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Highly stereoselective construction of spiro[cyclopropane-1,4′-pyrazolin-5′-one]with 4-arylidene-3-methyl-1-phenyl-pyrazolin-5-one and arsonium ylide

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ABSTRACT

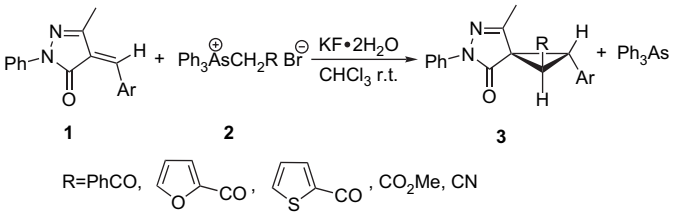
A highly stereoselective synthesis of *exo*-spiro[cyclopropane-1,4′-pyrazolin-5′-one] from 4-arylidene-3-methyl-1-phenyl-pyrazolin-5-one and arsonium bromide in the presence of base has been achieved. The triphenylarsine-catalyzed cyclopropanation of 4-arylidene-3-methyl-1-phenyl-pyrazolin-5-one with bromide in the presence of $NaHCO_3$ has also been studied. Both *exo* and *endo* isomers were formed in this reaction. The structures of the products were characterized by IR, MS, ^1H NMR, elemental analysis, and X-ray diffraction analysis.

1. Introduction

Spirocyclopropyl moiety has attracted much attention due to its wide range of biological activities and pharmacological properties.[1] Therefore, considerable efforts have been made to explore new approaches to construct spirocyclopropyl heterocycles. The compounds incorporating pyrazole ring system continue to attract considerable attention because of their broad range of biological activities.[2] The procedures for the synthesis of spiropyrazole derivatives have been reported.[3] A number of synthetic approaches to spirocyclopropyl heterocycles have been reported in recent years, such as transition-metal catalyzed cyclopropanation of alkenes with diazo compounds, 1,3-dipolar cycloaddition reaction, and Diels–Alder reaction. But these methods are often not highly stereoselective and a mixture of cis/trans isomers is generally obtained.[4–6] To our knowledge, little effort has been expended in the synthesis of spirocyclopropyl pyrazole derivatives and only one paper has been reported for the synthesis of *cis*-dihydro-spiro[cyclopropanepyrazolin]ones from 4-arylidene-3-methyl-1-phenyl-pyrazolin-5-one with sulfur ylide by Croce and Pocar.[7] Therefore, the development of a new approach to highly stereoselective synthesis of spirocyclopropyl pyrazole derivatives is still demanded.

2. Results and discussion

In this paper, we present an approach for highly stereoselective construction of *exo-trans*-2,3-dihydro-spiro[2,3-disubstituted-cyclopropane-1,4′-3′-methyl-1′-phenyl-pyrazolin-5′-one] with 4-arylidene-3-methyl-1-phenyl-pyrazolin-5-one and arsonium salt in the presence of $KF\cdot 2H_2O$ (Scheme 1). In addition, the triphenylarsine-catalyzed cyclopropanation of 4-arylidene-3-methyl-1-phenyl-pyrazolin-5-one with bromide in the presence of $NaHCO_3$ is also studied. In this case, both *exo* and *endo* isomers are obtained (Scheme 2).



Scheme 1.

Our studies began with screening the optimum reaction condition. First, a couple of bases were tested. In the model experiment, compound **3a** was obtained when a mixture of 4-(4-chlorobenzylidene)-3-methyl-1-phenyl-pyrazolin-5-one **1a** (1 equiv), benzoyl methyltriphenylarsonium bromide **2** (1.1 equiv), and base (3 equiv) in $CHCl_3$ was stirred at room temperature for the time indicated in Table 1. As summarized in Table 1, $KF\cdot 2H_2O$ was the most efficient base among the tested bases (Table 1, entry 1). Next, several solvents were examined with $KF\cdot 2H_2O$ as base. The best yield was obtained in $KF\cdot 2H_2O/CHCl_3$ system (Table 1, entry 1).

To determine the scope of this approach, a number of arsonium salts were tested under the optimized reaction condition. As shown

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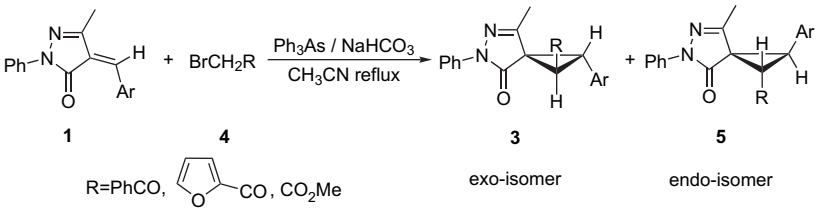


Scheme 2.

