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Copper-Catalyzed [5 + 1] Annulation of 2-Ethynylanilines with an *N,O*-Acetal Leading to Construction of Quinoline Derivatives

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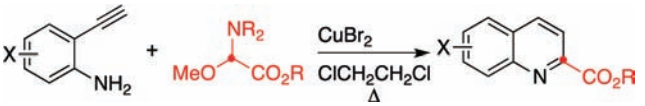
ABSTRACT



A novel copper-catalyzed [5 + 1] annulation of 2-ethynylanilines with an *N,O*-acetal, which functioned as a C1 part, leading to the preparation of quinoline derivatives with an ester substituent on the 2-position is described. A combination of $CuBr_2$ and trifluoroacetic acid (TFA) promoting [5 + 1] annulation of the 2-ethynylaniline with ethyl glyoxylate is also demonstrated.

A practical synthesis of polysubstituted quinolines is of considerable interest in the fields of organic and pharmaceutical chemistry, since this basic skeleton is widespread in natural products and biologically active substances.[1] Thus far, a number of approaches, using the Conrad–Limpach–Knorr synthesis,[2] the Skraup–Doebner–Von Miller synthesis,[3] the Friedländer synthesis,[4] and other methods[5,6] have been developed for the preparation of this skeleton. By extension, recently, intramolecular cyclization between an alkyne moiety and an *o*-substituted nitrogen-containing group through a benzene ring has also been attempted (Scheme 1). For example, palladium-catalyzed intramolecular cyclization of an *o*-amino-substituted propargylic compound produced a quinoline derivative (1,2-bond-forming reaction: path a).[7] The combination of *o*-alkynylisocyanobenzene with an appropriate nucleophile, such as an alcohol and an amine, has also been achieved both with and without a basic promoter (2,3-bond-forming reaction: path b).[8] Although a 2-ethynylaniline derivative has been widely utilized as a central and key synthetic building block to construct a typical nitrogen-containing heterocycle,

(1) (a) Glasby, J. S., Ed. *Encyclopedia of the Alkaloids*; Plenum Press: New York, 1975. (b) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Oxford, 2000; pp 616–624. (c) See also ref 6a and references cited therein.

(2) Selected papers for Conrad–Limpach–Knorr-type reactions, see: (a) Curran, A. C. W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 975. (b) Misani, F.; Bogert, M. T. *J. Org. Chem.* **1945**, *10*, 347.

(3) Selected recent papers for Skraup–Doebner–Von Miller-type reactions, see: (a) Sakai, N.; Aoki, D.; Hamajima, T.; Konakahara, T. *Tetrahedron Lett.* **2006**, *47*, 1261. (b) Wu, Y.-C.; Liu, L.; Li, H.-J.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2006**, *71*, 6592. (c) Denmark, S. E.; Venkatraman, S. *J. Org. Chem.* **2006**, *71*, 1668. (d) Eisch, J. J.; Dluzniewski, T. *J. Org. Chem.* **1989**, *54*, 1269.

(4) Selected recent papers for Friedländer-type reactions, see: (a) Ryabukhin, S. V.; Naumchik, V. S.; Plaskon, A. S.; Grygorenko, O. O.; Tolmachev, A. A. *J. Org. Chem.* **2011**, *76*, 5774. (b) Luo, W.; Mu, Q.; Qiu, W.; Liu, T.; Yang, F.; Liu, X.; Tang, J. *Tetrahedron* **2011**, *67*, 7090. (c) Martínez, R.; Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2007**, 1599. (d) Atechian, S.; Nock, N.; Norcross, R. D.; Ratni, H.; Thomas, A. W.; Verron, J.; Masciadri, R. *Tetrahedron* **2007**, *63*, 2811. (e) Wu, J.; Xia, H.-G.; Gao, K. *Org. Biomol. Chem.* **2006**, *4*, 126. (f) Wu, J.; Zhang, L.; Diao, T.-N. *Synlett* **2005**, 2653. (g) Yadav, J. S.; Reddy, B. V. S.; Premalatha, K. *Synlett* **2004**, 963. (h) Arcadi, A.; Chiarini, M.; Giuseppe, S. D.; Marinelli, F. *Synlett* **2003**, 203. (I) Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371. (j) Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467. (k) Cho, C. S.; Kim, B. T.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2003**, *59*, 7997. (l) Jiang, B.; Si, Y.-G. *J. Org. Chem.* **2002**, *67*, 9449. (m) Gladiali, S.; Chelucci, G.; Mudadu, M. S.; Gastaut, M. A.; Thummel, R. P. *J. Org. Chem.* **2001**, *66*, 400.

