Tetrahedron Letters 50 (2009) 2261–2265

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Sulfuric acid promoted condensation cyclization of 2-(2-(trimethylsilyl) ethynyl)anilines with arylaldehydes in alcoholic solvents: an efficient one-pot synthesis of 4-alkoxy-2-arylquinolines

Yong Wang, Changlan Peng, Lanying Liu, Jiaji Zhao, Li Su, Qiang Zhu *

Institute of Chemical Biology, Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou 510663, People's Republic of China

ARTICLE INFO

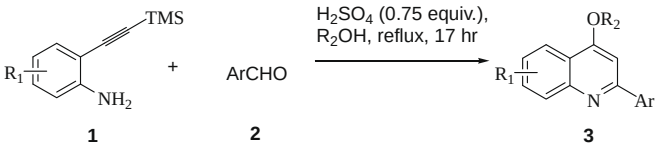
Article history:
Received 18 December 2008
Revised 24 January 2009
Accepted 27 February 2009
Available online 4 March 2009

ABSTRACT

An efficient method for the synthesis of 4-alkoxy-2-arylquinolines has been developed. The reaction proceeds smoothly by heating a mixture of easily accessible 2-(2-(trimethylsilyl) ethynyl)anilines and arylaldehydes in alcoholic solvents in the presence of sulfuric acid.

Quinoline derivatives are found to possess a broad spectrum of biological activities such as antimalarial,[1] antibacterial,[2] antifungal,[3] and anticancer.[4] Consequently, many classical methods such as Skraup, Doebner–von Miller, Friedländer, and Combes syntheses have been developed for the preparation of quinoline derivatives.[5] However, many of these methods suffer from the need of high temperatures, prolonged reaction times, and drastic reaction conditions and also the unsatisfied yields. To overcome the aforementioned drawbacks, more efficient methods such as modified Friedlander strategies,[6] hetero-Diels–Alder reaction of imines,[7] and transition-metal catalyzed reactions[8] have been developed. Owing to the fascinating biological properties of quinolines, new catalytic systems are being continuously explored to improve efficiencies and cost effectiveness.[9]

4-Alkoxy-2-arylquinoline derivatives have important biological activities,[10] such as antiplatelet.[11] But only a limited number of methods are available in the literature and most of them involve multiple steps or toxic reagents.[12] Herein we report an efficient method for the synthesis of 4-alkoxy-2-arylquinolines from easily accessible 2-(2-(trimethylsilyl)ethynyl)anilines **1** and arylaldehydes **2** in alcohols promoted by sulfuric acid (Scheme 1).

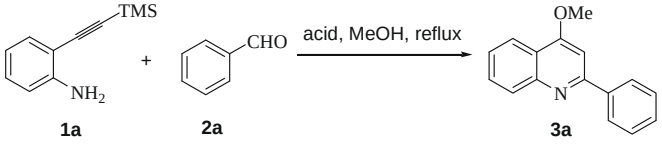


1 2 3

Scheme 1. 4-Alkoxy-2-arylquinolines from 2-(2-(trimethylsilyl)ethynyl)anilines **1** and arylaldehydes **2**.

In the course of studying a 3-component Passerini reaction using *o*-(trimethylsilylethynyl) isocyanobenzene **4,** benzaldehyde **2a,** and acetic acid in methanol,[13] no reaction product was

Table 1
Acid catalyzed cyclization of 2-(2-(trimethylsilyl)ethynyl)aniline **1a** with benzaldehyde **2a** in methanol under various conditions[a]



