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A new access to quinazolines from simple anilines

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Abstract—A new synthetic pathway to quinazolines is described. This new method uses hexamethylenetetramine in TFA and potassium ferricyanide in aqueous ethanolic KOH, starting from simple *N*-protected anilines. The method affords substituted quinazolines with high selectivities and good yields, reducing reaction-time and work-up operations.

1. Introduction

In the last few years, we have been interested in synthesizing benzoquinazolinic derivatives in search of new antiproliferative drugs. The interest in the quinazolinic structure, due to its wide range of biological activities,[1] led to a number of different synthetic pathways to access this nucleus (e.g., Niementowski's synthesis,[2] Bischler's synthesis,[3] and Riedel's synthesis).[4] However, all these methods suffer from the disadvantage that the starting naphthylamines need an appropriate *ortho* functional group in order to cyclize to the pyrimidine ring of the quinazoline nucleus.

During our studies we found a novel ring closure of the benzoquinazoline system starting from simple naphthylamines.[5] This new synthetic approach consisted in reacting the appropriate *N*-protected α-naphthylamines or β-naphthylamines with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA), followed by treatment with potassium ferricyanide in aqueous ethanolic potassium hydroxide to give, respectively, benzo[*f*]quinazoline or benzo[*h*]quinazoline in good yield. The final products were achieved via the corresponding dihydrobenzoquinazoline intermediates, which were directly reacted with the oxidizing agent without intermediate isolation.

This method represents a new improved and straightforward route to the benzoquinazoline nucleus. To expand the scope of this method in order to access new heterocyclic scaffolds, in this paper we also describe further investigations on simple anilines to find an efficient synthetic route to quinazolines. Particular attention was paid to study the various parameters of this new synthetic strategy in order to standardize the reaction conditions.

2. Results and discussion

To verify if the HMTA/TFA/$K_3Fe(CN)_6$ method could have widespread application and to set up standard reaction conditions, *N*-protected anilines were chosen as starting products. The protection of the amino group is necessary because it is well known that aromatic amines treated with HMTA in TFA gave only Tröger's bases.[6] As a general procedure, the *N*-protected aniline was treated with HMTA in TFA, and then directly refluxed in aqueous ethanolic potassium hydroxide with potassium ferricyanide.

In order to investigate reaction conditions avoiding *para* formylation, 4-methylaniline was chosen as reference compound: in fact, as reported in the literature,[7] aniline itself undergoes only *para* formylation. Even the HMTA/TFA/$K_3Fe(CN)_6$ method runs through an initial formylation step,[5] but this must occur at the *ortho*-position in order to achieve the desired pyrimidine annulation. In fact the reaction mechanism involves aminomethylation at both the *ortho*-position and the nitrogen atom of the carbamoyl group. The successive dehydrogenation of *ortho*-aminomethyl to aldimino group promotes an intramolecular cyclization to dihydropyrimidine ring. Finally oxidative dehydrogenation of the dihydropyrimidine derivative affords the desired quinazoline (Scheme 1).

To constrain *ortho* formylation and then pyrimidine ring closure, 4-methylaniline (**1a**) was first tested with the amino

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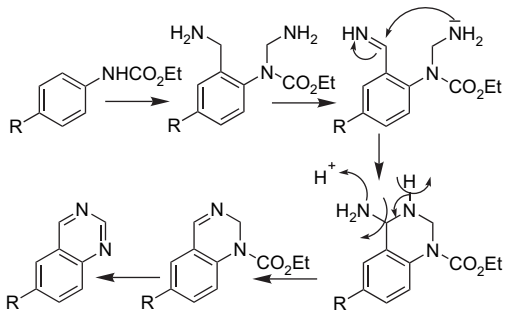
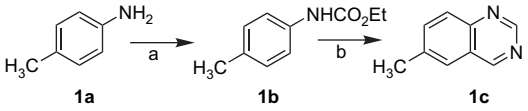


Scheme 1. Proposed reaction mechanism.

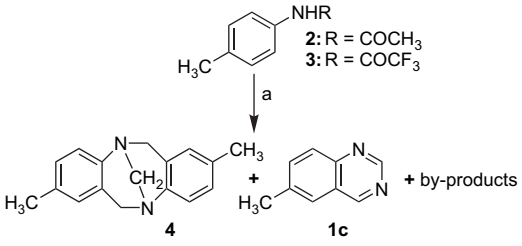
group protected as an ethyl carbamate. Thus, the *N*-protected 4-methylaniline (**1b**) gave 6-methylquinazoline (**1c**) in good yield (49%) (Scheme 2).



