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Efficient Room-Temperature One-Pot Synthesis of 2-Amino-3-alkyl(3-aryl)-quinazolin-4(*3H*)-ones

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Keywords: Heterocycles / Fused-ring systems / Amination / Thioureas / Guanidines

Starting from anthranilates, the one-pot successive addition of ethoxycarbonylisothiocyanate, alkyl- or arylamines, and the coupling reagent EDCI led to the clean, room-temperature formation of carbamate-protected 2-amino-3-alkyl(3-aryl)quinazolin-4(3*H*)-ones in up to 93 % yield. This method provides a practical alternative to previously reported procedures for the synthesis of 2-amino-3-substituted quinazolin-4(3*H*)-ones.

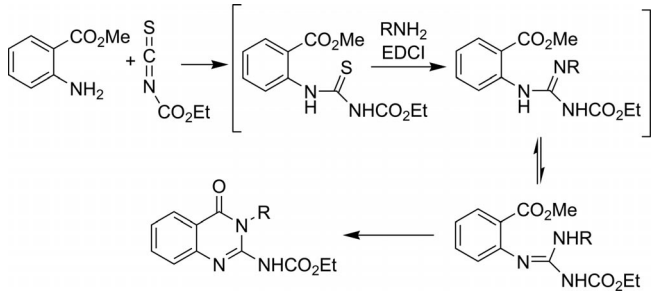
Introduction

Numerous quinazoline-containing compounds display important biological activities; some are marketed such as gefitinib (Iressa)[1] and erlotinib (Tarceva),[2] which are two EGFR inhibitors used in the treatment of cancer. Among quinazoline-containing compounds, 2-aminoquinazolin-4(*3H*)-one derivatives are biologically relevant and have been reported as dopamine agonists,[3] histamine H_4 receptor inverse agonists,[4] K_{ATP} channel modulators,[5] CCK-B antagonists,[6] and antitumor,[7] anti-inflammatory,[8] antihypertensive,[9] antihyperglycemic,[10] or antibacterial agents.[11]

For these reasons, several methodologies have been developed for their synthesis, which has been recently reviewed.[12] These methods can be classified into three main groups including (1) nucleophilic substitution of 2-chloroquinazolin-4(*3H*)-ones,[13] 2-alkylthio-quinazolin-4(3*H*)-ones,[14] or 2-cyanoquinazolin-4(*3H*)-ones[15] by amines; (2) ring-closure reaction from anthranilic acid derivatives with a number of one-carbon reagents such as isothioureas,[3,16] guanidines,[9a] haloformamidines,[11,17] or diphenylcarbonimidates;[18] and (3) the tandem aza-Wittig reaction using iminophosphoranes.[19] These procedures suffer from some limitations such as multistep reactions, harsh conditions, toxicity, or limited availability of reagents such as isocyanates.

More recently, several new routes have been reported, including the copper-catalyzed amination of 2-halobenzoic acids,[20] intramolecular Friedel–Crafts acylation of *N*-carbethoxy-protected arylguanidines,[21] the base-promoted intramolecular ring closure of *ortho*-fluorobenzoylguanidines,[22] and tandem amination/palladium-catalyzed cyclocarbonylation from carbodiimide derivatives.[23]

Although these methods offer multiple entries to the synthesis of 2-aminoquinazolin-4(3*H*)-ones, most of them are limited regarding the synthesis of 2-amino-3-substituted-quinazolin-4(3*H*)-ones. Solid-phase approaches to their synthesis have been reported using multistep procedures, and the cleavage from the resin most often requires strongly acidic conditions.[24] Moreover, in these methods, the ring-closure reaction, mainly from guanidine intermediates, may be nonregioselective depending on the nucleophilicity of both the nitrogen atoms.[24b,24c] It has been shown that *N*-acyl-protected guanidines can easily be obtained in a two-step procedure involving the formation of a thiourea intermediate with commercially available ethoxycarbonylisothiocyanate followed by amination of the latter by using EDCI as a coupling reagent.[25] We thought we could take advantage of this procedure to synthesize diversely substituted 2-amino-3-substituted-quinazolin-4(*3H*)-ones in a one-pot reaction according to Scheme 1.



Scheme 1. One-pot synthesis of 3-alkyl(3-aryl)-2-aminoquinazolin-4(*3H*)-ones.

