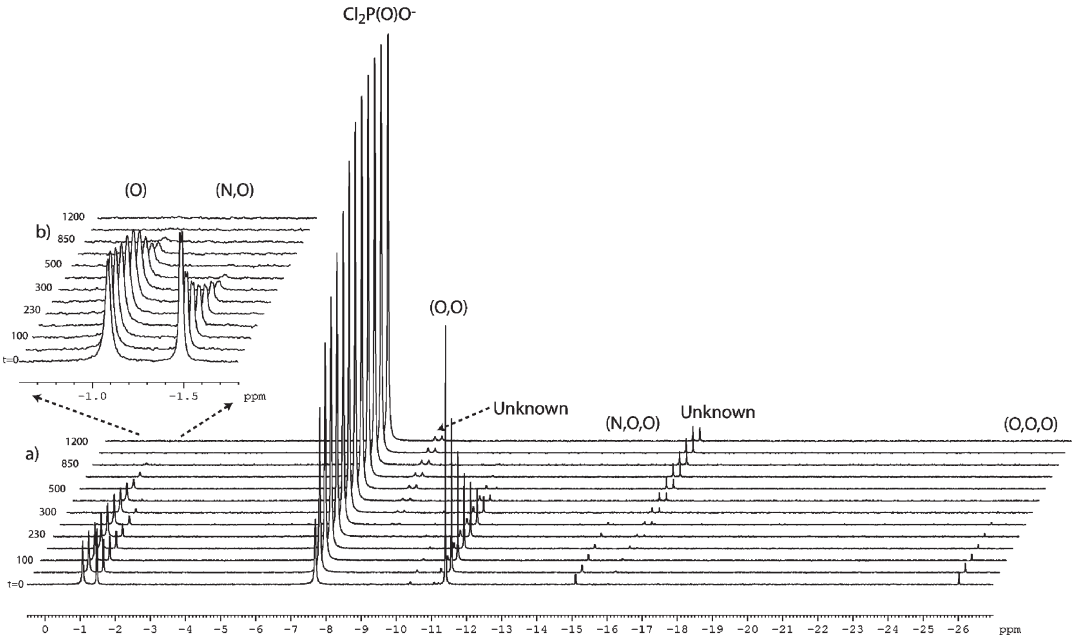


Figure 2. ^{31}P spectra showing the progress of the reaction under the experimental conditions (70 °C, hence the chemical shifts shown are slightly different from those described in Table 1 which are obtained at 20 °C): (a) full spectrum (excluding $POCl_3$); (b) expansion of the region containing (***O***) and (***N,O***).

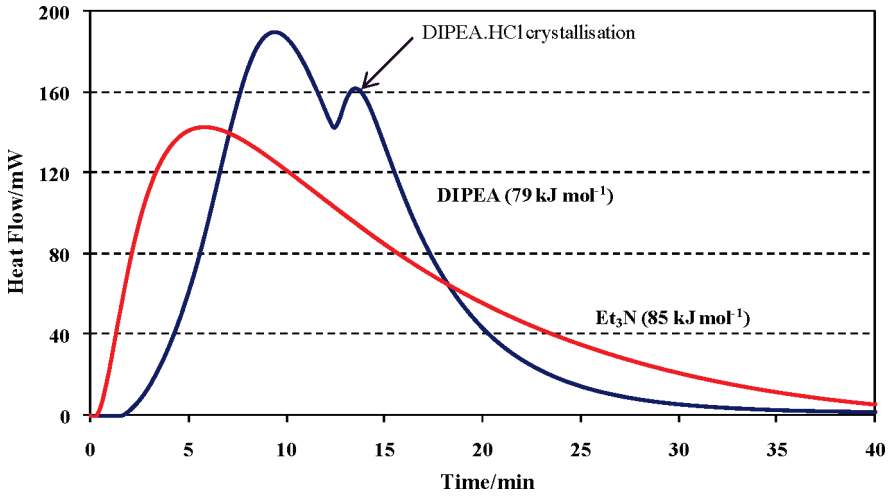


Figure 3. Heat flow for reaction of quinazolone, **12**, with $POCl_3$ (1.5 equiv) and R_3N (1.2 equiv) in PhCl at 20 °C: diisopropylethylamine (DIPEA) (blue); triethylamine (red).

of QOH to phosphorylated intermediates with negligible formation of dimer **6** (<0.5%) (the relevant NMR spectra are available in the Supporting Information).

