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Copper(I)-Catalyzed Intramolecular *N-N* Coupling of Cyclopropyl *O*-Acyl Ketoximes: Synthesis of Spiro-fused Pyrazolin-5-ones

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A convenient copper-catalyzed approach has been developed for the synthesis of substituted spiro-fused pyrazolin-5-ones from readily available cyclopropyl *O*-acyl ketoximes via an intramolecular N—N bond formation reaction. These catalytic reactions proceed in excellent yields with a broad scope.

Keywords copper-catalyzed, *N-N* bond formation, *O*-acyl ketoximes, pyrazolin-5-ones, cyclopropyl oximes

Introduction

Pyrazolones are very important nitrogen-containing intermediates and products. They have been widely used in analytical, dye, biological and pharmaceutical chemistry owing to the broad biological activities and structural complexity.[1] To date, numerous effective methods have been built for the synthesis of pyrazolones.[1a,1b,2] However, a systematic review of the literature showed that it remains lack of alternative methods for the synthesis of spiro-fused pyrazolin-5-ones, although their potential applications are included in organic synthesis and pharmaceutical chemistry. A multi-step strategy for the synthesis of spiro-fused pyrazolin-5-ones was first reported by Wamhoff and Korte[3] in 1966. Subsequently, in order to test the pharmacological activity of several 3-pyrazolone analogues, as the key intermediates, Krogsgaard-Larsen and co-works[4] prepared the spiro-fused pyrazolin-5-ones via multi-step (Figure 1). In 2010, Rao and Reddy[5] reported a multicomponent cascade approach (involves simultaneous cyclization, leading to the formation of thiazole, pyrazolone, and cyclopropane rings) for the synthesis of spiro-fused pyrazolin-5-ones in a single step from aryl bromomethylketones, heteroarylbromomethylketones with thiosemicarbazide and α-bromoacetyl-γ-butyrolactone in $POCl_3$ under heating (Figure 1). Dong's group[6] developed a tandem ketoxime tosylation and intramolecular cyclization for the synthesis of fully substituted spiro-fused pyrazolin-5-ones by treatment of cyclopropyl *O*-acetyl oximes with *p*-toluenesulfonyl chloride in the presence of potassium hydroxide (Figure 1). The development of new methods for the synthesis of spiro-fused pyrazolin-5-one derivatives is of considerable interest, although several useful methods have been established.

Very recently, we have achieved a convenient iron(III)-catalyzed intramolecular cyclization of 1-(*N*-arylpyrrol-2-yl)ethanone *O*-acyl oximes (**1**) for the synthesis of substituted pyrrolo[1,2-*a*]quinoxalines (**2**) through N—O bond cleavage and directed C—H arylation reactions in acetic acid (Eq. 1).[7] Combined with other recent researches on the copper-catalyzed oxime acetates participated reactions,[8] we speculated that the dinitrogen-containing seven-membered ring benzo[*b*]-[1,4]diazepin-2-one derivatives (**4**) should be synthesized via an intramolecular cyclization reaction using 1-carbamoyl-1-*O*-acyl ketoximylcycloalkanes (**3**) (Eq. 2).

In this paper, we present our efforts toward the copper-catalyzed intramolecular directed N—N bond formation of cyclopropyl *O*-acetyl oximes for the synthesis of spiro-fused pyrazolin-5-ones (Figure 1).

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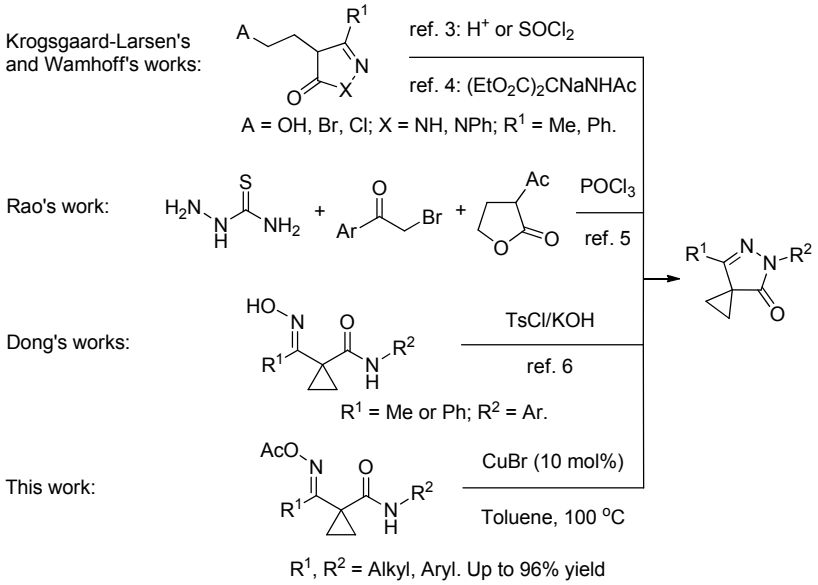
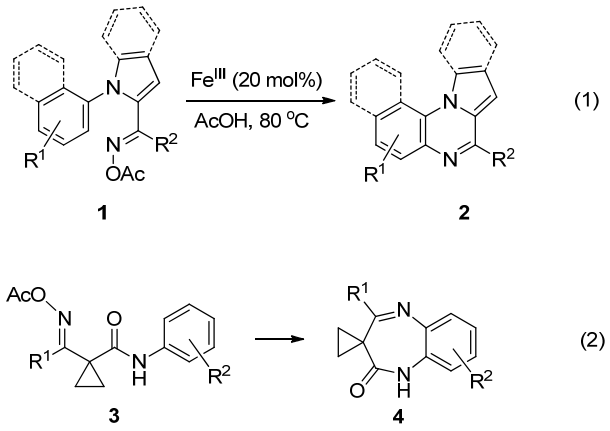


Figure 1 General synthetic routes to the spiro-fused pyrazolin-5-one derivatives.



Experimental

General

All reactions were carried out under an air atmosphere, unless otherwise indicated. All the reagents were commercially available, and toluene was distilled from sodium. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance/400 (^{1}H: 400 MHz, ^{13}C: 100 MHz at 25 ℃) with TMS as internal standard. Data are represented as follows: chemical shift, integration, multiplicity (br＝broad, s＝singlet, d＝doublet, dd＝double doublet, t＝triplet, q＝quartet, m＝multiplet), coupling constants in Hertz (Hz). All high-resolution mass spectra (HRMS) were measured on a mass spectrometer by using electrospray ionization (ESI-oa-TOF), and the purity of all samples used for HRMS (＞95%) were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic analysis. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All reactions were monitored by TLC with GF254 silica gel coated plates. Flash chromatography was carried out on SiO_2 (silica gel 200－300 mesh).

General procedure for the synthesis of 6 and 3

To a round-bottom flask (25 mL) was added **5** (2.0 mmol) in EtOH (6.0 mL)/H_2O (0.24 mL), hyoxylamine hydrochloride (4.0 mmol, 2.0 equiv.) and NaOAc (4.0 mmol, 2.0 equiv.). The mixture was heated at 100 ℃ for 12－24 h. After cooling to room temperature, the reaction was quenched by water, the mixture was extracted with dichloromethane (DCM) (4.0 mL×3), the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel to provide the desired product **6**.

Then to a 25 mL flask was added **6** (0.5 mmol), triethylamine (TEA, 1.0 mmol, 2.0 equiv.) and DCM (5 mL) at 0 ℃, a solution of acetyl chloride (0.75 mmol, 1.5 equiv.) in DCM (1.0 mL) was added dropwise to this stirred cooled solution. The reaction mixture was stirred at 0 ℃ for 5 min. After the reaction was quenched by water, the mixture was extracted with DCM (5.0 mL×3), and the combined extracts were washed with $NaHCO_3$ (aq.) (5.0 mL) and brine (5.0 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to provide the desired product **3**.

General procedure for the synthesis of 7

A solution of *O*-acyl oxime **3** (0.3 mmol) and CuBr (4.3 mg, 10 mol%) in toluene (3.0 mL, 0.1 mol/L) was heated at 100 ℃ until **3** was completely consumed (monitored by TLC). After cooling to room temperature, the mixture was quenched with water (10 mL), and then it was extracted with dichloromethane (DCM) (5 mL×3). The organic extracts were dried over anhydrous

Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, PE/EtOAc).

