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Article

Silver-catalyzed carboxylative cyclization of alkynic hydrazones with carbon dioxide

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ABSTRACT

The development of new catalytic methodologies to synthesize heterocyclic fine chemicals using carbon dioxide as a synthon has attracted considerable attention. Herein, we report the silver(I)-catalyzed carboxylative cyclization of a variety of alkynic hydrazones with carbon dioxide to produce the corresponding 1,3,4-oxadiazin-2-ones under mild reaction conditions. In this reaction, silver(I) salts play a π -Lewis acid role for the highly efficient activation of the alkyne moiety in the hydrazone substrates. Single-crystal X-ray analysis and NOE experiments confirm that the newly formed oxadiazinone products exhibit Z configuration. Based on control experiments and NMR studies, a mechanism including the formation of a reactive carbazate intermediate, electrophilic cyclization, and subsequent protonation is proposed. This study offers an efficient and atom-economical method for the synthesis of biologically important 1,3,4-oxadiazin-2-ones.

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1. Introduction

The catalytic transformation of carbon dioxide (CO_2) into valuable chemicals has attracted much attention as CO_2 is an abundant, inexpensive, and renewable C1 feedstock [1–7]. Compared to the industrial large-scale transformation of CO_2 into bulk chemicals, such as urea, salicylic acid, carbonate, and methanol, the preparation of fine chemicals using CO_2 as a synthetic unit remains scarce [8]. Therefore, the development of more efficient reactions to catalytically convert CO_2 into various valuable compounds is of high relevance [9,10]. Among these strategies, cyclization reactions represent the most commonly used and powerful approach as heterocycles offer tremendous diversity and are widely present in biologically important molecules [11,12]. Since CO_2 usually serves as an electrophile, it can be incorporated into heterocyclic com-

pounds via the reaction with nitrogen [13–15], oxygen [16–20], or carbon nucleophiles [21–26].

1,3,4-Oxadiazin-2-ones are important structural subunits found in many pharmacologically potent and biologically active compounds. Those compounds can be used as selective Ca^{2+} sensitizers, anticonvulsants, anxiolytic, antiulcer agents [27,28], and useful 1,2-diaza-1,3-butadiene precursors for the construction of other fine chemicals [29]. Typically, 1,3,4-oxadiazin-2-ones are prepared by the reaction of cyclic carbonate with hydrazine or by using carbazates through laborious multistep procedures [30,31]. Therefore, the development of more efficient and atom-economical approaches using CO_2 as the carboxylative reagent is highly desirable. As a continuation of our interest in catalytic transformations of CO_2 into fine chemicals [32–34], herein we report a silver-catalyzed carboxylative cyclization of alkynic hydrazones with CO_2 to give

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1,3,4-oxadiazin-2-ones in good yield under mild reaction conditions.

2. Experimental

2.1. General information

Unless otherwise stated, all manipulations were performed using standard Schlenk techniques under dry nitrogen or CO₂ atmosphere. DMF and DMSO were distilled under N₂ atmosphere with CaH₂. CH₃CN was distilled with P₂O₅. THF was distilled from sodium/benzophenone. All solvents were stored over 4 Å molecular sieves before use. Column chromatography was performed on silica gel (200–300 mesh). Thin layer chromatography was performed on 0.20 mm GF254 plates, which were visualized under UV light (254 nm). Unless otherwise stated, CO₂ (99.999%), commercial silver, copper, and palladium salts, and various bases were used without further purification.

NMR spectra were recorded on a 400M or 500M (¹H NMR, 400 or 500 MHz; ¹³C NMR, 101 or 126 MHz) spectrometer in CDCl₃ at ambient temperature, and the chemical shifts are expressed in parts per million (δ, ppm). The proton chemical shifts have been referenced to 7.26 ppm (CHCl₃) or 2.50 ppm (DMSO) and carbon chemical shifts to 77.0 ppm (CHCl₃) or 39.5 ppm (DMSO). The data is reported using the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; hept, heptet; and *J*, coupling constant in Hz. High resolution mass spectra (HRMS) were recorded on a Q-TOF mass spectrometer equipped with a Z-spray ionization source. Infrared (IR) spectra were measured using a Nicolet NEXUS FT-IR spectrophotometer.

Substrates **1** and **4** were prepared according to reported procedures [35].