(5) Selected recent papers for halogen-mediated preparation of quinolines, see: (a) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177. (b) Li, X.; Mao, Z.; Wang, Y.; Chen, W.; Lin, X. *Tetrahedron* **2011**, *67*, 3858.

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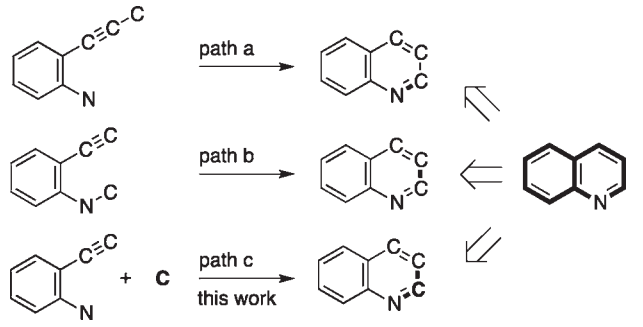
a polysubstituted indole,[9] the extensive annulation that produces a quinoline skeleton through a combination of the 2-ethynylaniline with a reaction substrate, such as an aldehyde and a ketone, has not been studied extensively (1,2- and 2,3-bond forming reaction: path c).[10] In this context, we previously reported that use of a 2-ethynylaniline with a trimethylsilyl group or with no substituent group on the terminal triple bond exclusively afforded polysubstituted quinoline derivatives via indium-promoted intermolecular dimerization of the ethynylaniline[11] and developed a $Hf(OTf)_4$-doped Me_3SiCl system-catalyzed aminomethylation of heterocycles with several *N*,*O*-acetals that led to the preparation of a variety of non-natural aromatic amino acid derivatives.[12]

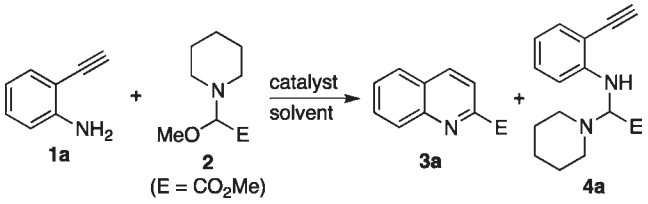
Scheme 1. Approach to a Quinoline Skeleton Through an Intramolecular Cyclization Mode of an Alkyne



We report herein a novel copper-catalyzed [5 + 1] annulation of 2-ethynylanilines with an *N*,*O*-acetal, which functions as a C1 unit, leading to the preparation of quinoline derivatives. We also disclosed that the combination of a Lewis acidic metal and a Brønsted acid, trifluoroacetic acid (TFA), promoted the [5 + 1] annulation of 2-ethynylaniline with ethyl glyoxylate in the presence of piperidine. This method is the first example for the preparation of a quinoline skeleton through copper-catalyzed [5 + 1] annulation and the direct introduction of an ester substituent at the 2-position on the skeleton.

