ORGANIC LETTERS

2013
Vol. 15, No. 14
3710–3713

Efficient Preparation of 4-Hydroxyquinolin-2(1*H*)-one Derivatives with Silver-Catalyzed Carbon Dioxide Incorporation and Intramolecular Rearrangement

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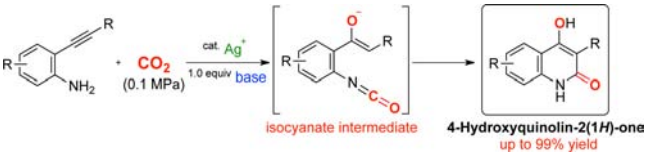
Received June 4, 2013

ABSTRACT



Although 4-hydroxyquinolin-2(1*H*)-one derivatives have attracted much attention due to their biological benefits, conventional reactions under harsh heat conditions must be employed to provide these key compounds. In the presence of a catalytic amount of silver salt, various *o*-alkynylanilines were treated with carbon dioxide and a base under mild reaction conditions to afford the corresponding 4-hydroxyquinolin-2(1*H*)-one derivatives in high yield.

Interest in 4-hydroxyquinolin-2(1*H*)-one derivatives has been growing due to their potential biological benefits. Studies on their medicinal properties have been promising, for example, in treatment of central nervous system disorders,[1] sex hormone-related conditions,[2] and suppression of allergy-associated inflammations,[3] and some of their derivatives have been reported as HIV-1 inhibitors.[4] Their preparations have been based on conventional heterocyclic chemistry including nucleophilic addition−elimination reactions under harsh heat conditions, such as the reaction of 4-halocarbostyril with potassium hydroxide,[5] or an aniline derivative and a carbonyl compound with high leaving-group ability.[6]

The rearrangement reaction is one of the most effective strategies for the preparation of heterocycles in industrial and academic laboratories. Various complex natural products and pharmaceutical agents have been synthesized by drastic transformation of the molecular framework induced by a rearrangement reaction.[7] Among these rearrangement

(1) (a) McQuaid, L. A.; Smith, E. C. R.; Lodge, D.; Pralong, E.; Wikel, J. H.; Calligaro, D. O.; O'Malley, P. J. *J. Med. Chem.* **1992**, *35*, 3423–3425. (b) Rowley, M.; Kulagowski, J. J.; Watt, A. P.; Rathbone, D.; Stevenson, G. I.; Carling, R. W.; Baker, R.; Marshall, G. R.; Kemp, J. A.; Foster, A. C.; Grimwood, S.; Hargreaves, R.; Hurley, C.; Saywell, K. L.; Tricklebank, M. D.; Leeson, P. D. *J. Med. Chem.* **1997**, *40*, 4053–4068.

(2) (a) DeVita, R. J.; Hollings, D. D.; Goulet, M. T.; Wyvratt, M. J.; Fisher, M. H.; Lo, J.-L.; Yang, Y.-T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2615–2620. (b) DeVita, R. J.; Goulet, M. T.; Wyvratt, M. J.; Fisher, M. H.; Lo, J.-L.; Yang, Y.-T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2621–2624.

(3) Sherlock, M. H.; Kaminski, J. J.; Tom, W. C.; Lee, J. F.; Wong, S.-C.; Kreutner, W.; Bryant, R. W.; McPhail, A. T. *J. Med. Chem.* **1988**, *31*, 2108–2121.

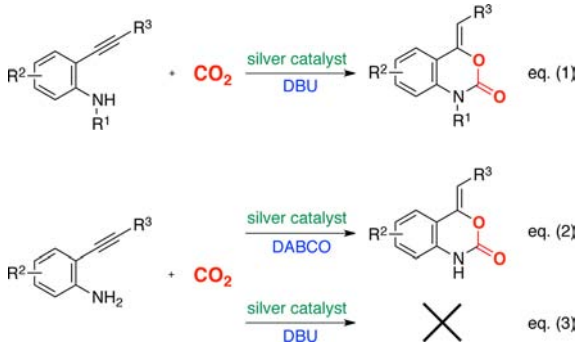
(4) McCormick, J. L.; McKee, T. C.; Cardellina, J. H., II; Boyd, M. R. *J. Nat. Prod.* **1996**, *59*, 469–471.

(5) Okamoto, T.; Kimura, E.; Iwasaki, S.; Yamamoto, K. *Chem. Pharm. Bull.* **1969**, *17*, 2083–2087.