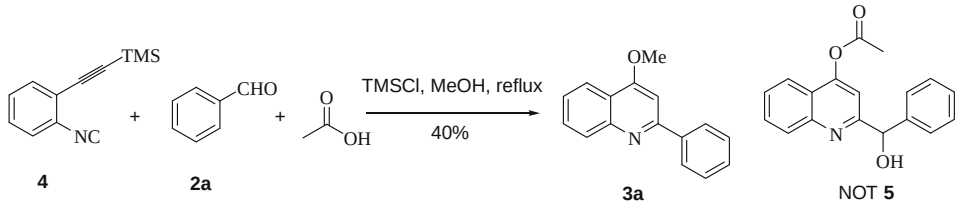
1a **2a** **3a**

Entry	Acid (equiv)	Ratio (**1a**/**2a**)	Time (h)	**3a** Yield[b] (%)
1	TMSCl (1.0)	3	17	42
2	TMSCl (1.5)	3	17	50
3	TFA (1.0)	3	17	24
4	PTSA (1.0)	3	17	40
5	BF_3·OEt (1.5)	3	17	46
6	Concd HCl (1.0)	3	17	34
7	CF_3SO_3H (1.0)	3	17	56
8	Concd H_2SO_4 (0.1)	3	17	Trace
9	Concd H_2SO_4 (0.3)	3	17	24
10	Concd H_2SO_4 (0.5)	1	17	36
11	Concd H_2SO_4 (0.5)	2	17	41
12	Concd H_2SO_4 (0.5)	3	17	65
13	Concd H_2SO_4 (0.5)	4	17	60
14	Concd H_2SO_4 (0.5)	5	17	59
15	Concd H_2SO_4 (0.75)	3	17	70
16	Concd H_2SO_4 (0.75)	3	4	38
17	Concd H_2SO_4 (0.75)	3	7	40
18	Concd H_2SO_4 (1.0)	3	17	69
19	Concd H_2SO_4 (1.5)	3	17	67
20	Concd H_2SO_4 (2.0)	3	17	52

[a] Reaction conditions: 2-(2-(trimethylsilyl)ethynyl)aniline (0.5 mmol) **1a**, benzaldehyde **2a**, and acid in 10 mL of dry methanol, reflux.
[b] Yield of isolated product.

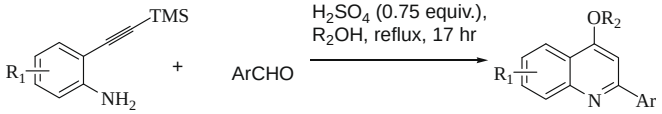
* Corresponding author. Tel.: +86 020 32290511; fax: +86 020 32290606.
E-mail address: zhu_qiang@gibh.ac.cn (Q. Zhu).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.206



Scheme 2. Unexpected 4-methoxy-2-phenylquinoline **3a** from an isocyano based multi-component reaction.

Table 2
Sulfuric acid catalyzed cyclization of 2-(2-(trimethylsilyl)ethynyl)anilines **1** with aldehydes **2** in alcohols[a]



1 **2** **3**

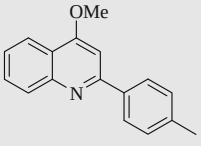
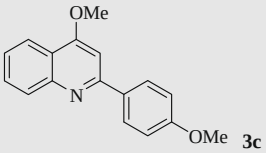
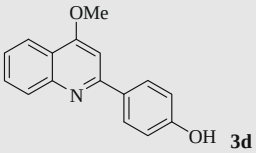
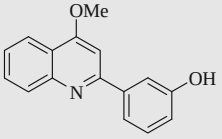
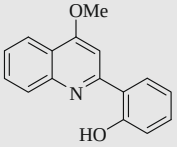
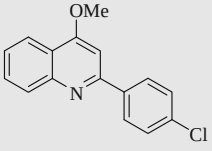
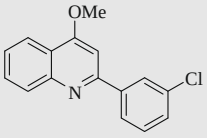
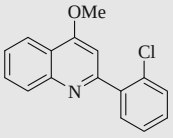
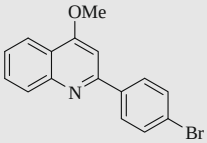
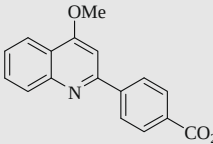
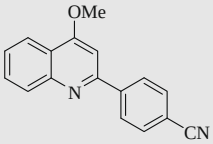
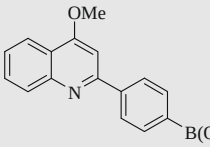
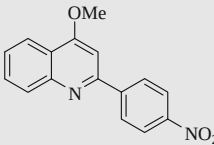
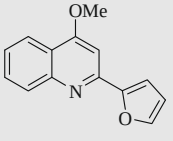
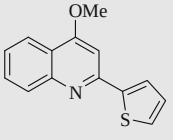
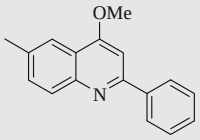
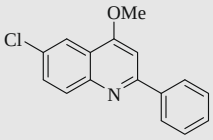
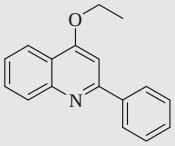
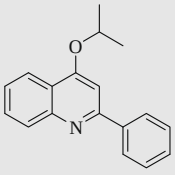
Entry	R_1	R_2	Ar	Product	Yield[b] (%)
1	H	Me	4-MeC_6H_4	 **3b**	65
	1a		**2b**		
2			4-$MeOC_6H_4$	 **3c**	68
			2c		
3			4-HOC_6H_4	 **3d**	81
			2d		
4			3-HOC_6H_4	 **3e**	68
			2e		
5			2-HOC_6H_5	 **3f**	31
			2f		
6			4-ClC_6H_4	 **3g**	78
			2g		

