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Acid catalyzed synthesis of 2-(2-aminophenyl)quinazoline-4-amine and reaction with aromatic aldehydes

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The hydrochloride salt of 2-(2-aminophenyl)quinazoline-4-amine, prepared from a quinazolino[3,4-*a*]quinazoline, was reacted with aromatic aldehydes under conventional heating or microwave irradiation, leading to high yields of tetracyclic dihydroquinazolines.

Introduction

The quinazoline motif is widely present in naturally occurring alkaloids isolated from plants, in commercial drugs and in a diversity of bioactive compounds. The synthetic strategies to prepare different quinazoline derivatives and their biological properties have been extensively documented in reviews and monographs.[1] The reported activities that include anticancer, antimicrobial, anti-inflammatory, antiviral, antitubercular, anticonvulsant or anti-depressant, highly depend on the substitution pattern and/or on the fused heterocyclic system associated to the quinazoline skeleton. This observation continues to inspire researchers in the development of new and eco-friendly methods to create diversity-oriented libraries of highly functionalized compound. Conventional heating methods have been generally applied,[2] as well as other strategies that include the use of efficient and greener catalysts,[3] multicomponent reactions[4] or microwave irradiation.[5]

The importance of 1,2-dihydroquinazoline derivatives has been documented and different methods have been reported for their synthesis, involving heating conditions or microwave irradiation. These compounds have been previously prepared from the reaction of 2-aminobenzamidine with aldehydes or ketones in refluxing ethanol[6] or from 2-aminobenzonitrile and Grignard reagents, followed by condensation with an aldehyde.[7] 1,2-Dihydroquinazolines were also prepared from the reaction of 2-aminobenzophenone with aldehydes in urea, under microwave irradiation[8] or in the presence of ammonium acetate catalyzed by DMAP, in ethanol at 40 ºC.[9] A different strategy used the microwave-promoted reaction of 2-aminoarylalkanone *O*-phenyl oximes with aldehydes in toluene.[10]

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The presence of reactive functional groups in the quinazoline core has been widely used to explore the preparation of structurally novel types of derivatives and/or the combination with recognized pharmacophores, to modify traditional drugs. The amino group, in particular, can be regarded as an important synthon and a recent publication reports the selective amidation of 2,4-diaryl quinazolines.[11] The reaction uses sulfonyl azides as the amine source and proceeds with exceptional regioselectivity in the ortho position of the 2-aryl group, induced by a rhodium catalyst and assisted by a meta substituent on the ring.

As a continuation of our ongoing study on the synthesis of quinazolino[3,4-*a*]quinazolines[11] herein we report their transformation into 2-aminophenyl quinazolines. These compounds were used in the reaction with aromatic aldehydes to generate novel and highly stable dihydro-quinazolino[3,4-*a*]quinazolines by two different eco-friendly methods.

Results and discussion

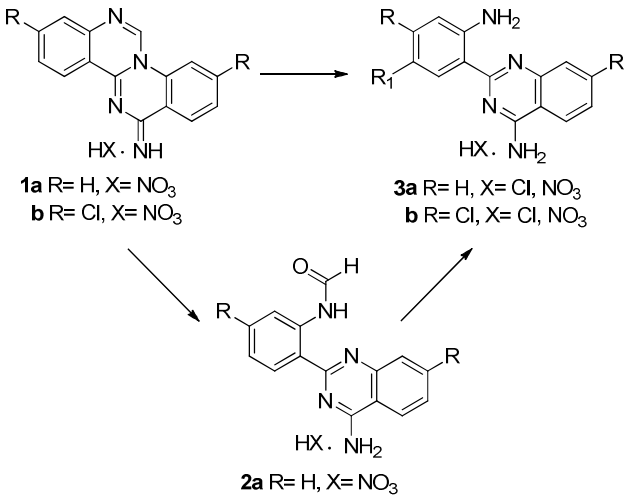
Quinazolino[3,4-*a*]quinazolines **1**, used as starting material for the preparation of 2-(2-amino)quinazolines **3**, were previously prepared from the reaction of anthranilonitrile and triethylorthoformate (TEOF). The product was isolated in 80 % yield from ethanol and 1 molar equivalent of nitric acid, after 3h (**1a**) or 3 days (**1b**) at 40 ºC.[12]

In the present work, the reactivity of the dimeric quinazoline **1** was studied in ethanol/methanol or aqueous solution, in the presence of inorganic acid or base (Table 1).

