JOC Article
pubs.acs.org/joc

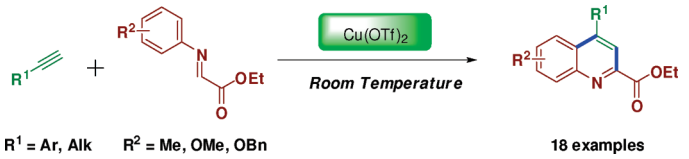
A Simple and Convenient Copper-Catalyzed Tandem Synthesis of Quinoline-2-carboxylates at Room Temperature

He Huang, Hualiang Jiang, Kaixian Chen, and Hong Liu*

Drug Discovery and Design Centre, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, and Graduate School, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China

hliu@mail.shcnc.ac.cn

Received May 25, 2009



We developed a simple and convenient copper-catalyzed method for the synthesis of quinoline-2-carboxylate derivatives through sequential intermolecular addition of alkynes onto imines and subsequent intramolecular ring closure by arylation. The efficiency of this system allowed the reactions to be carried out at room temperature.

Introduction

The quinoline-2-carboxylate framework is a motif common to biologically active compounds and valuable synthetic intermediates (Scheme 1).[1−4] For example, kynurenic acid **1**[1a] is a useful agent for the potential control of neurodegenerative disorders; compound **2**[1b] can be used as a potent 5-hydroxytryptamine antagonist; and compound **3**[1c] is a potent lead compound for inhibiting the binding of Insulin-like Growth Factor (IGF) to IGF-binding proteins. In addition, quinoline-2-carboxylates are key intermediates for the preparation of quinox ligands which were widely applied in asymmetric catalysis.[2a−2d] In particular, 2-quinolinecarboxylic acid **4** has been shown to be a promising ligand for the ruthenium-catalyzed dehydrative allylation of alcohols.[2e] As a consequence of their unique chemical and biological properties, quinoline-2-carboxylates have attracted wide interest from pharmaceutical and synthetic materials. Traditionally, the quinoline-2-carboxylate framework has been prepared through oxidative reactions of 2-methylquinolines,[5] 2-carbonylquinolines,[6] and 4-oxo-1,4-dihydroquinolines[7] in the presence of strong oxidants or the hydrolyzation of 2-cyanoquinolines[8] with bases. In addition, the Doebner−von Miller reaction is also a useful method to construct quinolines.[9] Although these methods are effective, harsh reaction conditions are necessary, and some depend on the availability of the requisite substituted quinoline derivatives.[5−8] Many starting materials are also sometimes difficult to prepare, so more convenient and efficient approaches

*To whom correspondence should be addressed. Phone: +86-21-50807042. Fax: +86-21-50807088.

(1) (a) Manfredini, S.; Vertuani, S.; Pavan, B.; Vitali, F.; Scaglianti, M.; Bortolotti, F.; Biondi, C.; Scatturin, A.; Prasad, P.; Dalpiaz, A. *Bioorg. Med. Chem.* **2004**, *12*, 5453. (b) Horchler, C. L.; McCauley, J. P.; Hall, J. E.; Snyder, D. H.; Moore, W. C.; Hudzik, T. J.; Chapdelaine, M. J. *Bioorg. Med. Chem.* **2007**, *15*, 939. (c) Zhu, Y. F.; Wang, X. C.; Connors, P.; Wilcoxen, K.; Gao, Y. H.; Gross, R.; Strack, N.; Gross, T.; McCarthy, J. R.; Xie, Q.; Ling, N.; Chen, C. *Bioorg. Med. Chem.* **2003**, *13*, 1931.

(2) (a) Abrunhosa, I.; Delain-Bioton, L.; Gaumont, A. C.; Gulea, M.; Masson, S. *Tetrahedron* **2004**, *60*, 9263. (b) Muller, P.; Chappellet, S. *Helv. Chim. Acta* **2005**, *88*, 1010. (c) Park, S. W.; Son, J. H.; Kim, S. G.; Ahn, K. H. *Tetrahedron: Asymmetry* **1999**, *10*, 1903. (d) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076. (e) Saburi, H.; Tanaka, S.; Kitamura, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1730.

(3) (a) Contour-Galcera, M. O.; Sidhu, A.; Plas, P.; Roubert, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3555. (b) Wang, Y. D.; Boschelli, D. H.; Johnson, S.; Honores, E. *Tetrahedron* **2004**, *60*, 2937. (c) Chan, B. K.; Ciufolini, M. A. *J. Org. Chem.* **2007**, *72*, 8489.