Table 1
Optimization of condition for the cyclopropanation reaction

Entry	Base	Solvent	Time (h)	Yield[a] **3a** (%)	Entry	Base	Solvent	Time (h)	Yield[a] **3a** (%)
1	$KF{\cdot}2H_2O$	$CHCl_3$	3	97	4	$KF{\cdot}2H_2O$	DME[b]	10	85
2	$NaHCO_3$	$CHCl_3$	52	70	5	$KF{\cdot}2H_2O$	EtOAc	24	46
3	K_2CO_3	$CHCl_3$	6	97	6	$KF{\cdot}2H_2O$	CH_3CN	3	93

[a] Isolated yield by silica gel chromatography.
[b] DME=dimethoxyethane.

in Table 2, the desired spirocyclopropanes **3a–j** were obtained. In all cases, the *exo-trans*-2,3-dihydro-spirocyclopropane **3** was obtained as the sole product. The structures of compounds (**3a–j**) were characterized by ^1H NMR, ^{13}C NMR, MS, IR, elemental analysis, and X-ray diffraction analysis (Figs. 1 and 2).[8]

Based on the above results, we turned our attention to investigate triphenylarsine-catalyzed cyclopropanation reaction for synthesis of spirocyclopropyl-pyrazolin-5-one. At first, we examined the reaction of pyrazolinone **1a** (1 mmol) and phenacyl bromide **2** (1.2 mmol) with catalytic amount of triphenylarsine (10% mmol) in $KF{\cdot}2H_2O/CHCl_3$ system. At room temperature, no reaction occurred. Whereas the mixture of *exo* and *endo* isomers (**3a** and **5a**) was obtained in chloroform at reflux in 53 and 30% yields, respectively. The further optimization of the reaction conditions was carried out. The results are summarized in Table 3. Higher total yield of *exo* and *endo* isomers was obtained when the reaction was performed in $KF{\cdot}2H_2O/CHCl_3$ (Table 3, entry 1), however, the best yield of *endo* isomer was obtained in $NaHCO_3$/CH_3CN system (Table 3, entry 5). To get more *endo* isomer from

Table 2
Synthesis of spirocyclopropyl-pyrazolin-5-one **3** from pyrazolinone **1** and arsonium ylide

Entry	Ar	R	Time (h)	Yield[a] **3** (%)	Entry	Ar	R	Time (h)	Yield[a] **3** (%)
1	$4\text{-}ClC_6H_4$	COPh	3	**3a**, 97	6	$4\text{-}CH_3OC_6H_4$	CO_2CH_3	36	**3f**, 54
2	C_6H_5	COPh	5	**3b**, 84	7	$4\text{-}ClC_6H_4$		34	**3g**, 67
3	$4\text{-}CH_3OC_6H_4$	COPh	24	**3c**, 85	8	$4\text{-}ClC_6H_4$		15	**3h**, 71
4	$4\text{-}ClC_6H_4$	CO_2CH_3	14	**3d**, 70	7	$4\text{-}ClC_6H_4$	CN	35	**3i**, 60
5	C_6H_5	CO_2CH_3	36	**3e**, 84					

[a] Isolated yield by silica gel chromatography.

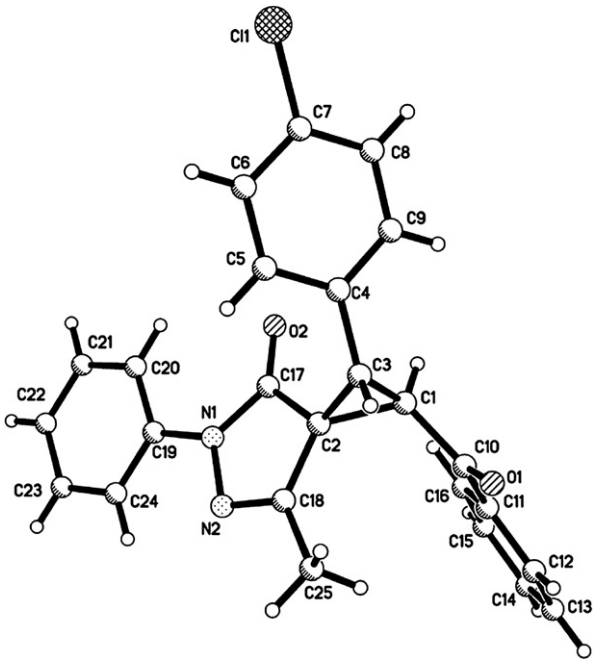


Figure 1. X-ray crystal structure of **3a**.