The reaction of **1a**, used as the nitrate salt, was initially performed in water, at room temperature, for 18 h. The formamide unit was maintained in the product (**2a**), isolated in 70% yield upon hydrolysis (entry 1). The yield was considerably improved using 3M NaOH under similar experimental conditions (entry 2, 96%). The synthesis was equally successful from the neutralized quinazolino[3,4-*a*]quinazolines **1a**, leading to the same product **2a** in 92% yield either upon heating at 60 ºC in water or in aqueous base at room temperature (entries 3 and 4). Compounds **1a** and **1b**

were also combined with conc. hydrochloric acid in methanol, at room

Table 1 Optimized experimental conditions for the synthesis of quinazolines **2** and **3** from quinazolino[3,4-*a*]quinazolines **1**



Entry	Reagents	Reaction conditions	Product (yield)
1	**1a**.HNO_3	H_2O, r.t, 18 h	**2a**, X= NO_3 (70%)
2	**1a**.HNO_3	NaOH (aq) 3M, r.t, 18 h	**2a** (96%)
3	**1a**	H_2O, 60 ºC, 18 h	**2a** (92%)
4	**1a**	NaOH (aq) 3M, r.t, 18 h	**2a** (92%)
5	**1a**.HNO_3	MeOH, HCl, r.t., 4 h	**3a**, X= Cl (93%)
6	**1a**.HNO_3	H_2O, EtOH, HNO_3, r.t, 6 days	**3a**, X= NO_3 (91%)
7	**1b**.HNO_3	MeOH, HCl, r.t., 16 h	**3b**, X= Cl (93%)
8	**2a**.HNO_3	H_2O, HNO_3, 110 ºC, 1 day	**3a**, X= NO_3 (70%)

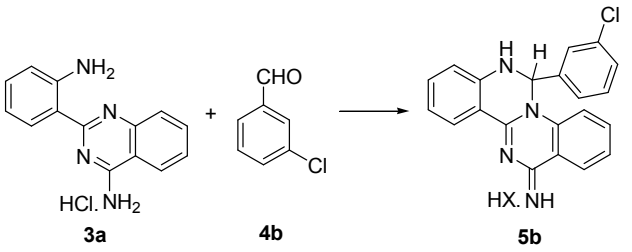
temperature (entries 5 and 7). The hydrochloride salt of the corresponding products **3a** and **3b** precipitated from solution and were isolated as yellow solids by simple filtration after 4 h (**3a**) or 16 h (**3b**), both in 93% yield. The use of nitric acid in ethanol/water (Table 1, entry 6) led to the nitrate salt of **3a**, isolated in 91% yield after 6 days, at room temperature. These results indicate that, in acidic medium, hydrolysis is followed by cleavage of the formyl group, leading to the diamine **3** in excellent yield. This was confirmed by the isolation of **3a** when **2a** was heated in aqueous nitric acid (entry 8). The hydrochloride salt of **3a** was neutralized in acetone and 3M NaOH solution and the product was isolated in 77% yield.

The synthesis of 2-(2-aminophenyl)quinazolin-4-amine **3a** was previously reported from the reaction of anthranilonitrile with sodium hydride in dimethyl sulphoxide, at 0 ºC (3 h) followed by 21 h at 25 ºC.[13] The product was isolated in almost quantitative yield after addition of aqueous HCl. This reaction was equally successful using sodium methoxide in dioxane, but the product was isolated in 75% yield.[14] Combining anthranilonitrile with 10 mol % of potassium t-butoxide[15] under microwave irradiation (700 W) for 1 minute led also to compound **3a**, isolated in 82% yield.

The reaction between the neutral pyrimidine **3a** and 2-methoxybenzaldehyde **4f** was initially followed by ^{1}H NMR, in deuterated DMSO (600 µl; **3a**, 10 mg; **4f**, 1.1 equiv.). No reaction was observed after 7h at 60 ºC and addition of a catalytic amount of TFA was equally unsuccessful, after 20 h at 60 ºC. The experiment was reproduced in ethanol and the reagents (**3a**:**4f**, 1:1.1 molar ratio) were refluxed for 30 h. TLC showed no evidence for product formation and **5f** was only quantitatively generated after addition of HCl (1 molar equivalent) and reflux for 30 min. This result indicates that the presence of one equivalent of acid is essential for a smooth reaction to occur and all the experiments were performed from the hydrochloride salt of **3a.** The quinazolino[3,4-*a*]quinazolines **5** were generated by nucleophilic attack of the most reactive amino group to the carbonyl function, followed by intramolecular cyclization to the neighbouring quinazoline nitrogen, with elimination of water.