General procedure for the radical trapping experiments

A solution of *O*-acyl oxime **3g** (97 mg, 0.3 mmol), CuBr (4.3 mg, 10 mol%) and radical scavenger (47 mg, 100 mol% and 470 mg, 1000 mol% TEMPO) in toluene (3.0 mL) was heated at 100 ℃ until **3g** was completely consumed (monitored by TLC). After cooling to room temperature, the mixture was quenched with water (10 mL), and then it was extracted with dichloromethane (DCM) (5 mL×3). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, PE/EtOAc)

(*E*)-1-((Acetoxyimino)(4-methoxyphenyl)methyl)-*N*-phenylcyclopropane-1-carboxamide (3a) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (146.2 mg, 83%), m.p. 49−51 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.71 (s, 1H), 7.63 (d, *J*=7.6 Hz, 2H), 7.47 (d, *J*=8.8 Hz, 2H), 7.28 (t, *J*=8.0 Hz, 2H), 7.06 (t, *J*=7.4 Hz, 1H), 6.92 (d, *J*=8.8 Hz, 2H), 3.82 (s, 3H), 2.10 (s, 3H), 1.77 (q, *J*=4.4 Hz, 2H), 1.16 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.4, 167.9, 167.8, 161.0, 138.4, 130.4, 128.7, 123.9, 122.7, 119.7, 113.7, 55.2, 30.4, 19.4, 16.3. HRMS (ESI) calcd for $C_{20}H_{20}N_2O_4$ ([M+Na]$^+$) 375.1315, found 375.1302.

(*E*)-1-((Acetoxyimino)(4-methoxyphenyl)methyl)-*N*-(*p*-tolyl)cyclopropane-1-carboxamide (3b) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (152.1 mg, 83%), m.p. 112−114 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.55 (s, 1H), 7.49 (t, *J*=7.4 Hz, 4H), 7.08 (d, *J*=8.4 Hz, 2H), 6.92 (d, *J*=8.8 Hz, 2H), 3.82 (s, 3H), 2.28 (s, 3H), 2.10 (s, 3H), 1.76 (q, *J*=4.2 Hz, 2H), 1.16 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.4, 167.7, 167.7, 161.0, 135.8, 133.4, 130.4, 129.2, 122.8, 119.8, 113.7, 55.2, 30.4, 20.7, 19.4, 16.1. HRMS (ESI) calcd for $C_{21}H_{22}N_2O_4$ ([M+Na]$^+$) 389.1472, found 389.1472.

(*E*)-1-((Acetoxyimino)(4-methoxyphenyl)methyl)-*N*-(4-chlorophenyl)cyclopropane-1-carboxamide (3c) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (164.4 mg, 85%), m.p. 65−67 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.06 (s, 1H), 7.65−7.60 (m, 2H), 7.43−7.38 (m, 2H), 7.25−7.20 (m, 2H), 6.93−6.89 (m, 2H), 3.81 (s, 3H), 2.08 (s, 3H), 1.75 (q, *J*=4.4 Hz, 2H), 1.12 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.5, 168.3, 168.0, 161.0, 137.1, 130.3, 128.6, 128.6, 122.4, 120.9, 113.7, 55.2, 30.2, 19.3, 16.5. HRMS (ESI) calcd for $C_{20}H_{19}ClN_2O_4$ ([M+Na]$^+$) 409.0926, found 409.0932.

(*E*)-1-((Acetoxyimino)(*p*-tolyl)methyl)-*N*-(4-chlorophenyl)cyclopropane-1-carboxamide (3d) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (153.9 mg, 83%): m.p. 106−108 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.41 (s, 1H), 7.65 (d, *J*=8.8 Hz, 2H), 7.26−7.20 (m, 6H), 2.37 (s, 3H), 2.04 (s, 3H), 1.75 (q, *J*=4.0 Hz, 2H), 1.11 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.7, 168.2, 167.8, 140.5, 137.1, 129.0, 128.6, 128.5, 127.8, 127.4, 120.9, 29.7, 21.3, 19.2, 16.6. HRMS (ESI) calcd for $C_{20}H_{19}ClN_2O_3$ ([M+Na]$^+$) 393.0976, found 393.0975.

(*E*)-1-((Acetoxyimino)(*m*-tolyl)methyl)-*N*-(4-chlorophenyl)cyclopropane-1-carboxamide (3e) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (150.2 mg, 81%), m.p. 61−63 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.64 (s, 1H), 7.66 (d, *J*=8.8 Hz, 2H), 7.28 (t, *J*=7.8 Hz, 1H), 7.24−7.18 (m, 3H), 7.07−7.01 (m, 2H), 2.35 (s, 3H), 2.00 (s, 3H), 1.74 (q, *J*=4.2 Hz, 2H), 1.09 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.7, 168.0, 167.6, 138.1, 137.2, 130.7, 130.3, 128.6, 128.5, 128.2, 127.7, 124.5, 120.9, 29.4, 21.3, 19.1, 16.8. HRMS (ESI) calcd for $C_{20}H_{19}ClN_2O_3$ ([M+Na]$^+$) 393.0976, found 393.0981.

(*E*)-1-((Acetoxyimino)(4-chlorophenyl)methyl)-*N*-(4-chlorophenyl)cyclopropane-1-carboxamide (3f) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (170.2 mg, 87%), m.p. 98−100 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.43 (s, 1H), 7.69−7.63 (m, 2H), 7.45−7.41 (m, 2H), 7.29−7.25 (m, 4H), 2.07 (s, 3H), 1.80 (q, *J*=4.4 Hz, 2H), 1.09 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.9, 167.5, 167.3, 137.1, 136.4, 129.1, 129.0, 128.9, 128.8, 128.7, 121.0, 29.6, 19.2, 16.7. HRMS (ESI) calcd for $C_{19}H_{16}Cl_2N_2O_3$ ([M+Na]$^+$) 413.0430, found 413.0437.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-phenylcyclopropane-1-carboxamide (3g) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (153.1 mg, 95%), m.p. 144−146 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.25 (s, 1H), 7.69 (d, *J*=8.4 Hz, 2H), 7.45−7.38 (m, 3H), 7.36−7.26 (m, 4H), 7.06 (t, *J*=7.4 Hz, 1H), 2.02 (s, 3H), 1.78 (q, *J*=4.2 Hz, 2H), 1.13 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.29, 167.95, 167.46, 138.39, 130.58, 129.99, 128.68, 128.29, 127.54, 123.82, 119.69, 29.68, 19.07, 16.42. HRMS (ESI) calcd for $C_{19}H_{18}N_2O_3$ ([M+Na]$^+$) 345.1210, found 345.1201.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(*p*-tolyl)cyclopropane-1-carboxamide (3h) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (143.0 mg, 85%), m.p. 115−117 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.07 (s, 1H), 7.55 (d, *J*=8.4 Hz, 2H), 7.45−7.39 (m, 3H), 7.36−7.33 (m, 2H), 7.10 (d, *J*=8.4 Hz, 2H), 2.29 (s, 3H), 2.03 (s, 3H), 1.77 (q, *J*=4.2 Hz, 2H), 1.14 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.30, 168.00, 167.29, 135.87, 133.36, 130.71, 130.03, 129.20, 128.32, 127.62, 119.70, 29.73, 20.74, 19.14, 16.33.