(4) (a) Povarov, L. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1966**, 337. (b) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (c) Alves, M. J.; Azoia, N. G.; Fortes, A. G. *Tetrahedron* **2007**, *63*, 727. (d) Osborne, D.; Stevenson, P. J. *Tetrahedron Lett.* **2002**, *43*, 5469. (e) Twin, H.; Batey, R. A. *Org. Lett.* **2004**, *6*, 4913.

(5) (a) Ladner, D. W. *Synth. Commun.* **1986**, *16*, 157. (b) Warpehoski, M. A.; Gebhard, I.; Kelly, R. C.; Krueger, W. C.; Li, L. H.; Mcgovren, J. P.; Prairie, M. D.; Wicnienski, N.; Wierenga, W. *J. Med. Chem.* **1988**, *31*, 590.

(6) Deeming, A. J.; Rothwell, I. P. *J. Organomet. Chem.* **1981**, *205*, 117.

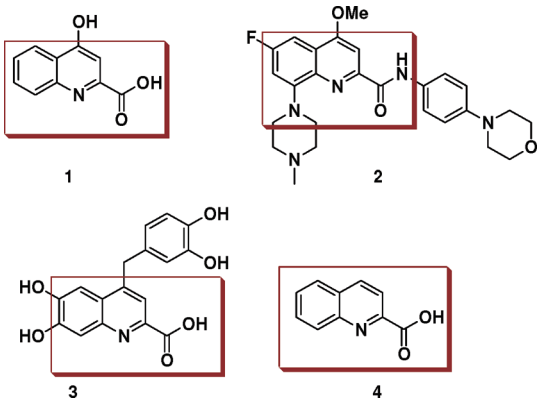
(7) (a) Wright, R. G. M. *Synthesis* **1984**, 1058. (b) Molinski, T. F.; Faulkner, D. J. *Tetrahedron Lett.* **1988**, *29*, 2137.

(8) (a) Rao, A. V. R.; Chavan, S. P.; Sivadasan, L. *Tetrahedron* **1986**, *42*, 5065. (b) Shrader, W. D.; Celebuski, J.; Kline, S. J.; Johnson, D. *Tetrahedron Lett.* **1988**, *29*, 1351.

(9) (a) Mackenzie, A. R.; Moody, C. J.; Rees, C. W. *Tetrahedron* **1986**, *42*, 3259. (b) Itoh, S.; Fukui, Y.; Haranou, S.; Ogino, M.; Komatsu, M.; Ohshiro, Y. *J. Org. Chem.* **1992**, *57*, 4452. (c) Boger, D. L.; Chen, J. H. *J. Org. Chem.* **1995**, *60*, 7369.

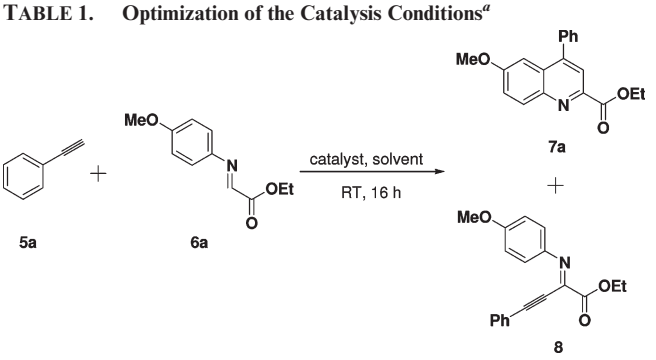
Published on Web 07/02/2009 DOI: 10.1021/jo901101v

SCHEME 1. Representative Quinoline-2-carboxylates in Medicinal Chemistry and Organic Synthesis