2.2. General procedure for the carboxylative cyclization of alkynic hydrazones with CO₂

A 20 mL oven-dried autoclave containing a stir bar was charged with hydrazone (0.30 mmol), Cs₂CO₃ (4.9 mg, 5 mol%), AgOAc (2.5 mg, 5 mol%), and 3.0 mL DMSO in a glove box. After removal from the glove box, the autoclave was purged with CO₂ three times and then pressurized at 2.0 MPa CO₂. The reaction mixture was stirred at 25 °C for 2 h, after which the remaining gas was vented slowly in the hood. The reaction mixture was diluted with 10 mL water and extracted with diethyl ether (3 × 10 mL). The combined organic phase was washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using petroleum/ethyl acetate as the eluent to afford the following oxadiazinone products.

(*Z*)-6-Benzylidene-3-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2a**). White solid (0.30 mmol scale, 59 mg, 85% yield). *R*_f = 0.4 (EtOAc/petroleum ether = 2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.68 (d, *J* = 7.3 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.32–7.30 (m, 1H), 7.23 (s, 1H), 5.76 (s, 1H), 3.97–3.92 (m, 4H), 2.59 (s, 1H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 144.52,

141.09, 138.07, 132.29, 129.68, 128.73, 128.64, 113.05, 60.39, 53.01 ppm. HRMS (ESI, *m/z*) calculated for C₁₂H₁₃N₂O₃ [M+H]⁺: 233.0926, found: 233.0924. IR (neat): ν 3443, 2925, 1732, 1275 cm⁻¹.

(*Z*)-6-Benzylidene-3-(2-cyanoethyl)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2b**). White solid (0.30 mmol scale, 56 mg, 77% yield). *R*_f = 0.3 (EtOAc/petroleum ether = 1:1). ¹H NMR (400 MHz, CDCl₃): δ 7.68 (d, *J* = 7.6 Hz, 2H), 7.43–7.28 (m, 4H), 5.82 (s, 1H), 4.06 (t, *J* = 6.8 Hz, 2H), 2.79 (t, *J* = 6.8 Hz, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 143.62, 140.74, 138.57, 132.03, 129.78, 128.98, 128.67, 116.89, 114.00, 46.59, 16.38 ppm. HRMS (ESI, *m/z*) calculated for C₁₃H₁₂N₃ [M+H]⁺: 242.0930, found: 242.0929. IR (neat): ν 2924, 2250, 1738, 1630 cm⁻¹.

(*Z*)-6-Benzylidene-3-isopropyl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2c**). White solid (0.30 mmol scale, 48 mg, 69% yield). *R*_f = 0.5 (EtOAc/petroleum ether = 1:5). ¹H NMR (400 MHz, CDCl₃): δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.32–7.24 (m, 2H), 5.73 (s, 1H), 4.70 (p, *J* = 6.7 Hz, 1H), 1.30 (d, *J* = 6.7 Hz, 6H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 143.57, 141.21, 137.59, 132.67, 129.57, 128.64, 128.45, 111.85, 50.46, 19.96 ppm. HRMS (ESI, *m/z*) calculated for C₁₃H₁₄N₂NaO₂ [M+Na]⁺: 253.0953, found: 253.0953. IR (neat): ν 3443, 2921, 1732 cm⁻¹.

(*Z*)-3-Benzyl-6-benzylidene-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2d**). White solid (0.30 mmol scale, 75 mg, 90% yield). *R*_f = 0.4 (EtOAc/petroleum ether = 1:5). ¹H NMR (400 MHz, CDCl₃): δ 7.70 (d, *J* = 7.5 Hz, 2H), 7.45–7.31 (m, 8H), 7.23 (s, 1H), 5.76 (s, 1H), 4.94 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 144.03, 141.39, 138.09, 135.97, 132.43, 129.70, 128.70, 128.64, 128.55, 128.53, 128.08, 112.85, 54.55 ppm. HRMS (ESI, *m/z*) calculated for C₁₇H₁₅N₂O₂ [M+H]⁺: 279.1134, found: 279.1130. IR (neat): ν 3424, 2914, 1732 cm⁻¹.