Scheme 2. Reagents and conditions: (a) $ClCO_2Et$, THF, 98% and (b) (1) HMTA, TFA and (2) KOH aqueous EtOH, $K_3Fe(CN)_6$, 49%.

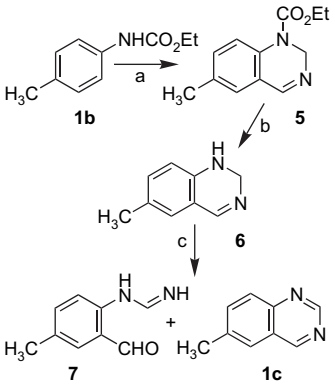
The reaction was even attempted with different protecting groups on the amino function and different acid conditions to evaluate their influence on the reaction course.

If the amino group was protected as an acetyl or trifluoroacetyl (**2** and **3**), the HMTA/TFA/$K_3Fe(CN)_6$ reaction afforded a complex mixture, in which the quinazoline **1c** was present in low concentration together with the Tröger's base **4** and other unidentified by-products (Scheme 3). In this case, the acid hydrolysis of the protecting groups became competitive with cyclization: the portion of still protected molecules yielded the final quinazoline, while the portion of deprotected molecules gave rise to the Tröger's base and other unidentified by-products.



Scheme 3. Influence of N-protection on reaction products (A). Reagents and conditions: (a) (1) HMTA, TFA and (2) KOH aqueous EtOH, $K_3Fe(CN)_6$.

On the other hand, the ethyl carbamate group is stable in TFA in such a way to afford the *N*-protected dihydroquinazoline intermediate from which the final quinazoline is derived. Hence, the stability of the *N*-protected intermediate is crucial for the quinazoline formation: in our hypothesis, the intermediate arising from N-deprotection is not stable in acid conditions, owing to the hydrolysis of the imine bond, and does not survive long enough to be aromatized to the quinazoline nucleus. To prove this hypothesis, compound **1b** was reacted with HMTA in TFA and the stable intermediate **5** was hydrolyzed in alkaline medium to dihydroquinazoline **6**, immediately isolated from the reaction mixture and kept in toluene solution, due to its high instability (Scheme 4).



Scheme 4. Influence of N-protection on reaction products (B). Reagents and conditions: (a) HMTA, TFA, 80%; (b) KOH aqueous, 92%; and (c) AcOH, 13% (**7**) and 13% (**1c**).

Compound **6** in acid solution was converted into a mixture of the quinazoline **1c** and formamidine **7**: compound **1c** derived from spontaneous oxidation of **6**,[8] while compound **7** derived from the hydrolysis of the imine bond of dihydropyrimidine ring.[9] Therefore, to avoid undesired side reactions, it is essential that the amino group of the starting anilines remained protected until the aromatization step: this condition is satisfied only when ethyl carbamate, stable in the strong acid conditions needed for the initial cyclization step, is used.

The influence of different acid conditions on the HMTA/TFA/$K_3Fe(CN)_6$ reaction was also studied. Performing the reaction in acetic acid or in a mixture of formic and acetic acids, no reaction occurred, while in methanesulfonic acid, the reaction afforded the same complex mixture as observed with acyl as the protecting group (Scheme 3). This fact was ascribed to the strength of the acid medium, which causes partial hydrolysis of the amino protection. Even diluting methanesulfonic acid with another acid (e.g., acetic acid), a complex mixture was obtained, while dilution with a solvent (e.g., THF) led to no reaction.

Using TFA in lower quantity, the reaction did not reach completion, while dilution with solvent led to no reaction.

Finally, the reaction was attempted even on compound **1a**, but, as expected,[6] in TFA only the Tröger's base **4** was isolated, while in acetic acid a mixture of the quinazoline **1c** and formamidine **7** was obtained, demonstrating that intermediate **6** could be formed but is not stable in acid conditions.

Various *N*-carbethoxy anilines were submitted as starting materials to the HMTA/TFA/$K_3Fe(CN)_6$ synthetic pathway to test its applicability.