Table 1 shows the results of intermolecular annulation of ethynylaniline (**1a**) with *N*,*O*-acetal **2**, which was prepared from methyl 2-bromo-2-methoxyacetate and piperidine in the presence of a base by the procedure previously reported under several conditions.[12c] Initially, when the reaction ran in chloroform without a catalyst, the adduct **4a** was obtained in a 62% yield (entry 1). No trace of either the indole or quinoline derivative was observed. To promote intramolecular cyclization of the adduct **4a**, the addition of 10 mol % of $InBr_3$ to the reaction system was then examined under similar conditions. Interestingly, a slight formation of quinoline derivative **3a** was observed (entry 2). Thus, the additive effect of several copper catalysts, which may be able to undergo intramolecular cyclization,[13] was investigated. When the reaction was performed with CuCl, the selective formation of the corresponding quinoline derivative was observed in a 51% yield (entry 3). Also, the use of CuBr and $CuBr_2$ showed a similar annulation effect (entries 4 and 5). When the reaction was conducted with $CuBr_2$ under 1,2-dichloroethane reflux conditions, the yield of the quinoline was improved to 76% (entry 6). Moreover, the reaction time was dramatically shortened. The use of $CuCl_2$ also showed a similar effect (entry 7).

Table 1. Examinations of Reaction Conditions



entry	cat.	solv	temp[a] (°C)	time (h)	yield[b] (%) 3a	4a
1	–	$CHCl_3$	65	18	ND	62
2	$InBr_3$	$CHCl_3$	65	18	5	33
3	CuCl	$CHCl_3$	65	1	51	ND
4	CuBr	$CHCl_3$	65	5	52	ND
5	$CuBr_2$	$CHCl_3$	65	24	58	ND
6	$CuBr_2$	$ClCH_2CH_2Cl$	85	0.5	(76)	ND
7	$CuCl_2$	$ClCH_2CH_2Cl$	85	0.5	70	ND

[a] Bath temperature. [b] NMR (Isolated) yield.

(6) Selected recent papers for copper-catalyzed preparation of quinolines, see: (a) Huang, H.; Jiang, H.; Chen, K.; Liu, H. *J. Org. Chem.* **2009**, *74*, 5476. (b) Patil, N. T.; Raut, V. S. *J. Org. Chem.* **2010**, *75*, 6961.

(7) (a) Pisaneschi, F.; Sejberg, J. J. P.; Blain, C.; Ng, W. H.; Aboagye, E. O.; Spivey, A. C. *Synlett* **2011**, 241. (b) Mahanty, J. S.; De, M.; Das, P.; Kundu, N. G. *Tetrahedron* **1997**, *53*, 13397. (c) Torii, S.; Xu, L. H.; Sadakane, M.; Okumoto, H. *Synlett* **1992**, 513.

(8) (a) Zhao, J.; Peng, C.; Liu, L.; Wang, Y.; Zhu, Q. *J. Org. Chem.* **2010**, *75*, 7502. (b) Mitamura, T.; Nomoto, A.; Sonoda, M.; Ogawa, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 822. (c) Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1977.

(9) Selected reviews for intramolecular preparation of indoles, see: (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641. (b) Barluenga, J.; Rodriguez, F.; Fananas, F. J. *Chem. Asian J.* **2009**, *4*, 1036. (c) Kruger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153. (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.

(10) (a) Okamoto, N.; Takeda, K.; Ishikura, M.; Yanada, R. *J. Org. Chem.* **2011**, *76*, 9139. (b) Wang, Y.; Peng, C.; Liu, L.; Zhao, J.; Su, L.; Zhu, Q. *Tetrahedron Lett.* **2009**, *50*, 2261. (c) Lee, J. H.; Lee, B. S.; Shin, H.; Nam, D. H.; Chi, D. Y. *Synlett* **2006**, 65.

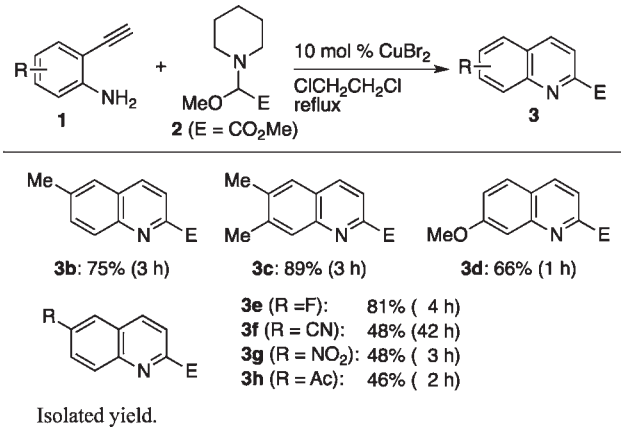
(11) (a) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160. (b) Sakai, N.; Annaka, K.; Konakahara, T. *J. Org. Chem.* **2006**, *71*, 3653.

