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Direct Synthesis of Quinazolines through Copper-Catalyzed Reaction of Aniline-Derived Benzamidines

Yusuke Ohta, Yusuke Tokimizu, Shinya Oishi, Nobutaka Fujii,* and Hiroaki Ohno*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

hohno@pharm.kyoto-u.ac.jp; nfujii@pharm.kyoto-u.ac.jp

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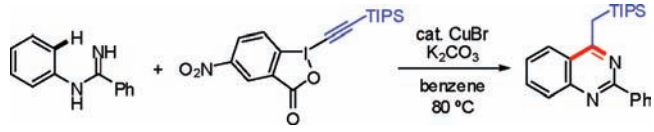
ABSTRACT



A novel synthesis of 2-phenyl-4-[(triisopropylsilyl)methyl]quinazolines from monosubstituted arenes has been developed. Treatment of *N*-phenylbenzamidines with 5-nitro-1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one and K_2CO_3 in the presence of a catalytic amount of CuBr in benzene gives 2-phenyl-4-[(triisopropylsilyl)methyl]quinazolines in moderate to good yields.

Many biologically active compounds contain the quinazoline motif, including the potent anti-lung cancer agent, gefitinib,[1] and the α-adrenergic blocker, prazosin.[2] Most of the synthetic routes to quinazolines depend on the use of anilines bearing an *ortho*-functional group.[3] This limitation prompted us to develop a direct synthesis of these compounds from *ortho*-unfunctionalized aniline derivatives.

Since the pioneering works on C−H alkynylation of heteroarenes using a stoichiometric amount of metal by Kalinin and Trofimov[4] and using transition-metal catalyst by Gevorgyan,[5] significant advances have been made in the field of aromatic C−H alkynylation.[6−8] Recently, Waser reported gold-catalyzed C−H alkynylation of indoles and pyrroles at the 3-position by use of alkynyliodoxolone reagent.[9] We postulated that the amidine group in *N*-phenylbenzamidine **1a** could function as both a directing group for copper-catalyzed C−H alkynylation[10] with an appropriate alkyne **2** and a nucleophilic group for cyclization of **3a** to directly give substituted quinazoline **4** (Scheme 1). Otherwise, nitrogen alkynylation[11] might promote tautomerization−electrocyclization cascade[12] of **3b** to give the same quinazoline **4**. The challenges of this strategy include predominant alkyne introduction over benzimidazole forma-

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(3) For recent reviews, see: (a) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223.

(4) For C−H alkynylation of heteroarenes in the presence of a stoichiometric amount of metal, see: (a) Kalinin, V. K.; Pashchenko, D. N.; She, F. M. *Mendeleev Commun.* **1992**, *2*, 60. (b) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. I.; Ushakov, I. A. *Tetrahedron Lett.* **2004**, *45*, 6513. (c) Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Vakul'skaya, T. I.; Kazheva, O. N.; Aleksandrov, G. G.; Dyachenko, O. A.; Mikhaleva, A. I. *Tetrahedron* **2008**, *64*, 5541. For a related radical reaction, see: (d) Martelli, G.; Spagnolo, P.; Tiecco, M. *J. Chem. Soc. B* **1970**, 1413.

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(8) For a recent review, see: Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096.

(9) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346.

(10) For related C−H alkynylation of anilines, see refs 6b and 6c.

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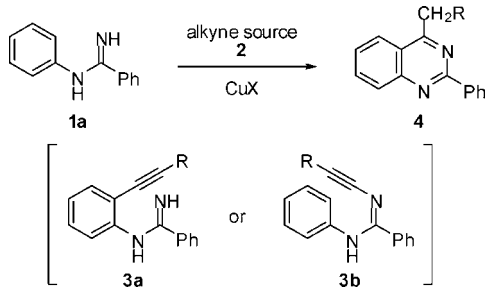
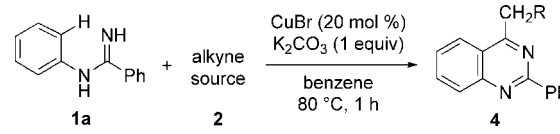
Scheme 1. Direct Synthesis of Quinazoline through Copper-Catalyzed Alkynylation and Cyclization

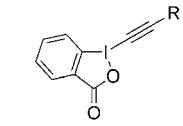
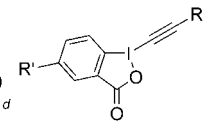


tion[13] and regioselective cyclization[14] or alkynylation in the presence of two nitrogen atoms.