The total heat output ($\Delta H \sim -80$ kJ mol^{-1}) includes the heat of reaction and the heat of crystallization of the accompanying amine hydrochlorides, $RNH_3^+Cl^-$. The reaction in the presence of *n*-Bu_3N, for which the hydrochloride is soluble, gave $\Delta H \sim -70$ kJ mol^{-1}, indicating that the major portion of the heat comes from the phosphorylation reaction. The hydrochloride of DIPEA is moderately soluble and crystallization occurs as a delayed event, but for Et_3N the much lower solubility of the hydrochloride results in precipitation occurring throughout the reaction rather as a separate event. It should be noted that the amine hydrochloride formed during the phosphorylation provides the chloride ion required for subsequent product formation.

The observed rates of phosphorylation depend upon the pK_a of the base (water values,[7] 25 °C, bracketed), DIPEA (11.0) ≈ Et_3N (10.5) > *n*-Bu_3N (9.0), and completion of reaction on a practical time scale requires a base with aq p$K_a \geq 9$. The use of weaker bases, such as *N*-methylmorpholine (7.6), produces only a very sluggish reaction at 20 °C. These observations suggest that the quinazolone phosphorylates via its anion, QO^-. It was also found that it is essential to have ≥1.0 equiv of R_3N to keep conditions basic *throughout* $POCl_3$ addition: acidic conditions leads to not only slower phosphorylation but also much more side product dimer **6**.

In summary, in the presence of a strong base (aq p$K_a \geq 9$), rapid reaction occurs between QOH and $POCl_3$ to give phosphate intermediates at room temperature. The use of temperatures in the range 0−25 °C effectively "freezes out" all reactions

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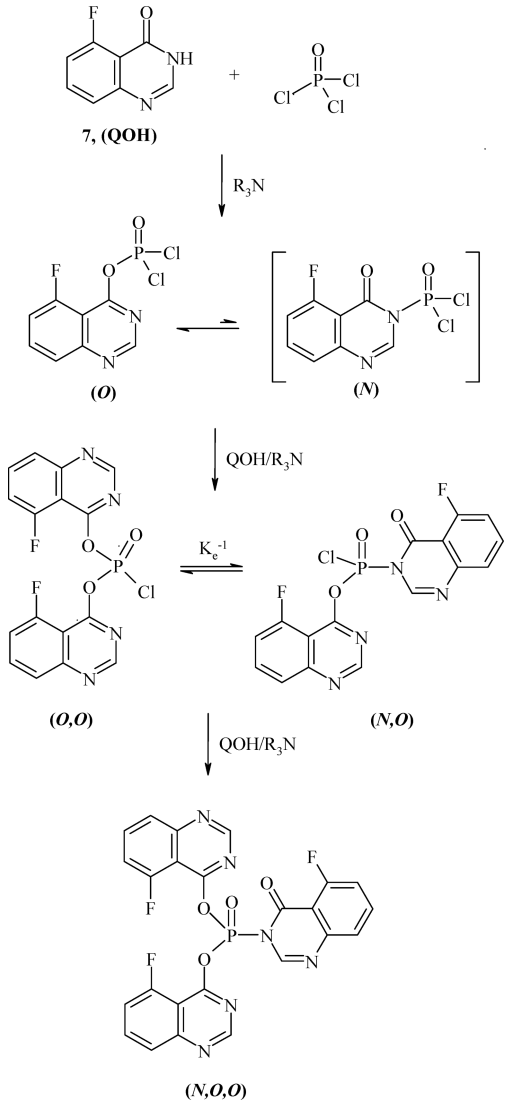
Scheme 2. Phosphorylation of Quinazolone 7



except phosphorylation: a *slow*, direct addition of $POCl_3$ is therefore possible (addition times of up to 120 min are tolerated). This is especially important on a manufacturing scale because of the highly exothermic nature of the phosphorylation reaction ($\Delta H \sim -80$ kJ mol^{-1}).