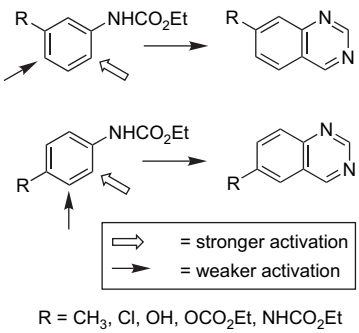
The course of the reaction and the obtained products depend on the starting aniline: in fact, in this study we worked with anilines substituted with activating and deactivating groups in order to understand their influence on reactivity and orientation.

If starting anilines have position 4 substituted with *ortho*/*para*-directing groups (such as methyl, methoxy, chloro, and amino groups), the quinazoline nucleus was obtained in moderate to good yields. For example, the *N*-protected 4-methylaniline (**1b**), 4-chloroaniline (**8b**), 4-methoxyaniline (**9b**), and 4-*O*-carbethoxyaniline (**10b**) gave, respectively, 6-methyl (**1c**), 6-chloro (**8c**), 6-methoxy (**9c**), and 6-hydroxyquinazoline (**10c**) (Scheme 2 and Table 1, entries 1–3). In particular compound **10b**, in which both amino and hydroxyl groups were protected with ethyl chloroformiate, gave only 6-hydroxyquinazoline with deprotection of the hydroxyl function during the oxidative step (entry 3), while compound **11b** carrying only N-protection led to a complex reaction mixture (entry 4). Moreover, it was observed that in the case of 1,4-phenylendiamine (**12a**), despite the presence of two amino functions, only one pyrimidine ring was formed to give 6-aminoquinazoline (**12c**) (Table 1, entry 5).

As expected, if starting anilines have position 4 substituted with deactivating groups, such as nitro or carboxylic groups, no reaction was observed (Table 1, entries 6 and 7).

The influence of methoxy or amino substitution on position 3 of aniline was also tested: even if the *para* position was free, only quinazoline formation was observed, probably due to the activation of the *para* position in the respect of the 3-substituent. From *N*-protected 3-methoxyaniline (**15b**), *N*,*N*′-diprotected 1,3-phenylenediamine (**16b**), and *N*,*N*′-diprotected 2-methyl-1,3-phenylenediamine (**17b**), respectively, 7-methoxy (**15c**), 7-aminoquinazoline (**16c**), and 7-amino-8-methylquinazoline (**17c**) were obtained (Table 1, entries 8–11). In particular, no trace of the isomeric 5-aminoquinazoline was recovered in the reaction mixture of entry 9, so proving the regioselectivity of pyrimidine annulation. This high regioselectivity was again observed in the presence of further substituents: when the reaction was carried out on *N*,*N*′-diprotected 1,3-phenylenediamines susbstituted in 4 position with methyl group (**18b**), and methoxy group (**19b**), only 7-amino-6-methylquinazoline (**18c**), and 7-amino-6-methoyquinazoline (**19c**) were achieved without traces of the other two possible quinazoline isomers (Table 1, entries 11 and 12). This last observation demonstrates the selectivity of the reaction toward the *para* position with respect to the second amino group, and/or a steric hindrance exerted by the *meta* substituent.

The effect of aniline substituents on the reaction course is summarized in Scheme 5.

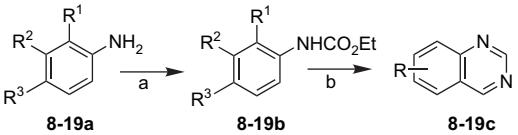


Scheme 5. Effect of aniline substituents.

3. Conclusions

We report further investigations on a versatile and improved method[5] for the synthesis of substituted quinazoline derivatives to verify its general applicability. This new method uses HMTA in TFA and potassium ferricyanide in aqueous ethanolic KOH, starting from anilines with the amino group protected as an ethyl carbamate, without isolating reaction intermediates. Both *N*-ethoxycarbonyl protection and TFA are crucial to the success of the reaction. Various 6- and 7-substituted quinazolines were obtained in yields higher than that previously reported:[10–14] even when the yields were comparable, the old methods were time and solvent-consuming, running through almost 4–5 steps. Moreover, our method starts from cheaper and easily available starting materials. Finally, three new methyl- or methoxy-7-aminoquinazoline was synthesized. This novel method afforded

Table 1. Reaction products[a]