HRMS (ESI) calcd for $C_{20}H_{20}N_2O_3$ ([M + Na]$^+$) 359.1366, found 359.1368.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(*m*-tolyl)cyclopropane-1-carboxamide (3i) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (144.7 mg, 86%), m.p. 69−71 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.16 (s, 1H), 7.58 (s, 1H), 7.44 (d, *J*=8.4 Hz, 1H), 7.42−7.37 (m, 3H), 7.35−7.31 (m, 2H), 7.16 (t, *J*=7.8 Hz, 1H), 6.88 (d, *J*=7.6 Hz, 1H), 2.31 (s, 3H), 2.00 (s, 3H), 1.77 (q, *J*=4.4 Hz, 2H), 1.14 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.0, 167.8, 167.3, 138.3, 138.2, 130.5, 129.9, 128.4, 128.2, 127.4, 124.5, 120.2, 116.7, 29.6, 21.3, 18.9, 16.2. HRMS (ESI) calcd for $C_{20}H_{20}N_2O_3$ ([M+Na]$^+$) 359.1366, found 359.1362.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(*o*-tolyl)cyclopropane-1-carboxamide (3j) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶6] as a white solid (146.3 mg, 87%), m.p. 84−86 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.18 (s, 1H), 7.68 (d, *J*=8.0 Hz, 1H), 7.45 (s, 5H), 7.16 (t, *J*=8.0 Hz, 2H), 7.07−7.01 (m, 1H), 2.17 (s, 3H), 2.02 (s, 3H), 1.80 (q, *J*=4.4 Hz, 2H), 1.28 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.7, 167.6, 166.9, 135.7, 130.9, 130.2, 130.1, 130.0, 128.3, 127.7, 126.1, 125.0, 123.4, 29.7, 19.1, 17.6, 16.4. HRMS (ESI) calcd for $C_{20}H_{20}N_2O_3$ ([M+Na]$^+$) 359.1366, found 359.1377.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-mesitylcyclopropane-1-carboxamide (3k) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶6] as a white solid (153.0 mg, 84%), m.p. 106−108 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.36 (s, 1H), 7.59−7.55 (m, 2H), 7.47−7.43 (m, 3H), 6.81 (s, 2H), 2.23 (s, 3H), 2.04 (s, 3H), 1.98 (s, 6H), 1.75 (q, *J*=4.4 Hz, 2H), 1.36 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.9, 167.8, 166.1, 136.2, 134.7, 131.2, 131.1, 130.2, 128.4, 128.3, 128.1, 29.8, 20.6, 19.2, 17.7, 15.4. HRMS (ESI) calcd for $C_{22}H_{24}N_2O_3$ ([M+Na]$^+$) 387.1679, found 387.1687.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(4-methoxyphenyl)cyclopropane-1-carboxamide (3l) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (146.2 mg, 83%), m.p. 117−119 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.04 (s, 1H), 7.58−7.52 (m, 2H), 7.42−7.38 (m, 3H), 7.34−7.30 (m, 2H), 6.84−6.78 (m, 2H), 3.73 (s, 3H), 2.00 (s, 3H), 1.74 (q, *J*=4.2 Hz, 2H), 1.11 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.3, 168.0, 167.2, 155.9, 131.7, 130.6, 123.0, 128.3, 127.6, 121.2, 113.8, 55.2, 29.6, 19.1, 16.2. HRMS (ESI) calcd for $C_{20}H_{20}N_2O_4$ ([M+Na]$^+$) 375.1315, found 375.1304.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(3-methoxyphenyl)cyclopropane-1-carboxamide (3m) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (137.4 mg, 78%), m.p. 114−116 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.30 (s, 1H), 7.46 (s, 1H), 7.42−7.39 (m, 3H), 7.34−7.29 (m, 2H), 7.20−7.16 (m, 2H), 6.65−6.60 (m, 1H), 3.77 (s, 3H), 2.01 (s, 3H), 1.76 (q, *J*=4.2 Hz, 2H), 1.13 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.1, 167.9, 167.5, 159.8, 139.6, 130.5, 123.0, 129.4, 128.3, 127.5, 111.9, 110.1, 105.0, 55.0, 29.7, 19.1, 16.4. HRMS (ESI) calcd for $C_{20}H_{20}N_2O_4$ ([M+Na]$^+$) 375.1315, found 375.1310.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(2-methoxyphenyl)cyclopropane-1-carboxamide (3n) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (144.5 mg, 82%), m.p. 77−79 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.02 (s, 1H), 8.23 (q, *J*=1.2 Hz, 1H), 7.52−7.47 (m, 2H), 7.42−7.38 (m, 3H), 6.99−6.94 (m, 1H), 6.88−6.84 (m, 1H), 6.79 (q, *J*=1.2 Hz, 1H), 3.77 (s, 3H), 2.08 (s, 3H), 1.74 (q, *J*=4.2 Hz, 2H), 1.34 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.7, 167.3, 164.7, 148.0, 131.2, 130.1, 128.2, 127.9, 127.4, 123.6, 120.4, 119.6, 109.7, 55.3, 30.7, 19.3, 16.1. HRMS (ESI) calcd for $C_{20}H_{20}N_2O_4$ ([M+Na]$^+$) 375.1315, found 375.1312.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(4-chlorophenyl)cyclopropane-1-carboxamide (3o) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (153.4 mg, 86%), m.p. 119−121 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.58 (s, 1H), 7.69−7.65 (m, 2H), 7.46−7.43 (m, 3H), 7.31−7.27 (m, 3H), 7.26−7.24 (m, 1H), 2.04 (s, 3H), 1.78 (q, *J*=4.2 Hz, 2H), 1.12 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.6, 168.1, 167.6, 137.2, 130.4, 130.1, 128.7, 128.6, 128.4, 127.5, 121.0, 29.5, 19.1, 16.8. HRMS (ESI) calcd for $C_{19}H_{17}ClN_2O_3$ ([M+Na]$^+$) 379.0820, found 379.0796.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(4-chlorophenyl)cyclopropane-1-carboxamide (3p) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶6] as a white solid (157.0 mg, 88%), m.p. 79−81 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.60 (s, 1H), 7.91 (s, 1H), 7.50−7.45 (m, 1H), 7.44−7.38 (m, 3H), 7.29−7.26 (m, 2H), 7.19 (t, *J*=8.2 Hz, 1H), 7.04−7.01 (m, 1H), 2.00 (s, 3H), 1.76 (q, *J*=4.2 Hz, 2H), 1.11 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.3, 168.0, 167.8, 139.6, 134.2, 130.3, 130.0, 129.7, 128.3, 127.4, 123.8, 119.8, 117.8, 29.5, 19.0, 16.7. HRMS (ESI) calcd for $C_{19}H_{17}ClN_2O_3$ ([M+Na]$^+$) 379.0820, found 379.0821.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(2-chlorophenyl)cyclopropane-1-carboxamide (3q) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (160.6 mg, 90%), m.p. 73−75 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.09 (s, 1H), 8.17 (d, *J*=8.0 Hz, 1H), 7.52−7.48 (m, 2H), 7.44−7.39 (m, 3H), 7.27 (d, *J*=8.0 Hz, 1H), 7.17 (t, *J*=7.8 Hz, 1H), 7.00−6.92 (m, 1H), 2.05 (s, 3H), 1.77 (q, *J*=4.4 Hz, 2H), 1.35 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.9, 167.6, 164.9, 134.4, 130.9, 130.3, 128.8, 128.3, 128.0, 127.2, 124.7, 123.5,

122.0, 30.6, 19.2, 16.5. HRMS (ESI) calcd for $C_{19}H_{17}ClN_2O_3$ ([M+Na]$^+$) 379.0820, found 379.0817.