A preliminary study on the effect of solvent, temperature and acid/base catalysis on the product yield was performed using the reaction of **3a** with **4b** (Table 2). When **3a** and **4b** were combined in

Table 2 Optimization of the experimental conditions for the reaction of compound **3a** with aldehyde **4b**.



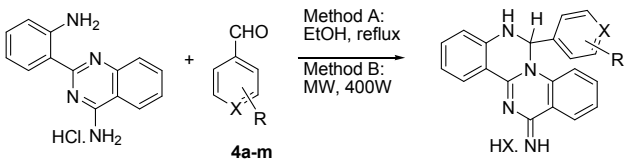
Entry	Reagents (equiv.)	Reaction conditions	Product (yield)
1	**3a** + **4b** (1:2)	THF, HNO_3, r.t., 6 days	**3a** + **5b** (1:1.4)[a]
2	**3a** + **4b** (1:2)	EtOH, HNO_3, r.t., 3 days	**5b** (85%)
3	**3a** + **4b** (1:2)	EtOH, NEt_3, r.t., 1.5 days	Complex Mixture[b]
4	**3a** + **4b** (1:2)	EtOH, DBU, r.t., 1.5 days	**3a** + **5b** (1:2.7)[b]
5	**3a** + **4b** (1:1.1)	EtOH, reflux, 2 h	**5b** (86%)
6	**3a** + **4b** (1:1.2)	EtOH, MW, 400W, 5 min	**5b** (94%)

[a] By ^{1}H NMR. [b] By TLC.

a 1:2 molar ratio, using THF as solvent and nitric acid catalysis, the quinazoline **3a** was still present after 6 days at room temperature (entry 1). Changing the solvent to ethanol under similar reaction conditions led to the isolation of **5b** in 85% yield after 3 days at room temperature (entry 2). Ethanol was definitely a better solvent than THF and was selected for the remaining experiments where trimethylamine or DBU were used as base catalysts (entries 3 and 4 respectively). After 1.5 days at room temperature, experiment 3 resulted in a complex mixture while experiment 4 allowed the isolation of a solid product that proved to be a combination of **3a** and **5b** in a 1:2.7 molar ratio, by ^{1}H NMR. Refluxing the reagents in ethanol proved to be the most convenient approach, resulting in 86% isolated yield of **5b** after 2 h (entry 5). The use of microwave irradiation (400 W for 5 min) was equally successful leading to 94% yield of the product (entry 6).

Experiments 5 and 6 were considered the optimal reaction conditions and compound **3a** was reacted with a variety of aromatic aldehydes (**4a-m**) either under conventional heating conditions in ethanol (method A) or under microwave irradiation at a constant power of 400 W (method B). Table 3 summarizes the individual experimental conditions that were used and the overall yield of product **5**, isolated as a yellow solid. Products **5a-m** were collected by simple filtration in excellent yield from both methods A or B.

Table 3 Selected of experimental conditions for the reaction of compound **3** with aldehydes **4**.



3a **4a-m** **5a-m**

a, R= 2-Cl, X= CH
b, R= 3-Cl, X= CH
c, R= 4-Cl, X= CH
d, R= 4-CN, X= CH
e, R= 4-NO_2, X= CH
f, R= 2-OMe, X= CH
g, R= 3-OMe, X= CH
h, R= 4-OMe, X= CH
i, R= 4-OH, X= CH
j, R= 4-Me, X= CH
k, R= 3,4-OH, X= CH
l, R= H, X= N
m, R= H, X= CH