(*Z*)-6-(4-Fluorobenzylidene)-3-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2e**). White solid (0.30 mmol scale, 52 mg, 69% yield). *R*_f = 0.3 (EtOAc/petroleum ether = 2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.67–7.63 (m, 2H), 7.21 (s, 1H), 7.03 (t, *J* = 8.7 Hz, 2H), 5.71 (s, 1H), 3.95–3.90 (m, 4H), 2.63 (s, 1H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 162.54 (d, *J* = 251.49 Hz), 144.43, 140.77, 137.93, 131.54 (d, *J* = 8.1 Hz), 128.57 (d, *J* = 4.1 Hz), 115.75 (d, *J* = 22.2 Hz), 111.77, 60.29, 53.02 ppm. HRMS (ESI, *m/z*) calculated for C₁₂H₁₁FN₂NaO₃ [M+Na]⁺: 273.0651, found: 273.0652. IR (neat): ν 3430, 2921, 1720 cm⁻¹.

(*Z*)-6-(4-Chlorobenzylidene)-3-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2f**). White solid (0.30 mmol scale, 61 mg, 76% yield). *R*_f = 0.3 (EtOAc/petroleum ether = 2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.23 (s, *J* = 10.0 Hz, 1H), 5.72 (s, 1H), 3.96–3.94 (m, 4H), 2.37 (s, 1H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 144.31, 141.47, 137.79, 134.60, 130.88, 130.85, 128.96, 111.76, 60.61, 53.16 ppm. HRMS (ESI, *m/z*) calculated for C₁₂H₁₂ClN₂O₃ [M+H]⁺: 267.0536, found: 267.0533. IR (neat): ν 3358, 2923, 1656 cm⁻¹.

(*Z*)-3-(2-Hydroxyethyl)-6-(4-methylbenzylidene)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2g**). White solid (0.30 mmol scale, 52 mg, 71% yield). *R*_f = 0.4 (EtOAc/petroleum ether = 2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.21 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.74 (s, 1H), 3.96–3.93 (m, 4H), 2.53 (s, 1H), 2.35 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 144.71,

140.60, 139.06, 138.26, 129.69, 129.53, 129.41, 113.25, 60.51, 52.99, 21.37 ppm. HRMS (ESI, m/z) calculated for $C_{13}H_{15}N_2O_3$ $[M+H]^+$: 247.1083, found: 247.1077. IR (neat): ν 3430, 3054, 1728, 1464 cm^{-1} .

(*Z*)-3-(2-Hydroxyethyl)-6-(4-methoxybenzylidene)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2h**). White solid (0.30 mmol scale, 63 mg, 80% yield). R_f = 0.4 (EtOAc/petroleum ether = 2:1). 1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.8 Hz, 2H), 7.22 (s, 1H), 6.91 (d, J = 8.8 Hz, 2H), 5.76 (s, 1H), 3.99–3.96 (m, 4H), 3.84 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.99, 144.84, 139.83, 138.42, 131.39, 125.14, 114.21, 113.11, 60.77, 55.29, 52.99 ppm. HRMS (ESI, m/z) calculated for $C_{13}H_{15}N_2O_4$ $[M+H]^+$: 263.1032, found: 263.1028. IR (neat): ν 3437, 3065, 1719, 1594, 1275 cm^{-1} .

(*Z*)-3-(2-Hydroxyethyl)-6-pentylidene-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2i**). Colorless liquid (0.30 mmol scale, 50 mg, 78% yield). R_f = 0.4 (EtOAc/petroleum ether = 2:1). 1H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 5.05–5.01 (m, 1H), 3.93–3.88 (m, 4H), 2.23–2.19 (m, 2H), 1.40–1.30 (m, 4H), 0.91–0.87 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.57, 141.77, 137.51, 116.17, 60.26, 52.68, 30.56, 23.75, 22.16, 13.66 ppm. HRMS (ESI, m/z) calculated for $C_{10}H_{17}N_2O_3$ $[M+H]^+$: 213.1239, found: 213.1235. IR (neat): ν 3448, 2956, 1724, 1654 cm^{-1} .

(*Z*)-6-Hexylidene-3-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2j**). Colorless liquid (0.30 mmol scale, 53 mg, 78% yield). R_f = 0.4 (EtOAc/petroleum ether = 2:1). 1H NMR (400 MHz, $CDCl_3$): δ 7.06 (s, 1H), 5.01 (t, J = 7.8 Hz, 1H), 3.85 (s, 4H), 2.73 (s, 1H), 2.20–2.14 (m, 2H), 1.39–1.24 (m, J = 44.2 Hz, 6H), 0.85 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.58, 141.76, 137.53, 116.26, 60.33, 52.68, 31.26, 28.13, 24.02, 22.26, 13.82 ppm. HRMS (ESI, m/z) calculated for $C_{11}H_{19}N_2O_3$ $[M+H]^+$: 227.1396, found: 227.1386. IR (neat): ν 3440, 2926, 1724, 1652 cm^{-1} .