We initially explored appropriate alkyne sources for the reaction. After considerable experimentation using various terminal and internal alkynes in combination with series of copper(I and II) salts and solvents (see the Supporting Information),[15] we obtained promising results by use of alkynyl halides or related reagents and CuBr in benzene (Table 1). When *N*-phenylbenzamidine **1a** was reacted with 2-(triisopropylsilyl)ethynyl bromide **2a** in the presence of CuBr (20 mol %) and K_2CO_3 (1 equiv) in benzene, ^{1}H NMR indicated formation of the desired quinazoline **4a** as an inseparable mixture with an unidentified compound (entry 1). The use of alkynyl iodonium salt **2b** led to the decomposition of the amidine **1a** (entry 2). Iodoxolone derivatives **2c**−**f** were tested as alkyne sources based on Waser's reports on C−H alkynylation of indoles with **2c**.[9,16] As expected, **2c** bearing a TIPS group was a favorable alkyne

Table 1. Optimization of Reaction Conditions[a]



entry	alkyne source **2**	R	R'	product **4**	yield (%)[b]
1	TIPS—≡—Br	**2a**		**4a**	ND[c]
2	TIPS—≡—$^+$IPh $^-$OTf	**2b**		**4a**	0
3		**2c**	TIPS	**4a**	20
4[d]		**2c**	TIPS	**4a**	31
5		**2d**	TMS	**4b**	0
6		**2e**	Ph	**4c**	0
7		**2f**	*t*-Bu$_2$	**4d**	0
8		**2g**	TIPS Me	**4a**	*ca.* 61
9		**2h**	TIPS F	**4a**	*ca.* 61
10		**2i**	TIPS NO_2	**4a**	44−61
11[d]		**2i**	TIPS NO_2	**4a**	62

[a] All reactions were conducted with **1a** (0.13 mmol) and **2** (1.5 equiv) in the presence of CuBr (20 mol %) in benzene at 80 °C for 1 h. [b] Isolated yields. [c] ND = not determined. [d] MS4Å (300 mg) was added.

source and provided the desired quinazoline **4a** in 20% yield (entry 3). Addition of 4 Å molecular sieves (MS4Å) slightly improved the yield to 31% (entry 4). The reaction of *N*-phenylbenzamidine **1a** with **2d** bearing a TMS group did not produce the desired quinazoline **4b** (entry 5). The same result was obtained when **2e** (phenyl group) and **2f** (*t*-butyl group) were used (entries 6 and 7, respectively). These results prompted our investigation of an appropriate substituent on the aryl ring of **2c**. Both 5-methyl- and 5-fluorobenziodoxolones (**2g** and **2h**) increased the yield of **4a** to ca. 61% with some impurities (entries 8 and 9). 5-Nitrobenziodoxolone **2i** showed a clear conversion to **4a** in 44−61% yield (entry 10). With the addition of MS4Å, this direct synthesis of quinazoline was a reproducible reaction (entry 11).

Having established the reaction conditions (Table 1, entry 11),[17] we next examined the substrate scope of this reaction using substituted *N*-phenylbenzamidines **1b**−**m** (Table 2). These can be readily prepared by Lewis acid mediated addition of anilines to benzonitrile. The reactions using amidines **1b**−**e**, which were derived from anilines containing a halogen atom at the 4-position, gave the corresponding 6-fluoro-, chloro-, bromo-, and iodoquinazolines **4e**−**h** in moderate yields (entries 1−4). Amidines substituted with an electron-donating methyl, methoxy, or *t*-butyl group at the 4-position of the aryl ring were found to be good reaction components and provided the quinazolines **4i**−**k** in 60−67% yields (entries 5−7). Substitution at the *meta* position was investigated using amidine **1i** prepared from 3-bromoaniline. In the reaction, this gave a mixture of 5-bromo- and 7-bromoquinazoline derivatives **4l**, which shows that the

(11) For selected examples of nitrogen alkynylation using alkynyliodonium salts, see: (a) Murch, P.; Williamson, B. L.; Stang, P. J. *Synthesis* **1994**, 1255. (b) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440. (c) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426. For a reaction including 1,2-silyl migration, see: (d) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed* **1998**, *37*, 489. For reviews, see: (e) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927. (f) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev* **2010**, DOI: 10.1021/cr100003s.

(12) For a related arene-ynamide cyclization, see: (a) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047. See also: (b) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572.

(13) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932.

(14) (a) Palladium-catalyzed quinazolin-2-one formation by rearrangement of benzo[*d*][1,3]oxazinamine derivatives: Costa, M.; Della Cá, N.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, *69*, 2469. (b) Platinum-catalyzed quinazolin-2-one formation from alkoxy-substituted urea derivatives: Nakamura, I.; Sato, Y.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 4198. (c) TfOH-mediated quinazolin-2-one formation: Wang, H.; Liu, L.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *Tetrahedron Lett.* **2009**, *50*, 6841. (d) Gold-catalyzed selective synthesis of quinazolin-2-ones over indoles: Gimeno, A.; Medio-Simón, M.; Ramírez de Arellano, C.; Asensio, G.; Cuenca, A. B. *Org. Lett.* **2010**, *12*, 1900.

(15) In this study, we focused on the reaction using copper salts (especially halides), generally cheaper than many other transition-metal salts/complexes including those of palladium, nickel, and gallium.

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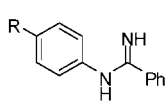
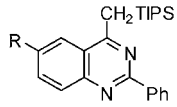
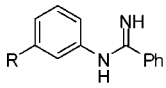
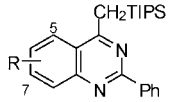
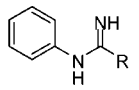
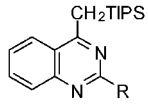
(17) The reaction conditions including solvent, base, and catalyst loading were not optimized with **2i**.