Entry	Reagents (equiv.)	Reaction conditions	Product (yield)
1	**3a** + **4a** (1:1.2)	EtOH, reflux, 2 h	**5a** (84%)
2	**3a** + **4a** (1:1.2)	EtOH, MW, 400W, 5 min	**5a** (85%)
3	**3a** + **4b** (1:1.1)	EtOH, reflux, 2 h	**5b** (86%)
4	**3a** + **4b** (1:1.2)	EtOH, MW, 400W, 5 min	**5b** (94%)
5	**3a** + **4c** (1:1.2)	EtOH, reflux 12 h	**5c** (91%)
6	**3a** + **4c** (1: 1.2)	EtOH, MW, 400W, 5 min	**5c** (94%)
7	**3a** + **4d** (1:1.1)	EtOH, reflux 1.5h	**5d** (86%)
8	**3a** + **4d** (1:1.2)	EtOH, MW, 400W, 5 min	**5d** (84%)
9	**3a** + **4e** (1:1.32)	EtOH, reflux 5 h	**5e** (92%)
10	**3a** + **4e** (1:1.2)	EtOH, MW, 400W, 5 min	**5e** (90%)
11	**3a** + **4f** (1:1.1)	EtOH, reflux 15 min	**5f** (97%)
12	**3a** + **4f** (1:1.2)	EtOH, MW, 400W, 5 min	**5f** (96%)
13	**3a** + **4g** (1:1.1)	EtOH, reflux 25 min	**5g** (94%)
14	**3a** + **4g** (1:1.2)	EtOH, MW, 400W, 5 min	**5g** (96%)
15	**3a** + **4h** (1:1.1)	EtOH, reflux 50 min	**5h** (86%)
16	**3a** + **4h** (1:1.2)	EtOH, MW, 400W, 5 min	**5h** (90%)
17	**3a** + **4i** (1:1.2)	EtOH, reflux 4 h	**5i** (83%)
18	**3a** + **4i** (1:1.2)	EtOH, MW, 400W, 5 min	**5i** (84%)
19	**3a** + **4j** (1:1.2)	EtOH, reflux 12.5h	**5j** (86%)
20	**3a** + **4j** (1:1.2)	EtOH, MW, 400W, 5 min	**5j** (90%)
21	**3a** + **4k** (1:1.1)	EtOH, reflux, 1.5 h	**5k** (91%)
22	**3a** + **4k** (1:1.2)	EtOH, MW, 400W, 5 min	**5k** (93%)
23	**3a** + **4l** (1:1.1)	EtOH, reflux, 4 h	**5l** (92%)
24	**3a** + **4j** (1:1.2)	EtOH, MW, 400W, 5 min	**5l** (95%)
25	**3a** + **4m** (1:1.1)	EtOH, reflux, 4 h	**5m** (74%)
26	**3a** + **4m** (1:1.1)	EtOH, MW, 400W, 5 min	**5m** (76%)

The quinazolines **5** proved to be highly stable in air and heat. A solution of **5b** in deuterated DMSO was heated to the boiling point of the solvent with no detected degradation of the product, by ^{1}H NMR performed when the solution reached room temperature. Products **5** clearly showed the presence of a sp^3 carbon and two characteristic protons on NH and CH in adjacent positions (by ^{1}H NMR, δ 8.65 and 7.72 ppm, *J* 4 Hz). The feasibility to generate the aromatic tetracyclic skeleton in the presence of an oxidizing agent was also tested. Studies on the evolution of **5b** were conducted by ^{1}H NMR spectroscopy in DMSO-d_6 solution and in the presence of DDQ. A catalytic amount of DDQ was added to a solution of **5b** (3 mg) in deuterated DMSO (650 μL) and the NMR tube was allowed to stand at 20 ºC. The spectrum was registered after 1 and 5 days, evidencing that the composition of the solution remained unchanged. The sample was placed at 60 °C and after 7 days, the two doublets were still clearly present. The mixture was heated to the boiling point of the NMR solvent during 1 to 5 minutes. Again no evolution was observed in the ^{1}H NMR spectrum and the coupling between the NH and CH protons was undoubtedly present.

Compound **5b** demonstrated a high stability to temperature and to oxidation but in the ^{1}H NMR spectrum, some of the compounds **5** consistently showed the presence of trace amounts of aldehyde and quinazoline **3a** in a 1:1 molar ratio. This observation led us to study the effect of temperature on the chemical composition of the NMR solution of a selection of these compounds in DMSO-d_6. The solutions were prepared using 3 mg of solid material in 650 μL of deuterated solvent and the ^{1}H NMR spectra were registered at 20 °C and 80 °C. Table 4 summarizes the relative percentage of tetracyclic compound **5** and starting material **3a**, calculated from the integration of the triplet at δ 7.47-7.50 ppm corresponding to C9-H (**5b**, **5h**, **5m**) of the doublet at δ 6.98-7.03 ppm corresponding to C8-H (**5c**, **5d**, **5j**) or the doublet at δ 6.56 ppm for C6'-H of **5g**. Compound **3a** was quantified from the triplet at δ 6.71 ppm for C5-H. For each compound, the relative percentage of the tetracyclic structure and of starting material (**5:3a**), present in solution at 80 °C and 20 °C, was calculated**.**