Conversion of Phosphates to Product Chloroquinazoline: Kinetic and Mechanistic Studies. Once complete phosphorylation has occurred at 20 °C, the mixture of phosphates can be heated to 70−90 °C to bring about clean turnover to 4-chloro-5-fluoroquinazoline, (**13**) QCl, by attack of Cl^-. Reaction profiles were obtained by NMR and kinetic modeling has been carried out for the chlorination of 5-fluoroquinazolin-4(3*H*)-one, **7**, with $POCl_3$/diisopropylethylamine in chlorobenzene, PhCl, at 70 °C. This combination of base/solvent gave homogeneous solutions with reasonable concentrations ([QOH] ~ 0.3 M), allowing direct monitoring of the reaction by NMR. The reaction scheme for the phosphorylation and the abbreviations used for the intermediate species are shown in Scheme 2. Small amounts of (***N***) (≤1%) and di- or trisubstituted phosphates, other than those included in Scheme 2, were observed.

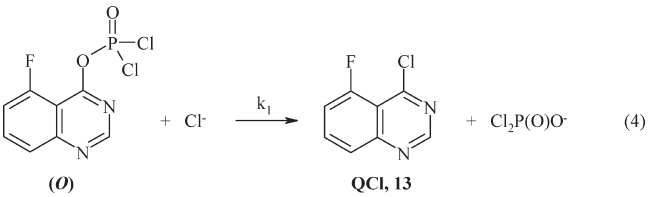
There is clear evidence for an equilibration of (*O,O*) and (*N,O*) species which is rapid on the time scale of the reaction; the equilibrium constant K_e, eq 3, has a value of 2.8_1 at 70 °C.

$$K_e = \frac{[(O,O)]}{[(N,O)]} = 2.8_1 \qquad (3)$$

Thus, the ratio [(***O,O***)]/[(***N,O***)] was independent of the initial distribution of intermediates and remained constant throughout the conversion of the intermediates to the product, QCl. We assume that the interconversion must be *intramolecular*. Alternative potential mechanisms involving, for example, reversion of (***O,O***) to (***O***) and QO^- by reaction at P with Cl^-, followed by a recombination of (***O***) and QO^- to give (***N,O***), are not feasible, as they would be disrupted by a competitive reaction of the liberated QO^- with $POCl_3$ to give (***O***). We also assume that this interconversion is general for *N*-/*O*-substituted species.[8]

Kinetic modeling was consistent with the following reactions occurring for the various intermediate phosphates.

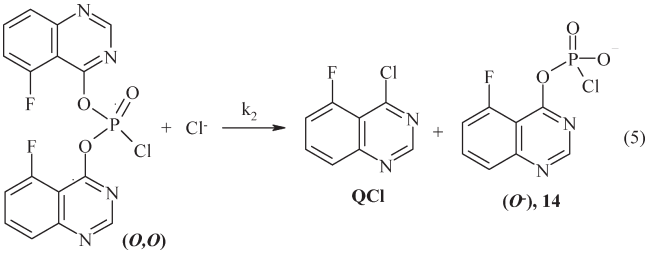
(a). (O)-Phosphate. Direct conversion to product by S_NAr reaction with Cl^-, eq 4:



(4)

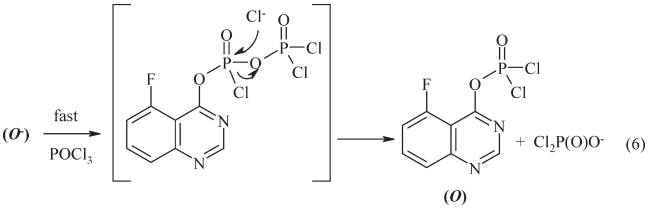
An analogous reaction of (***O***) with the dichlorophosphate anion $Cl_2P(O)O^-$ is also possible but merely leads to phosphate exchange.

*(b). (**O,O**)/(**N,O**)-Phosphates.* Two possible reactions occur: (i) S_NAr reaction with Cl^- to give product and (O^-)/(N^-), illustrated for (O^-), **14** (5-fluoroquinazolin-4-yl) chloridophosphate, eq 5:



(5)

In the presence of excess $POCl_3$, however, (O^-)/(N^-) react rapidly in a non-rate-determining step to give (***O***) and $(Cl)_2P(O)O^-$, eq 6.