(6) (a) Zeigler, E.; Wolf, R.; Kappe, J. *Monatsh. Chem.* **1965**, *96*, 418–422. (b) Yamaguchi, S.; Yoshimoto, Y.; Murai, R.; Masuda, F.; Yamada, M.; Kawase, Y. *J. Heterocycl. Chem.* **1984**, *21*, 737–739. (c) Mitsos, C. A.; Zografos, A. L.; Igglessi-Markopoulou, O. *J. Org. Chem.* **2003**, *68*, 4567–4569. (d) Leeson, P. D.; Baker, R.; Carling, R. W.; Kulagowski, J. J.; Mawer, I. M.; Ridgill, M. P.; Rowley, M.; Smith, J. D.; Stansfield, I.; Stevenson, G. I.; Foster, A. C.; Kemp, J. A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 299–304. (e) Jung, J.-C.; Jung, Y.-J; Park, O.-S. *Synth. Commun.* **2001**, *31*, 1195–1200. (f) Dittmer, D. C.; Li, Q.; Avilov, D. V. *J. Org. Chem.* **2005**, *70*, 4682–4686. (g) Arya, K.; Agarwal, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 86–93. (h) Zhang, S.-L.; Huang, Z.-S.; Li, Y.-M.; Chan, A. S. C.; Gu, L.-Q. *Tetrahedron* **2008**, *64*, 4403–4407. (i) Im, I.; Lee, E. S.; Choi, S. J.; Lee, J.-Y.; Kim, Y.-C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3632–3636.

10.1021/ol401571r
Published on Web 07/02/2013

reactions, isocyanates have been employed as effective intermediates because of their high reactivity,[8] e.g., in Schmidt rearrangement,[9] Hofmann rearrangement,[10] Curtius rearrangement,[11] Lossen rearrangement,[12] and Bucherer–Bergs reaction.[13]



We recently reported the silver-catalyzed preparation of benzoxazin-2-one derivatives from *o*-alkynylaniline derivatives and carbon dioxide.[14] It was considered that the amino group and carbon dioxide would form the corresponding carbamate followed by 6-*exo*-*dig* cyclization on the alkyne activated by a silver catalyst. Upon optimization, it was found that DBU was the most effective base for the reaction of secondary *o*-alkynylanilines to afford the corresponding benzoxazin-2-one derivatives in high yield (eq 1). However, for primary *o*-alkynylanilines, DABCO was the most suitable base (eq 2). When DBU was employed for the reaction of primary *o*-alkynylanilines, the corresponding products were not obtained at all (eq 3); nevertheless, the starting material was completely consumed. After carefully investigating the reaction mixture, 4-hydroxyquinolin-2-one was surprisingly generated as the sole product. Single-crystal X-ray diffraction analysis revealed the structure of this product (Figure 1).[15] A few quinoline syntheses from *o*-alkynylaniline derivatives have been reported, for example, using Masamune–Bergman type cyclization of enyne-isocyanates synthesized from *o*-alkynylanilines,[16] carbocyclization of *N*-(*o*-alkynyl)-malonamides with base[17a] or an electrochemical method,[17b] and Michael Addition of NH group of carbamate to conjugated enones from alkyne-carbonyl metathesis of *o*-alkynylanilines and aldehydes.[18] These reactions are considered to be conceptually different from the present reaction with carbon dioxide incorporation and rearrangement. Herein, we would like to report an efficient preparation of 4-hydroxyquinolin-2(1*H*)-one derivatives from *o*-alkynylanilines and carbon dioxide.

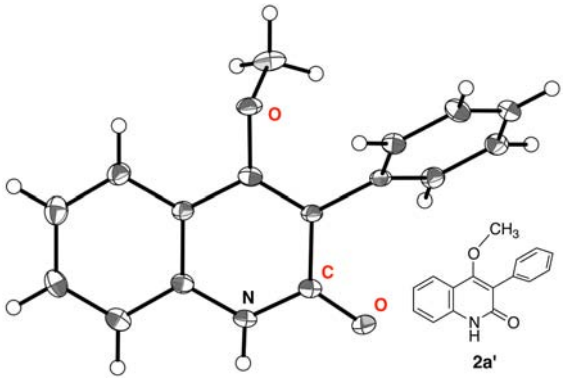


Figure 1. Single-crystal X-ray diffraction analysis for **2a′**. Thermal ellipsoids are shown at the 50% probability level. The single crystal was obtained after methylation of **2a** with trimethylsilyldiazomethane.