In an attempt to understand if the nature and position of the substituent on the aromatic ring of the aldehyde influenced the relative amounts of the species in solution at 80 °C and 20 °C we used the Hammett-Brown parameter (σ*), calculated for the aryl group using the "ACD Lab Sigma Predictor" program. The relationship of this parameter with log K, defined as the ratio K = [**5**] / [**3a**], is depicted in scheme 1. A linear relationship was observed between these values, either at 80 °C or at 20 °C, confirming that the polar effect of the aromatic substituent influences this equilibrium.

Considering that the Hammett-Brown parameter (σ*) reflects the polar effect of the aromatic substituent incorporating the R group, the analysis of these results suggests that as the electron-withdrawing character of the substituent increases, the ratio of the tetracyclic structure **5** increases when compared to the precursor **3a**. This effect is more evident at 20 °C than at 80 °C.

The equilibrium may be due to a strong interaction between the two nitrogen atoms of the dihydropyrimidine unit in compound **5** with a water molecule, as is represented in scheme 2. In this association, the inter-conversion boat-chair must be accelerated as the temperature is raised. At 80 ºC, a higher contribution of the boat conformation is expected, favouring the intramolecular nucleophilic attack of the oxygen atom to the sp^3 carbon, regenerating the reagents **3a** and **4**.

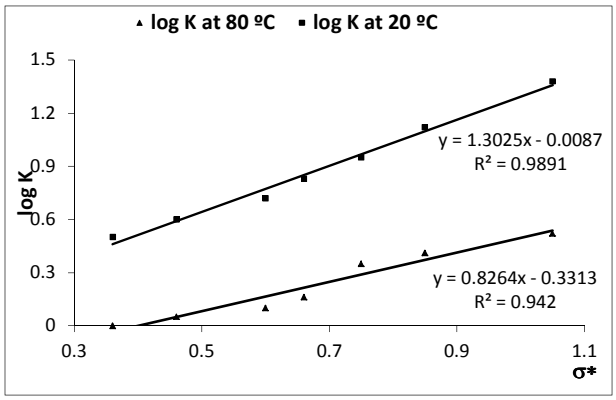
The presence of electron withdrawing substituents in the aromatic ring decreases the basicity of the adjacent amino groups, and the stability of the association with the water molecule is consequently

reduced, leading to an enhanced concentration of the tetracyclic structure **5**. When the sample studied at 80 ºC was allowed to cool to 20 ºC, the compound ratio reproduced the values initially registered by ^{1}H NMR at this temperature, clearly evidencing an equilibrium that favours the tetracyclic structure.

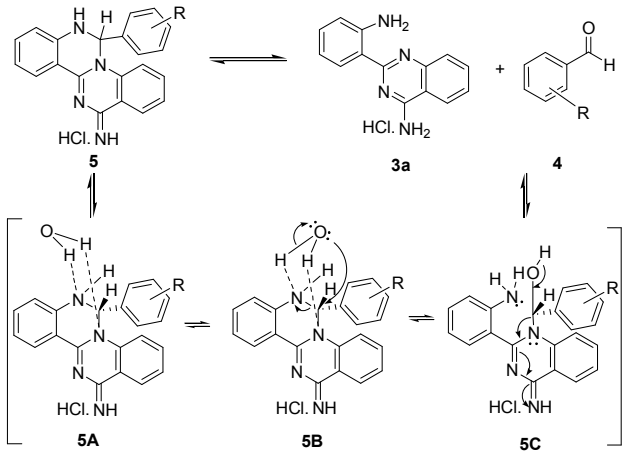
Table 4 Relative ratio of **5** and **3a** (in DMSO-d_6 at 20 ºC and 80 ºC) and Hammett-Brown parameters (σ*) for the aromatic substituents of aldehyde **4**

Comp	R (aldehyde)	σ*[a]	20 ºC				80 ºC			
			5 (%)	**3a** (%)	K[b]	Log K	**5** (%)	**3a** (%)	K[b]	Log K
5h	***p*-OMe**	0.36	76	24	3.17	0.50	50	50	1	0
5j	***p*-Me**	0.46	80	20	4.00	0.60	53	47	1.12	0.05
5m	**H**	0.60	84	16	5.25	0.72	55	45	1.27	0.10
5g	***m*-OMe**	0.66	87	13	6.69	0.83	59	41	1.44	0.16
5c	***p*-Cl**	0.75	90	10	9.00	0.95	69	31	2.23	0.35
5b	***m*-Cl**	0.85	93	7	13.29	1.12	72	28	2.57	0.41
5d	***p*-CN**	1.05	96	4	24.00	1.38	77	23	3.35	0.52

[a] Calculated using the "ACD Lab Sigma Predictor" program. [b] K = [**5**] / [**3a**].