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Results and Discussion

We initiated our studies with methyl anthranilate (**1a**) as starting material. The reaction of **1a** with ethoxycarbonyl isothiocyanate (1.2 equiv.) in acetonitrile at room temperature led to complete conversion into the corresponding thiourea within 4 h.[26] Adding benzylamine (1.5 equiv.) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 2 equiv.) to the reaction mixture afforded quinazolinone **2a** after 12 h at room temperature. The reaction proceeded probably through the cyclization of the guanidine intermediate, which was not detected. The use of 1 equiv. of benzylamine led only to partial conversion of the isothiocyanate into quinazolinone. It is noticeable that quinazolinone **2a** was obtained in 93% yield after a simple extractive workup and crystallization from diethyl ether. We then explored the reaction by using different primary amines. The results are summarized in Table 1.

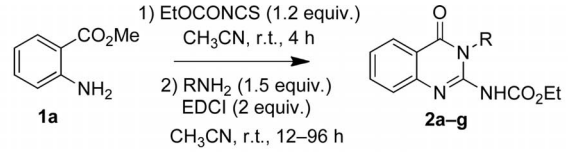
Aliphatic amines, even bulky 2,6-dichlorobenzylamine (Table 1, Entry 2) led to the corresponding quinazolinones in good yields. Interestingly, aromatic amines such as aniline proved to be efficient in this transformation (Table 1, Entry 4), even if the use of less nucleophilic arylamines such as methyl anthranilate (Table 1, Entry 5) and 3-nitroaniline (Table 1, Entry 6) resulted in lower yields and prolonged reaction times.[27] We then evaluated hexamethyldisilazane (HMDS), which has already been shown to be a nitrogen source in the synthesis of guanidines from thioureas.[28] Using 10 equiv. of HMDS led to the formation of *N*-3 unsubstituted quinazolinone **2g** in 71% yield (Table 1, Entry 7). Complete conversion of the thiourea intermediate to the quinazolinone varied from 12 h to 4 d depending on the nucleophilicity of the amine and steric parameters.

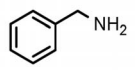
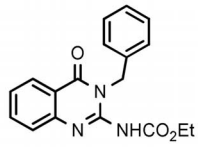
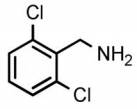
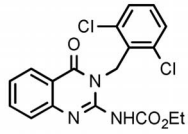
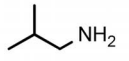
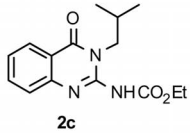
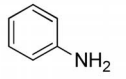
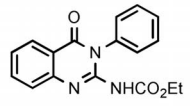
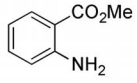
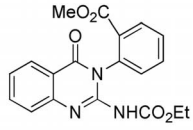
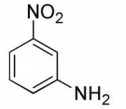
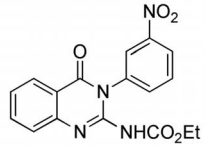
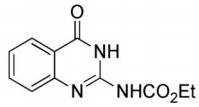
We then evaluated this procedure with anthranilates substituted with either electron-donating or electron-withdrawing groups to explore the generality of the reaction. For each anthranilate, four representative amines were chosen (benzylamine, isobutylamine, aniline, and HMDS). The results are summarized in Table 2.

For each representative anthranilate substituted with either an electron-donating (i.e., **1b**) or an electron-withdrawing group (i.e., **1c**), the reaction worked well, leading to the corresponding quinazolinones **2h**–**o** in high yields. 5-Chloro-substituted anthranilate **1d** led to similar results, and the lower yield observed with aniline was probably due to the partial solubility of resulting quinazolinone **2r** in diethyl ether. However, purification of the quinazolinones by flash chromatography appeared to be very easy and would allow the loss of material due to crystallization workup to be overcome.

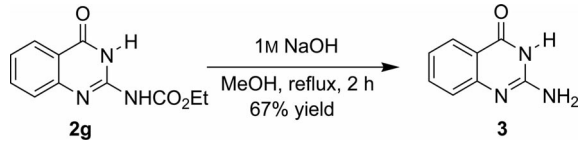
The 2-aminoquinazolinones were obtained as ethyl carbamates; thus, we envisaged their deprotection on a representative compound. Heating protected quinazolinone **2g** at reflux in a mixture of methanol and 1 M NaOH afforded 2-aminoquinazolinone **3** in 67% yield. The free 2-amino group could be further elaborated to create an additional point of diversity (Scheme 2).