(12) (a) Sakai, N.; Watanabe, A.; Ikeda, R.; Nakaike, Y.; Konakahara, T. *Tetrahedron* **2010**, *66*, 8837. (b) Sakai, N.; Sato, A.; Konakahara, T. *Synlett* **2009**, 1449. (c) Sakai, N.; Asano, J.; Kawada, Y.; Konakahara, T. *Eur. J. Org. Chem.* **2009**, 917. (d) Sakai, N.; Asano, J.; Shimano, Y.; Konakahara, T. *Synlett* **2007**, 2675. (e) Sakai, N.; Hirasawa, M.; Hamajima, T.; Konakahara, T. *J. Org. Chem.* **2003**, *68*, 483. (f) Sakai, N.; Hamajima, T.; Konakahara, T. *Tetrahedron Lett.* **2002**, *43*, 4821.

(13) Selected papers for intramolecular cyclization of an ethynylaniline with a copper catalyst, see: (a) Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958. (b) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126. (c) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277.

Next, to extend the generality of this reaction, the annulation of various ethynylanilines with *N*,*O*-acetal **2** was carried out under optimal conditions, with the results shown in Scheme 2. Most cases with the ethynylaniline having an electron-donating group, such as a methyl, dimethyl and methoxy group, were completed within 3 h to produce the desired quinoline derivatives in good yields. The use of a substrate with a fluoro electron-withdrawing group gave the product in good yield. However, attempts to cyclize ethynylaniline with a stronger electron-withdrawing group, such as cyano and nitro groups, and the *N*,*O*-acetal led to a decrease in both yields. In particular, the reaction of the substrate with a cyano group prolonged the reaction time. The reaction of the substrate containing an acetyl group also produced the corresponding quinoline derivative in moderate yield. These results strongly implied that the nucleophilicity of the tethered amino group on the ethynylaniline had an effect on both the first intermolecular substitution and the subsequent intramolecular cyclization.

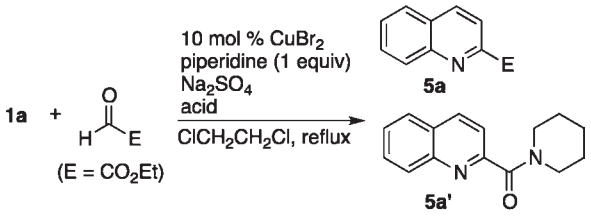
Scheme 2. Synthesis of Quinolines with Ethynylanilines **1** and *N*,*O*-Acetal **2**



To extend this procedure further, a single-step synthesis of the quinoline derivative from a 2-ethynylaniline derivative and ethyl glyoxylate was examined. We anticipated that an *N*,*O*-acetal from the glyoxylate ester and a secondary amine in the presence of an acid promoter was initially generated in situ, followed by annulation of the formed *N*,*O*-acetal and the aniline **1a**, leading to a quinoline derivative. After screens using several Brønsted acids, a cooperative catalytic system of $CuBr_2$ and TFA in the presence of piperidine promoted annulation through formation of the *N*,*O*-acetal to produce the desired quinoline **5a** in good yield (Scheme 3). Also, when the reaction was carried out without the acidic catalyst, the yield of quinoline **5a** decreased to 46% and the byproduct **5a′** having an amide part was obtained in 16% yield after 24 h. These results imply that the TFA acts as a promoter to generate the *N*,*O*-acetal from the aldehyde and piperidine.