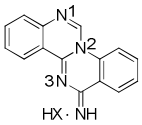
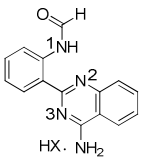
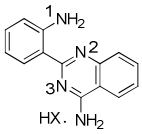
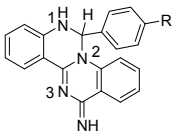
Scheme 1 Plot of log K (K = [**5**]/[**3**]) in DMSO-d_6 versus the Hammett-Brown parameters σ*.



Scheme 2 Mechanistic proposal for the equilibrium between the reagents **3a** and **4** and the tetracyclic structure **5**, induced by heating.

All compounds were characterized by the usual analytical and spectroscopic techniques and a selection was also studied by ^{15}N/^{1}H HMBC correlation spectra (Table 5).

Table 5 Data for ^{15}N chemical shifts by HMBC correlation to ^{1}H NMR signals, obtained in DMSO-d_6 solution.

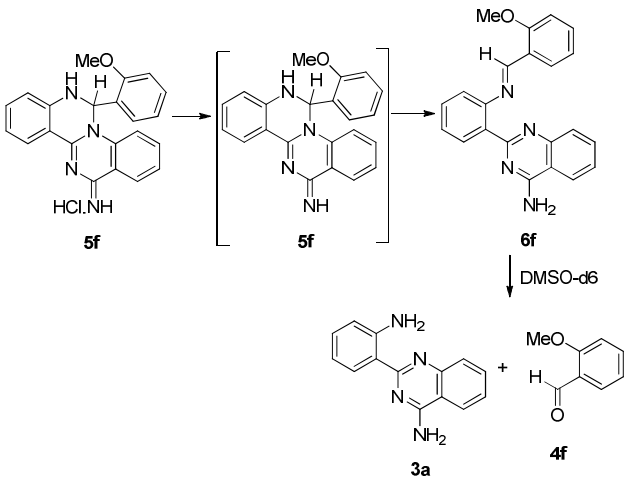
Compound		δ N1	δ N2	δ N3
	**1a** HX = HNO_3	262.81	169.57	252.82
	neutral	249.81	160.30	-
	**2a** HX = TFA	136.00	240.10	-
	neutral	133.81	-	-
	**3a** HX = HNO_3	74.06	146.74	-
	HX = TFA	73.47	145.45	220.58
	**5c** R = Cl	75.05	145.32	216.31
	5h R = OMe	76.20	146.30	216.40

The N_1 and N_3 nitrogen atoms in the protonated form of **1a** exhibit high chemical shifts (δ 252.82 and 262.81 ppm) while a considerably lower chemical shift was assigned to N_2 (δ 169.59 ppm). The specific assignments were based on the correlations of N_1 and N_2 with the neighbouring ring protons and the remaining signal was assigned to N_3. The signal for the exocyclic amino group on the quinazoline ring could never be detected. Protonation affects all the nitrogen atoms of the tetracyclic ring of **1a**, with a decrease of 10-13 ppm observed for the chemical shift of N_1 and N_2. For compound **2a**, protonation has only a minor effect on the signal for N_1, suggesting that the proton must be centrally located on the quinazoline ring. Compound **3a** (protonated), **5b** and **5h** all share comparable chemical shifts for N_1 (the sp^3 nitrogen of an amino group), N_2 (a sp^3 nitrogen partially involved in the aromatic π system) and N_3 (a sp^2

ring nitrogen). This observation suggests that protonation of **3a** is predominantly occurring on N_2.

