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Report

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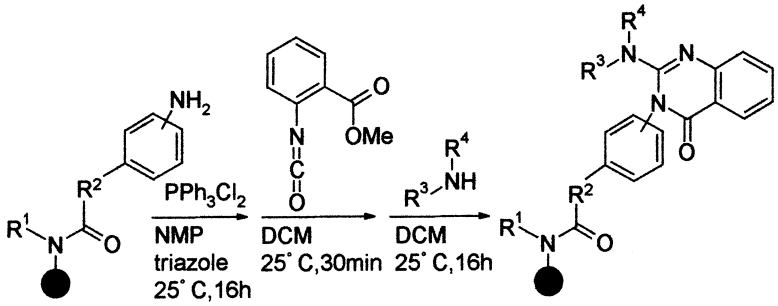

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Efficient Solid-Phase Synthesis of Diverse 2-Aminoquinazolin-4-ones from Resin-Bound Anilines

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Introduction

Combinatorial chemistry for the synthesis of non-peptide organic compounds has emerged as an important tool for drug discovery.[1] Solid-phase synthesis of heterocyclic compounds in particular has been a focus of recent investigations with application toward a variety of drug targets.[2] Among various solid-phase syntheses of heterocycles, we are especially interested in the synthesis of quinazoline-2,4-dione analogues from resin-bound compounds with primary amines, incorporating the amines in the rings of the 3N-position of the quinazoline-2,4-dione analogues[3] (Figure 1). In addition to the fact that these solid-phase syntheses can be applicable to a number of resin-bound compounds with primary amines, a compound with a primary amine can be easily derivatized into compounds with various quinazoline-2,4-dione analogues; therefore, the bioactivities of these derivatized compounds can be compared efficiently. As a part of our project to develop solid-phase syntheses of quinazoline-2,4-dione analogues, we decided to investigate the synthesis of 2-aminoquinazolin-4-ones.[4] Previously, two prominent strategies for the solution-phase synthesis of 2-aminoquinazolin-4-ones were reported, employing an aza-*Wittig* reaction with 2-iminophosphoranebenzoic acid derivatives (**1**,**5**) as a key reaction in both cases[5] (Scheme 1). In route A,[5a,b] 2-aminoquinazolin-4-ones **4** were obtained via intramolecular cyclization by the nucleophilic attack of the nitrogen atom of the amide (**3**), while in route B,[5c] they were obtained via the nucleophilic attack of the amines **8** to the carbodiimide **7** and the subsequent intramolecular cyclization of **9**. Although these two synthetic routes were applied to solid-phase synthesis,[6] the previously reported methods were not applicable to the derivatization of a resin-bound compound with a primary amine. In addition, it was not possible to derivatize the R^1 substitutions on solid-support using the previous methods. Therefore, we decided to develop a solid-phase synthesis for 2-aminoquinazolin-4-ones from a resin-bound primary amine, where derivatization of the R^1 substitutions was possible.

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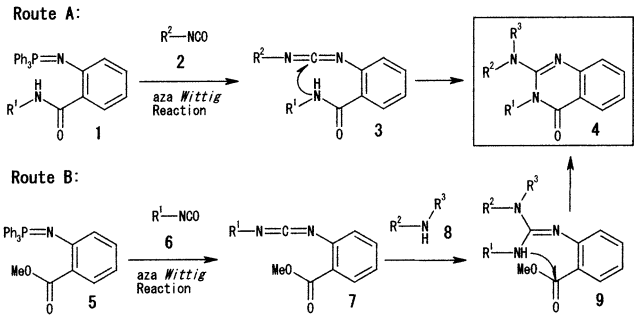
Scheme 1. Two Prominent Solution-Phase Syntheses of 2-Aminoquinazolin-4-ones **4**