(*Z*)-6-(5-Chloropentylidene)-3-(2-hydroxyethyl)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2k**). White solid (0.30 mmol scale, 55 mg, 75% yield). R_f = 0.3 (EtOAc/petroleum ether = 2:1). 1H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 1H), 5.01 (t, J = 7.8 Hz, 1H), 3.87 (s, 4H), 3.52 (t, J = 6.5 Hz, 2H), 2.58 (s, 1H), 2.26–2.21 (m, 2H), 1.81–1.52 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.43, 142.18, 137.31, 115.00, 60.41, 52.76, 44.54, 31.88, 25.73, 23.32 ppm. HRMS (ESI, m/z) calculated for $C_{10}H_{16}ClN_2O_3$ $[M+H]^+$: 247.0849, found: 247.0845. IR (neat): ν 3450, 2935, 1727, 1654 cm^{-1} .

(*Z*)-3-(2-Hydroxyethyl)-6-(2-phenoxyethylidene)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2l**). White solid (0.30 mmol scale, 45 mg, 57% yield). R_f = 0.3 (EtOAc/petroleum ether = 2:1). 1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.27 (m, 2H), 7.18 (s, 1H), 6.99–6.89 (m, 3H), 5.30 (t, J = 6.4 Hz, 1H), 4.78 (d, J = 6.4 Hz, 2H), 3.95–3.91 (m, 4H), 2.02 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.92, 144.58, 142.70, 136.26, 129.56, 121.28, 114.56, 109.90, 60.79, 60.40, 53.08 ppm. HRMS (ESI, m/z) calculated for $C_{13}H_{14}N_2NaO_4$ $[M+Na]^+$: 285.0851, found: 285.0851. IR (neat): ν 3408, 2924, 1737, 1236 cm^{-1} .

(*Z*)-6-Benzylidene-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**5a**). Pale white solid (0.30 mmol scale, 47 mg, 83% yield). R_f = 0.3 (EtOAc/petroleum ether = 1:2). 1H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.41–7.31 (m, 3H), 7.24 (s,

1H), 5.85 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.38, 149.91, 143.79, 141.00, 138.09, 132.15, 129.88, 128.99, 128.75, 114.15 ppm. HRMS (ESI, m/z) calculated for $C_{10}H_9N_2O_2$ $[M+H]^+$: 189.0664, found: 189.0654. IR (neat): ν 2921, 1727, 1630 cm^{-1} .

(*Z*)-6-(4-Fluorobenzylidene)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**5b**). White solid (0.30 mmol scale, 54 mg, 87% yield). R_f = 0.3 (EtOAc/petroleum ether = 1:2). 1H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.72–7.69 (m, 2H), 7.22 (s, 1H), 7.09–7.06 (m, 2H), 5.81 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.77 (d, J = 252 Hz), 143.65, 140.67, 137.95, 131.77 (d, J = 7.6 Hz), 128.44, (d, J = 3.8 Hz), 115.90 (d, J = 22.7 Hz), 112.75 ppm. HRMS (ESI, m/z) calculated for $C_{10}H_6FN_2O_2$ $[M-H]^-$: 205.0413, found: 205.0420. IR (neat): ν 2925, 1729, 1590 cm^{-1} .

(*Z*)-6-(4-Chlorobenzylidene)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**5c**). White solid (0.30 mmol scale, 53 mg, 79% yield). R_f = 0.3 (EtOAc/petroleum ether = 1:2). 1H NMR (500 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.23 (s, 1H), 5.80 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.40, 141.28, 137.79, 134.83, 131.02, 130.67, 129.02, 112.63 ppm. HRMS (ESI, m/z) calculated for $C_{10}H_6ClN_2O_2$ $[M-H]^-$: 221.0118, found: 221.0131. IR (neat): ν 2933, 1737, 1599 cm^{-1} .

(*Z*)-6-(4-Methylbenzylidene)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**5d**). White solid (0.30 mmol scale, 52 mg, 85% yield). R_f = 0.3 (EtOAc/petroleum ether = 1:2). 1H NMR (500 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.21–7.18 (m, 3H), 5.82 (s, 1H), 2.37 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.03, 140.47, 139.32, 138.25, 129.86, 129.50, 129.40, 114.13, 21.44 ppm. HRMS (ESI, m/z) calculated for $C_{11}H_9N_2O_2$ $[M-H]^-$: 201.0664, found: 201.0679. IR (neat): ν 2924, 1763, 1616 cm^{-1} .