Entry	Starting amine				Intermediate carbamate				Product		Yield
	R^1	R^2	R^3		R^1	R^2	R^3				
1	H	H	Cl	**8a**	H	H	Cl	**8b**	6-Chloroquinazoline	**8c**	15
2	H	H	OCH_3	**9a**	H	H	OCH_3	**9b**	6-Methoxyquinazoline	**9c**	19
3	H	H	OH	**10a**	H	H	OCO_2Et	**10b**	6-Hydroxyquinazoline	**10c**	24
4	H	H	OH	**11a**	H	H	OH	**11b**	Complex mixture		
5	H	H	NH_2	**12a**	H	H	$NHCO_2Et$	**12b**	6-Aminoquinazoline	**12c**	54
6	H	H	NO_2	**13a**	H	H	NO_2	**13b**	No reaction		
7	H	H	COOH	**14a**	H	H	COOH	**14b**	No reaction		
8	H	OCH_3	H	**15a**	H	OCH_3	H	**15b**	7-Methoxyquinazoline	**15c**	22
9	H	NH_2	H	**16a**	H	$NHCO_2Et$	H	**16b**	7-Aminoquinazoline	**16c**	45
10	CH_3	NH_2	H	**17a**	CH_3	$NHCO_2Et$	H	**17b**	7-Amino-8-methylquinazoline	**17c**	38
11	H	NH_2	CH_3	**18a**	H	$NHCO_2Et$	CH_3	**18b**	7-Amino-6-methylquinazoline	**18c**	44
12	H	NH_2	OCH_3	**19a**	H	$NHCO_2Et$	OCH_3	**19b**	7-Amino-6-methoxyquinazoline	**19c**	43

[a] Reagents and conditions: (a) $ClCO_2Et$, THF; (b) (1) HMTA, TFA and (2) KOH aqueous EtOH, $K_3Fe(CN)_6$.

substituted quinazolines with high selectivities and good yields, reducing reaction-time and work-up operations.

4. Experimental

4.1. General

Melting points were determined on a Gallenkamp MFB-595-010M melting point apparatus and are uncorrected. Analytical TLC was performed on pre-coated 60 F_{254} silica gel plates (0.25 mm; Merck) developing with a $CHCl_3$/MeOH mixture (9:1). Preparative column chromatography was performed using silica gel 60 (0.063–0.100 mm; Merck), eluting with $CHCl_3$. ^1H NMR spectra were recorded on a Bruker AMX300 spectrometer with TMS as an internal standard. Chemical shift values are reported in parts per million and coupling constants are reported in hertz. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer. HRMS spectra were obtained using an ESI-TOF Mariner 5220 (Applied Biosystem) mass spectrometer with direct injection of the sample and collecting data in the positive ion mode. GC–MS analysis of samples were carried out using a Varian CP-3800 gas chromatograph with a Mass Selective Detector (EI), equipped with an Agilent HP-INNOWax column (30 m length, 0.25 mm I.D., and 0.25 μm film thickness) using helium as carrier gas (1 mL/min) and a temperature program from 100 °C (3 min) to 300 °C (10 °C/min) for a total run length of 28 min. Elemental analyses were performed on a Perkin–Elmer 2400 Analyser and are within ±0.4% of theoretical values.

Analytical data for compounds **1c**,[10] **8c**,[11] **9c**,[10] **10c**,[12] **12c**,[13] **15c**,[10] and **16c**[14] were compared with literature data.

For the synthesis of carbamates **1b** and **8–19b**, and for experiments with different acids, see the Supplementary data.

4.2. General procedures for quinazolines

A mixture of carbamate **1b** or **8–19b** (5 mmol) and HMTA (35 mmol) in TFA (35 mL) was refluxed for 1 h. After cooling, the mixture was diluted with 4 M HCl (200 mL). The undissolved residue was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in aqueous ethanolic (water/EtOH, 1/1) 10% KOH (300 mL), added of $K_3Fe(CN)_6$ (12.5 g, 38 mmol) and refluxed for 4 h. After cooling, the mixture was diluted with water (300 mL), extracted with organic solvent (see below) (5×100 mL), and the organic phase was evaporated under reduced pressure.