Ethyl (*E*)-4-(1-((acetoxyimino)(phenyl)methyl)-cyclopropane-1-carboxamido)benzoate (3r) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶6] as a white solid (159.7 mg, 81%), m.p. 94−96 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.76 (s, 1H), 8.03−7.97 (m, 2H), 7.81−7.76 (m, 2H), 7.46−7.41 (m, 3H), 7.31−7.25 (m, 2H), 4.34 (q, *J*=7.2 Hz, 2H), 2.03 (s, 3H), 1.80 (q, *J*=4.4 Hz, 2H), 1.37 (t, *J*=7.2 Hz, 3H), 1.12 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6, 168.0, 168.0, 166.3, 142.6, 130.6, 130.4, 130.1, 128.5, 127.6, 125.6, 119.0, 60.7, 29.7, 19.2, 17.1, 14.3. HRMS (ESI) calcd for $C_{22}H_{22}N_2O_5$ ([M+Na]$^+$) 417.1421, found 417.1421.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(4-bromophenyl)cyclopropane-1-carboxamide (3s) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (162.5 mg, 81%), m.p. 68−70 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.57 (s, 1H), 7.63−7.58 (m, 2H), 7.44−7.40 (m, 3H), 7.40−7.36 (m, 2H), 7.29−7.26 (m, 2H), 2.01 (s, 3H), 1.76 (q, *J*=4.2 Hz, 2H), 1.10 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.5, 168.0, 167.6, 137.6, 131.6, 130.4, 130.0, 128.4, 127.5, 121.3, 116.3, 29.6, 19.1, 16.7. HRMS (ESI) calcd for $C_{19}H_{17}BrN_2O_3$ ([M+Na]$^+$) 423.0315, found 423.0314.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(4-fluorophenyl)cyclopropane-1-carboxamide (3t) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (141.3 mg, 83%), m.p. 93−95 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.43 (s, 1H), 7.68−7.62 (m, 2H), 7.44−7.40 (m, 3H), 7.32−7.28 (m, 2H), 6.97 (t, *J*=8.6 Hz, 2H), 2.01 (s, 3H), 1.75 (q, *J*=4.2 Hz, 2H), 1.11 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.5, 168.1, 167.5, 158.9 (d, *J*=241 Hz), 134.6 (d, *J*=2.7 Hz), 130.4, 130.0, 128.3, 127.5, 121.3 (d, *J*=7.8 Hz), 115.3 (d, *J*=22.2 Hz), 29.5, 19.1, 16.5. HRMS (ESI) calcd for $C_{19}H_{17}FN_2O_3$ ([M+Na]$^+$) 363.1115, found 363.1115.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(4-(trifluoromethyl)phenyl)cyclopropane-1-carboxamide (3u) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (158.1 mg, 81%), m.p. 57−59 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.87 (s, 1H), 7.85 (d, *J*=8.8 Hz, 2H), 7.55 (d, *J*=8.8 Hz, 2H), 7.46−7.41 (m, 3H), 7.29−7.25 (m, 2H), 2.02 (s, 3H), 1.79 (q, *J*=4.4 Hz, 2H), 1.12 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6, 168.1, 168.1, 141.6, 130.3, 130.1, 128.4, 127.5, 126.0 (q, *J*=3.5 Hz), 125.6, 125.5, 125.3, 122.8, 119.5, 29.6, 19.1, 17.0. HRMS (ESI) calcd for $C_{20}H_{17}F_3N_2O_3$ ([M+Na]$^+$) 413.1083, found 413.1083.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(3-chloro-4-methoxyphenyl)cyclopropane-1-carboxamide (3v) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (164.3 mg, 85%), m.p. 69−71 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.33 (s, 1H), 7.84 (d, *J*=2.8 Hz, 1H), 7.45 (dd, *J*=9.2, 2.8 Hz, 1H), 7.42−7.39 (m, 3H), 7.31−7.25 (m, 2H), 6.83 (d, *J*=8.8 Hz, 1H), 3.82 (s, 3H), 2.00 (s, 3H), 1.73 (q, *J*=4.2 Hz, 2H), 1.09 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 168.0, 167.4, 151.3, 132.2, 130.4, 130.0, 128.3, 127.5, 122.0, 122.0, 119.2, 111.9, 56.1, 29.5, 19.1, 16.5. HRMS (ESI) calcd for $C_{20}H_{19}ClN_2O_4$ ([M+Na]$^+$) 409.0926, found 409.0937.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-benzyl-cyclopropane-1-carboxamide (3w) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (131.2 mg, 78%), m.p. 73−75 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 (s, 1H), 7.44−7.38 (m, 5H), 7.28−7.19 (m, 3H), 7.10−7.05 (m, 2H), 4.40 (d, *J*=5.6 Hz, 2H), 1.99 (s, 3H), 1.68 (q, *J*=4.2 Hz, 2H), 1.24 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.5, 168.0, 166.2, 137.9, 131.1, 130.1, 128.3, 127.9, 127.3, 127.0, 43.9, 29.6, 19.2, 15.6. HRMS (ESI) calcd for $C_{20}H_{20}N_2O_3$ ([M+Na]$^+$) 359.1366, found 359.1351.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-butyl-cyclopropane-1-carboxamide (3x) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a yellow oil (136.1 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37−7.32 (m, 5H), 7.28 (s, 1H), 3.18−3.11 (m, 2H), 1.95 (s, 3H), 1.57 (q, *J*=4.2 Hz, 2H), 1.37−1.28 (m, 2H), 1.19−1.11 (m, 2H), 1.08 (q, *J*=4.2 Hz, 2H), 0.77 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 168.0, 167.1, 131.1, 130.0, 128.2, 127.8, 39.8, 31.00, 29.4, 19.7, 19.1, 15.4, 13.5. HRMS (ESI) calcd for $C_{17}H_{22}N_2O_3$ ([M+Na]$^+$) 325.1523, found 325.1508.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-cyclo-hexylcyclopropane-1-carboxamide (3y) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (139.6 mg, 85%), m.p. 47−49 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (s, 5H), 7.1 (d, *J*=7.2 Hz, 1H), 3.70−3.57 (m, 1H), 1.97 (s, 3H), 1.75−1.65 (m, 2H), 1.62−1.52 (m, 4H), 1.52−1.44 (m, 1H), 1.28−1.17 (m, 2H), 1.12−1.08 (m, 2H), 1.06−0.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2, 168.0, 167.2, 131.2, 130.0, 128.2, 127.8, 48.7, 32.4, 29.5, 25.2, 24.5, 19.2, 15.4. HRMS (ESI) calcd for $C_{19}H_{24}N_2O_3$ ([M+Na]$^+$) 351.1679, found 351.1667.

(*E*)-1-((Acetoxyimino)(phenyl)methyl)-*N*-(*tert*-butyl)cyclopropane-1-carboxamide (3z) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (136.1 mg, 90%), m.p. 53−55 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (s, 5H), 6.74 (s, 1H), 1.97 (s, 3H), 1.52 (q, *J*=4.2 Hz, 2H), 1.16 (s, 9H), 1.11 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 167.9, 166.7, 131.5, 130.0, 128.2, 127.8, 51.3, 30.2, 28.3, 19.2, 15.0. HRMS (ESI) calcd for $C_{17}H_{22}N_2O_3$ ([M+Na]$^+$) 325.1523, found 325.1514.

(*Z*)-2-((Acetoxyimino)(phenyl)methyl)-*N*-(4-

chlorophenyl)butanamide (3a') The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a yellow oil (163.2 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.34 (s, 1H), 7.61 (d, *J*=8.8 Hz, 2H), 7.42−7.36 (m, 3H), 7.33−7.29 (m, 2H), 7.22 (d, *J*=8.8 Hz, 2H), 3.67 (t, *J*=7.2 Hz, 1H), 2.03 (s, 3H), 2.01−1.98 (m, 1H), 1.92−1.82 (m, 1H), 0.96 (t, *J*=7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.5, 167.8, 167.3, 136.6, 131.1, 130.1, 128.9, 128.7, 128.3, 127.3, 120.9, 55.8, 24.1, 19.2, 11.6. HRMS (ESI) calcd for $C_{19}H_{19}ClN_2O_3$ ($[M+Na]^+$) 381.0976, found 381.0976.

(*E*)-1-(1-(Acetoxyimino)ethyl)-*N*-(4-methoxyphenyl)cyclopropane-1-carboxamide (3b') The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (124.8 mg, 86%), m.p. 64−69 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.12 (s, 1H), 7.55 (d, *J*=9.2 Hz, 2H), 6.83 (d, *J*=9.2 Hz, 2H), 3.76 (s, 3H), 2.22 (s, 3H), 1.92 (s, 3H), 1.69 (q, *J*=4.2 Hz, 2H), 1.21 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.8, 167.1, 166.2, 156.0, 131.8, 121.3, 113.9, 55.3, 29.5, 19.3, 15.5, 14.1. HRMS (ESI) calcd for $C_{15}H_{18}N_2O_4$ ($[M+Na]^+$) 313.1159, found 313.1137.

(*E*)-1-(1-(Acetoxyimino)ethyl)-*N*-(4-chlorophenyl)-cyclopropane-1-carboxamide (3c') The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (132.6 mg, 86%): m.p. 81−83 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.78 (s, 1H), 7.63 (d, *J*=8.8 Hz, 2H), 7.23 (d, *J*=8.8 Hz, 2H), 2.22 (s, 3H), 1.87 (s, 3H), 1.71 (q, *J*=4.4 Hz, 2H), 1.22 (q, *J*=4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 167.7, 167.5, 165.8, 137.2, 128.6, 128.5, 121.0, 29.2, 19.2, 16.1, 13.5. HRMS (ESI) calcd for $C_{14}H_{15}ClN_2O_3$ ($[M+Na]^+$) 317.0663, found 317.0646.

7-(4-Methoxyphenyl)-5-phenyl-5,6-diazaspiro-[2.4]hept-6-en-4-one (7a) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow solid (78.4 mg, 89%), m.p. 107−109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.06 (d, *J*=8.0 Hz, 2H), 7.55 (d, *J*=8.8 Hz, 2H), 7.43 (t, *J*=7.8 Hz, 2H), 7.20 (t, *J*=7.4 Hz, 1H), 6.93 (d, *J*=8.8 Hz, 2H), 3.83 (s, 3H), 2.09 (q, *J*=4.2 Hz, 2H), 1.89 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.7, 161.0, 157.4, 138.6, 128.8, 127.2, 124.8, 123.1, 118.8, 114.3, 55.3, 32.9, 20.9. HRMS (ESI) calcd for $C_{18}H_{16}N_2O_2$ ($[M+Na]^+$) 315.1104, found 315.1100.

7-(4-Methoxyphenyl)-5-(*p*-tolyl)-5,6-diazaspiro-[2.4]hept-6-en-4-one (7b) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow solid (83.6 mg, 91%), m.p. 105−107 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.92 (d, *J*=8.4 Hz, 2H), 7.57−7.52 (m, 2H), 7.23 (d, *J*=8.0 Hz, 2H), 6.94−6.90 (m, 2H), 3.83 (s, 3H), 2.36 (s, 3H), 2.07 (q, *J*=4.4 Hz, 2H), 1.87 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.5, 160.9, 157.2, 136.3, 134.4, 129.3, 127.1, 123.1, 118.8, 114.2, 55.2, 32.8, 20.9, 20.8. HRMS (ESI) calcd for $C_{19}H_{18}N_2O_2$ ($[M+Na]^+$) 329.1260, found 329.1254.

5-(4-Chlorophenyl)-7-(4-methoxyphenyl)-5,6-diazaspiro[2.4]hept-6-en-4-one (7c) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (89.2 mg, 92%), m.p. 101−103 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.05−8.00 (m, 2H), 7.57−7.52 (m, 2H), 7.41−7.35 (m, 2H), 6.96−6.92 (m, 2H), 3.85 (s, 3H), 2.11 (q, *J*=4.4 Hz, 2H), 1.90 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.7, 161.2, 157.7, 137.3, 129.9, 128.8, 127.3, 122.9, 119.8, 114.4, 55.4, 33.0, 21.1. HRMS (ESI) calcd for $C_{18}H_{15}ClN_2O_2$ ($[M+Na]^+$) 349.0714, found 349.0710.