(*Z*)-6-(4-Methoxybenzylidene)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**5e**). Pale white solid (0.30 mmol scale, 41 mg, 63% yield). R_f = 0.2 (EtOAc/petroleum ether = 1:2). 1H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.67 (d, J = 8.6 Hz, 2H), 7.19 (s, 1H), 6.91 (d, J = 8.6 Hz, 2H), 5.80 (s, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.12, 144.07, 139.68, 138.35, 131.53, 124.97, 114.24, 113.86, 55.32 ppm. HRMS (ESI, m/z) calculated for $C_{11}H_9N_2O_3$ $[M-H]^-$: 217.0613, found: 217.0625. IR (neat): ν 2930, 1755, 1611, 1147 cm^{-1} .

(*Z*)-6-(Biphenylmethylene)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**5f**). White solid (0.30 mmol scale, 49 mg, 62% yield). R_f = 0.3 (EtOAc/petroleum ether = 1:2). 1H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.79 (d, J = 8.1 Hz, 2H), 7.64–7.61 (m, 5H), 7.48–7.35 (m, 3H), 5.89 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.71, 141.59, 141.05, 140.19, 138.09, 131.19, 130.35, 128.88, 127.74, 127.34, 127.01, 113.66 ppm. HRMS (ESI, m/z) calculated for $C_{16}H_{11}N_2O_2$ $[M-H]^-$: 263.0821, found: 263.0834. IR (neat): ν 2922, 1738, 1635 cm^{-1} .

(*Z*)-6-(Cyclohexylmethylene)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**5g**). White solid (0.30 mmol scale, 40 mg, 69% yield). R_f = 0.3 (EtOAc/petroleum ether = 1:2). 1H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.03 (s, 1H), 4.94 (d, J = 9.6 Hz, 1H), 2.61–2.59 (m, 1H), 1.72–1.61 (m, 14.0 Hz, 5H), 1.34–1.28 (m, 2H), 1.20–1.09 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.10, 140.28, 137.75, 122.46, 33.39, 32.09, 25.77, 25.41 ppm. HRMS (ESI, m/z) calculated for $C_{10}H_{13}N_2O_2$ $[M-H]^-$: 193.0977, found: 193.0987. IR (neat): ν 2930, 1762, 1242 cm^{-1} .

(*Z*)-6-Hexylidene-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**5h**). White solid (0.30 mmol scale, 39 mg, 71% yield). R_f = 0.3 (EtOAc/petroleum ether = 1:4). ^1H NMR (400 MHz, CDCl_3): δ 8.63 (s, 1H), 7.07 (s, 1H), 5.08 (t, J = 7.7 Hz, 1H), 2.21 (q, J = 7.4 Hz, 2H), 1.43–1.29 (m, 6H), 0.88 (t, J = 6.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ 145.37, 141.65, 137.52, 117.10, 31.32, 28.18, 24.02, 22.34, 13.91 ppm. HRMS (ESI, m/z) calculated for $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_2$ [$\text{M}-\text{H}$] $^-$: 181.0977, found: 181.0988. IR (neat): ν 2924, 1747, 1659 cm^{-1} .

(*Z*)-6-(4-Chlorobutylidene)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**5i**). White solid (0.30 mmol scale, 33 mg, 54% yield). R_f = 0.3 (EtOAc/petroleum ether = 1:4). ^1H NMR (400 MHz, CDCl_3): δ 8.39 (s, 1H), 7.09 (s, 1H), 5.09 (t, J = 7.8 Hz, 1H), 3.55 (t, J = 6.6 Hz, 2H), 2.40 (q, J = 7.6 Hz, 2H), 1.91 (p, J = 6.9 Hz, 2H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ 144.79, 142.45, 137.09, 114.50, 44.04, 31.28, 21.60 ppm. HRMS (ESI, m/z) calculated for $\text{C}_7\text{H}_8\text{ClN}_2\text{O}_2$ [$\text{M}-\text{H}$] $^-$: 187.0274, found: 187.0290. IR (neat): ν 2930, 1747, 1659, 1059 cm^{-1} .