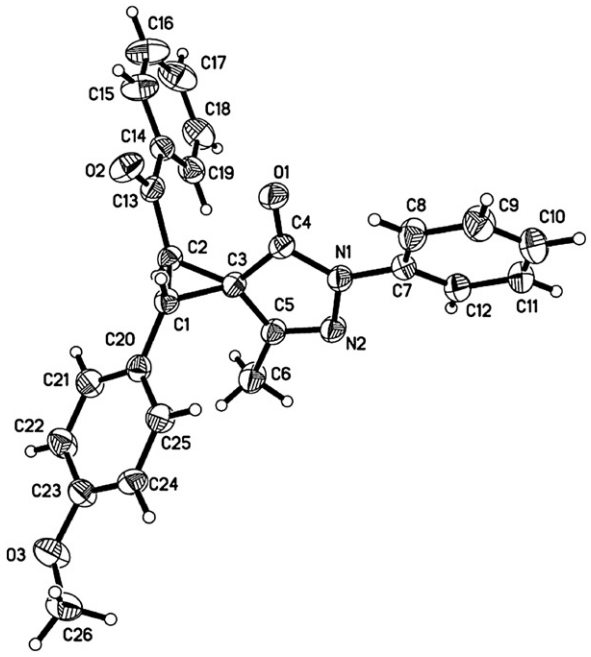


Figure 2. X-ray crystal structure of **5c**.

Table 3
Optimization of condition for triphenylarsine-catalyzed cyclopropanation reaction

Entry	Base	Solvent	Temperature (°C)	Time (h)	Yield[a] **3a** (%)	Yield[a] **5a** (%)
1	$KF·2H_2O$	$CHCl_3$	60	96	53	30
2	$NaHCO_3$	$CHCl_3$	60	72	61	12
3	K_2CO_3	$CHCl_3$	60	16	2	11
4	$KF·2H_2O$	CH_3CN	80	18	44	30
5	$NaHCO_3$	CH_3CN	80	10	15	55
6	K_2CO_3	CH_3CN	80	3	18	12
7	$NaHCO_3$	EtOH	80	2	23	13
8	$NaHCO_3$	Benzene	80	26	3	0
9	$NaHCO_3$	DME[b]	80	24	0	0
10	$NaHCO_3$	CH_3NO_2	100	4	33	9

[a] Isolated yield by silica gel chromatography.
[b] DME=dimethoxyethane.

this reaction, we chose $NaHCO_3/CH_3CN$ system as a standard protocol.

Several bromides were tested to determine the scope and limitation of this reaction. There were no corresponding spiro compounds observed when bromoacetonitrile and 2-bromo-1-thiophen-2-yl-ethanone were employed as starting materials (Table 4, entries 8 and 9). We found that the reaction condition for preparing arsonium salts[9] was different from the condition for triphenylarsine-catalyzed cyclopropanation reaction. We studied the formation of the arsonium salts with bromoacetonitrile or 2-bromo-1-thiophen-2-yl-ethanone under the catalytic condition. There were no corresponding arsonium salts formed when equal molar of triphenylarsine and bromoacetonitrile or 2-bromo-1-thiophen-2-yl-ethanone were stirred at reflux in CH_3CN. Thus, these cyclopropanation reactions were unsuccessful. The plausible mechanism for this reaction is proposed and depicted in Scheme 3. The arsonium ylide may be produced by deprotonation of arsonium salt **2**, which could be formed from triphenylarsine and bromide under triphenylarsine-catalyzed condition, in the presence of $KF·2H_2O$ or $NaHCO_3$. The ylide could nucleophilically attack the 4-arylidene-3-methyl-1-phenyl-pyrazolin-5-one 1 to result in the transition states (**TS-A**) and (**TS-B**). The *exo*-spirocyclopropane **3** could be formed via **TS-A**, while *endo* isomer **5** could be formed through **TS-B**. It is obvious that the reaction temperature plays a key role in controlling the pathway. At room temperature, **TS-A** may be favored over **TS-B** due to the hydrogen bond formed between hydrogen and oxygen anion, and the *exo*-spirocyclopropane **3** would be formed as the sole product. At higher temperature, both **TS-A** and **TS-B** could be existed. Because part of **TS-A** could be transformed into **TS-B** due to the steric repulsion between methyl group and bulky R group in the conformation of **TS-A** when the hydrogen bond in **TS-A** may be weaker at higher temperature in solution. The fact that higher yield of *endo* isomer was obtained in acetonitrile at reflux showed that the possibility of **TS-B** increased with the rise of reaction temperature.