5-(4-Chlorophenyl)-7-(*p*-tolyl)-5,6-diazaspiro-[2.4]-hept-6-en-4-one (7d) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow solid (90.4 mg, 97%), m.p. 100−102 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.06−7.99 (m, 2H), 7.47 (d, *J*=8.4 Hz, 2H), 7.39−7.34 (m, 2H), 7.22 (d, *J*=8.0 Hz, 2H), 2.38 (s, 3H), 2.10 (q, *J*=4.4 Hz, 2H), 1.88 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.7, 157.9, 140.6, 137.2, 129.8, 129.6, 128.8, 127.4, 125.6, 119.8, 33.0, 21.3, 21.1. HRMS (ESI) calcd for $C_{18}H_{15}ClN_2O$ ($[M+Na]^+$) 333.0765, found 333.0764.

5-(4-Chlorophenyl)-7-(*m*-tolyl)-5,6-diazaspiro-[2.4]hept-6-en-4-one (7e) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow solid (83.0 mg, 89%), m.p. 84−86 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.07−8.00 (m, 2H), 7.46 (s, 1H), 7.39−7.35 (m, 2H), 7.31−7.29 (m, 2H), 2.40 (s, 3H), 2.10 (q, *J*=4.4 Hz, 2H), 1.89 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.6, 158.1, 138.7, 137.2, 131.1, 130.1, 129.8, 128.7, 126.5, 122.7, 119.8, 33.1, 21.4, 21.1. HRMS (ESI) calcd for $C_{18}H_{15}ClN_2O$ ($[M+Na]^+$) 333.0765, found 333.0761.

5,7-Bis(4-chlorophenyl)-5,6-diazaspiro[2.4]hept-6-en-4-one (7f) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (90.4 mg, 91%), m.p. 136−138 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.02−7.97 (m, 2H), 7.53 (d, *J*=8.8 Hz, 2H), 7.43−7.37 (m, 4H), 2.10 (q, *J*=4.4 Hz, 2H), 1.93 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.5, 156.8, 137.1, 136.5, 130.2, 129.3, 128.9, 128.8, 127.0, 119.9, 33.0, 21.2. HRMS (ESI) calcd for $C_{17}H_{12}Cl_2N_2O$ ($[M+Na]^+$) 353.0219, found 353.0219.

5,7-Diphenyl-5,6-diazaspiro[2.4]hept-6-en-4-one (7g) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (74.0 mg, 94%), m.p. 57−59 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.09−8.02 (m, 2H), 7.64−7.58 (m, 2H), 7.48−7.41 (m, 5H), 7.22 (t, *J*=7.4 Hz, 1H), 2.12 (q, *J*=4.4 Hz, 2H), 1.92 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.8, 157.7, 138.6, 130.5, 130.2, 128.9, 128.8, 125.8, 125.0, 118.8, 33.1, 20.9. HRMS (ESI) calcd for $C_{17}H_{14}N_2O$ ($[M+Na]^+$) 285.0998, found 285.0985.

7-Phenyl-5-(*p*-tolyl)-5,6-diazaspiro[2.4]hept-6-en-4-one (7h) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (79.6 mg, 96%), m.p. 108－110 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.96－7.92 (m, 2H), 7.63－7.58 (m, 2H), 7.44－7.40 (m, 3H), 7.24 (d, *J*=8.4 Hz, 2H), 2.37 (s, 3H), 2.09 (q, *J*=4.4 Hz, 2H), 1.89 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.5, 157.4, 136.1, 134.5, 130.5, 130.0, 129.2, 128.8, 125.6, 118.8, 32.9, 20.9, 20.8. HRMS (ESI) calcd for $C_{18}H_{16}N_2O$ ([M＋Na]$^+$) 299.1155, found 299.1149.

7-Phenyl-5-(*m*-tolyl)-5,6-diazaspiro[2.4]hept-6-en-4-one (7i) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow solid (77.1 mg, 93%): m.p. 81－83 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.62－7.55 (m, 2H), 7.46－7.40 (m, 4H), 7.35－7.28 (m, 3H), 2.36 (s, 3H), 2.15 (q, *J*=4.4 Hz, 2H), 1.94 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 173.2, 157.6, 136.1, 135.0, 131.1, 130.6, 129.9, 128.8, 128.3, 126.6, 126.4, 125.5, 31.7, 20.6, 18.4. HRMS (ESI) calcd for $C_{18}H_{16}N_2O$ ([M＋Na]$^+$) 299.1155, found 299.1150.

7-Phenyl-5-(*o*-tolyl)-5,6-diazaspiro[2.4]hept-6-en-4-one (7j) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a yellow oil (73.8 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.90－7.87 (m, 2H), 7.65－7.58 (m, 2H), 7.46－7.41 (m, 3H), 7.33 (t, *J*=7.8 Hz, 1H), 7.04 (d, *J*=7.8 Hz, 1H), 2.42 (s, 3H), 2.10 (q, *J*=4.2 Hz, 2H), 1.90 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.7, 157.5, 138.6, 138.4, 130.4, 130.0, 128.8, 128.6, 125.8, 125.7, 119.4, 116.0, 33.0, 21.5, 20.8. HRMS (ESI) calcd for $C_{18}H_{16}N_2O$ ([M＋Na]$^+$) 299.1155, found 299.1143.

5-Mesityl-7-phenyl-5,6-diazaspiro[2.4]hept-6-en-4-one (7k) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (74.9 mg, 82%), m.p. 103－105 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.60－7.57 (m, 2H), 7.45－7.38 (m, 3H), 6.98 (s, 2H), 2.33 (s, 3H), 2.22 (s, 6H), 2.16 (q, *J*=4.2 Hz, 2H), 1.94 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 173.4, 157.7, 138.8, 136.4, 132.5, 130.8, 129.9, 129.1, 128.9, 125.5, 31.4, 21.1, 20.3, 18.0. HRMS (ESI) calcd for $C_{20}H_{20}N_2O$ ([M＋Na]$^+$) 327.1468, found 327.1460.

5-(4-Methoxyphenyl)-7-phenyl-5,6-diazaspiro-[2.4]hept-6-en-4-one (7l) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a yellow oil (81.6 mg, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.95－7.89 (m, 2H), 7.60－7.57 (m, 2H), 7.45－7.39 (m, 3H), 6.99－6.93 (m, 2H), 3.82 (s, 3H), 2.10 (q, *J*=4.2 Hz, 2H), 1.89 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.4, 157.5, 156.9, 132.0, 130.5, 130.0, 128.9, 125.7, 120.7, 113.9, 55.4, 32.9, 20.8. HRMS (ESI) calcd for $C_{18}H_{16}N_2O_2$ ([M＋Na]$^+$) 315.1104, found 315.1088.

5-(3-Methoxyphenyl)-7-phenyl-5,6-diazaspiro-[2.4]hept-6-en-4-one (7m) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow solid (80.7 mg, 92%), m.p. 74－76 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.70 (t, *J*=4.0 Hz, 1H), 7.68 (d, *J*=8.0 Hz, 1H), 7.61－7.58 (m, 2H), 7.43 (q, *J*=1.6 Hz, 3H), 7.33 (t, *J*=8.6 Hz, 1H), 6.77 (dd, *J*=8.4, 2.4 Hz, 1H), 3.85 (s, 3H), 2.11 (q, *J*=4.4 Hz, 2H), 1.90 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.7, 159.9, 157.5, 139.7, 130.4, 130.1, 129.6, 128.9, 125.7, 104.3, 55.3, 33.1, 20.9. HRMS (ESI) calcd for $C_{18}H_{16}N_2O_2$ ([M＋Na]$^+$) 315.1104, found 315.1094.

5-(2-Methoxyphenyl)-7-phenyl-5,6-diazaspiro-[2.4]hept-6-en-4-one (7n) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow solid (77.2 mg, 88%), m.p. 127－129 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.59－7.53 (m, 2H), 7.44 (d, *J*=7.6 Hz, 1H), 7.42－7.34 (m, 4H), 7.04 (t, *J*=7.8 Hz, 2H), 3.85 (s, 3H), 2.10 (q, *J*=4.4 Hz, 2H), 1.91 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 173.5, 157.6, 155.0, 130.7, 129.8, 129.8, 128.7, 128.4, 126.0, 125.7, 120.6, 112.3, 55.9, 31.6, 20.5. HRMS (ESI) calcd for $C_{18}H_{16}N_2O_2$ ([M＋Na]$^+$) 315.1104, found 315.10095.

