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Silver-Catalyzed Incorporation of Carbon Dioxide into *o*-Alkynylaniline Derivatives

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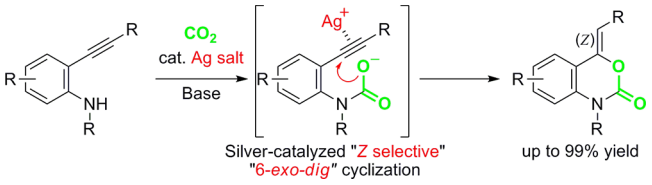
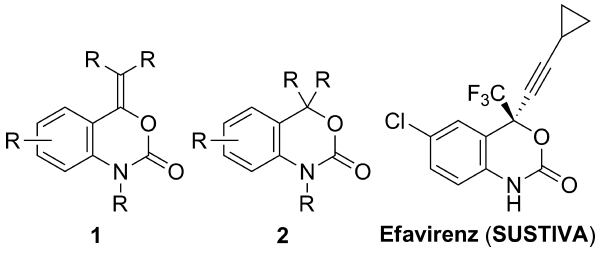
ABSTRACT



Benzoxazine-2-one derivatives are important heterocycle structures because of their various pharmaceutical activities, though their synthetic methods had been limited. In some cases, toxic reagents, such as phosgene or carbon monoxide, are required. It was found that a silver catalyst successfully promoted the incorporation of CO_2 into *o*-alkynylanilines to afford the corresponding benzoxazine-2-ones bearing *Z exo*-olefin via 6-*exo-dig* cyclization at the activated C−C triple bond.

Benzoxazine-2-one derivatives have attracted much attention as some of the most important heterocycle structures in pharmaceutical science; for example, one derivative bearing an *exo*-olefin, 4-ylidene-1,4-dihydro-2*H*-3,1-benzoxazine-2-one **1**, were reported active as osteoclast differential induction inhibitors or anti-inflammatory agents, as well as osteoclasis inhibitors and antirheumatic agents.[1] The analogues of **1**, 4-alkylsubstituted 1,4-dihydro-2*H*-3,1-benzoxazine-2-one derivatives **2**, also indicated biological behaviors with a modest progesterone receptor (PR) agonist activity, which have been applied used for contraceptives and hormone therapy, often in combination with estrogen.[2−5] Efavirenz (SUSTIVA), composed of the benzoxazine-2-one system, is the first anti-HIV drug approved by the FDA in the United States.[6] In spite of the importance of the benzoxazine-2-one components, their methods in organic synthesis have been limited. Several preparative reactions employing phosgene,[1,6−9] carbon monoxide,[10,11] carbonyldiimidazole,[5] or a hypervalent iodine compound[12] were reported for the synthesis of the 4-alkyl-substituted benzoxazine-2-one derivatives. The synthetic reaction for benzoxazine-2-ones containing *exo*-olefin **1** has been only rarely reported in which their scope was limited and toxic phosgene must be employed.[1,8] Carbon dioxide is regarded as safe, easy handled, and reasonable C1 resource especially for constructing carbonyl functionalities as an alternative to the use of toxic chemical reagents.



We recently reported that carbon dioxide could be employed in the presence of a silver salt[13] to efficiently afford the cyclic carbonates, oxazolidinones, and lactones

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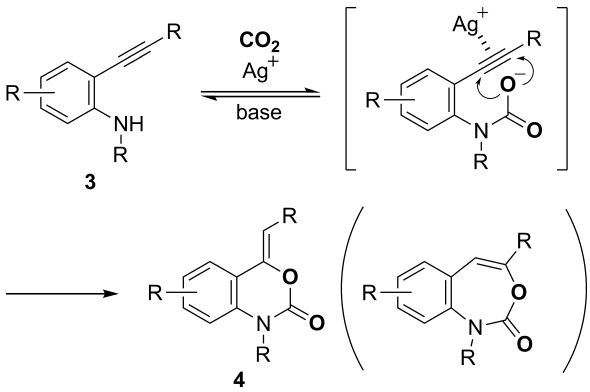
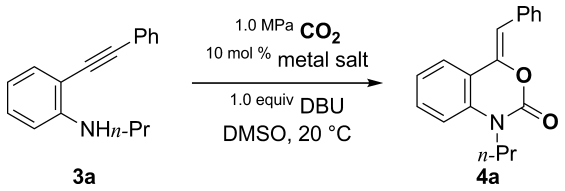
Scheme 1. Postulation Reaction Mechanism of *o*-Alkynylaniline and CO_2



with a *Z exo*-olefin from the corresponding alkyne derivatives. In these reactions, the silver catalyst effectively activates the C−C triple bond[14] to afford the 5-*exo-dig* cyclized products in high yield. A DFT calculation study[15] supported these mechanisms. Therefore, when *o*-alkynylaniline derivatives **3** are used as the starting substrates for the silver-catalyzed carbon dioxide incorporation reaction, the desired benzoxazine-2-one derivatives bearing the *Z exo*-olefin **4** would be obtained via the 6-*exo-dig* cyclization on the activated C−C triple bond (Scheme 1). We now report a new synthetic method to produce benzoxazine-2-one derivatives possessing the *Z exo*-olefin in the presence of a silver catalyst from *o*-alkynylanilines and carbon dioxide.