Scheme 4 shows the results of a single-step synthesis of the quinoline derivative from several ethynylanilines with

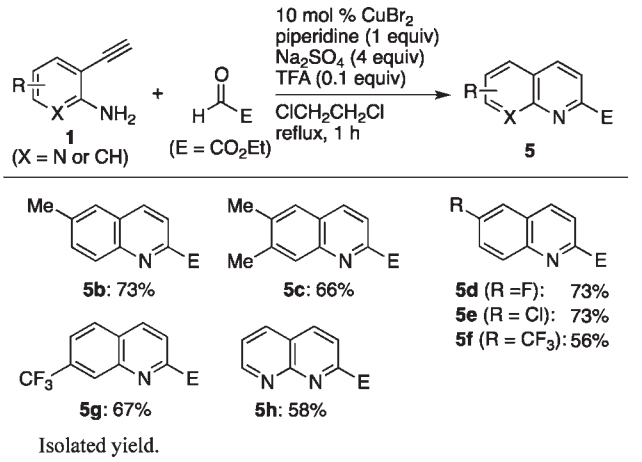
Scheme 3. Single-Step Synthesis of a Quinoline Derivative from an Ethynylaniline and Ethyl Glyoxylate



acid	time	yield
TFA (0.1 equiv)	1 h	**5a**: 78%, **5a'**: ND
without acid	24 h	**5a**: 46%, **5a'**: 16%

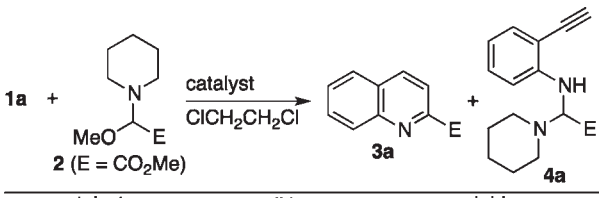
ethyl glyoxylate and piperidine in the presence of a catalytic amount of both $CuBr_2$ and TFA. All reactions were cleanly completed within 1 h to give the corresponding quinoline derivatives **5** selectively in moderate to good yields. The electronic effect of the substituent group on the ethynylaniline does not have a direct influence on the reaction time of the annulation and the product yield. No formation of a corresponding amide product was observed in all cases. This method could be applied to preparation of 1,8-naphthyridine derivative **5h**, which was widely found in a basic skeleton of biologically active substances.[1a]

Scheme 4. Direct Synthesis of Quinolines and a Naphthyridine with Ethynylanilines **1** and Ethyl Glyoxylate



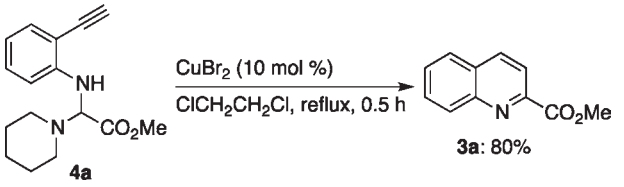
To understand the reaction pathway for the annulation, several control experiments were conducted. When the reaction of the ethynylaniline **1a** and the *N*,*O*-acetal **2** was treated without a catalyst under the $ClCH_2CH_2Cl$ refluxed conditions for 18 h, a selective formation of the 1:1 adduct, *N*,*N*-aminal **4a** was observed (Scheme 5). Most of the reactions described above were completed within 3 h, which implied that the copper catalyst activated the formation of an *N*,*O*-acetal to a certain extent. In contrast, when a similar reaction was carried out with 10 mol % of $CuBr_2$, the reaction was completed within 0.5 h to give only the quinoline **3a** in a 76% yield. Additionally, when the

Scheme 5. Effect of the Copper Catalyst for Intermolecular Substitution



catalyst	conditions	yield
without $CuBr_2$	reflux, 18 h	**3a**: 0% **4a**: 62%
with 10 mol % of $CuBr_2$	reflux, 0.5 h	**3a**: 76% **4a**: 0%

