JOC*Note*

Concise Synthesis of 2-Amino-4(3*H*)-quinazolinones from Simple (Hetero)aromatic Amines

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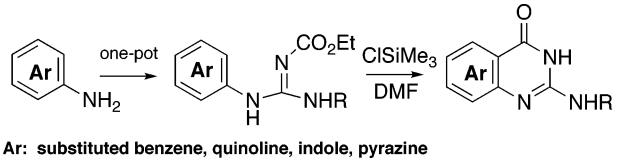


Ar: substituted benzene, quinoline, indole, pyrazine

A novel and simple method of preparation of 2-alkylaminoquinazolin-4-ones with fused heteroaromatic rings from easily accessible (hetero)aromatic amines is described. The method is very efficient, and the 2-alkylaminoquinazolinone derivatives are obtained in three steps without chromatographic purification. The key step is the ring closure of the N-protected guanidine intermediates by intramolecular Friedel−Craft's type substitution.

Introduction

The quinazoline skeleton is found in a number of biologically active molecules. In particular, 2-amino-4(3*H*)-quinazolinone derivatives display a large range of biological properties such as antitumor (thymidylate synthase inhibition1), antibacterial and antifungal activities,[1] antihypertensive effects,[2] or dopamine agonist activity.[3] Very recently this class of compounds was shown to interfere with insulin secretion and smooth muscle contractile activity by targeting K_{ATP} channel activity,[4] and such molecules were tested as analgesic and anti-inflammatory agents.[5] Leonard[6] and, more recently, Kool[7] have also used imidazo[*d*]quinazoline (benzoguanine) as a fluorescent analogue of guanine. Several groups (both from academy and industry) have been involved in the synthesis and study of this family of compounds. Despite their simple skeleton, 2-aryl- and 2-alkylaminoquinazolinones are not easily accessible. Several synthetic methodologies, including recent solid-phase applications, have been reported.[8] As shown in Figure 1, most of them are based on three disconnections. Their major limitations are the availability of diversely substituted aromatic starting materials (mainly anthranilic acid derivatives) and the reactivity and toxicity of the reagents, such as the alkyl- or aryl isocyanates, required in paths **b** or **c**.

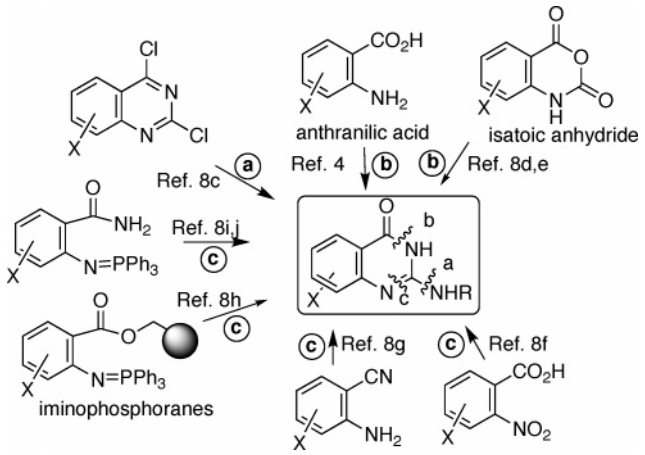
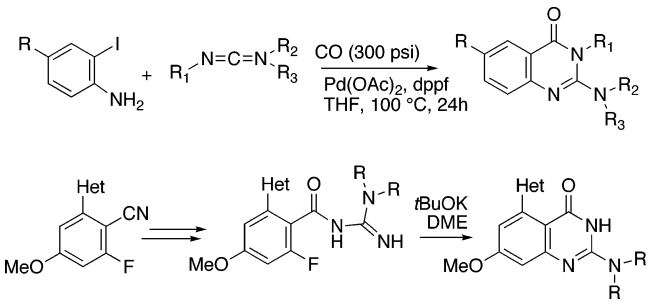


FIGURE 1. Literature data for the preparation of 2-alkylaminoquinazolin-4-one derivatives.[8a−j]

More recently, two new methods were reported (Scheme 1), the palladium-catalyzed cyclocarbonylation of *o*-iodoanilines with heterocumulenes[9] and the base-promoted ring closure of *o*-fluorobenzoylguanidines.[10] This first strategy is dependent on the availability and stability of carbodiimines and requires prolonged heating and high temperature, whereas the other is compatible with the presence of various substituents but gives moderate to low yields of cyclization.

SCHEME 1. Syntheses of 2-Alkylaminoquinazolin-4-one Derivatives from *o*-Iodoanilines and *o*-Fluorobenzoylguanidines



Our research interests focus on the design of biologically active nitrogen heterocycles. In the past years, taking advantage of the regioselective reactivity of aminoacridines with electrophilic reagents, we have prepared several acridine-fused heterocycles of biological interest.[11] We are currently studying the chemical and biological properties of guanidino-substituted acridines. As exemplified in Scheme 2, these compounds are

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(7) Liu, H.; Gao, J.; Kool, E. T. *J. Org. Chem.* **2005**, *70*, 639−647.