Table 4
Triphenylarsine-catalyzed cyclopropanation of pyrazolinone **1** with bromide

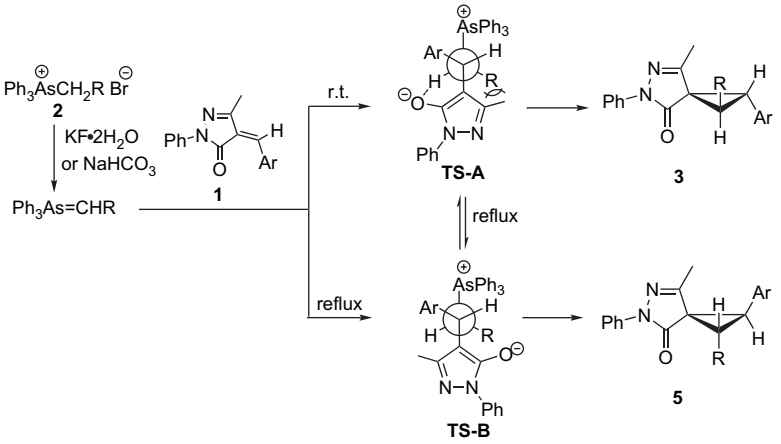
Entry	Ar	R	Solvent	Time (h)	Yield[a] **3** (%)	Yield[a] **5** (%)
1	$4\text{-}ClC_6H_4$	Ph	CH_3CN	10	**3a**, 15	**5a**, 55
2	C_6H_5	Ph	CH_3CN	10	**3b**, 8	**5b**, 25
3	$4\text{-}CH_3OC_6H_4$	Ph	CH_3CN	48	**3c**, 8	**5c**, 32
4	$4\text{-}ClC_6H_4$	OCH_3	CH_3CN	8	**3d**, 29	**5d**, 45
5	C_6H_5	OCH_3	CH_3CN	32	**3e**, 32	**5e**, 43
6	$4\text{-}CH_3OC_6H_4$	OCH_3	CH_3CN	72	**3f**, 5	**5f**, 10
7	$4\text{-}ClC_6H_4$		CH_3CN	10	**3g**, 8	**5g**, 11
8	$4\text{-}ClC_6H_4$		CH_3CN	10	0	0
9	$4\text{-}ClC_6H_4$	CN	CH_3CN	10	0	0

[a] Isolated yield by silica gel chromatography.

3. Experimental

3.1. General

All reagents and solvents were obtained from commercial sources and used without purification. All melting points were uncorrected. Melting points were determined on WRS-1 digital melting point apparatus made by Shanghai physical instrument factory (SPOIF), China. IR spectra were measured on a Bruker spectrometer and expressed in cm^{-1} (KBr disc). ^1H NMR spectra were recorded at a Bruker AM-500, using $CDCl_3$ as solvent and TMS as internal reference. *J* values are given in hertz. Mass spectra were taken with a HP5989A mass spectrometer at an ionizing voltage of 70 eV. Elemental analyses were measured on the elemental vario EL III. X-ray crystal data were collected with Bruker Smart Apex2 CCD.



Scheme 3.

3.2. Preparation of 4-arylidene-3-methyl-1-phenyl-pyrazolin-5-ones

These compounds were prepared by condensing 3-methyl-1-phenyl-pyrazolin-5-one with aromatic aldehydes under Knoevenagel reaction condition. The *Z* configuration of 4-arylidene-3-methyl-1-phenyl-pyrazolin-5-one was established from the corresponding NOESY correlations between the methyl proton and the methylene proton.

3.3. General procedure for the preparation of compounds 3

A mixture of pyrazolinone **1** (1 mmol), arsonium salt **2** (1.1 mmol), and $KF\cdot 2H_2O$ (284 mg, 3 mmol) was stirred at room temperature in $CHCl_3$ (5 mL). The completion of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 8:1). Triphenylarsine could be recovered and the desired product **3** was obtained.

*3.3.1. exo-trans-2,3-Dihydro-1-benzoyl-2-(4-chlorophenyl)-7-methyl-5-phenyl-5,6-diaza-spiro[2,4]hept-6-en-4-one (**3a**)*

As a white solid; mp (°C): 159–160 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.00 (s, 3H), 4.18 (d, *J*=8.5, 1H), 4.21 (d, *J*=8.5, 1H), 7.13–7.16 (m, 1H), 7.28–7.37 (m, 6H), 7.48–7.51 (m, 2H), 7.61–7.64 (m, 1H), 7.86 (d, *J*=8.0, 2H), 7.98 (d, *J*=8.0, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.0, 38.2, 41.3, 46.5, 118.6, 125.1, 127.2, 128.6, 128.9, 129.2, 129.5, 129.7, 129.9, 130.8, 132.4, 134.2, 134.5, 135.9, 138.3, 156.2, 167.3, 191.7; IR (KBr) ν: 3445, 1710, 1679, 1594 cm^{-1}; MS *m*/*z* (%) (EI): 416 (M^++1, 1), 106 (8), 105 (100), 91 (2), 78 (3), 77 (43), 51 (7), 44 (14), 43 (2). Anal. Calcd for $C_{25}H_{19}ClN_2O_2$: C, 72.37; H, 4.62, N, 6.75. Found: C, 72.41; H, 4.46; N, 6.83.