Scheme 6. Effect of the Copper Catalyst for Intramolecular Cyclization



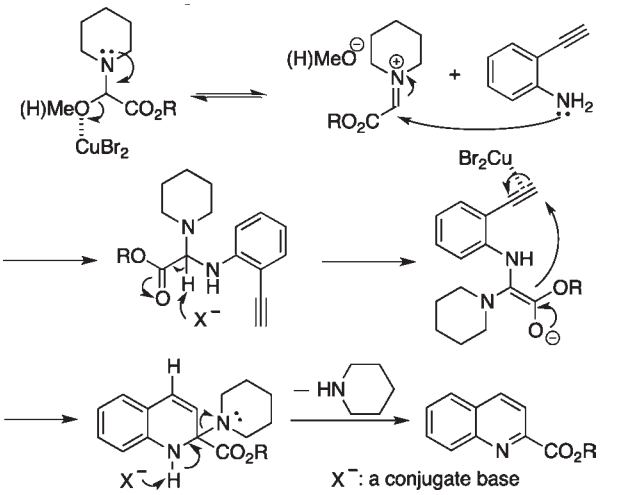
isolated *N*,*N*-aminal derivative **4a** was treated with 10 mol % of $CuBr_2$ in $ClCH_2CH_2Cl$, the intramolecular cyclization proceeded smoothly to afford the desired quinoline **3a** in an 80% yield (Scheme 6). Apparently, the copper catalyst activated the alkyne moiety to facilitate the intramolecular cyclization of the tethered amino group, and it was found that the *N*,*N*-aminal was a key intermediate in the annulation series.

On the basis of these results, we present a plausible mechanism for the [5 + 1] annulation as shown in Scheme 7. The central key in this mechanism is the enolization of the ester part. An intramolecular attack of the formed enolate anion onto the terminal alkyne carbon activated by $CuBr_2$ allowed construction of a quinoline skeleton. Also, when a similar reaction with nonenolizable aldehydes, such as benzaldehyde and trichloroethanal, instead of ethyl glyoxylate, was carried out under optimal conditions, no annulation was observed to recover the starting ethynylaniline. These results strongly support the reaction mechanism shown in Scheme 7.[14] The role of TFA would be to promote both condensation of a glyoxylate ester and piperidine and elimination of piperidine.

(14) When the reaction with an ethynylaniline having a substituent group on the terminal alkyne moiety was examined, no annulation was observed.

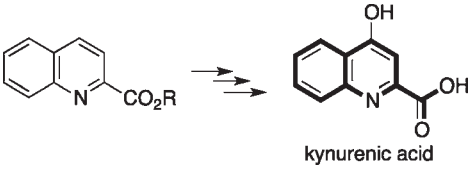
(15) (a) Manfredini, S.; Pavan, B.; Vertuani, S.; Scaglianti, M.; Compagnone, D.; Biondi, C.; Scatturin, A.; Tanganelli, S.; Ferraro, L.; Prasad, P.; Dalpiaz, A. *J. Med. Chem.* **2001**, *45*, 559. (b) Leeson, P. D.; Baker, R.; Carling, R. W.; Curtis, N. R.; Moore, K. W.; Williams, B. J.; Foster, A. C.; Donald, A. E.; Kemp, J. A.; Marshall, G. R. *J. Med. Chem.* **1991**, *34*, 1243.

Scheme 7. Proposed Reaction Path of the Annulation



As shown in Scheme 8, this procedure would be to provide facile approach to a basic skeleton of a biologically active substance, such as kynurenic acid.[15]

Scheme 8. Biologically Active Substance Containing a Quinoline Skeleton with 2-Carboxylic Acid Substituent



We have demonstrated a copper-catalyzed [5 + 1] annulation of 2-ethynylanilines with an *N*,*O*-acetal, leading to the preparation of quinoline derivatives having an ester substituent on the 2-position. We also found that a combination of the Lewis and Brønsted acids consisting of a copper catalyst and TFA promoted both intermolecular substitution and a subsequent intermolecular cyclization of 2-ethynylanilines with ethyl glyoxylate to give the quinoline or naphthyridine skeleton.

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Supporting Information Available. Experimental details and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.