(6)

The net reaction is therefore given by eq 7.

$$(O,O)/(N,O) + Cl^- \xrightarrow[POCl_3]{k_2} QCl + (O) + Cl_2P(O)O^- \qquad (7)$$

dx.doi.org/10.1021/jo102262k |*J. Org. Chem.* 2011, 76, 1653–1661

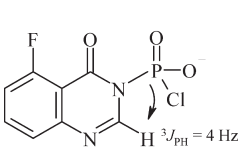
(ii) Reaction analogous to eq 5 of $(O,O)/(N,O)$ occurred, but with $Cl_2P(O)O^-$ attacking $(O,O)/(N,O)$ rather than Cl^-, to give (O) and $(O^-)/(N^-)$. The latter again reacts with excess $POCl_3$ (eq 6) to form another 1 mol of (O). The net reaction is, therefore, given by eq 8:

$$(O,O)/(N,O) + Cl_2P(O)O^- \xrightarrow[POCl_3]{k_3} 2(O) + Cl_2P(O)O^- \quad (8)$$

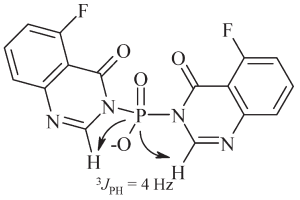
*(c). (**N,O,O**)-Phosphate.* Reactions with Cl^- or $Cl_2P(O)O^-$, analogous to those in eq 7 and 8, occur giving product QCl and $(O,O)/(N,O)$. The relatively low levels of (N,O,O) present in the initial phosphate distribution (<2% on ^{31}P, 6% on ^{19}F (QOH)) meant that we were unable sensibly to distinguish between the reactivity of Cl^- and $(Cl)_2P(O)O^-$. The disappearance of (N,O,O) was therefore represented by a single, average rate constant, k_4, eq 9.

$$(N,O,O) + Cl^-/Cl_2P(O)O^- \xrightarrow[POCl_3]{k_4} QCl + (O,O)/(N,O) + (O) + Cl_2P(O)O^- \quad (9)$$

It is important to note that reactions of di- and trisubstituted phosphorylated intermediates give initially anionic phosphates (e.g., (O^-) and (N^-) from $(O,O)/(N,O)$, eq 5), which under our reaction conditions of excess $POCl_3$ ($\geq$1 molar equiv relative to QOH, typically 1.5 equiv) are observed transiently in trace quantities only. In the absence of an excess of $POCl_3$, however, although phosphorylation proceeds readily (1/3 equiv $POCl_3$ only is required), conversion to product stalls. Instead, there is a progressive build-up of two predominant, unreactive intermediates, whose NMR is consistent with the anionic species (N^-), **15** (5-fluoro-4-oxoquinazolin-3(4*H*)-yl)phosphonochloridate) (^{31}P NMR δ = −10.1 ppm, d, J = 4 Hz), and (N,N^-), **16** (bis-(5-fluoro-4-oxoquinazolin-3(4*H*)-yl)phosphinate) (^{31}P NMR δ = −15.1 ppm, t, J = 4 Hz).



(*N*), **15**



(*N,N*), **16**

This observation is consistent with the involvement of $POCl_3$ in the conversion of the initial products resulting from the reactions of $(O,O)/(N,O)$ and (N,O,O) with Cl^- and $Cl_2P(O)O^-$ to (O) and $(O,O)/(N,O)$, as in eqs 5−9 of the proposed reaction scheme.

A further important point is that ***only*** *O-substituted Phosphate intermediates can react with Cl⁻ or $Cl_2P(O)O^-$ to give product or further intermediates on the reaction pathway*; *N*-substituted intermediates react indirectly via equilibration to the corresponding *O*-substituted species.

Reactions were modeled on the basis of eqs 4 and 7−9 for two different starting phosphate distributions resulting from (a) a "normal" $POCl_3$ addition at 20 °C over 30 min, followed by heating to 70 °C, and (b) a dump-charge of $POCl_3$ at 20 °C, followed by heating to 70 °C. The former addition profile for $POCl_3$ produces higher levels of di- and trisubstituted phosphate intermediates.