would be helpful. In recent years, transition metal-catalyzed coupling reactions have emerged as a powerful tool for the synthesis of heterocyclic compounds.[10] Chan et al. have developed silver- or copper-catalyzed efficient alkynylation of α-imino ester with arylacetylenes.[11] These methods provide an effective route to propargylic amines, which are key intermediates to the construction of quinoline derivatives. Recently, Fujiwara et al. reported an efficient synthesis of quinolin-2(1*H*)-ones by using Pd^{II} via the activation of aromatic C−H bonds for addition to C−C multiple bonds.[12a] Also, an efficient synthesis of 2,4-disubstituted quinoline derivatives from *N*-aryl-2-propynylamines has been reported by Takai and Kuninobu in which Au^{I} and Cu^{I} were used together.[12b] By using $AuCl_3$/CuBr catalysis, Wang described a sequential catalytic process for the synthesis of quinolines through a three-component reaction of aldehydes, amines, and alkynes.[12c] Although these approaches provide efficient access to quinolines, there is considerable room for improvement. For example, an aryl or alkyl group at position 2 of the quinoline ring is predominant in these protocols. To the best of our knowledge, there is no example of constructing a quinoline-2-carboxylate framework under ligand-free copper catalysis at room temperature. The numerous advantages of copper catalysts make them highly attractive for chemical synthesis from environmental and economic points of view.[13] Herein, we report a straightforward and practical copper-catalyzed tandem reaction for the efficient synthesis of quinoline-2-carboxylates via activation of C−H bonds under mild conditions, wherein the Grignard-type imine addition is followed by a Friedel−Crafts alkenylation of arenes with alkynes. The method only requires one metal catalyst, which is both simpler and less costly than those methods that use two metals for both steps. These reactions represent an environmentally friendly and atom-economical concept when performed under mild conditions. The 2-carboxyl group makes this method particularly appealing, since this substituent can be used for further synthetic manipulations.

TABLE 1. Optimization of the Catalysis Conditions[a]



entry	catalyst	solvent	yield **7a**/**8** [%]
1	CuI	CH_2Cl_2	0/0
2	$Cu(OAc)_2$	CH_2Cl_2	0/78
3[b]	$Cu(acac)_2$	CH_2Cl_2	0/73
4[c]	$Cu(tmhd)_2$	CH_2Cl_2	0/59
5[d]	$Cu(OTf)_2$	CH_2Cl_2	87/0
6	$Cu(OTf)_2$	dioxane	15/0
7	$Cu(OTf)_2$	furan	28/0
8	$Cu(OTf)_2$	toluene	37/0
9	$Cu(OTf)_2$	DMSO	0/27
10	$Cu(OTf)_2$	DMF	0/81
11[e]	$Cu(OTf)_2$	CH_2Cl_2	54/0
12[f]	$Cu(OTf)_2$	CH_2Cl_2	31/0
13[g]	$Cu(OTf)_2$	CH_2Cl_2	64/0
14[h]	$Cu(OTf)_2$	CH_2Cl_2	52/0
15[i]	$Cu(OTf)_2$	CH_2Cl_2	85/0

[a]Reaction condition: phenylacetylene (100 μL), *N*-PMP α-iminoethyl glyoxylate (2.0 equiv), catalyst (0.2 equiv), solvent (2 mL), room temperature, reaction time (16 h). [b]acac = acetylacetonate. [c]tmhd = 2,2,6,6-tetramethyl-3,5-heptanedione. [d]OTf = trifluoromethanesulfonate. [e]10% mol $Cu(OTf)_2$ was used. [f]4% mol $Cu(OTf)_2$ was used. [g]1.0 equiv of *N*-PMP α-iminoethyl glyoxylate was used. [h]Reaction time (10 h). [i]Reaction time (24 h).

Results and Discussion

Initially, we chose phenylacetylene **5a** and *N*-PMP α-iminoethyl glyoxylate (PMP = *p*-methoxyphenyl) **6a** as the model substrates to optimize the reaction conditions at room temperature.[14] As shown in Table 1, we tested various copper catalysts in CH_2Cl_2. When the reaction was attempted with

(10) For recently reported methods or reviews for the synthesis of substituted quinolines, see: (a) Cui, S. L.; Wang, J.; Wang, Y. G. *Tetrahedron* **2008**, *64*, 487. (b) István, S.; Ferenc, F. *Synthesis* **2009**, 775. (c) Ghorbani-Vaghei, R.; Akbari-Dadamahaleh, S. *Tetrahedron Lett.* **2009**, *50*, 1055. (d) Vander Mierde, H.; Van Der Voort, P.; Verpoort, F. *Tetrahedron Lett.* **2009**, *50*, 201. (e) Ghassamipour, S.; Sardarian, A. R. *Tetrahedron Lett.* **2009**, *50*, 514. (f) Qi, C. M.; Zheng, Q, W.; Hua, R. M. *Tetrahedron* **2009**, *65*, 1316. (g) Likhar, P. R.; Subhas, M. S.; Roy, S.; Kantam, M. L.; Sridhar, B.; Seth, R. K.; Biswas, S. *Org. Biomol. Chem.* **2009**, *7*, 85. (h) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *J. Org. Chem.* **2007**, *72*, 6873. (i) Gabriele, B.; Mancuso, R.; Salerno, G.; Lupinacci, E.; Ruffolo, G.; Costa, M. *J. Org. Chem.* **2008**, *73*, 4971. (j) Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.* **2008**, *12*, 1116. (k) Kouznetsov, V. V.; Méndez, L. Y. V.; Gómez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141.