Scheme 1 shows the hypothetical reaction mechanism to explain these observations. First, the corresponding benzoxazin-2-one would form from the *o*-alkynylaniline and carbon dioxide catalyzed by the silver catalyst. In the second step, the benzoxazine would immediately be deprotonated with DBU base to generate the isocyanate and the enolate from C–O bond cleavage of the carbamate functionality. The enolate would then attack the carbon atom of the isocyanate to afford the 1,3-diketone intermediate, which would produce the corresponding 4-hydroxyquinolin-2(1*H*)-one after enolization. Thus, in this proposed mechanism, a new C–C bond is formed with carbon dioxide. It is expected that the corresponding quinoline derivative should contain carbon dioxide.

On the basis of our previous report, if a benzoxazin-2-one is formed as an intermediate, a silver-catalyzed process should be required. Various metal salts expected to activate

(7) (a) Aucejo, A.; Burguet, M. C.; Corma, A.; Fornes, V. *Appl. Catal.* **1986**, *22*, 187–200. (b) Curtin, T.; McMonagle, J. B.; Hodnett, B. K. *Appl. Catal., A* **1992**, *93*, 75–89. (c) Kob, N.; Drago, R. S. *Catal. Lett.* **1997**, *49*, 229–234. (d) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597–1598. (e) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103–1106.

(8) Delebecq, E.; Pascault, J.-P.; Boutevin, B.; Ganachaud, F. *Chem. Rev.* **2013**, *113*, 80–118.

(9) (a) Schmidt, K. F. *Z. Angew. Chem.* **1923**, *36*, 511. (b) Schultz, A. G.; Wang, A.; Alva, C.; Sebastian, A.; Glick, S. D.; Deecher, D. C.; Bidlack, J. M. *J. Med. Chem.* **1996**, *39*, 1956–1966.

(10) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2725–2736. (b) Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009–3012.

(11) (a) Buchner, E.; Curtius, T. *Chem. Ber.* **1885**, *18*, 2371–2377. (b) Carda, M.; Gonzalez, F.; Sanchez, R.; Marco, J. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1005–1010.

(12) (a) Lossen, W. *Liebigs Ann. Chem.* **1869**, *150*, 313–325. (b) Ohmoto, K.; Yamamoto, T.; Horiuchi, T.; Kojima, T.; Hachiya, K.; Hashimoto, S.; Kawamura, M.; Nakai, H.; Toda, M. *Synlett* **2001**, 299–301.

(13) (a) Bucherer, H. T.; Fischbeck, H. T. *J. Prakt. Chem.* **1934**, *140*, 69. (b) Sarges, R.; Goldstein, S. W.; Welch, W. M.; Swindell, A. C.; Siegel, W. S.; Beyer, T. A. *J. Med. Chem.* **1990**, *33*, 1859–1865.

(14) Ishida, T.; Kikuchi, S.; Tsubo, T.; Yamada, T. *Org. Lett.* **2013**, *15*, 848–851.

(15) Crystallographic data reported in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-904718. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U.K.; Fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

(16) Li, H.; Yang, H.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2004**, *69*, 4500–4508.

(17) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett* **1998**, 446–448. (b) Arcadi, A.; Inesi, A.; Marinelli, F.; Rossi, L.; Verdecchia, M. *Eur. J. Org. Chem.* **2007**, 2430–2437.

(18) Saito, A.; Kasai, J.; Odaira, Y.; Fukaya, H.; Hanzawa, Y. *J. Org. Chem.* **2009**, *74*, 5644–5647.

Scheme 1. Hypothetical Reaction Mechanism

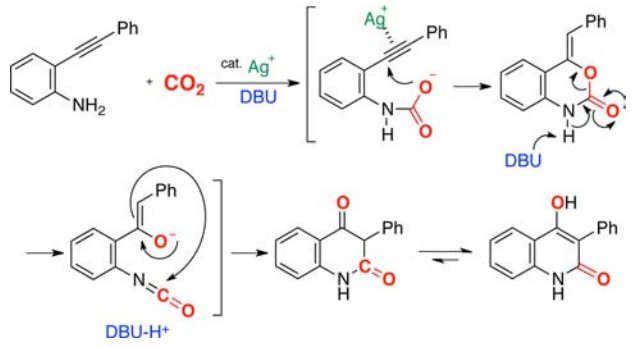
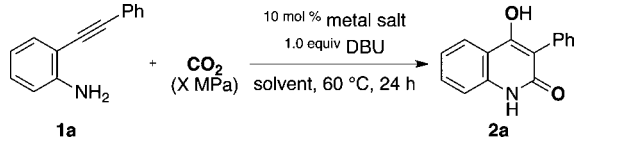