Table 2. Rate Constants Derived from the Reaction of Quinazolone 7 with $POCl_3$ in Chlorobenzene at 70°C[a]

reaction	rate constant/M^{-1} s^{-1}
$(O) + Cl^-$ (eq 4)	$k_1 = 1.1_7 \times 10^{-3}$
$(O,O)/(N,O) + Cl^-$ (eq 7)	$k_2 = 3.4_7 \times 10^{-4}$
$(O,O)/(N,O) + Cl_2P(O)O^-$ (eq 8)	$k_3 = 2.1_1 \times 10^{-4}$
$(N,O,O) + Cl^-/Cl_2P(O)O^-$ (eq 9)[b]	$k_4 = 2.1 \times 10^{-4}$
$(N,O) \rightleftharpoons (O,O)$	$K_e = 2.8_1$

[a] Diisopropylethylamine as base. [b] Average rate constant for attack by Cl^- and $(Cl)_2P(O)O^-$.

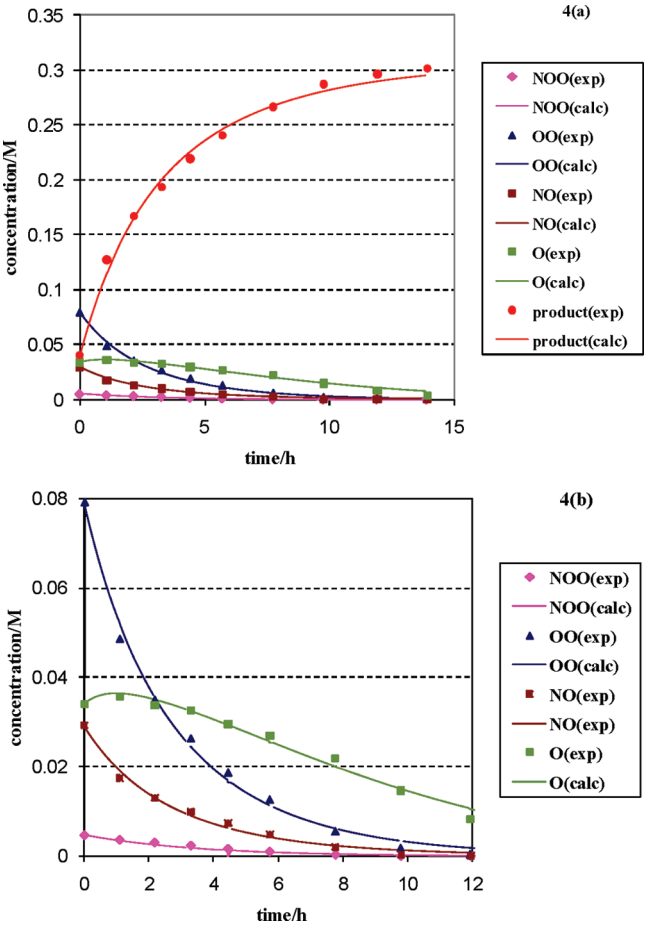


Figure 4. Reaction profiles for intermediates and product for quinazolone 7 at 70 °C in chlorobenzene following 30 min addition of $POCl_3$ at 20 °C (see text); [7] = 0.301 M, $POCl_3$ (1.5 equiv), diisopropylethylamine (1.5 equiv). Full lines are calculated using the rate constants from Table 2: (a) intermediates and products; (b) expanded view of intermediates.

Full details of the kinetic model are given in the Supporting Information. Rate constants for reactions of the various phosphate intermediates derived from quinazolone 7 in chlorobenzene are listed in Table 2.

The reaction profiles are shown in Figures 4 and 5, which include the NMR-derived species concentrations, together with those calculated from the kinetic model using the rate constants listed in Table 2.