5-(4-Chlorophenyl)-7-phenyl-5,6-diazaspiro[2.4]-hept-6-en-4-one (7o) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (84.6 mg, 95%), m.p. 90－92 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.03 (d, *J*=9.2 Hz, 2H), 7.59 (q, *J*=2.0 Hz, 2H), 7.47－7.42 (m, 3H), 7.41－7.36 (m, 2H), 2.12 (q, *J*=4.4 Hz, 2H), 1.91 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.7, 157.9, 137.2, 130.3, 130.3, 129.9, 129.0, 128.8, 125.8, 119.8, 33.1, 21.1. HRMS (ESI) calcd for $C_{17}H_{13}ClN_2O$ ([M＋Na]$^+$) 319.0609, found 319.0610.

5-(3-Chlorophenyl)-7-phenyl-5,6-diazaspiro[2.4]-hept-6-en-4-one (7p) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (80.1 mg, 90%), m.p. 70－72 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.11 (t, *J*=2.0 Hz, 1H), 8.03－8.00 (m, 1H), 7.63－7.57 (m, 2H), 7.47－7.41 (m, 3H), 7.34 (t, *J*=8.2 Hz, 1H), 7.17 (dd, *J*=8.0, 1.2 Hz, 1H), 2.13 (q, *J*=4.4 Hz, 2H), 1.92 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.8, 158.0, 139.6, 134.5, 130.4, 130.2, 129.9, 129.0, 125.8, 124.9, 118.6, 116.5, 33.2, 21.2. HRMS (ESI) calcd for $C_{17}H_{13}ClN_2O$ ([M＋Na]$^+$) 319.0609, found 319.0604.

5-(2-Chlorophenyl)-7-phenyl-5,6-diazaspiro[2.4]-hept-6-en-4-one (7q) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow solid (69.5 mg, 78%), m.p. 87－89 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.60－7.51 (m, 4H), 7.44－7.40 (m, 3H), 7.39－7.32 (m, 2H), 2.15 (q, *J*=4.4 Hz, 2H), 1.95 (dd, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 173.2, 158.2, 134.9, 131.8, 130.5, 130.4, 130.1, 129.7, 128.9, 128.9, 127.4, 125.8, 31.8, 20.7. HRMS (ESI) calcd for $C_{17}H_{13}ClN_2O$ ([M＋Na]$^+$) 319.0609, found 319.0600.

Ethyl 4-(4-oxo-7-phenyl-5,6-diazaspiro[2.4]hept-6-en-5-yl)benzoate (7r) The product was isolated by

flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶7] as a white solid (79.2 mg, 79%), m.p. 120−122 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.2−8.16 (m, 2H), 8.15−8.09 (m, 2H), 7.64−7.59 (m, 2H), 7.48−7.43 (m, 3H), 4.38 (q, *J*=7.2 Hz, 2H), 2.15 (q, *J*=4.4 Hz, 2H), 1.95 (q, *J*=4.4 Hz, 2H), 1.41 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 173.1, 166.2, 158.4, 142.3, 130.6, 130.5, 130.3, 129.1 126.5, 126.0, 117.8, 60.9, 33.2, 21.2, 14.4. HRMS (ESI) calcd for $C_{20}H_{18}N_2O_3$ ($[M+Na]^+$) 357.1210, found 357.1208.

5-(4-Bromophenyl)-7-phenyl-5,6-diazaspiro[2.4]-hept-6-en-4-one (7s) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (89.1 mg, 87%), m.p. 80−82 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.02−7.93 (m, 2H), 7.62−7.56 (m, 2H), 7.54−7.49 (m, 2H), 7.48−7.42 (m, 3H), 2.11 (q, *J*=4.4 Hz, 2H), 1.90 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.7, 157.9, 137.6, 131.7, 130.3, 130.2, 128.9, 125.8, 120.1, 117.7, 33.1, 21.1. HRMS (ESI) calcd for $C_{17}H_{13}BrN_2O$ ($[M+Na]^+$) 363.1003, found 363.1001.

5-(4-Fluorophenyl)-7-phenyl-5,6-diazaspiro[2.4]-hept-6-en-4-one (7t) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow solid (75.7 mg, 90%), m.p. 97−99 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.05−7.99 (m, 2H), 7.61−7.57 (m, 2H), 7.46−7.41 (m, 3H), 7.15−7.07 (m, 2H), 2.12 (q, *J*=4.4 Hz, 2H), 1.90 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.5, 159.8 (d, *J*=242.6 Hz), 157.8, 134.8 (d, *J*=2.7 Hz), 130.3, 130.2, 128.9, 125.7, 120.5 (d, *J*=7.9 Hz), 115.4 (d, *J*=22.4 Hz), 33.0, 21.0. HRMS (ESI) calcd for $C_{17}H_{13}FN_2O$ ($[M+Na]^+$) 303.0904, found 303.0894.

7-Phenyl-5-(4-(trifluoromethyl)phenyl)-5,6-diazaspiro[2.4]hept-6-en-4-one (7u) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (90.2 mg, 91%), m.p. 88−90 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.23 (d, *J*=8.8 Hz, 2H), 7.68 (d, *J*=8.8 Hz, 2H), 7.61 (q, *J*=2.0 Hz, 2H), 7.47−7.44 (m, 3H), 2.15 (q, *J*=4.4 Hz, 2H), 1.94 (q, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 173.1, 158.4, 141.3, 130.5, 130.2, 129.0, 128.7, 126.1 (q, *J*=3.7 Hz), 125.9, 118.2, 33.2, 21.3. HRMS (ESI) calcd for $C_{18}H_{13}F_3N_2O$ ($[M+Na]^+$) 353.0872, found 35.0873.

5-(3-Chloro-4-methoxyphenyl)-7-phenyl-5,6-diazaspiro[2.4]hept-6-en-4-one (7v) The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (84.3 mg, 86%), m.p. 135−137 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.08 (d, *J*=2.4 Hz, 1H), 7.94 (dd, *J*=8.8, 2.6 Hz, 1H), 7.61−7.56 (m, 2H), 7.47−7.40 (m, 3H), 6.97 (d, *J*=9.2 Hz, 1H), 3.91 (s, 3H), 2.12 (q, *J*=4.4 Hz, 2H), 1.90 (q, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 172.4, 157.9, 152.3, 132.4, 130.3, 130.2, 129.0, 125.8, 122.5, 121.1, 118.2, 111.9, 56.3, 33.0, 21.0. HRMS (ESI) calcd for $C_{18}H_{15}ClN_2O_2$ ($[M+Na]^+$) 349.0714, found 349.0709.

Mixture of 5-benzyl-7-phenyl-5,6-diazaspiro[2.4]-hept-6-en-4-one (7w) and 5w The mixture of **7w** and **5w** was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid and the yield of **7w** was calculated according to the ^{1}H NMR (*ca*. 45.6 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.51−7.46 (m, 2H), 7.43−7.41 (m, 2H), 7.39−7.32 (m, 5H), 7.31−7.28 (m, 1H), 5.04 (s, 2H), 2.03 (q, *J*=4.2 Hz, 2H), 1.83 (q, *J*=4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 174.0, 157.3, 136.7, 130.7, 129.8, 128.9, 128.5, 128.2, 127.5, 125.5, 48.6, 20.3, 15.3. HRMS (ESI) calcd for $C_{18}H_{16}N_2O$ ($[M+Na]^+$) 299.1155, found 299.1155.

Mixture of 5-butyl-7-phenyl-5,6-diazaspiro[2.4]-hept-6-en-4-one (7x) and 5x The mixture of **7x** and **5x** was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow oil and the yield of **7x** was calculated according to the ^{1}H NMR (*ca*. 51.6 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.51−7.46 (m, 2H), 7.39−7.34 (m, 3H), 3.82 (t, *J*=7.2 Hz, 2H), 1.99 (q, *J*=4.4 Hz, 2H), 1.78 (q, *J*=4.4 Hz, 2H), 1.77−172 (m, 2H), 1.39−1.35 (m, 2H), 0.94 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 173.9, 156.9, 130.8, 129.6, 128.8, 125.4, 44.5, 30.6, 20.0, 19.8, 13.6. HRMS (ESI) calcd for $C_{15}H_{18}N_2O$ ($[M+Na]^+$) 265.1311, found 265.1301.

Mixture of 5-cyclohexyl-7-phenyl-5,6-diazaspiro-[2.4]hept-6-en-4-one (7y) and 5y The mixture of **7y** and **5y** was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid and the yield of **7s** was calculated according to the ^{1}H NMR (*ca*. 47.5 mg, 59%); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.51−7.47 (m, 2H), 7.39−7.34 (m, 3H), 4.22−4.11 (m, 1H), 1.99 (q, *J*=4.4 Hz, 2H), 1.90−1.81 (m, 6H), 1.78 (q, *J*=4.2 Hz, 2H), 1.54−1.44 (m, 2H), 1.28−1.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 173.3, 156.5, 129.5, 128.7, 128.5, 125.5, 53.1, 35.3, 31.2, 25.5, 20.0, 15.2. HRMS (ESI) calcd for $C_{17}H_{20}N_2O$ ($[M+Na]^+$) 291.1468, found 291.1459.