*3.3.2. exo-trans-2,3-Dihydro-1-benzoyl-7-methyl-2,5-diphenyl-5,6-diaza-spiro[2,4]hept-6-en-4-one (**3b**)*

As a white solid; mp (°C): 131–132 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.03 (s, 3H), 4.25 (d, *J*=9.0, 1H), 4.27 (d, *J*=9.0, 1H), 7.14–7.17 (m, 2H), 7.34–7.37 (m, 6H), 7.49–7.52 (m, 2H), 7.62–7.66 (m, 1H), 7.86–7.88 (m, 2H), 8.00–8.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.0, 39.2, 41.3, 46.7, 118.5, 125.0, 128.3, 128.4, 128.6, 129.4, 131.3, 134.4, 136.0, 138.3, 156.4, 167.4, 192.0; IR (KBr) ν: 3447, 1690, 1676, 1594 cm^{-1}; MS *m*/*z* (%) (EI): 380 (M^+, 2), 115 (2), 106 (6), 105 (100), 78 (2), 77 (39), 76 (2), 51 (6), 44 (7). Anal. Calcd for $C_{25}H_{20}N_2O_2$: C, 78.93; H, 5.30; N, 7.36. Found: C, 78.79; H, 5.12; N, 7.18.

*3.3.3. exo-trans-2,3-Dihydro-1-benzoyl-2-(4-methoxyphenyl)-7-methyl-5-phenyl-5,6-diaza-spiro[2,4]hept-6-en-4-one (**3c**)*

As a white solid, mp (°C): 144–145 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.04 (s, 3H), 3.83 (s, 3H), 4.23 (d, *J*=9.0, 1H), 4.27 (d, *J*=9.0, 1H), 6.89–6.91 (m, 2H), 7.16–7.19 (m, 1H), 7.31–7.33 (m, 2H), 7.37–740 (m, 2H), 7.51–7.55 (m, 2H), 7.65–7.68 (m, 1H), 7.90 (d, *J*=7.5, 2H), 8.02 (d, *J*=7.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.0, 39.1, 41.5, 46.9, 55.2, 113.8, 118.5, 123.1, 125.0, 128.6, 128.8, 129.2, 130.6, 134.4, 136.0, 138.4, 156.5, 159.5, 167.5, 192.1; IR (KBr) ν: 3448, 1709, 1679, 1596 cm^{-1}; MS *m*/*z* (%) (EI): 411 (M^++1, 6), 410 (M^+, 1), 408 (7), 106 (8), 105 (100), 78 (3), 77 (47), 51 (8), 44 (23). Anal. Calcd for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82. Found: C, 76.35; H, 5.08; N, 6.65.

*3.3.4. exo-trans-2,3-Dihydro-2-(4-chlorophenyl)-4-methyl-7-oxo-6-phenyl-5,6-diaza-spiro[2,4]hept-4-ene-1-carboxylic acid methyl ester (**3d**)*

As a white solid; mp (°C): 190–191 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.22 (s, 3H), 3.40 (d, *J*=9.0, 1H), 3.83 (s, 3H), 3.88 (d, *J*=9.0, 1H), 7.13–7.16 (m, 1H), 7.23–7.24 (m, 2H), 7.28–7.32 (m, 2H), 7.35 (d, *J*=7.5, 2H), 7.80 (d, *J*=7.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.2, 37.4, 38.7, 44.9, 53.0, 118.6, 125.1, 128.5, 128.8, 129.3, 130.6, 134.2, 138.1, 156.1, 167.1 168.1; IR (KBr) ν: 3455, 1737, 1701, 1595 cm^{-1}; MS *m*/*z* (%) (EI): 370 (M^++2, 4), 369 (M^++1, 2), 368 (M^+, 9), 338 (21), 336 (50), 308 (17), 128 (20), 105 (19), 77 (100), 51 (19), 44 (59). Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.44; H, 4.63; N, 7.66.

*3.3.5. exo-trans-2,3-Dihydro-4-methyl-7-oxo-2,6-diphenyl-5,6-diaza-spiro[2,4]hept-4-ene-1-carboxylic acid methyl ester (**3e**)*

As a white solid; mp (°C): 120–121 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.23 (s, 3H), 3.70 (d, *J*=8.5, 1H), 3.83 (s, 3H), 3.95 (d. *J*=8.5, 1H), 7.12–7.15 (m, 1H), 7.29–7.35 (m, 7H), 7.82–7.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.2, 37.5, 39.7, 45.0, 52.8, 118.5, 124.9, 128.2, 128.3, 128.7, 129.2, 130.8, 138.2, 156.7, 167.2, 168.3; IR (KBr) ν: 4354, 1737, 1694, 1596 cm^{-1}; MS *m*/*z* (%) (EI): 334 (M^+, 15), 303 (24), 302 (75), 274 (33), 121(27), 115 (32), 102 (33), 77 (100), 51 (35). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.79; H, 5.39; N, 8.36.