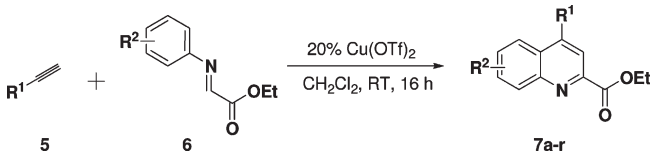
(11) (a) Ji, J. X.; Au-Yeung, T. L.; Wu, J.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 42. (b) Ji, J. X.; Wu, J.; Chan, A. S. C. *Proc. Natl Acad. Sci. U.S.A.* **2005**, *102*, 11196. (c) Shao, Z.; Wang, J.; Ding, K.; Chan, A. S. C. *Adv. Synth. Catal.* **2007**, *349*, 2375.

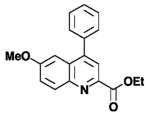
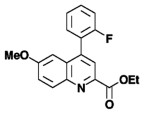
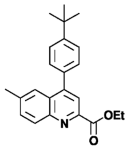
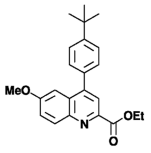
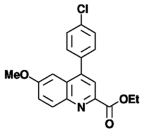
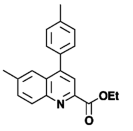
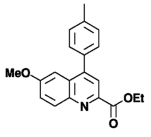
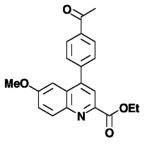
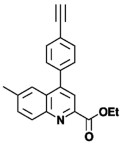
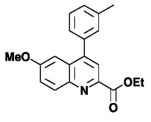
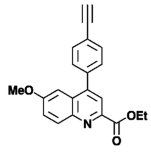
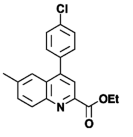
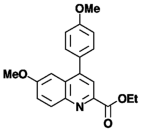
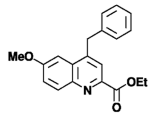
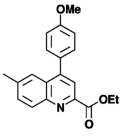
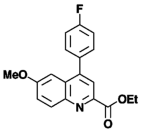
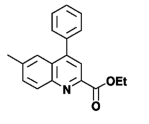
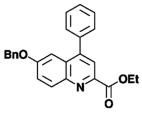
(12) (a) Jia, C. G.; Piao, D. G.; Oyamada, J. Z.; Lu, W. J.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Kuninobu, Y.; Inoue, Y.; Takai, K. *Chem. Lett.* **2007**, *36*, 1422. (c) Xiao, F. P.; Chen, Y. L.; Liu, Y.; Wang, J. B. *Tetrahedron* **2008**, *64*, 2755.

(13) For recent reviews on copper-catalyzed reactions, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Ma, D. W.; Cai, Q. A. *Acc. Chem. Res.* **2008**, *41*, 1450. (c) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359. (d) Yamada, K.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874. (e) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (f) Poulsen, T. B.; Jorgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (g) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796. (h) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(14) *N*-Aryl iminoethyl glyoxylates were prepared by a condensation reaction through the ethyl glyoxylate and aromatic amines in CH_2Cl_2 at temperature.

TABLE 2. Copper-Catalyzed Synthesis of Quinoline-2-carboxylates



Entry	Product	Yield [%]	Entry	Product	Yield [%]	Entry	Product	Yield [%]
1	 **7a**	87	7	 **7g**	79	13	 **7m**	84
2	 **7b**	92	8	 **7h**	83	14	 **7n**	79
3	 **7c**	85	9	 **7i**	69	15	 **7o**	85
4	 **7d**	83	10	 **7j**	90	16	 **7p**	76
5	 **7e**	88	11[a]	 **7k**	52	17	 **7q**	83
6	 **7f**	81	12	 **7l**	81	18	 **7r**	85

[a]Reacted at 50 °C.