Mixture of 5-(*tert*-butyl)-7-phenyl-5,6-diazaspiro-[2.4]hept-6-en-4-one (7z) and 5z The mixture of **7z** and **5z** was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a yellow solid and the yield of **7z** was calculated according to the ^{1}H NMR (*ca*. 17.0 mg, 23%); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.56 (t, *J*=7.4 Hz, 3H), 7.48 (dd, *J*=7.2, 3.6 Hz, 2H), 1.95 (q, *J*=4.2 Hz, 2H), 1.70 (q, *J*=4.2 Hz, 2H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 174.1, 155.0, 133.2 (s), 128.7, 128.5, 125.3, 51.7, 36.1, 28.3, 14.9. HRMS (ESI) calcd for $C_{15}H_{18}N_2O$ ($[M+Na]^+$) 243.1492, found 240.1491.

2-Benzoyl-*N*-phenylbutanamide (5a') The product was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶8] as a white solid (31.7 mg, 35%); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.83 (s, 1H), 8.05 (d, *J*=7.6 Hz, 2H), 7.65 (t, *J*=7.2 Hz, 1H), 7.55−7.50 (m, 4H), 7.30−7.26 (m, 2H), 4.43 (t, *J*=7.2 Hz, 1H), 2.20−2.03 (m, 2H), 1.03 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 200.8, 167.0, 136.2, 134.4, 129.3,

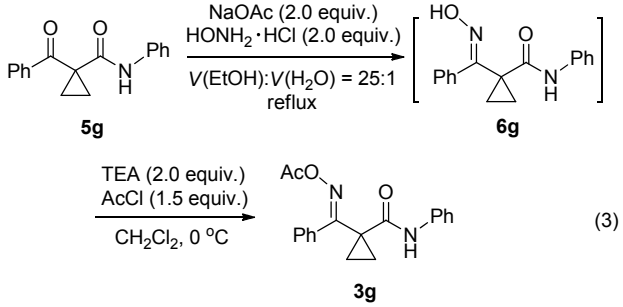
129.0, 129.0, 128.7, 121.3, 121.2, 56.9, 27.1, 12.0. HRMS (ESI) calcd for $C_{13}H_{14}N_2O_2$ ($[M + Na]^+$) 324.0762, found 324.0766.

Mixture of 5-(4-methoxyphenyl)-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (7b') and 5b' The mixture of **7b'** and **5b'** was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶10] as a yellow solid and the yield of **7b'** was calculated according to the ^{1}H NMR (*ca*: 57.8 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81−7.76 (m, 2H), 6.94−6.89 (m, 2H), 3.79 (s, 3H), 1.94 (s, 3H), 1.77−1.71 (m, 2H), 1.66−1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.1, 156.7, 132.0, 121.8, 120.5, 113.9, 55.4, 33.6, 18.6, 12.5. HRMS (ESI) calcd for $C_{13}H_{14}N_2O_2$ ($[M + Na]^+$) 253.0947, found 253.0947.

Mixture of 5-(4-chlorophenyl)-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (7c') and 5c' The mixture of **7c'** and **5c'** was isolated by flash chromatography [eluent: *V*(EtOAc)∶*V*(PE)=1∶10] as a yellow solid and the yield of **7c'** was calculated according to the ^{1}H NMR (*ca*: 52.8 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95−7.88 (m, 2H), 7.38−7.32 (m, 2H), 1.97 (s, 3H), 1.81−1.74 (m, 2H), 1.71−1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.36, 160.05, 129.57, 128.75, 121.36, 119.58, 33.7, 18.91, 12.52. HRMS (ESI) calcd for $C_{12}H_{11}ClN_2O$ ($[M+Na]^+$) 257.0452, found 257.0452.

Results and Discussion

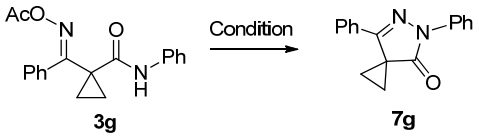
With this assumption in mind, compound 1-(1- (acetoxyimino)ethyl)-*N*-phenylcyclopropane-1-carboxamide (**3g**), which could be easily synthesized from 1-benzoyl-*N*-phenylcyclopropane-1-carboxamide (**5g**) via an intermediate product 1-((hydroxyimino)(phenyl)-methyl)-*N*-phenylcyclopropane-1-carboxamide (**6g**) by a two-step reaction following the literatures (Eq. 3),[6,9] was selected as the model compound to evaluate its ability to give the seven-membered ring compound **4g**. After many attempts, however, compound 5,7-diphenyl-5,6-diazaspiro[2.4]hept-6-en-4-one (**7g**) instead of **4g** was isolated in the yield of 94% when we treated **3g** with CuBr (10 mol%) at 100 ℃ in toluene for 2 h (Table 1, Entry 2). The yield of **7g** was reduced when the reaction was performed at a higher or lower temperature (120 or 80 ℃) (Table 1, Entries 1 and 3). Similar result was also observed in case of increasing the amount of catalyst (Table 1, Entry 4). However, the reaction could not afford **7g** in the absence of CuBr catalyst, and 89% of **3g** was recovered (Table 1, Entry 5). Other copper salts including CuCl, CuI, Cu_2O, $CuBr_2$, $Cu(OAc)_2$ and $CuSO_4$•$5H_2O$ were screened against the reaction. They were less effective than CuBr for the desired reaction (Table 1, Entries 6−11). The reaction was also tested against various solvents, including DMF, DMSO, xylene, 1,4-dioxane, and EtOH. The experiments disclosed that they were all found to be less efficient than toluene for the conversion (Table 1, Entries 12−16). It is noteworthy that compound **6g** cannot cyclize to the corresponding pyrazolone **7g** under our optimal conditions (Table 1, Entry 2), and most of **6g** was recovered at present.[9c]



(3)

With the optimized conditions in hand (Table 1, Entry 2), the scope of this intramolecular N-N cyclization using different *O*-acetyl oximes **3** was then investigated (Table 2). It was found that satisfactory yields of **7a**−7**f** (89%−97%) were obtained when starting materials (**3a**−**3f**) with various aryl substituents (R^1) were employed for the reactions, and no deprotection by-products **5a**−**5f** were detected by means of HRMS and ^{1}H NMR. The variation of the R^2 group was then examined. The results revealed that the reaction was well tolerant

Table 1 Survey of the reaction conditions[a]

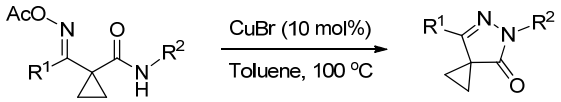


Entry	Cat. (equiv.)	*T*/℃	Time/h	Solvent	Yield of **7a**/%
1	CuBr (0.1)	120	1	toluene	91
2	CuBr (0.1)	100	2	toluene	94
3	CuBr (0.1)	80	12	toluene	81
4	CuBr (0.2)	100	1.5	toluene	90
5	CuBr (0)	100	2	toluene	0[b]
6	CuCl (0.1)	100	5	toluene	92
7	CuI (0.1)	100	8	toluene	87
8	Cu_2O (0.1)	100	24	toluene	75[c]
9	$CuBr_2$ (0.1)	100	1	toluene	82
10	$Cu(OAc)_2$ (0.1)	100	20	toluene	80
11	$CuSO_4·5H_2O$ (0.1)	100	24	toluene	18[d]
12	CuBr (0.1)	100	24	DMF	0[e]
13	CuBr (0.1)	100	8.0	DMSO	77
14	CuBr (0.1)	100	4.0	xylene	85
15	CuBr (0.1)	100	6.0	1,4-dioxane	74
16	CuBr (0.1)	100	24	EtOH	42[f]