Table 1. Examination of Metal Salts and Condition Optimization



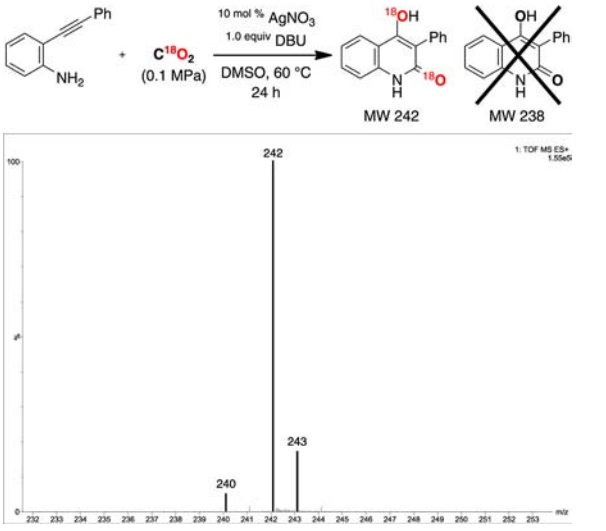
entry	metal salt	solvent	X/MPa	yield[a] (%)
1	none	DMSO	1.0	0
2	CuI	DMSO	1.0	0
3	$RhCl_3 \cdot 3H_2O$	DMSO	1.0	0
4	$PdCl_2$	DMSO	1.0	0
5	$PtCl_2$	DMSO	1.0	0
6	AuCl	DMSO	1.0	0
7	$AgNO_3$	DMSO	1.0	94
8	$AgNO_3$	tolune	1.0	82
9	$AgNO_3$	EtOH	1.0	9
10	$AgNO_3$	DCE	1.0	3
11	$AgNO_3$	THF	1.0	70
12	$AgNO_3$	MeCN	1.0	93
13[b]	$AgNO_3$	MeCN	0.1	93
14	**$AgNO_3$**	**DMSO**	**0.1**	**97**
15	$AgBF_4$	DMSO	0.1	91
16	$AgOC(O)CF_3$	DMSO	0.1	95
17	AgOAc	DMSO	0.1	92

[a] Isolated yield. [b] The reaction was carried out for 48 h.

the C−C triple bond were examined (Table 1). In the absence of any metal salts, the corresponding hydroxyquinoline was not obtained (entry 1). Although copper(I), rhodium(III), palladium(II), platinum(II), and gold(I) salts were expected to activate the C−C triple bond, the corresponding products were not afforded at all (entries 2−6). Silver(I) nitrate effectively promoted the reaction in DMSO or MeCN (entries 7 and 12). The hydroxyquinoline was generated in good yield in toluene or THF; however, the reaction proceeded inadequately in EtOH or DCE (entries 8−11). Under atmospheric pressure of carbon dioxide, the product was afforded in MeCN or DMSO; however, a longer reaction time was required in MeCN compared to DMSO (entries 13 and 14). It was found that other silver salts also promoted the reaction to produce the corresponding 4-hydroxyquinolin-2(1*H*)-one derivative in high yield (entries 15−17). These results would suggest that a silver salt effectively activates the C−C triple bond to generate a benzoxazin-2-one from the *o*-alkynylaniline and carbon dioxide in the earlier stage of the reaction.

Isotopic labeling experiments with $C^{18}O_2$ were conducted to reveal whether the quinoline contained carbon dioxide (Scheme 2). As a result, the ^{18}O-labeled quinoline (MW 242) was detected by mass spectral analysis, and the nonlabeled quinoline (MW 238) was not detected at all, which strongly suggested that the quinoline was derived from the *o*-alkynylaniline and carbon dioxide. In addition, in situ IR measurement of the reaction of the benzoxazin-2-one and DBU was carried out. After DBU was added to the THF solution of the benzoxazine, absorption at 2150 cm^{-1} assigned as isocyanate group was observed.[19] This result would also support the proposed reaction mechanism.