CuI as the catalyst, no conversion was observed. Under Cu(OAc)$_2$, Cu(acac)$_2$, and Cu(tmhd)$_2$ catalysis, no desired product was observed. Instead, the major product was ethyl 2-(4-methoxyphenylimino)-4-phenylbut-3-ynoate **8**, which was formed from the oxidation of propargylic amine (Table 1, entries 2−4). However, switching to Cu(OTf)$_2$ as the catalyst resulted in ethyl 6-methoxy-4-phenylquinoline-2-carboxylate **7a** in good yield (Table 1, entry 5). We also investigated the effect of solvents (Table 1, entries 5−10). The choice of solvent influenced both the activity and selectivity of the catalytic system: the desired products were obtained when the reactions were conducted in dioxane, furan, and toluene, albeit in lower yield (Table 1, entries 6−8). The use of DMSO and DMF gave 27% and 81% oxidation product **8**, respectively, and none of the desired product (Table 1, entries 9 and 10). A satisfactory result (i.e., 87% yield of desired product **7a**) occurred when CH_2Cl_2 was used (Table 1, entry 5). Then the amount of catalyst required was also investigated. We were unable to reduce the catalyst loading below 20 mol % (relative to the phenylacetylene) without adversely affecting the product yield

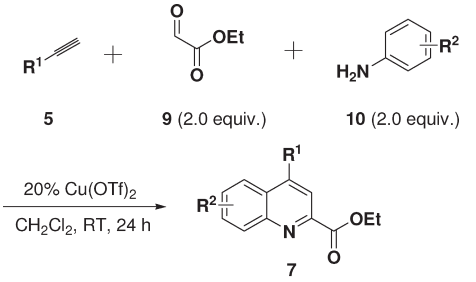
(Table 1, entries 5, 11, and 12). When 1.0 equiv of **6a** was performed, the reaction also works well but with a lower yield (Table 1, entry 13). Finally, shortening reaction time to 10 h led to a decrease in yield (Table 1, entry 14). No improvement was observed when the reaction time was further prolonged (Table 1, entry 15). Therefore, our optimal reaction conditions for the synthesis of quinoline-2-carboxylates is as follows: 20 mol % of $Cu(OTf)_2$ as the catalyst, CH_2Cl_2 as the solvent, and carrying out the reaction at room temperature for 16 h. For determining whether compound **8** was a possible intermediate, we performed the reaction of isolated **8** under the optimal reaction conditions, and observed no formation of product **7a**.

Having established suitable reaction conditions, we explored the scope and generality of the methodology starting with alkynes (Table 2). As shown in Table 2, most substrates examined under the standard reaction condition provided moderate to excellent yields at room temperature. Several functional groups, including halogens and electron-donating or electron-withdrawing substituents on the aryl ring of the alkynes, were tolerated well. Generally, the substituted aromatic alkynes containing electron-neutral (Table 2, entry 1) or electron-rich groups, for example, substrates with groups such as *tert*-butyl (Table 2, entry 2), methyl (Table 2, entries 3 and 4), and methoxy (Table 2, entry 5) proceeded well. Electron-withdrawing substituents, including fluoro (Table 2, entries 6 and 7) and chloro groups (Table 2, entry 8), were tolerated, although with slightly weaker reactivity, while 1-(4-ethynylphenyl)ethanone provided lower yields (Table 2, entry 9). Notably, the alkynyl group was also tolerated (Table 2, entry 10). A wide range of aromatic alkynes readily participated in the reaction with the aniline rings at ambient temperatures. However, the catalytic process was unsatisfactory with aliphatic substrates, and a higher temperature was necessary for achieving sufficient conversion. The corresponding product was obtained in moderate yields when temperature was raised to 50 °C (Table 2, entry 11). We also found that compounds substituted by electron-donating or electron-neutral substituents such as methoxy, benzyloxy, or methyl groups at the 4-position on the phenyl ring attached to the nitrogen proceeded well. In each case, we obtained satisfactory product yields from the catalytic reactions (Table 2, entries 12−18).

We were also pleased to observe that the present protocol could be readily used in a three-component reaction[12c,15] in one pot. As shown in Scheme 2, ethyl glyoxylate **9** and aniline **10** reacted with alkynes **5** in the presence of a $Cu(OTf)_2$ catalyst to afford quinoline-2-carboxylates **7** under mild conditions (room temperature, 24 h). It is important to note that good yields can be obtained for these reactions by using representative aromatic alkynes and anilines as starting materials (Scheme 2). Consistent with the results of previous studies, the electron-neutral or electron-rich aromatic alkynes were found to be more efficient.