Table 1. Scope of amines in the one-pot synthesis of 3-alkyl(3-aryl)-2-ethoxycarbonylaminoquinazolin-4(*3H*)-one derivatives from methyl anthranilate.



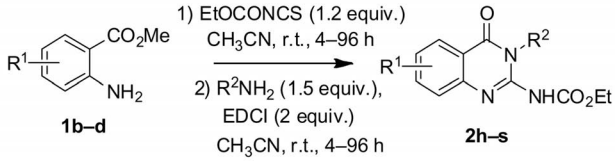
Entry	Amine	Product	Yield [%]
1		 **2a**	93
2		 **2b**	76
3		 **2c**	83
4		 **2d**	86
5		 **2e**	60
6		 **2f**	66
7	$(TMS)_2NH$[a]	 **2g**	71

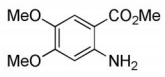
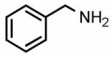
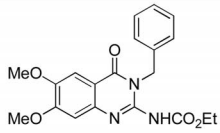
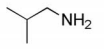
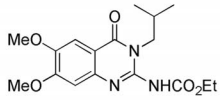
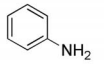
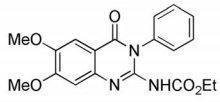
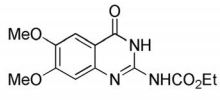
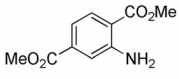
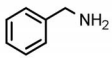
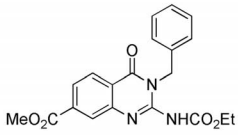
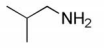
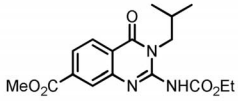
[a] 10 equiv. were used.

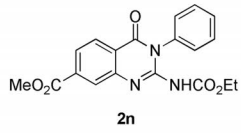
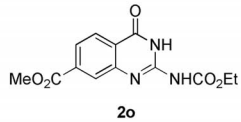
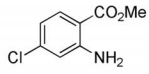
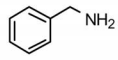
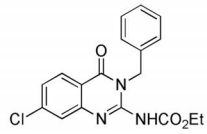
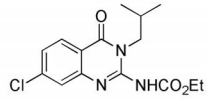
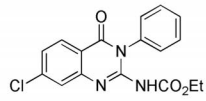
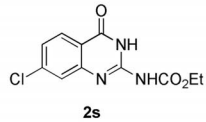


Scheme 2. Deprotection of the carbamate group on a representative example.

Table 2. Synthesis of 2-amino-3-substituted-quinazolin-4(*3H*)ones from diversely substituted anthranilates.



Anthranilate	Amine	Product	Yield [%]
 **1b**		 **2h**	80
1b		 **2i**	70
1b		 **2j**	88
1b	$(TMS)_2NH$[a]	 **2k**	75
 **1c**		 **2l**	85
1c		 **2m**	89

Anthranilate	Amine	Product	Yield [%]
1c		 **2n**	79
1c	$(TMS)_2NH$[a]	 **2o**	69
 **1d**		 **2p**	59
1d		 **2q**	70
1d		 **2r**	36
1d	$(TMS)_2NH$[a]	 **2s**	67

[a] 10 equiv. were used.

Conclusions

In summary, we have developed an efficient route to diverse 2-amino-3-alkyl(3-aryl)quinazolin-4(*3H*)-ones through a mild, room-temperature, three-step, one-pot procedure by combining a variety of anthranilates and primary amines. Owing to the interest of the 2-aminoquinazoline scaffold for the design of biologically relevant compounds, this methodology offers a new practical route for the synthesis of large and diverse chemical libraries. The synthetic applications of this procedure are under investigation in our laboratory.

Experimental Section

General Procedure for the Synthesis of Quinazolinones 2a–s: Ethoxycarbonyl isothiocyanate (1.2 equiv.) was added to a solution of appropriate anthranilate **1a–d** (1 equiv., 1 mmol) in CH_3CN (10 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere until no starting material remained (monitored by LC–MS). The amine (1.5 equiv.) or HMDS (10 equiv.) and EDCI (2 equiv.) were then successively added. The resulting mixture was stirred at room temperature for 24–96 h. The solvent was then removed in vacuo, and the residue was dissolved in EtOAc. The organic layer was successively washed with 1 N HCl/H_2O (2×) and water (1×), dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was either crystallized from dry diethyl ether or purified by silica gel chromatography to afford quinazolinones **2a–s**.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^1H and ^{13}C NMR spectra of the compounds.

Acknowledgments

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