4.2.1. 6-Methylquinazoline (1c). Extraction solvent: toluene; yield: 49%; mp: 62 °C (lit.[10] 62–63 °C); ^1H NMR ($CDCl_3$): δ 9.32 (s, 1H, 4-H), 9.27 (s, 1H, 2-H), 7.95 (d, J=8.6 Hz, 1H, 8-H), 7.76 (dd, J=8.6, 1.8 Hz, 1H, 7-H), 7.69 (d, J=1.8 Hz, 1H, 5-H), 2.58 (s, 3H, CH_3); HRMS (ESI-TOF) for $C_9H_9N_2$ (M^++1): calcd: 145.0760, found: 145.0674. Anal. Calcd for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.00; H, 5.50; N, 19.50.

4.2.2. 6-Chloroquinazoline (8c). Extraction solvent: toluene; yield: 15%; mp: 137 °C (lit.[11] 143 °C); ^1H NMR ($CDCl_3$): δ 9.36 (s, 1H, 4-H), 9.34 (s, 1H, 2-H), 8.02 (d, J=9.0 Hz, 1H, 8-H), 7.94 (d, J=2.2 Hz, 1H, 5-H), 7.87 (dd, J=9.0, 2.2 Hz, 1H, 7-H); HRMS (ESI-TOF) for $C_8H_6{}^{35}ClN_2$ (M^++1): calcd: 165.0214, found: 165.0197. Anal. Calcd for $C_8H_5ClN_2$: C, 58.38; H, 3.06; Cl, 21.54; N, 17.02. Found: C, 58.34; H, 3.09; Cl, 21.51; N, 17.06.

4.2.3. 6-Methoxyquinazoline (9c). Extraction solvent: cyclohexane; yield: 19%; mp: 71 °C (lit.[10] 71–72 °C); ^1H NMR ($CDCl_3$): δ 9.29 (s, 1H, 4-H), 9.20 (s, 1H, 2-H), 7.94 (d, J=9.2 Hz, 1H, 8-H), 7.56 (dd, J=9.2, 2.8 Hz, 1H, 7-H), 7.13 (d, J=2.5 Hz, 1H, 5-H), 3.95 (s, 3H, OCH_3); HRMS (ESI-TOF) for $C_9H_9N_2O$ (M^++1): calcd: 161.0709, found: 161.0622. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.44; H, 5.06; N, 17.52.

4.2.4. 6-Hydroxyquinazoline (10c). After washing with chloroform (3×100 mL), the aqueous solution was neutralized with 1 M HCl, extracted with EtOAc (3×100 mL), and evaporated under reduced pressure. Yield: 24%; mp: 235 °C (lit.[12] 239 °C); ^1H NMR ($CDCl_3$): δ 9.28 (s, 1H, 4-H), 9.18 (s, 1H, 2-H), 8.14 (d, J=2.5 Hz, 1H, 5-H), 7.99 (d, J=9.1 Hz, 1H, 8-H), 7.61 (dd, J=9.1, 2.5 Hz, 1H, 7-H); HRMS (ESI-TOF) for $C_8H_7N_2O$ (M^++1): calcd: 147.0553, found: 147.0693. Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.68; H, 4.17; N, 19.17.

4.2.5. 6-Aminoquinazoline (12c). Extraction solvent: toluene; yield: 54%; mp: 212 °C (lit.[13] 213 °C); ^1H NMR ($CDCl_3$): δ 9.20 (s, 1H, 4-H), 9.13 (s, 1H, 2-H), 7.90 (d, J=9.1 Hz, 1H, 8-H), 7.35 (dd, J=9.1, 2.6 Hz, 1H, 7-H), 6.95 (d, J=2.6 Hz, 1H, 5-H); HRMS (ESI-TOF) for $C_8H_8N_3$ (M^++1): calcd: 146.0713, found: 146.0693. Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.23; H, 4.80; N, 28.97.

4.2.6. 7-Methoxyquinazoline (15c). Extraction solvent: cyclohexane; yield: 22%; mp: 90 °C (lit.[10] 87 °C); ^1H NMR (MeOD-d_4): δ 9.30 (s, 1H, 4-H), 9.10 (s, 1H, 2-H), 7.97 (d, J=9.0 Hz, 1H, 5-H), 7.53 (dd, J=9.0, 2.5 Hz, 1H, 6-H), 7.31 (d, J=2.5 Hz, 1H, 8-H), 4.01 (s, 3H, OCH_3); HRMS (ESI-TOF) for $C_9H_9N_2O$ (M^++1): calcd: 161.0709, found: 161.0699. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.53; H, 5.00; N, 17.50.