Table 2. Reaction of Various *N*-Phenylbenzamidines[a]

entry	substrate **1**	product **4**	yield (%)[b]
			
1	**1b**: R = F	**4e**	52
2	**1c**: R = Cl	**4f**	46
3	**1d**: R = Br	**4g**	49
4	**1e**: R = I	**4h**	57
5	**1f**: R = Me	**4i**	60
6	**1g**: R = OMe	**4j**	61
7	**1h**: R = *t*-Bu	**4k**	67
			
8	**1i**: R = Br	**4l**	48[c]
9	**1j**: R = OMe	**4m**	77[d]
			
10	**1k**: R = 4-(CF$_3$)C$_6$H$_4$	**4n**	50
11	**1l**: R = 4-(MeO)C$_6$H$_4$	**4o**	61
12	**1m**: R = thiophen-2-yl	**4p**	46

[a] All reactions were conducted with **1** (0.13 mmol) and **2i** (1.5 equiv) in the presence of MS4Å (300 mg) and CuBr (20 mol %) in benzene at 80 °C for 1 h. [b] Isolated yields. [c] A 3.7:1 mixture of 5- and 7-bromoquinazolines. [d] A 1.25:1 mixture of 5- and 7-methoxyquinazolines.

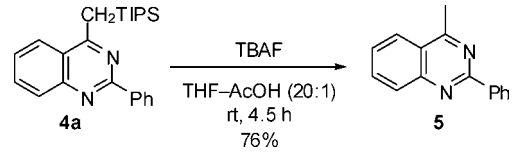
reaction proceeds with moderate regioselectivity (48%, 3.7:1, entry 8). The use of *N*-(3-methoxyphenyl)benzamidine **1j** resulted in the highest yield of the desired 5-methoxy- and 7-methoxyquinazolines **4m** without regioselectivity (77%, 1.25:1, entry 9). Quinazolines **4n** and **4o** with a substituted arene at the 2-position were produced in 50 and 61% yield, respectively, from amidines prepared using *p*-trifluoromethyl- or *p*-methoxybenzonitrile (entries 10 and 11). This reaction is applicable to the synthesis of 2-(heteroaryl)quinazolines. For example, amidine **1m** was allowed to react with **2i** in the presence of CuBr to give 2-(thiophen-2-yl)quinazoline **4p** in 46% yield. In all cases, benzimidazole formation was not observed. The moderate yields of the reaction are due to formation of highly polar byproducts (unidentified).

Finally, desilylation of the resulting 2-phenyl-4-(triisopropylsilyl)methylquinazoline **4a** was investigated (Scheme 2). The reaction of **4a** with TBAF in THF−AcOH (20:1) at room temperature led to efficient cleavage of the TIPS group to give known quinazoline **5**[18] in 76% yield.

It should be noted that the amidine **3a** bearing a (TIPS)-ethynyl group at the *ortho*-position (Scheme 1, R = TIPS),

(18) Anderson, R. K.; Carter, S. D.; Cheeseman, G. W. H. *Tetrahedron* **1979**, *35*, 2463.

Scheme 2. Removal of the TIPS Group



identically prepared through Sonogashira reaction of iodoaniline, did not produce the quinazoline **4a** under standard reaction conditions. Accordingly, C−H alkynylation of **1a** is not promoted in this system. At present, we can only say that other reaction pathways, including nitrogen alkynylation to produce **3b**,[19] would be more likely than the C−H alkynylation pathway.

In summary, we have developed a novel synthesis of quinazolines through copper-catalyzed alkynylation and cyclization of *N*-phenylbenzamidines. This reaction is synthetically useful since functionalized quinazolines can be directly constructed from *ortho*-unsubstituted amidines, readily prepared from commercially available anilines. Further studies that include an investigation of the exact reaction mechanism and elaboration of 4-(silylmethyl)quinazolines including carbon−carbon bond formation are now in progress.

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Supporting Information Available: A general experimental procedure, details of the reaction optimization, and ^{1}H and ^{13}C NMR spectra for all new compounds (**1h**, **1i**, **1k**, **2g**−**i**, **4a**, **4e**−**p**) and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For related electrophilic reactions with iodoxolane reagents, see: (a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.—Eur. J.* **2006**, *12*, 2579. (b) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754. (c) Eisenberger, P.; Kieltsch, I.; Armanino, N.; Togni, A. *Chem. Commun.* **2008**, 1575. (d) Stanek, K.; Koller, R.; Togni, A. *J. Org. Chem.* **2008**, *73*, 7678. (e) Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4332. (f) Niedermann, K.; Welch, J. M.; Koller, R.; Cvengroš, J.; Santschi, N.; Battaglia, P.; Togni, A. *Tetrahedron* **2010**, *66*, 5753. See also: (g) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett.* **1995**, *36*, 7975.