dx.doi.org/10.1021/jo102262k |*J. Org. Chem.* 2011, 76, 1653–1661

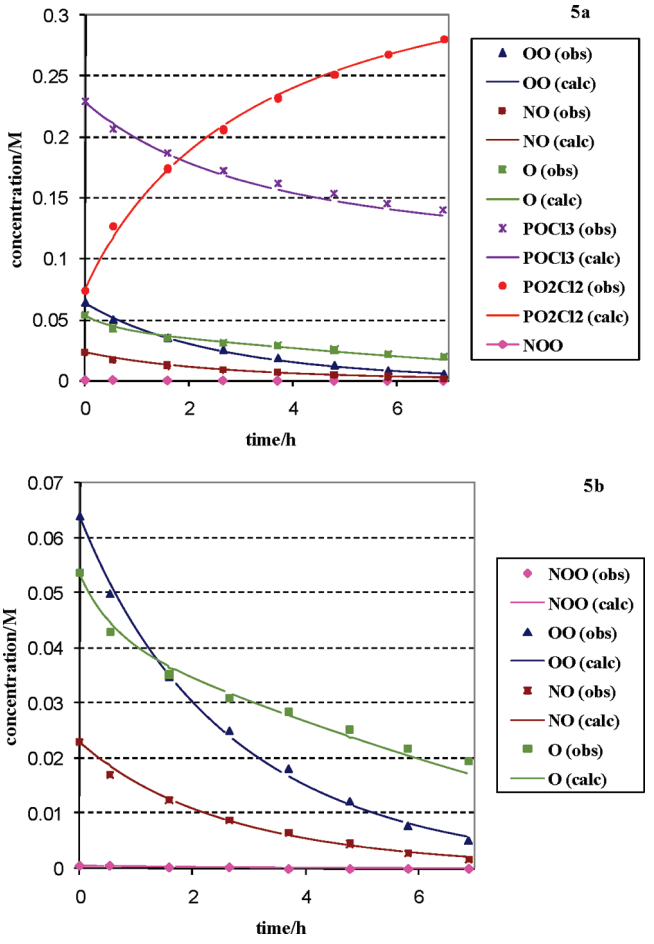


Figure 5. Reaction profiles for phosphate-containing intermediates and product for quinazolone **7** at 70 °C in chlorobenzene following rapid addition of $POCl_3$ at 20 °C (see text); [**7**] = 0.301 M, $POCl_3$ (1.5 equiv), diisopropylethylamine (1.5 equiv). Full lines are calculated using the rate constants from Table 2: (a) intermediates and products; (b) expanded view of intermediates.

The most obvious difference between the profiles in Figure 4 and 5 is to be seen in the behavior of (***O***), which initially increases in Figure 4 (Figure (4a)) but falls continuously in Figure 5 (Figure 5b). This is a consequence of the initially higher levels of di- and trisubstituted intermediates observed upon relatively slow addition of $POCl_3$ (Figure 4); the result is that initially its rate generation from (***O,O***)/(***N,O***) exceeds its rate of reaction with Cl^- to give product QCl.

The good agreement between the experimentally derived values and those calculated using the rate constants in Table 2, especially given the relatively complicated reaction profiles for the two different phosphate distributions, provides strong support for the reaction scheme described in eqs 4−9. We explored a number of possible alternative reaction sequences but were unable to find any that gave similar agreement. Two key features in particular must be accounted for by any successful model: the first is the variation of the concentration of the monosubstituted phosphate (***O***), which clearly reflects both its reaction to products and its formation from the more highly substituted intermediates during reaction; the second is that the decrease in the (***O,O***)/(***N,O***) species is close to exponential and far from the second-order curve that would result from simple reaction of these species with chloride. This

Scheme 3. Influence of Solvent on Dimer Formation

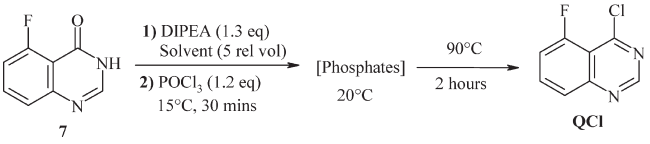


Table 3. Solvent Dependence of Dimer Formation in the Chlorination of 7

solvent	% chloroquinazoline[a]	% dimer[a]
chlorobenzene	>99	<1
methoxybenzene	>99	<1
dimethyl ether	98	2
butyronitrile	97	3
acetonitrile	89	11

[a] Yields are calculated from ^{19}F NMR integrals.