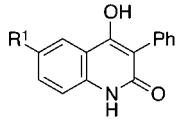
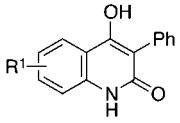
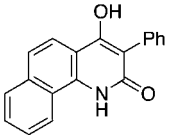
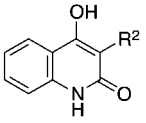
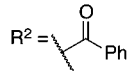
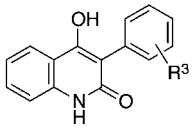
Scheme 2. Isotopic Labeling Experiments with $C^{18}O_2$



Under the optimized reaction conditions, various *o*-alkynylaniline derivatives were applied to the C−C bond-forming carbon dioxide incorporation reaction (Table 2). In the presence of 10 mol % of $AgNO_3$ and 1.0 equiv of DBU under atmospheric pressure of carbon dioxide in DMSO, aniline derivative **1a** was transformed into 4-hydroxyquinoilne-2-one derivative **2a** in excellent yield (entry 1). Anilines with substituents (**R**[1]) at the *para*-position relative to the amino group were next subjected to the reaction. When *o*-alkynylaniline **1b** substituted with an electron-donating group on the phenyl group was employed, the corresponding product **2b** was obtained in high yield (entry 2). The 4-hydroxyquinoline derivatives with electron-withdrawing groups at the 6-position, **2c**, **2d**, and **2e,** derived from **1c**, **1d**, and **1e,** respectively, were also generated in high to excellent yields (entries 3−5). The *meta*- and *ortho*-substituted substrates **1f** and **1g** were converted into the corresponding products **2f** and **2g** in high yields

(19) The details about the experiment were described in the Supporting Information.

Table 2. CO_2 Incorporation with C−C Bond Formation through Intramolecular Rearrangement with Various *o*-Alkynylaniline Derivatives

entry	product		yield[a] (%)
1		R^1 = H (**2a**)	97
2		R^1 = CH_3 (**2b**)	82
3		R^1 = F (**2c**)	98
4		R^1 = Cl (**2d**)	99
5		R^1 = CF_3 (**2e**)	90
6		R^1 = 7-CH_3 (**2f**)	84
7		R^1 = 8-CH_3 (**2g**)	85
8		(**2h**)	99
9		R^2 = H (**2i**)	75
10		R^2 = *n*-Bu (**2j**)	69
11		R^2 = 2-Py (**2k**)	96
12		R^2 = 1-Np (**2l**)	98
13		(**2m**)	91
14		R^3 = *p*-OMe (**2n**)	98
15		R^3 = *p*-NO_2 (**2o**)	97
16		R^3 = *m*-CF_3 (**2p**)	92

[a] Isolated yield.

despite the steric hindrance of the substituents (entries 6−7). The highly conjugated aniline derivative **1h** was also an excellent substrate for this reaction, and the corresponding three-ring fused compound **2h** was produced quantitatively (entry 8).

Substituents $\mathbf{R^2}$ on the alkynyl terminal were examined next. The substrate with terminal alkyne **1i** was transformed into quinoline derivative **2i** containing the trisubstituted olefin in 75% yield (entry 9). An alkyl group on alkyne **1j** was subjected to the conditions to afford the corresponding 3-alkyl-4-hydroxyquinoline **2j** in 69% yield (entry 10). Substrates with a 2-pyridyl group **1k** and a 1-naphthyl group **1l** successfully afforded the corresponding products **2k** and **2l**, respectively, in excellent yields (entries 11 and 12). The product having an enone structure **2m** derived from the corresponding ynone-substituted aniline **1m** was formed in satisfactory yield.

Substituent $\mathbf{R^3}$ effects were examined on the phenyl ring attached to the alkyne terminus. An electron-donating group at the *para*-position **1n** afforded the corresponding product **2n** quantitatively. Substrates with electron-withdrawing groups, e.g., nitro **1o** or trifluoromethyl **1p**, were subjected to the reaction conditions to produce the quinoline derivatives **2o** and **2p**, respectively.

In conclusion, we developed a conceptually new synthetic method of 4-hydroxyquinolin-2-one derivatives, which have been reported as biologically active compounds for treatment of several diseases, from *o*-alkynylanilines, DBU, silver catalyst, and atmospheric pressure of carbon dioxide under mild reaction conditions. The key step in the reaction mechanism is proposed as the generation of the isocyanate and the enolate through C−O bond cleavage and new C−C bond formation induced by deprotonation of the amide after formation of the benzoxazin-2-one. The obtained quinoline derivatives were composed of the starting *o*-alkynylaniline and carbon dioxide as revealed by isotopic labeling experiments. Various substrates could be subjected to the optimized reaction conditions and smoothly transformed into the corresponding quinoline derivatives in high yields. Further applications are currently being investigated in our laboratory.

Note Added after ASAP Publication. Scheme 2 contained an error in the version published ASAP on July 2, 2013; the correct version reposted on July 9, 2013.

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

The authors declare no competing financial interest.