*3.3.6. exo-trans-2,3-Dihydro-2-(4-methoxy-phenyl)-4-methyl-7-oxo-6-phenyl-5,6-diaza-spiro[2,4]hept-4-ene-1-carboxylic acid methyl ester (**3f**)*

As a white solid; mp (°C): 126–127 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.25 (s, 3H), 3.40 (d, *J*=9.0, 1H), 3.81 (s, 3H), 3.85 (s, 3H), 3.93 (d, *J*=9.0, 1H), 6.86–6.88 (m, 2H), 7.14–7.17 (m, 1H), 7.26 (d, *J*=8.0, 2H), 7.34–7.38 (m, 2H), 7.85 (d, *J*=8.0, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.2, 37.7, 39.6, 45.3, 52.9, 55.2, 113.8, 118.6, 122.6, 124.9, 128.8, 130.4, 138.3, 156.4, 159.5, 167.3, 168.4; IR (KBr) ν: 3444, 1735, 1703, 1596 cm^{-1}; MS *m*/*z* (%) (EI): 364 (M^+, 6), 362 (20), 332 (19), 135 (26), 132 (14), 128 (13), 118 (15), 44 (110), 77 (43). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.60; H, 5.51; N, 7.50.

*3.3.7. exo-trans-2,3-Dihydro-1-(4-chlorophenyl)-2-(2-furoyl)-7-methyl-5-phenyl-5,6-diaza-spiro[2,4]hepten-4-one (**3g**)*

As a white solid; mp (°C): 151–152 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.14 (s, 3H), 4.14 (d, *J*=8.5, 1H), 4.17 (d, *J*=8.5, 1H), 6.61–6.62 (m, 1H), 7.14–7.17 (m, 1H), 7.28–7.38 (m, 7H), 7.69 (s, 1H), 7.84–7.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.3, 37.9, 41.0, 46.7, 113.1, 118.5, 119.4, 125.1, 128.6, 128.8, 129.8, 130.7, 134.2, 138.2, 148.1, 152.2, 156.4, 167.2, 180.1; IR (KBr) ν: 3446, 1694, 1670, 1595 cm^{-1}; MS *m*/*z* (%) (EI): 406 (M^++2, 2), 405 (M^++1, 1), 404 (M^+, 5), 336 (4), 96 (6), 95 (100), 77 (16), 67 (3), 51 (6), 44 (20). Anal. Calcd for $C_{23}H_{17}ClN_2O_3$: C, 68.23; H, 4.23; N, 6.92. Found: C, 68.37; H, 3.99; N, 6.72.

*3.3.8. exo-trans-2,3-Dihydro-1-(4-chlorophenyl)-2-(2-thienoyl)-7-methyl-5-phenyl-5,6-diaza-spiro[2,4]hepten-4-one (**3h**)*

As a white solid; mp (°C): 140–141 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.09 (s, 3H), 4.12 (d, *J*=8.5, 1H), 4.17 (d, *J*=8.5, 1H), 7.14–7.18 (m, 2H), 7.28–7.37 (m, 6H), 7.75–7.77 (m, 1H), 7.82–7.85 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.1, 38.2, 41.9, 46.6, 118.5, 125.1, 128.6, 128.8, 128.9, 129.8, 130.7, 133.8, 134.2, 135.9, 138.2, 143.2, 156.3, 167.3, 184.2; IR (KBr) ν: 3445, 1691, 1659, 1595 cm^{-1}; MS *m*/*z* (%) (EI): 422 (M^++2, 2), 113 (6), 112 (8), 111 (100), 83 (5), 77 (13), 51 (6), 44 (16), 42 (3). Anal. Calcd for $C_{23}H_{17}ClN_2O_2S$: C, 65.63; H, 4.07; N, 6.66. Found: C, 65.63; H, 3.78; N, 6.50.

*3.3.9. exo-trans-2,3-Dihydro-2-(4-chlorophenyl)-4-methyl-7-oxo-6-phenyl-5,6-diaza-spiro[2,4]hept-4-ene-1-carbonitrile (**3i**)*

As a white solid; mp (°C): 61–62 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (s, 3H), 2.93 (d, *J*=9.0, 1H), 3.50 (d, *J*=9.0, 1H), 7.22–7.24 (m, 1H), 7.38–7.46 (m, 6H), 7.91–7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.3, 19.3, 37.0, 41.1, 114.5,

118.6, 125.6, 127.8, 129.0, 129.5, 130.9, 135.4, 137.8, 154.6, 168.3; IR (KBr) ν: 3446, 2242, 1696, 1596 cm^{-1}; MS m/z (%) (EI): 335 (M^+, 44), 336 (M^++1, 10), 337 (M^++2, 20), 93 (18), 77 (100), 67 (32), 64 (18), 51 (41), 44 (68). Anal. Calcd for $C_{19}H_{14}ClN_3O$: C, 67.96; H, 4.20; N, 12.51. Found: C, 68.03; H, 4.35; N, 12.17.