Table 2 (*continued*)

Entry	R_1	R_2	Ar	Product	Yield[b] (%)
7			3-ClC_6H_4	 **3h**	75
			2h		
8			2-ClC_6H_4	 **3i**	10
			2i		
9			4-BrC_6H_4	 **3j**	61
			2j		
10			4-$MeO_2CC_6H_4$	 **3k**	49
			2k		
11			4-NCC_6H_4	 **3l**	16
			2l		
12			4-$(HO)_2BC_6H_4$	 **3m**	20
			2m		
13			4-$NO_2C_6H_4$	 **3n**	0
			2n		
14			2-Furanyl	 **3o**	49
			2o		
15			2-Thiophenyl	 **3p**	53
			2p		

(*continued on next page*)

Table 2 (*continued*)

Entry	R_1	R_2	Ar	Product	Yield[b] (%)
16	4-Me		**2a**	 **3q**	57
	1b				
17	4-Cl			 **3r**	67
	1c				
18	**1a**	Et		 **3s**	65
19		*i*-Pr		 **3t**	58

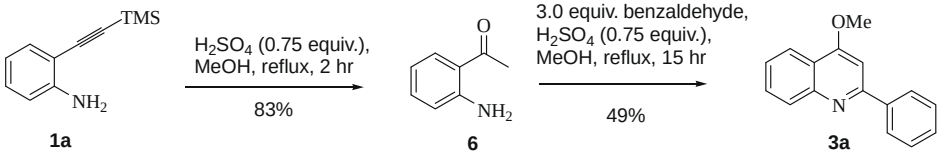
[a] Reaction conditions: 2-(2-(trimethylsilyl)ethynyl)anilines **1** (0.5 mmol), aldehydes **2** (1.5 mmol), and sulfuric acid (37 mg, 0.375 mmol) in 10 mL of dry alcohol, reflux for 17 h.

observed even under reflux overnight (Scheme 2). A new and clean spot appeared when 1.0 equiv of TMSCl was added to the reaction mixture and stirred for another 12 h under reflux. The product was isolated in 40% yield and identified as 4-methoxy-2-phenylquinoline **3a** not **5** as we originally designed. It was obvious that the terminal carbon of isocyanide was not present in the product, nor was acetic acid. We proposed that the isocyanide was hydrolyzed to formamide and further to amine first, and then imine was formed with benzaldehyde. Instead of isocyanide **4**, *o*-(trimethylsilylethynyl)aniline **1a** was used and the same product **3a** was obtained in similar yield.