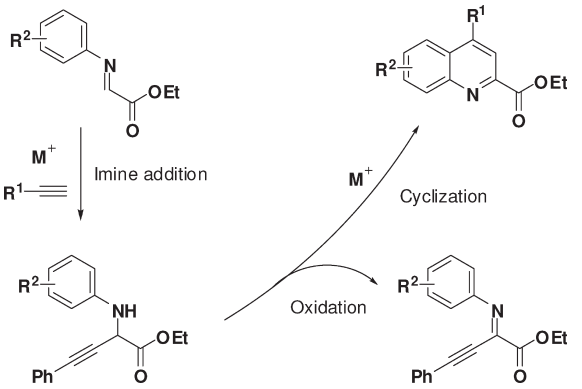
On considering the mechanism (Scheme 3), the first generally proposed step is the formation of propargylic amines. As proposed by Chan and co-workers,[11] propargylic amines were produced via an intermediate that was formed by successive complexation of substrates to the metal center. The propargylic amines were detected and identified in the

SCHEME 2. Copper-Catalyzed Three-Component Reactions



7a: $R^1 = C_6H_5$, R^2 = 4-OMe, yield = 76%
7b: R^1 = 4-*t*Bu-C_6H_4, R^2 = 4-OMe, yield = 83%
7e: R^1 = 4-MeO-C_6H_4, R^2 = 4-OMe, yield = 81%
7h: R^1 = 4-Cl-C_6H_4, R^2 = 4-OMe, yield = 71%
7l: $R^1 = C_6H_5$, R^2 = 4-Me, yield = 74%
7r: $R^1 = C_6H_5$, R^2 = 4-OBn, yield = 79%

SCHEME 3. Proposed Mechanism



reaction mixture by mass spectrum and TLC analysis. We then performed the reaction of isolated propargylic amines under the optimal reaction conditions, and obtained the desired quinoline-2-carboxylates. These results indicated that the propargylic amines were intermediates in the catalytic process. The subsequent cyclization step may then occur directly through a Friedel−Crafts-type addition leading to the desired products. Alternatively, the oxidation products would be obtained under the specific reaction conditions.

Conclusions

In summary, we have developed a simple and practical copper-catalyzed tandem Grignard-type imine addition/Friedel−Crafts alkenylation of arenes with alkynes for the efficient synthesis of quinoline-2-carboxylates via activation of C−H bonds. We obtained the target products in high yields from a variety of readily available alkynes and imines. This new method only requires one copper catalyst, which is both simpler and less costly than those methods with two metals for both steps, and tolerates a variety of useful functional groups. The system's efficiency allowed the reactions to be carried out at room temperature.

Experimental Section

General Procedure for the Synthesis of 7a (Table 2, entry 1). A mixture of *N*-PMP α-iminoethyl glyoxylate (377 mg) and phenylacetylene (100 μL) was dissolved in CH_2Cl_2 (2.0 mL).

(15) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598.

Subsequently, 0.2 equiv of $Cu(OTf)_2$ was added to this mixture. The reaction was then stirred at ambient temperature for 16 h. The crude reaction mixture was concentrated and purified by flash column chromatography (petroleum ether/ethyl acetate) to yield the expected product. The data obtained are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 9.3 Hz, 1H), 8.09 (s, 1H), 7.57−7.50 (m, 5H), 7.43 (dd, J = 9.3 Hz, J = 1.5 Hz, 1H), 7.21 (d, J = 1.5 Hz, 1H), 4.55 (q, J = 7.0 Hz, 2H), 3.80 (s, *3*H), 1.47 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 159.4, 147.9, 145.3, 144.2, 137.8, 132.6, 129.2, 129.1, 128.7, 128.6, 122.7, 121.7, 103.1, 62.0, 55.4, 14.3. MS (EI, m/z) 307 $[M]^+$; HRMS (EI) calcd for $C_{19}H_{17}NO_3$ $[M]^+$ 307.1208, found 307.1214.

General Procedure for the Synthesis of 7a through a Three-Component Reaction. A mixture of ethyl glyoxylate (372 μL, 50% solution in toluene), aniline (170 mg), and phenylacetylene (100 μL) was dissolved in CH_2Cl_2 (2.0 mL). Subsequently, 0.2 equiv of $Cu(OTf)_2$ was added to this mixture. The reaction was then stirred at ambient temperature for 24 h. The crude reaction mixture was concentrated and purified by flash column chromatography (petroleum ether/ethyl acetate) to yield the expected product. The data obtained are as mentioned above.

Acknowledgment. We gratefully acknowledge financial support from the National Natural Science Foundation of China (Grants 20721003 and 20872153), International Collaboration Projects (Grants 2007DFB30370 and 20720102040), and the 863 Hi-Tech Program of China (Grants 2006AA020602).

Supporting Information Available: Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.