3.4. General procedure for the catalytic preparation of compounds 3 and 5

A mixture of pyrazolinone **1** (1 mmol), bromide **4** (1.2 mmol), triphenylarsine (30 mg, 0.1 mmol), and $NaHCO_3$ (240 mg, 3 mmol) was stirred in CH_3CN (10 mL) at reflux. The completion of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 8:1). Triphenylarsine could be recovered and the products **3** and **5** were obtained, respectively.

*3.4.1. endo-trans-2,3-Dihydro-1-benzoyl-2-(4-chlorophenyl)-7-methyl-5-phenyl-5,6-diaza-spiro[2,4]hept-6-en-4-one (**5a**)*

As a white solid; mp (°C): 213–214 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60 (s, 3H), 3.87 (d, J=8.5, 1H), 4.12 (d, J=8.5, 1H), 7.12–7.15 (m, 1H), 7.30 (d, J=8.5, 2H), 7.32–7.34 (m, 2H), 7.38 (d, J=8.5, 2H), 7.42–7.47 (m, 2H), 7.54–7.57 (m, 1H), 7.79–7.85 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.1, 38.8, 39.5, 44.7, 118.5, 125.1, 128.3, 128.8, 129.0, 129.3, 130.6, 131.7, 134.0, 134.7, 135.8, 138.2, 155.6, 168. 189.7; IR (KBr) ν: 3453, 1709, 1681, 1595 cm^{-1}; MS m/z (%) (EI): 415 (M^++1, 1), 115 (2), 106 (7), 105 (100), 78 (3), 77 (38), 51 (8), 44 (12), 42 (2). Anal. Calcd for $C_{25}H_{19}ClN_2O_2$: C, 72.37; H, 4.62; N, 6.75. Found: C, 72.13; H, 4.45; N, 6.84.

*3.4.2. endo-trans-2,3-Dihydro-1-benzoyl-7-methyl-2,5-diphenyl-5,6-diaza-spiro[2,4]hept-6-en-4-one (**5b**)*

As a white solid; mp (°C): 179–180 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.56 (s, 3H), 3.91 (d, J=8.5, 1H), 4.19 (d, J=8.5, 1H), 7.12–7.15 (m, 1H), 7.32–7.39 (m, 7H), 7.43–7.47 (m, 2H), 7.54–7.57 (m, 1H), 7.81–7.83 (m, 2H), 7.86–7.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 39.5, 39.7, 44.6, 118.4, 124.8 128.2, 128.5, 128.7, 128.8, 128.9, 129.2, 133.0, 133.8, 135.9, 138.2, 155.9, 168.1, 189.9; IR (KBr) ν: 3455, 1712, 1684, 1595 cm^{-1}; MS m/z (%) (EI): 380 (M^+, 3), 106 (60), 105 (100), 77 (47), 57 (4), 51 (10), 44 (44), 43 (8), 42 (4). Anal. Calcd for $C_{25}H_{20}N_2O_2$: C, 78.93; H, 5.30; N, 7.36. Found: C, 79.12; H, 5.07; N, 7.01.

*3.4.3. endo-trans-2,3-Dihydro-1-benzoyl-2-(4-methoxyphenyl)-7-methyl-5-phenyl-5,6-diaza-spiro[2,4]hept-6-en-4-one (**5c**)*

As a white solid; mp (°C): 136–137 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.58 (s, 3H), 3.83 (s, 3H), 3.87 (d, J=8.5, 1H), 4.12 (d, J=8.5, 1H), 6.91 (d, J=8.5, 2H), 7.11–7.14 (m, 1H), 7.27 (d, J=8.5, 2H), 7.31–7.34 (m, 2H), 7.42–7.45 (m, 2H), 7.54–7.57 (m, 1H), 7.81–7.83 (m, 2H), 7.85–7.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 39.5, 39.7, 44.7, 55.2, 114.2, 118.3, 124.7, 124.8, 128.1, 128.6, 128.8, 130.2, 133.7, 135.8, 138.2, 156.0, 159.5, 168.2, 190.0; IR (KBr) ν: 3455, 1704, 1676, 1596 cm^{-1}; MS m/z (%) (EI): 411 (M^++1, 1), 219 (8), 106 (9), 105 (100), 91 (22), 77 (43), 57 (8), 51 (13), 44 (27). Anal. Calcd for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82. Found: C, 76.26; H, 5.23; N, 6.90.