Attempts to neutralize compound **5f** in 3M NaOH (Table 6, entry 1) led to an oily solid material identified by TLC as a mixture of **3a** and **4f**. In order to avoid the use of aqueous base, the neutralization was performed by DBU in acetonitrile (entry 2). A white solid was immediately formed and identified by NMR as the imine **6f**. The imine proton (δH 8.68 ppm and δC 155.59 ppm) correlates with the neighbouring carbon atoms in both aromatic rings. The product was always contaminated with the hydrochloride salt of DBU together with traces of the neutral species **5f**, as evidenced by a doublet at δH 7.56 ppm (*J* 4 Hz) and δC 59.29 ppm assigned to the sp^3 carbon. Keeping the NMR solution at room temperature for one week, resulted in complete evolution to **3a** and **4f** due to prompt imine hydrolysis induced by traces of water in the solvent.

Table 6 Optimization of the experimental conditions for the neutralization of compound **5f**.



Entry	Reagent	Reaction conditions	Product (yield)
1	**3a**.HCl	NaOH 3M, r.t., 15 min	**3a** + **4f** [a]
2	**3a**.HCl	DBU (1 equiv.), CH_3CN, r.t., 5 min	**6f** [b]

[a] By TLC of the oily off-white product; [b] Contaminated with hydrochloride salt of DBU

Experimental

General methods. All compounds were fully characterized by elemental analysis and spectroscopic data. The NMR spectra were recorded at room temperature, on a Varian Unity Plus (^{1}H: 300 MHz, ^{13}C: 75 MHz), or Bruker Avance III 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) including the ^{1}H–^{13}C and ^{1}H–^{15}N correlation spectra (HMQC and HMBC). Deuterated DMSO was used as solvent. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet and br, broad. The coupling constants, *J*, are reported in hertz (Hz). IR spectra were recorded on a FT-IR Bomem MB 104 using Nujol mulls and NaCl cells. The reactions under microwave irradiation were performed on a CEM microwave reactor, model Mars 5, using a quartz open vessel.

All reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F_{254} (Merck). The melting points were determined on a Stuart SMP3 melting point apparatus and are uncorrected. Elemental analyses were performed on a LECO CHNS-932 instrument. High resolution mass spectra (HRMS) were obtained from the C.A.C.T.I. - Universidade de Vigo (Spain).

Synthesis of [2-(4-aminoquinazolin-2-yl)phenyl]formamide (2a). A solution of the nitrate salt of 13*H*-quinazolino[3,4-*a*]quinazolin-13-imine nitrate **1a** (0.08 g, 0.26 mmol) in 3M NaOH (1 mL) was stirred at room temperature for 18 h, leading to a yellow solid suspension. The solid was filtered, washed with water and identified as 2-(4-aminoquinazolin-2-yl)phenyl]formamide **2a**.

General procedure for the synthesis of the hydrochloride salt of 2-(2-aminophenyl) quinazolin-4-amine (3). Concentrated HCl (5 µL) was added to a pale yellow suspension of the nitrate salt of 13*H*-quinazolino[3,4-*a*]quinazolin-13-imine **1** in methanol (2 mL). The reaction mixture was stirred at room temperature leading to a homogeneous yellow solution after 5-15 min. A yellow solid started to precipitate after 25-45 min and the suspension was stirred for a further 4-15 h. The solid was filtered and washed with diethyl ether, leading to the pure product **3**.

General procedure for the synthesis of the hydrochloride salt of 6-aryl-6,7-dihydro-13*H*-quinazolino[3,4-*a*]quinazolin-13-imine (5). The aldehyde **4** (1.1-1.2 equiv) was added to a yellow suspension of the hydrochloride salt of 2-(2-aminophenyl)quinazolin-4-amine **2a** in ethanol (2-3 mL). The suspension was refluxed for 15 min-12.5 h (method A) or irradiated at a constant power of 400 W for 5 min (method B). The solid was filtered and washed with diethyl ether, leading to the pure product **5**.

Conclusions

A simple and eco-friendly approach was developed for the synthesis of quinazolines **3**, prepared from the corresponding quinazolino[3,4-*a*]quinazolines **1**, in methanol and hydrochloric or nitric acid, at room temperature. The hydrochloride salt of the unsubstituted quinazoline **3a** was reacted with a slight excess of a selection of aromatic aldehydes, leading to a novel and highly stable tetracyclic structure **5**. The reaction was performed under reflux in ethanol (15 min to 12.5 h) or under microwave irradiation at a constant power of 400 W (5 min). All the products were isolated in a high purity form by simple filtration and in 74 to 97% yield. The stability of compounds **5** is associated with protonation, as neutralization results in the imine precursor that can be easily hydrolysed.

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Graphical Abstract