Based on previous research, we thought that the activation of C−C triple bond would be the key step for this reaction and several metal salts were initially examined on the reaction of *o*-alkynylaniline derivative **3a** (Table 1). The reaction did not proceed in the absence of metal salts (entry 1). When palladium(II),[16a−c] rhodium(II),[16d] platinum(II),[16e,f] and copper(I) salt,[16g,h] which would be expected to activate the C−C triple bond effectively, were investigated, no product formed and the starting material was recovered (entries 2−5). Although gold(I)[16i,j] and gold(III)[16k] salts did not work for this reaction (entries 6 and 7), the cationic gold(I) salt (AuCl with $AgNO_3$) could catalyze this reaction to afford the corresponding benzoxazine-2-one derivative in 30% yield (entry 8). The silver salts were also examined on this reaction, and consequently, it was found that they were the most effective catalysts for this reaction to produce the corresponding products in excellent yields (entries 9 and 10). Other silver salts were examined, and it was found that most of them could catalyze this reaction (Table S1, Supporting Information), so that $AgNO_3$ was chosen as a standard catalyst. The benzoxazepin-2-one derivative which might be generated via the 7-*endo-dig* cyclization was not detected at all.

Table 1. Examination of Various Metal Salts



entry	metal salt	yield[a] (%)
1	none	0
2	$Pd(OAc)_2$	0
3	$RhCl_2(PPh_3)_3$	0
4	$PtCl_2$	0
5	CuBr	0
6	AuCl	0
7[b]	$AuCl_3$	0
8	AuCl/$AgNO_3$	30
9	$AgNO_3$	97
10	AgOAc	97

[a] Isolated yield. [b] The reaction was carried out at 80 °C.

In the presence of $AgNO_3$ (10 mol %) and DBU (1.0 equiv) in DMSO under pressurized (1.0 MPa) carbon dioxide,[17] the CO_2 incorporation reaction of the *o*-alkynylaniline **3a** was carried out. The corresponding benzoxazine-2-one **4a** was obtained in excellent yield (Table 2, entry 1). Various *o*-alkynylaniline derivatives were then subjected to the present reaction conditions. The *N*-alkyl *o*-alkynylaniline derivatives could also be transformed into the corresponding products in excellent yields (entries 2−4). The *o*-alkynylanilines with *p*-substitution **3e**, **3f**, and **3g** were easily converted into the corresponding 6-substituted

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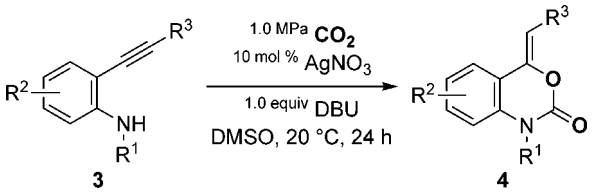
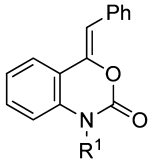
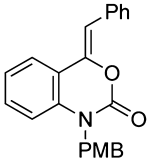
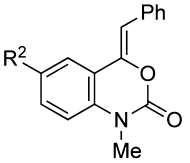
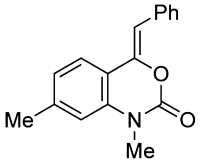
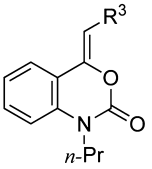
(17) Other reaction conditions were also investigated. The results are summarized in the Supporting Information.

Table 2. $AgNO_3$ Catalyzed the Reaction of Several *o*-Alkynylaniline Derivatives with CO_2



entry	product		t (°C)	yield[a] (%)
1		R^1 = *n*-Pr (**4a**)	20	97
2		R^1 = Me (**4b**)	20	97
3[b]		R^1 = *i*-Bu (**4c**)	40	96
4[c]		(**4d**)	20	96
5		R^2 = Me (**4e**)	20	87
6		R^2 = F (**4f**)	20	90
7		R^2 = CF_3 (**4g**)	40	87
8		(**4h**)	20	85
9[d]		R^3 = H (**4i**)	60	80
10[d]		R^3 = *n*-Bu (**4j**)	40	86
11		R^3 = 2-Py (**4k**)	20	99

[a] Isolated yield. [b] The reaction was carried out for 35 h. [c] PMB = *p*-methoxybenzyl. [d] The reaction was carried out for 49 h.