3. Results and discussion

3.1. Optimization of reaction conditions

Alkynic hydrazones were firstly synthesized by the reaction of alkynals with hydrazines according to reported procedures [35]. In an initial investigation, alkynic aryl hydrazone was found to react with CO_2 to give very low yields of the cyclization product under different reaction conditions due to the low nucleophilic reactivity of the nitrogen atom. As a consequence, phenylpropynal 2-hydroxyethylhydrazone (**1a**) was chosen as the model substrate for the reaction with CO_2 to identify the optimal conditions (Table 1).

Considering that silver(I) salts can function as an effective π -Lewis acid catalyst for alkyne activation in carboxylation and other reactions [36–41], various silver-based catalytic systems were screened. The reaction of **1a** with 2 MPa CO_2 using 5

mol% AgOAc as the catalyst and 1.5 equivalent Cs_2CO_3 as the base in DMSO at 25 °C was found to readily afford the carboxylative cyclization product 3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**2a**) in 87% isolated yield (Table 1, entry 1). It should be noted that the geometry of the C=N bond in hydrazone substrates had no effect on the reactivity, probably due to the rapid conversion of the two isomers **Z-1a** and **E-1a**. The structural assignment of the isolated product was further confirmed by single-crystal X-ray analysis of **2a** [42]. As shown in Fig. 1, the newly formed C=C bond in the product exhibits *Z* configuration, the typical structure obtained from Ag-catalyzed electrophilic cyclizations. Other silver(I) salts such as AgI, AgBF_4 , Ag_2CO_3 , and AgNO_3 displayed inferior catalytic performance than AgOAc (see SI). CuI showed lower catalytic activity than AgOAc (entry 2), while $\text{Pd}(\text{OAc})_2$ afforded no carboxylated product and **1a** was fully recovered (entry 3). The replacement of Cs_2CO_3 with K_2CO_3 or CsF resulted in a slight decrease in the yield of **2a** (entries 4 and 5). Although DBU is frequently employed as an efficient base in many carboxylation reactions using CO_2 , only 30% yield of **2a** was obtained when applied as the base (entry 6). Switching the base to KO^tBu and NaH led to the exclusive formation of the non-carboxylative cyclization product pyrazole **3a** (entries 7 and 8) [35,43]. The CO_2 pressure had an obvious effect on the reaction. A lower yield of **2a** was obtained when the reaction was conducted at low CO_2 pressure (entry 9). The reaction did not proceed in the absence of CO_2 , indicating that the carbonyl moiety in the resulting product originates from CO_2 rather than from the carbonate base (entry 10). Interestingly, **2a** in 75% yield was still obtained in the absence of a base (entry 11), implying that hydrazone **1a** itself may serve as a base in this process. To maintain the high efficiency of the reaction, a catalytic amount of base was added. The presence of 5 mol% Cs_2CO_3 was enough to achieve 85% yield of **2a** (entry 11), which is comparable to the result using stoichiometric bases (entries 1 and 4). No product was observed in the absence of the catalyst, confirming the catalytic role of the silver(I) salt (entry 12). Finally, further screening experiments revealed DMSO as the optimal solvent for this reaction (see SI).

3.2. Substrate scope

Under the optimized reaction conditions, the scope of the silver-catalyzed carboxylative cyclization with regard to alkynic hydrazone substrates was investigated (Table 2). In addition to phenylpropynal 2-hydroxyethylhydrazone (**1a**), other *N*-alkyl substituted hydrazones such as 2-cyanoethylhydrazone (**1b**),

Table 1

Optimization of the reaction conditions for the carboxylative cyclization of alkynic hydrazones with CO_2 .

Entry	Catalyst (mol%)	Base (equiv.)	Yield (%)
1	AgOAc (5)	Cs_2CO_3 (1.5)	87
2	CuI (5)	Cs_2CO_3 (1.5)	75
3 ^a	$\text{Pd}(\text{OAc})_2$ (5)	Cs_2CO_3 (1.5)	<1
4	AgOAc (5)	K_2CO_3 (1.5)	85
5	AgOAc (5)	CsF (1.5)	77
6	AgOAc (5)	DBU (1.5)	30
7 ^b	AgOAc (5)	KO^tBu (1.5)	<1
8 ^b	AgOAc (5)	NaH (1.5)	<1
9 ^c	AgOAc (5)	Cs_2CO_3 (1.5)	52
10 ^d	AgOAc (5)	Cs_2CO_3 (1.5)	0
11	AgOAc (5)	—	75
12	AgOAc (5)	Cs_2CO_3 (0.05)	85
13	—	Cs_2CO_3 (0.05)	<1

Reaction conditions: **1a** (0.3 mmol), 3 mL DMSO, 2.0 MPa CO_2 , 25 °C, 2 h, isolated yield. ^a **1a** was fully recovered. ^b Non-carboxylative cyclization product **3a** was obtained. ^c Using a CO_2 balloon. ^d In the absence of CO_2 .