Results and Discussion

The model reactant **13** was prepared according to a previous report[3l] (Scheme 2). First, a synthetic protocol similar to route A was investigated to convert **13** into **19**. The iminophosphorane **16** was obtained via the coupling between **13** and 2-azidobenzoic acid[6] **14** and subsequent *Staudinger* reaction.[8] However, the following aza-*Wittig* reaction between **16** and isocyanate **17** and the succeeding treatment of **18** under various reaction conditions for the intramolecular cyclization gave only a mixture of byproducts instead of **19**.[9] Because this type of cyclization was reported to require harsh reaction conditions even in solution-phase,[5b,6b] the cyclization on solid-support may be difficult. On the other hand, the cyclization from **9** to **4** (route B) was reported to proceed under mild conditions;[5c] therefore, the aza-*Wittig* reaction between **20** and **22** and the subsequent reactions in Scheme 3 were initially considered as the straightforward application of route B. However, we decided to perform an aza-*Wittig* reaction between **21** and **23**, exchanging the functionalities between **20** and **22**, because (1) handling of the stable iminophosporane **21** should be easier than isocyanate **20**, and (2) **23** was commercially available, while the solution-phase synthesis of **22** was required. Therefore, intensive investigation for the preparation of **21** was performed; finding the treatment of **13** with Ph_3PCl_2/triazole/DIEA gave iminophosphorane **21** with the best purity (*Kirzanov* reaction[10] was modified to increase the purity). The following aza-*Wittig* reaction between **21** and 2-methoxycarbonyl phenylisocyanate **23** was found to be completed within 30 min to give **24**. Then, treatment of **24** with various secondary amines **25** directly gave **27** via the nucleophilic attack of **25** and the subsequent cyclization of **26** due to the basicity of the excess amount of **25**. In the case that indoline was used as **25** (entry g), the additional treatment with DIEA was necessary because of the insufficient cyclization. Finally, compounds **28** were obtained by treatment of **27** with 95% TFA/H_2O. As shown in Table 1, this synthesis worked excellently with various secondary amines **25**. The limitation of this synthetic protocol is that amines **25** have to be secondary amines. When primary amines (R^2═H) were used as **25**, the cyclization from **26** to **27** was not selective due to the alternative nucleophilic attack

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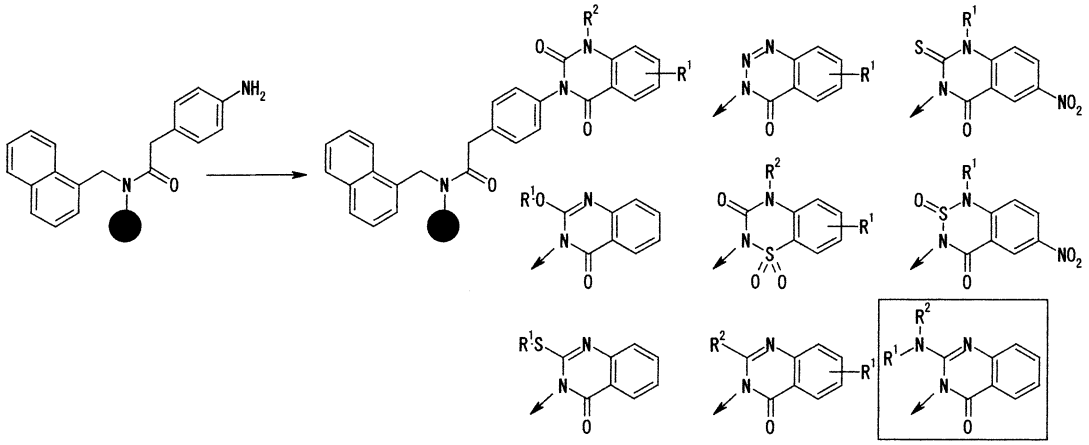
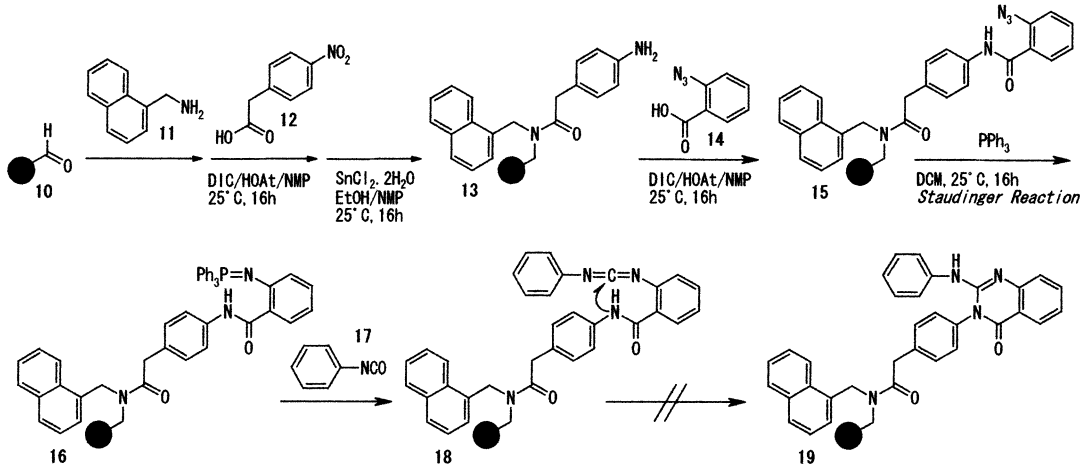
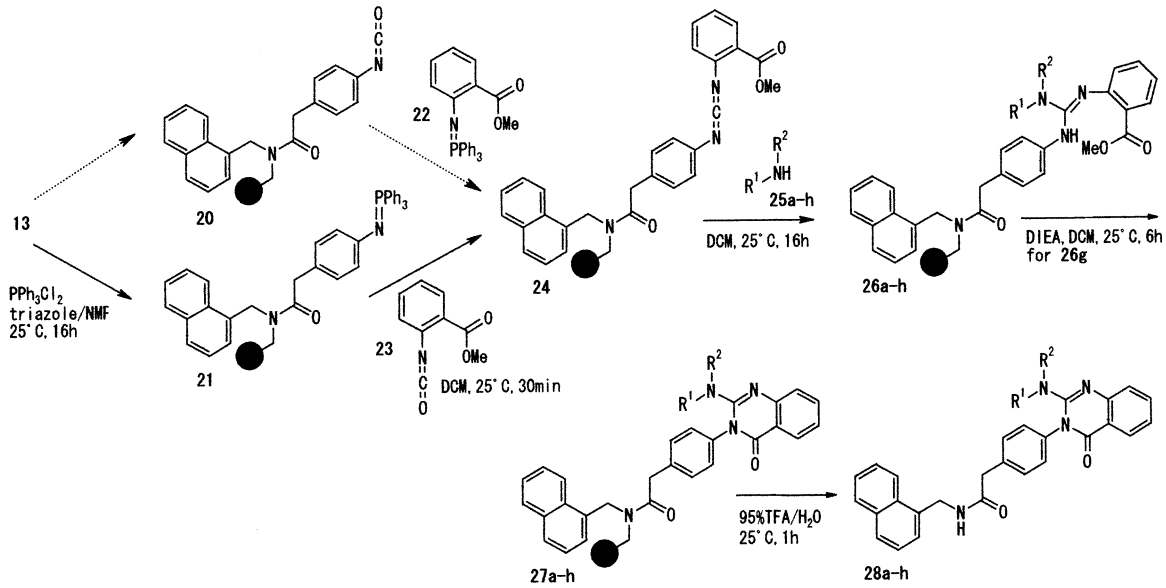