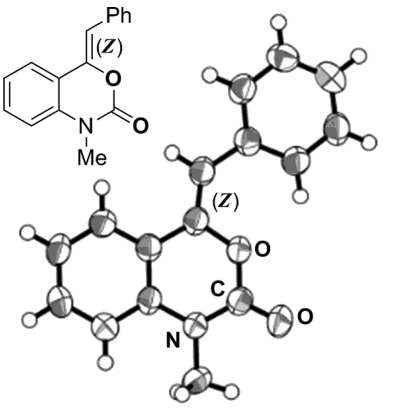
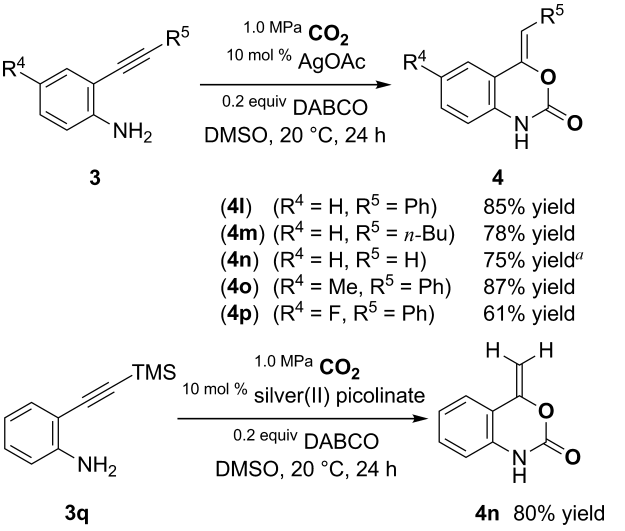


Figure 1. Single-crystal X-ray diffraction analysis for **4b**. Thermal elipsoids are shown at 50% probability.

Scheme 2. Silver-Catalyzed Reactions of Several Primary *o*-Alkynylaniline Derivatives with CO_2



[a] Silver(II) picolinate was used instead of AgOAc.

products **4e**, **4f**, and **4g** in high yields, respectively (entries 5−7). The *m*-substituted *o*-alknylaniline derivative **3h** was also a good substrate for this reaction, and the corresponding 7-substituted product **4h** was obtained in 85% yield (entry 8). The reactions of the substrates bearing the terminal alkyne **3i** and internal alkyne **3j** were smoothly performed to produce the corresponding products (**4i** and **4j**) in high yields (entries 9 and 10). The substrate having the 2-pyridyl group on the alkynyl terminal was also subjected to this catalytic system to afford the corresponding product **4k** in excellent yield (entry 11). The geometry of the *exo*-olefin in the product **4b** was confirmed by an X-ray diffraction analysis (Figure 1). This result revealed the product was benzoxazine-2-one containing *Z exo*-olefin as the sole compound.[18] All other products were suggested to be the *Z*-isomer based on NOE experiments. Taking into account our previous studies, this result would suggest that the silver catalyst could effectively activate the C−C triple bond during this reaction.

The present catalytic system was successfully applied to various primary *o*-alkynylaniline derivatives with carbon dioxide (Scheme 2). The reactions of the *o*-alkynylanilines with a free amino group possessing the phenyl-substituted alkyne **3l** and alkyl-substituted alkyne **3m** were catalyzed

(18) Crystallographic data reported in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-983361. 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, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

by AgOAc in the presence of DABCO as a base to generate the benzoxazine derivatives (**4l** and **4m**) in high yields, respectively. The substrate bearing the terminal alkyne **3n** was also converted into the corresponding benzoxazine derivative **4n**, but in insufficient yield. The yield of **4n** was improved to 75% when catalyzed by silver(II) picolinate instead of AgOAc. When the *o*-alkynylaniline derivatives with *p*-methyl and *p*-fluoro groups (**3o** and **3p**) were subjected to this catalytic system, the corresponding products (**4o** and **4p**) were obtained in 75% and 61% yields, respectively. When the reaction of the aniline **3q** substituted with trimethylsilylacetylenyl was carried out, the corresponding benzoxazine-2-one **4n** was obtained in 80% yield, though TMS group was removed.

In conclusion, it was revealed that the silver catalyst with bases could allow the reaction of carbon dioxide with the *o*-alkynylaniline derivatives to produce a series of benzoxazine-2-one derivatives containing the *Z exo*-olefin in high yields under mild reaction conditions, which were reported to show various biological activities. Primary as well as secondary anilines could be used with this catalytic system to afford the corresponding products in good yields. The structure of the product was verified by an X-ray diffraction analysis and NOE experiment to determine the product possesses the *Z exo*-olefin. Further applications for this silver catalytic system are being investigated.

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

The authors declare no competing financial interest.