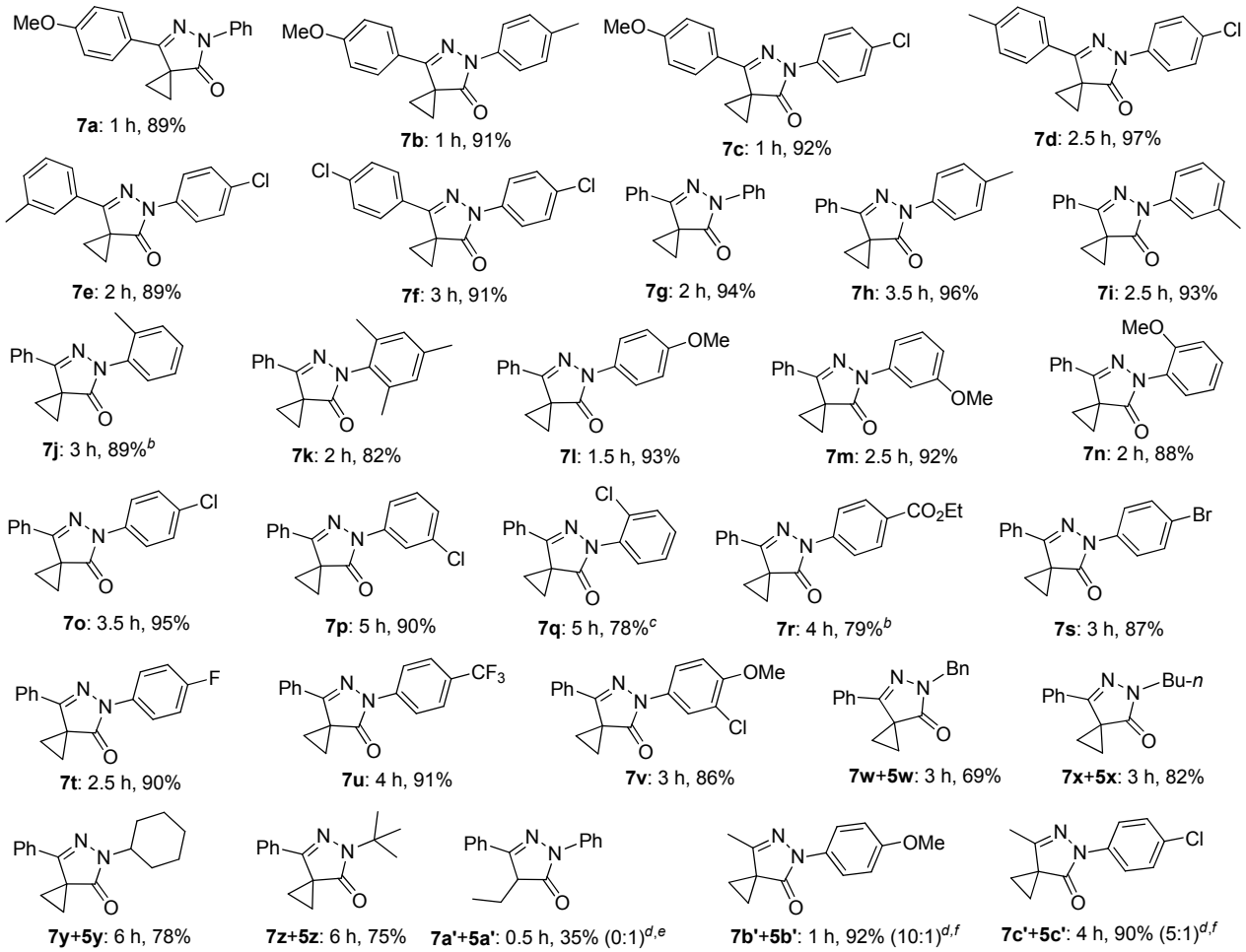
[a] Unless otherwise indicated, all reactions were carried out with **3** (0.3 mmol) in 3 mL solvent; [b] 89% of **3g** was recovered; [c] 8% of **3g** was recovered; [d] 65% of **3g** was recovered; [e] A trace amount of **3g** and complex mixture was observed; [f] 13% of **3g** was recovered.

towards various aryl bearing the electron-donating groups (EDG's) (*e.g.*, Me and OMe) and electron-withdrawing groups (EWG's) (*e.g.*, Cl, Br, F, CF_3 and CO_2Et) at the *ortho*-, *meta*- or *para*-position on the phenyl ring. Compounds **7g**—**7v** were isolated in moderate to good yields (78%—96%). It is noteworthy that *ortho*-chloro-substituted compound **3q** afforded a byproduct **5q** (8%). Furthermore, the starting materials (**3w**—**3z**) with aliphatic substituent R^2 also afforded the deprotection products **5w**—**5z** besides the desired **7w**—**7z**. And the yields showed an increasing tendency with the increasing steric hindrance of the substituents. Similar results were also observed for the starting materials **3b'**—**3c'** and **3a'**. Accordingly, several control experiments were conducted, using **3q** as the model compound, in order to minimise the amout of the deprotection products **5**. However, it was found that the reaction still produced **5q** in the yield of 23%, along with **7q** in 66% yield, when we treated **3q** under the optimized conditions in anhydrous toluene in the N_2 atomphere after 5 h. Additionally, the other two control experiments also showed that the yields of compounds **5q** and **7q** had almost no change when the reaction was performed in the presence of 4Å molecular sieves in anhydrous toluene in the N_2 atomphere or under open air in the presence of 10 equiv. of water. It was deduced according to these observations that the deprotection product **5** was unlikely formed during the work-up stage, and may be from the reaction period.

Table 2 Extension of the reaction scope[a]



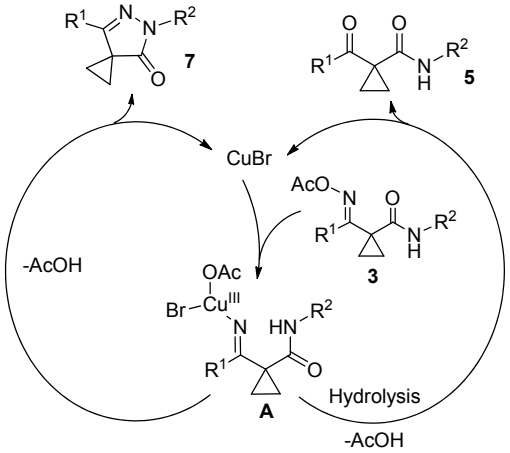
3 **7**



[a] Unless otherwise indicated, all of the reactions were carried out with **3** (0.3 mmol) and CuBr (4.3 mg, 0.03 mmol) in toluene (3 mL) at 100 ℃. [b] Reaction was performed in N_2. [c] 8% of **5q** was obtained. [d] The mixture of **7** and **5** could not be separated due to their same polarity, and the ratio of compounds **7** and **5** provided in the bracket was determined based on the ^{1}H NMR. [e] The reaction was performed at 100 ℃. [f] The reaction was performed at 120 ℃.

Limited extension was concerned on these starting materials of which methylene position was substituted by alkyl because the *O*-acetyl oxime derivatives are difficult to prepare under the current conditions. Obviously, they are competitive reactions of the N-N coupling reaction and hydrolysis. It was deduced that, comparatively, these compounds which are easily to hydrolyze (such as **3q** and **3w**－**3c')** will generate the byproducts **5**.[10] However, the hydrolyzate 5 could not be completely inhibited when we performed the reaction under the optimized conditions with **3q** in an ultra-dried toluene (H_2O＜0.3‰). Radical trapping experiments were also conducted to determine whether a radical process was involved in this reaction using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) radical scavenger. It was found that the reactions proceed smoothly to give **7g** in 69% and 62% yields in the presence of the 1 and 10 equiv. TEMPO, respectively. The observed results suggested that a radical process may not be involved in the transformation.[11] In addition, the experiments using Cu^{II} catalysts suggested that a Cu^{III} species might be involved in this transformation (Table 1, Entries 8－10). A plausible mechanism for this reaction was proposed based on these results of the current study and information from the literature (Scheme 1).[12] Oxidative additions to N－O bonded species are precedential.[13] Accordingly, we deduced that the oxidative addition of the *O*-acetyl oximes **3** to the Cu^{I} catalyst occurred first to form the Cu^{III} species **A**.[11b,14] Oxime acetates acted not only as a substrate, but also as an oxidant, thus the reaction needs no additional oxidants or additives. Then, the putative organo-copper(III) intermediate **A** formed the desired product **7** via the reductive elimination reaction and simultaneously released one molecule of AcOH.[11b,14] Alternatively, intermediate **A** underwent hydrolysis pathway to give the by-product **5**, the procedure is similar to those of several previous related works.[11a]

Scheme 1 Proposed mechanism



Conclusions

In summary, a copper(I)-catalyzed route for the facile synthesis of spiro-fused pyrazolin-5-ones has been developed. The reaction uses readily available *O*-acetyl oximes acting not only as a substrate, but also as an oxidant, without additional oxidants or additives, and proceeds under non-basic and non-oxidizing conditions thus complementing existing *N*-*N* bond forming reactions.

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[10] The yield of hydrolyzate **5q** increased from 8% to 24% when we performed reaction of **3q** in an aqueous solvent [toluene (3 mL), H_2O (1 equiv.)]. Additionally, it is noteworthy that the products **7w**—**7z**, **7b'**, and **7c'** were obtained as a mixture with the corresponding hydrolyzed products **5** due to their close molecular polarity. And starting material **3a'** gave product **5a'** in the yield of 35% after 0.5 h, instead of the desired compound **7a'**.

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