Figure 1. Solid-phase synthesis of quinazoline-2,4-diones and their analogues from a resin-bound compound with a primary amine, incorporating the amine as parts of these derivatized heterocycles.[3] Note that various resin-bound compounds with primary amines in the original reports are simplified to the single starting compound for explanation. Not all the solid-phase syntheses have been tested with these resin-bound amines.

Scheme 2. Attempted Solid-Phase Synthesis of the 2-Aminoquinazolin-4-one **19** According to the Straightforward Application of Route A in Scheme 1



Scheme 3. Solid-Phase Synthesis of 2-Aminoquinazolin-4-ones **28** Similar to Route B with Various Secondary Amines **25**



of the nitrogen atom adjacent to R^1 as described in previous reports[6a] (data not shown).

Furthermore, the synthesis of 2-aminoquinazolin-4-ones **32** was tested with various resin-bound anilines **31** (Scheme 4). As shown in Table 2, 2-aminoquinazolin-4-ones **32** were obtained with good to excellent purity, showing the feasibility of this solid-phase synthesis. Unfortunately, this synthesis did not work with resin-bound alkylamines (data not shown).

Scheme 4. Solid-Phase Synthesis of 2-Aminoquinazolin-4-ones **32** with Various Resin-Bound Reactants **31**

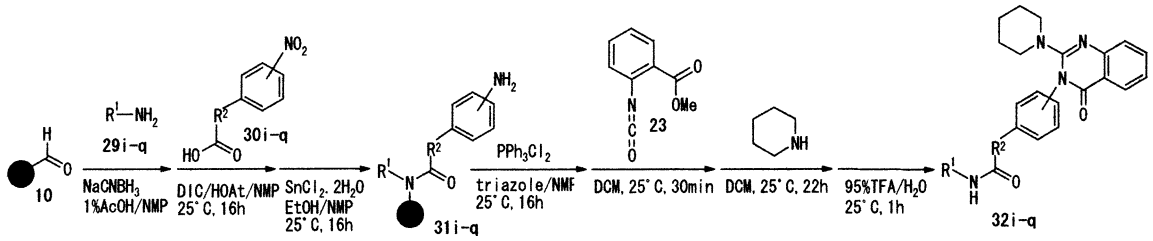
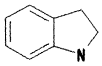
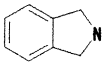
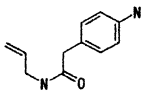
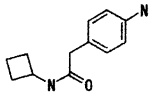
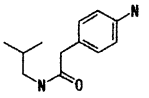
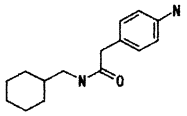
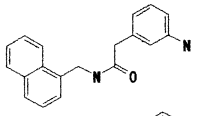
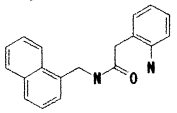
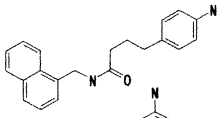
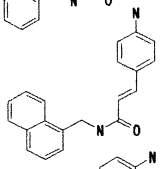
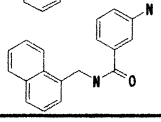


Table 1. Solid-Phase Synthesis of 2-Aminoquinazolin-4-ones with Various Secondary Amines **25**

Entry	28	purity[a] (%)	yield[b] (%)
a		90	92
b		77	76
c		87	88
d		> 95	92
e		81	90
f		87	94
g		81	90
h		84	77

[a] Reverse-phase HPLC was carried out using water/acetonitrile (0.04% TFA) linear gradients from 5 to 98% organic component over 5 min. Flow rate: 2 mL/min. Column: waters symmetry C_{18} (3.5 μm) 4.6 × 50 mm. HPLC purities were determined by summation of integrated HPLC peak areas at (210 + 2N) nm, $N = 0-45$. [b] Crude yields based on the theoretical loading weight of target molecules.

Table 2. Solid-Phase Synthesis of 2-Aminoquinazolin-4-ones with Various Resin-Bound Reactants **31**

Entry	32	purity (%)	yield (%)
i		> 95	94
j		91	89
k		93	91
l		> 95	90
m		86	95
n		74	95
o		> 95	84
p		77	89
q		88	92

It should be noted that the derivatization of the 3N-substitution of 2-aminoquinazolin-4-ones on solid support was easily achieved before the formation of 2-aminoquinazolin-4-ones in our strategy, while the derivatization of 3N-substitution on solid support was not possible in the previous methods.[6] In addition, the synthesis 2-aminoquinazolin-4-ones was demonstrated only from aldehyde-functionalized resin **10**; however, this method was found to work excellently with other types of resins such as Wang resin with ester linker, showing the generality of this solid-phase synthesis.

Conclusion

The solid-phase synthesis of 2-aminoquinazolin-4-ones from various resin-bound anilines, incorporating the nitrogen atom of the anilines in the rings of the 3N-position of 2-aminoquinazolin-4-ones, was developed. Although there are some limitations in terms of the building blocks, we believe that this synthesis, together with the solid-phase synthesis of quinazoline-2,4-dione analogues in Figure 1, would be especially useful for lead optimization/evolution in the pharmaceutical industry.

Abbreviations Used

N,*N*′-diisopropylcarbodiimide (DIC), hydroxy-7-azabenzotriazole (HOAt), *N*-methyl-2-pyrrolidone (NMP), dichloromethane (DCM), diisopropylethylamine (DIEA), trifluoroacetic acid (TFA).

Supporting Information Available. Experimental procedures for the synthesis of **28d**, NMR spectral and ESI mass spectra for the compounds in Tables 1 and 2. This information is available free of charge via the Internet at http://pubs.acs.org.

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(9) Because it was not possible to analyze the unstable intermediates **18**, **24**, and **26**, the purity of these intermediates was estimated indirectly as follows: the purity of **18** was estimated as the corresponding guanidine after treating **18** with piperidine/DCM. The reaction conditions for each synthetic step from **21** to **28** were optimized according to the purity of **28**. The iminophosphorane **21** was found to be stable under 95% TFA/H_2O; thus, the cleavage of compounds from solid supports and the LC-MS analysis were possible, while **16** was decomposed under the same cleavage condition, generating triphenylphosphineoxide.

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