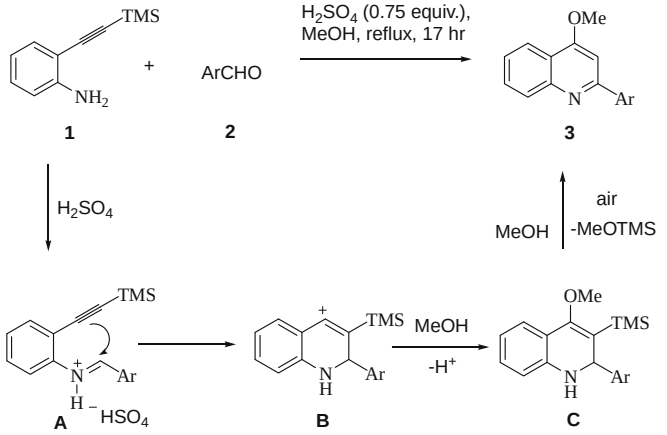
The reaction conditions were optimized and the results are summarized in Table 1. We first tested the effectiveness of different acids with 3 equiv of benzaldehyde **2a** in refluxing methanol overnight. Among the acids screened, sulfuric acid was found to be the most effective (Table 1, entries 1–7, 12) and **3a** was obtained in 65% yield. The amount of acid used was also crucial. By increasing the equivalent of H_2SO_4 gradually from 0.1 to 2.0, the yield reached its maximum of 70% at 0.75 equiv and then declined (Table 1, entries 8, 9, 12, 15, 18–20). Altering the equivalent of benzaldehyde **2a** and reaction time cannot push the yield further (Table 1, entries 10–14, 16, 17). So, the best conditions we optimized were heating a mixture of **1a** and 3 equiv of **2a** in dry methanol in the presence of 0.75 equiv of H_2SO_4 under reflux for 17 h.

The scope of the reaction was examined under the optimized conditions (Table 2). Arylaldehydes with electron-donating groups or halogens gave moderate to good yields (Table 2, entries 1–9), while electron-deficient aldehydes provided much lower yields (Table 2, entries 10–13). No desired products were observed when strong electron-deficient 4-nitrobenzaldehyde **2n** and 2-pyridinecarboxaldehyde (result not shown) were used as substrates. The major by-products in these cases were corresponding methoxyacetals. Stereo-hindered substrates were also unfavorable to the reaction (Table 2, entries 5 and 8). Electron-rich heteroaromatic aldehydes were suitable substrates for this reaction (Table 2, entries 14 and 15). There was no significant influence on yields when substituted 2-(2-(trimethylsilyl)ethynyl)anilines **1b** and **1c** were applied (Table 2, entries 16 and 17). Ethanol and 2-propanol were also suitable solvents for this reaction and the corresponding 4-ethoxy and 4-isopropoxy quinoline derivatives were formed in moderate yields (Table 2, entries 18 and 19). Aliphatic aldehyde such as isobutyraldehyde failed even as much as 10 equiv of it was used. We tried to extend this method for the synthesis of 3-substituted 4-alkoxy-2- arylquinolines by replacing the TMS group in **1a** with alkyl or phenyl substituents. Unfortunately, these substrates failed to give the desired products.[14]

It is reasonable to propose the reaction mechanism through intermediate 2'-aminoacetophenone **6**, since hydration of phenylacetylene with electron-donating groups to phenylketone is well documented.[15] 2'-Aminoacetophenone **6** was isolated in 83% yield under the same reaction conditions without aldehyde (Scheme 3). But the yield of **3a** was much lower (49%) when using **6** instead of



Scheme 3. Stepwise synthesis of 4-methoxy-2-phenylquinoline **3a**.



Scheme 4. Proposed mechanism for the acid promoted cyclization of 2-(2-(trimethylsilyl)ethynyl)aniline **1a** with arylaldehydes **2** in methanol.

1a as substrate. This result suggests that the mechanism in Scheme 4 is more reasonable, which involves: (1) imine formation under acid catalysis; (2) intramolecular attack of the alkyne to iminium **A**; (3) the resulting vinyl cation **B** quenched by methanol; and finally (4) desilylation and air oxidation of 1,2-dihydroquinoline **C** to give the final product.

In summary, we have demonstrated a convenient method for the construction of 4-alkoxy-2-arylquinolines from 2-(2-(trimethylsilyl)ethynyl)anilines **1** and arylaldehydes **2** in alcoholic solvents catalyzed by sulfuric acid. This novel three-component, one-pot reaction provides an efficient way for the synthesis of diversified 4-alkoxy-2-arylquinolines.

Acknowledgment

This work was financially supported by Start-up Foundation for New Investigators from Guangzhou Institutes of Biomedicine and Health (GIBH).