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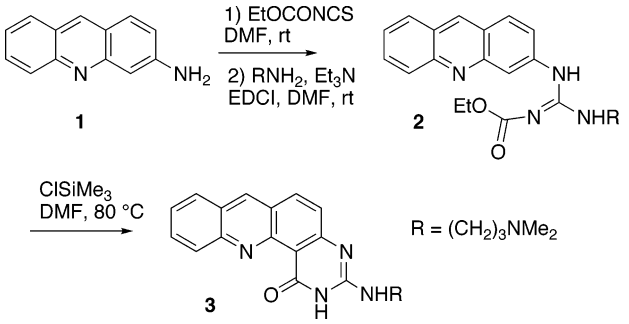
SCHEME 2. Formation of Quinolino[2,3-*f*]quinazolin-1-one Skeleton from 3-Aminoacridine



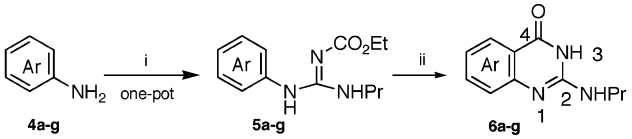
prepared following the Manimala and Anslyn's[12] methodology, by condensing the aminoacridines with ethoxycarbonyl isothiocyanate followed by coupling with aliphatic amines and deprotection of the guanidine function. It appeared to us that the ethoxycarbonyl group of the N-protected guanidino intermediates was ideally positioned to react by intramolecular Friedel−Craft's type substitution, to form, in one step, the fused pyrimidinone ring of 2-alkylaminoquinolino[2,3-*f*]quinazolinone **3** (Scheme 2).

The first attempt of cyclization was performed with guanidinoacridine **2**.[13] The reaction was successfully achieved by heating **2** at 80 °C in DMF in the presence of $ClSiMe_3$ (5 equiv). The desired quinazolinone **3** was isolated as the hydrochloride salt in 95% yield.[14]

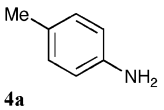
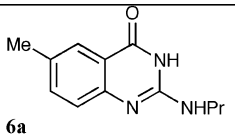
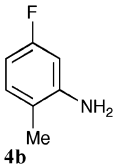
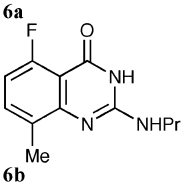
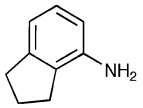
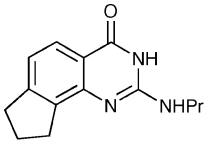
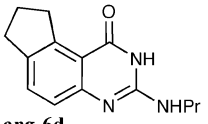
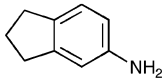
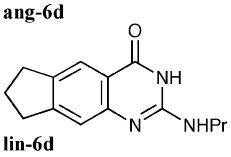
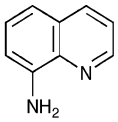
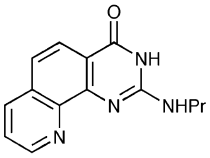
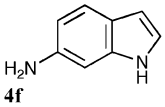
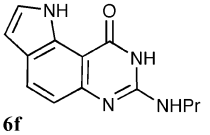
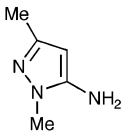
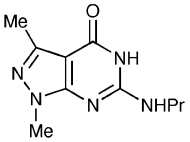
To assess the scope of this approach, we performed this cyclization process with various *N*-aryl and *N*-heteroaryl *N*′-propylguanidines. We report in this paper a new efficient methodology for the synthesis of substituted 2-propylaminoquinazolin-4-ones from simple aromatic and heteroaromatic amines. The results are summarized in Table 1.

The preparation of the ethoxycarbonyl-guanidines **5a**−**g** was performed in one pot by careful control of the stoichiometry of the reagents, successively added to the chosen aromatic amine dissolved in CH_2Cl_2. In most cases, the resulting protected guanidines **5a**−**g** were easily isolated in excellent levels of purity (>95% as shown by HPLC analysis) by simple precipitation from water. The same sequence of reactions was also performed using DMF as the solvent, with similar results. The next step of ring closure was achieved by heating the crude guanidines **5a**−**g** in DMF in the presence of an excess of $ClSiMe_3$. As indicated by HPLC analysis, the guanidines have been fully