4.2.7. 7-Aminoquinazoline (16c). Extraction solvent: toluene; yield: 45%; mp: 190 °C (lit.[14] 190.5–191 °C); ^1H NMR (MeOD-d_4): δ 9.01 (s, 1H, 4-H), 8.84 (s, 1H, 2-H), 7.79 (d, J=8.9 Hz, 1H, 5-H), 7.16 (dd, J=8.9, 2.0 Hz, 1H, 6-H), 6.90 (d, J=2.0 Hz, 1H, 8-H); HRMS (ESI-TOF) for $C_8H_8N_3$ (M^++1): calcd: 146.0713, found: 146.0589. Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.23; H, 4.85; N, 28.92.

4.2.8. 7-Amino-8-methylquinazoline (17c). Extraction solvent: toluene; yield: 38%; mp: 163 °C; ^1H NMR (MeOD-d_4): δ 8.96 (s, 1H, 4-H), 8.90 (s, 1H, 2-H), 7.65 (d, J=8.8 Hz, 1H, 5-H or 6-H), 7.16 (d, J=8.8 Hz, 1H, 5-H or 6-H), 2.43 (s, 3H, CH_3); IR (KBr) 3450, 3370, 3025, 2930, 2865, 1620, 1520, 1490, 1375, 1270, 1145, 1035, 940, 825 cm^{-1}; HRMS (ESI-TOF) for $C_9H_{10}N_3$ (M^++1): calcd: 160.0869, found: 160.0781. Anal. Calcd for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.94; H, 5.68; N, 26.38.

4.2.9. 7-Amino-6-methylquinazoline (18c). Extraction solvent: toluene; yield: 44%; mp: 175 °C; ^{1}H NMR (DMSO-d_6): δ 9.01 (s, 1H, 4-H), 8.91 (s, 1H, 2-H), 7.64 (s, 1H, 5-H or 8-H), 7.38 (s, 1H, 5-H or 8-H), 2.30 (s, 3H, CH_3); IR (KBr) 3430, 3345, 3030, 2930, 2865, 1625, 1530, 1345, 1235, 1145, 1100, 1015, 950, 845 cm^{-1}; HRMS (ESI-TOF) for $C_9H_{10}N_3$ (M^++1): calcd: 160.0869; found: 160.0912. Anal. Calcd for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.01; H, 5.67; N, 26.32.

4.2.10. 7-Amino-6-methoxyquinazoline (19c). Extraction solvent: EtOAc; yield: 43%; mp: 163 °C; ^{1}H NMR ($CDCl_3$): δ 9.01 (s, 1H, 4-H), 9.00 (s, 1H, 2-H), 7.07 (s, 1H, 5-H or 8-H), 7.00 (s, 1H, 5-H or 8-H), 4.02 (s, 3H, OCH_3); IR (KBr) 3420, 3395, 3040, 2930, 2865, 1690, 1575, 1490, 1380, 1320, 1235, 1215, 1170, 1025, 905, 835 cm^{-1}; HRMS (ESI-TOF) for $C_9H_{10}N_3O$ (M^++1): calcd: 176.0818, found: 176.0685. Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.68; H, 5.22; N, 24.02.

4.3. Synthesis from compounds 2 and 3

A mixture of carbamate **2**[15] or **3**[16] (5 mmol) and HMTA (35 mmol) in TFA (35 mL) was refluxed for 1 h. After cooling, the mixture was diluted with 4 M HCl (200 mL). The undissolved residue was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in aqueous ethanolic (water/EtOH, 1/1) 10% KOH (300 mL), added with $K_3Fe(CN)_6$ (12.5 g, 38 mmol) and refluxed for 4 h. After cooling, the mixture was diluted with water (300 mL), extracted with toluene (5×100 mL), and the organic phase was evaporated under reduced pressure to give a complex mixture, in which **1c** and Tröger's bases **4** were detectable by NMR analysis: ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1H, **1c**-4-H), 9.27 (s, 1H, **1c**-2-H), 7.95 (d, J=8.6 Hz, 1H, **1c**-8-H), 7.76 (dd, J=8.6, 1.8 Hz, 1H, **1c**-7-H), 7.69 (d, J=1.8 Hz, 1H, **1c**-5-H), 7.02 (d, J=8.8 Hz, 2H, **4**-3-H and 9-H or 4-H and 10-H), 6.96 (d, J=8.8 Hz, 2H, **4**-3-H and 9-H or 4-H and 10-H), 6.70 (s, 2H, **4**-1-H and 7-H), 4.64 (d, J=16.6 Hz, 2H, **4**-6-H and 12-H), 4.30 (s, 2H, **4**-N–CH_2–N), 4.10 (d, J=16.6 Hz, 2H, **4**-6-H and 12-H), 2.21 (s, 6H, 2H, **4**-2-CH_3 and 8-CH_3), 2.58 (s, 3H, **1c**-CH_3); peak assignment was made by comparison with NMR spectrum of an authentic sample of **4** prepared from literature method.[6]