Scheme 4. Influence of Base on Dimer Formation

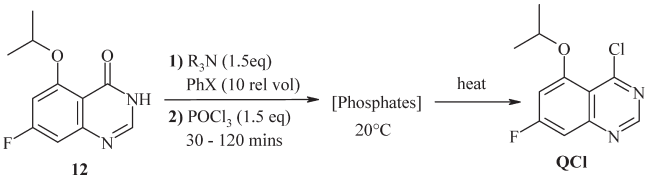


Table 4. Influence of Base upon Dimer Formation in the Chlorination of 12

base	% QCl[a]	% dimer[a]
diisopropylethylamine (80 °C)	99	1
tri-*n*-butylamine (20 °C)	99	1
triethylamine (80 °C)	94	6
triethylamine (20 °C)	88	12

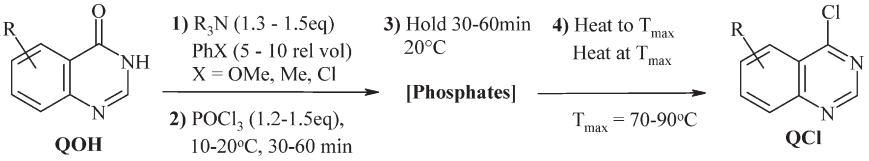
[a] Yields are calculated from ^{19}F NMR integrals.

latter feature is accommodated very well by the (chemically sensible) reaction of the intermediates with both Cl^- (decreasing during reaction) and $Cl_2P(O)O^-$ (increasing), as described in the model. An alternative postulate of nucleophilic catalysis of the substitution reactions by the tertiary amine bases, involving rate-determining reaction between (***O,O***)/(***N,O***) and R_3N, also fits the observed reaction profiles. The steric bulk of the amines would, however, make this very unlikely, and indeed, the reactions showed no rate acceleration upon addition of extra base.

The initial distribution of phosphates depends upon the substitution pattern of the parent quinazolone as well as the mode of addition of $POCl_3$, but in all cases a surprisingly strong tendency to form di- and trisubstituted intermediate phosphates was observed. We note, for example, that for the 5-fluoroquinazolone, **7**, the proportion of the simple monosubstituted derivative (***O***), **8**, corresponds to only 23% of the total quinazolone, even following rapid addition of $POCl_3$ to the quinazolone/base mixture. Alkoxy-substituted quinazolones, however, form a higher proportion of the monosubstituted analogues of **8**, up to

dx.doi.org/10.1021/jo102262k |*J. Org. Chem.* 2011, 76, 1653–1661

Scheme 5. Quinazolone Chlorination with $POCl_3$



65−70% under similar reaction conditions, and overall also give rise to a lower proportion of *N*-phosphorylated intermediates.

Dimer Formation. The optimized reaction conditions applied to the 5-fluoroquinazolone, **7**, namely direct addition of $POCl_3$ (1.2−1.5 equiv) over 30−60 min to a slurry of **7** and diisopropylethylamine (1.2−1.5 equiv) at 15−20 °C in chlorobenzene (5−40 vol), followed by warming to 70−90 °C, afforded the chloroquinazolone with only ∼0.5% dimer. The final outcome of the reaction was, however, sensitive to the nature of both the solvent and the base, despite the fact the almost complete absence of dimer immediately following phosphorylation. This is illustrated by the following examples: the influence of solvent on the chlorination of **7** (Scheme 3) and the influence of base on the chlorination of **12** (Scheme 4). The results are summarized in Tables 3 and 4.

The most pronounced solvent effect on the degree of dimer formation occurred with acetonitrile as solvent (Table 3). We may speculate that this is related to a lower degree of ion-pairing formation in this more polar solvent and that the resulting higher level of free chloride more readily promotes the reverse reaction at phosphorus, giving increased levels of QO^- during reaction.

It should be emphasized that in all cases reported in Tables 3 and 4, reaction mixtures at completion of phosphorylation were essentially completely free of dimer. Thus, dimer formation occurred during the conversion of phosphates to the product chloroquinazoline. This presumably arises from some reversibility of the phosphorylation reaction by reaction of Cl^- at P at higher temperatures to regenerate QO^-, which can then couple with the (*O*)-phosphate to give dimer. In keeping with this, it was confirmed that the use of larger excesses of $POCl_3$ reduced dimer formation in all cases, presumably by competitively converting any QO^- generated to (*O*)-phosphate. Use of aromatic solvents, such as chlorobenzene or anisole, and bases, such as tributylamine and diisopropylethylamine, whose hydrochlorides are soluble at reaction temperatures, minimizes the problem.

SUMMARY

We describe a general method for cleanly converting quinazolones (QOH) to 4-chloroquinazolines, illustrated in Scheme 5.