Fig. 1. Thermal ellipsoid plot for product **2a**.

Table 2Silver-catalyzed carboxylative cyclization of substituted alkynic hydrazones with CO₂.

Reaction conditions: **1** (0.3 mmol), AgOAc (5 mol%), Cs₂CO₃ (5 mol%), 3 mL DMSO, 2.0 MPa CO₂, reaction temperature 25 °C, reaction time 2 h, isolated yield.

isopropylhydrazone (**1c**), and benzylhydrazone (**1d**) were found to be suitable substrates for this reaction. Arylpropynal 2-hydroxyethylhydrazones bearing various functional groups including electron-withdrawing (fluoro, chloro) and electron-donating (methyl, methoxyl) substituents reacted smoothly to afford the corresponding 3,6-dihydro-2H-1,3,4-oxadiazin-2-ones (**2e–2h**) in good yield. Alkyl-substituted propynal 2-hydroxyethylhydrazones **1i–1l** participated efficiently in the carboxylative cyclization reaction furnishing the corresponding products in moderate to good yield.

Since nitrogen heterocycles in medicinal compounds frequently present NH moieties, many synthetic processes involve redundant nitrogen protection/deprotection steps. Therefore, carboxylative cyclization reactions of propynal hydrazone substrates **4** to give directly *N*-unsubstituted products **5** were then examined (Table 3). Using the same reaction conditions to those applied to *N*-substituted hydrazone substrates **1**, substrates **4** containing electron-withdrawing or electron-donating aryl and alkyl substituents on the alkyne moiety furnished the desired products **5** in satisfactory yield. The geometry of the newly formed C=C bonds in oxadiazinones **5** was also identified as that of *Z* isomers based on NOE experiments for products **5a** and **5g** (see SI).

This catalytic reaction is readily scalable for both types of substrates, as exemplified by the synthesis of **2a** (83% yield) and **5a** (85% yield) at gram scale with longer reaction times (Scheme 1). It should be mentioned that the isolated yield of **5a** at 0.8 mmol scale (Scheme 1) was slightly higher than the yield obtained at 0.3 mmol scale (Table 3).

3.3. Mechanistic studies

In addition to the control experiments in Table 1 illustrating the catalytic role of silver(I) salts and the need for CO₂ in this reaction, the reaction of **4a** with CO₂ in DMSO-*d*₆ was further

Table 3Silver-catalyzed carboxylative cyclization of alkynic hydrazones with CO₂.

Reaction conditions: **4** (0.3 mmol), AgOAc (5 mol%), Cs₂CO₃ (5 mol%), 3 mL DMSO, 2.0 MPa CO₂, reaction temperature 25 °C, reaction time 2 h, isolated yield.

examined to detect possible reactive intermediates by NMR spectroscopy.

As shown in Fig. 2, the ¹H NMR spectrum of **4a** saturated with atmospheric CO₂ in DMSO-*d*₆ (Fig. 2(a)) was found to be identical to that of **4a** without CO₂, implying that the formation of a carbazate intermediate in the absence of an external base is inefficient despite the hydrazone itself being able to act as a base. When a catalytic amount of Cs₂CO₃ was added to the reaction system, two obvious new signals appeared at 6.26 and 8.23 ppm, assigned to the carbazate intermediate (Fig. 2(b)). The amount of this species gradually increased to a 1:4 ratio relative to **4a** (Fig. 2(c)). When 10 mol% of AgOAc was added to the reaction system, the signals for the carbazate intermediate and **4a** began to disappear, while the signals of product **5a** started to emerge (Fig. 2(d)). After 2 h, the hydrazone substrate was completely converted into the oxadiazinone product and no obvious signals for the carbazate intermediate were detected anymore (Fig. 2(e)).

On the basis of the above experiments, a plausible mechanism for this reaction is proposed in Scheme 2. The *Z*-isomer of the hydrazone substrate enters a productive catalytic cycle where it interacts with the base. The reaction of the NH moiety of the hydrazone with CO₂ affords the reactive carbazate intermediate **B**. Then, the carboxylate oxygen atom conducts a nucleophilic attack on the silver(I)-activated alkyne moiety

Scheme 1. Gram-scale reactions.