*3.4.4. endo-trans-2,3-Dihydro-2-(4-chlorophenyl)-4-methyl-7-oxo-6-phenyl-5,6-diaza-spiro[2,4]hept-4-ene-1-carboxylic acid methyl ester (**5d**)*

As a white solid; mp (°C): 111–112 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.43 (s, 3H), 3.29 (d, J=8.5, 1H), 3.82 (s, 3H), 3.91 (d, J=8.5, 1H), 7.18–7.19 (m, 1H), 7.24 (d, J=8.5, 2H), 7.35 (d, J=8.5, 2H), 7.39–7.42 (m, 2H), 7.92–7.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.6, 34.9, 39.0, 42.9, 52.6, 118.2, 124.8, 128.6, 128.9, 130.1, 130.9, 134.3, 138.0, 155.4, 165.5, 168.2; IR (KBr) ν: 3458, 1741, 1701 cm^{-1}; MS m/z (%) (EI): 369 (M^++1, 1), 368 (M^+, 5), 336 (37), 136 (15), 128 (16), 105 (18), 77 (110), 59 (130), 51 (230), 44 (40). Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60; Found: C, 65.40; H, 4.60; N, 7.36.

*3.4.5. endo-trans-2,3-Dihydro-4-methyl-7-oxo-2,6-diphenyl-5,6-diaza-spiro[2,4]hept-4-ene-1-carboxylic acid methyl ester (**5e**)*

As a white solid; mp (°C): 106–107 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.37 (s, 3H), 3.34 (d, J=8.5, 1H), 3.82 (s, 3H), 3.97 (d, J=8.5, 1H), 7.17–7.19 (m, 1H), 7.28–7.41 (m, 7H), 7.93–7.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.0, 35.5, 40.4, 43.5, 53.0, 118.7, 125.1, 128.8, 129.0, 129.1, 129.3, 132.8, 138.6, 156.5, 166.3, 169.0; IR (KBr) ν: 3445, 1738, 1706, 1595 cm^{-1}; MS m/z (%) (EI): 334 (M^+, 5), 302 (30), 77 (74), 71 (36), 57 (56), 55 (34), 44 (82), 43 (100), 41 (26). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 72.06; H, 5.40; N, 8.46.

*3.4.6. endo-trans-2,3-Dihydro-2-(4-methoxy-phenyl)-4-methyl-7-oxo-6-phenyl-5,6-diaza-spiro[2,4]hept-4-ene-1-carboxylic acid methyl ester (**5f**)*

As a white solid; mp (°C): 120–121 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.41 (s, 3H), 3.30 (d, J=8.5, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 3.92 (d, J=8.5, 1H), 6.87 (d, J=8.5, 2H), 7.16–7.18 (m, 1H), 7.20 (d, J=8.5, 2H), 7.38–7.41 (m, 2H), 7.92–7.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.6, 35.3, 39.7, 43.1, 52.5, 55.0, 114.0, 118.2, 124.1, 124.6, 128.5, 130.0, 138.1, 156.1, 159.4, 165.9, 168.5; IR (KBr) ν: 3427, 1712, 1684, 1595 cm^{-1}; MS m/z (%) (EI): 364 (M^+, 21), 332 (82), 304 (48), 135 (37), 132 (43), 128 (27), 77 (100), 51 (24), 44 (89). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.15; H, 5.32; N, 7.44.

*3.4.7. endo-trans-2,3-Dihydro-1-(4-chlorophenyl)-2-(2-furoyl)-7-methyl-5-phenyl-5,6-diaza-spiro[2,4]hept-en-4-one (**5g**)*

As a white solid; mp (°C): 134–135 (methylene chloride/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.55 (s, 3H), 3.81 (d, J=9.0, 1H), 4.09 (d, J=9.0, 1H), 6.53–6.54 (m, 1H), 7.14–7.17 (m, 1H), 7.29–7.38 (m, 7H), 7.53 (s, 1H), 7.85–7.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.7, 38.1, 38.7, 43.9, 112.6, 117.8, 118.1, 124.6, 128.5, 128.9, 130.3, 131.3, 134.3, 138.0, 146.7, 152.0, 155.6, 167.8, 178.1; IR (KBr) ν: 3455, 1719, 1695, 1595 cm^{-1}; MS m/z (%) (EI): 404 (M^+, 4), 96 (7), 95 (100), 77 (17), 51 (8), 44 (33), 42 (7), 41 (6). Anal. Calcd for $C_{23}H_{17}ClN_2O_3$: C, 68.23; H, 4.23; N, 6.92. Found: C, 68.05; H, 4.16; N, 6.63.

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References and notes

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8. CCDC-648245 (**3a**) and CCDC-648246 (**5c**) contain all crystallographic details of this publication and are available free of charge at www.ccdc.cam.ac.uk or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk. Unit cell parameters (**3a**): *a*: 8.2396(2) Å; *b*: 10.9572(2) Å; *c*: 13.0351(3) Å; α: 73.5850(10); β: 81.840(2); γ: 68.5160(10); space group: *P*-1. Unit cell parameters (**5c**): *a*: 22.721(3) Å; *b*: 10.4745(12) Å; *c*: 21.675(4) Å; α: 90; β: 120.629(2); γ: 90; space group: *C*2/*c*.
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