4.4. Ethyl 6-methyl-2*H*-quinazoline-1-carboxylate (5)

A mixture of **1b** (1.0 g, 5.6 mmol) and HMTA (5.5 g, 39.1 mmol) in TFA (40 mL) was refluxed for 1 h. After cooling, the mixture was diluted with 4 M HCl (200 mL). The undissolved residue was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in water (200 mL), neutralized with $NaHCO_3$, and extracted with EtOAc (3×100 mL). The organic phase was evaporated under reduced pressure, and the solid was crystallized from cyclohexane to give **5** (0.98 g, 80%). ^{1}H NMR (DMSO-d_6): δ 8.32 (t, J=2.0 Hz, 1H, 4-H), 7.58 (d, J=8.3 Hz, 1H, 8-H), 7.35 (dd, J=8.3, 1.6 Hz, 1H, 7-H), 7.29 (d, J=1.6 Hz, 1H, 5-H), 5.29 (d, J=2.0 Hz, 2H, 2-H), 4.23 (q, J=7.1 Hz, 2H, COOCH_2CH$_3$), 2.35 (s, 3H, CH_3), 1.29 (t, J=7.1 Hz, 3H, COOCH$_2$$CH_3$). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.09; H, 6.42; N, 12.88.

4.5. 6-Methyl-1,2-dihydroquinazoline (6)

A solution of **5** (0.95 g, 4.3 mmol) in 10% KOH (200 mL) was refluxed for 2 h. After cooling, the mixture was extracted with toluene (3×100 mL) and the organic phase was evaporated under reduced pressure to give **6** (0.58 g, 92%). ^{1}H NMR (DMSO-d_6): δ 7.95 (t, J=1.6 Hz, 1H, 4-H), 6.96 (dd, J=8.1, 1.5 Hz, 1H, 7-H), 6.92 (d, J=1.5 Hz, 1H, 5-H), 6.45 (d, J=8.1 Hz, 1H, 8-H), 5.86 (d, J=1.6 Hz, 1H, NH), 4.77 (d, J=1.6 Hz, 2H, 2-H), 2.14 (s, 3H, CH_3). Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 74.00; H, 6.86; N, 19.14. Compound **6** easily decomposed if not kept in aprotic or non-polar solvent, such as toluene.

4.6. *N*-(2-Formyl-4-methylphenyl)formamidine (7)

A solution of **6** (0.55 g, 3.8 mmol) in acetic acid (30 mL) was refluxed for 1 h. After cooling, the mixture was diluted with water (100 mL), neutralized with $NaHCO_3$, and extracted with toluene (3×80 mL). The organic phase was evaporated under reduced pressure and the residue was analyzed by GC–MS, identifying **1c** (t_R=12.7 min) and **7** (t_R=13.9 min) as reaction products. The residue was further purified by column chromatography to give, in order of elution, **1c** (7.1 mg, 13%); GC–MS (EI): m/z 144, 117, 89, 90, 63 (see above for other analytical data) and **7** (7.9 mg, 13%); ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1H, CHO or CH=NH), 9.27 (s, 1H, CHO or CH=NH), 7.95 (d, J=8.6 Hz, 1H, 6-H), 7.76 (dd, J=8.6, 1.8 Hz, 1H, 5-H), 7.69 (d, J=1.8 Hz, 1H, 3-H), 2.58 (s, 3H, CH_3); GC–MS (EI): m/z 136, 135, 107, 106, 77; HRMS (ESI-TOF) for $C_9H_{11}N_2O$ (M^++1): calcd: 163.0866, found: 163.0901. Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.66; H, 6.18; N, 17.30.

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Supplementary data

Experimental details for compounds **1b** and **8**–**19b**, and experiments with different acids can be found in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.103.

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