Fig. 2. NMR studies of the reaction of **4a** with CO_2 .

Scheme 2. Proposed mechanism.

affording vinylic silver intermediate **C**. The following protonation reaction finally furnishes the carboxylative cyclization product, with concomitant regeneration of the catalyst and release of the base.

4. Conclusions

We have developed a silver(I)-catalyzed carboxylative cyclization of alkyne hydrazones under mild reaction conditions. Silver(I) salts show high activity in this reaction as π -Lewis acid catalysts for alkyne activation, and the use of catalytic amounts of a base such as cesium carbonate is sufficient to guarantee the

rapid formation of the reactive carbazate intermediate. This reaction provides a highly efficient and convenient approach to synthesize biologically important 1,3,4-oxadiazin-2-one compounds in good yield using CO_2 as the carboxylative reagent.

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Graphical Abstract

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Silver-catalyzed carboxylative cyclization of alkynic hydrazones with carbon dioxideWenzhen Zhang*, Yuqian Sun, Min Zhang, Hui Zhou, Xiaobing Lu
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A silver(I)-catalyzed carboxylative cyclization of alkynic hydrazones with carbon dioxide under mild reaction conditions was developed, which efficiently affords biologically important 1,3,4-oxadiazin-2-one compounds in good yield.

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银催化炔基肼与二氧化碳的羧化环化反应

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摘要: 将二氧化碳作为羰基合成子催化转化成重要的杂环精细化学品的的方法学研究受到广泛关注。1,3,4-噁二嗪-2-酮类化合物是一类具有重要生理活性的氮氧杂环化合物, 广泛用于医药如钙增敏剂、强心剂、杀菌及除草剂等。传统的合成此类化合物的方法包括环状碳酸酯与肼的反应、肼基甲酸酯化化合物的闭环反应等, 其反应步骤长, 效率低, 不够经济绿色。本文开发了一种银催化的炔肼类化合物与二氧化碳羧化环化新反应用于高效合成1,3,4-噁二嗪-2-酮。

首先选取苯乙炔基肼乙基肼与二氧化碳的羧化环化反应作为模式反应, 筛选出适用于此反应的最优反应条件为: 5 mol%醋酸银为催化剂, 5 mol%碳酸铯为碱, 二氧化碳压力为2.0 MPa, 二甲基亚砜为溶剂, 25 °C下反应2 h。炔肼分子中碳氮双键的顺反构型对其羧化反应活性没有影响。当使用化学当量的叔丁醇钾或氢氧化钠等作为碱时, 即使在2.0 MPa的二氧化碳存在下, 炔肼底物也几乎全部转化成非羧化闭环产物吡唑类化合物。在最优反应条件下, 氮原子上烷基取代或未取代的炔肼底物能与二氧化碳高效发生羧化环化反应, 以54%–90%的产率得到20多种1,3,4-噁二嗪-2-酮产物。反应放大到克级时依旧能高效进行。产物的X射线单晶衍射及氢核磁NOE实验证实, 新形成的碳碳双键为顺式结构。当使用氮原子上芳基取代的炔肼时, 由于底物中氮原子的亲核反应活性较差, 目标羧化产物产率很低。

一价银盐通常在二氧化碳参与的羧化反应中作为路易斯酸催化剂活化碳碳叁键。本文对照实验也证明在此羧化环化反应中银盐具有不可或缺的催化作用。改变反应气氛的实验也验证了1,3,4-噁二嗪-2-酮产物中的羰基来自二氧化碳。氢核磁跟踪实验观察到加入催化量碱能有效促进关键肼基甲酸根中间体的形成。以此为依据, 本文提出了包含二氧化碳插入炔肼底物形成肼基甲酸根、羧基氧亲核进攻银盐活化的碳碳叁键形成烯基银中间体、质子化得到1,3,4-噁二嗪-2-酮产物及再生银催化剂及碱的催化反应机理。

总之, 本文发展了一种银催化的简单易得的炔肼类化合物与二氧化碳的羧化环化新反应, 为1,3,4-噁二嗪-2-酮类化合物的合成提供了一种方便高效的方法。

关键词: 二氧化碳; 银催化; 羧化环化反应; 炔基肼; 噁二嗪酮; 均相催化

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