References and notes

1. (a) Bilker, O.; Lindo, V.; Panico, M.; Etiene, A. E.; Paxton, T.; Dell, A.; Rogers, M.; Sinden, R. E.; Morris, H. R. *Nature* **1998**, *392*, 289; (b) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, H. *Eur. J. Med. Chem.* **2000**, *35*, 1021; (c) Chen, Y.-L.; Fang, K.-C.; Sheu, J.-Y.; Hsu, S.-L.; Tzeng, C.-C. *J. Med. Chem.* **2000**, *44*, 2374; (d) Winstanley, P. A. *Parasitol. Today* **2000**, *16*, 146.
2. (a) Fang, K.-C.; Chen, Y.-L.; Sheu, J.-Y.; Wang, T.-C.; Tzeng, C.-C. *J. Med. Chem.* **2000**, *43*, 3809; (b) Chevalier, J.; Atifi, S.; Eyraud, A.; Mahamoud, A.; Barbe, J.; Pages, J.-M. *J. Med. Chem.* **2001**, *44*, 4023; (c) Phan, L. T.; Jian, T.; Chen, Z.; Qiu, Y.-L.; Wang, Z.; Beach, T.; Polemeropoulos, A.; Or, Y. S. *J. Med. Chem.* **2004**, *47*, 2965; (d) Benkovic, S. J.; Baker, S. J.; Alley, M. R. K.; Woo, Y.-H.; Zhang, Y.-K.; Akama, T.; Mao, W.; Baboval, J.; Rajagopalan, P. T. R.; Wall, M.; Kahng, L. S.; Tavassoli, A.; Shapiro, L. *J. Med. Chem.* **2005**, *48*, 7468.
3. (a) Majerz-Maniecka, K.; Oleksyn, B.; Musiol, R.; Podeszwa, B.; Polanski, J. *Abstracts of Papers*, Joint Meeting on Medicinal Chemistry, Vienna, Austria, June 20–23, 2005; *In Sci. Pharm.*, **2005**, *73*, 194; (b) Vargas, L. Y.; Castelli, M. V.; Kouznetsov, V. V.; Urbina, J. M.; Lopez, S. N.; Sortino, M.; Enriz, R. D.; Ribas, J. C.; Zacchino, S. *Bioorg. Med. Chem.* **2003**, *11*, 1531; (c) Singh, M.; Singh, M. P.; Ablordeppey, S. Y. *Drug Dev. Ind. Pharm.* **1996**, *22*, 377.
4. (a) Dassonneville, L.; Lansiaux, A.; Wattelet, A.; Wattez, N.; Mahieu, C.; Van Miert, S.; Pieters, L.; Bailly, C. *Eur. J. Pharmacol.* **2000**, *409*, 9; (b) Dassonneville, L.; Bonjean, K.; De Pauw-Gillet, M.-C.; Colson, P.; Houssier, C.; Quetin-Leclercq, J.; Angenot, L.; Ablordeppey, S. Y. *Bioorg. Med. Chem.* **2002**, *10*, 1337; (c) Bailly, C. *Biochemistry* **1999**, *38*, 7719; (d) Bailly, C.; Laine, W.; Bal-deyrou, B.; De Pauw-Gillet, M.-C.; Colson, P.; Houssier, C.; Cimanga, K.; Miert, S. V.; Vlietinck, A. J.; Pieters, L. *Anti. Cancer Drug Des.* **2000**, *15*, 191.
5. For reviews on quinoline synthesis, see: (a) Claret, P. A.. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 4, pp 1479–1489; (b) Jones, G.. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., McKillop, A., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, pp 167–300; (c) Larsen, R. D.. In *Science of Synthesis*; Black, D. S., Ed.; Thieme: Stuttgart, 2005; Vol. 15, pp 389–549; (d) Larsen, R. D.. In *Science of Synthesis*; Black, D. S., Ed.; Thieme: Stuttgart, 2005; Vol. 15, pp 551–660; (e) Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gómez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141–161; (f) Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.* **2008**, *12*, 1116–1183; (g) Arisawa, M.; Terada, Y.; Theeraladanon, C.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Organomet. Chem.* **2005**, *690*, 5398–5406; (h) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583–593; (i) Yamashkin, S. A.; Oreshkina, E. A. *J. Heterocycl. Chem.* **2006**, *42*, 701–718.
6. (a) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2001**, 2576–2577; (b) Cho, C. S.; Kim, B. T.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2003**, *59*, 997–8002; (c) Martinez, R.; Ramon, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8988–9001; (d) Vander, H. M.; Ledoux, N.; Allaert, B.; Voort, P. V. D.; Drozdzak, R.; Vos, D. D.; Verpoort, F. *New J. Chem.* **2007**, *31*, 1572–1574; (e) Martinez, R.; Ramon, D. J.; Yus, M. *Eur. J. Org. Chem.* **2007**, 1599–1605; (f) Martinez, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2008**, *73*, 9778–9780. and references cited therein.