The key concept underlying Scheme 5 is the separation of two distinct reaction phases, governed by control of reaction temperature. This allows a convenient, direct addition of $POCl_3$ and leads to greatly reduced dimer **6** formation and very high overall yields (>95% in all cases studied). The hold time following $POCl_3$ addition is necessary to ensure complete phosphorylation of QOH prior to heating. Important points may be summarized as follows: (1) An initial fast reaction between $POCl_3$ and QOH under strongly basic conditions at < 25 °C to prepare phosphate intermediates is followed by warming to induce turnover to QCl product. (2) The base must have a $pK_a \geq 9$ (aqueous pK_a); diisopropylethylamine is preferred. (3) Aromatic solvents are preferred, particularly those of higher polarity, such as anisole and chlorobenzene; avoid CH_3CN. (4) Good selectivity with respect to dimer formation and conversion of intermediates to product requires (i) ≥1.0 equiv of R_3N to ensure that conditions remain basic *throughout* $POCl_3$ addition and (ii) ≥1.0 equiv of $POCl_3$ to enable intermediates to funnel effectively to product.

The conditions have been applied successfully to a range of alkoxy- and fluoro-substituted quinazolones at laboratory and kilogram scales. It was noticeable that for the alkoxy-substituted quinazolones, e.g., 6,7-dimethoxyquinazolin-4(3*H*)-one, there was less separation between the rates of phosphorylation and the subsequent chlorination, with some product formation at 20 °C, but this did not affect the outcome. The conditions described may also be expected to be relevant to the chlorination of related systems, such as pyrimidones.

EXPERIMENTAL SECTION

Materials. 5,7-Difluoroquinazolone and inorganic chemicals were high-purity commercial reagents used without further purification.

A typical chlorination reaction with $POCl_3$ with quinazolone in anisole is described for preparation of 4-chloro-5,7-difluoroquinazoline. The chloroquinazoline is not isolated; instead, it is coupled with the appropriate aniline to give the corresponding anilide.

Preparation of 4-Chloro-5,7-difluoroquinazoline. To a cooled (10 °C) slurry of 5,7-difluoroquinazolone (20 g, 0.109 mol, 1.0 molar equiv) and DIPEA (24.90 mL, 0.143 mol, 1.3 molar equiv) in anisole (140 mL, 7 rel vol) was added $POCl_3$ (12.3 mL, 0.132 mols, 1.2 molar equiv) over 30 min, keeping the reaction temperature 20 °C. The mixture was stirred at 20 °C for 1 h, heated to 95 °C, and held at 95 °C for 2.5 h. The mixture is sampled for reaction completion by quenching the analytical sample with pyrrolidine and analyzing by HPLC. Generally, 98−99% (HPLC area %) conversion with ∼ <2% starting material is obtained.

HPLC Method for 4-Chloro-5, 7-difluoroquinazolone. Zorbax SB-C18, 1.8 μm (50 × 4.6 mm), gradient as in Table 5.

Table 5[a]

time/min	% water	% ACN	% TFA (1%)
0	85	5	10
1.0	70	20	10
8.0	45	45	10
8.90	45	45	10
9.0	85	5	10

[a] Run time = 9 min; post time = 2 min; flow rate = 1.5 mL/min; injection volume = 5 μL; column temperature = 30 °C; wavelength = 240 nm. Sample preparation: In a 25 mL volumetric flask, quench 25 μL of the reaction mixture with 0.5 mL of pyrrolidine. Fill to volume with ACN or 1:1 aqueous ACN; 5,7-fluoroquinazolone, rt, 2.22 min; 5,7-difluoro-4-(pyrrolidin-1-yl)quinazoline, rt, 2.57 min.

dx.doi.org/10.1021/jo102262k |*J. Org. Chem.* 2011, 76, 1653–1661

■ ASSOCIATED CONTENT

Supporting Information. Kinetic model, NMR spectra, and HPLC chromatograms for the phosphorylation of 7-fluoro-5-(propan-2-yloxy)quinazolin-4-(3*H*)-one **12** and the formation of 4-chloro-5-fluoroquinazolone, **13** and 4-chloro-5,7-difluoroquinazoline. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For example, reaction of related 5,7-difluoroquinazolin-4-ol with the less reactive P-Cl species $(PhO)_2P(O)Cl$ forms initially predominantly the (***N***)-substituted quinazolone, which then equilibrates with the (***O***)-substituted species ; Pointon, S. Unpublished work.