TABLE 1. Preparation of 2-Propylamino(3*H*)quinazolin-4-one Derivatives from Aromatic Amines



i) EtOCONCS (1.2 eq.), CH_2Cl_2, rt, 90 min, then Et_3N (3 eq.), $PrNH_2$ (2 eq.) and EDCI (1.2 eq.), 6h, rt; ii) $ClSiMe_3$ (5 or 10 eq.), DMF, 80 °C

Entry	Starting aromatic amine Ar-NH_2 **4a-j**	Product **6a-j**	Yield (%)
1	 **4a**	 **6a**	91[a]
2	 **4b**	 **6b**	86[a]
3	 **4c**	 **6c**	87[b]
		 **ang-6d**	
4	 **4d**	 **lin-6d**	89[b]
5	 **4e**	 **6e**	88[b]
6	 **4f**	 **6f**	90[b]
7	 **4g**	 **6g**	88[b]

[a] $ClSiMe_3$ (5 equiv), 5 h reaction. [b] $ClSiMe_3$ (10 equiv), overnight reaction.

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(12) Manimala, J. C.; Anslyn, E. V. *Tetrahedron Lett.* **2002**, *43*, 565−567.

(13) The synthesis and reactivity of compound **2** and other acridine analogues will be described elsewhere. The spectroscopic data of compounds **2** and **3** are given in the Supporting Information.

(14) Zeghida, W. Ph.D. thesis, Université Joseph Fourier, Grenoble, France, 2007.

converted into the corresponding quinazolinone analogues (**6a**−**g**), which were isolated as free bases in excellent yields by evaporation of the solvent and trituration of the residue in water in the presence of NH_4OH. As observed previously in the acridine series, the cyclization step was regioselective in the indole series (entry 6) and occurred on the carbon adjacent to the ring junction.[15] With the aminoindane isomer **5d**, a mixture of two regioisomers (linear **lin-6d** and angular **ang-6d**) was obtained. The two isomers were clearly characterized and quantified by ^1H NMR (two singlets for aromatic protons of **lin-6d** and two doublets for **ang-6d**). A 10/8 ratio in favor of the linear isomer was found.[16] It is worth noting that the proton NMR spectra of quinazolinones **6a**−**g** are characterized by the strong deshielding of the aromatic proton peri to the 4-oxo substituent, and the broadening of the aromatic proton peri to the N1 position, indicating an ongoing N1-H−N3-H tautomerism.

As shown in Table 1, the reaction is compatible with a wide range of aromatic cycles: phenyl and five- or six-membered fused heterocycles.

In conclusion, this unique cyclization process is very attractive because diversely substituted aromatic amines are easily available. Large quantities of N-ethoxycarbonyl guanidine intermediates can be prepared in one pot in good to high yields. It may be also worth isolating the thiourea intermediates (by simple precipitation from the reaction mixture), as they are key intermediates to build libraries of quinazolinones containing various 2-alkyl or arylamino groups. This methodology allows rapid preparation of large amounts of highly substituted quinazolinones with excellent purity and in good to high yields.

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(16) The two isomers are not separated in our HPLC conditions (reversed-phase C_{18} column, pH 2.5 H_2O−MeOH solvent gradient) and give two adjacent spots on TLC (silica gel, Et_2O). No attempt of separation was made as the mixture was well characterized and quantified by NMR.

Experimental Section

General Procedure for One-Pot Synthesis of Guanidine Derivatives. Ethyl isothiocyanatoformate (135 μL, 1.2 mmol) was added to a solution of the (hetero)cyclic amine (1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred at room temperature for 1.5 h. The disappearance of the starting amine was checked by TLC or HPLC analysis. To the solution, Et_3N (416 μL, 3 mmol), propylamine (166 μL, 2 mmol), and EDCI (229 mg, 1.2 mmol) were successively added. The resulting mixture was stirred for 6 h at room temperature or 60 °C (depending on the solubility of the thiourea intermediate). The solvent was then evaporated to dryness. The resulting oily residue was diluted with water. The guanidines were isolated either as solids by simple filtration or as oils after dilution with water and extraction with CH_2Cl_2. The purity of the guanidine was checked by HPLC analysis and was found to be >95%. The guanidines were used in the next step without further purification.

General Procedure for the Synthesis of Quinazolinone Derivatives. The protected guanidine **5a**−**g** (1 mmol) was dissolved in anhydrous DMF (3 mL), and $ClSiMe_3$ (5 or 10 mmol) was added to the solution and stirred at 80 °C. The reaction was monitored by HPLC. When the reaction was completed, water (2 mL) was added and the solvents were removed under reduced pressure. The residue was stirred in water, and aq. NH_4OH was added to reach neutral pH. The precipitate thus formed was filtered, washed with water, and dried to give the desired compound **6a**−**g**.

Supporting Information Available: Experimental details and full compound characterization data as well as copies of ^1H and ^{13}C spectra are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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