7. (a) Shindoh, N.; Tokuyama, H.; Takemoto, Y.; Takasu, K. *J. Org. Chem.* **2008**, *73*, 7451–7456; (b) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070; (c) Yadav, J. S.; Reddy, B. V. S.; Rao, R. S.; Naveenkumar, V.; Nagaiah, K. *Synthesis* **2003**, 1610–1614; (d) Zhao, Y.-L.; Zhang, W.; Wang, S.; Liu, Q. *J. Org. Chem.* **2007**, *72*, 4985–4988.
8. (a) Zhang, X.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763–766; (b) Luo, Y.; Li, Z.; Li, C.-J. *Org. Lett.* **2005**, *7*, 2675–2678; (c) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *J. Org. Chem.* **2007**, *72*, 6873–6877; (d) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* **2001**, *3*, 1109–1112; (e) Li, L.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 10707–10713; (f) Cho, C. S.; Kim, J. U. *Tetrahedron Lett.* **2007**, *48*, 3775–3778; (g) Zhang, Z.; Tan, J.; Wang, Z. *Org. Lett.* **2008**, *10*, 173–175. and references cited therein.
9. (a) Fan, J.; Wan, C.; Sun, G.; Wang, Z. *J. Org. Chem.* **2008**, *73*, 8608–8611; (b) Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1977–1979; (c) Fayol, A.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3633–3635; (d) Lin, X.-F.; Cui, S.-L.; Wang, Y.-G. *Tetrahedron Lett.* **2006**, *47*, 3127–3130.
10. (a) Goodwin, S.; Smith, A. F.; Valsquez, A. A.; Horning, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 6209–6213; (b) Fournet, A.; Vagneur, B.; Rilchomme, P.; Bruneton, J. *Can. J. Chem.* **1989**, *67*, 2116.
11. Ko, T.-C.; Hour, M.-J.; Lien, J.-C.; Teng, C.-M.; Lee, K.-H.; Kuo, S.-C.; Huang, L.-J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 279–282.
12. (a) Singh, O. V.; Kapil, R. S. *Synlett* **1992**, 751; (b) Verma, R. S.; Kumar, D. *Tetrahedron Lett.* **1998**, *39*, 9113–9116; (c) Mphahlele, M. J.; Mogamisi, F. K.; Tsanwani, M.; Hlatshwayo, M. S.; Mampa, M. R. *J. Chem. Res., Synop.* **1999**, 706–707; (d) Arcadi, A.; Marinelli, F.; Rossi, E. *Tetrahedron* **1999**, *55*, 13233–13250; (e) Kumar, K. H.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 9531–9535.
13. (a) Domling, A. *Chem. Rev.* **2006**, *106*, 17–89; (b) Kobayashi, K.; Takagoshi, K.; Kondo, S.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 553.
14. *General procedure*: To a solution of 2-(2-(trimethylsilyl)ethynyl)anilines **1** (0.5 mmol) and aldehydes **2** (1.5 mmol) in 10 mL of dry alcohols was added sulfuric acid (37 mg, 0.375 mmol). The reaction mixture was stirred at 65 °C for 17 h under air. After removal of most solvent under vacuum, 50 mL of EtOAc was added. The solution was washed successively with saturated $NaHCO_3$ twice and brine and then dried over Na_2SO_4. The residue was purified by column chromatography on silica gel after evaporation of solvent. Compound **3c** 4-methoxy-2-(4-methoxyphenyl)quinoline: ^1H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 8.4 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.14 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 4.11 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 162.7, 160.8, 158.4, 149.2, 132.9, 129.9, 129.0, 128.9, 125.1, 121.6, 120.2, 114.1, 97.5, 55.6, 55.4. MS (EI) 266 $[M+H]^+$. HRMS calcd for $C_{17}H_{15}O_2N$: 265.1103, found: 265.1097.
15. Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121–1150.